Carotid atherosclerotic disease: A systematic review of pathogenesis and management

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Abstract:
Carotid stenosis is an important contributor to ischemic stroke risk with resultant significant impact on neurological disability and death in adults and with worldwide implications. Management of carotid stenosis is impacted by whether there are associated symptoms along with the degree of stenosis. Understanding of the pathogenesis of carotid atherosclerosis or stenosis is important in management of carotid stenosis. Atherosclerotic plaque formation is a chronic insidious process with a number of potential contributors to the formation of such a plaque. The definition of atherosclerosis is not simply limited to abnormal deposition of lipid but also includes a chronic, complex, inflammatory process. Molecularly, in atherosclerosis, there is decreasing nitric oxide (NO) bioavailability, activity and/or expression of endothelial NO synthase, or increasing degradation of NO secondary to enhanced superoxide production. These above changes cause endothelial dysfunction leading to formation of foam cell followed by formation on lipid plaque. After lipid plaque formation, stable or unstable atherosclerotic plaque is formed depending on the calcium deposition over the lipid plaque. It continues to be clearly established that carotid intervention for symptomatic high-grade carotid stenosis is best managed with intervention either by carotid endarterectomy or carotid stenting. However, asymptomatic carotid stenosis is the subject of considerable controversy in terms of optimal management. This review of carotid atherosclerosis is an attempt to incorporate the information provided by more recent studies on pathogenesis and management which may help in the decision-making process for optimal management for protection against stroke.

Keywords:
Carotid stenosis, management, pathogenesis

Introduction

The most important aspect of addressing the evaluation and management of carotid stenosis is the assessment of risk of stroke and determining if the proposed treatment’s benefits justify the potential risk of serious complication. Obviously, clinical features help to define the stroke risk profile.[1] Coexistent factors can have a major impact on optimal management.[2] For example, one has to question the advisability of carotid intervention in a patient with coexistent atrial fibrillation who is best managed with chronic anticoagulant therapy. It is also well recognized that a patient presenting with vertebrobasilar TIA will not necessarily have protection against stroke with carotid intervention for coexistent carotid disease.

Pathophysiology of Carotid Atherosclerotic Plaque

The layers of the arterial walls, and their functions, are important in understanding the pathophysiology of carotid artery stenosis. The normal structure of the carotid artery, or arteries in general, is composed of three layers: from internal to external, the tunica intima, tunica media, and tunica adventitia.[3] Each of the layers has a specific
Atherosclerotic plaque formation is a chronic insidious process with a number of potential contributors to the formation of such plaques. The definition of atherosclerosis is not only limited to abnormal deposition of lipid but also includes a chronic, complex, inflammatory process. Of particular note, alteration of shear stress is an important initiating factor in atherosclerosis. The process is initiated at the abluminal surface, where metabolic, mechanical, or physical injury causes disruption of endothelial integrity. The resultant endothelial dysfunction can lead to intimal stress associated with an abnormal biochemical signal. Over time, disruption of the tunica media also occurs.\textsuperscript{[5,4]}

**Endothelial Dysfunction and the Cascade of the Atherosclerosis Process**

Endothelial cells are a key predictor of vascular health, in addition to being a barrier between luminal contents and the vessel wall. Normal functions of the endothelium include production of nitric oxide (NO), control of volume, regulation of platelet adhesion and coagulation, immune function, and electrolyte balance of the extravascular and intravascular spaces. Endothelial dysfunction is often related to impaired NO-mediated relaxation. The risk factors associated with atherosclerosis, which include diabetes mellitus, hypertension, hyperlipidemia, smoking, as well as genetic predisposition, often potentiate the endothelial dysfunction.\textsuperscript{[4,7]} Previous *in vivo* and *in vitro* studies have demonstrated that low shear stress and disturbed flow, including flow separation and turbulent flow, predispose to endothelial dysfunction.\textsuperscript{[4,7]} Endothelial dysfunction subsequently triggers atherosclerosis formation and extension.\textsuperscript{[8]}

