

**Effect of stent design on clinical and radiological outcomes of carotid artery stenting: a meta-analysis.**

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This study was presented at:

- 2017 MAC Munich Vascular Conference, München, December 7-9, 2017
- 2018 ICCA Stroke Conference, Warsaw, April 20-21, 2018.

Key words: carotid artery stenting, stent design, stroke, MR-DWI, meta-analysis

Word count: abstract: 360 words, body text: 3,063 words (introduction – contributions)

Tables: 1, figures: 4, online data supplements: 1.

## ABSTRACT

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**Objective:** Procedural characteristics, including stent design, may influence the outcome of carotid artery stenting (CAS). A thorough comparison of the effect of stent design on outcome of CAS is thus warranted to allow for optimal evidence-based clinical decision making. This study sought to evaluate the effect of stent design on clinical and radiological outcomes of CAS.

**Methods:** A systematic search was conducted in MEDLINE, Embase, and Cochrane databases in May 2018. Included were articles reporting on the occurrence of clinical short- and long-term major adverse events (MAE, any stroke or death) or radiological adverse events (new ischemic lesions on postprocedural magnetic resonance diffusion-weighted imaging (MR-DWI), restenosis or stent fracture) in different stent designs used to treat carotid artery stenosis. Random effects models were used to calculate combined overall effect sizes. Meta-regression was performed to identify the effect of specific stents on MAE rates.

**Results:** From 2,654 unique identified articles, two randomized controlled trials and 66 cohort studies were eligible for analysis (including 46,728 procedures). Short-term clinical MAE rates were similar for patients treated with open cell versus closed cell or hybrid stents. Use of Acculink stent was associated with a higher risk of MAE compared to Wallstent (RR: 1.51,  $p=0.03$ ), as was true for use of Precise stent versus Xact stent (RR: 1.55,  $p<0.001$ ). Long-term clinical MAE rates were similar for open versus closed cell stents. Use of open cell stents predisposed to a 25% higher chance (RR: 1.25;  $p=0.03$ ) of developing postprocedural new ischemic lesions on MR-DWI. No differences were observed in incidence of restenosis, stent fracture, or intraprocedural hemodynamic depression with respect to different stent design.

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**Conclusions:** Stent design does not affect short- or long-term clinical MAE rates in patients undergoing CAS. Furthermore, the division in open and closed cell stent design might conceal true differences in single stent efficacy. Nevertheless, open cell stenting resulted in a significantly higher number of MR-DWI-detected subclinical postprocedural new ischemic lesions compared with closed cell stenting. An individualized patient data meta-analysis, including future studies with prospective homogenous study design, is required to adequately correct for known risk factors and provide definite conclusions with respect to carotid stent design for specific subgroups.

## **ABBREVIATIONS**

CAS	carotid artery stenting
CI	confidence interval
ENDORSE	the Effect of steNt Design on outcomes of carOtid arteRy StEnting
EPD	embolic protection device
MeSH	medical subject headings
MR-DWI	magnetic resonance-diffusion weighted imaging
MRI	magnetic resonance imaging
NOS	Newcastle-Ottawa scale
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RCT	randomized controlled trial
RR	risk ratio

## INTRODUCTION

Randomized trials (RCTs) comparing carotid artery stenting (CAS) with endarterectomy demonstrated a higher benefit of endarterectomy with respect to 30-day stroke prevention.<sup>1</sup> Further, 50% of patients treated with CAS has new postprocedural cerebral white matter lesions on magnetic resonance diffusion-weighted imaging (MR-DWI).<sup>2,3</sup> However, CAS access techniques and devices are under continuous development,<sup>4</sup> and with the next generation stent designs being evaluated in phase III studies a significant reduction in periprocedural events and MR-DWI lesions with CAS is imaginable.

Literature on CAS devices focuses amongst others on stent designs, which are categorized according to strut interconnections: larger free cell area with fewer interconnections (“open cell”) versus smaller free cell area with more interconnections (“closed cell”). Open cell stents are more flexible while closed cell stents may offer better plaque coverage. Both designs are merged in “hybrid” stents, which theoretically combine both profits in one design. However, guidelines are inconclusive<sup>5</sup> and the debate on carotid stent design in relation to clinical outcomes, occurrence of new MR-DWI lesions or restenosis, is ongoing.<sup>6-17</sup>

This meta-analysis evaluated the effect of carotid stent design on early and late clinical adverse events as well as radiological outcomes in patients undergoing CAS for significant carotid artery stenosis, to allow for optimal evidence-based clinical decision making.

