

Review Article

Carotid Stenosis and Stroke: Historical Perspectives Leading to Current Challenges

David M. Pelz¹ , Allan J. Fox², J. David Spence^{3,4} and Stephen P. Lownie^{5,6}

¹Department of Medical Imaging, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada, ²University of Toronto, Toronto, ON, Canada, ³Neurology and Clinical Pharmacology, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada, ⁴Stroke Prevention and Atherosclerosis Research Centre, Robarts Research Institute, London, ON, Canada, ⁵Division of Neurosurgery, Department of Surgery, Dalhousie University, Halifax, NS, Canada and ⁶Schulich School of Medicine and Dentistry, Western University, Halifax, NS, Canada

ABSTRACT: The carotid artery is unique; it is the only vessel to bifurcate into a bulb larger than itself. The history of its anatomic description, understanding of its pathophysiology and evolution of its imaging are relevant to current controversies regarding measurement of stenosis, surgical/endovascular therapies and medical management of carotid stenosis in stroke prevention. Treatment decisions on millions of symptomatic and asymptomatic patients are routinely based on information from clinical trials from over 30 years ago. This article briefly summarizes the highlights of past research in key areas and discuss how they led to current challenges of diagnosis and treatment.

RÉSUMÉ : Sténose carotidienne et accidents vasculaires cérébraux : facteurs historiques à l'origine de controverses actuelles. L'artère carotide est unique en son genre, en ce sens qu'elle est le seul vaisseau sanguin à se diviser en un sinus [ou bulbe] plus gros qu'elle-même. Ainsi, l'historique de sa description anatomique, la compréhension que les chercheurs avaient de sa physiopathologie et l'évolution de l'imagerie médicale sont tous des éléments qui permettent de mieux saisir les controverses qui entourent les mesures du degré de sténose ainsi que le traitement chirurgical ou endovasculaire et la prise en charge médicale de la sténose carotidienne en prévention des accidents vasculaires cérébraux. Les décisions relatives au traitement de cette obstruction artérielle chez des millions de patients qui présentent ou non des symptômes reposent généralement sur des données provenant d'essais cliniques effectués il y a plus de 30 ans. Aussi présenterons-nous dans l'article un résumé des faits saillants qui ont marqué la recherche dans le passé dans des domaines clés, et discuterons-nous de la manière dont ces éléments principaux ont conduit aux problèmes actuels de pose de diagnostic et de traitement.

Keywords: carotid artery disease; carotid endarterectomy; history; stroke; stroke imaging

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Introduction

Atherosclerotic stenosis of the internal carotid artery is the cause of < 10%–20% of all acute ischemic strokes.^{1–3} The global prevalence of carotid atherosclerosis between the ages of 30–79 is now approximately 21%, nearly 1 billion people. Over 800 million people have carotid plaque, and 58 million have carotid stenosis.⁴ Although age-adjusted incidence of carotid disease has been declining with more intensive medical therapy,^{4–6} the prevalence has increased by approximately 59% since 2000, mainly due to an aging population.⁵ The incidence of severe, asymptomatic carotid stenosis is estimated to be approximately 3.1% in those 80 years or older.⁷ Treatment decisions to prevent stroke on millions of patients, both symptomatic and asymptomatic, are often based on evidence that is decades old, outdated and frequently flawed.^{8,9} Revascularization procedures including carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS) cost an estimated \$3.7 billion worldwide in 2007⁹ and are undoubtedly much higher today, including the hybrid procedure, transcarotid

artery revascularization (TCAR). This article will briefly summarize the history of pathophysiologic investigation, measurement, medical, surgical and interventional treatment of carotid stenosis in stroke, hopefully providing a context in which to better understand the controversies of today.

The large, historical randomized outcome trials that guide management today relate to stroke caused by atherosclerotic carotid stenosis. No similar trials to guide management of other carotid artery conditions in stroke, such as dissections, carotid webs, tandem cervical and intracranial disease exist and these entities will not be discussed in this article.

History

The carotid artery is unique in the human body. It is the only artery that bifurcates into a bulb larger than itself. It is subjected to unique hemodynamic and pathophysiologic forces and has been a source of fascination for centuries. In 438 BC, the Greeks depicted manual neck compression on the Parthenon as a battlefield technique to

Corresponding author: D. M. Pelz; Email: pelz@uwo.ca

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stun, stupefy or plunge an opponent into a deep sleep (*karos* or *karotides*). In the same century, Hippocrates recognized that lesions of one neck vessel resulted in contralateral hemiplegia and coined the term *apoplexy* (to *strike down*) to describe stroke. Rufus of Ephesus in 100 AD is credited with officially naming these vessels *carotid*^{10,11} and Vesalius in 1543 was the first to provide accurate illustrations and to recognize their significance for cerebral circulation.^{10–12} Wepfer in 1658 was the first to provide detailed descriptions of the cerebral and extracranial vasculature, and to describe extracranial carotid thrombosis in association with *apoplexy*.^{10,11} Willis in 1664 is credited with recognizing the physiologic and pathologic importance of his eponymous Circle at the base of the brain, including the potential for collateral circulation in proximal occlusion, a principle dramatically proven by John Hunter in the 1700s.

