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Meta-analysis of the Effect of Stent Design on 30-Day Outcome After Carotid Artery Stenting

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Abstract

Purpose: To review the contemporary literature and analyze whether stent cell design plays a role in 30-day outcomes after carotid artery stenting (CAS). **Methods:** A systematic review of the literature was undertaken that identified 9 studies comparing the effect of different cell design on 30-day outcome in patients undergoing CAS. Random-effects models were applied to calculate pooled outcome data for mortality and cerebrovascular morbidity. Results are reported as the odds ratio (OR) and 95% confidence interval (CI). **Results:** The 9 studies included 8018 patients who underwent 8028 CAS procedures (4018 open-cell stents, 4010 closed-cell stents). Six studies were retrospective in design, one was a registry, and only two studies prospectively compared the effect of different cell designs. Nearly half of the patients (3452, 43.1%) were symptomatic, with no significant difference between the closed- and open-cell stent groups (p=0.93). During the first month after the procedure, there were no significant differences in mortality (OR 0.69, 95% CI 0.39 to 1.24, p=0.21), transient ischemic attacks (OR 0.95, 95% CI 0.69 to 1.30, p=0.74), or strokes (OR 1.17, 95% CI 0.83 to 1.66, p=0.37). **Conclusion:** This meta-analysis showed that 30-day cerebrovascular complications after CAS were not significantly different for the open-cell group in comparison to the closed-cell group. Future prospective clinical trials comparing different free cell areas and other stent design properties are still needed to further investigate whether stent design plays a significant role in the results of carotid stenting.

Keywords

carotid artery stenting, closed cell, complications, open cell, mortality, stent design, stroke, transient ischemic attack

Introduction

Atherosclerotic stenosis of the carotid artery constitutes a major cause of ischemic stroke in the western world.[1] Carotid endarterectomy (CEA) had been used as a procedure for stroke prevention for many decades. The beneficial role of CEA in preventing strokes, mostly for symptomatic and to a lesser extent for asymptomatic patients, has been highlighted in all current guidelines.[2] In the era of less invasive procedures, carotid artery stenting (CAS) has emerged as an evolving alternative technique that may even be used as the first-line treatment in high-risk patients.[3]

Randomized controlled trials comparing CEA and CAS have produced diverging results.[2] The safety and efficacy of CAS have been debated, since some randomized trials reported high complication rates within the CAS arm.[3,4] On the contrary, several experienced centers continue to report low rates of neurologic complications from large CAS registries.[5–7] These discrepancies between studies may be the result of the operators' learning curve, but it also may be device-related.[8]

Carotid artery stenting can be performed with a number of stents of different structural cell design (Table 1). Different carotid stent designs create different vessel wall scaffolding, and as a result their plaque stabilization

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Table 1. Types of Stents Used for Carotid Artery Stenting.

Design	Stent	Free Cell Area, mm^2
Closed cell	Wallstent	1.08
	Xact	2.74
	NexStent	4.07
	Adapt	4.4
Open cell	Precise	5.89
	Exponent	6.51
	Protégé	10.71
	Acculink	11.48
Hybrid	Cristallo	3.24–15.17

properties vary, mainly in relation to the size of the free cell area between the struts of stents. Stents with small cell sizes have a dense, metallic mesh, which in theory may provide more effective plaque and wall coverage and reduce the risk for embolization of particles compared to stents with larger cell sizes. In one study, patients in the closed-cell arm exhibited a substantially lower risk for neurologic adverse events, supporting the hypothesis that stents with a small free cell area and dense, metallic meshes improve the safety of CAS.[9] Closed-cell stents, however, are less flexible and conformable to carotid anatomy and neck movement and thus are perhaps not the best choice for specific groups of patients.

In the absence of any clear evidence relating carotid stent design and neurologic adverse events and mortality, this study sought to review the literature concerning the results of CAS using open- and closed-cell stents and evaluate the 30-day mortality, stroke, and transient ischemic attack (TIA) rates of each stent design.

Methods

Eligibility Criteria

The objectives, methodology of the systematic review and analysis, and the inclusion criteria for study enrollment were documented in a protocol that followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. Studies comparing the effect of different stent design on outcome of patients after CAS were considered eligible; only comparative studies (open cell vs closed cell) were included in the final analysis. Two reviewers (G.N.K. and N.P.) performed eligibility assessment independently in an unblended, standardized manner. Disagreements between reviewers were arbitrated by discussion.

Search

An electronic search was conducted of the English-language medical literature from 1991 to October 2014 using the PubMed and EMBASE databases to find all studies comparing the effect of stent design on outcome of patients undergoing CAS for carotid stenosis. Search terms included "carotid," "stenting," "open cell," "closed cell," and "stent design." Related articles suggested by the PubMed search engine and reviews on this subject were searched for additional relevant articles. Further articles were also identified from the references cited in the initially identified reports.

