Intracranial atherosclerosis

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Atherosclerotic disease often involves the intracranial arteries including those encased by cranial bones and dura, and those located in the subarachnoid space. Age, hypertension, and diabetes mellitus are independent risk factors for intracranial atherosclerosis. Intracranial atherosclerosis can result in thromboembolism with or without hypoperfusion leading to transient or permanent cerebral ischaemic events. High rates of recurrent ischaemic stroke and other cardiovascular events mandate early diagnosis and treatment. Present treatment is based on a combination of antiplatelet drugs, optimisation of blood pressure and LDL cholesterol values, and intracranial angioplasty or stent placement, or both, in selected patients.

Introduction

Atherosclerotic lesions ranging from slight wall thickening and non-stenosing plaques to severe luminal narrowing often involve intracranial arteries encased by cranial bones and dura, or those located in the subarachnoid space. The most common sites, in order, are the basilar artery, the internal carotid arteries, the middle cerebral arteries, the intracranial vertebral arteries, the posterior cerebral arteries, and the anterior cerebral arteries.[1] Intracranial atherosclerosis can occur in isolation or as part of systemic atherosclerotic disease involving the coronary, extracranial, and other peripheral arteries.[2,3] A disproportionately high rate of stroke mortality occurs in Asian countries such as China, Japan, and South Korea where intracranial atherosclerosis is highly prevalent.[4] Therefore, intracranial atherosclerosis could be a major cause of regional variation in stroke mortality.

Epidemiology

Data for atherosclerotic disease prevalence are based on either studies of pathological changes in autopsy specimens or detection of arterial calcification or lumen narrowing by neuroimaging in population-based screening.[5] In a study,[6] atherosclerosis was evident in 10–30% of Europeans aged 20–29 years, and by the age of 65 years, 80–97% of the population had pathological evidence of intracranial atherosclerosis. In the population-based Rotterdam Study,[6] intracranial internal carotid artery calcification on CT scans that related to intracranial atherosclerosis was identified in 82% of individuals (95% in those aged ≥80 years). Luminal narrowing or stenosis of greater than 50% by transcranial Doppler (TCD) ultrasound was identified in about 7% of asymptomatic middle-aged and elderly individuals.[7–9] A review[5] of four studies that screened a total of 2593 asymptomatic individuals reported a prevalence of intracranial stenosis ranging from 3·5% to 13% depending on the age and ethnic origin of the population studied. In the Joint Study of Extracranial Arterial Occlusion,[10] investigators reported asymptomatic stenosis of 50% or greater (by catheter angiography) in 14% of intracranial internal carotid arteries and 8% of basilar arteries and middle cerebral arteries of 3788 patients with various symptoms of brain ischaemia.

Asian[11–13] and African-American patients[14,15] have disproportionately higher rates of intracranial atherosclerosis than white patients.[13,16] In the Northern Manhattan Study,[17] the prevalence of intracranial atherosclerosis that led to ischaemic stroke was three per 100 000 for white individuals and 15 per 100 000 for African-American individuals. A post-mortem study[13] in China identified severe intracranial atherosclerosis in at least one artery ranging from about 30% in the sixth and seventh decades to about 50% in the eighth and ninth decades. TCD-based studies have shown a 20–30% prevalence of asymptomatic intracranial stenosis in Chinese patients with hypertension, diabetes mellitus, and hyperlipidaemia.[7,18] About 15% of the Japanese population has asymptomatic intracranial atherosclerosis.[19]

The disproportionately high rate of uncontrolled hypertension, diabetes mellitus, and hyperlipidaemia in the African-American population[20,21] partly accounts for the increased incidence of intracranial atherosclerosis. The high rate in the Japanese population is attributed to the high frequency of hypertension with paradoxically low rates of hyperlipidaemia.[22,23] In the Chinese population, the rates of hypertension, diabetes mellitus, and hyperlipidaemia are not higher than that in the white population,[24–26] and therefore the excess burden of intracranial atherosclerosis is unaccounted for.

Pathological appearance

Fatty streaks and fibrous plaques in intracranial arteries are evident by age 24 years,[27] followed by intimal necrosis and thickenings in older individuals.[28] Proliferative fibrosis of the intima or adventitia is more prevalent than is lipid infiltration in intracranial atherosclerosis, and changes appear later than those seen in coronary arteries.[2,29] Well

Search strategy and selection criteria

We based our Seminar on personal knowledge of the subject supplemented by data derived from multicentre randomised trials and selected non-randomised or observational clinical studies that included ten or more patients. The information was identified by searches on Medline from January, 2004, to April, 2013, by cross-referencing keywords of "cerebral atherosclerosis", "ischaemic stroke", "intracranial stenosis", "intracranial atherosclerosis", "neuroimaging", "clinical studies", "randomised trials", "aspirin", "vitamin K antagonists", "cilostazol", "antiplatelets", "oral anticoagulants", "angioplasty", and "stent". Other articles were identified through reviews of bibliographies from selected articles. We also reviewed abstracts from pertinent scientific meetings.

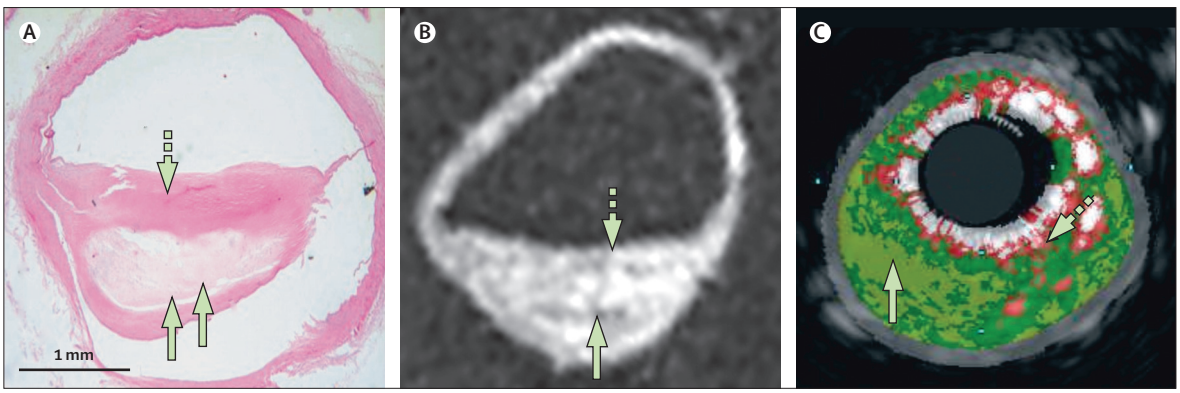

Figure 1: **Cross-section of intracranial atherosclerotic plaque**
(A) Histological section stained with haematoxylin and eosin. (B) High-resolution (7T) MRI imaging. (C) Intravascular ultrasonography. White component in imaging represents calcification and red component represents necrosis. Solid arrows=fibrous and adipose component. Dotted arrows=fibrous component.

defined plaques (figure 1) are most frequent in elderly people.[14,30] Vasa vasorum extending into the vascular media (neovascularisation) is frequently associated with intraplaque haemorrhage.[31] Dense mineral deposits, particularly calcium, are identified in the degenerated media of intracranial arteries,[32] but less often than in coronary arteries.[2] Plaques with high-lipid content, intraplaque haemorrhage, neovasculature, and macrophage and T lymphocyte infiltration are associated with ischaemic events.[33,34] Intracranial arteries might be more susceptible to inflammatory changes and plaque instability because of reduced expression of inhibitors of inflammation,[35] prominent expression of proinflammatory proteasomes,[36] and absence of an external elastic lamina.[37]

