Intimal Hyperplasia Post Carotid Endarterectomy

George H. Meier, MD RVT FACS
Professor and Chief, Vascular
University of Cincinnati COM
Disclosures

None
Anyone who says they understand Intimal Hyperplasia, is lying....
FIGURE 50.3 Intimal fibromuscular hypertrophy in a section of human coronary artery. The intimal thickening consists of an orderly layered intimal structure including both smooth muscle cells and matrix fibers and separated from the media by the internal elastic lamina.
FIGURE 50.4 Artery cross section with intimal hyperplasia and lumen stenosis. Widely spaced cells are surrounded with abundant matrix with few distinct collagen or elastin fibers and little geometric orientation.
Figure 3. Longitudinal (left) and cross-sectional (right) views of a restenotic ICA (patient 8), indicating an isoechoic lesion with concentric stenosis.
Associations with IH

• Embolectomy catheter induced, associated with endothelial denudation

• Common after endarterectomy in any location

• Common after balloon angioplasty (~30%)
Primary Restenosis

Carotid artery restenosis following endarterectomy and stenting ranges from 1-20% nationally
Technical Result of Carotid Endarterectomy*

Arteriographic Assessment

F. William Blaisdell, M.D., Robert Lim, Jr., M.D., and Albert D. Hall, M.D.,
San Francisco, California

From the Surgical Service, University of California School of Medicine, San Francisco Veterans Administration Hospital and San Francisco General Hospital. This work was supported by U.S.P.H.S. Grants No. HE-06996 and HE-11122-01.

In recent years numerous reports have described the morbidity, mortality, and neurologic sequelae of the operations for cerebrovascular occlusive disease [1–7]. A few others have documented the technical result of these procedures [8,9] but none have used arteriographic evaluation consistently. Even though a patient’s neurologic symptoms have abated, one is not justified in concluding that the vascular reconstruction is patent. Several authors have described how the conversion of a stenotic lesion to a complete occlusion may result in improvement or relief of symptoms, provided that the symptoms were caused by embolism [10,11]. The development of col-

Arteriograms were obtained before the incision was closed in all patients, as well as in the early postoperative period in ninety-one patients, and at five year follow-up study in all available patients. The findings of these arteriograms and the results of autopsies, when performed, are reported herein.

MATERIAL AND METHODS

All patients in this series had preoperative arteriographic evaluation. With rare exceptions, this consisted of four vessel angiography [13,14]. All the operations were performed upon stenotic lesions of the first portion of the internal carotid artery. These stenoses consisted of lesions which exceeded 30 per cent compromise of the diameter of the lumen, but excluded those lesions which resulted in complete occlusion since it is well documented that the technical success of operations on the completely occluded carotid artery differs significantly from that of operations on the stenotic carotid artery [11,15].
Review

Recurrent carotid stenosis after carotid endarterectomy

C. R. LATTIMER and K. G. BURNAND
Surgical Unit, St Thomas' Hospital (United Medical and Dental School), London, UK
Correspondence to: Mr C.R. Lattimer, Department of Vascular Surgery, Fremantle Hospital, PO Box 480, Fremantle, Western Australia 6160, Australia

Background This review examines the history, incidence, aetiology and pathology of recurrent carotid stenosis, and assesses the methods and results of managing patients with this condition.

Methods Over 200 references were retrieved from Medline from 1966 to 1996. Data were collected which reported the incidence, timing, method of diagnosis, follow-up, percentage of patients with symptoms and the indications for revisional surgery. The stroke rate and operative mortality rate following revisional carotid surgery were also recorded.

Results The overall incidence of symptomatic recurrent stenosis ranged from 0 to 8.2 per cent, with a symptomless recurrence rate between 1.3 and 37 per cent. Forty-three (78 per cent) of 55 studies indicated that revisional surgery was performed on patients with symptoms; only 21 (38 per cent) of 55 studies indicated that operations were carried out on asymptomatic patients. The stroke rate and mortality rate after 511 revisional procedures were 3.9 and 1.0 per cent respectively.