Pathophysiology

In 1905, Chiari provided autopsy confirmation of atheromatous plaque in the cervical vessels as the source of cerebral emboli in stroke, a condition he termed “*endarteritis chronica deformans*.”¹³ Chiari in 1906 and Hunt in 1914 both re-emphasized the importance of the extracranial carotid arteries,¹⁴ which were first imaged by Moniz in 1927 with direct puncture cerebral angiography.¹⁵ It was not until the 1940s that detailed clinico-pathological association between carotid atherosclerosis and stroke was observed, a correlation then firmly established by C Miller Fisher’s seminal reports from the 1950s.^{16,17} His descriptions of carotid plaque associated thrombus and intraplaque hemorrhage, and the observation that most symptomatic patients had at least a 75% stenosis, or luminal diameter of 1 millimeter (mm) or less, form the basis for our understanding of extracranial disease and cerebral ischemia.^{18,19} External to internal carotid artery (ICA) collaterals were first described in 1911, and leptomeningeal collaterals, initially postulated by Heubner in 1874, in 1953.²⁰

Carotid surgery

The earliest reports of surgery on the carotid artery appeared in 1793 and were usually related to trauma and hemorrhage. John Abernethy, a protégé of John Hunter demonstrated that ligation of the carotid artery was survivable because of collateral flow in 1803.²¹ C Miller Fisher was an early proponent of revascularization surgery for extracranial atherosclerosis, although initially for restoration of normal blood flow rather than prevention of cerebral emboli.¹⁷

The first successful surgical reconstruction of the carotid artery was performed in Buenos Aires in 1951,²¹ and the first published report of successful CEA was by Eastcott et al in 1954,²² an earlier claim by DeBakey from 1953 was not reported until 1975. Interestingly, Eastcott used systemic hypothermia of 28C during 28 minutes of carotid occlusion. The first use of a shunt during CEA, a technique still debated today, was by Cooley in 1956.²¹ Surgical pioneers such as DeBakey and Cooley initially believed that the problem of carotid stenosis was due to reduced cerebral blood flow, and that stenosed vessels should be opened to improve flow, not prevent emboli.²³ It was Francis Murphey in 1973²⁴ who championed the embolic theory of stroke, and Wesley Moore in 1978 who documented the significance of ulcerated carotid plaques.²⁵

Over the next several decades, the numbers of CEA procedures worldwide grew rapidly, with essentially no guidelines on who would benefit from the procedure, or what would be acceptable

complication rates. In the United States, surgical mortality in over 2,400 cases performed between 1961 and 1968 was approximately 4.5%.²⁶ By 1976, over 34,000 procedures were being performed annually, with persistent high morbidity and mortality rates, up to 21% in one community-based series.²⁷ By 1985, over 100,000 CEAs were done annually, the third most common operation in the United States (US), with morbidity and mortality estimated at 10%.^{26,27} General unhappiness with both medical and surgical treatments of stroke led to the Joint Study on Extracranial Occlusive Disease in the US between 1959 and 1976, which added a large amount of surgical information to the debate but showed no significant outcome difference between medical and surgical groups.^{12,28} Heterogeneity and unreliability of accumulated clinical data prompted calls for multicentre randomized controlled trials (RCTs).²⁷

Initial RCTs of CEA vs. medical therapy were negative for surgical benefit.^{28–30} It was not until the landmark RCTs, the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET), published in 1991, that CEA was clearly shown to effectively prevent strokes in symptomatic patients with carotid stenosis > 70%.^{31,32} In NASCET, perioperative stroke and mortality rates of 5.5% and 1.2% were achieved and generally accepted as the standard. Despite organizational and methodological differences, both studies showed significant benefit of CEA over medical therapy, with NASCET showing an absolute risk reduction of 16%, and the number needed to treat of 6 patients to prevent one stroke over 5 years in patients with 70%–95% stenosis. Both men and women with 70–99% stenosis had significant benefit, and men with 50%–69% stenosis had some benefit with CEA performed within 2–3 weeks of their ischemic event. A combined ECST-NASCET analysis also confirmed that the benefit of surgery was muted in patients with lesser degrees of stenosis (50%–69%) and those with near occlusions (95%–99%), and that there was harm from surgical intervention in those with < 50% stenosis.¹²

