

# Stent design, restenosis and recurrent stroke after carotid artery stenting in the International Carotid Stenting Study

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## **Abstract**

### **Introduction**

Open-cell carotid artery stents are associated with a higher peri-procedural stroke risk than closed-cell stents. However, the effect of stent design on long-term durability of carotid stenting (CAS) is unknown. We compared the medium- to long-term risk of restenosis and ipsilateral stroke between patients treated with open-cell stents versus closed-cell stents in the International Carotid Stenting Study (ICSS).

### **Methods**

Patients with symptomatic carotid stenosis were randomized to CAS or endarterectomy and followed with duplex ultrasound for a median of 4.0 years. We analysed data from patients with completed CAS procedures, known stent design, and available ultrasound follow-up. The primary outcome, moderate or higher restenosis ( $\geq 50\%$ ) was defined as a peak systolic velocity of  $>1.3\text{m/s}$  on ultrasound or occlusion of the treated internal carotid artery, and analysed with interval-censored models.

### **Results**

855 patients were allocated to CAS. 714 patients with completed CAS and known stent design were included in the current analysis. Of these, 352 were treated with open-cell and 362 with closed-cell stents. Moderate or higher restenosis occurred significantly less frequently in patients treated with open-cell ( $n=113$ ) than closed-cell stents ( $n=154$ ; 5-year risks were 35.5% vs. 46.0%, unadjusted hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.53-0.88). There was no significant difference in the risk of severe restenosis ( $\geq 70\%$ ) after open-cell stenting ( $n=27$ ) vs. closed cell stenting ( $n=43$ ; 5-year risks: 8.6% vs. 12.7%, unadjusted HR 0.63; 95% CI 0.37-1.05). The risk of ipsilateral stroke beyond 30 days after treatment was similar with open-cell and closed-cell stents (HR 0.78, 95% CI 0.35-1.75).

## **Conclusions**

Moderate or higher restenosis after CAS occurred less frequently in patients treated with open-cell stents than closed-cell stents. However, both stent designs were equally effective at preventing recurrent stroke during follow-up.

**Clinical Trial Registration:** URL: <http://www.isrctn.com/ISRCTN25337470>; Unique identifier: ISRCTN25337470.

## **Introduction**

Carotid artery stenting (CAS) is a less invasive alternative to carotid endarterectomy (CEA) for treatment of symptomatic carotid stenosis. Previous studies reported a higher risk of peri-procedural stroke associated with CAS, particularly in older patients.<sup>1</sup> Beyond the initial peri-procedural period, CAS and CEA were equally effective at preventing recurrent stroke.<sup>2, 3</sup> However, data pertaining to the long-term patency and restenosis of the carotid artery after CAS or CEA have been inconsistent.<sup>4-8</sup>

Various carotid stent devices, with different designs and configurations are available for CAS. Previous studies have shown a higher risk of peri-procedural stroke in patients treated with open-cell stent devices compared with those treated with closed-cell devices.<sup>9-11</sup> The effect of stent design on long-term patency of the internal carotid artery (ICA) and ipsilateral stroke risk following CAS is currently unclear. Larger open areas between struts in open-cell stents could in theory be associated with a higher risk of embolization due to incomplete coverage of the atheromatous lesion particularly in the peri-procedural period, but also potentially in the medium to longer-term.<sup>10</sup> Furthermore, open-cell and closed-cell stents have different mechanical properties,<sup>12, 13</sup> which might influence the risk of residual or recurrent stenosis after treatment. We therefore aimed to compare the medium- to long-term risk of ICA restenosis and recurrent stroke between patients treated with open-cell stents versus those treated with closed-cell stents in the International Carotid Stenting Study (ICSS).<sup>2</sup>

## **Methods**

### *Study centres, participants, randomisation and masking*

The International Carotid Stenting Study (ICSS) included patients with atherosclerotic carotid stenosis associated with ipsilateral TIA or stroke symptoms within 12 months prior to enrolment. The trial was approved by local ethics committees for non-UK centres and by the

