Optimal Treatment of the 'High Risk' Patient with Carotid Artery Stenosis

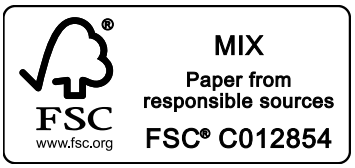
Talje Margriet Fokkema

Optimal Treatment of the 'High Risk' Patient with Carotid Artery Stenosis
Thesis, University of Utrecht, Faculty of Medicine, with a summary in Dutch
Proefschrift, Universiteit Utrecht, met een samenvatting in het Nederlands

ISBN/EAN 978-94-6108-534-4
Cover design: Esther Vinke
Printed by: Gildeprint Drukkerijen - The Netherlands

The printing of this thesis was financially supported by: Pie Medical Imaging B.V., Chipsoft B.V., Johnson & Johnson Medical B.V., Krijnen Medical Innovations B.V., W. L. Gore & Associates B.V., Chirurgisch Fonds UMC Utrecht

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowlegded.



Optimal Treatment of the 'High Risk' Patient with Carotid Artery Stenosis

De optimale behandeling van de 'hoog risico' patiënt met een carotis stenose
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus,
prof. dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen
op donderdag 28 november 2013 des ochtends te 10.30 uur

door

Talje Margriet Fokkema
geboren op 18 augustus 1986 te Rosmalen

Promotor:	Prof. dr. F.L. Moll
Co-promotoren:	Dr. G.J. de Borst Dr. M.L. Schermerhorn

CONTENTS

Introduction

Stroke is the leading cause of long-term disability in the western world with a significant proportion attributable to carotid artery stenosis.[1] Despite the decline in stroke mortality over time, the burden of stroke disability has major socio-economic consequences and will be an increasing public health priority.[2] This thesis focuses on the prevention of stroke or death due to carotid artery stenosis.

Carotid artery stenosis is usually caused by atherosclerosis, a systematic chronic inflammatory disease of the vessel wall in mainly medium and large sized arteries. Early lesions are initiated by intimal accumulation of lipoprotein particles and may remain asymptomatic for many years.[3] As the plaque continues to grow it expands in the arterial lumen and causes narrowing, or stenosis. Thrombus formation and plaque disruption contribute to progressive stenosis of the lumen and clinical symptoms. Symptoms that arise from the atherosclerotic carotid artery include cerebrovascular events such as transient ischemic attack (TIA) or ischemic stroke. Most extracranial atherosclerotic lesions develop in the internal carotid arteries at the level of the bifurcation.[4]

Carotid artery revascularization. Carotid endarterectomy (CEA), practiced since the 1950s, is an effective and durable revascularization procedure that consists of surgically removing the plaque that causes the stenosis. CEA eliminates a source of emboli, increases cerebral blood flow and prevents the progression of the stenosis. CEA compared to medically treated patients reduces future stroke in symptomatic patients with severe stenosis by more than half, despite the risk of stroke associated with surgery.[5,6] Also, for patients with moderate stenosis in the absence of neurological symptoms, CEA has been proven to be beneficial over best medical treatment, although the magnitude of benefit was considerably smaller than in symptomatic patients.[7,8] Over the past two decades, endovascular carotid artery stenting (CAS) has emerged as a less invasive alternative to CEA for the treatment of severe carotid artery stenosis. CAS has the potential advantages of a minimally invasive revascularization procedure, such as avoiding local surgical complications, reducing the risks of general anesthesia, and shortening hospital stay. Yet, CAS does not remove the atherosclerotic plaque, and may therefore be less durable than CEA. Independent of the use of embolic protection devices, CAS yields higher procedural stroke rates compared to CEA.[9,10]

Treatment strategy. The effectiveness of CEA over medical management for stroke prevention in patients with severe carotid artery disease has been extensively studied and has been widely adopted by clinicians. Yet, improvements in medical therapy and the addition of CAS to the surgical armamentarium has presented new patient selection challenges.[11] Currently, the CEA versus CAS comparison is a nuanced one requiring fine distinctions. Among an average risk population, CEA seems to exhibit lower rates of perioperative stroke and 'stroke or death' than CAS. On the other hand, CEA has increased risk for periprocedural cranial nerve injury (CNI) as well as myocardial infarction (MI).[10,12,13] Choosing a treatment strategy requires patient specific information regarding periprocedural risk of mortality and morbidity events. Preoperative symptom status has been shown to be one of the strongest predictors for postoperative outcome for both CAS and CEA.[14,15] A wide range of other patient related factors seem to influence

outcome, including demographics (gender, age and race), risk factors for vascular disease (e.g. hypertension, hypercholesterolemia, diabetes and smoking) and anatomical characteristics of the lesion (e.g. degree of stenosis, status of the contralateral carotid artery).[16] In addition, procedural variables (shunt use, practitioners' experience)[17] and histopathological factors of the carotid plaque itself seem to affect outcome.[18]

Rationale of this thesis

There has been significant effort to define the optimal treatment choices for individual patients. Critical in all discussions of procedural risk determination are the considerations of a subset of patients deemed 'high-risk' for surgery.[19,20] Patients with unfavorable anatomical features or medical comorbidities are usually considered as a high-risk group for CEA (Table).[21] The anticipated outcome of this subset of patients is poorer than their healthier counterparts, and therefore CAS is often proposed as an alternative, or even beneficial, treatment modality. While several high-risk criteria were used to enroll patients in CAS registries[22,23], the ability of these criteria to truly define high-risk remains unknown. Further, there is no clear evidence suggesting that the adverse event risk in these patients following CAS is lower than that of CEA.[24] Current guidelines from independent international organizations define 'high-risk' patients slightly differently and advocate different approaches to treatment.[25] Most studies were not able to report on outcomes stratified for the various subgroups among high-risk patients, since the vast majority were single center reports limited by small sample size. The larger registries and administrative databases may provide insight to these questions, but are often limited by the lack of detailed information on the particular high-risk variables.[26] In this thesis we sought to elucidate the concept of 'high-risk' and its impact on outcome. The main objective was to identify the optimal treatment strategy for the individual patient at 'high-risk' for carotid endarterectomy in the era of carotid stenting. Extensive research on the impact of particularly anatomical risk factors on outcome has been performed in order to identify the risks and benefits associated with different treatment modalities. In the search for the optimal treatment strategy, we consulted all available prospectively collected, non-randomized data. While a randomized study design may have been ideal to answer these questions; this is not feasible because of the small number of patients within the 'high-risk' subgroups, incombination with the low incidence of adverse events. Therefore, we critically assessed the consequences that were associated with carotid comparative analyses and risk stratification conducted in (large) datasets.

Outline of this thesis

This thesis is divided into three parts.
In part one we assessed two purported anatomic 'high-risk' factors, namely previous cervical radiation therapy and previous ipsilateral CEA. These factors have been identified as anatomical high-risk factors because they may result in a more difficult operation with subsequent less favorable outcome. We conducted a systematic review and meta-analysis of the current literature to identify all patients with a history of cervical radiation therapy that were treated for carotid artery disease. We did not find any differences in stroke rate between CAS and CEA. However, patients undergoing CEA were more likely to have cranial nerve injury, and patients

undergoing CAS had more restenosis **(Chapter 1).** In our own institutional carotid registry, we identified histological carotid plaque characteristics associated with radiation injury and showed a more stable plaque compared to the atherosclerotic plaque, which may account for the higher incidence of restenosis among these patients **(Chapter 2). Chapter 3 and 4** involved comparative analyses between CAS and CEA among patients who underwent revascularization for restenosis after prior ipsilateral CEA. While the risk of re-intervention was significantly increased compared to primary procedures, no differences in outcome were identified between CAS and CEA for both symptomatic and asymptomatic patients.

In part two we sought to identify the 'high risk' patient for carotid revascularization, among the 'normal' risk population. In **chapter 5** we assessed which anatomic or medical patient factors (as defined by the Centers for Medicaid and Medicare) may contribute to an increased stroke risk following CEA and/or CAS. In **chapter 6** we investigated whether the status of the contralateral artery impacts perioperative outcome in carotid revascularization procedures. We found that only certain patients were at increased risk due to contralateral artery stenosis or occlusion, depending on their degree of ipsilateral stenosis and symptom status. In **chapter 7** we assessed the clinical impact of CNI following CEA. While CNI may be seen as a disadvantage for CEA, we found the vast majority of lesions were transient. Contrary to prior work, we found that redo-CEA or prior cervical radiation therapy were not associated with increased risk for cranial nerve injury.

In part three we took a closer look at the consequences of research in large databases, specifically focusing on outcome analyses for carotid revascularization in frequently used databases. **Chapter 8** addressed the need for reporting and comparing 30-day outcomes after revascularization, since more than 30% of events appear to occur after hospital discharge. In **chapter 9** we showed the inability of state inpatient databases and the Nationwide Inpatient Sample to compare morbidity after revascularization procedures, despite the introduction of a present on admission indicator. We concluded this thesis with a general discussion and Dutch summary of our findings.

Table: Definition of 'high risk', adapted from the Centers for Medicare & Medicaid Services[27]

Patients at high risk for CEA are defined as having significant comorbidities and/or anatomic risk factors (i.e., recurrent stenosis and/or previous radical neck dissection), and would be poor candidates for CEA in the opinion of a surgeon. Significant comorbid conditions include but are not limited to:

Medical risk factors
Congestive heart failure (CHF) class III/IV;
Left ventricular ejection fraction (LVEF) < 30%;
Unstable angina;
Recent myocardial infarction (MI);

Anatomic risk factors
Contralateral carotid occlusion;
Previous CEA with recurrent stenosis;
Prior radiation treatment to the neck; and
other conditions that were used to determine patients at high-risk for CEA in the prior carotid artery stenting trials and studies.

References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation 2013;127:e6-e245.
2. Towfighi A, Saver JL. Stroke declines from third to fourth leading cause of death in the United States: historical perspective and challenges ahead. Stroke 2011;42:2351-5.
3. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993;362:801-9.
4. Perktold K, Resch M. Numerical flow studies in human carotid artery bifurcations: basic discussion of the geometric factor in atherogenesis. J Biomed Eng 1990;12:111-23.
5. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991;325:445-53.
6. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. Lancet 1991;337:1235-43.
7. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995;273:1421-8.
8. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004;363:1491-502.
9. Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet 2010;375:985-97.
10. Brott TG, Hobson RW, 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363:11-23.
11. Naylor AR. Is surgery still generally the first choice intervention in patients with carotid artery disease? Surgeon 2008;6:6-12.
12. Meier P, Knapp G, Tamhane U, Chaturvedi S, Gurm HS. Short term and intermediate term comparison of endarterectomy versus stenting for carotid artery stenosis: systematic review and meta-analysis of randomised controlled clinical trials. BMJ 2010;340:c467.
13. Economopoulos KP, Sergentanis TN, Tsivgoulis G, Mariolis AD, Stefanadis C. Carotid artery stenting versus carotid endarterectomy: a comprehensive meta-analysis of short-term and long-term outcomes. Stroke 2011;42:687-92.
14. Sidawy AN, Zwolak RM, White RA, Siami FS, Schermerhorn ML, Sicard GA. Risk-adjusted 30-day outcomes of carotid stenting and endarterectomy: results from the SVS Vascular Registry. J Vasc Surg 2009;49:71-9.
15. Halm EA, Tuhrim S, Wang JJ, Rockman C, Riles TS, Chassin MR. Risk factors for perioperative death and stroke after carotid endarterectomy: results of the new york carotid artery surgery study. Stroke 2009;40:221-9.
16. Bekelis K, Bakhoum SF, Desai A, Mackenzie TA, Goodney P, Labropoulos N. A risk factor-based predictive model of outcomes in carotid endarterectomy: the National Surgical Quality Improvement Program 2005-2010. Stroke 2013;44:1085-90.
17. Goodney PP, Wallaert JB, Scali ST, Stone DH, Patel V, Shaw P, et al. Impact of practice patterns in shunt use during carotid endarterectomy with contralateral carotid occlusion. J Vasc Surg 2012;55:61-71 e1.
18. Hellings WE, Peeters W, Moll FL, Piers SR, van Setten J, Van der Spek PJ, et al. Composition of carotid atherosclerotic plaque is associated with cardiovascular outcome: a prognostic study. Circulation 2010;121:1941-50.
19. Gasparis AP, Ricotta L, Cuadra SA, Char DJ, Purtill WA, Van Bemmelen PS, et al. High-risk carot-

id endarterectomy: Fact or fiction. Journal of Vascular Surgery 2003;37:40-6.
20. Mozes G, Sullivan TM, Torres-Russotto DR, Bower TC, Hoskin TL, Sampaio SM, et al. Carotid endarterectomy in sapphire-eligible high-risk patients: implications for selecting patients for carotid angioplasty and stenting. Journal of Vascular Surgery 2004;39:958-65.
21. Ricotta JJ, Malgor RD. A Review of the Trials Comparing Carotid Endarterectomy and Carotid Angioplasty and Stenting. Perspectives in Vascular Surgery and Endovascular Therapy 2008;20:299-308.
22. White CJ, Iyer SS, Hopkins LN, Katzen BT, Russell ME. Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. Catheter Cardiovasc Interv 2006;67:503-12.
23. Gray WA, Hopkins LN, Yadav S, Davis T, Wholey M, Atkinson R, et al. Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. J Vasc Surg 2006;44:258-68.
24. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493-501.
25. Paraskevas KI, Mikhailidis DP, Veith FJ. Comparison of the five 2011 guidelines for the treatment of carotid stenosis. J Vasc Surg 2012;55:1504-8.
26. Giles KA, Hamdan AD, Pomposelli FB, Wyers MC, Schermerhorn ML. Stroke and death after carotid endarterectomy and carotid artery stenting with and without high risk criteria. J Vasc Surg 2010;52:1497-504.
27. Centers for Medicare & Medicaid Services. (Accessed at http://www.cms.gov/medicare-coverage-database/.)

