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Does Free Cell Area Influence the Outcome in Carotid Artery Stenting?

M. Bosiers,[1*] G. de Donato,[2] K. Deloose,[1] J. Verbist,[3] P. Peeters,[3] F. Castriota,[4] A. Cremonesi[4] and C. Setacci[4]

[1]*Department of Vascular Surgery, AZ St-Blasius, Dendermonde, Belgium,* [2]*Department of Vascular and Endovascular Surgery, University of Siena, Italy,* [3]*Department of Cardiovascular and Thoracic Surgery of the Imelda Hospital in Bonheiden, Belgium, and* [4]*Interventional Cardio-Angiology Unit, Villa Maria Cecilia Hospital, Cotignola (RA), Italy*

Objectives. *To identify if carotid stent design, especially free cell area, impacts on the 30-day rates for stroke, death and TIA after carotid artery stenting (CAS).*
Material and methods. *A CAS database of 3179 consecutive CAS patients was retrospectively assessed. The distribution of neurological complications were analysed for association with the different stent types and designs. Events where subdivided into procedural and postprocedural events.*
Results. *The overall combined rate of TIA, stroke and death was 2.8% at 30 days (late events 1.9%). The post-procedural event rate analyzed for differences stents varied from 1.2% using BSCI Carotid Wallstent to 5.9% using Medtronic Exponent. The late event rates varied from 1.2% to 3.4% for free cell areas $<2.5\ mm^2$ and $>7.5\ mm^2$ respectively ($p < 0.05$). Post-procedural event rate was 1.3% for closed cells and 3.4% for open cells. All these differences were highly pronounced among symptomatic patients ($p < 0.0001$).*
Conclusions. *After carotid stenting, complication rates vary according to stent type, free cell area and cell design. In the symptomatic population (and also in the total population), post-procedural complication rates are highest for the open cell types and increase with larger free cell area.*

Keywords: Carotid artery stenting; Carotid stenosis; Neurological complications; Cell design; Free cell area; Late embolic events.

Introduction

Carotid angioplasty and stenting (CAS) is increasingly used in the treatment of severely stenotic carotid disease.[1–4] With growing experience and the introduction of dedicated CAS materials, recent research showed that in high volume centers, there has been a shift from intra- to post-procedural complications.[5] Approximately 2/3 all events occurred after the procedure, which are probably caused by late emboli through the struts of the stent. During carotid endarterectomy (CEA) the complete plaque is removed. With carotid stenting the plaque remains contained in between the stent and the vessel wall. The stent needs to offer sufficient scaffolding in order to prevent post-procedural plaque embolization through the stent struts. Logically stents with a smaller free cell area and hence a greater percentage of wall coverage may better contain the fractured and dilated plaque after CAS resulting in a lower number of post-procedural events.

To investigate this hypothesis we reviewed the 30 day outcome after CAS in four centers with high volume experience, excluding the bias of the learning curve.

Materials and Methods

Patients

3281 patients were scheduled to undergo percutaneous carotid revascularization of the internal carotid artery in the Department of Vascular Surgery of the AZ St-Blasius in Dendermonde, Belgium, in the Department of Cardiovascular and Thoracic Surgery of the Imelda Hospital in Bonheiden, Belgium, in the Department of Vascular and Endovascular Surgery, University of Siena, Italy, and in the Interventional

*Corresponding author. M. Bosiers, MD, Department of Vascular Surgery, AZ St-Blasius, Kroonveldlaan 50, 9200 Dendermonde, Belgium.
E-mail address: marc.bosiers@telenet.be

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Cardio-Angiology Unit, Villa Maria Cecilia Hospital, Cotignola, Italy. The interventionalists at the different sites all had an experience of over 50 CAS before the databases were set-up in their services.

In 11 out of 3281 patients (0.35%), CAS could not be performed due to unsuccessful common carotid engagement or embolic protection device delivery or deployment, all were converted to CEA. 91 where left out of the analysis because only a small number of procedures where done with these devices (Palmaz – Cordis $n = 12$, Symbiott - Boston Scientific $n = 1$, Conformexx - Bard $n = 3$, Memotherm - Bard $n = 1$, Vivexx - Bard $n = 6$) or the device was never commercially available (Zilver - Cook $n = 37$), or the treatment consisted only in angioplasty ($n = 31$).