## **METHODS**

The study and preplanned analyses were designed by the core study group, and the manuscript was approved by all collaborating authors of the ENDORSE (Effect of steNt Design on carOtid arteRy StEnting outcomes) study group. A systematic review and meta-analysis was conducted in accordance with the PRISMA statement.<sup>18</sup>

### ***Search strategy***

A systematic literature search was conducted in MEDLINE, Embase, and Cochrane databases in June 2016 (updated May 2018). The Medical Subject Headings (MeSH) terms “carotid stenosis” and “stents” were combined using various synonyms for different stent designs. The full search strategy can be found in the data supplement (I).

Included were studies concerning patients with significant (>50%) carotid artery stenosis undergoing CAS using different stent types (i.e., open, closed or hybrid cell stents). Exclusion criteria were implementation of only one stent type, animal studies, reviews, case reports, and case series with fewer than 10 patients. Articles in English, Dutch, German, and French were considered. If multiple articles referred to similar study populations (n = 18), the paper with the largest sample size or most relevant outcome measures (e.g., reporting of adverse events in different stent groups) was retained (data supplement (II)).

Two investigators (EEdV, AJAM) screened all titles and abstracts and independently assessed full-text eligibility. Judgment differences were resolved by discussion. Reference lists of included articles were screened for missing articles.

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### ***Data processing***

Prespecified quantitative data (numbers of events occurring in patients treated with different stent designs) were required for inclusion. If quantitative data were not provided, corresponding authors were contacted. We contacted 116 authors of 133 potentially eligible articles, 55 authors replied (response rate 47%), and 29 authors provided additional data for 30 papers (23%). Studies were excluded if authors could not provide additional quantitative data.

Descriptive variables were extracted and included: study characteristics, patient baseline demographic and clinical characteristics, and procedural characteristics (data supplement (III) and (IV)). Stents were categorized as open, closed, or hybrid cell according to the manufacturer's definition (data supplement (IV)).

Primary outcome: incidence of major adverse events (MAE, any stroke or death) during short-term (30-day) and long-term (1-year) follow-up. Secondary outcomes: other clinical outcomes such as transient ischemic attack and myocardial infarction, number of patients with any new MR-DWI lesion, occurrence of restenosis and stent fracture, and intraprocedural hypotension or bradycardia. Meta-analyses of which the pooled RR is shown in Figure 2 and Figure 3 are included as Supplementary figures in the data supplement (V).

### ***Quality assessment and statistical analysis***

Newcastle-Ottawa Scale (NOS) was used to assess quality of cohort studies<sup>19</sup> and Cochrane Collaboration's tool for RCTs.<sup>20</sup> Meta-analyses were performed using Review Manager (RevMan, version 5.3.5, Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using random effects models.  $\chi^2$  and  $I^2$  were calculated to determine (variance attributable to) heterogeneity.

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Funnel plots were assessed for publication bias. Meta-regression was subsequently performed to identify the effect of a single stent on observed 30-day MAE rates. A p-value below 0.05 was considered statistically significant. Unless otherwise specified, data is given in mean  $\pm$  standard deviation (SD).

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## RESULTS

### *Search results and comparability of studies*

The search yielded 2,654 articles, of which 326 were retrieved for more detailed evaluation (Figure 1). After exclusion, 68 studies using at least two of three stent designs were included, comprising 46,728 procedures (open cell: 51%, closed cell: 46%, hybrid: 3%) and 46,444 patients. Two studies were RCTs,<sup>21,22</sup> and 66 were cohort studies.<sup>3,7-9,12,13,15-17,23-79</sup>

Overall, baseline characteristics seemed to be fairly equally distributed between the different stent design groups. Patient age was similar in the groups (open cell: 70±3 years, closed cell: 70±3 years, hybrid: 70±2 years), as was the percentage of males (open cell: 69±11%, closed cell: 69±12%, hybrid: 66±17%). The percentage of symptomatic patients seemed equal in open and closed cell groups (open cell: 50±31%, closed cell: 55±30%), and lower in the hybrid group (41±31%). Nearly all patients were on double antiplatelet medication (open cell: 99±4%, closed cell: 100±2%, hybrid: 100±0%). Study characteristics and outcomes are listed in data supplement (III), procedural characteristics in data supplement (IV).

The methodological quality of included studies was moderate: for the cohort studies, 19/42 (45%) reached a NOS score of 5 or more out of 6, 18/24 (75%) reached a NOS score of 7 or more out of 9, and the two RCTs scored 5 and 6 of 7 (data supplement (VI)).