Concurrently, investigators were studying patients with asymptomatic carotid stenosis. The Veterans Affairs study of 1993³³ showed no benefit of CEA over medical therapy. The Asymptomatic Carotid Atherosclerosis Study (ACAS) in 1995 showed marginal benefit from CEA in patients with severe stenosis, with an annual risk reduction of 1% and a number needed to treat of > 65 to prevent one stroke over 2 years.³⁴ Only men aged 75–80 with 60%–99% stenosis were found to benefit from CEA. These studies did not recognize or analyze for near occlusions as did NASCET. The inclusion of transient ischemic attack as an endpoint in this study distinguished it from ECST and NASCET, weakening the conclusions. The Asymptomatic Carotid Surgery Trial (ACST), published in 2004 showed similar results with marginal benefit, but only if perioperative stroke and death did not exceed 3%.³⁵ These studies and others have justified intervention on vast numbers of asymptomatic patients despite impressive improvements in medical therapy³⁶ and evidence that complication rates in the community often exceed 3%.³⁷ Approximately 90% of carotid revascularization procedures are performed in asymptomatic patients in the USA.^{38,39} The rates of intervention elsewhere are much lower, estimated at 7% in the UK.⁴⁰ Contemporary RCTs of intervention vs. medical therapy for asymptomatic disease such as ACST-2, ECST-2 and Stent Protected Angioplasty versus Carotid Endarterectomy (SPACE-2) have shown inconclusive findings, and results of the most comprehensive trial, Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST-2) are pending.^{41,42}

Measurement of carotid stenosis

The measurement of carotid stenosis, historically so essential to clinical decision-making, has always been controversial. Absolute luminal diameter, cross sectional area, ratios, % reduction and “eyeball” techniques using a variety of modalities, beginning with angiography by direct puncture and then catheters, have all been used with varying degrees of validity. It is relatively easy to overestimate stenosis severity, and arbitrary criteria, with stenoses as low as 30%⁴³ were used to justify treatment. The Joint Study in the US was one of the first to rigorously define stenosis comparing the narrowest luminal diameter to the internal carotid artery beyond the bulb (28), but it was not until NASCET and ECST that validated measurement schemes were widely accepted.

NASCET used a ratio of the ICA diameter at the site of maximal stenosis to the ICA diameter well beyond the bulb where the walls are parallel⁴⁴ whereas ECST used a ratio of the maximal ICA stenosis to the carotid bulb, unseen on a catheter angiogram. There are pitfalls with both systems. For NASCET, interpretation of partial or complete collapse beyond a proximal stenosis,⁴⁵ resulting in “near occlusion” will produce otherwise fallacious ratios of percent stenosis. Near occlusions are common when recognized correctly.⁴⁶ NASCET percentage calculation uses a denominator of a normal ICA diameter well beyond the bulb where the walls are parallel, not commonly complied with and located outside the range of ultrasound windows. The ECST pitfall is to measure an imagined bulb diameter. These pitfalls lead to unique prognostic and therapeutic distortions.

There was initial confusion when comparing outcome results using NASCET and ECST systems, with a study in 1994 demonstrating their essential incompatibility, i.e., a 70% ECST stenosis was calculated as suggesting only 40% by NASCET, 75% ECST suggesting 50% NASCET, and 85% ECST suggesting 70% NASCET.⁴⁷ The NASCET method became the most durable and widely accepted for research and outside the bounds of clinical trials because endarterectomy clearly corrected the very serious stroke risk for the most severe stenoses. It was always relatively easy, however, to “fudge” the percent stenosis to exaggerate severity, thereby giving the appearance of surgical eligibility for patients with a stenosis that didn't meet the rigorous NASCET criteria. The denominator of the commonly used ratios has always been a source of ambiguity and unreliability.⁴⁴

The replacement of instrumented angiography and its intrinsic risks with less-invasive modalities such as duplex ultrasound, CTA and MRA permits much more accurate and detailed evaluation of carotid disease. Direct measurement in mms at the site of greatest stenosis is the key parameter, accurate from CTA without the stroke risk of catheter angiography, and nearly so with MRA. NASCET percentages can be extrapolated from CTA images,⁴⁸ but overestimation of percentage stenosis is common^{49,50} and the vagaries of percent stenosis continue. The real comparative measurement is the stenosis diameter without a ratio, as originally proposed by Miller Fisher.¹⁹

Ultrasound and MRI now provide detailed analysis of plaque morphology and composition, allowing demonstration of plaque progression, regression and vulnerability.⁵¹ More sophisticated, contemporary criteria are becoming available to determine the need for carotid intervention.^{52,53} Maximum wall thickness, lipid-rich necrotic core, intraplaque hemorrhage, fibrous cap rupture, plaque inflammation and neovascularity are all associated with increased stroke risk. The recently introduced Carotid Plaque-RADS scale⁵³ is a multi-modality scoring system that incorporates

these variables, as well as plaque burden, stenosis progression and calcification to produce an overall assessment of plaque vulnerability and stroke risk.