Risk factors

Age, hypertension, and type 2 diabetes mellitus are consistently identified as independent risk factors for TCD-documented intracranial stenosis in studies that include asymptomatic[8,38,39] or symptomatic patients.[40] Metabolic syndrome—a disorder of metabolic risk factors, insulin resistance, and vascular inflammation—is identified in almost half of patients.[41–43] In the Barcelona Asymptomatic Intracranial Atherosclerosis (AsIA) study,[44] diabetes mellitus and metabolic syndrome increased the risk of intracranial atherosclerosis. Cigarette smoking has a minor role in predisposition to intracranial atherosclerosis.[38,45] No clear relation with body-mass index (BMI) has been reported,[44,46] but physical activity of moderate or heavy intensity is associated with a reduced risk of ischaemic stroke.[47,48]

The high prevalence of intracranial atherosclerosis in patients with type 2 diabetes mellitus is at least partly attributed to the high prevalence of underlying hypertension and hyperlipidaemia in patients with diabetes mellitus.[18] However, the association is statistically significant even after adjustment for hypertension and hyperlipidaemia in several studies.[39,49,50] The severity and extent of intracranial atherosclerosis are not related to serum glucose or glycated haemoglobin A_{1C} (HbA_{1C}) concentrations,[18] and intensive glucose control in patients with type 2 diabetes does not reduce stroke events.[51] Other mechanisms such as increased expression of vascular cell adhesion molecule 1 and inflammatory cell infiltration associated with insulin resistance could predispose to intracranial atherosclerosis.[52,53]

Clinical manifestations

Intracranial stenosis presents with one or many recurrent ischaemic strokes and transient ischaemic attacks (TIA).[54] Intracranial plaques and stenoses on autopsy are identified in 45–62% of patients who have had an ischaemic stroke,[33,50] and are causal in about 10% of ischaemic strokes.[50] Other ischaemic strokes are probably related to concomitant proximal extracranial stenosis or atrial fibrillation identified in 10–20% of patients with intracranial atherosclerosis.[55–57] In the Northern Manhattan Study,[17] intracranial atherosclerosis caused ischaemic stroke in 9% of white individuals, 17% of African-American, and 15% of Hispanic. Intracranial stenosis was reported in 33–37% of Chinese patients admitted to hospital with ischaemic stroke.[58,59]

Patients with intracranial stenosis are more likely to develop one or many lacunar and subcortical infarctions (figure 2).[60–63] The underlying mechanisms are predominantly artery to artery emboli, in-situ thromboembolism, haemodynamic impairment, and local small arterial branch origin occlusion by atherosclerotic plaques.[61,63,45] Reduction of regional cerebral blood flow is identified in the presence of high-grade stenosis and contributes both to the occurrence and magnitude of ischaemic injury.[64] Half of patients have one lesion that can be either lacunar, subcortical, or cortical infarction.[62,65–67] The remaining patients with intracranial stenosis have several infarctions involving a combination of cortical, subcortical, and lacunar infarctions.[62,65–67] Lacunar infarctions identified in 10–19% of patients[57,67] are most often located in the pons followed by the corona radiata or centrum semiovale regions. Clinical presentation includes cortical function impairments such as

aphasia, neglect, and hemianopsia in almost half of patients with cortical and large subcortical infarctions.[62,65,66] In the remaining patients, signs of isolated motor or sensory deficits predominate, in association with lacunar and small subcortical infarctions. Up to 30% of patients undergoing coronary artery bypass grafting have asymptomatic intracranial stenosis,[68] and those with stenosis have a significantly increased risk of ischaemic stroke within 14 days of bypass surgery.[69]

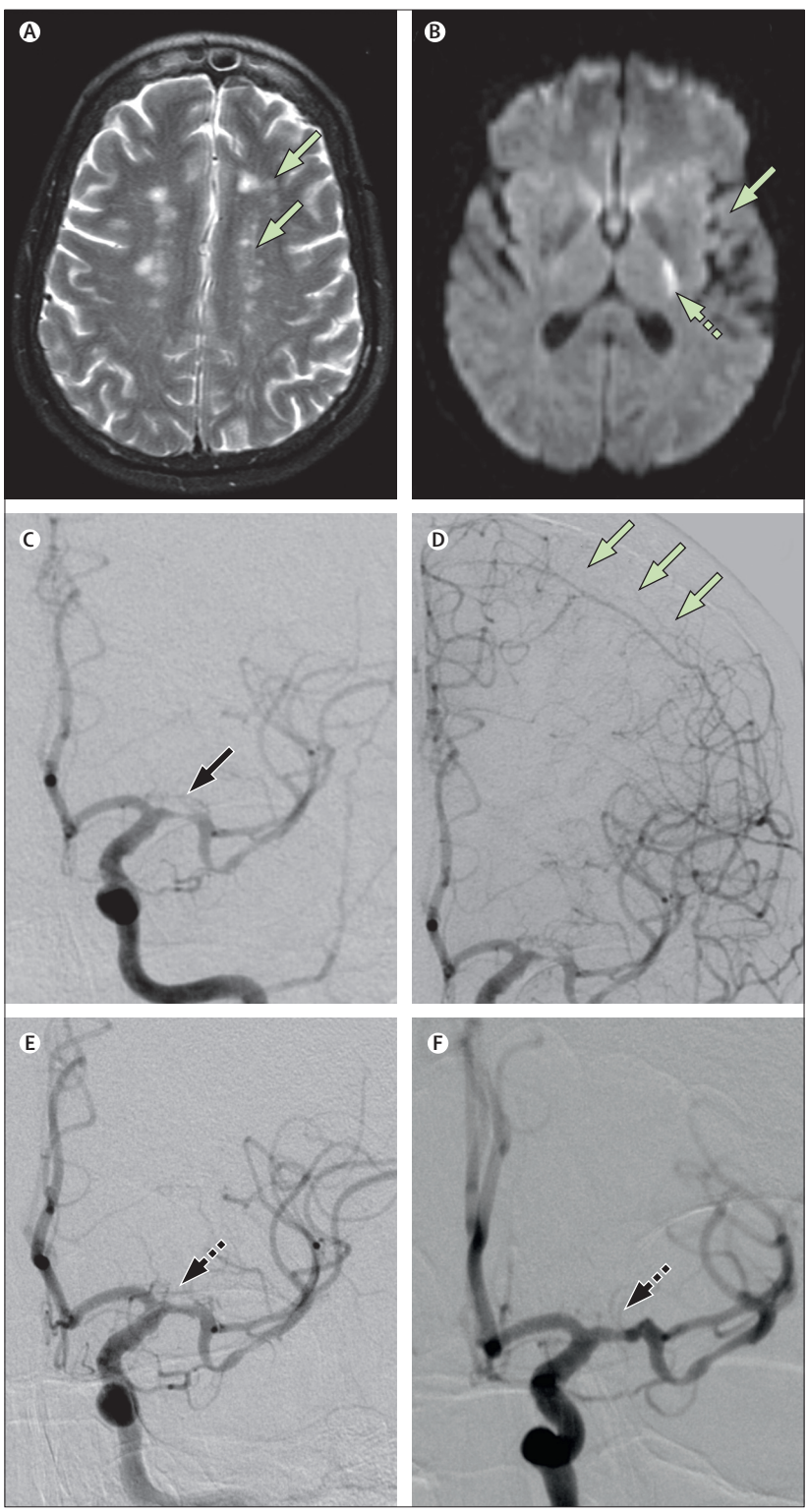

Figure 2: **Lacunar and subcortical infarctions associated with intracranial stenosis**
A 56-year-old woman presented with a new right-sided hemispheric transient ischaemic attack. Old (solid arrows) and new (dotted arrow) subcortical and lacunar infarctions are identified in the distribution of left middle cerebral artery on (A) T2-weighted MRI and (B) diffusion-weighted MRI images. Anteroposterior images from catheter angiography show (C) high-grade stenosis of proximal left middle cerebral artery (black solid arrow) with (D) absence of collateral flow from anterior cerebral artery (green solid arrows). Prominent reduction in severity of stenosis is seen at (E) immediate postangioplasty (black dotted arrows), and (F) 6-month postangioplasty (black dotted arrows) results.