Shear stress directly impacts endothelial cell pathophysiology and is associated with the change in cellular orientation, local concentration of different cytokines, growth factors, receptors and adhesion molecules as well as gene expression. In general, high-to-medium shear stress causes release of NO and prostacyclin which maintain the vascular tone. In addition, NO is recognized as an atheroprotective factor of the endothelium. Turbulent flow and low shear, particularly in branch points of arteries, have the opposite effects of high shear including decreasing NO bioavailability, activity and/or expression of endothelial NO synthase, or increasing degradation of NO secondary to enhanced superoxide production.\textsuperscript{[9]}

In addition, hyperglycemia associated with diabetes mellitus, atherosclerosis-associated lipid components in hyperlipidemia, excessive homocysteine, and superoxide formation, associated with smoking, are toxic to the endothelium. In one study, elevation of serum level of inflammatory markers was associated with carotid stenosis leading to induction of oxidative stress in the wall of carotid arteries.\textsuperscript{[10]}

Different cytokines, growth factors, and their receptors, as well as adhesion molecules, are released by dysfunctional endothelium. Release of vascular cell adhesion molecule (VCAM), intercellular adhesion molecule, and P-selectin triggers the adhesion of monocyte, platelets, and lymphocytes and increases cell permeability. This process further enhances the inflammatory process.\textsuperscript{[11]}

The increased endothelial permeability facilitates monocytes to migrate through endothelium and allows low-density lipoprotein (LDL)-cholesterol to enter into the intimal layer, where the LDL is oxidized by the superoxide molecules. The monocytes are then transformed to macrophages and ingest the oxidized LDL particles by phagocytosis. These cells are referred as “foam cells.” The foam cells, platelets, and T-lymphocytes release into the bloodstream the pro-inflammatory cytokines which include monocyte colony-stimulating factor (M-CSF) and platelet-derived epithelial growth factor.\textsuperscript{[12]} Oxidized LDL also promotes the recruitment and retention of monocytes and lymphocytes.\textsuperscript{[13]} The cytokines, growth factors, and adhesion molecules released by the above cells cause further recruitment and migration of the leukocytes and macrophages which potentiate the inflammatory reactions.\textsuperscript{[14]} In addition, the inflammatory cascade is further magnified by the local release of interleukin (IL)-1, tumor necrosis factor (TNF)-α, and M-CSF, which facilitates the adhesion, activation, and proliferation of leukocytes.\textsuperscript{[11]}

This cascade potently activates the subtypes of mitogen-activated protein kinase including extracellular signal-regulated kinase and P38 mitogen-activated protein kinase (MAPK) which induces cellular
adhesion, migration, proliferation, differentiation, apoptosis, and autophagy. Over time, the intimal layer becomes more permeable to circulating cells and triggers a pro-inflammatory condition with release of cytokines. These cytokines further attract monocytes, macrophages, and T-cells to potentiate the plaque formation.[16] [Figure 1].

Besides the above factors, angiotensin II is also involved in atherosclerosis. Angiotensin II stimulates atherosclerosis by formation of reactive oxygen species (ROS) in inframammary cells, which oxidizes the LDL and promotes pro-atherogenic, pro-inflammatory, and pro-coagulant activity of platelets and monocytes.[18]

**Smooth Muscle Cell Dysregulation**

Smooth muscle in the tunica media migrates and proliferates to the intimal layer and results in a neointima by platelet derived growth factor (PDGF), endothelial growth factor, and transforming growth factor-beta.[17,18] High shear also decreases the release of endothelin-1, which exerts both constricting and mitogenic effects of vascular smooth muscles. Reduced bioavailability of NO is associated with increased vascular tone and increased platelet activation, as well as intimal proliferation.[19] The usual functional state of media, including contractility, is altered to a synthetic state. Smooth muscle cells (SMCs) also ingest the oxidized LDL particles and become foam cells. Endothelin released by dysfunctional endothelium causes mitogenic activity to the SMCs and vasoconstriction. Angiotensin II promotes the vascular SMC proliferation by formation of ROS and enhances the activity of membrane-bound nicotinamide adenine dehydrogenase/nicotinamide adenine dinucleotide phosphate (NADH/NADPH) oxidase.[20]

In response to alteration in function of the intima, the media responds with proliferation of SMCs, as well as further promoting the migration of leukocytes and monocytes into this layer. MAPK pathways are associated with migration, proliferation, and differentiation of the SMCs.[15] Various inflammatory mediators are released by SMCs including IL-1β, IL-8, TNF-α and β, IL-6, M-CSF, monocyte chemoattractant factor-1 (MCP-1), and CD-40 ligand. These mediators diversely stimulate mitogenesis and intracellular matrix proliferation.[15] Within the media layer, the derangements of cells and extracellular matrix initiate formation of the carotid plaque. Both genetic and environmental risk factors contribute to the progression of lipid plaque [Figure 2].

