Optimal cut-off criteria for duplex ultrasound for the diagnosis of restenosis in stented carotid arteries in the International Carotid Stenting Study (ICSS): results from the CTA-substudy

Cover title: diagnosis of restenosis in stented carotid artery

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Abstract

Background and purpose: Previous studies reported that duplex-ultrasound cut-off criteria, based on blood velocity parameters, for the degree of stenosis in a stented carotid artery are higher than the established cut-offs used for unstented arteries. These studies were either retrospective, or the reference test was carried out only when a patient was suspected of having restenosis at duplex-ultrasound, which is likely to have resulted in verification bias. We performed a prospective study of diagnostic accuracy to find new blood velocity cut-offs in duplex-ultrasound for in-stent restenosis.

Materials and methods: Stented patients within the international carotid stenting study were eligible. Patients had a carotid CTA in addition to routine duplex-ultrasound performed at a yearly follow-up. Duplex-ultrasound bloodflow velocity parameters were compared to the degree of stenosis on CTA. The results were analysed using ROC curves.

Results: We included 103 patients in this study. On CTA, 30 (29.1%) patients had a 30-49% in-stent restenosis, 21 (20.4%) patients had 50-69% in-stent restenosis and 5 (4.9%) patients a ≥70% in-stent restenosis. The cut-off values for ≥30% and ≥50% stenosis were a peak systolic velocity of 92 cm/s, (sensitivity: 74% (95% CI: 59-86), specificity: 71% (95% CI: 58-82)) and 125 cm/s (sensitivity: 63% (95% CI: 41-79), specificity: 83% (95% CI: 72-90)).

Conclusion: The 125 cm/s cut-off value on duplex-ultrasound is lower than found in previous studies and equal to unstented arteries. Duplex-ultrasound measurements made in stented carotid arteries should not be corrected for the presence of a stent when determining the degree of stenosis.

Abbreviations

DUS: duplex ultrasound

ICSS: international carotid stenting study

PSV: peak systolic velocity

CAS: carotid angioplasty with stenting

CEA: carotid endarterectomy

CREST: carotid revascularization endarterectomy versus stent trial

ISR: in-stent restenosis

CCA: common carotid artery

ROC: receiver-operating-characteristic

Introduction

Carotid angioplasty with stenting (CAS) is an effective treatment for secondary prevention of stroke in patients with symptomatic carotid artery stenosis. Although CAS was associated with a higher rate of operative stroke than carotid endarterectomy (CEA) in trials such as the Carotid Revascularization Endarterectomy versus Stent Trial (CREST)[1] and the International Carotid Stenting Study (ICSS)[2], this risk increase appears to be limited to elderly patients[3]. In addition, CAS is still used in patients who are not suitable for CEA. Recently published data from ICSS shows that CAS is as effective as CEA in preventing recurrent stroke after the procedure[4].

An important factor in the follow-up of patients with stents is the occurrence of in-stent restenosis (ISR). Traditionally, the degree of stenosis in an untreated carotid artery was measured with conventional digital subtraction angiography (DSA). Because of a small but non-negligible risk of stroke or death, DSA has been replaced by non-invasive tests, such as duplex ultrasound (DUS), CT angiography (CTA) or MR angiography (MRA) [5,6,7]. For routine evaluation of unstented carotid arteries, DUS is a well-validated diagnostic test with established cut-off criteria for different degrees of stenosis[5,6]. For measurements within stents, however, these criteria might not suffice.

In a stenosed artery, narrowing of the lumen results in higher blood flow velocities at that point. Estimating the degree of stenosis with DUS is based on this principle. The peak systolic velocity (PSV) threshold is one of the main criteria for grading internal carotid stenosis, together with diameter on B-mode image; (absence of) flow on Color Doppler image; the average PSV; poststenotic PSV; and collateral flow.[8,9] However, it has been suggested that the use of PSV criteria validated in unstented arteries may overestimate the degree of (re)stenosis in stented arteries[10].

Aim

We hypothesise that blood flow and blood turbulence behaves differently in a stent than in a normal vessel because the stented carotid artery has a less elastic vessel wall than a stented one, because the metal struts of the stent will change the elastic properties of the artery. We therefore hypothesised that the PSV will be higher in a stented than in an unstented carotid artery with a similar degree of stenosis[11]. Previous studies reported higher PSV cut-offs for stented than for unstented arteries,[12-16] but these studies were often retrospective, or the reference test (DSA or CTA) was carried out only when a patient was suspected of having restenosis at DUS, which is likely to have resulted in verification bias.[17] Furthermore, different cut-off points have been suggested for different types of stent cell design (open versus closed)[18].We report the results of the ICSS-CTA-DUS substudy, a prospective diagnostic study in which DUS parameters in patients included in ICSS who were allocated and treated with a carotid stent were compared to the ipsilateral degree of carotid stenosis on CTA.