It is now time for stroke researchers to abandon ratios and percent stenosis, debated principles now decades old. NASCET outcomes were based on stenosis degree, and this remains valid. New studies in both symptomatic and asymptomatic patients, however, must work not only from stenosis assessed at the narrowest diameter in mms but should also incorporate current determinants of plaque vulnerability and stroke risk.⁵³

Carotid angioplasty and stenting

The earliest report of percutaneous transluminal balloon angioplasty of the carotid artery was in 1981.⁵⁴ The procedure was initially performed primarily by cardiologists and general interventional radiologists,⁵⁵ who soon realized that the carotid was not just another peripheral vessel, but one in which recoil, dissection and generation of emboli from friable atherosclerotic plaque following angioplasty could have major clinical consequences, eventually progressing to the routine use of stents and embolic protection devices (EPDs). CAS became a popular alternative to CEA, perceived as less invasive, particularly in high surgical risk patients.⁵⁶

RCTs of CEA vs. CAS soon followed, all defining primary endpoints as stroke or death and two including myocardial infarction. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) in 2001⁵⁷ showed no difference in outcomes between groups, but relatively high major adverse effects in both (9%–10%). The Stenting and Angioplasty with Protection in Patients at High risk for Endarterectomy (SAPPHIRE) in 2004 studied high surgical risk patients, 71% of whom were asymptomatic, and found that CAS was safer, mainly due to the lower incidence of myocardial infarction.⁵⁸ This study had a major influence on health care policy in the US, leading to regulatory approval of CAS as a valid alternative to CEA in this group of patients. SPACE and Endarterectomy versus Stenting in patients with Symptomatic Severe Carotid Stenosis (EVA 3-S) in 2006^{59,60} showed conflicting outcomes, the former demonstrating non-inferiority, the latter a higher risk of stroke and death at 30 days with CAS. The International Carotid Stenting Study (ICSS) in 2014 reported equivalent 5-year stroke and death rates, but twice as many non-disabling strokes with CAS.⁶¹ CREST, published in 2010, is considered to be the most informative comparison study, despite almost half of the 2,502 patients being asymptomatic. There was no significant difference in periprocedural and 4-year stroke and death rates, with more strokes in the CAS group and more myocardial infarcts in the CEA group.⁶² This study solidified the belief that CAS is equivalent to CEA in average surgical risk patients as well. However, there is evidence that stroke has a greater adverse effect on quality of life, so this represents a questionable equivalence.⁶³ CEA was safer than CAS in older patients (>75 yrs.) and those with multiple medical co-morbidities. This may seem paradoxical but is explained by the risk of emboli during balloon angioplasty and stenting of rigid, friable atherosclerotic arteries.⁶⁴ Up to 80% of patients undergoing CAS can show new diffusion weighted imaging lesions on MRI, with almost 7% worsening clinically in one series.⁶⁵

There are now multiple RCTs containing CAS arms specifically assessing asymptomatic patients. SPACE-2 and ECST-2 showed no difference between medical management and CAS,^{41,42} and

ACST-2 was reported as showing equivalent complication rates of CAS and CEA in these patients.⁶⁶ However, the periprocedural risk of stroke or death was 3.8% with CAS vs. 2.7% with CEA, and the 5-year risk was 5.5% with CAS vs. 3.6% with CEA.

Medical management

In the late 1800s, Sir William Osler and others were aware of the association of carotid disease and stroke, but it was not until the work of Miller Fisher and Adams in the 1950s and 1960s that the connection of atherosclerotic plaque as a source of embolism and therefore stroke was established, rather than vasospasm and hemodynamic alterations.^{67,68} The first use of anticoagulant therapy for threatened stroke was reported in 1955⁶⁹ but was eventually shown to be ineffective.^{70,71} The first successful trials, not for treatment but for prevention of stroke, occurred in the 1970s with the use of antiplatelet agents such as aspirin, dipyridamole, ticlopidine and clopidogrel, often with the active collaboration of vascular surgeons.^{72–75} Stroke risk was reduced by up to 20% in these studies. Statins have also figured prominently in stroke prevention in both asymptomatic and symptomatic patients since the 1990s.^{76–79} As imaging modalities became more sophisticated, the ability to determine features of plaque vulnerability dramatically improved. The American Heart Association developed well validated criteria of histologic classification in 1995 (80,51). Plaque echogenicity, neovascularity, ulceration, intraplaque hemorrhage, fibrous cap rupture and lipid-rich necrotic core are all associated with increased stroke risk. In combination with the presence of micro-emboli on transcranial Doppler, the ability to predict and monitor response to medical therapy has expanded the options available for the treatment of carotid disease.^{81–83}