The initial search identified 10 studies that compared the effects of stent cell design on CAS outcome[9–18]; one study[18] was excluded because the cohort was also included in a later report.

Data Extraction

Two authors (G.N.K. and N.P.) independently extracted data from the eligible full-text articles. Disagreements between reviewers were resolved by consensus. The variables extracted from each article included: stent type, stent models, patient age, gender, percent stenosis, symptom status, use of an embolic protection device (EPD), use of pre/post dilation, death, and cerebrovascular complications (TIA and stroke).

Data Synthesis and Analysis

Binary outcome measures (occurrence of stroke, TIA, and death) were calculated and reported as the odds ratio (OR) and 95% confidence interval (CI). A fixed-effects model was applied to calculate the pooled treatment effect. A random-effects model was used in the event that significant heterogeneity among the studies was identified. A forest plot for each treatment effect was created. Inter-study heterogeneity was assessed visually using the forest plots. Furthermore, heterogeneity was assessed using the Cochran Q test (chi-square) and by measuring inconsistency (I) of the effects of stent type; I^2 values <50% was considered to indicate low heterogeneity, 50% to 75% as moderate heterogeneity, and >75% as significant heterogeneity. A funnel was constructed using the included studies to visually assess any publication bias. Analyses were performed using the Review Manager 5.2 (Cochrane Information Management System; available at: *http://ims.cochrane.org/revman*)

Results

Study and Procedure Characteristics

The 9 studies that met the inclusion criteria included 8018 patients (mean age was 69.8±2.9 years; 5524 men) who underwent 8028 CAS procedures using 4018 open-cell and 4010 closed-cell stents (Table 2).[9–17] Six studies were retrospective, one was a registry, and only 2 studies prospectively compared the effect of different cell designs. The size

Table 2. Study and Patient Characteristics According to Stent Cell Design.

First Author, Year	Study Type	n	Stent Cell Type		Age, y[a]		Men[b]		Stenosis, %[a]		Symptoms[b]	
			Open	Closed	Open	Closed	Open	Closed	Open	Closed	Open	Closed
Bosiers, 2007	R	3179	937	2242	72.8±1	70.7±1.5	NR	NR	NR	NR	383 (41)	934 (42)
Schillinger, 2008	R	1684	825	859	71 (64–78)	72 (64–77)	524 (63)	599 (70)	85 (80–90)	85 (80–90)	381 (46)	293 (34)
Maleux, 2009	R	123	60	72	74.9±5.1	74.3±6.9	44 (73)	52 (72)	NR	NR	19 (32)	35 (49)
Timaran, 2011	P	40	20	20	67 (60–75)	65 (59–71)	20 (100)	20 (100)	NR	NR	9 (45)	8 (40)
Jim, 2011	Reg	2322	1775	547	NR	NR	NR	NR	NR	NR	796 (45)	265 (48)
Grunwald, 2011	R	120	84	36	68.9±1	66.5±1.4	NR	NR	88	86	25 (30)	7 (19)
Tadros, 2012	R	173	125	48	70.0±8.6	73.4±10.2	70 (56)	31 (65)	87.2±8	90.6±7.8	48 (38)	15 (52)
Sahin, 2013	R	282	144	138	66.6±9.2	66.6±8.3	102 (71)	110 (80)	83.6±11.6	86.8±10.8	86 (60)	72 (52)
Park, 2013	P	96	48	48	69.1±7.5	68.8±7.7	43 (90)	36 (75)	40% >70%	41% >70%	36 (75)	40 (83)

Abbreviations: NR, not reported; P, prospective; R, retrospective; Reg, registry.
[a]Data are presented as the means ± standard deviation or median (range).
[b]Data are given as the counts (percentage).

of the patient cohort in each study ranged from 40 to 3179, and the period during which these studies were published was from 2007 to 2013. Nearly half of the patients (3452, 43.1%) were symptomatic, with no significant difference between the open-cell (44.4%) and closed-cell (41.7%) groups (p=0.93).

The procedure characteristics are summarized in Table 3. An EPD was used in the vast majority of the procedures (90.7%), with no significant differences between the 2 groups (p>0.05). Data on the exact stent model were available in half of the study's cohort (4022, 50.3%; 1418 open-cell stents and 2604 closed-cell stents). In the open-cell group, the most frequently deployed stent was the Acculink (Guidant, Santa Clara, CA, USA; 540 stents, 38.1%) followed by Protégé (Medtronic/Covidien, Minneapolis, MN, USA; 381 stents, 26.9%), and Precise (Cordis, Miami, FL, USA; 369 stents, 26.4%). In the closed-cell group, the majority of the stents used were Wallstents (Boston Scientific, Marlborough, MA, USA; 2252 stents, 88.3%). Data on pre- and postdilation frequency were clearly reported in 5 studies. No significant differences were noted between the two groups either in prestent (p=0.75) or post-stent dilation frequencies (p=0.99).