Methods

The ICSS is a randomised multicentre international trial in which patients aged older than 40 years with symptomatic atherosclerotic carotid artery stenosis measuring at least 50% in diameter were randomly allocated treatment of the stenosis by CAS or CEA.[2] Exclusion criteria for the trial included contraindications to stenting or surgery.

Participating centres

The participating centres were the National Hospital for Neurology and Neurosurgery, London, United Kingdom; Academic Medical Center, Amsterdam, the Netherlands; University Medical Centre, Utrecht, the Netherlands; Erasmus MC, University Medical Center: Rotterdam, the Netherlands.

Patients

The diagnostic tests were performed during routine follow-up of the ICSS trial[2]. In addition to the general ICSS criteria, patients were excluded for the substudy if they had a contraindication to the contrast agent used for the CTA, such as renal failure. We asked patients who received a stent to participate in this diagnostic study at one of the yearly follow-up visits, at least 1 year after treatment. The substudy received approval from the Multicentre Research Ethics Committee in the UK and from the Ethics Committees of the participating centres in the Netherlands. Written informed consent was obtained from all participating patients.

Stent type

In ICSS stents and other devices used for carotid stenting were chosen at the discretion of the interventionist but had to have a CE mark. Open type stents were used as well as closed type stents. In this study 4 different open type stents were used, with an open space surface (OSS) >

5 mm^3: Smart stent (Cordis, Cashel, Ireland); Precision stents (Cordis, Cashel, Ireland); Protegé EV3 stents (Covidien, Plymouth, USA); and Acculink stents (Guidant, Indianapolis, USA). 2 different closed type stents were used (OSS < 5 mm^3): Carotid Wallstents (Boston scientific, Marlborough, USA) and next Stent (Boston scientific, Marlborough, United States).

Duplex ultrasound

DUS of the treated carotid arteries was performed by experienced vascular technician at the participating centres. They were blinded for CTA results. The PSV was recorded within the stent at the point of stenosis and in the unstented CCA. The ICA/CCA ratio was calculated with the analysis of the results.

Reference test

All CTAs were evaluated centrally by an experienced neuroradiologist at the UCL Institute of Neurology, blinded to all clinical data and the results of other diagnostic tests, at a workstation with reconstructions in the axial, sagittal and coronal direction. Sagittal and coronal reconstructions were evaluated for the presence of in-stent stenosis. Measurements to assess the severity of ISR were performed at the location with the most severe in-stent lumen reduction, either on the sagittal or coronal reconstruction. Wall-to-wall diameter measurements were performed by drawing a measurement line perpendicular to both vessel walls. A distal reference diameter was performed in the internal carotid artery distal to the stent where the lumen of the carotid artery has a constant diameter. These two measurements were used for calculating the degree of stenosis.

Analyses

Receiver-operating-characteristic (ROC) curves were made to find the highest sensitivity and specificity (Q* point) for the threshold of ≥30%, ≥50% and ≥70% ISR. In these curves the optimal cut-off criteria for different degrees of stenosis were determined. A different analysis will be made in optimal cut-off values for open versus closed type stents. To assess the effects of verification bias a subgroup analysis was performed in patients with ≥50% stenosis based on established DUS criteria. Optimal cut-off criteria was defined as the highest c

For all cut-off values sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and 95% CI were calculated. All data were analyzed using IBM SPSS statistics, version 21.

Results

103 patients in this study were included in ICSS between September 2003 and November 2008. The CTA and follow-up DUS were performed between November 2004 and July 2010. A flow chart of the inclusion is presented in figure 1. The baseline characteristics from the time of randomization are presented in table 1. On CTA, 47 (45.6%) patients had ISR of 0%-30%; 30 (29.1%) had ISR of 30%-49%; 21 (20.4%) of 50%-69%; and 5 (4.9%) of ≥70%. Scatter plot visualization with linear regression for the degree of stenosis on CTA and two different ultrasound characteristics (PSV and ICA/CCA ratio) are presented in figure 2.

On the ROC-curves, the best cut-off values for a ≥50% stenosis on CTA were a PSV of 125 cm/s (sensitivity: 62%, specificity: 83%) and an ICA/CCA ratio of 1.5 (sensitivity: 76%, specificity: 74%). (Table 2)

Of the five patients with ISR of >70% on CTA, two had a stenosis of 71% (PSV: 183 and 185 cm/s), one of 73% (PSV: 135 cm/s), one of 75% (PSV: 170 cm/s) and one of 76% (PSV: 220 cm/s).

