Author's response to reviews

**Title:** Optimal cut-off criteria for duplex ultrasound for the diagnosis of restenosis in stented carotid arteries: review and protocol for a diagnostic study

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**Version:** 3 **Date:** 2 July 2009

**Author's response to reviews:** see over
Revision 1, response to reviewer

OPTIMAL CUT-OFF CRITERIA FOR DUPLEX ULTRASOUND FOR THE DIAGNOSIS OF RESTENOSIS IN STENTED CAROTID ARTERIES. REVISION 1.

We would like to thank the reviewer for the very valuable comments. Each specific comment of the reviewer is listed separately; followed by our response.

The authors should comment on the SPACE and CAVATAS results, which show a high rate of in-stent stenosis, but on the other hand a low rate of clinical endpoints. This would make it easier for the reader to grasp the scope of the problem.

The SPACE-investigators indeed literally concluded in the abstract of their paper about the two years follow-up data (Lancet Neurol 2008) that the incidence of recurrent carotid stenosis at 2 years was significantly higher after carotid artery stenting but that it could not be excluded that the degree of in-stent stenosis is slightly overestimated by conventional ultrasound criteria. The CAVATAS-investigators also reported a higher restenosis rate after endovascular treatment than after endarterectomy (Stroke 2005), however, in this study the majority of patients in the endovascular arm were treated by angioplasty without stenting. We added a comment on the follow-up results of SPACE and CAVATAS (introduction, second paragraph on page 4) and we added two references (6 and 7).

The systematic literature search had the aim to identify all studies which used ultrasound and a reference test. The result of this is, that currently not enough data exists to define clear cut-off criteria for duplex diagnosis of in-stent stenosis. On this background I cannot really understand why the study of Kwon was excluded since the aim of this search was to identify all material as a starting point and the proposed study should yield definite results.

The study of Kwon et al. (J Endovasc Ther 2007) is discussed in the paper but could not be included in the table, because the study did not calculate new in-stent criteria. They used regular and previously defined criteria for non-stented arteries in the assessments of the patients treated with a stent; thus not derived from the present dataset. The reason of exclusion is discussed in the first sentence of the second paragraph on page 7 and in the last sentence of the first paragraph on page 8. The table contains those studies that calculated new in-stent criteria.

In the context of the proposed study it would also be necessary to comment on the accuracy of CTA in comparison to DSA in more depths, because CTA is planned to be used as reference. I am not sure, whether it is unethical to use DSA instead of CTA as reference. It is known that the accuracy of CTA in comparison with DSA is limited. So in the long run, we would end up with a non-invasive method with new ultrasound cut-off values which are of very limited accuracy compared to DSA because already the initial “goldstandard” was second best. In this respect it would also be necessary to take into account, that a therapeutic intervention would very likely need preinterventional or interventional DSA anyway. On the other hand I understand, that it would be difficult to enrol enough patients to bring such a study to an end.

We agree the point raised by the reviewer about the ‘gold’ or ‘reference’ test in diagnostic studies is difficult but crucial. First, as the reviewer suggested, we added information on the diagnostic accuracy of CTA (first paragraph, page 11). We agree that if you compare to DSA, the pooled diagnostic accuracy is limited (sensitivity 77% and specificity of 95% to diagnose a 70-99% stenosis).

Part of the limited accuracy compared to DSA, however, can be explained by methodological factors. CTA and also MRA provide more projections, often 12, (360° around the vessel) instead of the three in
the NASCET stenosis measurements in DSA (lateral, posteroanterior, or oblique). Measurements with CTA should preferably be done in a comparable manner, in order correctly apply the trial-data to the clinical decisions about CEA. By reducing the number of projections in the stenosis measurements, diagnostic accuracy compared to DSA will increase (Nederkoorn et al, J Vasc Surg 2002). The latter is explained in the last paragraph on page 13.

Moreover, it is likely that post-processed images and the use of 3D techniques in CTA or MRA reveal a more precise estimate of the actual degree of stenosis. However, with a potentially more precise estimate of the stenosis, the relation with DSA-based trial-results becomes more remote. DSA may not be the gold standard anymore with respect to state-of-the-art imaging and post-processing techniques, we agree with the reviewer that it is important to realise that it does remain the standard of reference with respect to clinical decision making on CEA, based upon what we know from the trials. Ideally, new 3D techniques should be compared with conventional DSA in sufficient large consecutive patient series. However, in clinical practice DSA is not routinely used anymore in all patients in whom CEA is considered. Therefore, such a diagnostic study would be unethical. Rapidly improvement techniques confront us with moving targets.

We felt it would be beyond the scope of this paper to discuss these methodological issues in detail. Crucial is the fact that we can compare DUS results to a technique that provides clear images of the lumen, in order to investigate if the PSV raises more in a stented artery than in an unstented artery when the remaining lumen in a stenosis is the same as. We added this last remark on page 11.

We do not completely agree that the use of DSA, in a study for diagnostic purposes only, could still be ethical. In the past, in the period of the large carotid surgery trials, a risk of 4% of TIA or minor stroke and 1% of major stroke, and even a small risk of death (<1%), was been reported (Hankey et al, JNNP 1990; Davies et al, JNNP 1993). More recently, a lower rate of neurological complications due to DSA was reported: 0.5% for stroke and 0.4% for TIA (Johnston et al, neurology 2001). On the other hand, even patients without apparent neurological complications after DSA have been shown to develop minor asymptomatic infarctions due to microembolisms (Bendszus et al, Lancet 1999). To expose patients to this risk for study and for diagnostic purposes only seems unethical to us.

The inaccuracy of ultrasound, which would be still acceptable obviously depends on the situation when a new therapeutic intervention is necessary. Perhaps the authors should comment on this last point and try to define “points of intervention” from the existing literature. Although it is not intended to use DSA as the sole standard, at least the postinterventional DSA result and DSA at the point of a planned new intervention or perhaps at the point of in-stent stenosis > 70% according CTA could serve as some “anchor points”.

We agree. But we would like to emphasis that the scope of the present study should is limited to define cut-off criteria; it does not yet study clinical consequences and is not designed to define points of intervention. However, precisely this will be done in the long-term follow-up of ICSS, using the new criteria. In ICSS data we will also look at DSA results available from re-interventions. But for the purpose of the present research question, obtaining valid PSV cut-off points avoiding verification-bias, in our study design we should limit to one suitable reference test carried out in all consecutive patients.

It seems that the authors intend to define velocity cut-offs only. However, since often in-stent stenosis is caused by intimal hyperplasia it might be better to try to also define additional duplex criteria. In-stent stenosis often is not localised such as in atherosclerotic proximal ICA stenosis.

We certainly agree and we will. However, this subject is also beyond the purpose of the present study. The other DUS characteristics will be studied in the ICSS follow-up data, particularly with respect to clinical consequences. We added a sentence to the discussion on this point (first paragraph page 6). In this study on purpose we limit to obtaining valid PSV cut-offs.