PART Ⅰ

Carotid stenting versus endarterectomy in the impaired neck

CHAPTER ONE

Stenting versus surgery in patients with carotid stenosis after previous cervical radiation therapy: systematic review and meta-analysis

Stroke
March 2012; Vol 43 Pages:793-801

Authors
Fokkema TM[1], den Hartog AG[1], Bots ML[2], van der Tweel I[2], Moll FL[1], de Borst GJ[1]

Affiliations
Department of Vascular Surgery[1] and Center for Health Sciences and Primary Care[2] University, Medical Center Utrecht, the Netherlands

ABSTRACT

Background and Purpose. Patients with both carotid stenosis and previously cervical radiation therapy (XRT) are considered 'high-risk' for carotid endarterectomy (CEA). Carotid angioplasty and stenting (CAS) seems a reasonable alternative, but neither the operative risk for CEA, nor the effectiveness of CAS has been proven. The purpose of this study is to evaluate perioperative and long-term outcome of both procedures in patients with XRT.

Methods. A systematic search strategy with the synonyms 'carotid artery stenosis' and 'cervical irradiation' was conducted in MEDLINE and EMBASE databases. To provide and compare estimates of outcomes, pooled and meta-regression analysis were performed.

Results. 27 Articles comprising 533 XRT patients (361 CAS and 172 CEA) fulfilled our inclusion criteria. Pooled analysis showed perioperative risk for 'any cerebrovascular adverse event' (CVE) of 3.9 % (95% Confidence Interval (CI) 2.3 – 6.7%) in CAS studies, against 3.5 % (95% CI 1.5 – 8.0%) in CEA studies ($p = 0.77$). Risk for cranial nerve injury (CNI) following CEA was 9.2% (95% CI 3.7 – 21.1%), versus none after CAS. Late outcome showed rates of CVE favoring CEA ($p = 0.014$). Rate of restenosis > 50% was significantly higher in patients treated with CAS procedure compared to CEA ($p < 0.005$).

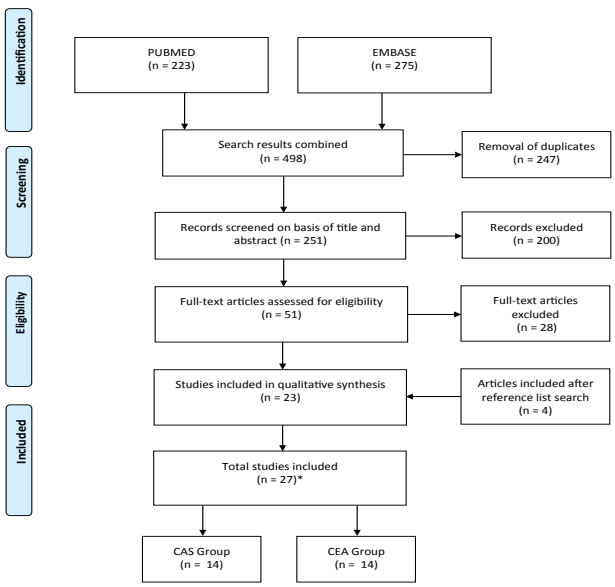
Conclusion. Both CAS and CEA proved to be feasible revascularization techniques with low risk for cerebrovascular adverse events. Although CEA patients suffered from more temporary CNI, higher rates of late CVE and restenosis were identified after CAS.

INTRODUCTION

The gold standard for treatment of symptomatic severe carotid stenosis is carotid endarterectomy (CEA), over medical treatment and carotid angioplasty and stenting (CAS). However, CAS has been proposed as the minimal invasive alternative for patients considered to be 'high-risk' for periprocedural events during CEA.[1-3] 'High-risk' is generally defined as anatomical or clinical factors that increase the risk of complications with surgery, ranging from stroke to peripheral nerve injury.[4] Several studies have been performed in these so-called 'high-risk' patients to evaluate safety and durability of CAS.[1, 2, 5-7] Despite favorable results on these aspects, generalizability is limited because no stratification was made within this group for the various different subgroups due to small patient populations.[8] Previous cervical radiation therapy is one assumed anatomical risk factor, resulting in a 'hostile' neck supposedly leading to technically more challenging surgery.[9] Reported causative factors include absent tissue planes in the diseased vessel wall and poor tissue healing through radiation-induced fibrosis. Whether these arguments are sufficiently valid to consider a previously irradiated patient (XRT) as a high-risk patient for surgery is questionable. After all, the concept of 'high-risk' remains confusing and should only be applied in the meaning of 'high-risk for adverse events in terms of periprocedural TIA or stroke'.

Patients with prior XRT form a small but important subgroup of the potential patients considered for either CEA or CAS, since radiation therapy seems to accelerate the development of severe stenosis, leading to an increased risk of stroke.[10] However, the optimal treatment strategy is not yet established, since no study to date has adequately assessed medical treatment options in primary and secondary stroke prevention in these patients.[11] In the present study, we reviewed current literature to investigate periprocedural and long-term outcome of CAS and CEA in patients with carotid stenosis and previous cervical radiation therapy.

Figure Flowchart of search strategy



* 1 Article included in both CAS and CEA Group

MATERIAL AND METHODS

The search strategy and collection of data in this study were performed according to the guidelines of MOOSE (Meta-analyses of observational studies in epidemiology).[12]

Search strategy. MEDLINE and EMBASE databases were searched on the 17th of October 2011, using the combination of synonyms for 'carotid artery stenosis' and 'cervical irradiation' to include all possible eligible studies. No restrictions or filters were applied. Additional studies were identified by searching the reference list of relevant studies. Studies published in books or abstracts of major meetings were searched using the search function on portable document formats. Final search queries are shown in Table I. A flowchart of the applied search strategy and selection process is summarized in Figure I.

Study selection. First, all duplicate articles were removed manually. Second, all citations were independently screened by two authors (MF and AGH), using predefined selection criteria. Inclusion criteria were: 1) Presenting data about XRT patients with carotid stenosis undergoing CEA and/or CAS, and 2) Reporting at least one relevant outcome measurement. Subsequently, the included articles were read full text and excluded if one of the following criteria were applicable: 1) Not meeting inclusion criteria; 2) Unsuitable study design (case report, review); 3) Articles under review. In case of disagreement regarding selection a third observer (GJB) was consulted to get consensus.

Table I Search queries

MEDLINE:

((carotid[tiab] OR extracranial[tiab]) AND (artery[tiab] OR vessel[tiab] OR bifurcation[tiab]) AND (stenosis[tiab] OR atherosis[tiab] OR disease[tiab]) OR "carotid stenosis"[tiab] OR "carotid atherosclerosis"[tiab]) AND ((neck[tiab] OR cervical[tiab] OR head and neck[tiab]) AND ((irradiation[tiab] OR radiation[tiab] OR radiotherapy[tiab])*

EMBASE:

(carotid:ab,ti OR extracranial:ab,ti AND (artery:ab,ti OR vessel:ab,ti OR bifurcation:ab,ti) AND (stenosis:ab,ti OR atherosis:ab,ti OR disease:ab,ti) OR 'carotid stenosis':ab,ti OR 'carotid atherosclerosis':ab,ti)*
AND (neck:ti,ab OR cervical:ti,ab OR 'head and neck':ti,ab) AND (irradiation:ti,ab OR radiation:ti,ab OR radiotherapy:ti,ab)

Data collection and items. The included articles were divided into two groups: 1) CAS group: studies on XRT patients undergoing CAS, and 2) CEA group: studies on XRT patients undergoing CEA. Additionally, we systematically extracted the following characteristics: author, publication date, number of patients, number of revascularizations, indication for intervention (symptomatic or asymptomatic stenosis), time interval between XRT and revascularization, length of follow up and outcome measures.

Primary outcome measures were: 1) Any cerebrovascular adverse event (CVE), defined as a composition of any stroke (fatal, disabling and non-disabling) and/or transient ischemic event (TIA), either ipsi- and/or contralateral of intervention site for periprocedural (< 30 days) and late (> 30 days) outcome. 2) Cranial nerve injury (CNI), specified in transient (no functional consequences and completely resolving < 30 days) and permanent (functional consequences and symptoms lasting > 30 days). 3) Restenosis and/or occlusion, where restenosis was defined as duplex ultrasound (US) derived > 50% stenosis, or otherwise if indicated, either symptomatic or asymptomatic.

Secondary outcome measures were procedural specific outcomes for both techniques. For CAS these included: technical success rate (defined as successful stent deployment with residual stenosis < 30% on control angiography or duplex US), vascular access site complication (haematoma or pseudo aneurysms) and cardiovascular complications (bradycardia or hypotension). For CEA these included: wound infection/ delayed healing and bleeding complications needing re-operation. Different descriptions across studies did not allow us to give more exact definitions for above outcome measures. Measure of outcome for perioperative outcomes was a 'proportion' (i.e. number of patients experiencing the event divided by total number of patients (n)); and for late outcome an 'incidence rate' (number of patients experiencing the event divided by total number of person-years (n x length of mean or median reported follow-up)).

Data presentation and statistical analysis. Data are presented as results per individual study in a descriptive manner and summarized systematically in tables. Results were evaluated separately for 1) early outcome (day of intervention (0) - 30 days) and 2) late outcome (> 30 days). Meta-analyses were performed to pool the primary outcome measures. A random effects model was chosen to adjust for heterogeneity between studies; I^2 was calculated as a measure for heterogeneity.[13] An I^2 value < 25% was considered as low heterogeneity.[14] To assess the difference between both procedures (CAS group and CEA group), meta-regression was performed with treatment procedure (CAS or CEA) as a factor. Meta-analyses were performed using SAS PROC NLMIXED (version 9.2). This procedure allows performance of an exact analysis using a binomial distribution for the early outcomes and a Poisson distribution for the late outcomes.[15]

RESULTS

MEDLINE and EMBASE search strategy yielded a total of 498 hits (Figure 1). After removal of duplicates and screening citations, 51 articles for full text evaluation remained. Of those, another 28 articles were excluded based on: not meeting inclusion criteria after critical full text evaluation (20), study design (7), article under review (1[16]). Four additional studies were retrieved from crossreferencing.[17-20] No additional studies were identified from books or abstract of major meetings. As a result, a total of 27 publications were included, comprising 533 patients divided in CAS group (14 articles[17, 19-31]; 361 patients, symptomatic: median 59% (Q_1-Q_3 = 51-75%)) and CEA group (14 articles[4, 9, 18, 21, 32-41]; 172 patients, symptomatic: median 67% (Q_1-Q_3 = 46-86%)).

Table II Study characteristics CAS

Author, year	Patients (n)	Procedures (n)	Symptomatic (%)	Dose (Gy) / interval (range) (years)	Use of embolic protection device (%)
Tallarita et al.[21] 2011	33	37	51	NA / 6.3 (NA)	68
Dorresteijn et al.[22] 2010	24	24	100	> 60 / 13.1 (NA)	NA
Sadek et al.[23] 2009	19	19	35*	NA	100
Favre et al.[24] 2008	135	149	34	NA /12 (NA)	59
Younis et al.[25] 2007	35	35	55*	NA	82.7*
Protack et al.[26] 2007	23	23	52	NA	75*
Ecker et al.[27] 2005	5	5	60	NA/ 16.6 (1 - 47)	80
Harrod-Kim et al.[28] 2005	16	19	75	NA	0
Hassen-Khodja et al.[29] 2004	13	13	80*	NA /15.2 (1- 41)	NA
McKevitt et al.[30] 2004	17	17	58*	NA	NA
Ting et al.[20] 2004	16	18	76	NA /12 (3 - 25)	22
Alric et al.[31] 2002	4	5	50	NA / NA (8 - 28)	75
Houdart et al.[17] 2001	7	10	86	NA / 8 (4 - 15)	20
Al Mubarak et al.[19] 2000	14	15	66	NA / 12.5 (NA)	0
Total	361	389	59†		

* data over entire study population, not specified for XRT patients; † Median; NA: no data available

1 Article was included in both groups.[21]All studies had an observational study design and were considered valid for inclusion. Characteristics of the individual studies are presented in table II (CAS group) and table III (CEA group).

Radiation therapy. Indications for XRT in general were head and neck squamous cell malignities (primary carcinoma's or lymph node metastases of unknown origin). Less common indications for cervical radiation were lymphoma's (Hodgkin and non-Hodgkin), parotid tumors and thyroid tumors. In most articles, radiation characteristics were poorly documented. Therefore, exact site (left or right carotid territory) of irradiation was not mentioned for all patients. The therapeutic dose was administered in only one article in CAS group (> 60 Gy in 71% of patients).[22] In the CEA group two articles reported 62 Gy resp. 43.5 Gy as a mean therapeutic dose.[34, 35] Range in the mean interval in years between RT and carotid revascularization was 6.3 – 16.6 years for the CAS group and 1.71 – 17.0 years for the CEA group. More than 50% of patients in the CEA group underwent previous neck surgery in combination with RT. For CAS group this was not clarified.