Cognitive deficits of varying severity including impaired executive function, slowing of activity and thinking, and anterograde amnesia are identified. In the Baltimore Longitudinal Study of Aging,[70] 34% of cases of dementia were attributable to intracranial atherosclerosis. Hemispheral infarcts alone or in conjunction with Alzheimer's disease accounted for 35% of these cases.[71] Such infarcts usually involve the anterior-medial thalamus, caudate nucleus, or cerebral cortical or white matter zones, which are important in memory, language, and other cognitive and behavioural functions.[72–74] In patients without infarcts, cognitive deficits are attributable to white matter degeneration, hypoperfusion (figure 3), and hypometabolism.[75] White matter degeneration is frequent,[76,77] and almost 18% of patients with asymptomatic middle cerebral artery stenosis have focal and 13% have diffuse confluent white matter disease without direct association with severity of stenosis.[76,78] Loss of microstructural integrity resulting in diffusion abnormalities in white matter that appears normal[79] is identified in patients with intracranial atherosclerosis, leading to further impairment of executive function and information processing.[79] In one study,[80] hypoperfusion related to intracranial stenosis was associated with cognitive deficits and with improvement in deficits after resolution of perfusion deficits. Propagation of Alzheimer's disease by increased expression of amyloid β protein and neuritic plaques in patients with intracranial atherosclerosis is also reported, although the mechanism is unclear.[81,82]

Depression is a common manifestation and is associated with higher disability than that identified in patients without vascular disease.[83,84] In the Second Manifestations of Arterial Disease-Memory, Depression and Aging (SMART-Medea) study,[85] 17% of patients with cerebral, coronary, or peripheral atherosclerosis had symptoms of depression. The presence of large subcortical infarcts and lacunar infarcts in deep white matter tracts increased the risk of depression by two-fold. Symptoms of depression might precede development of dementia related to vascular diseases.[86]

Diagnosis, quantification, and characterisation

Raised mean blood flow velocities on TCD or luminal narrowing and absence of flow, or both, on MRI, CT, and catheter angiography are used to identify and quantify the severity of intracranial atherosclerosis (table 1).[87–91] Because of high negative predictive values, non-invasive methods are good screening tests, but might be inadequate to measure the severity of disease in some circumstances. Other appropriate features, such as the presence of multiple cardiovascular risk factors or a history of established atherosclerotic disease in coronary or peripheral circulation in young patients, are needed to distinguish atherosclerotic disease from non-atherosclerotic vasculopathies.[92] In the acute stroke setting, regions of narrowing or occlusion might be mimicked by embolic occlusion or filling defects from a local thrombus.[93] These findings most frequently resolve on repeat vascular imaging studies after 5–7 days.[93,94]

Catheter angiography is needed for quantitation of stenosis[95,96] and assessment of collateral flow. Such precise information is most valuable in patients in whom intracranial angioplasty or stent placement is an option. The severity of stenosis is quantified as a ratio between the wall diameter at the point of maximum narrowing and the reference diameter of the proximal normal artery (or infrequently the distal artery or feeding artery).[97] This method is used because of good inter-observer and intraobserver agreements.[97] Collateral blood flow occurs through anastomoses between arteries either at the base or the cortical or cerebellar surfaces of the brain in the event of reduced antegrade flow through stenotic arteries. In patients with intracranial stenosis, 30% of affected arteries show reduced distal blood flow proportional to severity of stenosis.[98] In about 10% of patients, collaterals supply the complete distribution of the stenotic artery.[99]

Both the severity of stenosis and the extent of collateral blood flow are important measures for estimation of outcome and selection of treatment. In the WASID study,[100] the risk of recurrent ipsilateral stroke increased with severity of stenosis. The risk of recurrent ipsilateral stroke was 19% and 10% in patients with stenosis severity of 70% or greater and less than 70%, respectively, during a mean period of 1·8 years. In patients with stenosis ranging in severity from 70% to 99%, good retrograde flow through the collaterals supplying the complete distribution of the stenotic artery was associated with a four-fold lower risk of recurrent ischaemic stroke compared with patients with poor flow collaterals.[99] This association was independent of and stronger than was the severity of stenosis (≥70 *vs* <70%) and has been supported by other studies.[101] Because of pre-existing vasodilation in response to ischaemia, arteries and arterioles fail to dilate in response to stimuli such as acetazolamide in a third of patients with severe intracranial stenosis.[102]

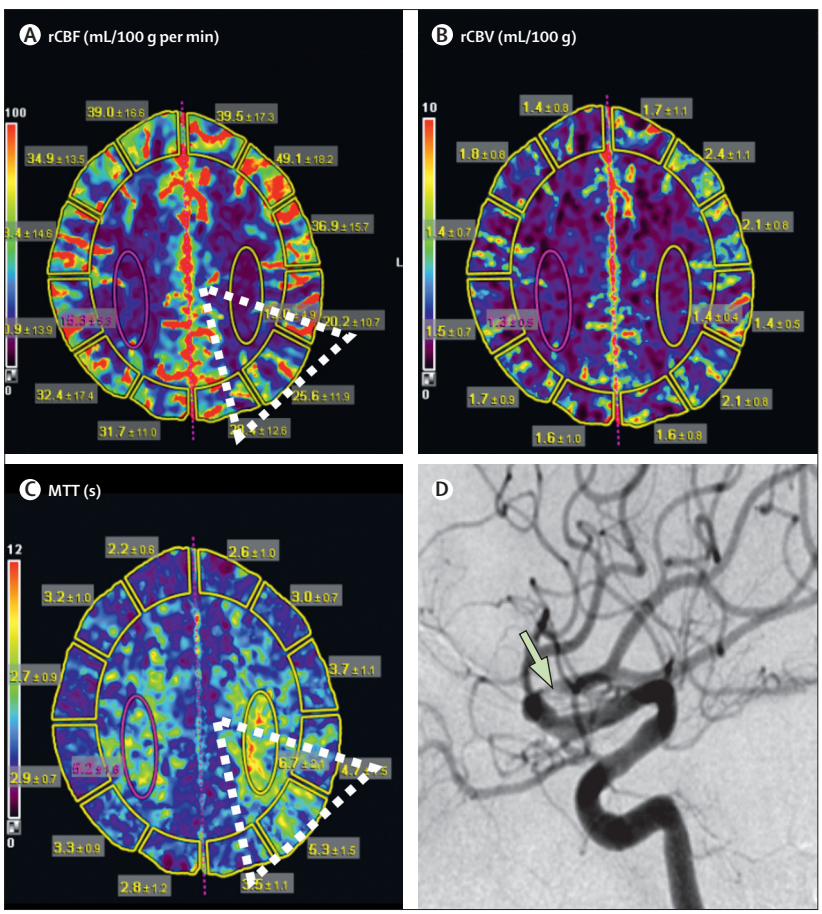

Figure 3: **Chronic hypoperfusion associated with intracranial stenosis**
A 46-year-old woman presented with a new right-sided hemispheric minor ischaemic stroke. (A) CT perfusion images show low rCBF with (B) preserved rCBV, and (C) delay in blood flow shown by increased MTT. White dotted triangular boundaries represent affected regions. (D) Lateral image from catheter angiography shows high-grade stenosis of distal left middle cerebral artery (arrow). rCBF=regional cerebral blood flow. rCBV=regional cerebral blood volume. MTT=mean transmit time.