An approach to treatment of atherosclerosis based on measurement of carotid plaque implemented in 2003,⁸⁴ was associated with a > 80% reduction of risk among patients with asymptomatic carotid stenosis: the 2-year risk of stroke declined from 8.8% to 1% (i.e., 0.5%/year), and the 2-year risk of myocardial infarction declined from 6.7% to 1%.⁸³ Meta-analyses reported more than 10 years ago that with more intensive medical therapy, the risk of stroke or death was well below the risk of CAS or CEA.⁸⁵ With truly optimal medical management including smoking cessation and a Mediterranean diet, most patients with asymptomatic carotid stenosis would not benefit from intervention. The risk of stroke from a severe, asymptomatic carotid stenosis is approximately 1% annually, or 4.7% over 5 years⁸⁶ and it seems likely that < 10% of asymptomatic patients require intervention.^{36,82}

Conclusions

Measurement standards, interventions and medical therapy of carotid stenosis have all advanced dramatically since the historical trials were performed decades ago.⁸⁷ TCAR, a more recent addition to interventional techniques, has yet to be tested in a controlled trial.⁸⁸ Guidelines for carotid stenting in the US and a recent decision of the Centres for Medicare and Medicaid Services have expanded indications for stenting despite the weakness of past evidence for benefit.^{89,90} There are many who believe that carotid artery revascularization procedures are now greatly over-utilized and that only CEA, in a very limited number of subgroups in trials from decades ago, has ever been shown to have a net benefit compared to noninvasive care alone.⁹⁰

New RCT evidence based on contemporary carotid stenosis measurement⁹¹ and treatment practice is needed. From many trials it is accepted that most stroke risk from carotid disease is via thromboembolism. Hence medical prevention against emboli is used, even in conjunction with revascularization management. Prediction of stroke risk from carotid stenosis has evolved from historical determination of mm diameters and percentages derived from catheter angiography. Although recent studies suggest that carotid revascularization has limited benefit in asymptomatic patients, and that the stroke risk from CAS remains greater than CEA in younger symptomatic patients, surgical/interventional treatments in both asymptomatic and symptomatic patients are becoming entrenched. Apart from the financial and logistical challenges, organization of a meaningful RCT requires equipoise between treatment options with participation and cooperation of practitioners open to alternative approaches.⁹² Surprising results can occur, overcoming widely accepted biases and conventional wisdom, when such trials are conducted with appropriate scientific rigor.^{32,93} Only when these obstacles are overcome will there be valid answers to the continuing controversies regarding carotid stenosis and interventions to prevent stroke.

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References

- Linxin L, Yiin GS, Geraghty OC, et al. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. *Lancet Neurol.* 2015;14:903–13.
- Warlow C, Sudlow C, Dennis M, Wardlaw J, Sandercock P. stroke. *Lancet.* 2003;362:1211–24.
- van Velzen TJ, Kuhrij LS, Westendorp WF, van de Beek D, Nederkoorn PJ. Prevalence, predictors and outcome of carotid stenosis: a sub study in the preventive antibiotics in stroke study (PASS). *BMC Neurol.* 2021;21:20–31.
- Song P, Fang Z, Cai Y, et al. Global and regional prevalence, burden and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. *Lancet Glob Health.* 2020;8:e721–e729.
- Hackam DG, Spence JD. Decline in the severity of carotid atherosclerosis and associated stroke risk factors from 2002–2014. *Stroke.* 2018;49:2786–88.
- Bogiatzi C, Hackam DG, McLeod AI, Spence JD. Secular trends in ischemic stroke subtypes and stroke risk factors. *Stroke.* 2014;45:3208–13.
- De Weerd M, Greving JP, Hedblad B, et al. Prevalence of asymptomatic carotid stenosis in the general population: an individual participant data meta-analysis. *Stroke.* 2010;41:1294–7.
- Abbott A, Paraskevas KI, Kakkos SK, et al. Systematic review of guidelines for the management of asymptomatic and symptomatic carotid stenosis. *Stroke.* 2015;46:3288–301.
- Abbott AL. Extra-cranial carotid artery stenosis: an objective analysis of the available evidence. *Front. Neurol.* 2022;739999:10.3389/neur.2022.739999.
- Robicsek F. The medical history of extracranial cerebrovascular disease. In: Robicsek F, ed. *Extracranial cerebrovascular disease*, New York: MacMillan Publishing Company; 1986:5–18.
- Gurdjian E, Gurdjian E. History of occlusive cerebrovascular disease: from Weper to Moniz. *Arch Neurol.* 1979;36:340–3.
- Barnett HJM. Reflections on the carotid artery: 438 BC to 2009 AD. The Karolinska 2008 Award lecture in stroke research. *Stroke.* 2009;40:3143–8.
- Chiari H. Ueber verhalten des teilung-swinkels der carotis communis bei der endarteritis chronica deformans. *Verh Dtsch Ges Path.* 1905;9:3–6.