Table III Study characteristics CEA

Author, year	Patients n	Procedures n	Symptomatic %	Dose (range) / interval (range) years
Tallarita et al.[21] 2011	27	29	56	NA /1.71 (NA)
Frego et al.[4] 2009	8	8	NA*	NA
Boules et al.[32] 2005	9	9	39	NA
Mozes et al.[33] 2004	6	6	73	NA
Leseche et al.[34] 2003	27	30	60	62 Gy (50-70) / 10 (1 - 26)
Cazaban et al.[35] 2003	11	11	27	43.5 Gy (30-50) / 12.3 (2.5 - 32)
Friedell et al.[9] 2001	10	11	46	NA/ 14 (1 - 44)
Hassen-Kodja et al.[36] 2000	17	18	67	6300 rad /17 (NA)
Kashyap et al.[37] 1999	24	26	69	NA
Rockman et al.[38] 1996	10	14	46	NA/10.4 (NA)
Andros et al.[18] 1996	4	4	67*	> 5000 rad / 9.4 (1 - 37)
Atkinson et al.[39] 1989	7	9	100	NA
Francfort et al.[40] 1989	5	6	100	NA
Silverberg et al.[41] 1978	7	9	100	6151 rad (4290 - 12000) / NA
Total	172	190	67†	

Rad: Röntgen-absorbed dose; Gy: gray, 1 Gy = 100 rad; * not specified: >70% stenose (asympomatic and symptomatic patients); † Median; NA: no data available

Early outcome. Early results are shown in Table IV. In the CAS group (13 studies with 361 patients, 389 procedures), pooled analysis estimated a risk of 3.9 % (95% CI 2.3 – 6.7 %, I^2 = 22.1%) for CVE. One fatal stroke was seen in a series of 16 patients.[20] Technical success rate was reported varying from 94% - 100%. Six failures occurred: three needed conversion to surgery[24], one stent became lodged in the curve of the introducer sheet (only balloon dilatation was performed)[31], one was abandoned owing to failure to pass the guide wire across a tight lesion[20] and one patient suffered for residual stenosis after the procedure.[26]

In the CEA group (14 studies with 172 patients, 190 procedures), pooled analysis showed a risk of 3.5 % (95% CI 1.5 – 8.0 %, I^2 = 0%) for CVE. One death occurred due to massive intracerebral haemorrhage.[34] No statistically significant difference was encountered in occurrence of CVE between CAS and CEA (p = 0.77).

Meta-analysis of CNI resulted in an estimated risk of 9.2 % (95% CI 3.7 – 21.1 %) in patients with CEA treatment (12 studies with 157 patients). All injuries were considered to be initial and completely resolved within several weeks, although one study reported 9% (1/11) permanent CNI.[35] Six studies reporting on this specific endpoint did not encounter any nerve problem at all.[9, 18, 34, 38, 40, 41] Other procedure specific complications were incidental, including wound infection and bleeding needing re-intervention (Table IV).[21, 34, 36, 37]

Late outcome.

Clinical outcome: Data for CVE on follow-up extending the post-procedural 30 days were reported in 20 studies (398 patients). Results are summarized in Table V. In CAS group (11 studies, 277 patients) a total of 15 events occurred over a total follow up period of 697.9 person-years, an estimated rate of 4.9 per 100 person-years (95% CI 3.6 – 6.6). Two disabling strokes were identified contralateral of the CAS site in a series of 24 patients with a mean follow-up of 39.6 months.[22] Three other strokes were related to restenosis and occurred in a series of 135 patients at a mean interval of 16 months.[24] Another three ipsilateral strokes (2 major, 1 minor; not further defined) were identified in a series of 30 patients after a mean follow-up of 58 months, were one patient had carotid stent occlusion after 38 months.[21] No further information was provided on two strokes observed in the study by Protack et al. (23 patients, mean follow-up: 14.4 months).[26] In total, five TIA's were identified: one contralateral and one ipsilateral of the CAS site[22], one related to restenosis and two due to carotid thrombosis[24].

In CEA group (9 studies, 121 patients) only 1 event (TIA)[36] over a total of 386.7 person-years of follow-up was reported, on average 2.8 per 100 person-years (95% CI 2.0 – 3.9). The difference in CVE rate between both procedures was significant (p = 0.014).

Mortality: Mortality rate for CAS group and CEA group varied between 0 and 33% and 0 and 44.4% respectively. This rate seemed to be highly influenced by non-vascular causes of death such as pre-existent cancer in both groups.[21, 22, 24, 34, 36]

Restenosis: In CAS group (13 studies, 319 patients), 72 patients were identified with restenosis and/or occlusion after a total of 725.2 person-years of follow-up, an average rate of 5.4 per 100 person-years (95% CI 4.3 – 6.6). Large differences among studies existed. Two small studies[17, 27] (n = 5 and n = 7) found no restenosis and no re-interventions performed during follow-up (9.3 resp. 6 months). Two slightly larger studies both monitored 16 patients for respectively 30 and 28 months and found restenosis rates of 17.6% and 21%.[20, 28] The study with the largest patient population (n = 135) yielded an overall restenosis (>50%) rate of 18% (n = 27) at 30 months.[24] Seven (5.2%) of these led to neurological complications. In the study by Protack et al.[26] (mean follow-up 14.4 months), 43% of XRT patients developed restenosis. Also Dorresteijn et al.[22] showed a high rate of 42% restenosis in a series of 24 patients, measured over a follow-up length of two years. Nevertheless, all lesions remained asymptomatic and only in one patient re-stenting was performed. In CEA group (9 studies, 121 patients), 13 patients were diagnosed with > 50% restenosis and/or occlusion after a period of 386.7 person-years of follow-up, an average rate of 2.8 per 100 person-years (95% CI 1.9 – 4.0). The highest reported rate of restenosis was 16.6%; after a mean follow up of 18 months, duplex scans showed asymptomatic recurrent stenosis >50% in three out of 27 patients.[34] Another study showed 4 patients (15%) with asymptomatic restenosis after a mean follow up of 58 months. Because of progressive asymptomatic lesions, two of these patients were treated with CAS.[21] In the remaining studies, four other patients reached this specific endpoint; two in a series of 17 patients and two in a series of 24 patients, resulting in 11.8% (n=17) and 8.3% (n=24) restenosis rate respectively at 52 and 13 months.[36, 37] In each of these studies, one patient was symptomatic. In total three patients developed an ipsilateral occlusion.[9, 37, 41] Comparison of outcomes for restenosis and/or occlusion showed a significant difference favoring CEA (p = 0.0025).

Table IV Early outcome (0 - 30 days)

CAS group	N, P	Success rate (%)	Stroke (n)	Tia (n)	Procedure specific outcome (n)
Tallarita et al.[21]	33, 37	100	2	0	0
Dorresteijn et al.[22]	24, 24	100	1[a]	2	0
Sadek et al.[23]	19, 19	NA	0	0	Haematoma: 1
Favre et al.[24]	135, 149	98	2	1	Haematoma: 4 Technical problems: 13 Seizure: 1
Younis et al.[25]	35, 35	NA	-	-	-
Protack et al.[26]	23, 23	96	2*	*	Haematoma: 1 Vasospasm: 2 Bradycardia: 2
Ecker et al.[27]	5, 5	100	0	0	0
Harrod-Kim et al.[28]	16, 19	100	1[a]	0	Haematoma: 1
Hassen-Khodja et al.[29]	13,13	100	0	0	NA
McKevitt et al.[30]	17, 17	NA	0	0	NA
Ting et al.[20]	16, 18	94	1[c]	1	Haematoma: 1 Hypotension: 1
Alric et al.[31]	4, 5	80	0	0	0
Houdart et al.[17]	7, 10	100	0	0	Seizure: 1
Al Mubarak et al.[19]	14, 15	100	1[a]	0	0

CEA group		Stroke (n)	Tia (n)	CNI initial (n)/ permanent (n)	Procedure specific outcome (n)
Tallarita et al.[21]	27,29	1	0	6 / NA	Wound complications: 3
Frego et al.[4]	8, 8	0	0	1 / 0 †	0
Boules et al.[32]	9, 9	NA ‡	NA ‡	NA	0
Mozes et al.[33]	6, 6	NA §	NA §	NA ‖	0
Leseche et al. [34]	27, 30	1[c]	1	0	Haematoma: 2
Cazaban et al. [35]	11, 11	0	0	02-jan	0
Friedell et al.[9]	10, 11	0	0	0	0
Hassen-Kodja et al.[36]	17, 18	0	0	2 / 0	Haematoma: 1
Kashyap et al.[37]	24, 26	0	0	6 / 0	Infection: 2
Rockman et al.[38]	10, 14	0	0	0	0
Andros et al.[18]	4, 4	0	0	0	0
Atkinson et al.[39]	7, 9	0	0	2 / 0	0
Francfort et al.[40]	5, 6	0	1	0	Respiratory problems: 2
Silverberg et al.[41]	7, 9	0	0	0	Postoperative thrombosis: 1

[a] non-disabling stroke; [b] disabling stroke; [c] fatal stroke/death; Tia: transient ischemic attack; CNI: cranial nerve injury; N: number of patients; P: number of procedures; * Any cerebrovascular event, not specified into stroke or tia; † Outcome not specified for XRT patients; ‡ 11% 'poor outcome': a composition of stroke, tia or death; § Odds ratio for tia/stroke: 15.2; ‖ CNI over entire study population (high-risk patients): 7.7%; NA: No data available

Table V Late outcome (> 30 days)

CAS group	Mean follow-up (range) (months)	Tia (n)	Stroke (n)	Death (n)	Restenosis (n) / occlusion (n)
Tallarita et al.[21]	58 (1 – 132)	0	3	11	6 / 2
Dorresteijn et al.[22]	39.6 (3.6 – 132)	2	2[b]	7	7 / 0
Sadek et al.[23]	9 (0.5 - 45)	NA	NA	NA	1 / 0
Favre et al.[24]	30 (3 - 95)	3	3	30	18 / 9
Younis et al.[25]	24 (6 - 99)	NA	NA	NA	7 / 0
Protack et al.[26]	14.4 (NA)	0	2	2	9 / 2
Ecker et al.[27]	9.3 (1 - 24)	0	0	0	0
Harrod-Kim et al.[28]	28 (5 - 78)	0	0	1	4 / 2
Hassen-Khodja et al.[29]	18 (NA)	0	0	0	1 / 0
McKevitt et al.[30]	1	-	-	-	-
Ting et al.[20]	30 (5 - 55)	0	0	2	3 / 0
Alric et al.[31]	10 (3 - 18)	0	0	0	1 / 0
Houdart et al.[17]	8 (3 - 24)	0	0	0	0
Al Mubarak et al.[19]	8 (NA)	0	0	3	0*
CEA group					
Tallarita et al.[21]	58 (1 – 132)	0	0	3	4 / 0
Frego et al.[4]	40 (0-156)	0	0	0	0†
Boules et al. [32]	1	-	-	-	-
Mozes et al.[33]	1	-	-	-	-
Leseche et al.[34]	40 (3 - 99)	0	0	12	3 / 0
Cazaban et al.[35]	1	-	-	-	-
Friedell et al.[9]	37 (12 - 60)	0	0	0	0 / 1
Hassen-Kodja et al.[36]	52 (12 - 108)	1	0	4	2 / 0
Kashyap et al.[37]	13 (1 - 156)	0	0	0	2 / 1
Rockman et al.[38]	NA	NA	NA	NA	NA
Andros et al.[18]	24.9 (NA)	0	0	1	0
Atkinson et al.[39]	49 (NA)	0	0	1	0
Francfort et al.[40]	26 (6 - 48)	0	0	2	0
Silverberg et al.[41]	NA	NA	NA	NA	NA

[a] non-disabling stroke; [b] disabling stroke; [c] fatal stroke/death; Tia: transient ischemic attack;
* Measured at 6 months of follow-up; † Defined as duplex US derived > 30% stenosis; NA: No data available

DISCUSSION

In this systematic review and meta-analysis we present an overview of 533 patients, treated with CAS or CEA for carotid stenosis after previous cervical radiation therapy (CAS group, n = 361; CEA group, n = 172). The risk for adverse cerebrovascular events was low following CEA and CAS for both perioperative and late outcome. However, results were statistically different for late outcome favoring CEA. CEA was hampered by a mean risk of 9.2 % of -mostly transient- cranial nerve injury, against none after CAS. Furthermore, higher rates of restenosis >50% and occlusion after CAS compared to CEA were identified (p = 0.0025). However, most in-stent restenoses behaved in a benign fashion and remained asymptomatic.

Treatment of carotid stenosis after cervical radiation needs special interest as in the past decennia survival after cervical malignancy has increased. Simultaneously, the risk for relevant carotid stenosis seems to increase.[42] Several carotid intervention studies defined XRT patients as a 'high-risk' group for carotid endarterectomy.[2, 43, 44] This classification remains controversial because definition was based on theoretical arguments and still no risk stratification for XRT patients exists today.[45] Additionally, the concept of high-risk is doubtful and multiple interpretable: patients can be either high-risk for stroke or high-risk for surgery, or both.[46] Notwithstanding, radiation was accepted as one of the anatomic high-risk criteria among contralateral occlusion, previous ipsilateral endarterectomy and high carotid bifurcation, thus XRT patients were included in studies investigating the effectiveness and safety of CAS in deemed high-risk groups.[1, 5] Although appraisal of subset analyses in these studies are not precise due to the small patient populations, yet, the XRT group often showed better but non significant perioperative results compared to the other high-risk subgroups. One study on CAS found the combined all stroke/death risk in the overall high-risk group (n =103) was 9.7%, versus 7% in a non-high-risk control group (n = 373) (p > 0.05).[30] However, the all stroke/death risk in the XRT subgroup (n = 17) was 0%. Others found that the periprocedural risk of CAS in XRT patients appeared to be comparable to CAS in non-XRT patients.[23, 47] By performing this review we aim to expand this evidence by identifying that CAS and CEA can be performed safely for revascularization of XRT patients with carotid stenosis, with no early deaths and low risk for CVE. On the other hand, even like in recent prospective randomized studies in symptomatic patients at 'normal risk',[48, 49] late clinical events happened more frequently after endovascular repair as compared to CEA (p = 0.014). Furthermore, rates for restenosis were higher after CAS as compared to both CEA and non-XRT references for the treatment of carotid artery stenosis. In four studies,[22, 24-26] CAS was initially feasible in XRT patients, but during follow-up, restenosis rates were significantly higher than in other deemed high-risk subgroups. The underlying mechanism leading to in-stent restenosis after CAS is explained by myointimal hyperplasia with smooth muscle cell proliferation. Stent deployment in a pre-existent fibrotic (post-radiation) process may be associated with faster and higher incidence of restenosis.[25] Contrary to CAS, rates for restenosis after CEA seem to be comparable to those with surgery in the absence of radiotherapy.[9, 29, 37] Only Leseche et al.[34] suggest that in patients who experienced cervical radiation, restenosis is markedly higher than in those patients without XRT. However, no data were provided on the exact location of restenosis why as these restenoses might have occurred somewhere else in the radiated plane or in-stent/ within the region of previous endarterectomy.

