Influence of stent design and use of protection devices on outcome of carotid artery stenting – a pooled analysis of individual patient data

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Keywords: Carotid artery stenting; stent design; protection system; stent optimization; plaque

ABSTRACT

Background and Purpose: Carotid artery stenting is an alternative to endarterectomy for treatment of symptomatic carotid stenosis but was associated with a higher risk of procedural stroke or death in randomized controlled trials (RCTs). Technical aspects of treatment may have partly explained these results. The purpose of this analysis was to investigate the influence of technical aspects such as stent design or the use of protection devices, as well as clinical variables, on procedural risk.

Methods: We pooled data of 1557 individual patients receiving stent treatment in three large RCTs comparing stenting versus endarterectomy for symptomatic carotid stenosis. The primary outcome event was any procedural stroke or death occurring within 30 days after stenting.

Results: Procedural stroke or death occurred significantly more often with use of open-cell stents (61/595 patients, 10.3%) than with use of closed-cell stents (58/962 patients, 6.0%; RR 1.76; 95% CI 1.23–2.52; p=0.002). Procedural stroke or death occurred in 76/950 patients (8.0%) treated with protection devices (predominantly distal filters) and in 43/607 (7.1%) treated without protection devices (RR 1.10; 0.71–1.70; p=0.67). Clinical variables predicting the primary outcome event were age, severity of the qualifying event, history of stroke and level of disability at baseline. The effect of stent design remained similar after adjustment for these variables.

Conclusions: In symptomatic carotid stenosis, the use of stents with a closed-cell design is independently associated with a lower risk of procedural stroke or death compared with open-cell stents. Filter-type protection devices do not appear to reduce procedural risk.

INTRODUCTION

Carotid artery stenting and carotid endarterectomy are equally effective in preventing recurrent stroke in patients with symptomatic carotid stenosis, but stenting carries a higher risk of procedure-related stroke than surgery. [1–4] Stenting is a newer procedure and less standardized than endarterectomy. A wide range of endovascular devices are available, and interventionalists use different technical approaches, with or without endovascular protection devices, using stents of different cell design, and either with or without balloon-dilatation of the stenosis before or after stent placement, which may have contributed to the higher procedural risk of stenting in clinical trials. We undertook a pooled analysis of data from individual patients receiving stent treatment in the EVA-3S, SPACE and ICSS trials to investigate the influence of these technical aspects on the risk of procedural stroke or death, also taking into account clinical and demographic risk factors.

METHODS

Trials

The pooled analysis of EVA-3S (NCT 00190398), SPACE (ISRCTN 57874028), and ICSS (ISRCTN 25337470) was prospectively agreed at the design stage of the trials.[5 6] All three trials were randomized, open clinical trials with blinded outcome adjudication. Eligible patients had moderate or severe carotid stenosis (≥50% according to the NASCET method),[7] associated with a recent, non-disabling ocular or cerebral ischemic event, and were considered equally suited to undergo stenting or endarterectomy. Interventionalists could choose the type of the stent and used pre- and post-dilatation by balloon angioplasty of the target vessel at their discretion, as long as all devices carried a CE (Conformité Européene) mark. The use of approved cerebral protection devices was optional in SPACE and recommended in ICSS whenever the operator thought one could safely be deployed. Protection devices were initially

optional in EVA-3S, but then made mandatory after an interim analysis revealed a higher risk of procedural stroke with unprotected stenting compared with protected stenting.[8] CREST allowed the use of only one type of stent and protection device and thus was not included in this analysis.

Outcome events and variables

The analysis plan was defined before the data were assembled and analyzed (see data supplement). We included only patients who were randomized to stenting, in whom a stent was deployed across the stenosis, and the type of stent and protection device use was known. The primary outcome event was any procedural stroke or death (occurring from initiation of stenting until 30 days thereafter).