However, the value of impaired vasodilatory capacity in identification of patients at risk of subsequent ischaemic events is not well established.[103]

Plaque characteristics have been studied by use of high-resolution MRI[104] and intravascular ultrasonography,[105,106] which allow visualisation of submillimetre intracranial arterial wall structures. The location, thickness, and pattern of protrusion (inwards or outwards) are identified with high-resolution MRI.[107,108] The high signal-to-noise ratio of 3T MRI improves spatial resolution and reduces the signal averaging requirements (shortened scan duration).[109] Recent intraplaque haemorrhage, high vascularity, and inflammation increase the signal on T1-weighted fat-suppressed images that enhance after administration of intravenous contrast.[104,110,111] Intravascular ultrasonography accurately identifies fibrous, lipid, and calcific components within plaques,[112] but present use is scarce because of the invasive nature and difficulties in the navigation of the probe in intracranial arteries.

	Transcranial Doppler ultrasound	MRI angiogram	CT angiogram	Catheter-based angiogram
Primary attribute	Detects cerebral flow velocity increase distal to arterial narrowing	Detects abnormalities based on flow effects (flow dependent), contrast agents, or flow into blood to generate contrast (flow independent)	Detects and quantitates intraluminal narrowing through opacification after contrast injection	Detects and quantitates intraluminal narrowing through opacification after contrast injection
Secondary attribute(s)	Detects microembolic signals, measures vasodilatory capacity of arteries and arterioles to stimuli, such as CO_2 inhalation or acetazolamide injection	Concurrent MRI might identify ischaemic lesions and regional hypoperfusion	Detects arterial wall calcification by characteristic signal intensity; concurrent CT/CT perfusion might identify ischaemic lesions and regional hypoperfusion	Detects irregularities, ulceration, and in-situ thrombus within narrowing by characteristic contrast opacification patterns with high spatial resolution; detects collateral flow accurately through sequential image acquisition
Limitations	Temporal acoustic bone window might be absent (no visualisation) or restricted for reliable detection of stenoses in distal segments of arteries; artifactual narrowing in a curved arterial segment because angle correction not possible; anatomical localisation of stenosis not accurate because of persistence of flow increase in poststenotic segments	Flow signal intensity decreases caused by poststenotic altered flow dynamics create a flow gap; overestimate the degree of stenosis because of the turbulent flow or differential flow velocities within the stenosis	Artifactual narrowing or non-visualisation of intracranial internal carotid artery because of susceptibility gradient near the sphenoid sinus, flow acceleration, and loss of laminar flow; poor visualisation of arterial lumen with circumferential calcification	Procedural risk of ischaemic stroke and access site complications; rarely, supra-aortic arterial catheterisation might not be possible because of excessive tortuosity or proximal stenosis
Contrast	Infrequent	Optional and can differentiate occlusion versus high-grade stenosis within flow gaps	Mandatory	Mandatory
2D and 3D acquisitions	Not applicable	Routinely available	Routinely available	Routinely available
Positive predictive value	50%*	66%*	93%†	Standard
Negative predictive value	85%*	87%*	100%†	Standard

2D=two-dimensional. 3D=three-dimensional. *Derived from multicentre study.[90,91] †Derived from single centre study.[90,91]

Table 1: **Comparative assessment of imaging modalities for detection and quantitation of intracranial atherosclerosis**

Stroke, cardiovascular events, and mortality

After an initial TIA or ischaemic stroke, brain ischaemia can recur in the distribution of the stenotic artery and infrequently in another distribution in patients with intracranial stenosis. The high rate of vascular events emphasises the importance of timely diagnosis and treatment in these patients. Several studies have investigated patients given antithrombotic treatment but without intensive medical management. Early progression in deficits and mortality is underestimated in studies that do not include patients within 7 days of the initial symptoms. Progression of neurological deficits is reported in 14% of patients with intracranial stenosis and subcortical infarctions within the first 2 days.[113] About 13% of patients develop another ischaemic stroke between 24 h and 7 days.[65] About 10% of patients die during initial hospital admission if patients with major ischaemic strokes are included.[114] The rate of hospital readmission is high because of recurrent ischaemic events, with one study showing a rate of 56% during a median period of 28 days.[115]

Investigators of the WASID trial[116] reported outcomes in 569 medically treated patients with intracranial stenosis and recent ischaemic events (<3 months; table 2). Ischaemic stroke in any vascular territory occurred in 106 (19%) of 569 patients, three-quarters of which occurred in the territory of symptomatic stenosis during a median period of 1·8 years.[116] The risk of stroke in the symptomatic vascular territory was highest for patients enrolled early (≤17 days) after the qualifying event.[100] Early enrolment of patients resulted in higher rates probably because of the identification of early recurrent ischaemic events, which were not detected in the late enrolment group. The Groupe d'Etude des Stenoses Intra-Craniennes Atheromateuses symptomatiques (GESICA) study[121] investigated 102 medically treated patients with intracranial stenosis and concurrent recent ischaemic events (<6 months). The investigators reported new TIAs or ischaemic stroke in 25% and 14% of patients, respectively. Half of the events occurred within 2 months and about 5% of the ischaemic events occurred in another vascular distribution.

The rate of events is higher in registries that are not influenced by patient selection bias. In a study,[122] the recurrent stroke rate in consecutive patients with intracranial stenosis enrolled within 7 days of symptom onset in the presence or absence of concurrent extracranial stenosis during the first year was 17·1% and 24·3%, respectively. The rate was much lower (10·9%) for patients without intracranial or extracranial atherosclerosis. Recurrent ischaemic stroke was the most common cerebral event followed by new TIAs and haemorrhagic stroke. New ischaemic lesions are frequently detected by MRI, which are asymptomatic in

	Patients	Treatment group 1	Treatment group 2	Primary outcome	Rate of events in treatment group 1	Rate of events in treatment group 2	Risk reduction
Fraxiparine in Ischaemic Stroke (FISS)-tris study[117]	353 patients who had had an ischaemic stroke within 48 h and large artery occlusive disease detected by neuroimaging; intracranial stenosis only (n=300), intracranial and extracranial stenoses (n=42), or extracranial stenosis only (n=11)	Subcutaneous nadroparin calcium 3800 anti-factor Xa IU twice daily for 10 days (n=180), followed by aspirin 80–300 mg once daily for 6 months	Oral aspirin 160 mg daily for 10 days (n=173), followed by aspirin 80–300 mg once daily for 6 months	None or low disability at 6 months	73%	69%	Absolute risk reduction 4%, 95% CI −5 to 13 in favour of aspirin
Warfarin-Aspirin Symptomatic Intracranial Disease Trial (WASID)[116]	569 patients within 90 days after TIA or stroke attributable to angiographically verified 50–99% intracranial stenosis	Oral vitamin K antagonists (target INR of 2·0–3·0; n=289)	Oral aspirin 650 mg twice daily (n=280)	Ischaemic stroke, brain haemorrhage, or vascular death during a mean period of 1·8 years	21·8%	21·1%	No difference (HR 1·04, 95% CI 0·7 to 1·5) with oral vitamin K antagonists
European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT)[118]	1068 patients within 6 months after TIA or ischaemic stroke of presumed arterial origin	Oral vitamin K antagonists (target INR of 2·0–3·0; n=536)	Oral aspirin (30–325 mg daily; n=532)	Vascular death, stroke, MI, or major bleeding complication during a mean period of 4·6 years	19%	18%	No difference (HR 1·0, 95% CI 0·8 to 1·4) with oral vitamin K antagonists
European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT)[119]	2739 patients within 6 months after TIA or ischaemic stroke of presumed arterial origin	Oral aspirin (30–325 mg daily) plus dipyridamole (200 mg twice daily; n=1363)	Oral aspirin (30–325 mg; n=1376)	Vascular death, stroke, MI, or major bleeding complication during a mean period of 3·5 years	13%	16%	Risk reduction (HR 0·8, 95% CI 0·7 to 1·0) in favour of oral aspirin plus dipyridamole
Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial[120]	20 332 patients within 90 days after ischaemic stroke (28% with large artery atherosclerosis)	Oral aspirin (25 mg) plus extended-release dipyridamole (200 mg) twice daily (n=10 181)	Oral clopidogrel (75 mg) daily (n=10 151)	Recurrent stroke during a mean period of 2·5 years	9%	8·8%	No difference (HR 1·0, 95% CI 0·9 to 1·1)

