Original article

Long-term restenosis rate after carotid endarterectomy: comparison of three surgical techniques and intraoperative shunt usage

Short title: Restenosis rate after carotid endarterectomy

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WHAT THIS PAPER ADDS

This study compares the long-term restenosis rate within a large clinical trial in patients undergoing conventional carotid endarterectomy with primary closure, patch angioplasty or eversion endarterectomy, and examines the effect of using an interoperative shunt. The study highlights the increased risk of restenosis after primary closure compared to patch angioplasty. The use of shunts did not have any effect on the risk of restenosis. Despite the increased risk of restenosis, however, primary closure after carotid endarterectomy was not associated with an increase in the long-term risk of ipsilateral stroke after the procedure.

ABSTRACT

Objective: Closure of the artery during carotid endarterectomy (CEA) can be done with or without patch, or performed with the eversion technique, while the use of intraoperative shunts is optional. The influence of these techniques on subsequent restenosis is uncertain. We compared long-term carotid restenosis rates and risk of future ipsilateral stroke in these techniques.

Methods: Patients who underwent CEA in the International Carotid Stenting Study were divided into patch angioplasty, primary closure, or eversion endarterectomy. Intraoperative shunt usage was reported. Carotid duplex ultrasound was performed at each follow-up. Primary outcomes were restenosis of ≥50% and ≥70%, and ipsilateral stroke after the procedure to the end of follow-up.

Results: In total, 790 CEA patients had restenosis data at 1- and 5-years. 511 (64.7%) had patch angioplasty, 232 (29.4%) primary closure, and 47 (5.9%) eversion endarterectomy. The cumulative incidence of ≥50% restenosis at 1-year was respectively 18.9%, 26.1%, 17.7% and at 5-years respectively 25.9%, 37.2%, and 30.0%. There was no difference in risk between the eversion and patch angioplasty group (hazard ratio [HR] 0.90, 95% CI 0.45–1.81, p=.77). Primary closure had a higher risk of restenosis than patch angioplasty (HR 1.45, 95% CI 1.06–1.98, p=.19). The cumulative incidence of ≥70% restenosis did not differ between primary closure and patch angioplasty (12.1% vs. 7.1%, HR 1.59, 95% CI 0.88–2.89, p=.124) or

between patch angioplasty and eversion endarterectomy (4.7%, HR 0.45, 95% CI 0.06–3.35, p=.438). There was no effect of shunt usage on the cumulative incidence of restenosis. Post-procedural ipsilateral stroke was not more common in either of the surgical techniques or shunt usage.

Conclusions: Restenosis was more common after primary closure than conventionally with a patch closure. Shunt usage had no effect on restenosis. Patch closure is the treatment of choice to avoid restenosis.

Key words: carotid stenosis, stroke, restenosis, carotid endarterectomy

INTRODUCTION

Background and rationale

Carotid endarterectomy (CEA) is known to reduce the risk of stroke in patients with symptomatic carotid stenosis.[1] The use of perioperative neuro-monitoring and improved perioperative blood pressure control have led to lower postoperative stroke and mortality rates to less than 2%.[2-4] Rates of carotid restenosis following endarterectomy vary from 2 to 34%.[5-7] Different factors have been associated with restenosis including female sex and smoking, whilst the use of statins and dual antiplatelet therapy post-operatively, and possibly the presence of calcification in the carotid plaque pre-operatively, reduces restenosis.[8-12]

The surgical procedure itself has been greatly discussed with regards to the closure technique whether: primary closure, the use of patch angioplasty or eversion endarterectomy, as well as the use of an intravascular shunt.[13] Endarterectomy with patch angioplasty reduces the risk of occlusion and restenosis compared to primary closure.[13-15] Data on restenosis in eversion endarterectomy are contradictory. Some studies reported no difference in rates of restenosis,[16,17] whilst others reported less restenosis in eversion endarterectomy.[18-20] One large

study, consisting of 9 897 eversion endarterectomies over 20 years, reported an incidence of ≥50% restenosis of 4.3%.[21]

Data on intraoperative shunt usage on restenosis are limited. Use of a shunt involves more manipulation of the vessel and use of clamps that may injury the vessel wall and lead to neo-intimal hyperplasia and early restenosis.[22] The literature does not support the use of routine shunting or selective shunting in CEA due to the lack of reliable evidence.[23] Current guidelines, therefore, recommend that the choice of shunting should be left to the decision of the operating surgeon.[1]

Objectives

We aim to determine the cumulative incidence of restenosis and ipsilateral stroke after CEA with patch angioplasty, primary closure without patch, or eversion endarterectomy in the International Carotid Stenting Study (ICSS). The effect of an intraoperative shunt on restenosis was also investigated.

MATERIALS AND METHODS

This study is reported as per the Strengthening the Reporting of Observational Studied in Epidemiology (STROBE) recommendations.[24]

Study design

The ICSS was a randomised clinical trial comparing CEA and carotid artery stenting in patients with symptomatic atherosclerotic carotid stenosis. The full details on the study have been described previously.[25,26] The ICSS was approved by the Northwest Multicentre Research Ethics Committee in the United Kingdom and all participating centres obtained

local ethics approval. ICSS is registered with the ISRCTN registry with the number ISRCTN25337470.