Northwest Multicentre Research Ethics Committee in the UK. All patients provided written informed consent to participate in the trial prior to randomisation. Details on centre requirements, patient eligibility criteria, randomisation and treatment have been published previously.<sup>2, 15, 16</sup> In short, patients with symptomatic  $\geq 50\%$  carotid stenosis (according to NASCET criteria<sup>17</sup>), who were considered equally suitable for either procedure, were randomly assigned to treatment with CAS or CEA in a 1:1 ratio. Randomisation was performed by telephone or fax using a computerised service provided by the Oxford Clinical Trials Service Unit.

#### *Stenting procedures and follow-up*

Prior to randomisation, patients required carotid imaging with either selective digital subtraction angiography or concordant findings on extracranial carotid duplex ultrasound and non-invasive angiography (magnetic resonance angiography [MRA] or computed tomography angiography [CTA]). Stents and cerebral protection devices were chosen at the discretion of the interventionist but had to be 'CE marked' (Communauté Européenne) and approved by the Steering Committee. Stent devices used were documented at each participating centre. All patients received optimal medical care, and control of vascular risk factors. Pre-medication before CAS was discretionary, but the combination of aspirin and clopidogrel was recommended. The use of intraprocedural heparin was mandatory, but the exact dose was also discretionary.

Patients were followed up clinically at 30 days after treatment, at 6 months after randomisation, and annually thereafter. Follow-up was initially planned for 5 years but was extended to 10 years after randomisation for patients who were able and willing to continue. The protocol specified carotid duplex ultrasound to be done at each follow-up visit. Peak systolic velocities in the common carotid artery (PSV CCA), in the internal carotid artery (PSV ICA) and the end

diastolic velocity in the ICA (EDV ICA) on duplex ultrasound were recorded at each site and reported to the central trial office.

### *Outcomes*

Degree of stenosis at each visit was determined centrally based on the ultrasound flow velocities recorded at each site, using pre-defined criteria which correlated well with the severity of carotid stenosis measured on catheter angiography using the NASCET method of estimating stenosis.<sup>17</sup> The PSV ICA cut-off values used to quantify the severity of stenosis were  $>1.3$  m/s for  $\geq 50\%$  stenosis, and  $> 2.1$  m/s for  $\geq 70\%$  stenosis, but the EDV ICA and the PSV ICA/PSV CCA ratio were also considered (Table 2).<sup>8, 18</sup> No correction was made for the presence of a stent or stent design when measuring stenosis.<sup>8</sup> Ultrasound velocity measurements were not available from a small number of centres; in these cases, the percent stenosis reported by the local ultrasonographer and investigator was used. For the purpose of this study, moderate or higher restenosis was defined as  $\geq 50\%$  stenosis or occlusion of the treated carotid artery seen at any time during follow-up after completion of treatment. Severe restenosis was defined as  $\geq 70\%$  stenosis or occlusion. This definition of restenosis did not differentiate between residual stenosis present immediately after treatment and recurrent 'true restenosis' which developed over time. CAS was defined as being completed when a stent was placed across the stenosis.

Major clinical outcome events were adjudicated by an independent end-point committee. Stroke was defined clinically as a rapidly developing clinical syndrome of focal retinal or cerebral dysfunction, lasting more than 24 hours or leading to earlier death, with no other apparent non-vascular cause.

### *Statistical analysis*

The present analysis was performed as a per-protocol analysis and only included patients randomly allocated to stent treatment in whom the stenting procedure was completed, stent type



was known and in whom at least one post-procedural ultrasound follow-up examination was available. Patients who did not undergo revascularisation, those with aborted procedures, and those crossing over to receive endarterectomy were excluded. For analyses of restenosis, patients were censored at the time of any further ipsilateral revascularisation procedure during follow-up or at the time of their last ultrasound examination. Censoring was assumed to be non-informative.