One of the main concerns towards CEA in patients with a history of cervical radiation is the potentially higher rate of cranial nerve injury. Outside standard conditions, theoretically cranial nerve deficits may be more frequent in hostile necks[4]; and perivascular soft tissue fibrotic changes probably explain the greater risk.[50] A literature review calculated a 9% risk (range 2-27%) of temporary palsy after CEA in patients without a hostile neck.[51] Two other extensive studies reported a rate of 5%, with only 0.5% lasting more than a few months in patients at normal risk.[52, 53] Furthermore, a rate of 7.7% in a high-risk group with local risk factors was observed, without significant difference with the reference low-risk group (6.6%)[33]. These outcomes were very comparable with our pooled estimate of 9.2% of initial deficits, which were transient in most cases. Therefore, the risk for permanent CNI should probably not being considered as a contraindication for CEA in irradiated patients. However, we should state that we were not informed about the exact preoperative tissue condition of the treated cervical region, and details on combined XRT and cervical surgery could not reliably be analyzed, possibly influencing this consideration. In a recent study[21] this issue was well documented, were patients with prior radical neck dissections had more wound complications (14% vs. 5%) and CNI (28% vs. 9%) compared to those without neck dissections. Thus, if the cervical anatomy is highly affected not only by XRT, but especially through previous surgery making redo-surgery hazardous, CAS might be considered as a suitable alternative. The relative impact of patients' characteristics on the risk of complications for CAS or CEA have led to different approach to perform meta-analysis.[54] Due to limited patient data for XRT induced carotid stenosis, we were not able to select best technique on the basis of particular patient characteristics. The role of medical treatment in limiting disease progression and prevention of stroke in previously radiated patients stays unclear at this point.

Study limitations. Main problem of lack of randomized studies is the inevitable confounding by indication. Patient selection must have resulted in differences in outcome, which favored CEA, probably since less appropriate surgical candidates (e.g. due to previous neck surgery) were excluded for this procedure and treated by CAS. Moreover, as a consequence of small individual sample sizes and lack of reporting specific details, we were not able to distinguish between results of symptomatic or asymptomatic status as the initial indication for revascularization. Also inherent to meta-analysis of observational studies is the chance of publication bias. Although we included all available study data in the literature of the past decades, we could have missed outcomes of a few patients, especially of articles where XRT patients were not well stratified from other high-risk groups. Furthermore, assessment of generally accepted duplex criteria for grading stenosis after CEA has been shown to be not reliable after CAS, because placement of a stent in the carotid artery can cause an increase in duplex velocities in the absence of residual or true in-stent stenosis.[55] This could have led to distorted outcomes in CAS group. Finally, decreasing trends in stroke and mortality are usually observed as techniques and technology is improving. Therefore older studies could possibly lead to worsened results for total outcome especially within the CAS treated cohort. Yet, there is a therapeutic dilemma that calls for a randomized comparison. Based on the low risks and the limited number of patients a trial needs to be a randomized interventional multicenter study.

Conclusions and recommendations. According to the available literature, both CAS and CEA proved to be feasible revascularization techniques with low risk for cerebrovascular adverse events in patients with previous XRT. CEA patients suffered from more temporary CNI, while patients treated with CAS showed to have a greater risk on late CVE and restenosis >50%. These results do not indicate a preferred revascularization treatment and therefore, in patients with previous cervical radiation the choice for revascularization therapy should be considered on an individual basis.

References

1. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351:1493-501.
2. Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2008;358:1572-9.
3. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke. *Circulation*. 2006;113:e409-49.
4. Frego M, Bridda A, Ruffolo C, Scarpa M, Polese L, Bianchera G. The hostile neck does not increase the risk of carotid endarterectomy. *J Vasc Surg*. 2009;50:40-7.
5. Gray WA, Hopkins LN, Yadav S, Davis T, Wholey M, Atkinson R, et al. Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. *J Vasc Surg*. 2006;44:258-68.
6. Shin SH, Stout CL, Richardson AI, DeMasi RJ, Shah RM, Panneton JM. Carotid angioplasty and stenting in anatomically high-risk patients: Safe and durable except for radiation-induced stenosis. *J Vasc Surg*. 2009;50:762-7; discussion 7-8.
7. Sadek M, Hynecek RL, Sambol EB, Ur-Rehman H, Kent KC, Faries PL. Carotid angioplasty and stenting, success relies on appropriate patient selection. *J Vasc Surg*. 2008;47:946-51.
8. Chen YY. Critical evaluation: Review of the SAPPHIRE trial and the role of stenting in carotid stenosis. *ANZ J Surg*. 2009;79:82-4.
9. Friedell ML, Joseph BP, Cohen MJ, Horowitz JD. Surgery for carotid artery stenosis following neck irradiation. *Ann Vasc Surg*. 2001;15:13-8.
10. Dorresteijn LD, Marres HA, Bartelink H, Kappelle LJ, Boogerd W, Kappelle AC. Radiotherapy of the neck as a risk factor for stroke. *Ned Tijdschr Geneeskd*. 2005;149:1249-53.
11. Plummer C, Henderson RD, O'Sullivan JD, Read SJ. Ischemic stroke and transient ischemic attack after head and neck radiotherapy: a review. *Stroke*. 2011;42:2410-8.
12. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of Observational Studies in Epidemiology. *JAMA*. 2000;283:2008-12.
13. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*. 2002;21:1539.
14. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-60.
15. Hamza TH, van Houwelingen HC, Stijnen T. The binomial distribution of meta-analysis was preferred to model within-study variability. *J Clin Epidemiol*. 2008;61:41-51.
16. Chiu YW, Lin MS, Kao HL. Carotid artery stenting in radiotherapy related stenosis: safe and durable. *Eur Heart J*. 2010;31:511.
17. Houdart E, Mounayer C, Chapot R, Saint-Maurice JP, Merland JJ. Carotid stenting for radiation-induced stenoses: A report of 7 cases. *Stroke*. 2001;32:118-21.
18. Andros G, Schneider PA, Harris RW, Dulawa LB, Oblath RW, Salles-Cunha SX. Management of arterial occlusive disease following radiation therapy. *Cardiovasc Surg*. 1996;4:135-42.
19. Al-Mubarak N, Roubin GS, Iyer SS, Gomez CR, Liu MW, Vitek JJ. Carotid stenting for severe radiation-induced extracranial carotid artery occlusive disease. *J Endovasc Ther*. 2000;7:36-40.
20. Ting AC, Cheng SW, Yeung KM, Cheng PW, Lui WM, Ho P, et al. Carotid stenting for radiation-induced extracranial carotid artery occlusive disease: efficacy and midterm outcomes. *J Endovasc Ther*. 2004;11:53-9.
21. Tallarita T, Oderich GS, Lanzino G, Cloft H, Kallmes D, Bower TC, et al. Outcomes of carotid artery stenting versus historical surgical controls for radiation-induced carotid stenosis. *J Vasc Surg*. 2011;53:629-36.e5.
22. Dorresteijn LD, Vogels OJ, de Leeuw FE, Vos JA, Christiaans MH, Ackerstaff RG, et al. Outcome of carotid artery stenting for radiation-induced stenosis. *Int J Radiat Onc Biol Phys*. 2010;77:1386-90.

23. Sadek M, Cayne NS, Shin HJ, Turnbull IC, Marin ML, Faries PL. Safety and efficacy of carotid angioplasty and stenting for radiation-associated carotid artery stenosis. *J Vasc Surg*. 2009;50:1308-13.
24. Favre JP, Nourissat A, Duprey A, Nourissat G, Albertini JN, Becquemin JP. Endovascular treatment for carotid artery stenosis after neck irradiation. *J Vasc Surg*. 2008;48:852-8.
25. Younis GA, Gupta K, Mortazavi A, Strickman NE, Krajcer Z, Perin E, et al. Predictors of carotid stent restenosis. *Catheter Cardiovasc Interv*. 2007;69:673-82.
26. Protack CD, Bakken AM, Saad WA, Illig KA, Waldman DL, Davies MG. Radiation arteritis: A contraindication to carotid stenting? *J Vasc Surg*. 2007;45:110-7.
27. Ecker RD, Donovan MT, Hopkins LN. Endovascular management of carotid artery disease after radiation therapy and radical neck dissection. *Neurosurg Focus*. 2005;18:e8.
28. Harrod-Kim P, Kadkhodayan Y, Derdeyn CP, Cross Iii DT, Moran CJ. Outcomes of carotid angioplasty and stenting for radiation-associated stenosis. *Am J Neuroradiol*. 2005;26:1781-8.
29. Hassen-Khodja R, Kieffer E. Radiotherapy-induced supra-aortic trunk disease: Early and long-term results of surgical and endovascular reconstruction. *J Vasc Surg*. 2004;40:254-61.
30. McKevitt FM, Macdonald S, Venables GS, Cleveland TJ, Gaines PA. Is the endovascular treatment of carotid stenosis in high-risk patients really safer than carotid endarterectomy? *Cerebrovasc Dis*. 2004;17:332-8.
31. Alric P, Branchereau P, Berthet JP, Mary H, Marty-Ane C. Carotid artery stenting for stenosis following revascularization or cervical irradiation. *J Endovasc Ther*. 2002;9:14-9.
32. Boules TN, Proctor MC, Aref A, Upchurch Jr GR, Stanley JC, Henke PK. Carotid endarterectomy remains the standard of care, even in high-risk surgical patients. *Ann Surg*. 2005;241:356-63.
33. Mozes G, Sullivan TM, Torres-Russotto DR, Bower TC, Hoskin TL, Sampaio SM, et al. Carotid endarterectomy in SAPPHIRE-eligible high-risk patients: Implications for selecting patients for carotid angioplasty and stenting. *J Vasc Surg*. 2004;39:958-66.
34. Leseche G, Castier Y, Chataigner O, Francis F, Besnard M, Thabut G, et al. Carotid artery revascularization through a radiated field. *J Vasc Surg*. 2003;38:244-50.
35. Cazaban S, Maiza D, Coffin O, Radoux JM, Mai C, Wen HY. Surgical treatment of recurrent carotid artery stenosis and carotid artery stenosis after neck irradiation: evaluation of operative risk. *Ann Vasc Surg*. 2003;17:393-400.
36. Hassen-Khodja R, Sala F, Declemy S, Lagrange JL, Bouillane PJ, Batt M. Surgical management of atherosclerotic carotid artery stenosis after cervical radiation therapy. *Ann Vasc Surg*. 2000;14:608-11.
37. Kashyap VS, Moore WS, Quinones-Baldrich WJ. Carotid artery repair for radiation-associated atherosclerosis is a safe and durable procedure. *J Vasc Surg*. 1999;29:90-6; discussion 7-9.
38. Rockman CB, Riles TS, Fisher FS, Adelman MA, Lamparello PJ. The surgical management of carotid artery stenosis in patients with previous neck irradiation. *Am J Surg*. 1996;172:191-5.
39. Atkinson JL, Sundt TM, Jr., Dale AJ, Cascino TL, Nichols DA. Radiation-associated atheromatous disease of the cervical carotid artery: report of seven cases and review of the literature. *Neurosurgery*. 1989;24:171-8.
40. Francfort JW, Gallagher JF, Penman E, Fairman RM. Surgery for radiation-induced symptomatic carotid atherosclerosis. *Ann Vasc Surg*. 1989;3:14-9.
41. Silverberg GD, Britt RH, Goffinet DR. Radiation-induced carotid artery disease. *Cancer*. 1978;41:130-7.
42. Cheng SW, Wu LL, Ting AC, Lau H, Lam LK, Wei WI. Irradiation-induced extracranial carotid stenosis in patients with head and neck malignancies. *Am J Surg*. 1999;178:323-8.
43. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA*. 1995;273:1421-8.
44. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. *Stroke*. 1991;22:711-20.

45. Gasparis AP, Ricotta L, Cuadra SA, Char DJ, Purtill WA, Van Bemmelen PS, et al. High-risk carotid endarterectomy: fact or fiction. *J Vasc Surg*. 2003;37:40-6.
46. de Borst GJ, Moll FL. Regarding: "carotid angioplasty and stenting in anatomically high-risk patients: safe and durable except for radiation-induced stenosis". *J Vasc Surg*. 2010;51:1077; author reply -8.
47. Bates ER, Babb JD, Casey DE, Jr., Cates CU, Duckwiler GR, Feldman TE, et al. ACCF/SCAI/SVMB/SIR/ASITN 2007 Clinical Expert Consensus Document on carotid stenting. *Vasc Med*. 2007;12:35-83.
48. Mas JL, Trinquart L, Leys D, Albucher JF, Rousseau H, Viguier A, et al. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol*. 2008;7:885-92.
49. Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet*. 2010;375:985-97.
50. Cheng SW, Ting AC, Ho P, Wu LL. Accelerated progression of carotid stenosis in patients with previous external neck irradiation. *J Vasc Surg*. 2004;39:409-15.
51. Sajid MS, Vijaynagar B, Singh P, Hamilton G. Literature review of cranial nerve injuries during carotid endarterectomy. *Acta Chir Belg*. 2007;107:25-8.
52. Cunningham EJ, Bond R, Mayberg MR, Warlow CP, Rothwell PM. Risk of persistent cranial nerve injury after carotid endarterectomy. *J Neurosurg*. 2004;101:445-8.
53. Greenstein AJ, Chassin MR, Wang J, Rockman CB, Riles TS, Tuhrim S, et al. Association between minor and major surgical complications after carotid endarterectomy: results of the New York Carotid Artery Surgery study. *J Vasc Surg*. 2007;46:1138-44; discussion 45-6.
54. Touze E, Trinquart L, Chatellier G, Mas JL. Systematic review of the perioperative risks of stroke or death after carotid angioplasty and stenting. *Stroke*. 2009;40:e683-93.
55. de Borst GJ, Meijer R, Lo RH, Vosmeer HW, Ackerstaff RG, Moll FL. Effect of carotid angioplasty and stenting on duplex velocity measurements in a porcine model. *J Endovasc Ther*. 2008;15:672-9.