**Histopathological Features of Carotid Atherosclerotic Plaque**

The pathology of carotid stenosis begins with fatty streak formation, followed by production of atheromatous fibrous plaque. Accumulation of foam cells and SMCs in the intimal layer and production of extracellular matrix by the foam cells creates a fatty streak, elevates the endothelium, and initiates the formation of atherosclerotic plaque. Detection of active inflammation in the lipid core is an indicator of unstable plaque. When the foam cell dies, it leaves an inert necrotic, atheromatous core within the plaque which is soft and unstable. Some atherogenic LDL may be retained and accumulates within the intimal layer.[21] The lipid-rich core is soft, avascular, hypocellular, and devoid of collagen. Apoptosis of foam cells and SMCs results in the formation of an unstable lipid core and the fragile and rupture-prone fibrous cap. The above process also stimulates high tissue factor activity and thrombogenicity within the lipid core. Advanced atherosclerosis plaque is composed of 68% fibrous tissue, 16% inert necrotic core, 1% foam cells, 7% inflammatory cells, and 8% calcium.[15,22,23]
Calcification

Calcification of the lipid core is an important prognostic indicator. Plaque calcification is active and controlled and resembles bony calcification. Clinical observations suggest that calcified atheroma is stable, while the less calcified atheroma is more prone to rupture and can be associated with thromboembolism.\[24,25\]

Remodeling of Vascular Wall

Remodeling of the vessel wall in the atherosclerotic process triggers formation of rupture-prone inflamed thin-cap fibroatheroma. Leukocyte-induced matrix metalloproteinase (MMP)-mediated remodeling of the vascular wall is also noted in the development of carotid atherosclerosis.\[15,26\]

Angiogenesis

Neovascularization and inflammation coexist and mediate plaque progression. Angiogenesis starts in the vasa vasorum of the adventitia with proliferation and extension into the base of the lipid plaque. Microvessels from angiogenesis are very fragile and leaky. VCAM-1 is expressed in this process and promotes local extravasation of proteins, inflammatory cells, and erythrocytes.\[15,27\]

Thrombosis and Hemorrhage

The fibrous cap usually prevents the exposure of the lipid-rich core to flowing blood. However, any gap in the fibrous cap or significant injury exposes the athermanous core.\[28\] Exposure of the subendothelial tissue of the plaque allows platelets to adhere, resulting in the formation of fibrin. Platelet aggregation causes thrombus formation associated with luminal obstruction. Fibrinous material can help to stabilize the platelet-induced thrombus. However, this process can also allow accumulation of hemorrhage into the plaque resulting in silent, episodic progression of the atherosclerotic lesion.\[28\]

Ulceration of Carotid Plaque

Imaging can identify carotid plaques as being either smooth, irregular, or ulcerated and can help in determining what has been termed “vulnerable plaque” in terms of stroke risk.\[29\] Ulcerated plaque represents the excavated necrotic core with discontinuous fibrous cap.\[30,31\] Ulcerated plaques are associated with a higher risk of rupture and can lead to thrombus formation and subsequent embolization causing stroke.\[32\]

Stable versus Unstable Carotid Plaque

There are certain pathological features of rupture-prone plaque. Stratification of risk includes (1) structural features: large lipid reach necrotic core, thin fibrous cap, expansive remodeling, and adventitial inflammation and angiogenesis; (2) cellular features: lack of SMCs and accumulation of macrophages in the plaque; and (3) functional features: impairment of SMC-induced matrix synthesis and breakdown of macrophage-derived MMPs.\[21\]

Grossly complicated plaques are classified as follows: (1) plaque rupture with intraplaque hemorrhage (IPH), (2) plaque rupture plus thrombosis, (3) plaque rupture with IPH and thrombosis, and (4) IPH without plaque rupture\[21\] [Figure 2]. Plaque analysis with sophisticated ultrasound (US), including adding transcranial Doppler (TCD) detection of microemboli potentially associated with the unstable plaque can help to identify high-risk plaques\[33\] and this can include densitometric analysis of carotid plaque composition.\[34\] Conversely, uncomplicated, i.e., “stable,” plaques tend to be smooth and calcified.\[21\]
Progression of Atherosclerosis Plaque