The relation of symptoms with 30-day cerebrovascular outcome and stent design was investigated in 4 studies (Table 4). Only 2 of these studies gave detailed data for 30-day outcome; the other 2 indicated only that there were no statistically significant differences in cerebrovascular events between symptomatic and asymptomatic patients receiving open-cell or closed-cell stents. In the study by Bosiers et al,[9] the differences in postprocedure event rates were highly pronounced among symptomatic patients (p<0.0001).

Perioperative Outcomes

Data on 30-day mortality were extracted from all studies (Table 5). No significant differences were found between the groups (OR 0.69, 95% CI 0.39 to 1.24, p=0.21; Figure 1). No significant heterogeneity among the studies existed (I^2=0%). Visual evaluation of the funnel plot suggested that the possibility of publication bias was low (Figure 2).

All 9 studies concerning 8028 procedures reported the occurrence of cerebrovascular events (stroke plus TIA) during the 30 days after the procedure (Table 5). No significant differences in TIA were noted between the different stent cell designs (OR 0.95, 95% CI 0.69 to 1.30, p=0.74; Figure 3). Moderate heterogeneity among the studies was indicated (I^2=66%), and no asymmetry in the funnel plot was found to indicate any significant publication bias (Figure 2).

The incidence of stroke was similar in the open-cell (87, 2.2%) vs closed-cell (61, 1.5%) groups (OR 1.17, 95% CI 0.83 to 1.66, p=0.37; Figure 4). Heterogeneity among studies was insignificant (I^2=16%), and the probability of publication bias was low (Figure 2). Similarly, when analysis was performed for all cerebrovascular events occurring

Table 3. Procedure Characteristics According to Stent Cell Design.

First Author, Year	n	EPD Usage[a]		Stent Type[a]		Pre/Post Stent Dilation[a]	
		Open	Closed	Open	Closed	Open	Closed
Bosiers, 2007	3179	921 (98)	2128 (95)	Precise: 293 (31) Protégé: 201 (21) Acculink: 409 (44) Exponent: 34 (4)	Wallstent: 2107 (94) Xact: 105 (5) NexStent: 30 (1)	NR	NR
Schillinger, 2008	1684	730 (89)	744 (84)	NR	NR	432 (52) / 814 (99)	674 (79) / 854 (99)
Maleux, 2009	123	46/60	10/72	Acculink: 37 (62) Precise: 18 (30) Exponent: 5 (8)	Wallstent: 72 (100)	NR	NR
Timaran, 2011	40	20 (100)	20 (100)	Acculink: 20 (100)	Xact: 20 (100)	18 (90) / 20 (100)	16 (80) / 20 (100)
Jim, 2011	2322	NR	NR	NR	NR	NR	NR
Grunwald, 2011	120	0 (0)	0 (0)	Zilver: 84 (70)	Wallstent: 36 (30)	NR / 84 (100)	NR / 36 (100)
Tadros, 2012	173	125 (100)	48 (100)	Precise: 15 (8) Protégé: 36 (21) Acculink: 74 (43)	Wallstent: 37 (21) Xact: 8 (5) NexStent: 3 (2)	NR	NR
Sahin, 2013	282	144 (100)	138 (100)	All Protégé	All Xact	16 (11) / 128 (89)	28 (20) / 127 (92)
Park, 2013	96	43 (90)	48 (100)	All Precise	All Wallstent	41 (85) / 48 (100)	43 (90) / 48 (100)

Abbreviations: EPD, embolic protection device; NR, not reported.
[a]Data are given as the counts (percentage).

Table 4. Outcome of the Study Population According to Treatment Indication.

First Author, Year	Open Cell[a]		Closed Cell[a]	
	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic
Bosiers, 2007	21 (5.5) events	12 (2.3) events	27 (2.9) events	30 (2.3) events
Schillinger, 2008	No difference stated, but no detailed data given			
Maleux, 2009	No difference stated, but no detailed data given			
Timaran, 2011	NR	NR	NR	NR
Jim, 2011	Stroke: 29 (3.6)	16 (1.6)	5 (1.9)	4 (1.4)
	TIA: 19 (2.4)	9 (0.9)	6 (2.3)	4 (1.4)
	Mort: 10 (1.3)	15 (1.5)	6 (2.3)	4 (1.4)
Grunwald, 2011	NR	NR	NR	NR
Tadros, 2012	NR	NR	NR	NR
Sahin, 2013	NR	NR	NR	NR
Park, 2013	NR	NR	NR	NR

Abbreviations: NR, not reported; TIA, transient ischemic attack; Mort: mortality
[a]Data are given as the counts (percentage of the subgroup in the column).

within 30 days of treatment, including both strokes and TIAs, no significant differences between open- and closed-cell stent design were demonstrated when a fixed effects model was applied (OR 1.05, 95% CI 0.83 to 1.33, p=0.69; Figure 5). The between-study heterogeneity was moderate (I^2=65%), whereas the funnel plot did not indicate significant publication bias (Figure 2). The combined incidence of cerebrovascular events and death was also similar between the two groups (OR 1, 95% CI 0.8 to 1.25, p=0.98; Figure 6), while no significant publication bias was depicted from the funnel plot (Figure 2).