Setting

1 713 patients were recruited from May 2001 to October 2008. Of those, 858 were randomly enrolled to CEA and 855 to carotid artery stenting. We analysed data with follow-up of the patients up to 5 years after randomisation. Patients were seen at 30 days after CEA, 6 months after randomisation and then annually by a neurologist or a physician interested in stroke. The number of patients for analysis were categorised into three groups: CEA with patch angioplasty, CEA with primary closure, or eversion endarterectomy. Operative technique, shunting practices, the use of general or local anaesthetics and type of patch used were based on the surgeon's personal preference or the standard at the individual centre and were not randomised. Shunt usage and shunt type were noted for the procedures.

Participants

Patients with carotid stenosis ≥50%, measured according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria were eligible.[27] All patients provided written informed consent prior to randomisation. We selected the patients who underwent CEA as the randomly assigned procedure for the current study. Patients who had a cross-over carotid stenting, whose type of CEA or shunt type was unknown, and those without sufficient follow-up duplex ultrasound to analyse restenosis rates, were excluded. In patients in whom procedural data on CEA were previously missing, additional data were collected retrospectively on the surgical technique if available. All patients received best medical treatment including antiplatelet therapy or anticoagulation when indicated and optimal control of vascular risk factors such as hypertension, smoking and hyperlipidaemia before CEA and

throughout the period of follow-up. All patients were advised regarding their risk factor control at every visit and recommendations were made to their general practitioner regarding target levels of risk factors, i.e. target blood pressure levels and serum cholesterol levels. Smoking cessation was advised throughout the study if applicable. There were no specific exclusion criteria for patients who were non-compliant in the study.

Variables

The primary outcome of this study was carotid restenosis on carotid duplex ultrasound post-procedure within 5-years follow-up. The degree of carotid stenosis was determined with velocity criteria equivalent to NASCET angiography measures prescribed previously, and included the peak systolic velocity of internal carotid artery, the end diastolic velocity of internal carotid artery and the peak systolic velocity of common carotid artery.[26,27] The assessor was unware of the procedure technique or shunt usage and the dates of ultrasound follow-up. Restenosis was defined in two categories as any residual or recurrent stenosis of at least 50% or at least 70%, including occlusion, of the ipsilateral carotid artery during follow-up. Restenosis was not distinguished from residual restenosis after intervention because immediate post-procedure ultrasound or angiography findings were not collected. Post-procedural stroke was defined as stroke of any severity occurring more than 30 days after CEA, and was analysed according to whether the stroke involved the territory supplied by the treated artery or another vascular territory. Stroke was defined as an acute developing clinical syndrome with disturbance of focal neurological function with symptoms lasting more than 24 hours or leading to early death, with no apparent non-vascular cause.

Data sources

The protocol specified carotid duplex ultrasound to be done at each follow-up visit. Peak systolic velocities in the common carotid artery and the internal carotid artery, and the end diastolic velocity in the internal carotid artery on the treated carotid artery and on the contralateral side were recorded for all patients.

Statistical analysis

The present analysis included patients in whom CEA was performed and at least one post-procedural DUS follow-up examination was performed and available for analysis. Patients were censored at the time of any further ipsilateral revascularisation procedure during follow-up or at the time of their last DUS. Censoring was assumed to be 'non-informative'. Because the restenosis outcome was interval-censored, i.e. restenosis was only known to have occurred at some point between the previous ultrasound scan and the one showing restenosis, time to restenosis was analysed using a generalised non-linear model, which assumes proportional hazards and whose treatment effect parameter estimate can be interpreted as a log hazard ratio (HR).[28,29] The treatment effect p-value was calculated using a likelihood ratio test. HRs for restenosis were calculated with and without adjustment for patient baseline characteristics independently associated with restenosis in the ICSS.[30] For the models on ≥50% restenosis, the following predictors were adjusted for: the degree of stenosis in the contralateral artery, non-insulin dependent diabetes, sex, cholesterol, blood pressure, smoking status and history of angina. For the models on ≥70% restenosis, the follow predictors were adjusted for: the degree of stenosis in contralateral artery and non-insulin dependent diabetes. The cumulative incidence of restenosis at one and five years after treatment was calculated using the Kaplan Meier method, with the time to restenosis set to the mid-point between the previous normal scan and the one showing restenosis. Kaplan Meier plots of time to restenosis were

truncated at 7 years because the number of patients in whom DUS follow-up was continued beyond this time point was relatively small. We additionally investigated the association of procedure type with post-procedural stroke in any territory and with post-procedural ipsilateral stroke using Cox proportional hazards models. For these models, we censored at the time of the first of any of the following: stroke, death or loss to follow-up or further ipsilateral revascularisation. All reported p-values are two-sided with a value <.05 considered to indicate statistical significance.

RESULTS

Participants

A total of 1 713 patients were enrolled in ICSS with 858 patients randomised to CEA. After excluding patients who did not have complete data regarding the procedure, shunt usage or restenosis data, 790 patients were included for analyses (Figure 1). Of these, 511 (64.7%) had patch angioplasty, 232 (29.4%) primary closure, and 47 (5.9%) eversion endarterectomy.

Descriptive data

Comparing the three types of endarterectomy procedures, there were no differences in vascular risk factors at baseline characteristics, except for the presence of angina in the last 6 months being more common in the eversion group (Table 1). There was no difference in the degree of stenosis of the treated carotid plaque according to procedure type. The individuals were followed up annually with duplex ultrasound for a median of 4.0 years (inter-quartile range, 2.3–5.0). Length of follow-up did not differ between surgical techniques or the groups with and without shunt usage.