As mentioned previously, formation of foam cells and SMCs in intimal layer and associated production of extracellular matrix creates fatty streaks, elevates the endothelium, and initiates the formation of atherosclerotic plaque. Over time, the repeated process of endothelial injury and alteration of shear stress, immune response, and smooth muscle function trigger the formation of a fibrous cap on lipid-laden plaque. After forming a fibrous cap, the lipid plaque begins to encroach on the lumen of carotid artery and can reduce the luminal diameter of the artery. The active atheroma or plaque may continuously grow with chronic inflammation, which is triggered by alteration of the arterial geometry by the atheroma. This is followed by modification of the local shear stress direction, oscillation, and magnitude. Chronic inflammation and remodeling can result in progressive focal carotid stenosis.

The carotid plaque can become susceptible to rupture if the fibrous cap is associated with MMP-induced remodeling of the membrane. Chronic ongoing inflammation in a noncalcified plaque is the key element of atherosclerotic plaque vulnerability and disruption. On the other hand, plaque calcification is an indicator of a stable plaque less likely to be associated with thromboembolism. Decreased NO bioavailability induced by dysfunctional endothelial cells is associated with decreased anticoagulant properties, dysregulation of vascular tone, and increased platelet aggregation. The presence of CD40L in atherosclerosis plaque stimulates the expression of tissue factor and potentiates thrombus formation. In addition, exposure of a ruptured plaque to thrombotic material initiates formation of thrombus by activating platelets and the clotting cascade. This cascade of events eventually results in atheroembolism and resultant cerebral, or retinal, ischemia.[35] [Figures 1, 2 and 3].

Genetic Basis of Carotid Atherosclerosis

Alteration in certain genes promotes the atherosclerotic process. Mutation in the gene-encoding LDL receptor induces hypercholesterolemia and premature atherosclerosis.[39] Studies have shown that epsilon polymorphism of the apolipoprotein E protein gene and angiotensin-converting enzyme insertion/deletion polymorphism are associated with carotid atherosclerosis.[40-42] Genetic factors, other than those for lipid metabolism, have also been implicated in atherosclerosis and thrombogenesis. In addition, genetic variation in coagulation factors and fibrinogen have been identified as promoters of thrombogenesis.[41] Moreover, certain genetic variants of endothelial NO synthase have been also associated with atherosclerosis.[40]

Diagnostic Approaches to Carotid Stenosis

Early detection of stenosis of carotid artery is crucial to prevent potential stroke associated with internal carotid artery (ICA) stenosis. Fortunately, there has been a significant advancement in the detection capability of ICA stenosis which includes carotid US, TCD, computed tomographic angiogram (CTA), magnetic resonance angiogram (MRA), and conventional four-vessel cerebral digital subtraction angiography (DSA).[43-45]

Carotid Ultrasound

Carotid duplex imaging, combining B-mode anatomical imaging with Doppler flow velocity characteristics, can be used to determine the presence of atherosclerosis and flow status of carotid artery. Grayscale US is utilized to assess the status of vessel wall including the presence and characteristics of plaque. Calcification (hyperechoic) and noncalcified portions of the plaque, as well as intimal and medial thickness of the wall, can also be determined by grayscale US.[46,47] Color Doppler US is used to determine the vascular flow direction and velocity. Continuous Doppler waveform assesses the flow characteristics, and pulsed Doppler determines the velocity in a specific field depth of the specific vascular region.[48] Peak systolic velocity is typically used to determine the degree of stenosis. However, end-diastolic velocity and carotid index are also useful. US is 89% sensitive and 84% specific determining 70%–90% stenosis while it is 36% sensitive and 91% specific to assess 50%–69% stenosis.[49] US remains a noninvasive and relatively cost-effective procedure for initial assessment of carotid stenosis.