CHAPTER TWO

Radiation-induced carotid stenotic lesions have a more stable phenotype than de novo atherosclerotic plaques

European Journal of Vascular and Endovascular Surgery
June 2012; Vol 43 Pages: 643-8

Authors
Fokkema M[1], den Hartog AG[1], van Lammeren GW[1,2], Bots ML[3], Pasterkamp G[2], Vink A[4], Moll FL[1], de Borst GJ[1]

Affiliations
Department of Vascular Surgery[1], Experimental Cardiology Laboratory[2], Julius Center for Health Sciences and Primary Care[3] and Department of Pathology[4], University Medical Center Utrecht, The Netherlands

ABSTRACT

Objective. To identify plaque characteristics of carotid artery radiation induced stenosis.

Materials and Methods. Nineteen carotid plaques were obtained during carotid endarterectomy (CEA) in 17 consecutive patients with prior cervical radiation therapy (XRT) (median interval 10 years) and compared with 95 matched control carotid plaques of patients without a history of XRT. The following histopathological factors were assessed: calcification, collagen, macrophages, smooth muscle cells, atheroma, microvessels and intraplaque hemorrhage. Association of individual histological parameters with XRT-plaque was analyzed through multivariable regression model.

Results. Less infiltration of macrophages (6/19 vs. 60/95, adjusted $p = 0.003$) and a smaller lipid core size (Atheroma > 10%: 10/19 vs. 80/95, adjusted $p = 0.006$) were independently associated with XRT plaque, compared to non-XRT plaques.

Conclusions. Carotid stenotic lesions in patients with previous cervical radiation are less inflammatory and more fibrotic than carotid atherosclerotic lesions in non-radiated patients.

INTRODUCTION

Severe carotid stenosis after previous cervical radiation is considered a high-risk condition for revascularization.[1] A causal relationship of cervical radiation therapy (XRT) and development of carotid stenosis has been shown in previous studies.[2, 3] Furthermore, in patients with carotid stenosis following prior XRT for head and neck malignancy, an increased stroke rate was demonstrated as compared to patients without a history of XRT.[4]

The underlying physiopathological mechanism of carotid stenosis after cervical XRT resulting in higher stroke risk remains unclear, although different pathways have been suggested.[5, 6] Differences between atherosclerotic induced stenosis (AIS) and carotid stenosis after XRT have mainly been based on description of macroscopic morphologic lesion components and clinical patient characteristics. Clinically, XRT patients are younger and have a lower incidence of other risk factors (except hyperlipidemia) for atherosclerosis compared to non-XRT patients. Morphologically, XRT lesions have a higher degree of stenosis, are likely to be longer and appear on non-typical atherosclerotic sites (more frequent in external and common carotid artery).[7-9] Additionally, lesions of XRT patients frequently demonstrated a hypoechoic focus and less often shadowing compared with plaques found in atherosclerotic patients.[8] These findings indicate that lesions in previously irradiated patients might act as a different disease entity compared to AIS. However, differences in histological plaque characteristics have not been reported to date.

Phenotype of carotid plaque has proven to be clinically relevant, due to close associations with presenting primary cerebrovascular events.[10] In addition, the local atherosclerotic plaque composition has been shown to be an independent predictor of both future cardiovascular events and restenosis.[10, 11] Thus far, only animal studies and high-resolution magnetic resonance imaging (MRI) studies have attempted to identify characteristics in carotid plaques after radiation. With help of our longstanding Athero-Express biobank[12] we aimed to study carotid plaques microscopically, to identify plaque phenotype of patients with prior cervical XRT.

METHODS

Design. This cross-sectional study was designed on patients who have been included in the Athero-Express biobank (2002-2009). Athero-Express is an ongoing longitudinal prospective study that includes patients undergoing CEA in the participating centers St. Antonius Hospital Nieuwegein and University Medical Center Utrecht.[12] After CEA, the carotid plaque is collected and subjected to histological examination. All patients were asked to participate and provided written informed consent. Data of patients were collected prospectively, except for specific radiation characteristics, which were gathered retrospectively. Baseline characteristics included 1) demographic data: gender, age (at time of surgery), preoperative clinical presentation (asymptomatic, TIA, stroke and ocular symptoms), time between last symptoms and CEA, degree of ipsilateral stenosis (diagnosed by carotid colour Doppler assisted duplex ultrasound and in most cases confirmed by magnetic resonance angiography (MRA) or computed tomography angiography (CTA)); and 2) risk factors for atherosclerotic disease: (current) smoking, hypertension, hypercholesterolemia, diabetes mellitus (DM), coronary artery disease (CAD), peripheral artery disease of the lower limbs, renal function (expressed in glomerular filtration rate, GFR (ml/min/1.73m2) and body mass index (BMI) (kg/m^2). Hypertension and hypercholesterolemia were

by definition restricted to those cases using blood pressure-lowering drugs respectively statins. DM was defined as use of insulin or oral glucose inhibitors.

Patients. All previously radiated patients (XRT group) underwent consecutively CEA with histological plaque analysis according to the Athero-Express protocol. All patients with previous cervical radiation and CEA were selected out of the Athero-Express database. They were matched to patients (out of the same database) without a history of cervical radiation therapy (non-XRT group) for 1) gender, 2) age (at time of surgery) and 3) clinical presentation. A control group of non-XRT plaques (1:5 ratio) was selected per XRT plaque, based on previously recommended criteria for case control studies.[13] In the total study period, 1250 CEA's were performed for 85% symptomatic and 15% asymptomatic patients. Of those, 19 carotid plaques (1.5% of total surgeries) from 17 consecutive patients (median age: 69 years (range 56-92), 15 males) with previous cervical XRT were compared to 95 matched controls (median age: 69 years (range 56-90), 76 males) without a history of cervical XRT. The same treatment regimen was followed for radiated and non-radiated patients.

Plaque assessment & outcome. Conform a standardized protocol, the carotid plaque obtained during CEA was divided into segments of 5 mm thickness along the longitudinal axis.[12] The segment with the greatest plaque burden, the culprit lesion, was subjected to histological examination. Outcome of plaque characteristics was analyzed microscopically by observers of the Athero-Express blinded for XRT status. Histological outcome parameters were widely accepted measures for atherosclerotic plaque stability and included: calcification, collagen, macrophages, smooth muscle cells (SMC), fat, microvessels and intraplaque hemorrhage (IPH). Semiquantitative estimation of the plaque morphology was performed for calcification (hematoxylin and eosin [H&E]), collagen (picro Sirius red [PSR]), macrophages (CD 68) and SMC (alpha actin). Plaque characteristics were scored as 1) no/minor staining or 2) moderate/heavy staining. In addition, atheroma (PSR and H&E) was analyzed as the percentage of the plaque occupied by the lipid core (<10% or >10%). Microvessels (CD 34) were determined by the average number of CD 34-immunopositive microvessels of three hotspots within every plaque. For multivariable analysis, amount of microvessels was dichotomized as either below or above the median. IPH (H&E and Elastin von Gieson stainings) was rated as being absent or present.
Finally, overall plaque phenotype was established by overall appearance. A plaque is considered more active and unstable when it reveals a strong staining for macrophages, a large atheroma and when it lacks collagen and smooth muscle cells.[14] The more fibrous stable lesion typically lacks inflammatory cells and fat and reveals strong staining for collagen and smooth muscle cells. The Athero-Express defines this as: fibrous plaque (<10% of the plaque is occupied by lipid with abundant presence of collagen and SMC), fibro-atheromatous plaque 10-40% (between 10-40% is occupied by fat) and atheromatous plaque (>40% of the plaque hides atheroma with presence of macrophages).[12]

Statistical analysis. SPSS 17.0 was used for all analyses (SPSS Inc, Chicago, Ill). For dichotomized factors we used crosstabs and Chi-square tests to calculate absolute risks (%) and p-values. Continuous characteristics were analyzed with non-parametric Mann-Whitney U test since

parameters were not normally distributed. P-values < 0.05 were considered statistically significant. The univariate analysis including baseline parameters served as the basis for a multivariable logistic regression model to test if the histological parameters were independently associated with XRT-plaque. Baseline characteristics showing association (P < 0.20) with XRT exposure in univariate analysis were included in the (unconditional) multivariable model to correct for confounders. Associations were calculated using 'enter' method and reported as adjusted odds ratios (ORs) with 95% confident intervals (CIs) for all variables in the final model.

RESULTS

XRT patients. Median interval between cervical radiation therapy and carotid revascularization was 10 years (range 1.8 – 24.0 years). The underlying malignant disease indicating XRT was: pharyngeal carcinoma (n=4, 23.6%), laryngeal carcinoma (n=4, 23.6%), cervical metastases of unknown primary tumor (n=3, 17.6%), oral cavity tumors (n=2, 11.8%), neck lymphoma's (n=2, 11.8%), carcinoma of the nose (n=1, 5.9%) and carcinoma of the jaw bone (n=1, 5.9%). The exact cervical levels that had been radiated were not always exactly defined but included the affected carotid region in all cases. Median radiation dose received was 355 Gy (range 30 - 7000). Patient characteristics are summarized in Table I.

Table I Characteristics of previously radiated patients

Age	Gender	Malignancy	Lesion side	Interval[a] (years)	Received dosis (cGy)
96	F	Glottis larynx ca	R	13.1	7000
86	M	Glottis larynx ca	R	20	n.a
70	F	Hypopharynx ca	R	1.8	n.a
78	M	Pharynx ca	L	8	n.a
68	M	Oropharynx ca	L	4.2	30
72	M	Larynx ca	L	18	n.a
77	M	Maligne lymphoma tongue base	R	10	40
60	M	Nasopharynx ca	R	9	n.a
*	*	*	L	11	n.a
64	M	Non Hodgkin Lymfoma	L	12.9	355
74	M	Sqaumouscell ca nose	L	3.5	70
66	M	Tongue base ca, metastasis lymfnode	R	24	n.a
85	M	Squamous cell metastase lymfnode	L	3.6	5000
73	F	Squamous cell metastase lymfnode	R	14	n.a
64	M	Tongue base ca, squamous	L	8.2	5000
75	M	Tongue base ca	R	6	n.a
*	*	*	L	6	n.a
69	F	Jaw bone ca	R	15	n.a
73	M	Larynx ca	R	21	n.a

cGy, centi-Gray; F, female; M, male; ca, carcinoma; R, right; L, left; n.a, no data available [a] Time between end of radiation therapy to carotid endartectomy *Same patient as 1 line above, bilateral stenosis

Baseline characteristics. Comparisons of demographic characteristics and risk factors between XRT group and non-XRT group are shown in Table II. Overall, 17 (94.4%) lesions of the XRT group and 90 (94.7%) lesions of the non-XRT group were symptomatic (p = 0.93). A tendency towards a shorter interval between last event and surgery for XRT group was identified compared to non-XRT group; 35 days (range: 2-205) versus 66 days (range 1-364, p = 0.099). Also, al lower percentage of previous radiated patients had a severe degree (90-99%) of preoperative ipsilateral stenosis as compared to control non-XRT patients (26.3% versus 47.4%, p = 0.091). Considering risk factors for atherosclerosis, BMI differed significantly between both groups. A median BMI of 24 was seen in XRT group, versus 27 in non-XRT group (p = 0.001). Other risk factors did not show any differences between two groups.

Table II Demographic and clinical characteristics of the study population [a]

	XRT-plaque (n = 19)	Non-XRT plaque (n = 95)	P-value
Demographic characteristics			
Age, years (median, range)	69 (56-92)	69 (56-90)	0.903
Sex			0.917
Male	15 (78.9)	76 (80.0)	
Clinical presentation			
Asymptomatic	1 (5.3)	5 (5.3)	0.929
Symptomatic	18 (94.7)	90 (94.7)	
Stroke	4 (21.1)	20 (21.1)	
TIA	11 (57.9)	60 (63.2)	
Ocular	3 (15.8)	10 (10.5)	
Time between event and surgery, days (median, range)	35 (2-205)	66 (1-364)	0.099
Degree of ipsilateral stenosis			0.091
70-90%	15 (73.7)	50 (52.6)	
90-99%	5 (26.3)	45 (47.4)	
Risk factors			
Current smoker	7 (38.9)	33 (37.5)	0.912
Hypertension	17 (89.6)	84 (88.4)	0.895
Hypercholesterolemia (statin use)	14 (82.4)	67 (71.3)	0.344
Diabetes mellitus	3 (15.8)	22 (23.2)	0.692
Coronary artery disease	3 (15.8)	19 (20.0)	0.671
Peripheral artery disease	4 (21.1)	26 (27.4)	0.568
GFR (median, range)	66 (46-110)	67 (17-124)	0.849
BMI (median, range)	24 (22-29)	27 (18-39)	0.001

TIA, transient ischemic accident; GFR, glomural filtration rate in ml/min/1.73m2; BMI, body mass index calculated as weight in kilograms divided by height in meters squared

[a] Data are presented as No (%) unless otherwise indicated

Histological plaque composition. In univariate analysis, a significant difference was identified for infiltration of macrophages and atheroma >10%. Marked infiltration of macrophages (moderate or heavy) was less frequently observed in XRT-plaques 31.6% (6/19) as compared with non XRT plaques 63.8% (60/95) (p = 0.009). More fibrous plaques were identified in the XRT group; XRT plaques were associated with a smaller lipid core size compared to non-XRT plaque. 84.2% (80/95) of the control plaques contained more than 10% atheroma, compared to only 52.6% (10/19) in the XRT plaque (p = 0.002). (Table III)

In multivariable logistic regression analysis, infiltration of macrophages and atheroma >10% were independently associated with XRT plaques after adjusting for time between event and surgery, ipsilateral degree of stenosis and BMI. (Adjusted OR 0.094 [95% CI 0.020-0.455] resp. 0.129 [95% CI 0.030-0.553] adjusted p = 0.003 resp. p = 0.006). The Figure represents result histological visualized. Other histological parameters, including calcification, collagen, SMC, microvessels and IPH were not significantly associated with XRT status.