The primary analysis compared open-cell versus closed-cell stent design and protected versus unprotected stenting. Stents were classified based on the manufacturers' product information into closed-cell design, if the open area between stent-struts was ≤ 5.0 mm^2 and all stent-struts were interconnected; or open-cell design, if the open area was >5.0 mm^2 without interconnection between all stent struts. Protected stenting included any type of protection device (filter or balloon based systems and systems exerting reversal of blood flow). Secondary analyses included dilation of the stenosis with an inflatable balloon before or after stent insertion (pre-dilatation and post-dilatation) and single versus dual procedural antiplatelet therapy.

In addition, we studied the association between occurrence of the primary outcome and the following clinical and demographic variables: age at the time of randomization and sex; history of hypertension, diabetes, hypercholesterolemia, smoking (either current or past), coronary heart disease, and peripheral artery disease; systolic blood pressure at randomization; type of the qualifying event (the most recent ipsilateral ischemic event before

randomization: retinal ischemia, TIA, or ischemic stroke); history of any stroke before the most recent ipsilateral ischemic event; functional disability at randomization measured by the modified Rankin Scale; side (left/right) and degree of ipsilateral carotid stenosis (moderate, 50-69%; or severe, 70-99%); and contralateral severe carotid stenosis or occlusion.

Statistical analysis

Individual patient data were pooled and analyzed with binomial regression models with fixed-effects for source trial. The log-link was used to obtain an overall unadjusted risk ratio (RR) and 95% confidence intervals (CI) of procedural stroke or death. P-values were calculated with the likelihood ratio test. Potential heterogeneity of effect measures in the contributing trials was examined by testing for interactions with source trial in the regression model. Associations between technical variables and the primary outcome were first assessed on a univariable level providing unadjusted RR. Secondly, RR were adjusted for the three clinical or demographic variables that changed the unadjusted risk ratio the most. In a first post-hoc analysis, the annual number of stent procedures performed by the treating interventionalist categorized in terciles was added into the multivariable model as a surrogate of operator experience, as this was shown to be inversely associated with the risk of procedural stroke or death in a prior study by the CSTC[9]. Differences between the effects of protection devices in older versus younger patients and in patients treated with open-cell stents versus those treated with closed-cell stents were investigated by testing for statistical interaction.

To rule out potential confounding of the observed effect of stent design by factors not measured in this analysis (such as vascular anatomy and morphology of the atherosclerotic plaque), we performed a second post-hoc analysis, in which the primary outcome was compared between patients randomized to stenting and patients randomized to endarterectomy in the contributing trials by study center, according to the frequency of closed-cell stent use in the stenting arm at the centers. Centers were classified into three

groups: those using closed-cell stents in >80% of patients, those using closed-cell stents in 20-80% of patients, and those using closed-cell stents in <20% of patients. The modification of the primary outcome risk ratio between stenting and endarterectomy by the frequency of closed-cell stent use was then tested via statistical interaction. Statistical significance was defined as a p-value <0.1 for interaction tests and p<0.05 for all other tests.

The trials contributing data to this analysis were reviewed and approved by the responsible national, regional, or institutional ethics committees.

RESULTS

1725 patients were randomly assigned to stent treatment in the three contributing trials. The present analysis included 1557 patients who received stent treatment and in whom information on stent type and use of protection devices was available (figure 1). Patients' baseline characteristics are provided in table 1.

In total, 962 procedures (61.8%) were performed with three different closed-cell stents and 595 procedures (38.2%) with seven different open-cell stents (supplementary table 1). Procedural stroke or death occurred in 61 of 595 patients in the group treated with open-cell stents (10.3%) compared with 58 of 962 patients treated with closed-cell design stents (6.0%, RR 1.76; 95% CI 1.23–2.52; p=0.002; figure 2). The effect of stent design was consistent in all three trials, without evidence for heterogeneity (interaction P-value 0.94; figure 3).