TIA=transient ischaemic attack. INR=international normalised ratio. HR=hazard ratio. MI=myocardial infarction.

Table 2: **Summary of clinical trials that investigated short-term and long-term antithrombotic treatment**

three-quarters of patients.[65,123] In one study,[65] 51% of patients with intracranial stenosis had a new ischaemic (predominantly cortical) lesion on MRI at 7 days that was not apparent on initial MRI within 24 h of ischaemic symptoms. In another study,[123] 19% of patients with symptomatic intracranial stenosis had a new ischaemic lesion on follow-up MRI within 7 months.

Several studies have attempted to identify the subpopulation at highest risk of recurrent ischaemic stroke beyond the severity of stenosis and presence of collaterals. In GESICA,[121] a subpopulation consisting of patients who developed ischaemic symptoms during a change of position (supine to prone), or effort, or the introduction of or increase in dose of an antihypertensive drug, had a subsequent rate of combined stroke and TIA of 61%. Microembolic signals can be detected as random short-duration and high-intensity signals by 30-min TCD measurements in 15% and 48% of patients with mild to moderate and severe stenosis, respectively, within 3 days of ischaemic symptom onset.[124] The odds of subsequent ischaemic stroke or TIA during 1 year are eight-fold higher in patients in whom microembolic signals are detected. Patients classified as not having responded to drug treatment (ischaemic events despite use of aspirin, clopidogrel, or vitamin K antagonists in therapeutic doses) could have a risk of recurrent ischaemic events as high as 52%.[125] However, a posthoc analysis of WASID[126] and other studies[127] have not identified a difference in the rates of stroke or vascular death or stroke only between patients who did or did not respond to antithrombotic medication at the time of their qualifying event. Concurrent existence of metabolic syndrome, increased high-sensitivity C-reactive protein serum concentration, or C-reactive protein gene 1444C→T polymorphism could be associated with an increased risk of subsequent cerebral ischaemic events in patients with first-ever TIA or stroke and intracranial atherosclerosis.[128,129]

The natural history of asymptomatic lesions has not been well studied. A risk of new ischaemic events of 3·5% (95% CI 0·8–9·0) per year was identified in territories supplied by 85 asymptomatic arterial stenoses detected in the WASID trial.[130] Other studies[131–133] identified a lower risk of ischaemic events of less than 2% per year in the distribution of asymptomatic intracranial stenoses detected by TCD, but progression in the severity of stenosis was reported in 20% of patients. A high rate of all-cause mortality and vascular death in patients with asymptomatic intracranial stenoses and raised LDL cholesterol or type 2 diabetes mellitus is reported.[133,134]