Discussion

Carotid stents have sequentially aligned annular rings interconnected by bridges.[17] The number and arrangement of these bridge connectors differentiate open-cell from closed-cell designs.[19] Closed-cell stents are characterized by smaller free cell areas between struts, thus leaving smaller gaps uncovered.[11] These stents are rigid and may be prone to kinking, while more flexible open-cell stents conform better to tortuous anatomy. Theoretically, closed-cell stents are characterized by an improved ability to scaffold plaque,

Table 5. Outcomes of the Study Population by Stent Cell Design.

	Mortality at 30 Days[a]			TIA[a]			Stroke[a]		
First Author, Year	Open	Closed	p	Open	Closed	p	Open	Closed	p
Bosiers, 2007	2 (0.2)	5 (0.2)	NR	25 (2.7)	24 (1.1)	NR	11 (1.2)	22 (1)	NR
Schillinger, 2008	0 (0)	1 (0.01)	NR	14 (1.7)	35 (4.1)	NR	21 (2.4)	26 (3)	NR
Maleux, 2009	0 (0)	1 (1.4)	NR	2 (3.3)	2 (2.8)	NR	4 (6.7)	1 (1.4)	NR
Timaran, 2011	0 (0)	0 (0)	NR	1 (5)	0 (0)	NR	1 (5)	0 (0)	NR
Jim, 2011	25 (1.4)	10 (1.8)	0.54	32 (1.8)	13 (2)	0.7	45 (2.5)	9 (1.6)	0.25
Grunwald, 2011	1 (1.2)	0 (0)	NR	3 (3.6)	1 (2.8)	NR	1 (1.2)	0 (0)	NR
Tadros, 2012	1 (0.8)	0 (0)	0.54	0 (0)	0 (0)	NR	0 (0)	2 (4.2)	0.16
Sahin, 2013	0 (0)	2 (1.4)	0.14	5 (3.5)	5 (3.6)	0.94	4 (2.8)	0 (0)	0.04
Park, 2013	0 (0)	1 (2.1)	1	0 (0)	2 (4.3)	0.49	0 (0)	1 (2.1)	1

Abbreviations: NR, not reported; TIA, transient ischemic attack.
[a]Data are given as the counts (percentage of the cell type).

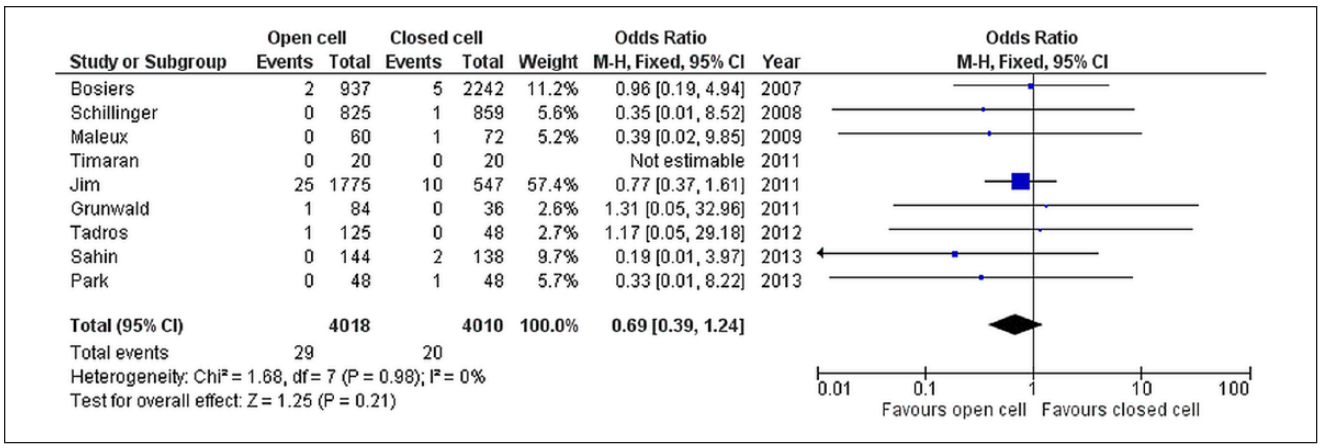

Figure 1. Differences in 30-day mortality rate between the open-cell and closed-cell groups.

thus reducing embolization in patients of high embolic risk.[9,16] However, the scaffolding benefits of a closed-cell design have a cost in flexion and conformability, just as the flexion benefits of an open-cell design have a cost in scaffolding uniformity.