### *Clinical adverse events*

Figure 2 shows the pooled RRs of several meta-analyses performed on stent design in relation to adverse outcome after CAS. The risk of MAE occurring within 30 days of CAS was similar in patients treated with open vs closed cell stents, or with hybrid stents vs open cell stents or closed

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cell stents. This result persisted in long-term analyses, as the 1-year risk of MAE remained equal for open and closed cell stents.

Insufficient data were available on asymptomatic and symptomatic subgroups to perform separate analyses on all outcomes. However, the *ratio* of 30-day MAE rates was comparable for open and closed cell stents between studies including 100% symptomatic patients versus <100% symptomatic patients (test for subgroup differences:  $p=0.30$ ; Supplemental figure 1). Thus, symptom status did not seem to influence the *ratio* of the 30-day MAE rate between open and closed cell stents. We did, however, find that *total* 30-day MAE rates (irrespective of stent design) were higher in studies including only symptomatic patients (7.0% versus 3.1%; Supplemental figure 1).

Figure 3 shows a summary of the pooled RRs of the 30-day MAE rate for individual stents, separated in terms of open vs closed cell stents, or two stents with the same open or closed design. Use of Acculink stent was associated with a higher risk of MAE compared to Wallstent (RR: 1.51, 95% CI: 1.05-2.26,  $p=0.03$ ). The same was true for use of Precise stent versus Xact stent (RR: 1.55, 95% CI: 1.21-1.98,  $p<0.001$ ). Within the open or closed cell design group, no direct comparisons between specific stents were associated with MAE risk.

We examined in more detail 16 studies ( $n=8,250$  patients) reporting specifically on timing of 30-day clinical events (data supplement (VII)). Of the 30-day adverse events reported (~200 events), 41% occurred during the procedure, and 75% occurred during or on the day of the procedure. Detailed information on stent design was available in 75 of ~200 procedural events. Of these 75 procedural events, 68% occurred in patients treated with closed cell stents compared with 32% in open cell stents.

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### ***MR-DWI lesions***

Eight studies reported pre- and postprocedural MRI outcomes (n=930 patients). Three included only symptomatic patients,<sup>3,24,36</sup> while the remaining five included symptomatic and asymptomatic patients in percentages varying from 30% to 100%. Meta-analysis revealed a higher incidence of any new postprocedural MR-DWI lesion (ipsi- and contralateral) in patients treated with open cell stents compared with closed cell stents (RR: 1.25, 95% CI: 1.02-1.54, p=0.03; Figure 4). This reflects a 25% higher chance of new ischemic MR-DWI lesions after CAS performed with open cell stents.

Certain potential confounders need to be accounted for (Table 1). Visual evaluation revealed no relationship between the percentage of symptomatic patients and accompanying effect estimates, nor between timing of postprocedural MRI, mean patient age, or routine use of EPDs and occurrence of new MR-DWI lesions. None of the studies provided information on time delay from last cerebrovascular event until CAS. A description of new MR-DWI lesions in the contralateral hemisphere was provided in five studies,<sup>3,23,24,36,52</sup> showing contralateral localization in 13% to 37% of patients.

### ***Restenosis and stent fracture***

Incidences of restenosis or stent fracture after CAS were reported in 15 (n=6,567 patients) and four (n=597 patients) studies, respectively. Follow-up duration was heterogeneous, averaging 6 months,<sup>57</sup> 12 months,<sup>26,32,37,51,52,54,55,61</sup> more than 12 months (range 15-42 months),<sup>16,17,39,59,70,73</sup> or was unclear.<sup>29,48</sup> Restenosis occurred in 5.0% of patients treated with open cell stents versus 3.2% of patients treated with closed cell stents. Incidence of stent fracture was 3.9% in the open cell stent group and 3.8% in closed cell stent group. These event rates were not significantly different (Figure 2).

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Presence of stent fracture was assessed by plain radiography in all studies. However, the imaging method (e.g. ultrasonography and/or computed tomography or angiography), and criteria used for diagnosis of restenosis (required diameter reduction or peak systolic velocity) varied greatly or were not reported. Nonetheless, we do not expect this influenced the outcomes related to stent design within one study.

### ***Hemodynamic depression***

Seven studies investigated the incidence of hypotension during stenting (n=2,334 patients). The incidence of intraprocedural bradycardia was additionally noted in four studies (n=1,851 patients). Both meta-analyses revealed no differences between patients treated with open or closed cell stents (Figure 2).

Applied definitions of hypotension and bradycardia were highly heterogeneous, as were pre-dilation rates and use of atropine intravenously. Visual inspection could not identify a trend toward an effect of routine pre-dilation or use of atropine intravenously on occurrence of hemodynamic depression.