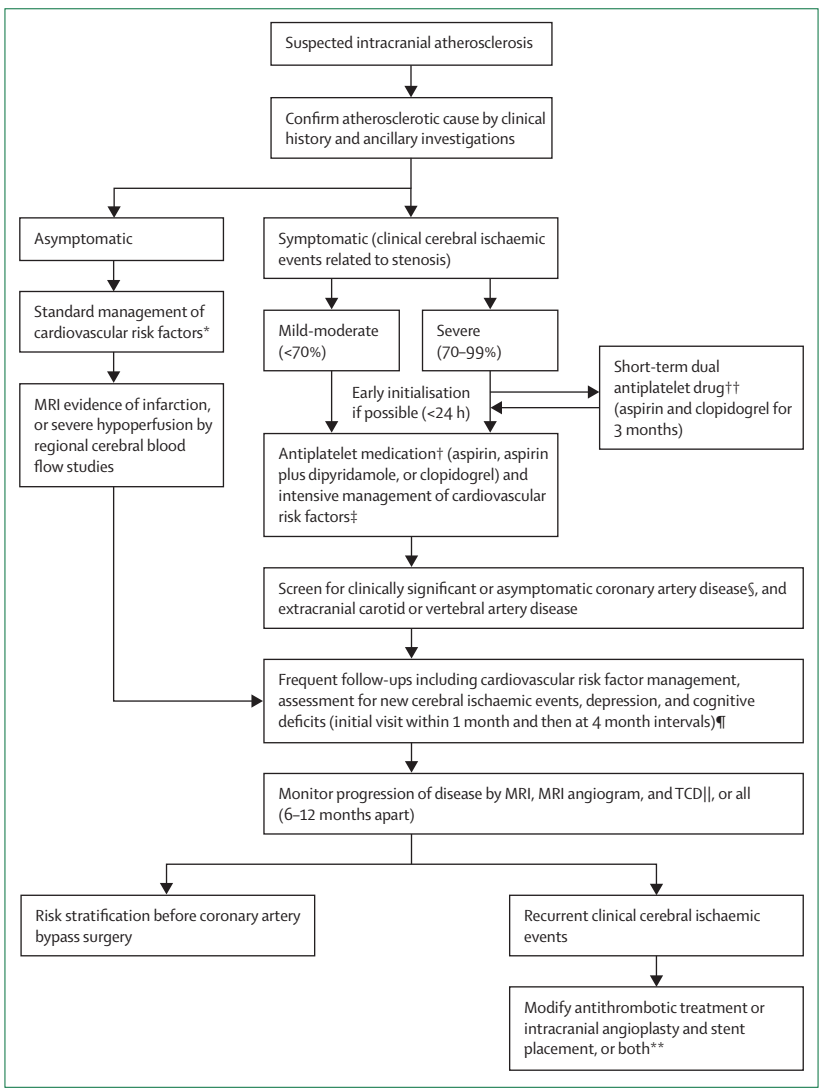

Figure 4: **Management algorithm for patients with suspected intracranial atherosclerosis**
Various components of management strategies are outlined. HbA_{1c}=haemoglobin A_{1c}. BMI=body-mass index. TCD=transcranial Doppler ultrasound. *The therapeutic value of antiplatelet drugs and intensive management of cardiovascular risk factors in this patient population has not been investigated; therefore, the goals of management of cardiovascular risk factors might depend on presence of other cardiovascular indications and associated risks. †Either aspirin (325 mg/day), aspirin plus dipyridamole (25 mg/200 mg twice daily), or clopidogrel (75 mg/day) are recommended as antiplatelet drugs;[135,136] because of the high rate of recurrent ischaemic stroke despite aspirin treatment, aspirin plus dipyridamole or clopidogrel is recommended as first-line treatment in some guidelines.[137,138] ‡Maintenance of blood pressure less than 140/90 mm Hg, LDL cholesterol less than 1·81 mmol/L, HbA_{1c} less than 7%, BMI less than 25 kg/m² (if BMI was 25–27 kg/m²), or 10% weight loss (if BMI was >27 kg/m²) by 30-min moderate intensity exercise sessions at least three times per week, and cigarette smoking cessation.[92] §Testing for asymptomatic coronary artery disease in patients who have had ischaemic events associated with intracranial atherosclerosis is recommended.[139] ¶Frequency of follow-up visits is based on the SAMMPRIS trial[92] for symptomatic patients and might not be applicable to asymptomatic patients. ||The appropriate frequency of serial neuroimaging is not known and incorporation into medical decision making is not validated; diffusion weighted MRI at 6 months for new silent ischaemic lesions[65] and MRI angiogrgam or TCD assessment at 6 months for progression in severity of intracranial stenosis[123] could provide information about the effectiveness of intensive medical treatment and identify the need for screening for depression and cognitive deficits. **The criteria for patient selection for intracranial angioplasty and stent placement, or both, vary between institutions; after the SAMMPRIS trial, the US Food and Drug Administration restricted the use of the Wingspan stent to patients aged 22–80 years who had had two or more ischaemic strokes related to 70–99% stenosis of the intracranial artery despite medical management; treatment is planned after 7 days of the most recent stroke.[140] ††Cautious use of a combination of aspirin (325 mg/day) and clopidogrel (75 mg/day) for 3 months can be considered for patients who are at high risk of recurrent brain ischaemic events;[92] ancillary findings, such as detection of microembolic signals[124] by TCD and absence of adequate collaterals[98] on angiography, could identify high-risk patients.

Medical treatment

Antithrombotic treatment

The present treatment of patients with ischaemic events attributable to intracranial stenosis is based on a combination of antiplatelet drugs and optimisation of blood pressure and LDL cholesterol values through lifestyle modification and drug treatment (figure 4).

Early initiation of antiplatelet drugs is preferred over parenteral anticoagulation in patients who present with brain ischaemic events related to intracranial atherosclerosis because of easy administration, similar efficacy, and better safety profile. The FISS-tris study[117] (table 2) did not identify a difference in rates of none or minimum disability at 6 months in patients with large artery occlusive disease during a 10-day course of either subcutaneous low molecular weight heparin (nadroparin twice daily) or daily oral aspirin initiated within 48 h of symptom onset. The rate of progression or recurrent stroke within the first week and 6 months was similar between the two groups.

Our understanding of long-term antithrombotic treatment is based on studies of patients who have had an ischaemic stroke or a TIA with documented intracranial atherosclerosis (WASID[116]), patients who have had a stroke of arterial origin with radiological detection of ischaemic lesions in large vessel distribution (large vessel disease; ESPRIT),[118,119] or patients who have had non-cardioembolic strokes related to large artery atherosclerosis (PRoFESS;[120] table 2). Continuation of antiplatelet treatment after the first 7–10 days for prevention of new or recurrent brain and coronary ischaemic events is preferred over oral anticoagulation.

In WASID[116] and ESPRIT,[118] no difference in rates of primary cumulative endpoints (combination of ischaemic stroke, brain haemorrhage, non-fatal myocardial infarction, major bleeding, or vascular death) was identified between patients who were randomly assigned either vitamin K antagonists or aspirin during a mean treatment and follow-up period of 1·8 years[116] or 4·6 years.[118] The results were similar in the ESPRIT subgroup analysis,[118] which included only patients with large vessel involvement (33% of randomly assigned patients). Major bleeding complications were two-fold higher in patients who were randomly assigned vitamin K antagonists in both trials. The rate of myocardial infarction or sudden death was increased in the group treated with vitamin K antagonists in the WASID trial. On the basis of the results of these trials, antiplatelet drugs are recommended in preference to oral anticoagulation for patients with stroke or TIA due to 50–99% stenosis of a major intracranial artery.[135] Although patients in the WASID trial were given aspirin 1300 mg/day, on the basis of data for general safety and efficacy, daily aspirin doses of 50–325 mg are recommended.[135]

However, the absence of superiority of vitamin K antagonists over aspirin should be interpreted with caution. The percentage of maintenance time that

patients given vitamin K antagonists spent within the international normalised ratio (INR) of 2·0–3·0 was 63%, whereas compliance with aspirin was reported in 94% of patients enrolled in WASID.[116] INRs of less than 2·0 were associated with a significantly increased risk of ischaemic stroke, whereas INRs greater than 3·0 were associated with a statistically significantly increased risk of major haemorrhages. Therefore, a more predictable therapeutic response, as reported with the new anticoagulants that do not depend on vitamin K inhibition (direct thrombin inhibitors and factor Xa inhibitors),[142] could provide a more optimum reduction in risk of ischaemic stroke with a better safety profile. Further studies are needed on the effectiveness and safety of these new oral anticoagulants in patients with severe intracranial artery stenosis.

Because of the high rate of recurrent ischaemic stroke despite aspirin treatment in WASID, aspirin plus dipyridamole combination or clopidogrel is recommended as the first-line treatment in long-term secondary prevention of stroke.[137,138] Some guidelines regard aspirin as an acceptable first-line drug along with aspirin plus dipyridamole or clopidogrel.[135,136] A meta-analysis[142] of five trials involving a total of 1774 patients with large artery disease showed a reduction of composite event of vascular death, non-fatal myocardial infarction, and non-fatal stroke (hazard ratio [HR] 0·7, 95% CI 0·6–0·9) with aspirin plus dipyridamole compared with aspirin alone in patients with ischaemic stroke. In ESPRIT,[119,141] there was a lower rate of vascular death, stroke, myocardial infarction, or major bleeding complication with aspirin plus dipyridamole compared with aspirin alone, and with aspirin plus dipyridamole compared with vitamin K antagonists.

In the PRoFESS trial, no difference in the rate of recurrent stroke or composite of stroke, myocardial infarction, or vascular death was identified in patients randomly assigned to clopidogrel compared with those randomly assigned to aspirin plus extended-release dipyridamole during a mean period of 2·5 years.[120] Intracranial haemorrhages were significantly more frequent in patients given aspirin plus dipyridamole (1·4% *vs* 1·0%, HR 1·4, 95% CI 1·1–1·8). In 5805 patients with large artery atherosclerosis, the rate of stroke recurrence was 10·6% in patients given aspirin-dipyridamole and 9·4% in those given clopidogrel. The compliance with treatment was lower with aspirin plus dipyridamole compared with clopidogrel because of a high occurrence of headaches. Titrated initiation of aspirin plus dipyridamole could be considered, particularly in women and patients who have had TIAs, to increase compliance to treatment.[143–145] In patients in whom clopidogrel is chosen as the antiplatelet drug, a loading dose of 300 mg or 600 mg could be necessary to ensure rapid therapeutic activity.[92]

A combination of aspirin and clopidogrel has been investigated for 3–6 month duration in the Stenting versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial[92] and the Trial of cilOstazol in Symptomatic intracranial Stenosis 2 (TOSS-2)[123] to achieve greater antiplatelet activity and reduce the early high risk of recurrence of ischaemic events in patients with intracranial stenosis. In a pilot trial,[146,147] 7-day clopidogrel and aspirin treatment in 70 patients with recent (within the past 7 days) ischaemic stroke or TIA related to intracranial stenosis significantly reduced microemboli detected by TCD on day 2 and day 7 compared with aspirin treatment alone. In the TOSS-2 study,[123] aspirin and clopidgrel combination for 7 months in 457 patients with acute symptomatic stenosis in the middle cerebral arteries or the basilar artery was compared with a combination of cilostazol and aspirin. Investigators reported no significant difference between the cilostazol and clopidogrel groups in rate of cardiovascular events (6·4% *vs* 4·4%), new cerebral ischaemic lesions (18·7% *vs* 12·0%), and major haemorrhagic complications (0·9% *vs* 2·6%). In view of the clinically significant risk of bleeding on even a short course of aspirin and clopidogrel,[138] the combination is recommended only in patients with concurrent unstable angina or non-Q-wave myocardial infarction, recent coronary stent placement, or those expecting intracranial angioplasty or stent placement.[135,137] Cautious use of a combination of aspirin and clopidogrel for 3 months could be considered in patients with recent brain ischaemic events and intracranial stenoses who have the same attributes as patients recruited in SAMMPRIS[92] in whom the rate of major haemorrhage was low (2·2%).