In most CAS procedures, either open-cell or closed-cell stents may be used.[20] The reports of the effect of stent design on cerebrovascular outcome have been controversial, and the theoretic advantage of plaque stabilization by the closed-cell stents has not been clinically established. While stent design may (albeit subtly) impact rates of TIA or stroke, it is unlikely that it can impact mortality, though some strokes may result in death. In 2006, Hart et al[18] suggested for the first time that carotid stents with a closed-cell design seem to be superior to those with open-cell design regarding 30-day stroke and death rate. In a consequent multicenter, retrospective, observational study, the same authors expanded their initial series to include 3179 CAS procedures.[9] The postprocedure event rates varied from 1.2% to 5.9% for free cell areas of 2.5 and 6.5 mm^2, respectively ($p<0.05$). To the contrary, these results were not confirmed in a later study of 1700 patients.[15] In this study,[15] open-cell carotid stent design was not associated with an increased risk for combined neurologic complications compared with closed-cell stent (open-cell 6.1% vs closed-cell 4.1%, p=0.077), though the statistical insignificance was marginal.[15] This disagreement between these 2 large studies may reflect differences in treatment strategies and patient selection between different centers and countries. In the present review encompassing nearly 8000 patients, the rates of stroke, death, and TIA during the first 30 days after the procedure were not different in patients receiving either open- or closed-cell carotid stents. Therefore, our results do not support the superiority of a specific stent cell design with respect to cerebrovascular complications and mortality risk.

Cerebral embolization has been used as a surrogate endpoint to compare different effects of CEA and CAS. A

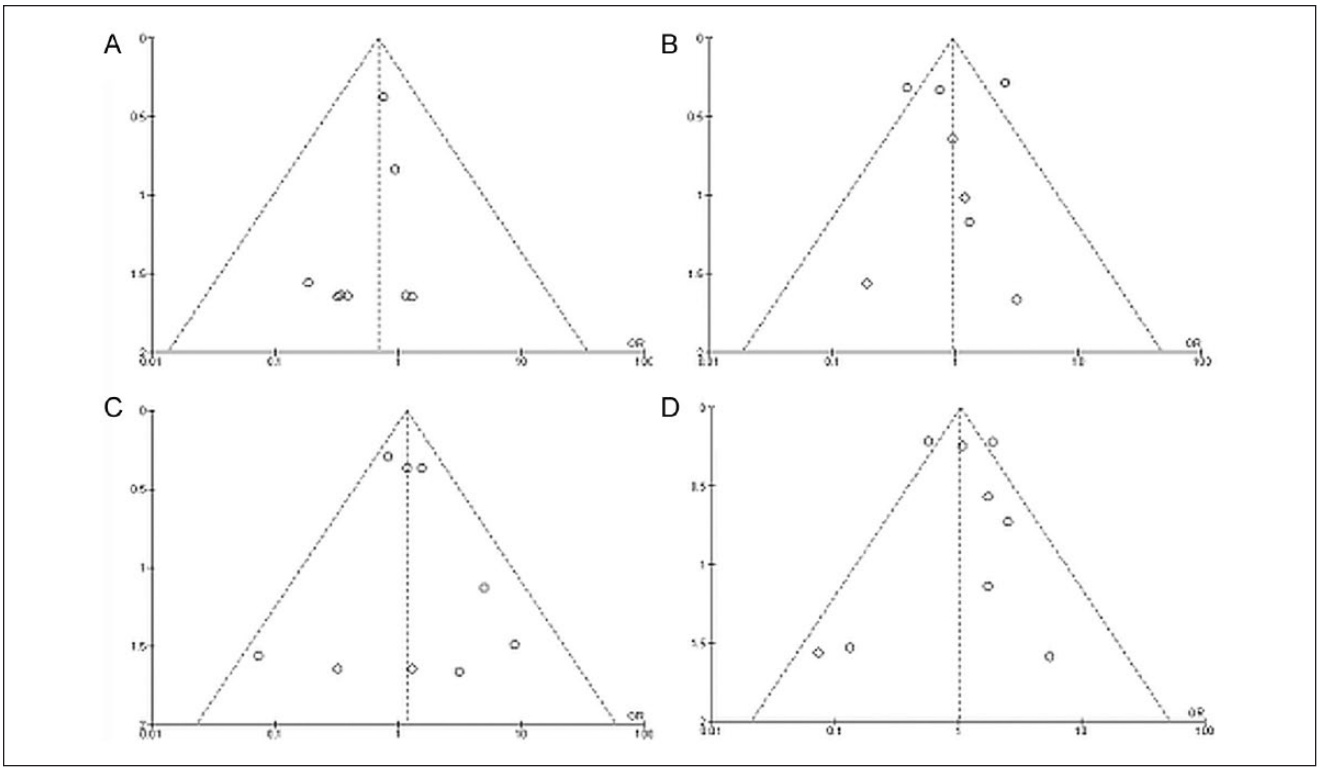

Figure 2. Funnel plots for (A) 30-day mortality, (B) transient ischemic attack, (C) stroke, and (D) cerebrovascular events.