Conclusion Symptomatic recurrent stenosis is rare but some patients may benefit from revisional surgery. Surgery for symptomless carotid restenosis should be considered only if a multicentre trial can demonstrate clear benefit in terms of patient survival or stroke reduction.
<table>
<thead>
<tr>
<th>Year</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Disease severity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>125</td>
<td>65</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>154</td>
<td>68</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>184</td>
<td>70</td>
<td>Critical</td>
<td></td>
</tr>
<tr>
<td>1989</td>
<td>214</td>
<td>72</td>
<td>Very Severe</td>
<td></td>
</tr>
</tbody>
</table>

### Table 1: Table of Treatment Outcomes in Published Cases

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Critical</td>
<td></td>
</tr>
<tr>
<td>Very Severe</td>
<td></td>
</tr>
</tbody>
</table>
Patterns of in-stent restenosis after carotid artery stenting: Classification and implications for long-term outcome

Brajesh K. Lal, MD, a,b,c,d Elias A. Kaperonis, MD, e Salvador Cuadra, MD, a,d Indravadan Kapadia, PA, d and Robert W. Hobson II, MD, a,b,d Newark, NJ, and Athens, Greece

Objectives: Factors predicting in-stent restenosis (ISR) and future need for target lesion revascularization (TLR) after carotid artery stenting (CAS) remain undetermined. We hypothesized that the patterns of restenotic lesions may provide prognostic information. In this study, we developed an ultrasound classification scheme for ISR based on lesion length and distribution and assessed factors that may predict the need for TLR.

Methods: Patients were followed up after CAS with B-mode ultrasound imaging, and ISR lesions (≥40% stenosis) were classified into type I (focal ≤10 mm end-stent lesions), II (focal ≤10 mm, intrastent), III (diffuse >10 mm, intrastent), IV (diffuse >10 mm proliferative, extending outside the stent), and V (total occlusion). The frequency of lesion types was assessed. Accuracy of the ultrasound classification was confirmed with angiography. We recorded patient (age, gender, comorbidities), lesion (severity, etiology, symptomatic status) and procedural features (type, number, length of stents), and the need for TLR.

Results: Eighty-five ISR lesions developed after 255 CAS procedures. Their percentage distribution was type I, 40; type II, 25.9; type III, 12.9; for type IV, 20; and type V, 1.2. Accuracy of the ultrasound classification was confirmed by angiography ($r^2 = 0.82$). Inter-rater agreement for the assignment of lesion type based on ultrasound was 0.88 (very good). TLR was performed in 13 that were ≥80% diameter reducing. On univariate analysis, the need for TLR was highest in type IV lesions (0%, 0%, 27.3%, and 58.8% [types I to IV, respectively]; $P = .001$). History of ISR (2.9%, 0%, 0%, and 41.2% [types I to IV]; $P = .003$) and diabetes mellitus (20.6%, 22.7%, 45.5%, and 52.9% [types I to IV]; $P = .02$) occurred more frequently with type IV ISR lesions. On multivariate analysis of all patient, lesion, and procedural characteristics, only the type of ISR (odds ratio, 5.1) and a history of diabetes (odds ratio, 9.7) were independent predictors of TLR.

Conclusions: The proposed classification accurately grades the magnitude of intimal hyperplasia after CAS and provides important prognostic information. Diffuse proliferative (type IV) ISR lesions and diabetes are important determinants of long-term outcome after CAS. This classification will facilitate a standardized description of recurrence after CAS and enable early identification of high-risk patients for additional monitoring, treatment, and investigation. (J Vasc Surg 2007;46:833-40.)
Type I: Focal end-stent
Type II: Focal intra-stent
Type III: Diffuse intra-stent
Type IV: Diffuse proliferative
Type V: Total occlusion
Fig 1. A, Schematic images show the five patterns of carotid in-stent restenosis based on the introduced classification. The shaded area represents the stent. B, Representative B-mode ultrasound images of in-stent restenosis correspond to the patterns I through IV.
### Table III. Target lesion revascularization