Restenosis was only known to have occurred at some point between the previous ultrasound scan and the one showing restenosis. We therefore used methods for interval-censored data and time to restenosis was analysed using a generalised non-linear model, which assumes proportional hazards. Based on this model the treatment effect parameter estimate can be interpreted as a log hazard ratio (HR).<sup>8, 18, 19</sup> Proportionality of hazards was tested via interactions with follow-up time periods.

The treatment effect p-value for restenosis was calculated using a likelihood ratio test. HRs for restenosis were calculated with closed-cell stents as the reference group without adjustment, as well as after adjustment for patient baseline characteristics which were previously identified to be independently associated with restenosis in ICSS.<sup>8</sup> The cumulative incidence of restenosis at one and five years after CAS was calculated using the Kaplan Meier method, with the time to restenosis set to the mid-point between the previous normal scan and the one showing restenosis. Kaplan Meier plots of time to restenosis were truncated at 7 years because the number of patients in whom ultrasound follow-up was continued beyond this time point was relatively small.

Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% CIs for ipsilateral stroke and stroke occurring in any territory, with closed-cell stenting as the reference group using all data to the end of follow-up. Kaplan-Meier estimates of cumulative risk 5 years after randomisation with 95% CIs were calculated. The proportionality for Cox models was

tested with Schoenfeld residuals and confirmed no significant departures from the proportionality assumption.

All reported p-values are two-sided, with a value  $<0.05$  considered to indicate statistical significance. No adjustment for multiple comparisons was made. ICSS is registered, number ISRCTN25337470.

## **Results**

Between May 2001 and October 2008, 1713 patients were enrolled in ICSS. Of those, 855 were randomly assigned to stenting, and 858 to endarterectomy (Figure 1). In 764 patients the CAS procedure was completed. Ultrasound follow-up was performed in 740 of these 764 patients. In 26 patients, no information on the type of stent used was available. We therefore included data from 714 patients with completed CAS procedures, known stent design and available ultrasound follow-up data in our analysis. Of these patients, 352 were treated with an open-cell and 362 with a closed-cell stent. Median duration of follow-up was 4.0 years (interquartile range 2.3-5.0), with a maximum of 10 years. Baseline characteristics of patients treated with open-cell and closed-cell stents as well as of patients excluded from analysis because the procedure was aborted, stent type was unknown or no ultrasound follow-up was available are provided in Table 1. Patients treated with open-cell and closed-cell stents were very similar in these characteristics. Excluded patients differed in some of the characteristics from our analysis population.

Moderate or higher restenosis occurred significantly less frequently in patients treated with open-cell stents (n=113) than in patients treated with closed-cell stents (n=154; 5-year risks 35.5% vs. 46%, unadjusted hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.53-0.88; Figure 2A). This difference remained after adjustment for baseline characteristics predicting restenosis (adjusted HR 0.58, 95% CI 0.44-0.76).

There was no significant difference in the incidence of severe restenosis ( $\geq 70\%$ ) or occlusion following open-cell (n=27) vs. closed-cell stenting (n=43; cumulative 5 year risks of 8.6% versus 12.7%; unadjusted HR 0.63, 95% CI: 0.37-1.05; adjusted HR 0.63, 95% CI: 0.37-1.06; Figure 2B).

There was no statistically significant difference in the occurrence of ipsilateral stroke beyond 30 days after treatment with open-cell (n=10, 5 year risk 4.6%, 95% CI 2.4-8.7) vs. closed-cell (n=14, 5 year risk 4.3, 95% CI 2.4-7.5) stenting (HR 0.78, 95% CI 0.35-1.75; Figure 3A), nor in the occurrence of stroke in any territory beyond 30 days after stenting in the 2 groups (n=17, 5 year risk 7.4%, 95% CI 4.5-12.0 vs. n=30, 5 year risk 9.3%, 95% CI 6.3-13.5, respectively; HR 0.62, 95% CI 0.34-1.12; Figure 3B).