Main results

Carotid endarterectomy closure type

At the five year follow up, 124 (cumulative incidence 25.9%) had restenosis of ≥50% in the patch angioplasty group, 80 (cumulative incidence 37.2%) in the primary closure group, and 11 (cumulative incidence 30.0%) in the eversion group (Table 2). The risk of ≥50% restenosis was greater after primary closure than after patch angioplasty (26.1% vs. 18.9% at 1-year, 37.2% vs. 25.9% at 5-year, HR 1.45, 95% CI 1.06–1.98, p=.019) (Figure 2). Comparing eversion endarterectomy with patch angioplasty, there was no difference in the cumulative incidence of restenosis (17.7% vs 18.9% at 1 year, 30.0% vs. 25.9% at 5-year, HR 0.90, 95% CI 0.45–1.81, p=.774). There were no differences between the groups when examining restenosis ≥70% with cumulative incidence at 5-year of 7.1%, 12.1%, and 4.7%, in the patch angioplasty, primary closure, and eversion endarterectomy respectively.

In those who received patch angioplasty, the type of patch was known in 377 (73.7%) of the cases. In 267 (52.2%) a synthetic patch was used, in the majority of these a Dacron patch was used (59.8%). Fourteen (2.7%) received the Bovine Pericardium patch and 96 (18.8%) received a venous autologous patch. Comparing those who received a synthetic patch versus venous autologous patch, it was found that synthetic patches were associated with less restenosis compared to the venous patch. The risk of ≥50% restenosis was smaller in the synthetic patch group compared to venous patch at 5 year follow-up (50.8% vs. 26.6%, HR 0.57, 95% CI 0.33–0.97, p=0.038) and the risk of ≥70% restenosis was also smaller (38.9% vs. 30.6%, HR 0.39, 95% CI 0.18–0.88, p=0.023).

Intraoperative shunt usage

A shunt was used in 316 patients (40.0%). Comparing baseline characteristics between the groups with and without shunt usage, it was found that the baseline blood pressure was higher in the group without shunt and the presence of treated hyperlipidaemia and atrial fibrillation more common in the shunt group (Table 3). There were no differences in incidence of restenosis ≥50% and ≥70% according to shunt usage (Table 4). On 199 patients data was available on the type of shunt used. The Pruitt Inahara shunt was used in 104 patients, the Javid shunt in 57, Sundt in 13 and on 25 patients other shunts were used (including Argyle, Brener, Bard and Vascushunt). There was no difference in restenosis rate between the type of shunt used. There was also no interaction found between endarterectomy closure type and shunt usage.

Post-procedural stroke

In the eversion group, no patients developed post-procedural stroke during follow-up. There were no differences in risk of post-procedural stroke at 1- and 5-years follow-up between the three surgical procedures (Table 5). In the patch angioplasty group, 13 patients (2.5%) developed post-procedural ipsilateral stroke, compared to 3 patients (1.3%) in the primary closure group (HR 0.49, 95% CI 0.14–1.72, p=.260). There was no difference in the risk of post-procedural stroke according to the use of a shunt intraoperatively.

DISCUSSION

This subgroup analysis of the ICSS indicates that primary closure after CEA is significantly associated with an increased long-term cumulative incidence of restenosis ≥50% compared to closure with patch angioplasty. There was no difference in the restenosis rate between eversion endarterectomy and patch angioplasty or the usage of an intraoperative shunt.

Severe restenosis of ≥70% was not found to be more common in CEA with primary closure. The long-term risk of post-procedural ipsilateral stroke was not more common in either of the surgical techniques or shunt usage.

In total, we included 790 CEA procedures in our analyses. The closure technique after CEA in our study was left to the surgeon's preference and primary closure was used in nearly one third of our study group. Our study is therefore the largest study to date with data on surgical technique and restenosis rates and post-operative ipsilateral stroke.[14,31] Our findings support previous systematic reviews and meta-analyses suggesting that patch angioplasty after longitudinal endarterectomy had benefit over primary closure in restenosis rates.[13,14,31] Our findings also support the current European guidelines recommending patch angioplasty over primary closure.[1,32] These guidelines are based on a meta-analysis consisting of 10 randomised controlled trails including 2 157 patients, suggesting that patch angioplasty was associated with a significant reduction in ipsilateral stroke (1.6% in patch angioplasty versus 4.8% in primary closure, odds ratio 0.32, 95% CI 0.16–0.63).[1,31] Our data did not replicate a similar result, which is most likely explained by the small numbers of outcome events in our population, with ipsilateral stroke occurring in 13 patients (2.5%) in the patch angioplasty group, compared to 3 patients (1.3%) in the primary closure group.