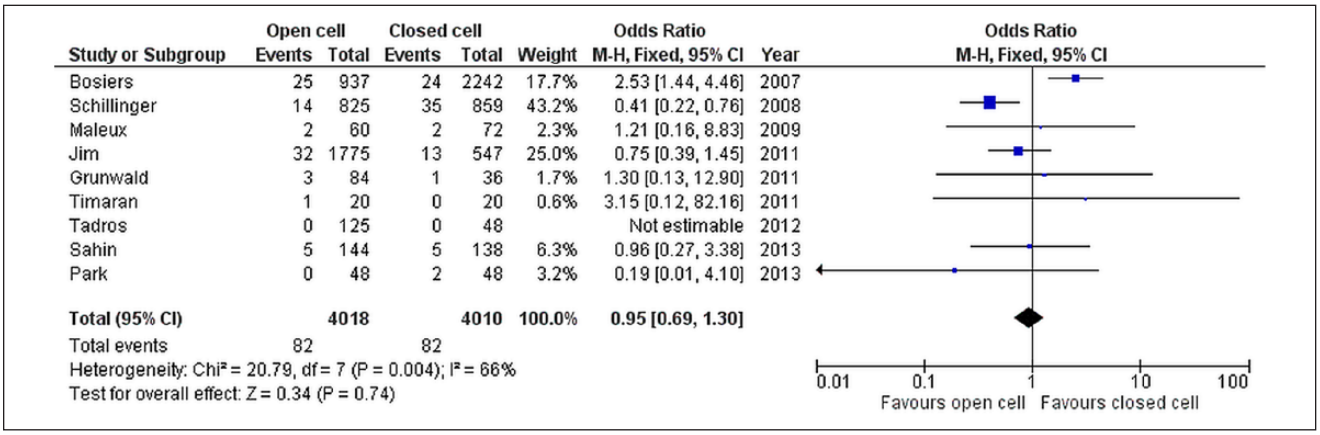

Figure 3. Differences in transient ischemic attack rate between the open-cell and closed-cell groups.

substudy of the International Carotid Stenting Study looked at 124 CAS and 107 CEA patients and reported about three times more patients in the stenting group than in the endarterectomy group having ischemic lesions on diffusion-weighted (DW) imaging.[21] The effect of stent design on cerebral embolization after CAS has not been sufficiently studied so far. In theory, an open-cell structure would increase the risk of plaque material extruding through the stent interstices. Still, in a prospective randomized study of 40 patients, Timaran et al[17] found that cerebral embolization, as depicted in DW magnetic resonance imaging, occurs with similar frequency after CAS with open- and closed-cell stents. On the contrary, Park et al[13] found that open-cell stents are associated with more frequent formation of new lesions on DW imaging after the procedure compared to closed-cell stents. Furthermore, Grunwald et al[10] reported that open-cell stents were related to a lower number and area of silent cerebral ischemic lesions in nearly 200 patients after unprotected CAS. However, clinical outcome, measured by incidence of adverse events and clinical neurologic assessment, in all these studies was not significantly