## **Discussion**

In the current analysis of patients who underwent CAS in ICSS, the risk of at least moderate restenosis or occlusion of the treated carotid artery was significantly lower in patients treated with open-cell stents than in those treated with closed-cell devices over a median follow-up period of 4 years. However, both stent designs appeared equally effective at preventing severe restenosis or recurrent ipsilateral stroke during follow-up.

Following the introduction of carotid artery stenting as a less invasive alternative to carotid endarterectomy for treatment of symptomatic carotid stenosis, stent design has evolved for optimised use in the carotid artery. Previous studies suggested that there is a higher risk of periprocedural stroke following open-cell compared with closed-cell CAS.<sup>9-11, 20</sup> However, one of the potential advantages of open-cell stents is that they are more flexible and better suited for tortuous supra-aortic vessels.<sup>21</sup> Closed-cell stents on the other hand have tighter meshes, which may provide better coverage of the atheromatous lesion, but are consequently more rigid. Prior

to conduct of this study, data pertaining to the influence of stent design on the medium- to long-term patency of the carotid artery and efficacy in preventing recurrent stroke were limited.

Some previous studies reported that CAS may change the mechanical characteristics of the vessel wall, thus rendering it less compliant and more rigid. This effect might be more pronounced with closed-cell stents than with open-cell stents. The change in vessel wall elasticity might lead to higher peak systolic blood flow velocities (PSV) in stented arteries at a given degree of narrowing compared with native arteries, and potentially to a higher PSV in arteries treated with closed-cell compared with open-cell stents. Such an effect might cause an apparent difference in the incidence of restenosis quantified by ultrasound alone. One observational study in patients without residual stenosis reported that PSVs were significantly higher in arteries treated with closed-cell stents compared with those treated with open-cell stents.<sup>21</sup> However, PSVs were measured immediately after the CAS procedure and no ultrasound follow-up was performed to assess the longer-term risk of restenosis in that study. In contrast, a prospectively-designed sub-study of ICSS comparing duplex-ultrasound flow velocities with degree of stenosis measured on computed tomography angiography (CTA) identified very similar optimal PSV cut-off values for moderate ( $\geq 50\%$ ) restenosis for open-cell stents (118cm/s) and closed-cell stents (128cm/s).<sup>14</sup> Moderate or higher restenosis on CTA was more common with closed-cell stents than with open-cell stents.<sup>14</sup>

These data support the conclusion that we observed a truly higher incidence of moderate or higher restenosis in CAS patients treated with closed-cell stents compared with patients receiving open-cell stenting. We can only speculate on possible mechanisms underlying this difference. The more rigid, more densely-packed material in closed-cell stents compared with open-cell stents might lead to greater irritation of the vessel wall which in turn might stimulate neo-intimal hyperplasia and result in a higher rate of restenosis. This hypothesis is supported by the fact that most of the divergence in the incidence of restenosis between the 2 stent designs

occurred in the first year after treatment (Figure 2A) when neo-intimal hyperplasia is considered to be the key mechanism causing carotid restenosis.<sup>22</sup>

The Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial found no significant association between the risk of moderate or higher ( $\geq 50\%$ ) restenosis and stent type.<sup>23</sup> However, this study only included 242 CAS patients and may have been underpowered to detect a difference. The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study did not investigate the potential association between stent design and the risk of restenosis after CAS, and only one stent device ('RX Acculink stent'), an open-cell device, was used throughout the Carotid Revascularization Endarterectomy *vs.* Stenting Trial (CREST).<sup>24</sup>

With regard to stroke prevention in the medium- to long-term after the peri-procedural period, we found no significant differences in the risk of recurrent ipsilateral stroke or stroke in any territory occurring beyond 30 days after treatment between open- versus closed-cell stents.