950 patients (61.0%) were treated with a protection device. The primary outcome event occurred in 76 patients (8.0%) treated with protected stenting and in 43 patients (7.1%) treated with unprotected stenting (RR 1.10; 0.71-1.70; p=0.67; figure 2). There was evidence for significant heterogeneity among the contributing trials; the comparison favored protected stenting in EVA-3S, and unprotected stenting in SPACE and ICSS (interaction P-value 0.036; supplementary figure 1). There was no significant difference in the effect of protection

devices between patients younger or older than 70 years, or between patients treated with open-cell or closed-cell stents (supplementary figure 2). The use of pre-dilatation or post-dilatation and whether or not patients received double antiplatelet therapy for the procedure did not alter procedural risk (figure 2). Of note, only a small proportion of patients (n=171, 11.2%) did not receive double antiplatelet therapy.

We observed a significant increase in the procedural stroke or death rate with increasing age (RR 1.53, 1.25-1.87, p<0.001, per 10 year increase); among patients with increasing severity of the qualifying event (retinal ischemia < TIA < stroke; p=0.004 for trend); in patients with a history of stroke prior to the qualifying event (RR 1.83, 1.13-2.97, p=0.02; figure 4); and with increasing level of functional disability at randomization measured by the modified Rankin Score (p=0.03 for trend). Patients who smoked at randomization or in the past were at lower risk of the primary outcome event (RR 0.63, 0.44-0.92, p=0.02). The effect of open versus closed-cell stents remained essentially the same after adjustment for age and type of qualifying event (n=1548 patients, RR 1.77, 1.24-2.51, p=0.002) as well as after additional adjustment for history of stroke before the qualifying event (which was unavailable in the SPACE trial; n=975 patients, RR 1.74; 95% CI 1.12–2.70; p=0.012). In our first post-hoc analysis, the effect of stent design also remained essentially unchanged after adjustment for the tercile of the annual number of in-trial stent procedures performed by the treating interventionalist, in addition to age and type of qualifying event (n=1450 patients, RR 1.85; 95% CI 1.29-2.66, p=0.001), and also in addition to age, type of qualifying event, and history of prior stroke (n=877 patients, RR 1.82; 95% CI 1.13-2.93, p=0.013).

In our second post-hoc analysis, the RR of procedural stroke or death in patients randomized to stenting versus patients randomized to endarterectomy continuously increased with decreasing use of closed-cell stents at the trial centers (>80% closed-cell stents: RR 1.31, 95%

CI 0.84-2.03; 20-80% closed-cell stents: 1.93, 1.25-3.00; <20% closed-cell stents: 3.24, 1.32-7.69; p=0.06 for interaction by trend; supplementary table 2).

DISCUSSION

Our study yielded the following main findings: first, procedural stroke or death occurred significantly less often if patients were treated with closed-cell stents (6.0%) compared with open-cell stents (10.3%). Second, the use of endovascular, mostly filter-type protection devices did not reduce these events. Third, clinical variables associated with procedural stroke or death were increasing age, severity of the qualifying event, history of prior stroke, and increasing level of functional disability at baseline. The effect of stent design remained essentially the same after adjustment for these factors, as well as for operator experience.

Our study had the following strengths; first, patients in all three contributing trials were followed by clinicians who were not involved in delivering treatment by stenting or endarterectomy, and outcome events were centrally adjudicated blinded to treatment allocation, thus minimizing potential ascertainment bias. Second, procedure-related technical variables and outcome events were defined before the data were assembled and analyzed. Third, the availability of individual patient data from three trials allowed investigating the independent impact of technical aspects of carotid artery stenting on procedural risk with greater statistical power than had been possible at the level of single studies, as well as to check for consistency across trials.