<table>
<thead>
<tr>
<th>Variables*</th>
<th>Patterns of in-stent restenosis by type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I, focal end-stent (n = 34)</td>
</tr>
<tr>
<td>Incidence of TLR, %*</td>
<td>0</td>
</tr>
<tr>
<td>Devices used for ISR, No.</td>
<td></td>
</tr>
<tr>
<td>Balloon angioplasty</td>
<td>0</td>
</tr>
<tr>
<td>Stent</td>
<td>0</td>
</tr>
<tr>
<td>Cutting balloon</td>
<td>0</td>
</tr>
<tr>
<td>Cutting balloon + stent</td>
<td>0</td>
</tr>
<tr>
<td>Post-treatment result, % residual stenosis</td>
<td>N/A</td>
</tr>
</tbody>
</table>

TLR, Target lesion revascularization; ISR, in-stent-restenosis; N/A, not applicable.

*P = .001.
Restenosis after Carotid Interventions and Its Relationship with Recurrent Ipsilateral Stroke: A Systematic Review and Meta-analysis

R. Kumar 1, A. Batchelor 1, A. Sarazin 2, A.F. AbasRahma 3, P. Ringlob 4, B.K. Lai 5, J.L. Mas 6, M. Steinbauer 7, A.R. Naylor 8

1 Department of Vascular Surgery at Leicester Royal Infirmary, Leicester, UK
2 Division of Vascular Surgery, West Virginia University, Charleston, WV, USA
3 Neurologische Klinik der Ruprecht-Karls-Universitaet, Heidelberg, Germany
4 Division of Vascular Surgery, University of Maryland, Baltimore, MD, USA
5 Hospital Sainte-Anne, Université Paris-Descartes, Paris, France
6 Department of Vascular and Endovascular Surgery, Regensburg, Germany

WHAT THIS PAPER ADDS
This meta-analysis of prospective surveillance data derived from nine randomised controlled trials found that CAS patients with an untreated asymptomatic > 70% restenosis had an extremely low rate of late ipsilateral stroke (0.8% over 50 months). CEA patients with an untreated, asymptomatic > 70% restenosis had a significantly higher risk of late ipsilateral stroke (compared with patients with no restenosis), but the risk was only 5% at 37 months. Overall, 97% of all late ipsilateral strokes after CAS and 85% after CEA occurred in patients with no evidence of a significant restenosis or occlusion.

Objective: Do asymptomatic restenoses > 70% after carotid endarterectomy (CEA) and carotid stenting (CAS) increase the risk of late ipsilateral stroke?

Methods: Systematic review identified 11 randomised controlled trials (RCTs) reporting rates of restenosis > 70% (and/or occlusion) in patients who had undergone CEA/CAS for the treatment of primary atherosclerotic disease, and nine RCTs reported late ipsilateral stroke rates. Proportional meta-analyses and odds ratios (OR) at end of follow-up were performed.

Results: The weighted incidence of restenosis > 70% was 5.8% after “any” CEA, median 47 months (11 RCTs; 4249 patients); 4.1% after patched CEA, median 32 months (5 RCTs; 1078 patients), and 10% after CAS, median 62 months (5 RCTs; 2716 patients). In four RCTs (1954 patients), one of 1.5% (0.6%) with restenosis > 70% (or occlusion) after CAS suffered late ipsilateral stroke over a median 50 months, compared with 37 of 1839 (2.0%) in CAS patients with no significant restenosis (OR 0.87; 95% CI 0.24–3.21; p = .8389). In seven RCTs (2810 patients), 13 out of 141 (9.2%) with restenosis > 70% (or occlusion) after CEA suffered late ipsilateral stroke over a median 37 months, compared with 33 out of 2669 (1.2%) in patients with no significant restenoses (OR 9.02; 95% CI 4.70–17.20; p < .0001). Following data correction to exclude patients whose surveillance scan showed no evidence of restenosis > 70% before stroke onset, the prevalence of stroke ipsilateral to an untreated asymptomatic > 70% restenosis was seven out of 135 (5.2%) versus 40 out of 2704 (1.5%) in CEA patients with no significant restenosis (OR 4.77; 95% CI 2.29–9.92).