The use of the type of patch in carotid patch angioplasty has been a well investigated topic with several meta-analyses conducted looking at the outcome data of synthetic patch use versus venous patch use. In our study, we found that the rate of the risk restenosis was also smaller in those who received a synthetic patch at 5 year follow-up. A recent meta-analysis by Texakalidis et al. consisting of 6 studies and 936 patients looking at the restenosis rate after 30-days in synthetic versus venous patch showed that the restenosis rate were similar (relative risk 0.48, 95% CI 0.19–1.20, p=0.11).[33] The mean follow-up in this group was 33.4 months. Ren et al. also conducted a meta-analysis on the restenosis rate and even though there was no

separate reporting on the short and long-term outcomes, no difference was found on the pooled early and late restenosis or stroke.[34] Despite the current practice is slowly shifting towards the use of Bovine Pericardium patch in CEA, our study does remain the largest study with restenosis data at long-term follow-up on synthetic patch versus venous autologous patch.[33,34]

Some studies have investigated the restenosis rate after eversion endarterectomy and these studies have shown contradictive results. One meta-analysis showed that eversion endarterectomy may be associated with a reduced risk of restenosis compared to the conventional technique (odds ratio 0.44, 95% CI 0.19–1.02).[20] In contrast, a more recent meta-analysis including combined randomised controlled trials and observational studies, showed that eversion endarterectomy was associated with late ≥50% restenosis (odds ratio 0.45, 95% CI 0.26–0.78).[35] This meta-analysis, however, did not state a specific time frame defined as late restenosis. Our study did not show any difference in restenosis rate between eversion and CEA with patch angioplasty in the long term. However, the small number of patients in our eversion group (5.9% of our total study patient population) and a low restenosis rate caused wide confidence intervals. Our eversion endarterectomy data should therefore be carefully interpreted and not compared with existing data.[16,35]

One meta-analysis by Kumar et al. showed that patients who had restenosis of >70% had a risk of 5% ipsilateral stroke at 37 months compared to patients without restenosis.[36] This study also showed that in 85% of the patients who had CEA with recurrent ipsilateral stroke, there was no evidence of significant carotid restenosis or occlusion. Some other studies do not report any significant association between restenosis and ipsilateral stroke,[28,37] whilst the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) showed that restenosis in CEA had a higher prevalence of recurrent ipsilateral stroke.[38] This raises the question whether patients who are asymptomatic from their restenosis need intervention. An additional analysis of the ICSS, has shown that restenosis ≥50% was associated with a

significant increased risk of ipsilateral stroke after CEA.[39] This risk of ipsilateral stroke in patients with restenosis, however, remained relatively low with a risk of 1% per year. Currently there are no distinct guidelines for re-intervention in patients with asymptomatic restenosis after CEA.[40] Surveillance with duplex ultrasound after CEA is therefore also not recommended, except when there is a presence of a significant contralateral stenosis prior to CEA which requires monitoring of disease progression.[1]

The decision to use a shunt during the procedure is often based on the surgeon's preference or based on the outcome of neuro-monitoring intraoperatively. In our study, 40% of the patients received a shunt during endarterectomy. There were no differences in incidence of restenosis compared to the groups with and without shunt usage. There is little evidence available on the association between the use of a shunt and restenosis and a common hypothesis is that the insertion of a shunt or the use of arterial clamps during shunt insertion could cause early myo-intimal hyperplasia. However, our study suggests that there might not be any association, especially in the long-term after surgery. Overall, there is very little evidence on the usage of shunts and restenosis rate. Data from the National Surgical Quality Improvement Programme (NSQIP) database did suggest that there is no association between the usage of shunts and perioperative stroke.[41] The use of intraoperative neuro-monitoring such as transcranial Doppler, could aid in the decision making for intraoperative shunt usage.[42] Cerebral flow velocity can be monitored during surgery to establish haemodynamic status over time and flow patterns can be compared before and after releasing the clamp on the internal carotid artery. Another benefit of using transcranial doppler intraoperatively is the detection of microembolic signals during CEA, which is an independent predictor of stroke risk when found present during surgical dissection and wound closure.[40]

There are several limitations to this study. Firstly, the ICSS was not designed to randomise patients for a comparison of outcomes based on the type of CEA procedure or shunt

usage. Therefore, a number of patients were excluded for analyses due to the unknown type of surgery and unknown usage of shunt. Differences in carotid plaque morphology or vascular anatomy prior to surgery could not have been assessed in our study, which could have influenced the risk of restenosis. However, there was no substantial differences found in the baseline characteristics between the surgical groups or shunt usage included for analyses. Secondly, the outcome of the follow-up duplex ultrasound imaging was not confirmed with a second imaging modality for comparison. Due to the variability in the measurement of ultrasound examinations between the sonographers in the study, this could have led to inaccurate restenosis rates. Additionally, a high carotid bifurcation, proximal or distal carotid disease could have led to misinterpretations of the results leading to additional bias to the study. However, we do not believe that this variability is any different between the surgical groups or shunt usage and therefore we consider that the risk of restenosis in primary closure we have shown is convincing. Thirdly, we acknowledge that the data is on average 10 to 20 years old. The understanding of the effect of blood pressure control and glucose control is increasing and the lack of the data is a limitation of the study. In addition, the ongoing improvement of surgical technique and advancements of imaging technology, and the improved understanding of the importance of individualised best medical treatment could influence the findings.

CONCLUSION

Restenosis was more common in primary closure compared to patch angioplasty during CEA. Primary closure is likely to be associated with a higher risk of restenosis compared to patch angioplasty. A higher incidence of ipsilateral stroke in this group was however not demonstrated. The use of a shunt does not seem to have any association with restenosis rate. The surgical technique and shunt usage did not differ in terms of long-term post-procedural stroke risk.