14. Hunt JR. The role of the carotid arteries in the causation of vascular lesions of the brain, with remarks on certain special features of the symptomatology. *Am J Med Sci.* 1914;147:704–13.
15. Moniz E. L'encephalographie arterielle, son importance dans la localisation des tumeurs cerebrales. *Rev Neurol.* 1927;2:72–90.
16. Fisher M. Occlusion of the internal carotid artery. *Arch Neurol Psychiat.* 1951;65:346–77.
17. Fisher M. Occlusion of the carotid arteries: further experiences. *Arch Neurol Psychiat.* 1954;72:187–204.
18. Fisher C, Gore I, Okabe N, White P. Atherosclerosis of the carotid and vertebral arteries-extracranial and intracranial. *J Neuropath Exp Neurology.* 1965;24:455–76.
19. Fisher C, Ojemann R. A clinico-pathologic study of carotid endarterectomy plaques. *Rev Neurol (Paris).* 1986;142:573–89.
20. Vander Eecken H, Adams R. The anatomy and functional significance of the meningeal arterial anastomoses of the human brain. *J Neuropath Exp Neurol.* 1953;12:132–57.
21. Thompson JE. The evolution of surgery for the treatment and prevention of stroke. *Stroke.* 1996;27:1427–34.
22. Eastcott HG, Pickering GW, Rob C. Reconstruction of the internal carotid artery in a patient with intermittent attacks of hemiplegia. *Lancet.* 1954; 267:994–6.
23. Robertson JT. Carotid endarterectomy: a saga of clinical science, personalities, and evolving technology: the willis lecture. *Stroke.* 1998;29:2435–41.
24. Murphey F. The scotomata of carotid artery disease as I remember them. *J Neurosurg.* 1973;39:390–3.
25. Moore WS, Boren C, Malone JM, et al. Natural history of Nonstenotic, asymptomatic ulcerative lesions of the carotid artery. *Arch Surg.* 1978;113:1352–9.
26. Easton JD. History of carotid endarterectomy: then and now. *Stroke.* 2014;45:101–3.
27. Barnett HJM, Plum F, Walton JN. Carotid endarterectomy – an expression of concern. *Stroke.* 1984;15:941–3.
28. Fields WS, Maslenikov V, Meyer JS, Hass WK, Remington RD, Macdonald M. Joint study of extracranial arterial occlusion. V. Progress report of prognosis following surgery or nonsurgical treatment for transient cerebral ischemic attacks and cervical carotid artery lesions. *JAMA.* 1970;211: 1993–2003.
29. Kurtzke J. Formal discussion. In: Whisnant JP, Sandok BA, ed. *Cerebral vascular disease-ninth princeton conference.* New York: Grune & Stratton; 1974:190–3.
30. Shaw DA, Venables GS, Carlidge NEF, Bates D, Dickinson PH. Carotid endarterectomy in patients with transient cerebral ischaemia. *J Neurol Sci.* 1984;64:45–53.
31. European Carotid Surgery Trialists' Collaborative Group. MRC European carotid surgery trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. *Lancet.* 1991;337:1235–43.
32. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med.* 1991;325:445–53.
33. Hobson RW, Weiss DG, Field WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *N Engl J Med.* 1993;328:221–7.
34. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA.* 1995; 273:1421–8.
35. MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal stroke by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet.* 2004;363:1491–502.
36. Hackam DG. Optimal medical management of asymptomatic carotid stenosis. *Stroke.* 2021;52:2191–8.
37. Kresowik TF, Bratzler D, Karp HR, et al. Multistate utilization, process, and outcomes of carotid endarterectomy. *J Vasc Surg.* 2001;33:227–35.
38. Golnari P, Nazari P, Hurley MC, et al. Continued dominance of carotid endarterectomy over stenting in the United States: volumes, outcomes, and complications from the national inpatient sample (1997–2015). *World Neurosurg.* 2022;163:e238–e252.
39. Otite FO, Khandelwal P, Malik AM, Chaturvedi S. National patterns of carotid revascularization before and after the carotid revascularization endarterectomy vs stenting trial (CREST). *JAMA Neurol.* 2018;75:51–7.