The main result of this analysis was that the use of closed-cell stents was independently associated with a lower risk of procedural stroke or death compared with open-cell stents. This observation had already been made in a retrospective study in 2006, where the authors reported a procedural stroke or death rate of 2.2% for closed-cell and 7.0% for open-cell design stents.[10] In the SPACE trial the risk of procedural stroke or death was 5.6% in patients

treated with closed-cell stents and with 11.0% in patients treated with open-cell stents.[11] In ICSS, the procedural stroke or death risks were 5.1% and 9.5% with closed-cell and open-cell stents, respectively.[12] Our findings provide the most robust evidence to date that the risk of procedural stroke or death depends on stent design, by consistently demonstrating this effect in all three contributing trials and independently of other patient characteristics. Our observed procedural 6% risk of stroke or death with closed cell stents is only slightly above the 4.4% risk in patients receiving endarterectomy in the same trials.[6]

Stroke attributable to atherosclerotic carotid disease usually occurs through embolization of plaque debris or locally formed thrombus following plaque rupture. The primary aim of carotid stenting should therefore be to stabilize the plaque by sealing off its surface. The tight meshes of closed-cell stents might be better suited to achieve this aim. With open-cell stents, plaque debris or appositional thrombus might escape into the blood stream, causing cerebral embolism during or shortly after the procedure. While speculative, the proposed mechanism of protection against embolism through tight stent architecture is supported by favorable results of new hybrid stent designs consisting of open cells covered with a very tight mesh, e.g. the CGuard Stent®[13].

The question whether intraluminal protection devices can reduce the risk of procedural thromboembolism during stenting is a matter of ongoing controversy. The results of our analysis showed no significant difference in the occurrence of procedural stroke or death whether CAS was performed with or without the use of a protection device. However, there was evidence of heterogeneity among the contributing trials, likely explained by the different policies used. The neutral effect of protection devices was independent of patient age and stent design. As most devices used in the contributing trials (87.3%) were distal filters, we cannot draw any conclusions as to the efficacy of other types of protection devices, for example devices exerting arrest or reversal of blood flow.[14–17]

In line with the findings of previous research, age was the strongest clinical predictor of the primary outcome event in the present analysis.[12,18,19] Age increases the procedure-related stroke risk in stenting, but not in endarterectomy.[6] In contrast, age has no significant effect on long-term stroke risk following stenting or endarterectomy.[20] Changes in vascular anatomy or plaque composition might render elderly patients more susceptible to thromboembolic complications during CAS; increased tortuosity of supra-aortic vessels and the target artery has been described in elderly patients.[21] At the same time, difficult vascular anatomy might lead some interventionalists to use open-cell stents which are more flexible and easier to insert. Importantly, our study showed no evidence for a confounding effect of age, as the effect of stent design on the risk of procedural stroke or death remained essentially the same after adjustment for age.

Although life-time case numbers of individual interventionalists were unavailable in the pooled CSTC data set, we previously showed that the annual in-trial volume of stent procedures (as a potential surrogate of operator experience) was inversely associated with the risk of procedural stroke or death in stenting.[9] At the same time, experience may also influence the choice of stent design. Precise implantation of closed-cell stents is more difficult because of their nature to shorten during delivery. Since inexperienced interventionalists may favor the use of open-cell stents, the effect of experience may have theoretically confounded our data. However, our first post-hoc analysis showed that the risk increase for procedural stroke or death associated with use of open-cell stents did not change after adjustment for annual in-trial volume of procedures.

Likewise, open-cell carotid stents may be preferred by some interventionalists in patients with unfavorable vascular anatomy or plaque morphology, which represented a potential source of bias for our analysis. For this reason, we performed a second post-hoc analysis by center, comparing the risk of procedural stroke or death between patients treated by stenting with

patients treated by endarterectomy as a randomized comparison group. This demonstrated a steady increase in excess events associated with stenting compared with endarterectomy the less often closed-cell stents were used. These results argue against confounding as it is unlikely that the distribution of vascular anatomy or lesion morphology differed between trial centers.