The remaining 3179 patients were available for analysis, including 1317 (41.4%) patients with symptomatic disease and 1862 (58.6%) patients with asymptomatic disease. A demographic analysis of all subgroups was performed (Table 1), showing no difference in the presence of any specific risk factors in any of the investigated stent groups.

CAS was performed via each unit's existing standards of care as described previously.[6–9] Protected CAS with an embolic protection device (EPD) was performed in 3049 patients (95.9%): distal filtrations systems were used in 2831 (92.9%) [FilterWire - Boston Scientific, Angioguard - Cordis, Accunet - Guidant, Emboshield - Abbott Vascular, Rubicon Filter - Rubicon Medical, Spider - ev3, Trap - ev3, Interceptor - Medtronic], proximal occlusion in 192 (6.4%) [Mo. Ma - Invatec, Parodi Anti Emboli System - Gore] and distal occlusion in 26 (0.8%) [Percusurge - Medtronic] patients.

Closed cell stents (i.e. all stent-struts are interconnected: Carotid Wallstent - Boston Scientific Corp, Natick, MA, USA; X-act - Abbott Vascular Devices, Redwood City, CA, USA; NexStent - Endotex, Cupertino, CA, USA) were used in 2242 cases (70.5%) and open cell stent (i.e. not all stent-struts are interconnected: Precise - Cordis, Miami Lakes, FL, USA; Exponent - Medtronic Vascular, Santa Rosa, CA, USA; Protégé - ev3, Plymouth, MN, USA; Acculink - Guidant, Santa Clara, CA, USA) implantation was performed in 937 (29.5%) procedures. Table 2 gives a detailed overview of the selected stents.

130 patients were intented to be treated without EPD: 112 received Carotid Wallstent, 7 Acculink, 6 Precise, 3 Protègè, 1 NexStent, 1 X-act. The majority of these cases dated from the period that no protection devices were available.

Events where subdivided into procedural (until removal of all endovascular material) and post-procedural (until 30 days) events. The distribution of

Table 1. Demographic analysis of all subgroups analyzed

Device	Number	Symptoms (%)	Smoke (%)	Hypertension (%)	Diabetes (%)	History of coronary/peripheral artery disease (%)	Hypercholesterolemia (%)	Calcification (%)	Non de-novo lesion (%)	Mean age (y)
X-act	105	44	38	66	26	62	63	27	2	71
Nexstent	30	20	33	67	27	53	77	30	3	69
Wallstent	2107	42	37	72	27	44	62	25	7	72
Precise	293	49	38	67	23	35	60	17	8	74
Protégé	201	30	43	78	29	58	62	18	4	72
Acculink	409	41	43	74	24	46	68	22	5	72
Exponent	34	32	24	62	18	59	56	21	6	73
Total	3179	41	38	72	26	45	63	24	6	72

Table 2. Overview of the selected stents

Type	Name	*N* (%)
Closed cell	Carotid Wallstent (Boston Scientific Corp, Natick, MA, USA)	2107 (66.2%)
	X-act (Abbott Vascular Devices, Redwood City, CA, USA)	105 (3.3%)
	NexStent (Endotex, Cupertino, CA, USA)	30 (0.9%)
Open cell	Precise (Cordis, Miami Lakes, FL, USA)	293 (9.2%)
	Exponent (Medtronic, Vascular, Santa Rosa, CA, USA)	34 (1.1%)
	Protégé (ev3, Plymouth, MN, USA)	201 (6.3%)
	Acculink (Guidant, Santa Clara, CA, USA)	409 (12.9%)

neurological complications were analysed for association with the different stents (X-act, Nexstent, Wallstent, Precise, Protégé, Acculink, Exponent), different free cell areas (0–2.5 mm^2; 2.5–5 mm^2; 5–7.5 mm^2 and >7.5 mm^2) and different cell design (open versus closed cell stents).