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CONFLICTS OF INTEREST

None.

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Figure 1. Study flowchart for long term restenosis rate after carotid endarterectomy (CEA)

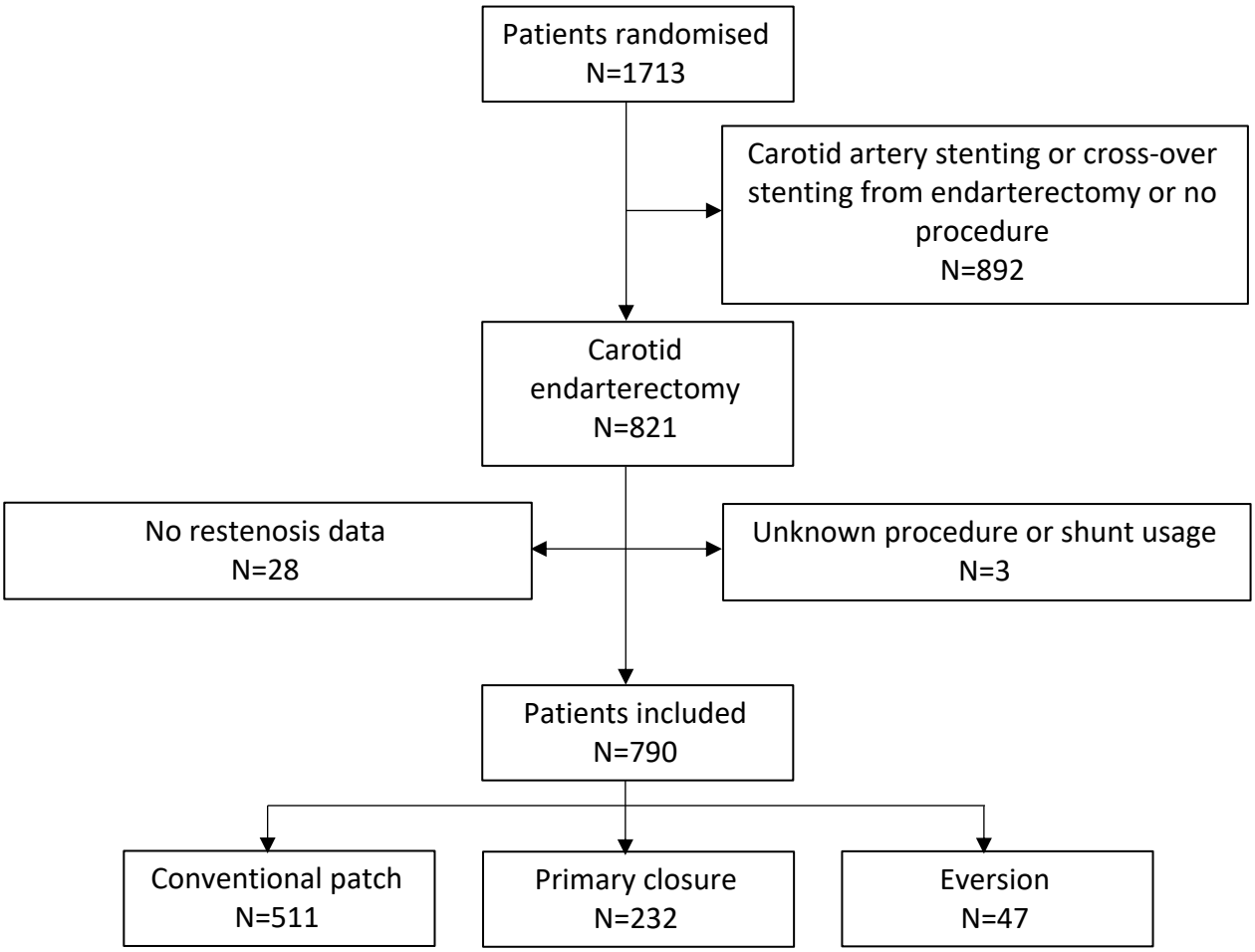
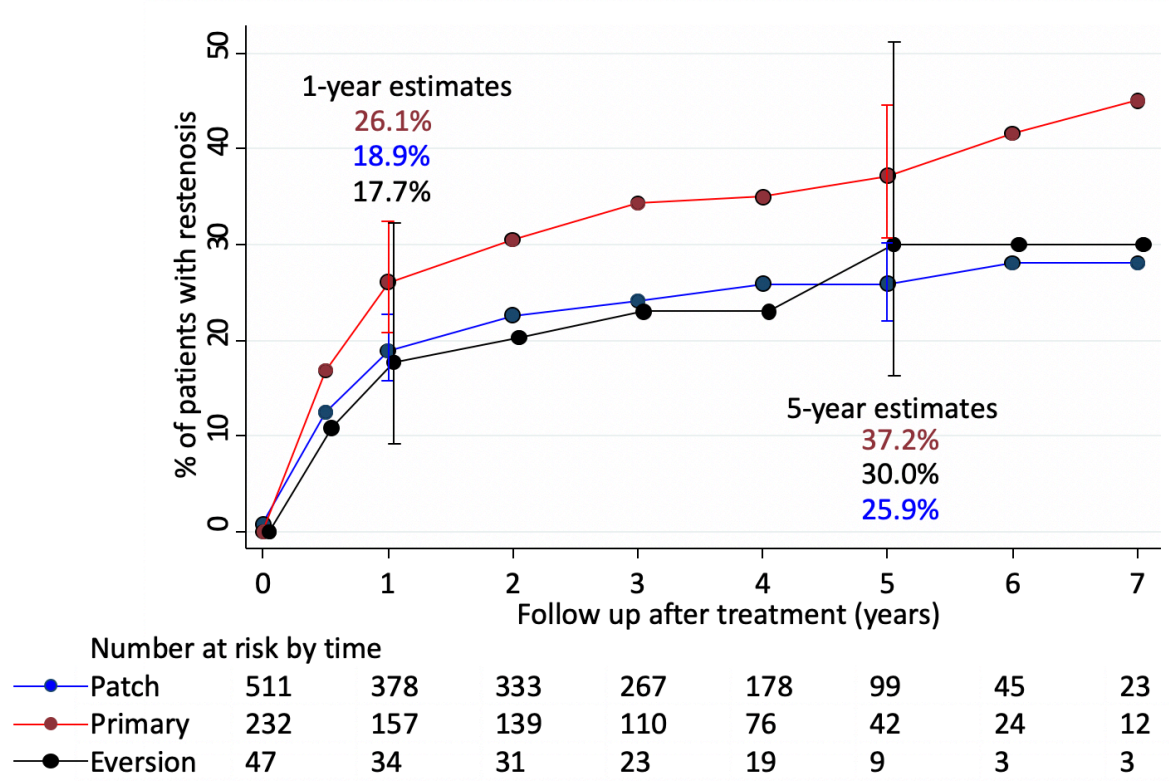


