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EDITORIAL

Surrogate Markers and Reporting Standards for Outcome After Carotid Intervention

Recently, a focus on the timing of intervention, as well as improvements in medical therapy, have changed the clinical treatment algorithm of carotid revascularisation. The debate remains alive when it comes to the optimal treatment strategy, including early (<14 days) *vs.* expedited (<48 h) revascularisation, the role of plaque vulnerability in decision making, and alternative (endovascular) revascularisation approaches. In weighing up the relative contribution and relevance of these strategies on outcome, it is of utmost importance to apply universally accepted and clear endpoints. As the classic clinical endpoints of "procedural stroke and death" and "recurrent stroke" now occur less often, very large numbers of patients would be required to demonstrate a significant outcome effect of new diagnostic and treatment algorithms. As such, there is a strong need for the redefinition of study endpoints and for surrogate markers for ischaemic stroke, both in the semi-acute and late phases.

It is important to stipulate that a distinction should be made between surrogate endpoints for peri-procedural stroke and surrogate markers for long term outcome after revascularisation or best medical treatment (BMT). Diffusion weighted imaging (DWI) lesions have emerged as a promising surrogate endpoint of peri-procedural cerebral ischaemia. The main advantage of DWI is that ischaemic areas can be identified within minutes of a hypoxic episode and will be visible for several days. Most DWI lesions are small, do not cause clinical neurological symptoms, and do not result in permanent ischaemic changes on follow up imaging.[1] DWI lesions are related to the procedure and far more prevalent than post-procedural strokes.[2]

The MRI substudy of the International Carotid Stenting Study demonstrated that the presence of any new (ipsilateral or contralateral) post-procedural DWI lesion was considerably higher after carotid stenting (50%) than after endarterectomy (17%).[2] DWI lesions qualify as a strong surrogate measure as they meet three conditions: (i) a plausible biological relationship with stroke;[3] (ii) an association with increased risk of post-procedural stroke/transient ischaemic attack);[4] and (iii) the treatment effect on DWI lesions correlates with that on stroke.[5] According to these three qualifications, DWI lesions quantified as number and/or volume are an excellent surrogate endpoint for studies evaluating treatment modifications.

A 2019 meta-analysis established that for an underlying 3% absolute difference in procedural stroke risk among revascularisation techniques, a 90% sample size reduction could be achieved when using DWI lesions rather than classic endpoints.[5] Of note, little is known about the optimal timing of the post-procedural scan as both ongoing haemodynamic disturbance and thrombo-embolic events days after the procedure are common. Also, magnetic resonance (MR) field strength may influence the number of DWI lesions,[2] and thus timing and image acquisition protocols should be harmonised in future research. A complete report of DWI data in randomised control trials of carotid interventions is required to use DWI as a valid surrogate endpoint.

As the appearance of hyperintensities on MR DWI is time limited, this modality is not suitable to investigate brain damage related to the natural course of atherosclerotic carotid artery disease. Instead, silent brain infarcts (SBIs) defined as cerebral infarcts on MR imaging (MRI; T2 or fluid attenuated inversion recovery) or computed tomography (CT) without corresponding clinical symptoms could be used for this purpose. Sensitivity for detection of silent infarcts is higher for MRI than for CT,[6] and the reported prevalence of ipsilateral lesions is as high as 38% in patients with asymptomatic carotid stenosis >50%.[7] Silent brain infarct, and especially cortical (micro-)infarcts are caused by emboli from proximal sources such as the heart and atherosclerotic lesions in the aortic arch, origin of supra-aortic arteries, carotid bifurcation, and intracranial arteries. New silent and clinical brain infarcts in the ipsilateral hemisphere during follow up could be used as a surrogate endpoint to evaluate the beneficial effects of carotid intervention *vs.* BMT in newly defined high risk subgroups based on atherosclerotic plaque imaging.

A third possibility for determining long term outcome in carotid interventions is assessment of white matter lesions (WMLs). WMLs have been used widely as a marker for small vessel disease and are closely associated with ageing and risk factors for atherosclerosis,[8] with hypertension being an important independent predictor for WML.[9] WMLs may result from embolic events from unstable carotid plaques, but may also be an expression of generalised atherosclerotic disease, and until now evidence for causality between plaque instability and WML has been fragile.[10]

All three surrogate markers have been associated with increased risk of future cerebrovascular events in patients with carotid artery disease specifically.[4,7,11] Both SBIs and WMLs have been associated with increased risk of cognitive decline.[6,12]

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In conclusion, there is a need for the establishment of well defined surrogate endpoints for stroke in patients with carotid artery disease. DWI lesions, SBIs, and WMLs are promising and complementary surrogate markers. Standardisation of imaging protocols and reporting of outcome is required. We recommend differentiating and reporting both "any" *vs.* new "ipsilateral" lesion. DWI lesions are most suitable for assessment of peri-procedural outcome, whereas both silent brain infarcts and white matter lesions can be used for long term outcome. In our view, pre- and post-procedural brain MRI should be implemented in standard care to encourage and facilitate employment of these surrogate markers in research and clinical practice when treating patients with carotid artery disease.

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