Medical treatment

Pre-procedure: All patients were treated with acetylsalicylic acid (ASA) at a mean dosage of 125 mg/day, associated with clopidogrel or ticlopidine at a mean dosage of 75 mg/day or 500 mg/day respectively at least 4–5 days prior to admission.

During the procedure: Weight-adjusted (70 IU/kg) heparin was administered and repeated as necessary to maintain an activated clotting time of 225 to 250 seconds throughout the procedure. Atropine (0.5–1 mg IV) was given to most patients just before the post-stenting dilation phase in order to reduce the bradycardia and hypotension potentially associated with carotid dilation. Atropine was not administered in patients with tachycardia and uncontrolled systemic hypertension.

Post procedure: Clopidogrel (75 mg/day) or ticlopidine (500 mg/day) was continued for at least 30 days after the interventional procedure (Haemoglobin and white blood count were checked 7–10 days following the percutaneous intervention). Mono anti-platelet therapy (either aspirin, clopidogrel or ticlopidine) was continued indefinitely.

Patient assessment

Neurological examinations were performed by an independent team of neurologists. Prior to treatment the patients underwent careful neurological examination (including NIH Stroke Scale), echo/color flow Doppler (lesion site and intracranial cerebral blood flow assessment), cerebral CT/MR scan. These tests were used to determine the degree of stenosis, rule out coexistent proximal or distal disease, and assess the lesion for echolucency, thrombus, and ulceration. All findings were subsequently confirmed by digital subtraction angiography at the time of CAS.

Within 24 hours of the procedure and at 30 days post-discharge the patients underwent a neurological examination and a complete echo/color flow Doppler evaluation. The neurological complications were defined as death, major stroke (i.e. persisting >24 hours), minor stroke (i.e. persisting <24 hours) and TIA (i.e. immediate recuperation of complaints).

A post-procedure cerebral CT/MR scan was performed only in patients with documented neurological complications.

Statistical analysis

Comparison of event rates between different groups was based on Pearson's Chi-square test whenever appropriate (i.e. whenever the expected cell counts exceeded 5 in at least 80% of all cells). Fisher's exact test was used in all other cases. The analysis of the total population was considered as the primary analysis. To allow for multiple testing, the subgroup and post-hoc analyses were applied using Bonferoni corrections. All analyses were conducted in SPSS Version 12.0.0.

Results

1. Comparison of event rates between stents

The detailed overview of the complications per stent are listed in Table 3. Table 4 reports the event rates related to the different stents for the total population, symptomatic and asymptomatic subgroups in absolute numbers and percentage. From the 48 complications that occurred in the group treated with the

Table 3. Detailed overview of the event rates per carotid stent

Device	Number	Death (%)	Major (%)	Minor (%)	TIA (%)	Combined (%)
X-act	105	1,0	0,0	0,0	1,0	1,9
Nexstent	30	0,0	3,3	0,0	0,0	3,3
Wallstent	2107	0,2	0,4	0,6	1,1	2,3
Precise	293	0,7	0,3	0,7	2,4	4,1
Protégé	201	0,0	0,0	1,5	1,5	3,0
Acculink	409	0,0	0,5	0,7	2,9	4,2
Exponent	34	0,0	0,0	2,9	8,8	11,8
Total	3179	0,2	0,4	0,7	1,5	2,8