Cardiovascular risk factor control

The American Heart Association (AHA) Stroke Council[135] and the European Stroke Organisation[137] consistently recommend regular monitoring of blood pressure and glucose. More than 50% of patients who have had an ischaemic stroke or TIA associated with intracranial stenosis have blood pressure of 140/90 mm Hg or greater or HbA_{1c} of 7% or greater and 90% have LDL cholesterol 2·33 mmol/L or greater at baseline and 1 year follow-up;[148] about 20% are cigarette smokers at baseline. An analysis[148] identified that systolic blood pressure of 140 mm Hg or greater was associated with a higher rate of recurrent ischaemic stroke (23% *vs* 15%, HR 1·6, 95% CI 1·1–2·4) in patients with intracranial stenosis. Therefore, initiation of antihypertensive drugs is recommended after the acute phase, including in patients with normal blood pressure with a goal to maintain blood pressure lower than 140/90 mm Hg.[135] Intensive goal for statin treatment (LDL cholesterol of <1·81 mmol/L) is recommended[135] based on results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL[149]) trial that showed that LDL cholesterol less than 1·81 mmol/L was associated with a 28% reduction in stroke risk compared with a concentration of greater than 2·59 mmol/L. In the WASID study,[148] patients with LDL cholesterol of 1·81 mmol/L or greater had a three-fold

higher rate of stroke, myocardial infarction, and vascular death (23% *vs* 7%). Furthermore, in the randomised Regression of Cerebral Artery Stenosis study,[133] of 132 patients with asymptomatic middle cerebral arteries stenosis and raised LDL cholesterol (3·00–5·00 mmol/L), LDL cholesterol concentration decreased by 1·42 mmol/L in patients given simvastatin and 0·13 mmol/L in patients given placebo within 2 years. The rates of progression of cerebral white matter lesions, asymptomatic brain infarcts, all-cause mortality, and any clinical events were significantly lower in the simvastatin-treated group.[76,150] Optimisation of blood pressure control and LDL cholesterol reduction synergistically reduced recurrent stroke and cardiovascular events as shown in the posthoc analysis of the SPARCL trial.[149]

The effect of intensity of serum glucose control in patients with diabetes mellitus and intracranial stenosis is unclear. In the WASID study,[148] patients with HbA_{1C} of 7% or greater had a higher rate of recurrent stroke (26% *vs* 15%, HR 1·7, 95% CI 0·8–3·6). On the basis of these data, reduction of HbA_{1C} to less than 7% with either insulin or pioglitazone is recommended.[137] Other recommended measures include BMI goals of less than 25 kg/m² (if BMI was 25–27 kg/m²) or 10% weight loss (if BMI was >27 kg/m²) by 30-min moderate intensity exercise sessions at least three times per week, and cigarette smoking cessation.[135] Initiation of fibrates should be considered if HDL cholesterol of 2·59 mmol/L or more or triglycerides of 2·26 mmol/L or more are identified after optimisation of LDL cholesterol.[92,148]

Investigators of the SAMMPRIS trial[92,148] recorded a 1-year rate of 12·2% stroke or death within 1 month and ipsilateral stroke between 1 and 12 months in patients with intensive medical treatment. The rate was lower than that recorded in the WASID trial (17%), which did not mandate intensive medical treatment. In patients who have had a minor stroke or TIA, early initiation (within 24 h) of both antihypertensive drugs and statins is supported by Early Use of Existing Preventive Strategies for Stroke (EXPRESS)[151] and SOS-TIA studies.[152] In the SOS-TIA study,[153] with early initiation of antiplatelet, antihypertensive, and statin drugs, the incidence of recurrent vascular events (recurrent TIA, stroke, or myocardial infarction) was only 7% in 160 patients with intracranial narrowing or occlusion at 1 year.

The AHA Stroke Council[139] support identification of atherosclerotic disease in coronary, extracranial, and other peripheral arteries because these patients are at high risk of vascular events[3,154] (panel). Almost a third of deaths in patients with intracranial stenosis are attributed to coronary artery disease and a fifth of vascular events are acute coronary syndromes during 2 years.[122] About 13% of patients with intracranial atherosclerosis and cerebral ischaemic events have known ischaemic heart disease.[154] In previous studies, 52% of patients with intracranial atherosclerosis had evidence of silent myocardial ischaemia measured by regional myocardial perfusion studies[155] and 60% have asymptomatic moderate to severe coronary artery stenosis.[156,157]

Intracranial angioplasty and stent placement

Intracranial angioplasty and stent placement are used for patients with high grade (70–99%) stenosis of a major intracranial artery such as the vertebral or basilar arteries, and internal carotid and middle cerebral arteries with recurrent ischaemic symptoms. Additional criteria such as the occurrence of ischaemic symptoms despite the use of antithrombotic treatment or severe hypoperfusion by regional blood flow studies are often used.[158] No data support the use of these procedures in asymptomatic

Panel: Management of concurrent disorders in patients with intracranial atherosclerosis

Cognitive deficits

Any patients with ischaemic symptoms should be screened with any of the available screening instruments (Cambridge cognitive examination or Vascular Dementia Assessment Scale cognitive subscale), supported by additional cognitive assessment. Treatment with multifaceted cognitive-linguistic therapies including compensatory strategies could be beneficial.

Depression

Any patients with ischaemic symptoms should be screened with self-report instruments (Beck Depression Inventory and Inventory of Depressive Symptomatology). Once diagnosed, treatment with psychotherapy and pharmacotherapy, or both, could be needed. Selective serotonin reuptake inhibitors are the preferred drugs.

Coronary artery disease (symptomatic or asymptomatic)

Patients with one or more cardiovascular risk factors or those with coronary artery calcification should be screened with stress and rest perfusion MRI or coronary CT angiography. If diagnosed, aspirin or clopidogrel (if aspirin contraindicated) is usually preferred over dipyridamole-based drug treatment. Coronary artery bypass grafting or percutaneous coronary intervention could be indicated for patients with acute coronary syndrome, pronounced symptoms and ischaemia, or both.

Extracranial carotid or vertebral arterial disease

Concurrent imaging of extracranial arteries by CT or MRI angiography is recommended. Carotid endartectomy, stent placement, or vertebral artery stent placement could be indicated if ischaemic symptoms are more probably attributed to extracranial stenoses based on clinical or imaging characteristics and severity of stenosis, or both.

Peripheral arterial disease

Intermittent claudication or signs and symptoms of critical limb ischaemia particularly in individuals with diabetes mellitus should be identified. Examination of the femoral, popliteal, and foot pulses and measurement of the the ankle brachial pressure index is reasonable in all patients. Revascularisation with angioplasty or bypass surgery could be indicated in patients with pronounced symptoms and ischaemia, or both.