There were no adverse events reported in this study

Open cell versus closed cell design stents

6 different stents were used. In 6 patients, the type of stent used was unknown. 77 open cell stents, with an open space surface (OSS) > 5 mm^3 were used. 20 closed cell stents were used, with an OSS < 5 mm^3. There was a significant difference in >50% ISR measured with CTA in open vs closed cell stents. 14 out of 77 (18%) patients with an open cell stent had a >50% ISR on CTA, versus 10 out of 20 (50%) in closed cell stents (p=0.003). The PSV in open cell stents ranged from 40 to 220 cm/s versus 78 to 220 cm/s in closed cell stents. ROC curves for open and close stents were separately made. The cut-off value for >50% ISR in open cell stents was 118 cm/s, sensitivity: 65% (95% CI: 35-87), specificity: 78% (95% CI: 66-87). The cut-off value for >50% ISR in closed cell stents was 128 cm/s, sensitivity: 80% (95% CI: 44-97), specificity: 70% (95% CI: 35-93).

Subgroup analysis

In an analysis limited to the 29 ICA's with a PSV >125 cm/s on DUS, for a >50% ISR the optimal cut-off PSV was 159 cm/s, sensitivity: 56% (95% CI: 25-81), specificity 56% (95% CI: 30-80) and an ICA/CCA ratio of 1.9, sensitivity: 63% (95% CI: 35-85), specificity: 62% (95% CI: 32-86)

Discussion

In this diagnostic substudy of the International Carotid Steniting Study, we found substantially lower cut-off values for flow velocity parameters on DUS in a stented ICA than previously reported, with cut-off values for a ≥50% stenosis of 125 cm/s for the PSV and 1.5 for the ICA/CCA ratio.

Over the period of one to five years after CAS, we only had 5 patients (4.9%) with a severe stenosis (>70%). There was no correlation in ISR and amount of years after procedure. In the whole ICSS trial, using commonly defined ultrasound criteria (not adjusted for stents), the cumulative incidence of severe restenosis 5 years after completed treatment was 10.8% in the CAS group, and 8.6% in the CEA group, a difference which was not statistically significant[4]. Therefore we were unable to determine a threshold PSV for severe stenosis.

As a reference test we chose CTA to compare to the velocity parameters measured with DUS. A diagnostic test that provides clear images of the lumen of the internal carotid artery is crucial, because a NASCET-like stenosis measurement is necessary as a reference to estimate the optimal PSV cut-offs for DUS. CTA offers high spatial resolution and contrast resolution, and it is a fast technique. We realise that CTA is better validated for unstented than for stented (carotid) arteries. The diagnostic accuracy of CTA compared to DSA, to diagnose a 70-99% stenosis for unstented arteries, was calculated in several studies[5,7]. A systematic review reported a sensitivity and specificity of 77% (95% CI: 68-84%) and 95% (95%CI: 91-97%) respectively[5], but these figures are likely to underestimate the accuracy of CTA in the present study because the quality of CTA has improved substantially since the studies included in the review.

One of the advantages of DUS for examining CAS-patients, is the ability to perform as much examination is wanted, since there is no risk for the patients. The comparison between DUS and CTA or DSA in a stented ICA has been done before and higher cut-off values were found in all degrees of stenosis, but previous studies often were retrospective, or the reference test (DSA or CTA) was carried out only when a patient was suspected of having restenosis at DUS, which may result in verification bias.[12-16] Verification bias is introduced if the decision to perform the reference standard procedure depends on the results of the test under investigation, precluding a reliable estimate of the diagnostic accuracy of the latter.[17] To our knowledge this is so far the only prospective study without any possibility of verification bias that compares DUS to a reference test for ISR in a stented ICA.

We identified 5 unique diagnostic series on in-stent stenosis measurements with DUS compared to a reference test (CTA or DSA) whom all proposed new criteria[12-16]. Table 3 summarises the 5 series and this study. In general, the cut-off values are higher than those reported for unstented arteries. But these studies where either retrospective or included the patients if they had a >50 stenosis on DUS. Only Kwon *et al* reported a series of patients all undergoing both DUS and the reference test, CTA. This study, however, was too small (n=27) to provide new in-stent cut-off criteria[19].

To emphasise the importance of avoiding verification bias we did a sub group analysis with only patients with a PSV >125 cm/s, to mimic a study with DUS as a selection criterion. This shows a difference in optimal cut-off value of 34 cm/s only by using different selection criteria (table 4). This could be one explanation for the higher cut-off values for the same degree of stenosis observed in previous studies.

Although differences in PSV's in open cell stent designs versus closed cell stent designs are well reported, in this study the difference between these two groups remained small, with an optimal cut-off value for a ≥50% of 118 cm/s for open cell stents versus 128 cm/s in closed cell stents.

A limitation of this study is that we had very few severe in-stent restenosis (≥70%). Theferore, we could not relaible estimate cut-off values for severe in-stent restenosis. In general, in the entire ICSS study, instent restenosis occured less frequently, later in time, and with lower degree of stenosis, than expected.[4]

The optimum cut off value of 125 cm/s we report for stented arteries is identical to the "strandness" velocity criteria widely used in ultrasound laboratories to identify ≥50% stenosis in unstented arteries. Our data therefore suggest that DUS measurements made in stented carotid arteries should not be corrected for the presence of a stent when determining the degree of carotid stenosis.