Table 4. Overview of event rates related to the different stents

	Total population			Symptomatic population			Asymptomatic population		
	Patients	All events	Post-procedural events	Patients	All events	Post-procedural events	Patients	All events	Post-procedural events
Stent name									
X-Act	105	2	2	46	1	1	59	1	1
Nexstent	30	1	1	6	0	0	24	1	1
Wallstent	2107	48	26	882	20	11	1225	28	15
Precise	293	12	9	144	9	7	149	3	2
Protégé	201	6	6	60	4	4	141	2	2
Acculink	409	17	15	168	13	12	241	4	3
Exponent	34	4	2	11	1	1	23	3	1
Total	3179	90	61	1317	48	36	1862	42	25
Stent name									
X-act		1.9%	1.9%		2.2%	2.2%		1.7%	1.7%
Nexstent		3.3%	3.3%		0.0%	0.0%		4.2%	4.2%
Wallstent		2.3%	1.2%		2.3%	1.2%		2.3%	1.2%
Precise		4.1%	3.1%		6.3%	4.9%		2.0%	1.3%
Protégé		3.0%	3.0%		6.7%	6.7%		1.4%	1.4%
Acculink		4.2%	3.7%		7.7%	7.1%		1.7%	1.2%
Exponent		11.8%	5.9%		9.1%	9.1%		13.0%	4.3%
Total	3179	2.83%	1.9%	1317	3.6%	2.73%	1862	2.25%	1.3%

Wallstent, 3 were treated without EPD (1 symptomatic and 2 asymptomatic). These three patients were before the year 2000 (no EPD available). All three occurred during the procedure (1 TIA, 2 minor stroke), and were included in the final analysis.

Table 5 reports *p*-values for the comparison of event rates between stents. The primary analysis of the total population reveals significant differences in event rates between stents, most obvious for the post-procedural events.

Highest post-procedural event rates were observed for Exponent (5.9%), Acculink (3.7%), NexStent (3.3%), Precise (3.1%) and Protégé (3.0%). Lowest post-procedural event rates were observed for Wallstent (1.2%) and X-act (1.9%). Secondary analyses revealed that differences in complication rates between stents were much more pronounced among symptomatic patients. However, there was no evidence of differences between stents in the asymptomatic population.

We subsequently performed post-hoc analyses to investigate precisely which stents are different in terms of event rates. Given that Table 5 revealed no significant differences in event rates in the asymptomatic population, no post-hoc comparisons were performed for this population. Due to small samples available for each comparison and by the need to adjust for multiple testing error, little power is available for detecting differences in event rates between each pair of stents. After adjustment for multiple testing, significant differences could only be established between Wallstent and Acculink in terms of post-procedural events for the total population (event rates 1.2% vs 3.7%, $p = 0.0079$), in terms of all events for the symptomatic patient population (event rates 2.3% vs 7.7%, $p = 0.0041$) and in terms of post-procedural events for the symptomatic patient population (event rates 1.2% vs 7.1%, $p = 3.6\ 10^{-5}$).

Table 5. *P*-values for the test that event rates differ between stents

Population	Outcome	*p*-value
Total	All events	0.018
	Post-procedural events	0.002
Symptomatic	All events	0.006
	Post-procedural events	<0.0001
Asymptomatic	All events	0.248
	Post-procedural events	0.790

2. *Comparison of event rates by free cell area*

The different stents where than subdived in 4 subgroups according to free cell area:

- <2.5 mm^2: Wallstent (1.08 mm^2), X-Act (2.74 mm^2)
- 2.5–5 mm^2: NexStent (4.07 mm^2)
- 5–7.5 mm^2: Precise (5.89 mm^2), Exponent (6.51 mm^2)
- >7.5 mm^2: Protégé (10.71 mm^2), Acculink (11.48 mm^2)

Table 6 reports the values of all and post-procedural event rates by free cell area in the total, symptomatic and asymptomatic population. The primary analysis of the total population reveals significant differences in event rates according to free cell area, again most importantly for the post-procedural events. Post-procedural event rates equal 1.2%, 2.2%, 3.4% and 3.4% for free cell areas lower than 2.5 mm^2, between 2.5 mm^2 and 5 mm^2, between 5 mm^2 and 7.5 mm^2, and higher than 7.5 mm^2, respectively. A secondary subgroup analysis shows that differences in