Transcranial Doppler

TCD is another noninvasive method to determine the hemodynamic effect of extracranial ICA stenosis on intracranial circulation.[50-52] The Doppler signal can be obtained through transtemporal and transorbital windows. Flow direction measurement of the ophthalmic, middle cerebral, and anterior cerebral arteries can allow indirect assessment of potential collateral circulation adjustments to ipsilateral severe ICA stenosis or occlusion.[53,54]

Computed Tomographic Angiography

Studies have demonstrated that CTA is highly sensitive and specific to diagnose ICA stenosis when compared with standard DSA.[53,56] CTA (R = 0.95) was comparable to DSA (R = 0.89) to detect stenosis. It is now routinely used in rooms during stroke codes to
detect extra- and intracranial carotid stenosis. CTA has higher sensitivity (98% vs. 70%) and positive predictive value (93% vs. 65%) than MRA, respectively, to detect ICA stenosis. CTA is also generally more accurate in assessing the posterior circulation compared to DSA in the presence of poor flow. However, the exact degree of ICA stenosis is more accurately measured by DSA. CTA has a tendency to underestimate the higher grade (CTA, 78% vs. DSA, 86%) and moderate grade stenosis (CTA, 57% vs. DSA, 63%).

Magnetic Resonance Angiography

MRA can be done with or without contrast to determine carotid stenosis with the time of flight MRA without contrast and gadolinium contrast-enhanced (CE) MRA available with the contrast-enhanced study viewed as being more accurate for extracranial ICA stenosis. MRA is not generally viewed as accurate as CTA as noncontrast MRA is not as sensitive to calcification resulting in underestimation of the carotid stenosis. On the other hand, contrast-enhanced MRA is more impacted by artifacts which can overestimate the stenosis. With either CTA or DSA, North American Symptomatic Carotid Endarterectomy Trial (NASCET) or European carotid surgery trial (ECST) criteria can be used to calculate the degree of ICA stenosis. Of note in acknowledgment of potential iodine-based contrast contraindication, contrast-enhanced MRA is 94% sensitive and 93% specific for identifying 70%–90% ICA stenosis. However, for 50%–69% stenosis, CE MRA is 77% and 97% sensitive and specific, respectively. MRA can thus be a reasonable option for relatively noninvasive evaluation of the carotid circulation, especially in those having a contraindication to iodine-based contrast.

Intra-arterial Cerebral Angiography (Digital Subtraction Angiography)

DSA is the gold standard, but invasive, method to determine the extent of carotid atherosclerotic occlusive disease in an accurate fashion. In addition to diagnostic assessment, this procedure is used during carotid stenting and angioplasty. There are generally two views including lateral and anterior–posterior with DSA. Rotational view is also performed for assessing severe carotid stenosis and better visualization of cerebral aneurysm. The sensitivity, specificity, and accuracy of DSA for detection of carotid stenosis are 95%, 99%, and 97%, respectively. In the NASCET and European Carotid Surgery Trial (ECST) DSA procedure was utilized. The NASCET criteria to calculate ICA stenosis is \( A - B / A \times 100 \) (%) and ECST criteria to calculate ICA stenosis is \( C - B / C \times 100 \) (%) [Figure 4]. In the NASCET criteria, severe ICA stenosis is defined as 70%–99% stenosis and moderate stenosis as 50%–69% stenosis.

Assessment and Treatment of Stroke Risk with Symptomatic Carotid Stenosis

One must first define symptomatic carotid stenosis in terms of its presentation. The presentation can be a cerebral hemispheric TIA, a cerebral hemispheric infarct, or a retinal TIA, termed amaurosis fugax or transient monocular blindness, or retinal infarction. The risk of stroke or TIA with carotid stenosis is related to the degree of stenosis along with plaque characteristics, including thrombus formation, in association with the carotid plaque. The term TIA has undergone some recent revision. Traditionally, TIA represents temporary neurological dysfunction, on a vascular basis in a single artery territory, that completely remits within 24 h. However, because of the potential presence of tissue infarction on diffusion-weighted MRI brain scan, the tissue-based definition of TIA is now a transient episode of neurological impairment associated with either focal brain, spinal cord, or retinal ischemia without acute
in patients >70 years of age (OR = 1.11 for those <70 vs. 2.23 for those >70, P = 0.007).[73]