40. Naylor AR. Which patients with asymptomatic carotid stenosis benefit from revascularization? *Curr Opin Neurol.* 2017;30:15–21.
41. Rieff T, Eckstein H-H, Mansmann U, et al. Carotid endarterectomy or stenting or best medical treatment alone for moderate to-severe asymptomatic carotid stenosis: 5-year results of a multicentre, randomised controlled trial. *Lancet Neurol.* 2022;21:877–88.
42. Nederkoorn PJ, Donners S, van Velzen T, Cheng, Gregson J et al. Immediate revascularization versus optimised medical therapy alone in patients with carotid stenosis at low to intermediate risk of stroke: interim results of ECST-2. (Abstr. 0313/2283). Presented at the 9th European Stroke Organization Conference, Munich, Germany, May 24–26, 2023. *European Stroke Journal* 2023; 8(2) suppl: ESOC Abstract Book, Sage Publications.
43. Bauer RB, Boulous RS, Meyer JS. Natural history and surgical treatment of occlusive cerebrovascular disease evaluated by serial arteriography. *Am J Roentgenol.* 1968;104:1–17.
44. Fox AJ. How to measure carotid stenosis. *Radiology.* 1993;186:316–8.
45. Fox AJ, Eliasziw M, Rothwell PM, Schmidt MH, Warlow CP, Barnett HJM. Identification, prognosis, and management of patients with carotid artery near occlusion. *AJNR Am J Neuroradiol.* 2005;26:2086–94.
46. Johansson E, Fox AJ. Near-occlusion is a common variant of carotid stenosis: study and systematic review. *Can J Neurol Sci.* 2022;49:55–61.
47. Rothwell PM, Gibson RJ, Slattery J, Sellar RJ, Warlow CP. Equivalence of measurement of carotid stenosis. A comparison of three methods on 1001 Angiograms. *Stroke.* 1994;25:2435–9.
48. Bartlett ES, Walters TD, Symons SP, Fox AJ. Quantification of carotid stenosis on CT angiography. *AJNR Am J Neuroradiol.* 2006;27:13–9.
49. Horev A, Honig C, Goldbart JE, et al. Overestimation of carotid stenosis on CTA - real world experience. *J Clin Neurosci.* 2021;85:36–40.
50. Jareczek FJ, Farrell MB, Lehman EB, et al. Variation in carotid artery stenosis measurements among facilities seeking carotid stenting facility accreditation. *Stroke.* 2023;54:1578–86.
51. Brijnikji W, Huston J, Rabinstein AA, Kim G-M, Lerman A, Lanzino G. Contemporary carotid imaging: from degree of stenosis to plaque vulnerability. *J Neurosurg.* 2016;124:27–42.
52. Saba L, Moody AR, Saam T, et al. Vessel wall-imaging biomarkers of carotid plaque vulnerability in stroke prevention trials. *JACC, Cardiovascular Imaging.* 2020;13:2445–56.
53. Saba L, Cau R, Murgia A, et al. Carotid plaque-RADS. A novel stroke risk classification system. *JACC Cardiovasc Imaging.* 2024;17:62–75. DOI: [10.1016/j.jcmg.2023.09.005](https://doi.org/10.1016/j.jcmg.2023.09.005).
54. Mathias K. Perkutane transluminale Katheterbehandlung supra-aortaler Aterienobstruktionen. *Angiology.* 1981;3:47–50.
55. Yadav JS, Roubin GS, Iyer S, et al. Elective stenting of the extracranial carotid arteries. *Circulation.* 1997;95:376–81.
56. Bettmann MA, Katzen BT, Whisnant J, et al. Carotid stenting and angioplasty. *Circulation.* 1998;97:121–3.
57. CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the carotid and vertebral artery transluminal angioplasty study (CAVATAS): a randomised trial. *Lancet.* 2001;357:1729–37.
58. Yadav JS, Wholey MH, Kuntz RE, et al. Stenting and angioplasty with protection in patients at high risk for endarterectomy investigators. Protected carotid-artery stenting versus endarterectomy on high-risk patients. *N Engl J Med.* 2004;351:1493–501.
59. The SPACE Collaborative Group. 30-day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet.* 2006;368: 1239–47.
60. Mas J-L, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med.* 2006;355:16601671–1671.
61. Bonati LH, Dobson J, Featherstone RL, et al. International carotid stenting study investigators. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the