Table 6. Overview of event rates related to the different free cell area

	Total population			Symptomatic population			Asymptomatic population		
	Patients	All events	Post-procedural events	Patients	All events	Post-procedural events	Patients	All events	Post-procedural events
Free cell area									
<2,5 mm^2	2107	48	26	882	20	11	1225	28	15
2,5–5 mm^2	135	3	3	52	1	1	83	2	2
5–7,5 mm^2	327	16	11	155	10	8	172	6	3
>7,5 mm^2	610	23	21	228	17	16	382	6	5
Total	3179	90	61	1317	48	36	1862	42	25
Free cell area									
<2,5 mm^2		2.3%	1.2%		2.3%	1.2%		2.3%	1.2%
2,5–5 mm^2		2.2%	2.2%		1.9%	1.9%		2.4%	2.4%
5–7,5 mm^2		4.9%	3.4%		6.5%	5.2%		3.5%	1.7%
>7,5 mm^2		3.8%	3.4%		7.5%	7.0%		1.6%	1.3%
Total	3179	2.83%	1.9%	1317	3.6%	2.73%	1862	2.25%	1.3%

complication rates are again substantially more pronounced among symptomatic patients. However, there was no evidence of differences according to free cell area in the asymptomatic population. Very similar results were obtained using trend tests which tend to be more powerful.

Table 7 reports *p*-values for the test for the association of event rates and free cell area.

We subsequently performed post-hoc analyses to investigate precisely which groups of stents (as defined in terms of free cell area) are different in terms of event rates. Given that Table 7 revealed no significant differences in event rates in the asymptomatic population, no post-hoc comparisons were performed for this population. After adjustment for multiple testing important significant differences are observed in the symptomatic population between stents with free cell areas lower than 2.5 mm^2 on one the hand and larger than 5 mm^2 on the other hand, and this for both event types (all events and post-procedural events) (see Table 8). Specifically, all event rates equal 2.3%, 6.5% and 7.5% for free cell areas lower than 2.5 mm^2, between 5 mm^2 and 7.5 mm^2, and higher than 7.5 mm^2, respectively, in the symptomatic patient population. Post-procedural event rates equal 1.2%, 5.2% and 7.0%, respectively, in that population. Because these differences get diluted with the absence of differences in the asymptomatic population, differences are much weaker and usually non-significant in the total study population.

Table 7. *P*-values for the test that event rates differ by free cell area

Population	Outcome	*p*-value
Total	All events	0.024
	Post-procedural events	0.002
Symptomatic	All events	0.002
	Post-procedural events	<0.0001
Asymptomatic	All events	1.00
	Post-procedural events	1.00

3. Comparison of event rates by cell types

Table 9 reports values of all and post-procedural event rates between cell types (open vs. closed) in the total, symptomatic and asymptomatic population.

The primary analysis of the total population reveals significant differences in event rates according to cell type, again especially for the post-procedural events. Post-procedural event rates were observed to be 1.3% for closed cells and 3.4% for open cells (Table 10).

The secondary analysis shows that differences in complication rates between cell types are highly pronounced among symptomatic patients, but there was no evidence of differences between cell types in the asymptomatic population.

Study Limitation

Although this study involves a large cohort of patients, it is a retrospective non-randomized analysis. The majority of the CAS procedures where performed in the perspective of clinical trials and carotid training

Table 8. *P*-values for post-hoc comparisons of event rates by free cell area

Free cell area	Total population		Symptomatic population	
	All events	Post-procedural events	All events	Post-procedural events
<2.5 vs [2.5, 5]	1.00	1.00	1.00	1.00
<2.5 vs [5, 7.5]	0.054	0.072	0.048	0.024
<2.5 vs >7.5	0.27	0.006	0.0006	$2.8\ 10^{-6}$
[2.5 − 5] vs [5, 7.5]	1.00	1.00	1.00	1.00
[2.5 − 5] vs >7.5	1.00	1.00	1.00	1.00
[5 − 7.5] vs >7.5	1.00	1.00	1.00	1.00

Table 9. Overview of event rates related to the cell design

	Total population			Symptomatic population			Asymptomatic population		
	Patients	All events	Post-procedural events	Patients	All events	Post-procedural events	Patients	All events	Post-procedural events
Open cell	937	39	32	383	27	24	554	12	8
Closed cell	2242	51	29	934	21	12	1308	30	17
Total	3179	90	61	1317	48	36	1862	42	25
Cell type									
Open cell		4.2%	3.4%		7.0%	6.3%		2.2%	1.4%
Closed cell		2.3%	1.3%		2.2%	1.3%		2.3%	1.3%
Total	3179	2.83%	1.9%	1317	3.6%	2.73%	1862	2.25%	1.3%

programs sponsored by different companies. During these sessions the interventions where performed with the sponsor's device, except for cases presenting with extreme anatomy (example: open cell flexible stent in tortuous bifurcation or closed cell stent in plaques considered as vulnerable). So even though one could argue that devise selection was biased, the majority of the stents where assigned randomly.