We are aware of several limitations of our study. Most importantly, the choice of stent type and use of a protection device was not subject to randomization. Neither data on the anatomy of the supra-aortic vessels nor the morphology of the stenotic plaque were systematically assessed. Thus, despite our post-hoc analysis by center, a residual risk of confounding remains. Importantly, the peri-procedural stroke or death rate in the stent group of the CREST trial was lower than in the trials included in the present study, even though an open-cell stent was used. However, the same was true for the endarterectomy group of the CREST trial. Hence, it is likely that the CREST trial also differed from the trials included here in factors unrelated to technical aspects of the procedure, e.g. in the selection of centers, operators and patients. Furthermore, the analysis of the effect of protection devices was limited, first, by significant heterogeneity between trials and second, by the fact that in the vast majority of patients in whom protection was applied, distal filters were used. Thus, we cannot draw any conclusions about the effect of other types of protection devices. Finally, the mechanisms which we propose might explain the lower peri-procedural risk with use of closed-cell stents are speculative and warrant further research. Despite these limitations, the present study provides the most robust evidence to date that closed-cell carotid stents are superior to open-cell stents in terms of procedural safety. These findings bear relevance for ongoing and future clinical trials of carotid artery stenting as well as for the development of safer carotid stents by the manufacturers.

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Competing Interests Statement

We declare that we have no conflicts of interest.

Contributorship Statement

FW wrote the first draft of the report and was supervised by OJ and LHB. FW, OJ and ELT designed the statistical analysis plan. ELT and JD undertook the statistical analyses. JLM, PAR, ELT, and LHB extracted patients' data from contributing trials. All the authors listed in the writing committee made substantial contributions to conception and design of the study, acquisition of data, or analysis and interpretation of data; and also contributed to drafting the report or revising it critically for important intellectual content. JLM, OJ, and LHB

contributed equally to the report. OJ and LHB had the final responsibility for the analyses and the content of the report.

Data Sharing Statement

N/A

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Figure Legends:

Figure 1. Patient flow diagram.

1557 of 1725 randomised patients could be included in the present analysis.

Figure 2. Influence of technical parameters on risk of procedural stroke or death.

Patients with deployed stents and available data on stent type and protection device use are included. Crude risks (number of events divided by number of patients) and binomial regression estimates of risk ratios and 95% confidence intervals (CI) of any stroke or death within 30 days of treatment are provided for each technical parameter of interest. All models are adjusted for source trial. Missing data were: pre-dilatation (n=1 patient), post-dilatation (n=246), antiplatelet therapy (n=29).

Figure 3. Effect of open-cell versus closed-cell stent design on risk of procedural stroke or death in contributing trials.

Percentages are number of events divided by number of patients. Squares and horizontal bars represent within-trial treatment risk ratios and 95% CIs, respectively, with closed-cell stenting as the reference group, on a log scale. The size of squares represents study weight. The diamond represents the pooled risk ratio and 95% CI, adjusted for source trial. In the investigation of heterogeneity, the interaction p value represents the significance of the interaction between source trial and treatment effect in the regression model (likelihood ratio test); a significant p value suggests heterogeneity. CAS=carotid stenting. EVA-3S=Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid

Stenosis. SPACE=Stent-Protected Angioplasty versus Carotid Endarterectomy. ICSS=International Carotid Stenting Study.

Figure 4. Influence of clinical and demographic variables on risk of procedural death or stroke.

Patients with deployed stents and available data on stent type and protection device and available clinical data are included. Crude risks (number of events divided by number of patients) and binomial regression estimates of relative risks (RR) and 95% confidence intervals (CI) of any stroke or death within 30 days of treatment are provided for each variable of interest. All models are adjusted for source trial. *Data not available in the SPACE trial. †P-value for trend across categories.