This study has some limitations. Velocity measurements were analysed as recorded by local investigators, and we were not able to review duplex images to check whether angle correction had been performed in all cases. However, our methodology was similar to other studies,<sup>8</sup> and all duplex ultrasound follow-up examinations were performed in accordance with pre-specified ultrasound criteria (Table 2) in well-established vascular laboratories at the participating centres. Second, this was not a randomised comparison of outcomes following open-cell *vs.* closed-cell stenting and the criteria used by individual practitioners to choose one stent type over the other were unknown. Therefore, we cannot be certain that there were no differences in original plaque morphology or vascular anatomy between those who had closed-cell *vs.* open-cell stenting which might have differentially influenced the risk of restenosis in one subgroup. However, there were no significant differences in any baseline demographic or vascular risk factor profiles, including stenosis severity, between patients treated with open-cell versus

closed-cell stents. Third, we did not reassess our entire study population with another non-invasive imaging modality to confirm or refute our ultrasound findings. Fourth, our analysis may have been underpowered to detect a true difference in the risk of severe restenosis after open-cell compared with closed-cell stenting.

## **Conclusions**

Moderate or higher restenosis occurred significantly less frequently in patients treated with open-cell stents compared with those treated with closed-cell stents. However, both stent designs were equally effective at preventing severe restenosis and recurrent stroke in the medium- to long-term.

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## **Disclosure**

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## Tables

*Table 1 – Baseline characteristics according to stent design*

		<b>Open-cell stent (N=352)</b>	<b>Closed-cell stent (N=362)</b>	<b>Excluded patients (N=114)</b>
<b>Age (years)</b>		69.3 (8.9)	70.0 (9.1)	72.7 (9.3)
<b>Female sex</b>		108/352 (30.7%)	110/362 (30.4%)	34/139 (24.5%)
<b>Treated hypertension</b>		237/348 (68.1%)	249/359 (69.4%)	101/136 (74.3%)
<b>Systolic blood pressure (mmHg)</b>		151 (25)	145 (22)	144 (23)
<b>Diastolic blood pressure (mmHg)</b>		81 (12)	78 (12)	79 (11)
<b>Diabetes mellitus</b>		73/352 (20.7%)	86/362 (23.8%)	25/139 (18.0%)
- <b>Non-insulin dependent</b>		50/348 (14.4%)	64/359 (17.8%)	20/136 (14.7%)
- <b>Insulin dependent</b>		23/348 (6.6%)	22/359 (6.1%)	5/136 (3.7%)
<b>Treated hyperlipidaemia</b>		217/348 (62.4%)	227/359 (63.2%)	78/136 (57.4%)
<b>Total cholesterol (mmol/l)</b>		4.8 (1.2)	5.0 (1.3)	4.5 (1.1)
<b>Current smoker</b>		89/348 (25.6%)	87/359 (24.2%)	29/136 (21.3%)
<b>Ex-smoker</b>		171/348 (49.1%)	170/359 (47.4%)	67/136 (49.3%)
<b>Angina in last 6 months</b>		31/348 (8.9%)	35/359 (9.7%)	17/136 (12.5%)
<b>Previous myocardial infarction</b>		65/348 (18.7%)	54/359 (15.0%)	32/136 (23.5%)
<b>Previous CABG</b>		52/348 (14.9%)	37/359 (10.3%)	20/136 (14.7%)
<b>Atrial fibrillation</b>		19/348 (5.5%)	23/359 (6.4%)	15/136 (11.0%)
<b>Other cardio-embolic source</b>		8/348 (2.3%)	7/359 (1.9%)	4/136 (2.9%)
<b>Cardiac failure</b>		11/348 (3.2%)	8/359 (2.2%)	4/136 (2.9%)
<b>Peripheral artery disease</b>		59/348 (17.0%)	62/359 (17.3%)	18/136 (13.2%)
<b>Degree of symptomatic carotid stenosis*</b>	50-69%	38/352 (10.8%)	35/362 (9.7%)	19/139 (13.7%)
	70-99%	314/352 (89.2%)	327/362 (90.3%)	120/139 (86.3%)
<b>Degree of contralateral carotid stenosis*</b>	0-49%	231/350 (66.0%)	245/362 (67.7%)	89/135 (65.9%)
	50-69%	50/350 (14.3%)	52/362 (14.4%)	26/135 (19.3%)
	70-99%	46/350 (13.1%)	47/362 (13.0%)	12/135 (8.9%)
	Occluded	23/350 (6.6%)	18/362 (5.0%)	8/135 (5.9%)
<b>Most recent ipsilateral event</b>	Ischaemic hemispheric stroke	151/347 (43.5%)	167/358 (46.6%)	75/135 (55.6%)