Assessment and Treatment of Stroke Risk with Asymptomatic Carotid Stenosis

In terms of the natural history of asymptomatic higher grade, i.e., >70% stenosis, Cheng et al.[74] reported that the 5-year risk of stroke or TIA associated with ipsilateral stenosis was 5.3%. This was based upon serial carotid duplex scan with a progression rate of stenosis, over time, of 24.1%. With such a relatively low overall risk of stroke in asymptomatic carotid stenosis, the approach to possible intervention remains perplexing.[75] In a Veterans Administration study reported in 1993, in a male population with 50% ICA stenosis or greater, the rate of what was termed “combined ipsilateral neurological events” was 8% with CEA versus 20.6% in the medical group (P < 0.001). During follow-up, the stroke rate was 4.7% for CEA versus 9.4% for the medical group although there was no difference in combined stroke and death at 30 days.[74] There has been additional support for intervention in carefully selected patients, who have relatively low surgical risk for complication, based on additional studies.[76] However, optimization of alternative medical therapy, in this patient group, is still an evolving process, particularly with success in managing dyslipidemia with statins or other lipid-lowering agents.[77] CAS versus CEA is under investigation for asymptomatic stenosis. To date, there has been reported a borderline significant increase in stroke or death, within 30 days of the procedure, with CAS compared to CEA with OR = 1.72, P = 0.05.[73]

A recent study by Saba et al. showed that imaging techniques including MRI, CTA, and US of carotid artery can detect carotid plaque volume, maximum wall thickness, plaque inflammation, IPH, neovascularization, ulceration, lipid-rich necrotic core, fibrous cap, plaque calcification, and microembolization.[78] Moreover, Schindler et al. showed that IPH is common in both symptomatic and asymptomatic carotid stenosis, and it is a strong predictor of stroke.[70] Currently, carotid assessment depends on not only about degree of stenosis but also carotid plaque vulnerability. Therefore, MRI or CTA-based detection of carotid plaque vulnerability may be beneficial for determination of carotid revascularization.

Current Patient Selection between Carotid Artery Stenting and Carotid Endarterectomy

Carotid stenting is usually preferring in patients with restenosis after prior CEA, prior radical neck surgery, radiation therapy in the neck, young patients less than 70 years old, and concomitant heart disease.
Alternatively, CEA is preferred in elderly patients older than 70 years.\textsuperscript{[59,80]}

### Transcarotid Artery Revascularization

Transcarotid artery revascularization (TCAR) is now available as an alternative to routine CEA or CAS for the treatment of CA stenosis. Anatomic requirements and eligibility for TCAR include diameter of carotid artery \(>6\) mm, distance between access site and the lesion \(>5\) cm and common carotid artery (CCA), and carotid occlusion sites free of thrombus or calcification. Recent studies\textsuperscript{[81‑83]} reported that the stroke, cranial nerve injury, or death rate is favorable for T-CAR compared to CAS. In the cases with symptomatic CA stenosis, new stroke determined within 24–48 h of procedure was 12.9% in TCAR compared to 33.3% in CAS.\textsuperscript{[81]} A previous study showed that TCAR significantly reduces the rate of MI compared to CEA, and that would be choice of treatment for the particular compared to CEA or CAS as there is no head-to-head randomized control trial between the procedures.

### Summary

The approach to the patient with carotid stenosis must be individualized. The medical stability of the patient and the availability of outstanding expertise in the interventional process are of utmost importance. There is increasing support for a conservative approach to management of asymptomatic carotid stenosis. However, one must factor in extenuating factors. For a relatively young and healthy patient with bilateral high-grade carotid stenosis, one might well want to consider intervention, especially if serial imaging of the carotid bifurcation shows progression of the stenosis over time despite optimal medical management. Conversely, if a patient with high-grade asymptomatic carotid stenosis, or symptomatic moderate stenosis, who is not receptive to acceptable medical management (e.g., optimal hypertension and diabetic control, optimal lipid profile, smoking cessation, dietary modification as well as use of anti-thrombotic therapy), then an interventional procedure becomes much more attractive to prevent a major cerebral infarct. Enhanced imaging of the plaque characteristics can now certainly help in the decision making process with either advanced neurosonology\textsuperscript{[84]} or MR imaging of the plaque\textsuperscript{[85]} with assessment of its potential vulnerability\textsuperscript{[86]}, as well as quantitative assessment of carotid plaque morphology with CTA.\textsuperscript{[87]}

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### Conflicts of interest

There are no conflicts of interest.

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