Conclusion

This study showed an optimal cut-off value of a PSV of 125 cm/s on DUS for the diagnosis of a 50% ISR and 92 cm/s for a 30% stenosis, which is lower than found in previous studies and equal to unstented arteries. The difference in results with the previous studies may be explained by avoiding verification bias. Ultrasound measurements made in stented carotid arteries should not be corrected for the presence of a stent when determining the degree of carotid stenosis.

Contributions

This study was designed by Nederkoorn and Brown. The data were analysed by Davagnanam and Hendrikse. Bosch wrote the manuscript and it was reviewed by the co-authors.

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Conflicts of interest

The authors declare no conflicts of interest

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TABLES

Table 1. Baseline characteristics

	No. of patients *(%)* *n=103*
Age (SD)	67 *(9)*
Age <70	67 *(64,4)*
Male	75 *(72.1)*
Median days between DUS and CTA	0 (0-29)
Median years between CAS and CTA	2 (1-5)
Ipsilateral carotid stenosis *	
50-69%	94 *(89,4)*
70-99%	10 *(9,7)*
Contralateral carotid stenosis †	
0-49%	67 *(62,2)*
50-69%	15 *(14,5)*
70-99%	15 *(13,5)*
occluded	5 *(4,9)*
Prior ipsilateral stroke *	23 *(22,1)*
Treated hypertension *	63 *(60,6)*
Cardiac failure *	3 *(2,9)*
Angina *	12 *(11,5)*
Previous myocardial infarction *	12 *(11,5)*
Atrial fibrillation *	5 *(4,8)*
Cardio-embolic source of stroke *	4 *(3,8)*
Diabetes type 2	17 *(16,3)*

Insulin-dependent diabetes *	5 (4,8)
Non-insulin-dependent diabetes *	12 *(11,5)*
Current smoker *	35 *(33,7)*
Ex-smoker *	42 *(40,4)*
Previous CABG *	13 *(12,5)*
Peripheral arterial disease *	12 *(11,5)*

* data of 1 patient missing

† data of 2 patients missing

Table 2. cut-off values for blood velocity parameters on DUS for ≥30% and ≥50% stenosis in a stented carotid artery

	Cut-of value	Sensitivity %	95% CI	Specificity %	95% CI	PPV	NPV
⩾30%							
PSV	92 cm/s	74	59-86	71	58-82	76	69
ICA/CCA	1.2	69	54-80	67	51-79	70	65
⩾50%							
PSV	125 cm/s	62	41-79	83	72-90	55	86
ICA/CCA	1.5	76	54-90	76	65-85	51	91

Table 3. Previously reported DUS cut-off values for stenosis measurements within a stent.

First Author	Year	Population size (n)	Prospective	Subgroup selection*	Subgroup (n)	Reference test	PSV** ≥30%	PSV ≥50%	PSV ≥70%	PSV ≥80%
Stanziale[17]	2005	605	No	Yes	118	DSA		225	350	
Chi[16]	2007	260	Yes	Yes	13	DSA		240	450	
Aburhama[1]	2008	144	Yes	Yes	144	CTA	178	278		403
Lal[14]	2008	225	No	Yes	99	CTA/DSA		220		340
Zhou[15]	2008	256	No	Yes	22	DSA			300	
Bosch	2015	103	Yes	No	-	CTA	92	125		

* Selection of a subgroup based on DUS results (the test under evaluation) indicates possible verification bias. These subgroups are compared to the reference test in order to obtain the listed DUS cut-off values.

** Suggested cut-offs for in-stent restenosis measurements based on the peak systolic velocity (PSV); in cm/sec

Table 4. Optimal cut-off criteria with and without verification bias

No verification bias			Verification bias		
PSV	Sensitivity	specificity	PSV Cm/s	sensitivity	specificity
38	100	0	128	100	0
49	100	8	129	94	0
56	94	12	131	94	23
77	85	31	133	88	23
81	85	47	138	69	23
97	77	62	146	63	23
109	65	75	154	56	46
125 *	**62**	**83**	**159 ***	**46**	**63**
131	58	87	168	39	63
145,	39	87	177	39	75
158	35	92	181	39	61
177	15	,94	184	13	61
187	4	94	192	4	69
197	4	96	197	4	84
221	0	100	221	0	100

Left: optimal cut-off criteria for a ≥50% stenosis in this study. Right: hypothetical optimal cut-off criteria if only patients with a PSV >125cm/s on DUS would have been included in this study

*****Optimal cut-off criteria for a >50 stenosis with (right) and without (left) verification bias

FIGURES