### ***Publication bias***

Visual evaluation of the funnel plots of the abovementioned meta-analyses (data supplement (VIII)) revealed overall symmetrical plots, suggesting little influence of publication bias.

## **DISCUSSION**

The results of this meta-analysis, based on 46,728 procedures, suggest that stent design does not affect short- or long-term MAE rates in patients undergoing CAS. However, meta-regression revealed that patients treated with Acculink or Precise stents had a higher risk for short-term MAE compared to patients treated with Wallstent or Xact stents, respectively. Furthermore, the use of open cell stents resulted in a significantly higher number of patients with any new postprocedural MR-DWI-detected lesion compared with closed cell stenting. No differences were observed in incidence of restenosis, stent fracture, or intraprocedural hemodynamic depression with respect to different stent designs. Unfortunately, the specified data precluded separate relevant analyses on asymptomatic versus symptomatic subgroups.

Given that carotid revascularization is performed to prevent future stroke, the occurrence of short- or long-term stroke or death is generally considered the primary and most relevant outcome measure for treatment efficacy and safety. A recent meta-analysis demonstrated comparable 30-day clinical adverse event rates between patients treated with open or closed cell stents.<sup>80</sup> Furthermore, a recently published individualized patient data meta-analysis on 1557 symptomatic patients showed lower risk of MAE in patients treated with closed cell stents.<sup>81</sup> Alongside the addition of radiological outcomes and provision of a comprehensive search strategy, current analyses confirmed these short-term clinical results in a larger patient sample, including symptomatic as well as asymptomatic patients, and revealed that long-term adverse event rates remained equal. In addition, our meta-regression shows that certain specific stents might provide better outcomes than others. Thus, the commonly used arbitrary division in open versus closed cell stent design might conceal differences in efficacy of specific stents. These

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differences might also be based on other stent characteristics than solely the free cell area, such as stent material.

Despite their theoretical advantages, hybrid stents did not seem to influence short-term MAE rates. However, relatively few data were available on adverse events in hybrid stents, also reflected in high heterogeneity in the analyses. Only 16 of 53 studies reported on timing of periprocedural adverse events. Of all periprocedural adverse events, 75% occurred on the day of the procedure. This might suggest an important role for procedural characteristics in the pathophysiology of periprocedural events and may warrant intensified neuromonitoring on the day of the procedure, allowing early detection and consequently early intervention.

The incidence of new MR-DWI lesions after carotid revascularization is clinically relevant as they are associated with increased risk of recurrent stroke<sup>82</sup> and possibly cognitive decline.<sup>83,84</sup>

When open cell stents were used, patients had a 25% higher chance of developing any new postprocedural ischemic MR-DWI lesion, compared with closed cell stenting. This did not result in different long-term clinical adverse event rates in our analysis, probably because of insufficient follow-up data.

Stent design is expected to influence only the occurrence of new ipsilateral MR-DWI lesions, as the contralateral lesions are more likely caused by guidewire and catheter manipulation.

Furthermore, other procedural characteristics such as use of EPD, differences in delivery devices, procedure time, and operator experience, are also suggested to influence incidence of new MR-DWI lesions. Therefore, results of our analysis have to be interpreted with caution. In addition, one large study with relatively homogenous study design demonstrated opposite outcomes, but could not be included due to insufficient data.<sup>42</sup> Nevertheless, this supports our hypothesis that procedural characteristics affect the development of new postprocedural MR-

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DWI lesions and warrants the evaluation of stent design, among other procedural characteristics, as potential marker for new ischemic MR-DWI lesions.

The occurrence of restenosis is associated with an increased stroke risk and is a major drawback of carotid revascularization.<sup>85</sup> We revealed that stent design did not affect restenosis rates.

However, follow-up duration was heterogeneous or not reported. Stent fracture is a potentially predictive marker of restenosis,<sup>26,39</sup> and closed cell stents are hypothesized to be more prone to fracture because of their inflexibility.<sup>15</sup> We demonstrated that closed cell stents did not predispose to higher incidences of stent fracture. However, both conclusions need to be interpreted with caution because of heterogeneous outcome definitions, cut-off values, and insufficient follow-up duration.

### ***Limitations***

Most included studies were of observational design, where stent allocation was left to the interventionalist. Selection bias may thus have influenced our results. Differences in procedure- and patient-related characteristics (e.g., symptomatology, vascular anatomy, EPD use, pre-/post-dilation) are therefore likely to have affected study outcomes. Only an individualized patient data meta-analysis (IPD-MA) would allow analysis of these characteristics in relation to outcomes. In addition, although symptomatic status negatively influences total 30-day complication risks (irrespective of stent design),<sup>72</sup> we hypothesize that symptomatic status has less influence on the *ratio* of 30-day adverse events occurring in different types of stents, which was shown in the non-significant test for subgroup differences. Furthermore, the lack of (universal) reporting of the interval between last cerebral event and revascularization might have influenced the risk of adverse events.<sup>86</sup> Despite aforementioned limitations, this meta-analysis provides the most

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comprehensive overview of studies reporting on CAS outcomes in relation to carotid stent design.