Conclusions: CAS patients with untreated asymptomatic > 70% restenosis had an extremely low rate of late ipsilateral stroke (0.8% over 50 months). CEA patients with untreated, asymptomatic > 70% restenosis had a significantly higher risk of late ipsilateral stroke (compared with patients with no restenosis), but this was only 5% at 37 months. Overall, 97% of all late ipsilateral strokes after CAS and 85% after CEA occurred in patients without evidence of significant restenosis or occlusion.

© 2017 European Society for Vascular Surgery. Published by Elsevier Ltd. All rights reserved.
Article history: Received 26 October 2016, Accepted 13 February 2017, Available online 28 March 2017
Figure 1. Times when carotid restenosis was detected on sonography.

<table>
<thead>
<tr>
<th>Yr</th>
<th>Number of arteries with restenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2wk</td>
<td>241</td>
</tr>
<tr>
<td>3M</td>
<td>241</td>
</tr>
<tr>
<td>1</td>
<td>237</td>
</tr>
<tr>
<td>2</td>
<td>154</td>
</tr>
<tr>
<td>3</td>
<td>104</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
</tr>
</tbody>
</table>

Number of examined arteries: 241, 241, 237, 154, 104, 67, 49, 28
The Problem
Neointimal Hyperplasia

Acute s/p PTCA, Elastic van Giesen stain

30 days s/p PTCA, Elastic van Giesen stain

Schwartz et.al. Rev Cardiovasc Med. 2002;3:S4
In-stent restenosis is almost exclusively the result of neointimal formation.

Pathophysiology
Neointimal Hyperplasia

- Platelets accumulate on denuded region
- Endothelial cells proliferate
- SMCs also proliferate and migrate into intima, causing intimal thickening
Pathophysiology
Neointimal Hyperplasia

Arterial injury

Platelet adhesion/activation

Thrombosis

Thrombus develops endothelial layer

Leukocytes demarginate from bloodstream, migrate into subendothelial mural thrombus

Smooth muscle cells proliferate and migrate into intima

New matrix synthesized
Pathophysiology
Neointimal Hyperplasia

Arterial injury

Platelet adhesion/activation

Thrombosis

Thrombus develops endothelial layer

Leukocytes demarginate from bloodstream, migrate into subendothelial mural thrombus

Smooth muscle cells proliferate and migrate into intima

New matrix synthesized

Conde et al. Cath & Cardiovasc Int. 2003;60:236
Pathophysiology
Neointimal Hyperplasia

Arterial injury

\[ \downarrow \]

Platelet adhesion/activation

\[ \downarrow \]

Thrombosis

\[ \rightarrow \]

Thrombus develops endothelial layer

\[ \downarrow \]

Leukocytes demarginate from bloodstream, migrate into subendothelial mural thrombus

\[ \downarrow \]

Smooth muscle cells proliferate and migrate into intima

\[ \downarrow \]

New matrix synthesized

Conde et al. Cath & Cardiovasc Int. 2003;60:236
Pathophysiology
Neointimal Hyperplasia

Arterial injury

Platelet adhesion/activation

Thrombosis

Thrombus develops endothelial layer

Leukocytes demarginate from bloodstream, migrate into subendothelial mural thrombus

Smooth muscle cells proliferate and migrate into intima

New matrix synthesized

Conde et al. Cath & Cardiovasc Int. 2003;60:236
Pathophysiology
Neointimal Hyperplasia

Arterial injury
↓
Platelet adhesion/activation
↓
Thrombosis
↓
Thrombus develops endothelial layer
↓
Leukocytes deaggregate from bloodstream, migrate into subendothelial mural thrombus
↓
Smooth muscle cells proliferate and migrate into intima
↓
New matrix synthesized
Pathophysiology
Neointimal Hyperplasia