Tables:

Table 1. Patient characteristics

	Total (n=1557)
Age (years; mean, SD)	69.1 (±8.9)
Male sex	1111 (71)
History of hypertension	1113 (72)
Systolic blood pressure at randomisation (mm Hg; mean, SD)	145 (±21.1)
History of diabetes	371 (24)
History of hypercholesterolaemia*	599 (61)
History of smoking	996 (64)
History or coronary heart disease	362 (23)
History of peripheral artery disease*	161 (17)
Stenosis on the left side	823 (53)
Ipsilateral degree of stenosis	
Moderate (50-69%)	307 (20)
Severe (70-99%)	1250 (80)
Contralateral severe carotid stenosis or occlusion	216 (15)
Qualifying event	
Amaurosis fugax or retinal stroke	281 (18)
Transient ischemic attack	537 (35)
Hemispheric stroke	730 (47)
History of stroke prior to qualifying event*	162 (16)
Modified Rankin score at baseline†	
0	762 (49)
1	421 (27)
2	258 (17)
3	88 (6)
4 + 5	14 (1)

Legend: Patients with deployed stents and available data on stent type and protection device use are included. Data are n/N (%), unless otherwise indicated. Percentages exclude missing data (N=number of patients for whom data were available). *Data were not gathered in the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial. †Modified Rankin scores at baseline might indicate non-stroke impairments; protocols of contributing trials excluded patients with disabling strokes. Missing data were: history of hypertension, history of diabetes, history of smoking, history of coronary heart disease, type of qualifying event (n=9 patients); modified Rankin score at baseline (n=14); systolic blood pressure at baseline

(n=43); contralateral severe carotid stenosis or occlusion (n=134); history of hypercholesterolaemia and history of peripheral artery disease (n=582); history of stroke prior to qualifying event (n=573).

Figures

Figure 1. Patient flow diagram.

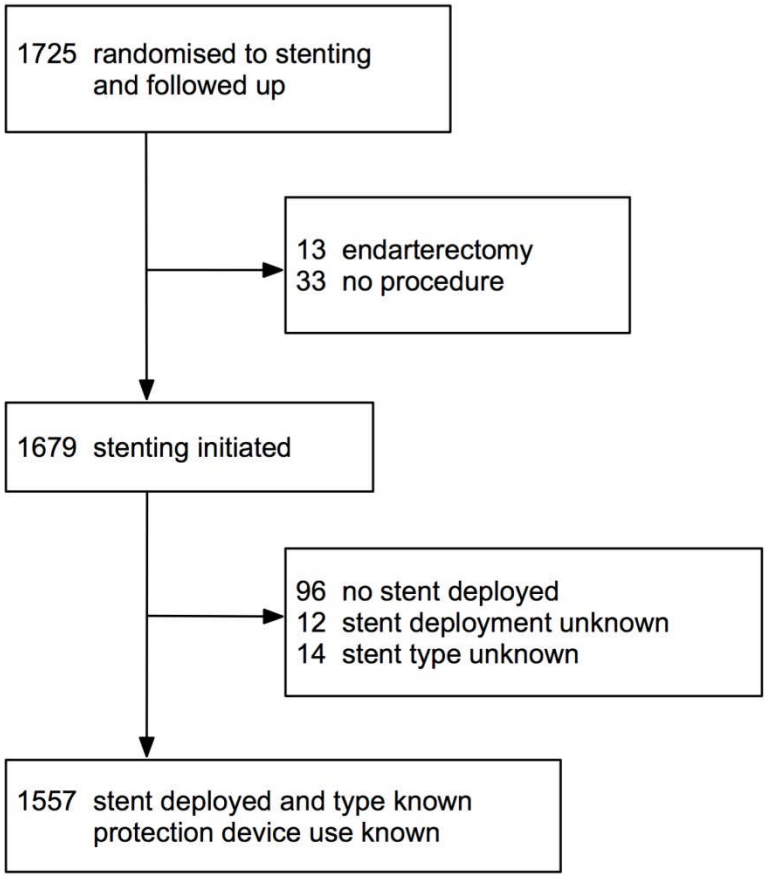

Figure 2. Influence of technical parameters on risk of procedural stroke or death.