<b>before randomisation</b>				
†				
	Retinal stroke	16/347 (4.6%)	5/358 (1.4%)	5/135 (3.7%)
	TIA	113/347 (32.6%)	123/358 (34.4%)	37/135 (27.4%)
	AFX	67/347 (19.3%)	63/358 (17.6%)	18/135 (13.3%)

*Data are either medians (Interquartile Range [IQR]), numbers of patients/total number (%), or means (Standard Deviation [SD]). \*Degree of stenosis reported by randomizing centre correlating with the measurement of stenosis used in the North American Symptomatic Carotid Endarterectomy Trial or an equivalent non-invasive imaging modality. † If two events were reported on the same day, the more severe event was recorded as the index event. TIA indicates Transient Ischaemic Attack; AFX Amaurosis Fugax, CABG Coronary Artery Bypass Graft*

**Table 2 – Duplex ultrasound velocity criteria used for grading the degree (%) of carotid stenosis**

<b>Band of stenosis (%)</b>	<b>PSV ICA (m/s)</b>	<b>EDV ICA (m/s)</b>	<b>PSV ICA / PSV CCA</b>
0 – 29	<1.1	<0.4	<3.2
30 – 49	1.1 – 1.3	<0.4	<3.2
50 – 59	>1.3 – 2.1	<0.4	<3.2
60 – 69	>1.3 – 2.1	0.4 – 1.1	3.2 – 4.0
70 – 79	>2.1	>1.1 – 1.4	>4.0
80 – 95	>2.1	>1.4	>4.0
96 – 99	String Flow	String Flow	String Flow
100	Occluded	Occluded	Occluded

*The degree of stenosis is expressed in values considered equivalent to the NASCET measurement of stenosis on catheter angiography. Velocity measurements are in meters per second. In cases where the flow velocity criteria spanned more than one category of stenosis, the higher category of stenosis was chosen if the PSV ICA and either the EDV ICA or the PSV ICA/CCA ratio were within the higher band. PSV – peak systolic velocity, EDV – end diastolic velocity, ICA – internal carotid artery, CCA – common carotid artery.*

## Figures

**Figure 1 – Patient flow.** *Study flow chart depicting all patients enrolled in the International Carotid Stenting Study (ICSS) as well as events precluding patients from this analysis.*

**Figure 2 – Moderate or higher ( $\geq 50\%$ ) restenosis or occlusion and severe ( $\geq 70\%$ ) restenosis or occlusion.** *Figure 2: (A) Cumulative incidence of ipsilateral moderate or higher ( $\geq 50\%$ ) carotid restenosis or occlusion, and (B) severe ( $\geq 70\%$ ) carotid restenosis or occlusion after completed carotid artery stenting, estimated by life-table analysis. Error bars represent standard errors. Graphs stop at 7 years' follow-up because the number of patients at risk beyond that time was less than 100, but analyses were based on all follow-up data (maximum duration of follow up was 10 years).*

**Figure 3 – Ipsilateral or any post-procedural stroke (beyond 30 days after treatment).** *(A) Cumulative incidence of post-procedural ipsilateral stroke beyond 30 days after treatment, and (B) post-procedural stroke in any territory after completed carotid artery stenting, estimated by life-table analysis. Patients with any stroke within 30 days after treatment ( $n=44$ ) were excluded from this analysis. Graphs stop at 7 years' follow-up because the number of patients at risk beyond that time was less than 100, but analyses were based on all follow-up data (maximum duration of follow-up was 10 years).*

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