- Factors from platelets, leukocytes, smooth muscle cells, and extracellular matrix interact and regulate the process of intimal hyperplasia, making each step a potential therapeutic target.
Pathophysiology
Neointimal Hyperplasia

Arterial injury

Platelet adhesion/activation

Thrombosis

Thrombus develops endothelial layer

Leukocytes demarginate from bloodstream, migrate into subendothelial mural thrombus

Smooth muscle cells proliferate and migrate into intima

New matrix synthesized

Injury

EC/SMC Disruption

Platelet Adherence/Degranulation

Angiotensin II

Quiescence

Proliferation

Migration

Intimal Hyperplasia

Matrix Deposition
MCAM deficiency abrogated neointimal hyperplasia in the carotid ligation model in mice.
Treatment

Restenosis and Drug-Eluting Stents

A. Rapamycin (Sirolimus):

- A macrolide produced by *Streptomyces hygroscopicus*
- Found in soil from Easter Island in 1974
- Inhibits migration and proliferation of vascular smooth muscle cells
- Anti-inflammatory properties
Restenosis and Drug-Eluting Stents

A. Rapamycin:

Rapamycin inhibits neointimal hyperplasia in porcine coronary restenosis model at 30 days.

mTOR Pathway

- Target for sirolimus
- Dysregulation associated with intimal hyperplasia
- Complicated!
FIG. 1. Decoy-ODN strategy as exemplified by edifoligide. In the cytoplasm, E2F is bound to a regulatory complex in quiescent cells involving cyclins, cyclin-dependent kinases (cdk), and the retinoblastoma gene product (Rb). With phosphorylation of this complex, E2F is released. At this point edifoligide can bind E2F and sequester it in the cytoplasm where it is subsequently degraded. If E2F is not bound by edifoligide, it migrates to the nucleus where binding its consensus sequence activates multiple cell cycle regulatory genes.
Edifoligide: A Transcription Factor Decoy to Modulate Smooth Muscle Cell Proliferation in Vein Bypass

Andrew W. Hoel and Michael S. Conte

Division of Vascular and Endovascular Surgery, Brigham and Women’s Hospital, Boston, MA, USA

Keywords: E2F — Intimal hyperplasia — Oligonucleotides — Smooth muscle cells — Transcription factor decoy — Vein bypass graft.

ABSTRACT

The era of genomics and recombinant DNA technology has ushered in an entirely new class of therapeutic agents designed to influence disease progression at a genetic level. The scope and utility of this technology is not fully realized. However, multiple trials of therapeutic agents have been completed and many more are ongoing. Here we report on edifoligide, a double-stranded oligodeoxynucleotide (ODN) that competitively inhibits the transcription factor E2F, a critical regulator of the cell cycle. Edifoligide has undergone extensive clinical testing for the treatment of intimal hyperplasia following vascular bypass procedures. In this review we address the rationale for targeting E2F in vascular disease, the pharmacology of edifoligide, and the results of preclinical and clinical studies using this novel compound.
Efficacy and Safety of Edifoligide, an E2F Transcription Factor Decoy, for Prevention of Vein Graft Failure Following Coronary Artery Bypass Graft Surgery

PREVENT IV: A Randomized Controlled Trial

Context Coronary artery bypass graft (CABG) surgery with autologous vein grafting is commonly performed. Progressive neointimal hyperplasia, however, contributes to considerable vein graft failure. Edifoligide is an oligonucleotide decoy that binds to and inhibits E2F transcription factors and thus may prevent neointimal hyperplasia and vein graft failure.

Objective To assess the efficacy and safety of pretreating vein grafts with edifoligide for patients undergoing CABG surgery.

Design, Setting, and Participants A phase 3 randomized, double-blind, placebo-controlled trial of 3014 patients undergoing primary CABG surgery with at least 2 planned saphenous vein grafts and without concomitant valve surgery, who were enrolled between August 2002 and October 2003 at 107 US sites.