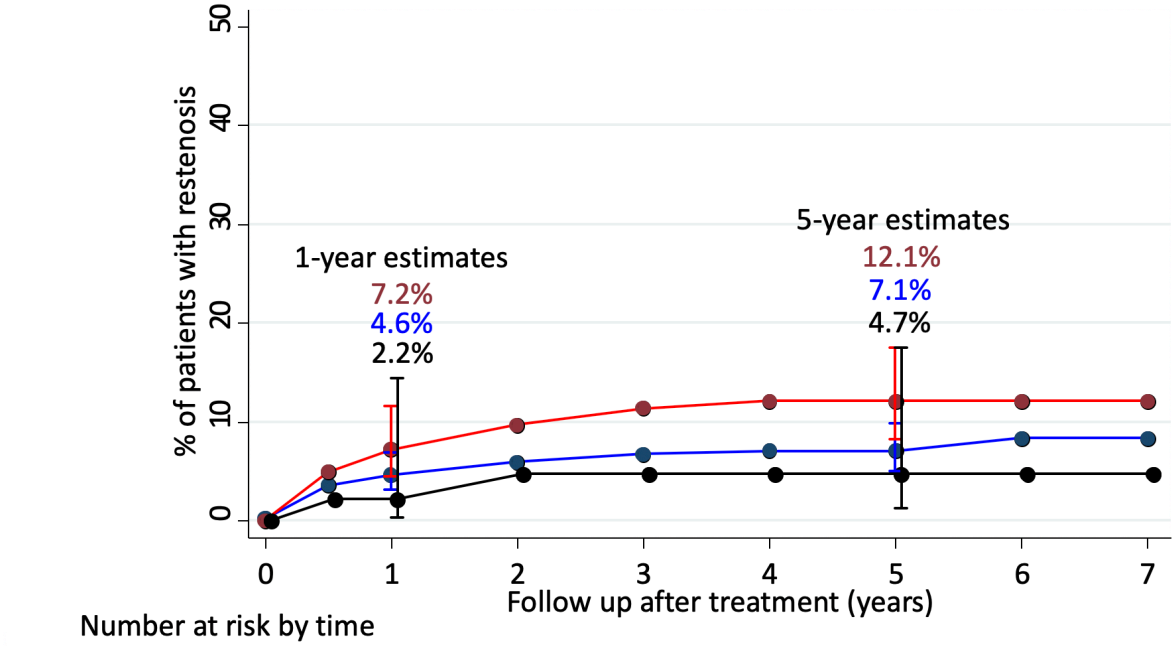
Figure 2. Lifetables for ≥50% (A) and ≥70% (B) restenosis, primary closure compared to patch angioplasty.

A. ≥50% restenosis



Number at risk by time								
Patch	511	378	333	267	178	99	45	23
Primary	232	157	139	110	76	42	24	12
Eversion	47	34	31	23	19	9	3	3

B. ≥70% restenosis



Number at risk by time								
Patch	511	443	395	315	213	118	52	26
Primary	232	198	179	140	98	59	35	19
Eversion	47	41	38	30	22	11	4	3

Table 1. Patient demographics by procedure technique.