Table III Histological outcome [a]

	XRT plaque (n = 19)	Non-XRT plaque (n = 95)	P-value
Histological characteristics			
Calcification, moderate/heavy	8 (42.1)	58 (61.1)	0.127
Collagen, moderate/heavy	14 (73.7)	73 (86.8)	0.768
Macrophages, moderate/heavy	6 (31.6)	60 (63.8)	0.009
SMC, moderate/heavy	11 (57.9)	59 (62.1)	0.731
Atheroma > 10%	10 (52.6)	80 (84.2)	0.002
Microvessels (median, range)	4.3 (0.3- 25.0)	7.0 (1.3 – 40.3)	0.06
IPH present	5 (26.3)	31 (32.6)	0.589
Overall plaque phenotype			
Fibrous	11 (57.9)	28 (29.5)	0.058
Fibro-atheromatous	3 (15.8)	27 (28.4)	
Atheromatous	5 (26.3)	40 (42.1)	

SMC, smooth muscle cells; IPH, intraplaque haemorrhage

[a] Data are presented as No (%) unless otherwise indicated

DISCUSSION

In this study we compared histological characteristics of carotid plaques of patients with prior cervical radiation therapy with plaques from non-radiated patients. A more fibrous and less inflammatory plaque was observed in XRT patients compared to plaques derived from non-XRT patients.

Soon after the introduction of radiation therapy around 1940, cardiovascular changes following radiation were recognized and discussed in animal studies.[15, 16]An experimental study on the large vessels of irradiated mice found progressive changes consisting of intimal proliferation, fragmentation of the elastic lamina, overproduction of elastic tissue, necrosis, hyaline thickening

and production of collagen.[15] Lindsey et al. irradiated localized segments of the abdominal aorta in dogs.[16] They observed arteriosclerotic changes consisting of selective disruption of the internal elastic layer and the development of intimal thickening without histological demonstrable injury to other layers of the vessel wall. Although above described changes were all short to mid term effects (< 17 months following radiation), response of radiation may have latency up to 20 years before the onset of clinical symptoms. This delay is probably related to the diameter of the irradiated artery; the interval being longer for larger arteries.[17] Based on these early experimental findings and additional information of non-invasive imaging techniques on human, arterial damage after radiation have been reported to be similar to non-irradiated atherosclerotic lesions in more recent human studies.[18-20] These studies suggested that radiation only accelerates the normal process of atherosclerotic stenosis. This theory is questionable, considering our results in human plaques. Results showed important differences between XRT plaques (at a median time interval of 10 years after radiation) and non-XRT plaques in a very comparable, mainly symptomatic (94.7%) patient population. After matching, baseline characteristics 'time interval between last event and surgery', 'degree of ipsilateral stenosis' and 'BMI' varied between both groups. For BMI, no differences in plaque composition have been described in literature. Unexpected, degree of preoperative stenosis was less severe in XRT group compared to non-XRT group. Results were not significant and should be interpreted with caution because of small groups. Time interval differences seem to be more relevant because histological studies have shown that remodeling of the plaque after a symptomatic event leads to more stable plaques over time. After stroke, the content of macrophages decreases significantly over relatively short time.[21, 22] However, despite 'time between last event and CEA' being shorter in the XRT group compared with non-XRT patients (35 vs. 66 days), we observed less macrophage infiltration and a more fibrous plaque in XRT group. Previous evidence emphasizes the strength of our observations in differences between atherosclerotic and radiated plaques. Due to our ongoing database, the effect of timing of intervention will become clear in the future since CEA is now recommended to be performed within two weeks of a first clinical event.[23]

Table IV Histological outcome, adjusted Odds Ratios for the presence of plaque parameters in patients with previous XRT as compared with controls.

Histological characteristics	Adjusted Odds Ratio* (95%CI)	Adjusted P – value*
Calcification	0.340 (0.087-1.328)	0.121
Collagen	0.612 (0.144 – 2.601)	0.506
Macrophage infiltration	0.094 (0.020-0.455)	0.003
SMC	0.595 (0.158 – 2.245)	0.443
Atheroma > 10%	0.129 (0.030-0.553)	0.006
Microvessels > median (number per hotspot)	0.480 (0.120-1.915)	0.299
IPH present	1.074 (0.286 – 4.039)	0.916

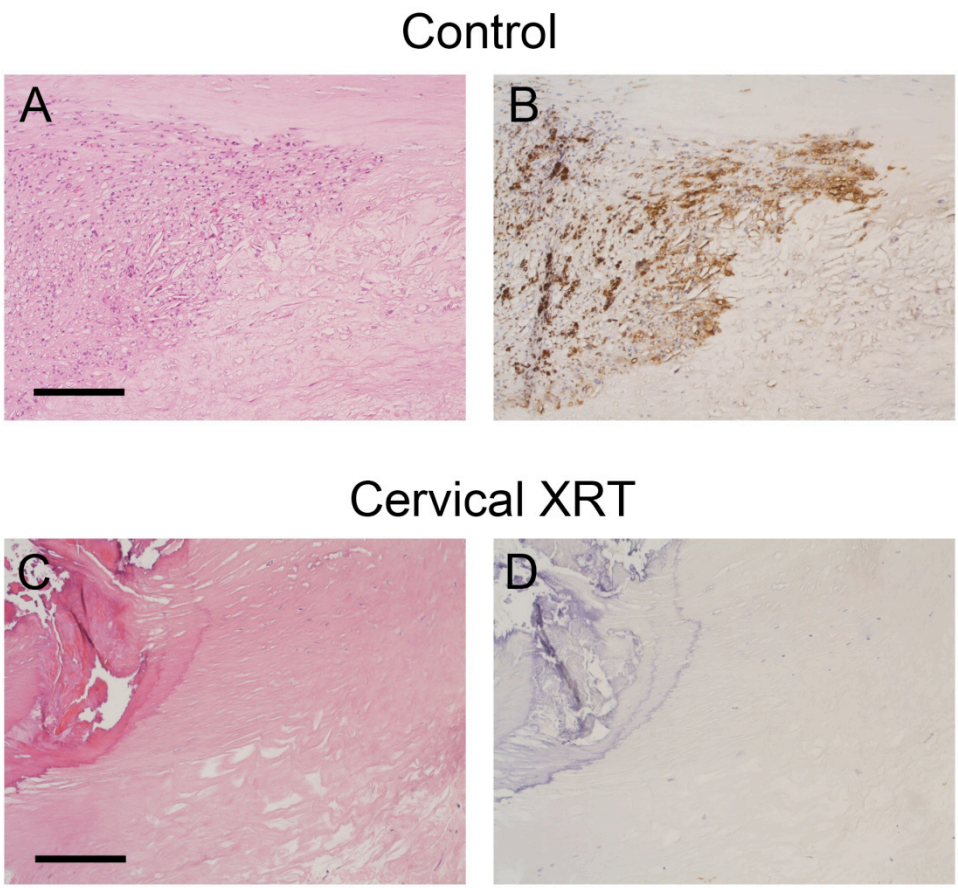
CI, confidence interval; SMC, smooth muscle cells; IPH, intraplaque hemorrhage
*Adjusted for time between last event and surgery, ipsilateral preoperative degree of stenose and body mass index (kg/m^2)

Since plaque characteristics are associated with clinical presentation but also with outcome after CEA, our findings might be of interest in the light of risk for further cardiovascular manifestations due to carotid stenosis like TIA or stroke. Cerebrovascular events are often a result of thrombus formation superimposed on a so called 'vulnerable' plaque.[24] Although radiation therapy increases the risk of symptomatic carotid stenosis, our observation suggests that XRT plaques are less vulnerable, or more stable and less active compared to non-radiated atherosclerotic lesions.[10] The explanation for this difference between reported clinical observations on increased stroke rate and our histology assessment remains a matter of debate. Possibly, other factors than plaque rupture of thrombus formation might lead to neurological symptoms, like progressive stenosis through intima-media thickening.[25] Our findings however do fit the clinical fact that radiated arteries do create restenosis faster than non-radiated plaques, as we also know that relatively stable and fibrous plaques cause restenosis more often than vulnerable plaques. More specifically, low macrophage infiltration and small or absent lipid core is associated with higher risk of restenosis (>50%) after CEA.[11] Applying this evidence for XRT plaques, patients could hypothetically be more prone to develop restenosis after revascularization following prior cervical radiation therapy. Although current literature is conflicting, some data suggest that previously radiated patients indeed have a higher risk for restenosis than non-XRT patients after CEA.[26] Evidence is more clear for XRT patients treated with carotid angioplasty and stenting (CAS), since rate of restenosis or occlusion was calculated as 5.4 per 100 person-years (95% CI 4.3 – 6.6) compared to 2.8 per 100 person-years (95% CI 1.9 – 4.0) after CEA ($p = 0.0025$) in a recent literature review.[27] Possibly, high rates of restenosis after CAS can be partly attributed to previous XRT status besides endovascular technique.

In this study, we were able to perform analyses on 19 plaques of 17 patients. Small sample sizes are known for its lack of precision and thus over- and underestimation of the relations under study. Analyzing a small number of patients is inevitable since incidence of patients with previous cervical radiation therapy who underwent CEA is low. However, we believe this is an important group to report on. Furthermore, despite the small sample size, we believe this data is valuable and sufficient to meet with our study goal. Ideally, our results need to be confirmed in a prospective and a preferable larger cohort. Because limited data on follow-up were available, we were not able to analyze the possible consequences for clinical outcome and restenosis. Also, we are not aware of the exact time course of the development of radiation induced lesions. Consequently, findings on histological level only apply for plaques at a mean time interval after radiation of 10 years. For some cases poor information of radiation characteristics (site and dose) was reported. However, this seems to be a minor problem since radiation induced stenosis was detected not only at the ipsilateral side, but also to a same severe amount at the contralateral side of irradiation for cervical malignancies by others.[28, 29] Findings can be explained by the so-called 'bystander effect', whereas radiation of cells damages not only the target cells, but also non-targeted bystander cells.[30] Lastly, because of segments with the greatest plaque burden were histological analyzed, different segments of the carotid artery could be analyzed in the XRT group and in the non-XRT group. However, examination of a single culprit segment of the plaque is reasonably representative for the plaque as a whole.[22] Because physiopathological pathways of initial lesion stay the same, histology will reflect either atherosclerotic or radiation origin.

Conclusions. Lipid poor, non-inflammatory plaque is distinctive for carotid plaques of previously irradiated and symptomatic patients, compared to a non-irradiated atherosclerotic plaque. Consequences for clinical outcome and restenosis after CEA need to be objectified in larger cohorts with longer follow-up.

Figure Carotid plaque histology of radiated and non-radiated patients



Histological analysis of carotid endarterectomy specimens. A and B, control plaque. A, Hematoxylin and eosin staining showing macrophages (left) at the border of an atheroma (right). Bar = 200 µm. B, immunohistochemical detection of macrophages (in brown; CD68 immunostain) in the same plaque as A with heavy staining of macrophages. C and D, XRT-plaque. C, Hematoxylin and eosin staining showing connective tissue and calcification in the plaque. Bar = 200 µm. D, no macrophages are present in the macrophage staining (CD68 immunostain) of the same area as C.