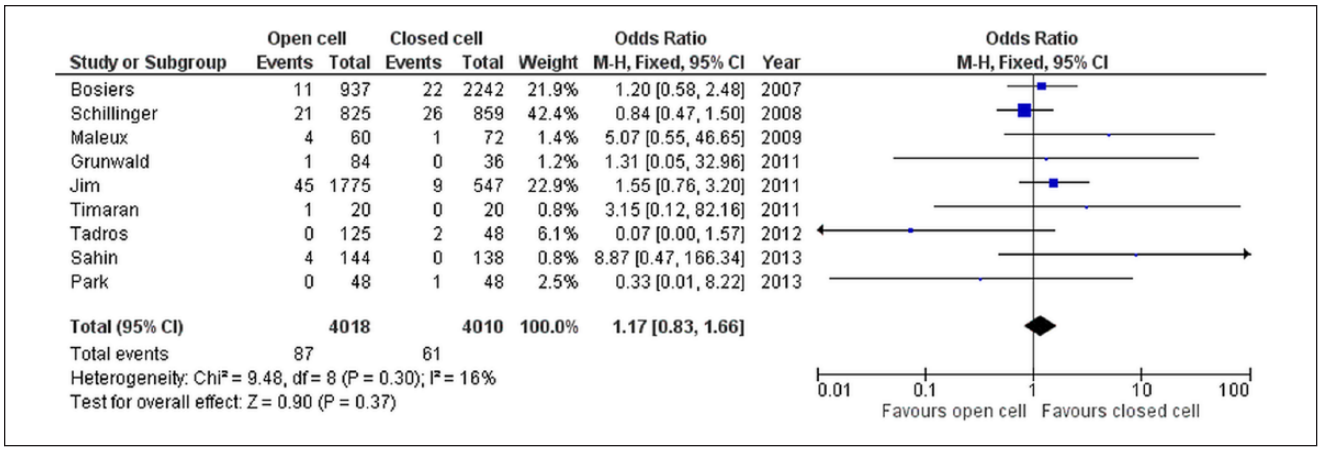

Figure 4. Differences in stroke rate between the open-cell and closed-cell groups.

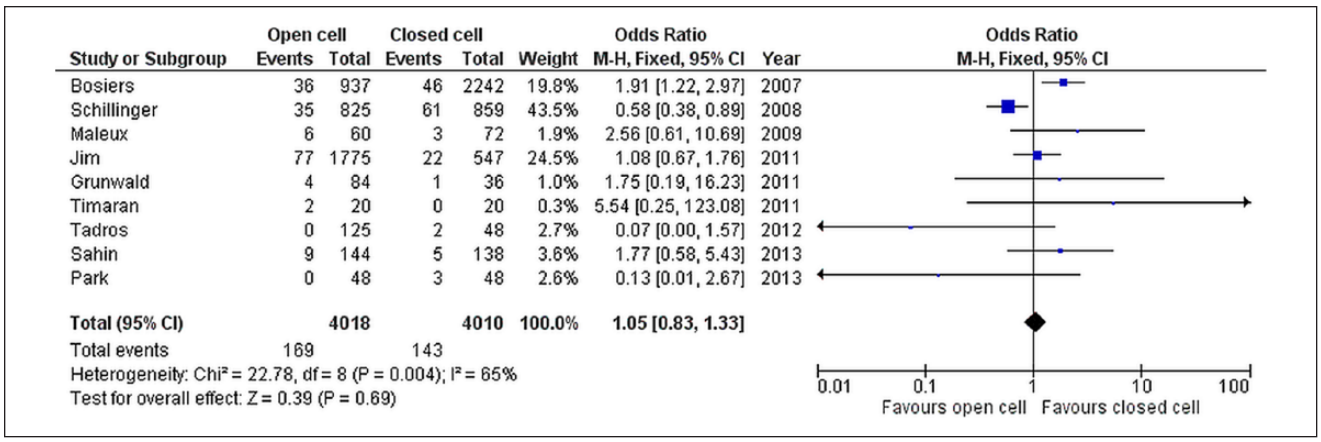

Figure 5. Differences in cerebrovascular events (stroke plus transient ischemic attack) between the open-cell and closed-cell groups.

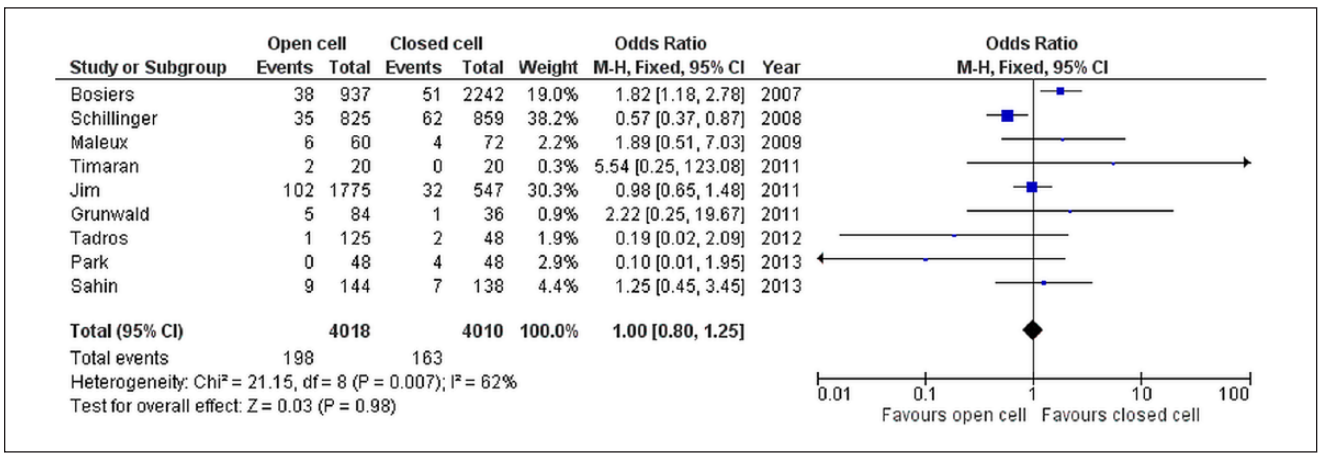

Figure 6. Differences in all events (death, stroke, transient ischemic attack) between the open-cell and closed-cell groups.

different between patients with different stent designs, implying that these clinically silent embolic lesions do not affect cerebrovascular outcome.