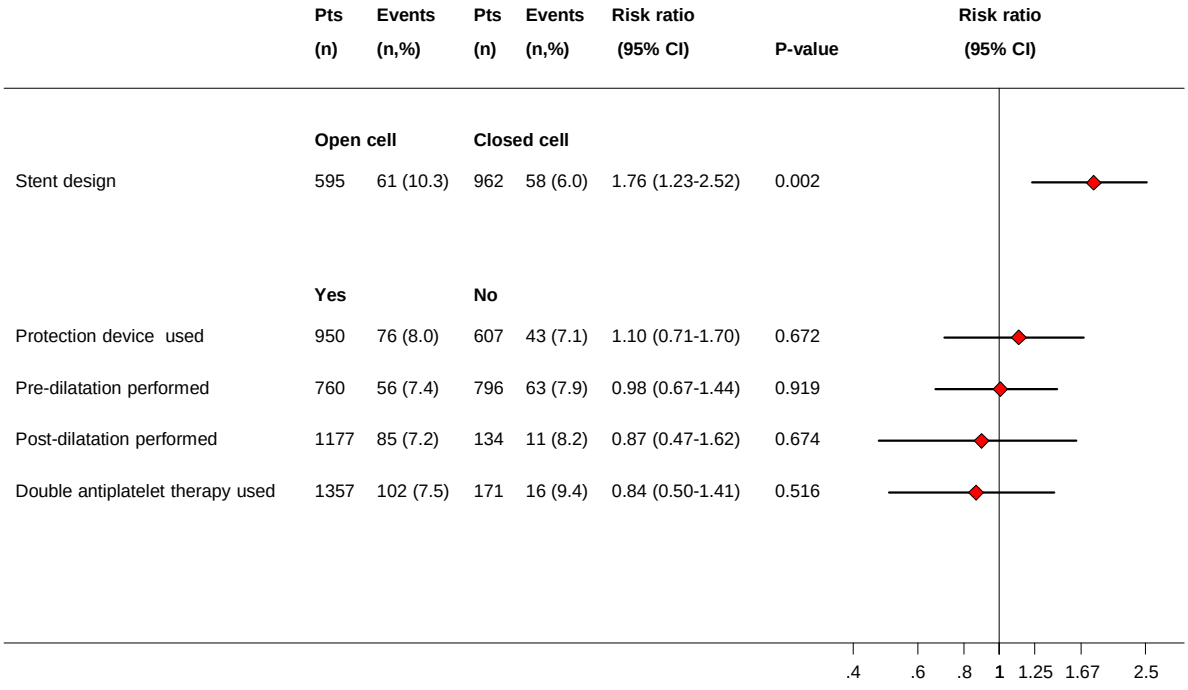

Figure 3. Effect of open-cell versus closed-cell stent design on risk of procedural stroke or death in contributing trials.

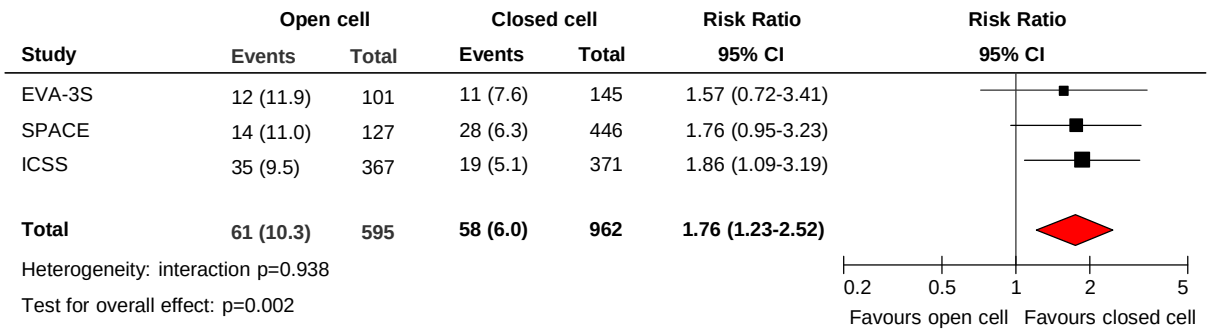

Figure 4. Influence of clinical and demographic variables on risk of procedural stroke or death.