Characteristic		n/N (%), mean (SD) or median (IQR)			P-value
		Eversion (n=47)	**Patch angioplasty (n=511)**	**Primary closure (n=232)**	
Age (years)		72.3 (8.7)	69.8 (9.3)	70.0 (8.8)	.194
Female sex		11/47 (23.4)	158/511 (30.9)	62/232 (26.7)	.356
Years from procedure to last duplex ultrasound		3.0 (1.0 to 4.4)	3.0 (1.1 to 4.9)	3.0 (1.0 to 4.8)	.740
Treated hypertension		31/46 (67.4)	361/508 (71.1)	158/230 (68.7)	.727
Systolic blood pressure (mmHg)		142 (22)	147 (25)	145 (21)	.200
Diastolic blood pressure (mmHg)		76 (11)	79 (13)	78 (12)	.245
Diabetes mellitus		7/47 (14.9)	105/511 (20.5)	53/232 (22.8)	.487
Non-insulin dependent		5/46 (10.9)	81/508 (15.9)	42/230 (18.3)	.455
Insulin dependent		2/46 (4.3)	24/508 (4.7)	11/230 (4.8)	1.000
Treated hyperlipidaemia		26/46 (56.5)	346/508 (68.1)	149/230 (64.8)	.230
Total cholesterol (mmol/l)		4.9 (1.5)	4.9 (1.3)	4.9 (1.3)	.969
Current smoker		9/46 (19.6)	116/508 (22.8)	58/230 (25.2)	.674
Ex-smoker		22/46 (47.8)	255/508 (50.2)	113/230 (49.1)	.934
Angina in last 6 months		10/46 (21.7)	40/508 (7.9)	19/230 (8.3)	**.014**
Previous myocardial infarction		13/46 (28.3)	96/508 (18.9)	35/230 (15.2)	.105
Previous CABG		11/46 (23.9)	69/508 (13.6)	25/230 (10.9)	.067
Atrial fibrillation		3/46 (6.5)	32/508 (6.3)	17/230 (7.4)	.831
Other cardiac embolic source		1/46 (2.2)	10/508 (2.0)	5/230 (2.2)	.918
Cardiac failure		2/46 (4.3)	32/508 (6.3)	6/230 (2.6)	.098
Peripheral artery disease		7/46 (15.2)	85/508 (16.7)	30/230 (13.0)	.463
Degree of symptomatic carotid stenosis	50-69%	5/47 (10.6)	43/511 (8.4)	23/232 (9.9)	.740
	70-99%	42/47 (89.4)	468/511 (91.6)	209/232 (90.1)	
Degree of contralateral carotid stenosis	0-49%	31/47 (66.0)	335/507 (66.1)	154/230 (67.0)	.360
	50-69%	9/47 (19.1)	76/507 (15.0)	46/230 (20.0)	
	70-99%	6/47 (12.8)	68/507 (13.4)	24/230 (10.4)	
	Occluded	1/47 (2.1)	28/507 (5.5)	6/230 (2.6)	
Most recent ipsilateral event before randomisation	Stroke	23/45 (51.1)	217/503 (43.1)	107/230 (46.5)	.371
	Retinal Stroke	2/45 (4.4)	12/503 (2.4)	8/230 (3.5)	
	TIA	16/45 (35.6)	192/503 (38.2)	71/230 (30.9)	
	AFX	4/45 (8.9)	82/503 (16.3)	44/230 (19.1)	
Statin use (1-month post-procedure)		36/45 (80)	390/482 (80.9)	169/215 (78.6)	0.759
Dual antiplatelet use (1-month post-procedure)		5/45 (11.1)	134/482 (27.8)	57/215 (26.5)	0.041

*p-value is for differences across any of the 3 categories.

Table 2. Cumulative incidence and hazard ratios for restenosis outcomes by type of endarterectomy.

Severity of restenosis		Patch angioplasty (n=511)	Primary closure (n=232)	Eversion (n=47)
50%	Total cases	124	80	11
	Cumulative incidence (95% CI) at 1-year – %	18.9 (15.7 to 22.7)	26.1 (20.8 to 32.4)	17.7 (9.3 to 32.3)
	Cumulative incidence (95% CI) at 5-years – %	25.9 (22.1 to 30.2)	37.2 (30.7 to 44.5)	30.0 (16.3 to 51.2)
	Unadjusted hazard ratio	Reference	1.54 (1.14 to 2.09) p =.005	1.03 (0.52 to 2.04) p =.927
	Adjusted hazard ratio*	Reference	1.45 (1.06 to 1.98) p =.019	0.90 (0.45 to 1.81) p =.774
70%	Total cases	34	25	2
	Cumulative incidence (95% CI) at 1-year – %	4.6 (3.1 to 6.8)	7.2 (4.5 to 11.5)	2.2 (0.3 to 14.4)
	Cumulative incidence (95% CI) at 5-years – %	7.1 (5.0 to 9.8)	12.1 (8.3 to 17.4)	4.7 (1.2 to 17.5)
	Unadjusted hazard ratio	Reference	1.56 (0.86 to 2.80) p =.140	0.44 (0.06 to 3.23) p =.417
	Adjusted hazard ratio*	Reference	1.59 (0.88 to 2.89) p =.124	0.45 (0.06 to 3.35) P =.438

*Adjusted for predictors of restenosis.

Table 3. Baseline characteristics by shunt usage.