References

1. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. Stroke. 1991;22:711-20.
2. Carmody BJ, Arora S, Avena R, Curry KM, Simpkins J, Cosby K, et al. Accelerated carotid artery disease after high-dose head and neck radiotherapy: is there a role for routine carotid duplex surveillance? J Vasc Surg. 1999;30:1045-51.
3. Cheng SW, Ting AC, Lam LK, Wei WI. Carotid stenosis after radiotherapy for nasopharyngeal carcinoma. Arch Otolaryngol Head Neck Surg. 2000;126:517-21.
4. Scott AS, Parr LA, Johnstone PA. Risk of cerebrovascular events after neck and supraclavicular radiotherapy: a systematic review. Radiother Oncol. 2009;90:163-5.
5. Louis EL, McLoughlin MJ, Wortzman G. Chronic damage to medium and large arteries following irradiation. J Can Assoc Radiol. 1974;25:94-104.
6. Zidar N, Ferluga D, Hvala A, Popovic M, Soba E. Contribution to the pathogenesis of radiation-induced injury to large arteries. J Laryngol Otol. 1997;111:988-90.
7. McGuirt WF, Feehs RS, Bond G, Strickland JL, McKinney WM. Irradiation-induced atherosclerosis: a factor in therapeutic planning. Ann Otol Rhinol Laryngol. 1992;101:222-8.
8. Lam WW, Liu KH, Leung SF, Wong KS, So NM, Yuen HY, et al. Sonographic characterisation of radiation-induced carotid artery stenosis. Cerebrovasc Dis. 2002;13:168-73.
9. Shichita T, Ogata T, Yasaka M, Yasumori K, Inoue T, Ibayashi S, et al. Angiographic characteristics of radiation-induced carotid arterial stenosis. Angiology. 2009;60:276-82.
10. Verhoeven B, Hellings WE, Moll FL, de Vries JP, de Kleijn DP, de Bruin P, et al. Carotid atherosclerotic plaques in patients with transient ischemic attacks and stroke have unstable characteristics compared with plaques in asymptomatic and amaurosis fugax patients. J Vasc Surg. 2005;42:1075-81.
11. Hellings WE, Moll FL, De Vries JP, Ackerstaff RG, Seldenrijk KA, Met R, et al. Atherosclerotic plaque composition and occurrence of restenosis after carotid endarterectomy. Jama. 2008;299:547-54.
12. Verhoeven BA, Velema E, Schoneveld AH, de Vries JP, de Bruin P, Seldenrijk CA, et al. Athero-express: differential atherosclerotic plaque expression of mRNA and protein in relation to cardiovascular events and patient characteristics. Rationale and design. Eur J Epidemiol. 2004;19:1127-33.
13. Pang D. A relative power table for nested matched case-control studies. Occup Environ Med. 1999;56:67-9.
14. Davies MJ, Richardson PD, Woolf N, Katz DR, Mann J. Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. Br Heart J. 1993;69:377-81.
15. Sams A. Histological Changes in the Larger Blood Vessels of the Hind Limb of the Mouse after X-Irradiation. Int J Radiat Bil Relat Stud Phys Chem Med. 1965;9:165-74.
16. Lindsay S, Kohn HI, Dakin RL, Jew J. Aortic arteriosclerosis in the dog after localized aortic x-irradiation. Circ Res. 1962;10:51-60.
17. Murros KE, Toole JF. The Effect of Radiation on Carotid Arteries: A Review Article. Arch Neurol. 1989;46:449-55.
18. Elerding SC, Fernandez RN, Grotta JC. Carotid artery disease following external cervical irradiation. Annals of Surgery. 1981;194:609-15.
19. Silverberg GD, Britt RH, Goffinet DR. Radiation-induced carotid artery disease. Cancer. 1978;41:130-7.
20. Lam WWM. Radiation-Induced Extracranial Carotid Stenosis. Vascular Disease Prevention. 2006;3:27-32.
21. Peeters W, Hellings WE, de Kleijn DPV, de Vries JPPM, Moll FL, Vink A, et al. Carotid Atherosclerotic Plaques Stabilize After Stroke: Insights Into the Natural Process of Atherosclerotic Plaque Stabilization. Arterioscler Thromb Vasc Biol. 2009;29:128-33.

22. Redgrave JNE, Lovett JK, Gallagher PJ, Rothwell PM. Histological Assessment of 526 Symptomatic Carotid Plaques in Relation to the Nature and Timing of Ischemic Symptoms: The Oxford Plaque Study. Circulation. 2006;113:2320-8.
23. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. Stroke. 2011;42:227-76.
24. Virmani R, Kolodgie FD, Burke AP, Finn AV, Gold HK, Tulenko TN, et al. Atherosclerotic Plaque Progression and Vulnerability to Rupture: Angiogenesis as a Source of Intraplaque Hemorrhage. Arterioscler Thromb Vasc Biol. 2005;25:2054-61.
25. Gianicolo ME, Gianicolo EA, Tramacere F, Andreassi MG, Portaluri M. Effects of external irradiation of the neck region on intima media thickness of the common carotid artery. Cardiovasc Ultrasound. 2010;8:8.
26. Lesèche G, Castier Y, Chataigner O, Francis F, Besnard M, Thabut G, et al. Carotid artery revascularization through a radiated field. J Vasc Surg. 2003;38:244-50.
27. Fokkema M, den Hartog AG, Bots ML, van der Tweel I, Moll FL, de Borst GJ. Stenting Versus Surgery in Patients With Carotid Stenosis After Previous Cervical Radiation Therapy: Systematic Review and Meta-Analysis. Stroke. 2011. In press.
28. Brown PD, Foote RL, McLaughlin MP, Halyard MY, Ballman KV, Collie AC, et al. A historical prospective cohort study of carotid artery stenosis after radiotherapy for head and neck malignancies. Int J Radiat Oncol Biol Phys. 2005;63:1361-7.
29. Martin JD, Buckley AR, Graeb D, Walman B, Salvian A, Hay JH. Carotid artery stenosis in asymptomatic patients who have received unilateral head-and-neck irradiation. Int J Radiat Oncol Biol Phys. 2005;63:1197-205.
30. Olsson MG, Nilsson EJ, Rutardottir S, Paczesny J, Pallon J, Akerstrom B. Bystander cell death and stress response is inhibited by the radical scavenger alpha(1)-microglobulin in irradiated cell cultures. Radiat Res. 2010;174:590-600.

CHAPTER THREE

Carotid stenting versus endarterectomy in patients undergoing re-intervention after prior carotid endarterectomy

Journal of Vascular Surgery
August 2013; Epub ahead of print

Authors
Margriet Fokkema MD[1], Gert Jan de Borst MD PhD[2], Brian W. Nolan MD[3], Ruby C. Lo MD[1], Robert A. Cambria MD[4], Richard J. Powell MD[3], Frans L. Moll MD PhD[2], Marc L. Schermerhorn MD[1].
on behalf of the Vascular Study Group of New England

Affiliations
Department of Vascular and Endovascular Surgery, [1]Beth Israel Deaconess Medical Center, Boston, MA, [2]University Medical Center Utrecht, Utrecht, the Netherlands, [3]Dartmouth-Hitchcock Medical Center, Lebanon, MA, [4]Eastern Maine Medical Center, Bangor, ME

ABSTRACT

Introduction. Outcomes for patients undergoing intervention for restenosis after prior ipsilateral carotid endarterectomy (CEA) in the era of carotid stenting (CAS) are unclear. We compared perioperative results and durability of CAS versus CEA in patients with symptomatic or asymptomatic restenosis after prior CEA and investigated the risk of re-intervention compared to primary procedures.

Methods. Patients undergoing CAS and CEA for restenosis between January 2003 and March 2012 were identified within the Vascular Study Group of New England (VSGNE) database. Endpoints included any stroke, death or myocardial infarction (MI) within 30 days, cranial nerve injury at discharge and restenosis ≥70% at 1-year follow-up. Multivariable logistic regression was done to identify whether prior ipsilateral CEA was an independent predictor for adverse outcome.

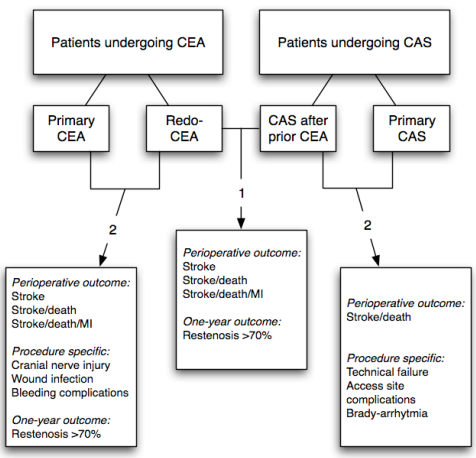
Results. Out of 9305 CEA procedures, 212 patients (2.3%) underwent redo-CEA (36% symptomatic). Of 663 CAS procedures, 220 patients (33%) underwent CAS after prior ipsilateral CEA (31% symptomatic). Demographics of patients undergoing redo-CEA were comparable to patients undergoing CAS after prior CEA. Stroke/death/MI rates were statistically similar between redo-CEA vs CAS after prior CEA in both asymptomatic (4.4% vs 3.3%, P=0.8) and symptomatic patients (6.6% vs 5.8%, P=1.0). No significant difference in restenosis ≥70% was identified between redo-CEA and CAS after prior CEA (5.2% vs. 3.0%, P = 0.5). Redo-CEA vs primary CEA had increased stroke/death/MI rate in both symptomatic (6.6% vs 2.3%, P=0.05) and asymptomatic patients 4.4% vs 1.7%, P=0.03). Prior ipsilateral CEA was an independent predictor for stroke/death/MI among all patients undergoing CEA (OR 2.1, 95% CI 1.3 – 3.5). No difference in cranial nerve injury was identified between redo-CEA and primary CEA (5.2% vs 4.7%, P=0.8).

C**onclusions.** In the VSGNE, CEA and CAS showed statistically equivalent outcomes in asymptomatic and symptomatic patients treated for restenosis after prior ipsilateral CEA. However, regardless of symptom status, the risk of re-intervention was increased compared to patients undergoing primary CEA.

INTRODUCTION

The reported incidence of restenosis after carotid endarterectomy (CEA) ranges from 6 to 15%, depending on the duration of follow-up and its measurement criteria[1,2]. Although most lesions remain asymptomatic, results from the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) showed the clinical significance of recurrent stenosis ≥70%, with increased risk of ipsilateral stroke within two years of surgery.[3] The management of restenotic lesions remains unclear[4-6]. Since redo-surgery after prior ipsilateral CEA potentially leads to a more challenging operation, prior CEA has been considered a 'high-risk' condition for CEA with increased risk of cranial nerve injury (CNI) and other local complications[7,8]. Yet, only few studies also report an increased stroke risk for redo-CEA compared to primary CEA[9,10]. In patients for whom re-intervention is indicated, carotid angioplasty and stenting (CAS) might be a suitable alternative to re-operation. CAS has been increasingly performed in restenotic lesions after the Centers for Medicare and Medicaid Services (CMS) approved reimbursement for CAS in patients with symptomatic restenosis after CEA.[11] Relative safety has been shown in early results,[12] but long-term outcome remains undefined.[13] Few analyses have directly compared outcomes of redo-CEA versus CAS in patients with restenosis after prior CEA[14-17]. Most studies that reported on outcome after CAS and/or CEA in restenotic lesions have been limited to single institution series with insufficient power to detect differences in outcome. Further, these studies did not distinguish symptomatic from asymptomatic disease. Nor did they report on the benefit of intervention beyond the perioperative period. In a recent study by the Vascular Study Group of New England (VSGNE), a history of prior ipsilateral CEA predicted stroke or death following carotid revascularization.[17] In the current study, we aimed to further investigate this observation. Our primary goal was to compare perioperative major adverse events and one year patency between redo-CEA and CAS for patients with restenosis after prior ipsilateral CEA, stratified by symptom status. Secondly, we investigated the risk of re-intervention compared to primary procedures. (Figure 1)

Figure 1 Overview of study groups and outcome



1. To compare outcome between redo-CEA and CAS in patients undergoing restenosis after prior ipsilateral CEA, 2. To investigate the risk of re-intervention compared to the primary intervention

METHODS

Database. Data collected by the VSGNE were used for this analysis. The VSGNE is a regional quality improvement initiative developed in 2002 and currently involves over 180 physicians at 30 centers (14 academic, 16 community). Preoperative clinical characteristics, imaging studies, operative outcome and follow-up data are collected and entered in the registry by trained nurses, or clinical data abstractors. Surgeons enter operative details. Research analysts are blinded to patient, surgeon, and hospital identity. Further details on this registry have been published previously and are available at http://www.vascularweb.org/regionalgroups/vsgne.
VSGNE data have been validated for completeness using audits of discharge claims data from each participating institution.[17] Additionally, we have not identified any mortality bias by cases not initially captured.[18]

Patients. Our study sample included all patients in the VSGNE registry who underwent CEA (January 2003 and December 2011) or CAS (July 2005 and March 2012). . Patients undergoing CEA with a concomitant coronary bypass procedure (CABG) were excluded (n = 221). If both the initial CEA procedure and the re-intervention (CAS or redo-CEA) were reported for one patient, the initial CEA was excluded (n = 52). In total, 9305 CEAs from 26 centers performed by 136 surgeons, and 663 CAS' from 13 centers performed by 58 surgeons were available for analyses. Within this sample, patients with a prior ipsilateral CEA in their medical history were identified. This resulted in a 're-intervention group' of 432 patients including 212 redo-CEAs and 220 CAS, and a 'primary procedure group' of 9536 patients including 9093 primary CEAs and 443 primary CAS procedures. In those who underwent a third ipsilateral carotid intervention (n=6), only the secondary intervention after the initial CEA was included for analyses.