- international carotid stenting study (ICSS) randomised trial. *Lancet*. 2015;385:529–38.
62. Brott TG, Hobson RWII, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363:11–23.
 63. Cohen DJ, Stolker JM, Wang K, et al. Health-related quality of life after carotid stenting versus carotid endarterectomy: results from CREST (Carotid revascularization endarterectomy versus stenting trial). *J Am Coll Cardiol*. 2011;58:1557–65.
 64. Spence JD. Management of patients with an asymptomatic carotid stenosis—medical management, endovascular treatment, or carotid endarterectomy? *Curr Neurol Neurosci Rep*. 2016;16:3. DOI: [10.1007/s11910-015-0605-6](https://doi.org/10.1007/s11910-015-0605-6).
 65. Almekhlafi MA, Demchuk AM, Mishra S, et al. Malignant emboli on transcranial Doppler during carotid stenting predict postprocedure diffusion-weighted imaging lesions. *Stroke*. 2013;44:1317–22.
 66. Halliday A, Bulbulia R, Bonati LH, et al. Second asymptomatic carotid surgery trial (ACST-2): a randomised comparison of carotid artery stenting versus carotid endarterectomy. *Lancet*. 2021;398:1065–73.
 67. Grotta JC. Fifty years of acute ischemic stroke treatment: a personal history. *Cerebrovasc Dis*. 2021;50:666–80.
 68. Fisher CM, Adams RD. Cerebrovascular diseases. *Neuropathological progress. Res Cardiovasc*. 1964;10:425–6.
 69. Millikan C, Siekert R, Schick R. Studies in cerebrovascular disease. V. The use of anticoagulant drugs in the treatment of intermittent insufficiency of the internal carotid arterial system. *Proc Mayo Clin*. 1955;30:578–86.
 70. International Stroke Trial Collaborative Group. The international stroke trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19,435 patients with acute ischemic stroke. *Lancet*. 1997;349:1569–81.
 71. Acute Stroke Treatment (TOAST) Investigators. Low molecular weight heparinoid (danaparoid), and outcome after acute ischemic stroke. A randomized, controlled trial. *JAMA*. 1998;279:1265–72.
 72. Fields WS, Lemak NA, Frankowski RF, Hardy RJ. Controlled trial of aspirin in cerebral ischemia. *Stroke*. 1977;8:301–14.
 73. The Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. *N Engl J Med*. 1978;299:53–9.
 74. Gent M, Blakely JA, Easton JD, et al. The Canadian American ticlopidine study (CATS) in thromboembolic stroke. *Lancet*. 1989;1:1215–20.
 75. Haas WK, Easton JD, Adams HP, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med*. 1989;321:501–7.
 76. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of ldl cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–81.
 77. Furberg CD, Adams HP, Applegate WB, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation*. 1994;90:1679–87.
 78. paper. Salonen RKAPS, Nyyssonen K, Parkkala-Sarataho E, Salonen JT. The kuopio atherosclerosis prevention study (KAPS): effect of pravastatin treatment on lipids, oxidative resistance of lipoproteins, and atherosclerosis progression. *Am J Cardiol*. 1995;76:34C–39F.
 79. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549–59.
 80. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and histological classification of atherosclerosis. *Circulation*. 1995;92:1355–74.
 81. Kamtchum-Tatuene J, Noubiap JJ, Wilman AH, Saqqur M, Shuaib A, Jickling GC. Prevalence of high-risk plaques and risk of stroke in patients with asymptomatic carotid stenosis. *JAMA Neurol*. 2020;77:1–12.
 82. Paraskevas KI, Veith FJ, Spence JD. How to identify which patients with asymptomatic carotid stenosis could benefit from endarterectomy or stenting. *Stroke Vasc Neurol*. 2018;3:92–100.
 83. Spence JD, Coates V, Li H, et al. Effects of intensive medical therapy on Microemboli and cardiovascular risk in asymptomatic carotid stenosis. *Arch Neurol*. 2010;67:180–6.
 84. Spence JD, Hackam DG. Treating arteries instead of risk factors. A paradigm change in management of atherosclerosis. *Stroke*. 2010;41:1193–9.
 85. Naylor AR. Time to rethink management strategies in asymptomatic carotid artery disease. *Nat Rev Cardiol*. 2011;9:116–24.
 86. Chang RW, Tucker L-Y, Rothenberg KA, et al. Incidence of ischemic stroke in patients with asymptomatic severe carotid stenosis without surgical intervention. *JAMA*. 2022;327:1974–82.
 87. Cole TS, Mezher AW, Catapano JS, et al. Nationwide trends in carotid endarterectomy and carotid artery stenting in the post-CREST era. *Stroke*. 2020;51:579–87.
 88. Kashyap VS, So KL, Schneider PA, et al. One-year outcomes after transcarotid artery revascularization (TCAR) in the ROADSTER 2 trial. *J Vasc Surg*. 2022;76:466–73.
 89. Centres for Medicare and Medicaid Services Coverage and Analysis Group. Percutaneous transluminal angioplasty (PTA) of the carotid artery concurrent with stenting. <https://www.cms.gov/medicare-coverage-data-base/view/ncaal-decision-memo.aspx?proposed-N&ncaid-311>. Accessed October 11, 2023.
 90. Abbott A, Gao L, Budincevic H, Ricco J-B. Carotid artery overtreatment in the USA. *Lancet Neurol*. 2023;22:1102–1103. DOI: [10.1016/S1474-4422\(23\)00407-6](https://doi.org/10.1016/S1474-4422(23)00407-6).
 91. Saba L, Scicolone R, Johansson E, et al. Quantifying carotid stenosis: history, current applications, limitations, and potential: how imaging is changing the scenario. *Life*. 2024;14:73. DOI: [10.3390/life14010073](https://doi.org/10.3390/life14010073).
 92. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med*. 1987;317:141–5.
 93. The EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke – results of an international randomized trial. *N Engl J Med*. 1985;313:1191–200.