### ***Recommendations***

Decreasing the periprocedural incidence of clinical MAEs after CAS remains the real challenge. Recently introduced double-layer mesh stents show promising preliminary 30-day results<sup>87,88</sup> and could potentially reduce this periprocedural complication rate (although the effect on thrombogenicity needs to be determined). We hypothesize that a personalized approach in patient and device selection is likely to improve CAS outcomes. We believe that future experimental studies are needed for in-depth evaluation of stent effects in different carotid artery anatomies and that an IPD-MA is required to correct for risk factors, to ultimately select a specific stent for the individual patient. Finally, our results warrant future evaluations of carotid stent design in relation to occurrence of new MR-DWI lesions, the effect on cognitive changes and intensified follow-up after carotid interventions using MR-DWI. For such new studies a consensus on the applied imaging protocol is crucial to obtain for future individual patient data analyses.

### **CONCLUSION**

Carotid stent design does not seem to influence short- or long-term major clinical adverse event rates in patients with carotid artery stenosis who require endovascular revascularization.

However, the division in open and closed cell design might conceal true differences in single stent efficacy. Nevertheless, use of open cell stents resulted in a significantly higher number of MR-DWI-detected postprocedural new ischemic lesions compared with closed cell stenting.

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**CONFLICT OF INTEREST: none.**

**FUNDING: none.**

### **ACKNOWLEDGEMENTS**

We thank the collaborating authors of the ENDORSE study group for providing us with additional data, and critically reviewing the manuscript. We are grateful to other contributing authors for sharing their data.

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*Latacz 2017, Mammo 2017, Piazza 2018, Rasiova 2017, Simonte 2017, Tatli 2017*

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**TABLE**

**Table 1. Specification of studies included in the meta-analysis on new MR-DWI lesions.**

study	timing of MRI after CAS	symptomatic pts (%)	age (y)	time delay to CAS	MRI field strength (tesla)	use of EPD (%)	% of new lesions of contra-lateral origin	% of patients with any new lesion	
								open cell	closed cell
Bijuklic 2013 <sup>23</sup>	<24h	~28	69	U	1.5	97	25	26	26
Park 2013 <sup>21</sup>	<24h	~79	69	NR	3	95	NA*	51	27
Timaran 2011 <sup>22</sup>	<24h	~43	65	NR	1.5	100	NR	53	47
Blasel 2009 <sup>24</sup>	<48h	100	70	U	1.5	100	21	44	47
Du Mesnil de Rochemont 2005 <sup>36</sup>	<48h	100	70	NR	1.5	100	37	34	23
Leal 2012 <sup>52</sup>	<48h	69	68	NR	1.5	100	13	37	18
Gensicke 2013 <sup>3</sup>	<3d	100	71	U	1.5 or 3	40	23	49	39
Nii 2011 <sup>58</sup>	<5d	~60	76	NR	NR	100	NR	35	27

Studies reported on the number of patients who had  $\geq 1$  new ischemic MR-DWI lesion after CAS, and are sorted in order of ascending number of days between CAS and postprocedural MR-DWI.

Footnotes: \*Only ipsilateral lesions were included as an outcome measure.

Abbreviations: d=days; DWI=diffusion weighted imaging; EPD=embolic protection device;

h=hours; MRI=magnetic resonance imaging; NA=not applicable; NR=not reported; pts=patients;

U=unavailable (after contact with author); y=years.

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## FIGURE LEGENDS

**Figure 1. Flowchart showing selection of articles for review.**

**Figure 2. Overview of pooled RRs of 11 meta-analyses performed on stent design in relation to adverse outcome after CAS.**

**Figure 3. Overview of pooled RRs of the 30-day MAE rate for individual stents.** Stent comparisons are separated in terms of open vs closed cell stents, or two stents with the same open or closed design.

**Figure 4. Difference in number of patients with any new MR-DWI detected ischemic brain lesion, between patients treated with open or closed cell stents.** Studies are listed in order of declining percentage of symptomatic patients. Risk ratios are shown with 95% confidence intervals. The diamond in the forest plot indicates the total risk ratio and confidence interval; pts = patients; CI = confidence interval; MR-DWI: magnetic resonance-diffusion weighted imaging; Sx = symptomatic.