Intervention Vein grafts were treated ex vivo with either edifoligide or placebo in a pressure-mediated delivery system. The first 2400 patients enrolled were scheduled for 12- to 18-month follow-up angiography.

Main Outcome Measures The primary efficacy end point was angiographic vein graft failure (≥75% vein graft stenosis) occurring 12 to 18 months after CABG surgery. Other end points included other angiographic variables, adverse events through 30 days, and major adverse cardiac events.

Results A total of 1920 patients (80%) either died (n = 91) or underwent follow-up angiography (n = 1829). Edifoligide had no effect on the primary end point of per patient vein graft failure (436 [45.2%] of 965 patients in the edifoligide group vs 442 [46.3%] of 955 patients in the placebo group; odds ratio, 0.96 [95% confidence interval, 0.80-1.14]; P = 0.66), on any secondary angiographic end point, or on the incidence of major adverse cardiac events at 1 year (101 [6.7%] of 1508 patients in the edifoligide group vs 121 [8.1%] of 1506 patients in the placebo group; hazard ratio, 0.83 [95% CI, 0.64-1.08]; P = 0.16).

Conclusions Failure of at least 1 vein graft is quite common within 12 to 18 months after CABG surgery. Edifoligide is no more effective than placebo in preventing these events. Longer-term follow-up and additional research are needed to determine whether edifoligide has delayed beneficial effects, to understand the mechanisms and clinical consequences of vein graft failure, and to improve the durability of CABG surgery.

Clinical Trial Registration ClinicalTrials.gov Identifier: NCT00042081.

www.jama.com
Results of PREVENT III: A multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery

Michael S. Conte, MD, Dennis F. Bandyk, MD, Alexander W. Clowes, MD, Gregory L. Moneta, MD, Lynn Seely, MD, Todd J. Lorenz, MD, Hamid Namini, PhD, Allen D. Hamdan, MD, Sean P. Roldy, MD, Michael Belkin, MD, Scott A. Berceli, MD, Richard J. DeMasi, MD, Russell H. Sunson, MD, and Scott S. Berman, MD, for the PREVENT III Investigators, Boston, Mass; Tampa, Gainesville, and Sarasota, Fla; Seattle, Wash; Portland, Ore; South San Francisco, Calif; Albany, NY; Norfolk, Va; and Tucson, Ariz

Objective: The PREVENT III study was a prospective, randomized, double-blinded, multicenter phase III trial of a novel molecular therapy (edifoligide; E2P decoy) for the prevention of vein graft failure in patients undergoing infragenual revascularization for critical limb ischemia (CLI).

Methods: From November 2001 through October 2003, 1404 patients with CLI were randomized to a single intraoperative ex vivo vein graft treatment with edifoligide or placebo. After surgery, patients underwent graft surveillance by duplex ultrasonography and were followed up for index graft and limb end points to 1 year. A blinded Clinical Events Classification committee reviewed all index graft end points. The primary study end point was the time to nontechnical index graft reintervention or major amputation due to index graft failure. Secondary end points included all-cause graft failure, clinically significant graft stenosis (>70% by angiography or severe stenosis by ultrasonography), amputation/reintervention-free survival, and nontechnical primary graft patency. Event rates were based on Kaplan-Meier estimates. Time-to-event end points were compared by using the log-rank test.