Atrial fibrillation

Any patients with ischaemic symptoms should be screened by ECG. Long-term anticoagulation might be needed if ischaemic symptoms are attributable to atrial fibrillation or if the patient is regarded as high risk for thromboembolism. Low-dose aspirin (<100 mg/day) or clopidogrel (75 mg/day), or both, can be added to prevent myocardial or cerebral ischaemic events, but an increased risk of bleeding should be noted. Drugs for rate control (digoxin, β blocker, or non-dihydropyridine calcium channel antagonist) or ablation of the atrioventricular node or accessory pathway could be indicated.

patients.[158] Several angioplasty balloons, and self-expanding and balloon expandable stents increase lumen diameter, improve regional cerebral blood flow, and induce remodelling to reduce thrombogenicity in patients with intracranial stenosis.[158] Investigators of postmarketing registries[159,160] have reported technical success rates of 97% or greater with use of new generation angioplasty catheters and self-expanding stents with 6–9% periprocedural stroke or death rates. The rates of 1-month stroke or death and 1–6 month ipsilateral stroke in patients with severe intracranial stenosis were lower compared with matched controls from medically treated patients in the WASID trial.[160] However, investigators of these registries also identified a restenosis rate of 25–30% within 6 months to a year after the procedure.

The SAMMPRIS study[92] compared intensive medical therapy alone with intracranial stent placement combined with intensive medical therapy in patients with 70–99% intracranial stenosis who had had a TIA or stroke within 30 days before enrolment. Enrolment was discontinued after 451 (59%) of the planned 764 patients were enrolled because of a 14% rate of stroke or death within the first 30 days in patients who received stent placement compared with 6% in patients given medical therapy alone. Five stroke-related deaths and ten symptomatic intracranial haemorrhages occurred within 30 days after enrolment in the stent placement group. The 1-year rate of the primary endpoint (any stroke or death within 30 days or ipsilateral stroke after 30 days) was significantly higher in the stent treatment group than in the medically managed group (20% *vs* 12%). Another prospective single-centre study[161] randomly assigned 70 patients with symptomatic middle cerebral artery stenosis (severity ≥70%) to either intracranial angioplasty and stent placement or best medical treatment. The rate of disabling ischaemic stroke and TIAs, or both, was similar between the intracranial angioplasty and stent placement group and the medically treated group (19% *vs* 18%, p=0·85). After the SAMMPRIS trial, the US Food and Drug Administration restricted the use of the Wingspan stent to patients aged between 22 and 80 years who had had two or more strokes related to 70–99% stenosis of the intracranial artery despite medical management in whom the most recent stroke had to have occurred more than 7 days before planned treatment.[140] The time restriction was placed to avoid increased rates of stroke death that were observed in the SAMMPRIS trial in which half of stent treatments were done within 10 days of qualifying stroke or TIA.[162]

A more permissive policy towards primary angioplasty as the sole method or as an alternative to stent placement in selected patients, particularly those with long lesions and tortuous arteries, is another option.[162] In an analysis of data derived from three academic centres, the overall 30-day postprocedure stroke and death rate was 7·2% in the SAMMPRIS eligible patients when a mandatory policy of stent placement was not used.[163] The 30-day postprocedure stroke and death rate was 3·3% with primary angioplasty and 10·2% with stent placement in the SAMMPRIS eligible patients. Another trial[164] randomly assigned 18 patients with symptomatic moderate intracranial stenosis (stenosis ≥50%) with documented unresponsiveness to medical treatment or severe stenosis (≥70%) to either primary angioplasty (n=10) or stent placement (n=8). The 1-month stroke and death rate was very low in both patient groups (one of ten *vs* none of eight patients). Angiographic restenosis was reported in three patients with stent placement who had follow-up angiography.

However, outcomes should be tracked and reliably ascertained in centres who practise primary angioplasty and stent placement by use of metrics such as those proposed by the AHA Stroke Council.[165]

New therapeutic targets

Prevention of progression of stenosis

An increase in severity of stenosis due to continued inflammatory changes, lipid deposition, fibrosis, in-situ thrombus formation, and intraplaque haemorrhage is identified in 33% of patients during 2 years, and might result in occurrence of new ipsilateral ischaemic events.[166,167] In one study,[123] 457 patients with intracranial stenosis in the middle cerebral arteries or basilar artery and on aspirin were randomly assigned to either cilostazol or clopidogrel. The progression of intracranial stenosis by MRI angiograms at 7 months was similar in the cilostazol and clopidogrel groups (10 and 15%, respectively). High HDL cholesterol and low apolipoprotein B or A1 concentrations are associated with low rates of progression in severity of intracranial stenosis.[168] However, simvastatin 20 mg daily compared with placebo did not reduce the rate of regression of stenosis (22% *vs* 16%) as shown by serial MRI angiograms during 2 years in patients with asymptomatic middle cerebral artery stenosis and raised LDL cholesterol.[133] At present, no drugs show conclusive benefits in the prevention of plaque progression.

Optimisation of collateral flow

The EC/IC Bypass Study[169] did not identify a benefit of surgical anastomosis of the superficial temporal artery and the middle cerebral arteries to reduce the rate of ipsilateral or major strokes or deaths in patients who had had ischaemic events attributed to atherosclerotic narrowing or occlusion of the ipsilateral middle cerebral arteries. The Carotid Occlusion Surgery Study[170] recruited patients with internal carotid artery occlusion, measured by angiography, with recent ischaemic symptoms (within 120 days) and increased oxygen extraction fraction (marker of tissue ischaemia) by PET. Extracranial to intracranial (EC/IC) bypass substantially improved the oxygen extraction fraction, but the rate of all stroke and death within 30 days and ipsilateral ischaemic stroke within 2 years of randomisation did not differ in patients

randomly assigned to either EC/IC bypass or non-surgical treatment (21% *vs* 23%). The study further supported the absence of therapeutic benefit with EC/IC bypass even in patients selected by regional cerebral metabolic indices. Therefore, EC-IC bypass surgery is not recommended for patients with stroke or TIA due to stenosis or occlusion of a major intracranial artery.[135]

Less invasive methods such as augmentation of cerebral collateral flow by external counterpulsation have been investigated with several sessions of intermittent compression of air-filled cuffs on the legs.[171] External counterpulsation increases intracranial cerebral blood flow by TCD in patients with intracranial stenosis.[172] In one study,[172] patients who had had an ischaemic stroke and large artery occlusive diseases (predominantly intracranial) who were treated for 7 weeks within 3 months of symptom onset by external counterpulsation had greater improvement of neurological deficits compared with controls. In patients with progressive or fluctuating neurological deficits, external counterpulsation could be a temporary method to achieve neurological stability. Low serum concentrations of vascular endothelial growth factor are associated with increased severity of disease,[173] and thus administration could be a treatment for patients with diffuse intracranial atherosclerosis. Long-term reduction in cerebral ischaemic events has not been shown by either external counterpulsation or vascular endothelial growth factor treatment in patients with intracranial stenosis.

Conclusions

Intracranial atherosclerosis is a highly prevalent disorder that has gained recent attention because of the high risk of recurrent subclinical and clinical ischaemic events, and its association with cognitive deficits and dementia. Concurrent existence of extracranial and coronary artery atherosclerosis necessitates a targeted and global approach to reduce the risk of new or recurrent cerebral and coronary ischaemic events in patients with intracranial atherosclerosis.

Contributors

AIQ did the literature search, collected and synthesised the data, prepared the figures, and wrote the Seminar. LRC interpreted the data and revised the Seminar for important intellectual content.

Conflicts of interest

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