Discussion

The nature of most neurological events in patients with carotid artery stenosis are not related to hypoperfusion of the brain but have an emboligenic origin.

As demonstrated in multi-center prospective randomized trials,[10–14] carotid endarterectomy (CEA), removing the plaque and the source of emboli, is the gold standard to reduce stroke in symptomatic and asymptomatic patients with significant carotid stenosis.[15–16]

An effective endovascular approach should consequently either be able to remove the plaque completely or prevent it from embolization. The CAS procedure as performed now[17] opens the stenosis by dilatation and tries to prevent future embolization through the scaffolding of the ruptured plaque against the vessel wall by means of a stent. Therefore after completion of the procedure the struts of the stent are the only protection against post-procedural neurological events.[18–20]

Table 10. *P*-values for the test that event rates differ by cell type

Population	Outcome	*p*-value
Total	All events	0.005
	Post-procedural events	<0.0001
Symptomatic	All events	<0.0001
	Post-procedural events	<0.0001
Asymptomatic	All events	1.00
	Post-procedural events	1.00

The results of our retrospective statistical analysis suggest that especially in symptomatic patient, who are known to have an emboligenic plaque,[21] the choice of a stent with a small free cell area resulted in a significant decrease of the post-procedural events. In the symptomatic population free cell area was a significant predictor of the number of events (all events: $p = 0.002$ and post-procedural events $p < 0.0001$). A free cell area lower than 2.5 mm showed superiority for both event types (all and post-procedural events) (<2.5 vs. 5–7.5; all: $p = 0.048$ – post-procedural: $p = 0.024$ and <2.5 vs. >7.5; all: $p = 0.0006$; post-procedural: $p = 2.8\ 10^{-6}$). Significant differences could also be established between the stent with the smallest free cell area (Wallstent: 1.08 mm^2) and the one with the largest free cell area (Acculink: 11.48 mm^2) in terms of all events for the total population ($p = 0.0079$) and all ($p = 0.0041$) as well as post-procedural ($p = 3.6\ 10^{-5}$) events in the symptomatic population.

Comparing stents by cell types (open vs. closed) in the total (3.4% vs. 1.3%) and most of all in the symptomatic population (6.3% vs. 1.3%) resulted in a clear reduction of predominantly post-procedural events for the closed cell group.

In the asymptomatic population free cell area or cell type did not influence the event rate. The 30-day stroke and death rate for the asymptomatic group (42 events in 1862 patients: 2.2%) was considerably lower than in the symptomatic patients (48 events in 1317 patients: 3.6%).

In contrast with many single high volume centers who have reported low intra- and post-procedural adverse neurologic events after CAS,[22–25] recent update from randomized multi-center trial suggest higher rates of complications. The EVA-3S[26] and SPACE[27] trials reported poor results for CAS in symptomatic patients: stroke and death rate at 30 days respectively 9.6% and 6.8%. In these trials many different stents have been used. A sub-analysis of these trial results comparing free cell area with event rate could be of

interest to find a possible explanation for the high complication rate.

Conclusions

We conclude that there is substantial evidence for differences in complication rates between stents ($p = 0.002$ for the late events). This is almost entirely explained by differences in event rates in the symptomatic population as no important differences could be established in the asymptomatic population. In the symptomatic population late complication rates are highest for the open cell types and increase with larger free cell area. Prospective randomised trials comparing different free cell areas should be conducted in order to further investigate this question. For the time being consideration should be given to the use of stents with a small free cell area especially in symptomatic patients.

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