Results: Demographics, comorbidities, and procedural details reflected a population with CLI and diffuse atherosclerosis. Tissue loss was the presenting symptom in 78% of patients. High-risk conduits were used in 24% of cases, including an alternative vein in 20% (18% spliced vein and 8% non–great saphenous vein) and 6% less than 3 mm in diameter; 14% of the cases were reoperative bypass grafts. Most (65%) grafts were placed to infrapopliteal targets. Perioperative (30-day) mortality occurred in 2.7% of patients. Major morbidity included myocardial infarction in 4.7% and early graft occlusion in 5.2% of patients. Ex vivo treatment with edifoligide was well tolerated. There was no significant difference between the treatment groups in the primary or secondary trial end points, primary graft patency, or limb salvage. A statistically significant improvement was observed in secondary graft patency (estimated Kaplan-Meier rates were 83% edifoligide and 78% placebo; P = .016) within 1 year. The reduction in secondary patency events was manifest within 30 days of surgery (the relative risk for a 30-day event for edifoligide was 0.45; 95% confidence interval, 0.27–0.76; P = .005). For the overall cohort at 1 year, the estimated Kaplan-Meier rate for survival was 84%, that for primary patency was 61%, that for primary assisted patency was 77%, that for secondary patency was 80%, and that for limb salvage was 88%.

Conclusions: In this prospective, randomized, placebo-controlled clinical trial, ex vivo treatment of lower extremity vein grafts with edifoligide did not confer protection from reintervention for graft failure. (J Vasc Surg 2006;43:743-781.)
E2F in LEB

Conte et al

Index graft primary patency

Patients with primary patency of index graft (%)

Edifoligide (n=707)
Placebo (n=697)
Censor edifoligide
Censor placebo

Time (Days)

VASCULAR
Physicians
Healing • Teaching • Leading
B. Paclitaxel

- An anti-neoplastic drug derived from Pacific yew tree.
- Inhibits migration and proliferation by enhancing microtubule assembly.
Treatment

Restenosis and Drug-Eluting Stents

B. Paclitaxel

TAXUS I
- 61 patients with de novo or restenotic lesions
- Randomized to TAXUS stent or bare metal

Six-Month Edge Analysis: % Diameter Stenosis

Intimal hyperplasia is a complex response to injury.

Vascular reconstruction is effective in salvage of vein grafts if performed in time.

Antiplatelet agents are effective if given at or withing a short time of surgery.

Development of effective therapy requires an understanding of the underlying pathophysiology.
Restenosis after Carotid Interventions and Its Relationship with Recurrent Ipsilateral Stroke: A Systematic Review and Meta-analysis

R. Kumar a, A. Batchelder a, A. Saratzis a, A.F. AbuRahma b, P. Ringleb c, B.K. Lal d, J.L. Mas e, M. Steinbauer f, A.R. Naylor a,*

a Department of Vascular Surgery at Leicester Royal Infirmary, Leicester, UK
b Division of Vascular Surgery, West Virginia University, Charleston, VA, USA
c Neurologische Klinik der Ruprecht-Karls-Universität, Heidelberg, Germany
d Division of Vascular Surgery, University of Maryland, Baltimore, MD, USA
e Hospital Sainte-Anne, Université Paris-Descartes, Paris, France
f Department of Vascular and Endovascular Surgery, Regensburg, Germany

WHAT THIS PAPER ADDS
This meta-analysis of prospective surveillance data derived from nine randomised controlled trials found that CAS patients with an untreated asymptomatic > 70% restenosis had an extremely low rate of late ipsilateral stroke (0.8% over 50 months). CEA patients with an untreated, asymptomatic > 70% restenosis had a significantly higher risk of late ipsilateral stroke (compared with patients with no restenosis), but the risk was only 5% at 37 months. Overall, 97% of all late ipsilateral strokes after CAS and 85% after CEA occurred in patients with no evidence of a significant restenosis or occlusion.
Restenosis after Carotid Interventions