Overall neurologic complication rates varied between studies, ranging from 0% to 6.7%. This may reflect differences in patient selection and treatment strategies between

centers and countries. Certain parameters, such as postdilation frequency, oversizing rates, technical difficulties, and accurate timing of the events in relation to different phases of the procedure, have not been adequately reported and accounted in the majority of studies, probably due to their retrospective nature. Embolic debris can potentially be generated at multiple stages, including during wire and catheter passage, EPD and stent deployment, and pre- or postdilation. Future studies should focus on investigating other procedure parameters besides device characteristics that may affect outcome after CAS.

The present study supports the view that closed-cell stents do not improve the safety of CAS by providing increased wall coverage and optimal plaque stabilization. However, the large differences in free cell area, even in stents of the same group, should be acknowledged. For example, there is a large difference in free cell area between Wallstent (1.08 mm^2) and NexStent (4.07 mm^2) of the closed-cell group, as well as between Precise (5.69 mm^2) and Acculink (11.48 mm^2) of the open-cell group. These differences were taken into account in only one study. By directly comparing Wallstent (the smallest free cell area) to the Acculink stent system (the largest free cell area), Shillinger et al[15] found that the observed differences became even smaller than in the entire patient sample. Other stent-related factors may be relevant determinants of cerebrovascular outcome and certainly need further investigation.

The vast majority of the patients in this review underwent CAS under an EPD, which could have influenced the role of stent design in distal embolization during the procedure. CAS without an EPD has already been investigated.[22,23] In subgroup analyses, the complication rates for protected vs unprotected groups in SPACE 1 showed 8.3% vs 6.5%.[24] Several reports pointed out that EPDs do not completely eliminate the risk of cerebral embolization.[25] Notably, distal vasospasm and slow flow are described with incidences of up to 3.6% and 7.2%, respectively.[26] Lesion-related CAS with closed-cell design stents without an EPD has also been proven effective, especially when individual anatomical variance was considered.[27] The association of stent design with clinical outcome and radiological findings after unprotected CAS has been investigated in only one retrospective study of 194 patients treated between 2000 and 2006.[10] However, currently, an EPD constitutes an integral part of the CAS procedure. Therefore, the design of a study without embolic protection to investigate the exact effect of cell area on distal embolization is impossible due to ethical and regulatory considerations.

The relationship of symptomatic carotid artery lesions and stent design has been investigated in only 4 studies, producing diverging results. Detailed data were available in only two of these studies, so no reliable analysis could be performed. Jim et al[11] found that symptomatic patients had a higher stroke rate in-hospital for both the open- and closed-cell patients, with no differences when comparing the 2 stent designs. This finding has also been confirmed in other 2 studies.[12,15] On the contrary, in the Belgium-Italian (BIC) Registry, the difference between designs was primarily seen in symptomatic patients.[9] This finding has been partially supported in a prospective study by Park et al,[13] who found that new lesions on postoperative DW images were noted more frequently in the open-cell–stented symptomatic patients, without, however, having any effect on clinical outcome when comparing the two groups. Nevertheless, none of these studies was randomized, and stent selection according to physician preference may have certainly influenced their results.

The present meta-analysis associates data across studies to estimate treatment effects of stent design on cerebrovascular outcome after CAS with more precision than is possible in a single study. Unfortunately, very few studies report on the adjusted risk ratio for specific outcomes, thus pooling adjusted risk estimates, although more appropriate, was not possible. The main limitation of this review is that only 2 of 9 studies were prospective. The results are based mostly on synthesis of outcomes of observational retrospective studies with varied methodological quality and no detailed 30-day data. However, based on the results of the present meta-analysis, any randomized trial investigating the differences of cell design would be underpowered unless it is designed to include thousands of patients. Selection bias for specific stents in specific anatomic and clinical settings is evident, since the open-cell design is known to be more flexible and therefore more likely to be used in kinked morphologies, while closed-cell stents are more rigid and thus better suited for straight lesions. Moreover, in most studies, different devices are grouped within each category of open- or closed-cell stents; therefore, risks for device-specific complications have not been adequately studied.

Conclusion

There is continuous refinement in CAS techniques based on selection of different endovascular devices for varying anatomic and plaque characteristics. Selection of the stent design should be incorporated into CAS treatment planning. This meta-analysis showed that 30-day cerebrovascular complications after CAS are not significantly different for the open-cell stents in comparison to the closed-cell stents. Future prospective clinical trials comparing different free cell areas and other stent design properties are still needed to further investigate whether stent design constitutes a way to improve the results of CAS.

Declaration of Conflicting Interests

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