Characteristic		n/N (%), mean (SD) or median (IQR)		P-value
		No shunt used	**Shunt used**	
Age (years)		70.0 (9.2)	70.1 (9.0)	.947
Female sex		133/474 (28.1)	98/316 (31.0)	.380
Years from procedure to last duplex ultrasound		3.0 (1.0 to 4.5)	3.1 (1.1 to 5.0)	.098
Treated hypertension		318/471 (67.5)	232/313 (74.1)	.056
Systolic blood pressure (mmHg)		149 (25)	142 (21)	**<.001**
Diastolic blood pressure (mmHg)		79 (13)	76 (12)	**<.010**
Diabetes mellitus		100/474 (21.1)	65/316 (20.6)	.929
Non-insulin dependent		74/471 (15.7)	54/313 (17.3)	.622
Insulin dependent		26/471 (5.5)	11/313 (3.5)	.230
Treated hyperlipidaemia		297/471 (63.1)	224/313 (71.6)	**.014**
Total cholesterol (mmol/l)		4.9 (1.3)	4.9 (1.3)	.608
Current smoker		107/471 (22.7)	76/313 (24.3)	.667
Ex-smoker		244/471 (51.8)	146/313 (46.6)	.166
Angina in last 6 months		38/471 (8.1)	31/313 (9.9)	.371
Previous myocardial infarction		90/471 (19.1)	54/313 (17.3)	.572
Previous CABG		67/471 (14.2)	38/313 (12.1)	.454
Atrial fibrillation		24/471 (5.1)	28/313 (8.9)	**.040**
Other cardiac embolic source		9/471 (1.9)	7/313 (2.2)	.800
Cardiac failure		25/471 (5.3)	15/313 (4.8)	.867
Peripheral artery disease		66/471 (14.0)	56/313 (17.9)	.159
Degree of symptomatic carotid stenosis	50-69%	40/474 (8.4)	31/316 (9.8)	.509
	70-99%	434/474 (91.6)	285/316 (90.2)	
Degree of contralateral carotid stenosis	0-49%	315/470 (67.0)	205/314 (65.3)	.553
	50-69%	76/470 (16.2)	55/314 (17.5)	
	70-99%	64/470 (13.6)	34/314 (10.8)	
	Occluded	15/470 (3.2)	20/314 (6.4)	
Most recent ipsilateral event before randomization	Stroke	206/469 (43.9)	141/309 (45.6)	.978
	Retinal Stroke	19/469 (4.1)	3/309 (1.0)	
	TIA	167/469 (35.6)	112/309 (36.2)	
	AFX	77/469 (16.4)	53/309 (17.2)	
Statin use (1-month post-procedure)		356/451 (78.9)	239/291 (82.1)	0.301
Dual antiplatelet use (1-month post-procedure)		116/451 (25.7)	80/291 (27.5)	0.610

Table 4. Cumulative incidence and hazard ratios for restenosis outcomes by shunt usage.

Severity of restenosis		**No shunt**	**Shunt**
50%	Total cases	136	79
	Cumulative incidence (95% CI) at 1-year – %	21.5 (18.0 to 25.6)	20.2 (16.1 to 25.1)
	Cumulative incidence (95% CI) at 5-years – %	32.1 (27.6 to 37.1)	25.8 (21.1 to 31.2)
	Unadjusted hazard ratio	Reference	0.89 (0.66 to 1.20) p =.446
	Adjusted hazard ratio*	Reference	0.83 (0.61 to 1.14) p =.254
70%	Total cases	37	24
	Cumulative incidence (95% CI) at 1-year – %	5.4 (3.7 to 8.0)	4.9 (3.0 to 8.0)
	Cumulative incidence (95% CI) at 5-years – %	8.4 (6.1 to 11.5)	8.4 (5.7 to 12.3)
	Unadjusted hazard ratio	Reference	1.03 (0.57 to 1.86) p =.915
	Adjusted hazard ratio*	Reference	0.96 (0.52 to 1.74) p =.884

*Adjusted for predictors of restenosis.

Table 5. Frequency of post-procedural stroke by endarterectomy type and shunt usage.

Type of endarterectomy		**Eversion endarterectomy**	**Patch angioplasty**	**Primary closure**
Any post-procedural stroke	Total cases	0	27	6
	1-year Kaplan Meier rate – %	No events	1.9 (1.0 to 1.0)	
	5-years Kaplan Meier rate – %	No events	6.4 (4.3 to 4.3)	3.2 (1.5 to 1.5)
	Unadjusted hazard ratio vs patch (95% CI)			0.48 (0.20 to 1.17); p =.110
Post-procedural ipsilateral stroke	Total cases	0	13	3
	1-year Kaplan Meier rate – %	No events	1.0 (0.4 to 0.4)	
	5-years Kaplan Meier rate – %	No events	2.9 (1.7 to 1.7)	1.8 (0.6 to 0.6)
	Unadjusted hazard ratio vs patch (95% CI)			0.49 (0.14 to 1.72); p =.260
Use of shunt			**No shunt**	**Shunt**
Any post-procedural stroke	Total cases		16	17
	1-year Kaplan Meier rate – %		1.1 (0.5 to 0.5)	1.3 (0.5 to 0.5)
	5-years Kaplan Meier rate – %		4.1 (2.5 to 2.5)	6.5 (4.0 to 4.0)
	Unadjusted hazard ratio vs no shunt (95% CI)			1.53 (0.76 to 3.05); p =.230
Post-procedural ipsilateral stroke	Total cases		9	7
	1-year Kaplan Meier rate – %		0.5 (0.1 to 0.1)	1.0 (0.3 to 0.3)
	5-years Kaplan Meier rate – %		2.3 (1.2 to 1.2)	2.6 (1.2 to 1.2)
	Unadjusted hazard ratio vs no shunt (95% CI)			1.18 (0.44 to 3.17); p =.740