<table>
<thead>
<tr>
<th>Study</th>
<th>resten&gt;70%</th>
<th>resten&lt;70%</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-CI</th>
<th>W(fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREST_2012</td>
<td>1</td>
<td>58</td>
<td>18</td>
<td>1028</td>
<td>0.98 [0.13; 7.50]</td>
<td>37.0%</td>
</tr>
<tr>
<td>EVA_3S_2014</td>
<td>0</td>
<td>7</td>
<td>6</td>
<td>232</td>
<td>2.32 [0.12; 45.15]</td>
<td>7.9%</td>
</tr>
<tr>
<td>space_2009</td>
<td>0</td>
<td>54</td>
<td>12</td>
<td>553</td>
<td>0.40 [0.02; 6.80]</td>
<td>43.8%</td>
</tr>
<tr>
<td>Steinbauer_2008</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>26</td>
<td>1.31 [0.05; 35.97]</td>
<td>11.2%</td>
</tr>
<tr>
<td><strong>Fixed effect model</strong></td>
<td><strong>125</strong></td>
<td><strong>1839</strong></td>
<td></td>
<td></td>
<td><strong>0.87 [0.24; 3.21]</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: I-squared=0%, tau-squared=0, p=0.8529

Figure 2. Forest plot depicting the relationship between restenosis > 70% (or occlusion) or no restenosis > 70% after carotid artery stenting and the risk of late ipsilateral stroke in all randomised control trials.
Figure 3. Forest plot depicting the relationship between restenosis > 70% (or occlusion) or no restenosis > 70% after carotid artery stenting and the risk of late ipsilateral stroke in CREST, SPACE, and EVA-3S.
Figure 4. Forest plot depicting the relationship between restenosis > 70% (or occlusion) or no restenosis > 70% after carotid endarterectomy and the risk of late ipsilateral stroke all randomised control trials.
Table 4. Strokes associated with restenosis >70% or occlusion and whether a restenosis >70% was present on the DUS surveillance scan prior to stroke onset.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Restenosis &gt; 70% and ipsilateral stroke as published in RCTs</th>
<th>Restenosis &gt; 70% present on DUS scan prior to stroke onset (^a)</th>
<th>Revised stroke risk in patients with untreated &gt;70% restenosis (^b)</th>
<th>Revised stroke risk in patients with restenosis &lt; 70% (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbuRahma</td>
<td>200</td>
<td>1/15</td>
<td>0/1</td>
<td>0/14</td>
<td>1/186</td>
</tr>
<tr>
<td>AbuRahma</td>
<td>200</td>
<td>1/16</td>
<td>0/1</td>
<td>0/15</td>
<td>1/185</td>
</tr>
<tr>
<td>Naylor</td>
<td>272</td>
<td>2/11</td>
<td>1/2</td>
<td>1/10</td>
<td>7/262</td>
</tr>
<tr>
<td>CREST</td>
<td>1105</td>
<td>6/62</td>
<td>6/6</td>
<td>6/62</td>
<td>12/1043</td>
</tr>
<tr>
<td>EVA-3S</td>
<td>244</td>
<td>1/12</td>
<td>0/1</td>
<td>0/11</td>
<td>8/233</td>
</tr>
<tr>
<td>SPACE</td>
<td>589</td>
<td>2/23</td>
<td>0/2</td>
<td>0/21</td>
<td>10/568</td>
</tr>
<tr>
<td>Steinbauer</td>
<td>29</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/29</td>
</tr>
<tr>
<td>Stone</td>
<td>200</td>
<td>0/2</td>
<td>0/2</td>
<td>0/2</td>
<td>1/198</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2839</td>
<td>13/141 (9.2%)</td>
<td>7/13</td>
<td>7/135 (5.2%)</td>
<td>40/2704 (1.5%)</td>
</tr>
</tbody>
</table>

\(^a\) These additional data were provided by the PIs of the seven RCTs.

\(^b\) Revised calculation of the risk of late ipsilateral stroke in the presence of untreated restenoses > 70% and < 70% after CEA.
Figure 5. Forest plot depicting the relationship between restenosis > 70% (or occlusion) or no restenosis > 70% after carotid endarterectomy and the risk of late ipsilateral stroke in patients who did (or did not) have an untreated asymptomatic restenosis > 70% or occlusion prior to stroke onset.
Conclusions

• Carotid restenosis, although not uncommon, rarely leads to stroke

• Treating asymptomatic restenosis is unwarranted

• We need to know more….