Endpoints and Measurements. Our primary endpoints were any stroke, a composite of any stroke or death and a composite of stroke, death, or myocardial infarction (MI) at 30-days postoperatively. Secondary endpoints included restenosis ≥70% as assessed by duplex ultrasound (DUS) during follow-up. In addition, CEA and CAS specific perioperative outcomes were evaluated. For CEA these included any CNI (as assessed at discharge by the operating surgeon), wound infection and bleeding needing re-intervention. For CAS these included technical failure, access site complications and brady-arrhythmia requiring treatment during the procedure. The definition of stroke included ipsilateral or contralateral major strokes (cortical, vertebrobasilar, or ocular disability resulting in non-independent living status, or blindness) and ipsilateral or contralateral minor stroke (other strokes not defined as major). Neurologists did not routinely examined patients postoperatively, though this is part of the protocol for CAS at several of the participating institutions. Myocardial infarctions included clinical, electrocardiogram, and troponin-only MI. Indications for obtaining postoperative troponin are institution dependent and variable. Not all centers routinely screened all postoperative patients for MI with troponin. For the evaluation of restenosis, we studied patients who had undergone DUS evaluation during follow-up. Among CAS patients, we were able to analyze 376 patients (56.7%) at a median follow-up of 254 days. Of the 287 patients (43.3%) without DUS information, 228 patients (34.4%) underwent stenting procedures in 2011 or 2012 and had therefore not completed one year follow-up yet at time of data-analysis. The remaining missing 59 patients (8.9%) were lost to follow-up or they did

Table I Demographics and patient characteristics of patients undergoing redo-CEA or CAS after prior ipsilateral CEA in the VSGNE

	Redo-CEA *n = 212*		CAS after prior CEA *n =220*		
	n	%	n	%	P-value
Age, yr (mean ± SD)	68.8 ± 9.2		68.9 ± 8.5		0.4
Age >80 yr	26	12.3	25	11.4	0.9
Gender					0.3
Male	124	58.5	139	63.2	
Female	88	41.5	80	36.4	
Race (non-white)	2	0.9	3	1.4	1
Ipsilateral symptoms	76	35.9	69	31.4	0.3
TIA	54	25.5	55	25	
Stroke	22	10.4	14	6.4	
Ipsilateral degree of ICA stenosis					0.5
< 50%	7	3.3	3	1.4	
50 – 59%	5	2.4	5	2.3	
60 – 69%	7	3.3	6	2.7	
70 – 79%	37	17.5	29	13.2	
≥ 80%	151	71.2	174	79.1	
Occluded	3	1.4	3	1.4	
Symptomatic patients ≥ 50% stenosis	212	100	220	100	1
Asymptomatic patients ≥ 70% stenosis	197	93	209	95	0.4
Any Smoke (prior or current)	191	90.1	188	85.5	0.2
Hypertension (≥140/90 or history)	189	89.2	207	94.1	0.1
Diabetes (on medication)	70	33	70	31.8	0.8
Coronary artery disease	82	38.7	78	35.5	0.6
CABG/PCI	81	38.2	79	35.9	0.5
Congestive heart failure	19	9	22	10	0.7
COPD	69	32.6	44	20	**<.01**
Antiplatelet therapy	192	90.6	213	96.8	**<.01**
Statin	175	82.5	183	83.2	0.9
Stress test abnormal (MI or ischemia)	18	8.5	18	8.2	0.9
On dialysis	1	0.5	2	0.9	1
Creatinine (>1.78 mg/dL)	12	5.7	13	5.9	0.3
ASA 3 and 4	93	43.9	101	45.9	0.6
Contralateral occlusion	24	12.1	24	11.5	1
Urgent procedures	27	12.7	21	9.5	0.4
Prior radiation	107	1.2			
Eversion CEA	8	3.8			
One or more medical high risk factor(s)			58	26.4	
One or more anatomical high risk factor(s)			141	64.1	
Refused surgery			38	17.3	

TIA, transient ischemic attack, ICA, internal carotid artery, CABG, coronary artery bypass grafting, PCI, percutaneous coronary intervention, COPD, chronic obstructive pulmonary disease, MI, myocardial infarction, ASA, American Society of Anesthesiology. Bold: P-value <.05

not undergo DUS imaging during follow-up. For CEA, 6189 patients (67%) were available for restenosis analyses at a median of 370 days. Of those without DUS information (n=3116, 33.4%), 1256 patients (13.5%) had undergone CEA in 2011 and had therefore not completed one year follow-up. The remaining 1860 patients (20%) were lost to follow-up or did not undergo DUS imaging at their follow-up consult. Results for primary outcome were stratified by preoperative symptom status. Symptomatic patients were defined as having an ipsilateral neurologic event, including any hemispheric or ocular transient ischemic attack, major or minor stroke preceding the intervention.

Statistical Analysis. Patient characteristics and outcome from patients who underwent redo-CEA or CAS after prior ipsilateral CEA were compared using χ^2 or Fisher's exact test for categorical variables and two tailed *t* test for continuous variables. Within the CAS and CEA group, patient characteristics and outcomes of re-intervention were also compared to primary procedures.
Multivariable logistic regression was performed to evaluate whether prior ipsilateral CEA was predictive for adverse outcome (stroke/death and stroke/death/MI) following CEA. Candidate predictors were identified by bivariate analysis and included in the multivariable model if the P-value was <.1. (Appendix A) Backward step-wise selection was applied to generate odds ratios (OR) and corresponding 95% confidence intervals (CI). The multivariable models were adjusted for age and gender. Predicted probabilities for adverse outcome were calculated based on the final models. P-values <.05 were considered significant. SPSS version 19.0 statistical software (IBM Corp. SPSS Statistics, Armonk, NY) was used for statistical analyses.

RESULTS

Redo-CEA versus CAS after prior CEA.

Patient characteristics. Among patients who underwent re-intervention after prior ipsilateral CEA, preoperative characteristics were comparable between redo-CEA and CAS. (Table I) The mean age was 69 years in both groups; 58.5% were men in the CEA group and 63.2% in the CAS group. 36% of patients were symptomatic undergoing redo-CEA versus 31% undergoing CAS (P = 0.3). All symptomatic patients had ≥50% stenosis, while in asymptomatic patients, 93% of patients undergoing redo-CEA and 95% of CAS patients had high-grade ≥70% stenosis. Chronic obstructive pulmonary disease (COPD) was more common in the CEA group (32.5% vs 20% CAS, P <.01). A greater proportion of patients in the CEA group were on preoperative antiplatelet therapy (aspirin or clopidogrel). Time from initial CEA to re-intervention was available for 52 patients (26 CAS and 26 CEA). Median time-interval to CEA was 36 months compared to 17.5 months to CAS (P=0.08).
Outcomes. Among symptomatic patients, outcome after CEA vs CAS did not differ significantly; 30-day stroke and stroke/death rate were 3.9% vs 4.4% (P = 1.0) and stroke/death/MI rate was 6.6% vs 5.8% (P = 1.0). (Table II) For asymptomatic patients, outcome after CEA vs CAS was also statistically similar: 30-day stroke and stroke/death were 2.9% vs 2.0% (P = 0.7) and stroke/death/MI rate was 4.4% vs 3.3% (P = 0.8). Length of stay after CEA was 2.2 days, compared to 1.9 days after CAS (P = 0.4). During follow-up, rate of restenosis ≥70% was 5.2% after CEA and 3.0% after CAS (P = 0.5, OR 0.6, 95% CI 0.2-2.0). Only one symptomatic lesion (ipsilateral stroke at 13 months) was identified in a patient who underwent CAS.

Redo-CEA versus primary CEA.

Patient characteristics. Comparison of demographics and patient characteristics showed that COPD, smoking (current or prior), contralateral occlusion and previous CABG or percutaneous coronary intervention were more common in patients undergoing redo-CEA compared to primary CEA. Eversion CEA was more frequently used in primary procedures (9.8% vs 3.8% redo-CEA, P < .01). Patching was more common with redo-CEA (96% vs 87% primary CEA, P<.01). (Appendix B, online)

Outcomes. Among symptomatic patients undergoing redo-CEA vs primary CEA, 30-day stroke, stroke/death, and stroke/death/MI rates were higher after redo-CEA, but not statistically different (stroke: 4.0% vs 1.5%, P = 0.1, stroke/death: 4.0% vs 1.8%, P = 0.2 and stroke/death/MI: 6.6% vs 2.8%, P = 0.07). (Table III) Asymptomatic patients undergoing redo-CEA compared to those undergoing primary CEA had significantly higher rates for stroke (2.9% vs 0.8%, P = 0.03), stroke/death (2.9% vs 0.9%, P = 0.04) and stroke/death/MI (4.4% vs 1.7%, P = 0.03). CNI at discharge was similar after primary CEA (5.1%, n = 470) and redo-CEA (6.1%, n = 13, P = 0.8, OR 1.2, 95% CI 0.7 – 2.1). One wound infection (0.5%) was seen after redo-CEA versus 7 (0.1%) after primary procedure (P = 0.2). 1.4% (n = 3) had bleeding complications after redo-CEA versus 1.0% (n = 90) after primary CEA (P = 1.0). Restenosis ≥70% was statistically similar in patients undergoing primary CEA compared to redo-CEA (2.8% vs 5.2%, P = 0.2, OR 1.7, 95% CI 0.9 – 4.2).

Table II Thirty-day outcome of patients undergoing redo-CEA and CAS after prior ipsilateral CEA in the VSGNE

		Redo-CEA *n = 76*		CAS after prior CEA *n = 69*				
		n	%	n	%	P-value	OR	95% CI
Symptomatic	Stroke	3	3.9	3	4.4	1	1.1	0.2 - 5.7
	Stroke/Death	3	3.9	3	4.4	1	1.1	0.2 - 5.7
	Stroke/Death/MI	5	6.6	4	5.8	1	0.9	0.2 - 3.4
		Redo-CEA *n = 136*		CAS after prior CEA *n = 151*				
		n	%	n	%	P-value	OR	95% CI
Asymptomatic	Stroke	4	2.9	3	2	0.7	0.7	0.2 - 3.0
	Stroke/Death	4	2.9	3	2	0.7	0.7	0.2 - 3.0
	Stroke/Death/MI	6	4.4	5	3.3	0.8	0.7	0.2 - 2.5

OR, odds ratio, CI, confidence interval, MI, myocardial infarction

CAS after prior CEA versus primary CAS. Patients who underwent primary CAS had more medical comorbidities than patients undergoing CAS after prior CEA, such as coronary artery disease, congestive heart failure, COPD and an abnormal stress test. (Data not shown) No significant difference in stroke or death rate was identified for both symptomatic (4.4% vs 7.6% primary CAS, P=0.6) and asymptomatic (2.0% vs 0.7% primary CAS, P = 0.4) patients. Technical failure (2.3% vs 1.8% primary CAS, P=NS) and access site complications (8.6% vs 5.9% primary CAS, P=NS) were statistically similar, while significantly more patients required treatment for brady-arrhythmias during primary CAS compared to patients undergoing CAS after prior CEA (27.4% [n = 121] vs 12.8% [n = 28], P < .01).

Table III Thirty-day outcome of patients undergoing primary CEA versus redo-CEA in the VSGNE

		Primary CEA *n = 3033*		Redo-CEA *n = 76*				
		n	%	n	%	P-value	OR	95% CI
Symptomatic	Stroke	46	1.5	3	3.9	0.12	2.6	0.8 - 8.6
	Stroke/Death	53	1.7	3	3.9	0.16	2.3	0.7 - 7.5
	Stroke/Death/MI	71	2.3	5	6.6	0.05	2.4	0.96 - 6.1
		Primary CEA *n = 6059*		Redo-CEA *n = 136*				
		n	%	n	%	P-value	OR	95% CI
Asymptomatic	Stroke	49	0.8	4	2.9	0.03	3.7	1.3 - 10.5
	Stroke/Death	54	0.9	4	2.9	0.04	3.4	1.2 - 9.4
	Stroke/Death/MI	105	1.7	6	4.4	0.04	2.6	1.1 - 6.1

OR, odds ratio, CI, confidence interval, MI, myocardial infarction

Multivariable analyses. Among all patients undergoing CEA (symptomatic and asymptomatic), redo-CEA was an independent predictor for 30-day stroke/death (OR 2.6, 95% CI 1.4 – 4.7, P = .002) and stroke/death/MI (OR 2.1, 95% CI 1.3 – 3.5, P = .002). (Table IV) Other predictive factors for stroke/death were age > 80 years, symptomatic status, hypertension, contralateral occlusion and urgent procedures. Preoperative antiplatelet therapy proved to be protective. Other predictors for stroke/death/MI were female gender, symptomatic status, hypertension, congestive heart failure, contralateral occlusion and urgent procedures (<24 hours of admission). Patients undergoing redo-CEA vs primary CEA had a significantly higher predicted adverse outcome, reflecting they are a higher risk population in the redo-group (Figure 2).

DISCUSSION

In a large regional database, CAS and redo-CEA revealed equivalent perioperative and one year outcome in both asymptomatic and symptomatic restenosis after prior CEA. Adverse outcome of re-intervention was increased compared to primary CEA, regardless of symptom status.

Table IV Multivariable model for adverse outcome among symptomatic and asymptomatic patients undergoing CEA (n = 9305)

	Stroke/Death			Stroke/Death/MI		
	OR	95% CI	P-value	OR	95% CI	P-value
Age >80 yr	1.8	1.2 - 2.7	0.004	-	-	-
Female gender	-	-	-	1.4	1.1 - 1.9	0.013
Ipsilateral symptoms	2.1	1.4 - 3.0	<.001	1.7	1.2 - 2.2	0.001
Prior ipsilateral CEA	2.6	1.4 - 4.7	0.002	2.1	1.3 - 3.5	0.002
Hypertension	2.5	1.2 - 5.4	0.02	1.8	1.0 - 3.0	0.036
Congestive heart failure	-	-	-	2	1.4 - 2.9	<.001
Antiplatelet therapy	0.5	0.3 - 0.9	0.009	-	-	-
Contralateral occlusion	2.4	1.4 - 4.0	0.001	1.9	1.2 - 3.0	0.003
Urgency	1.8	1.2 - 2.8	0.008	1.6	1.1 - 2.2	0.014

MI, myocardial infarction, OR, odds ratio, CI, confidence interval

The results of the current study indicate that patients with symptomatic or asymptomatic restenosis after prior CEA form a high-risk group for intervention, regardless of revascularization procedure or symptom status. Despite the increased risk compared to primary CEA, both CAS and CEA proved to be suitable options to treat symptomatic patients with restenosis after prior CEA. In asymptomatic patients, the benefit of intervention is less clear with stroke/death rate of 2.9% after CEA, which is the upper limit acceptable for asymptomatic lesions based on societal guidelines For these patients, a non-operative approach with medical treatment might be considered to achieve optimal long-term stroke prevention given that the natural history of asymptomatic lesions seems generally benign and some may regress over time.[19] However, others have shown increased stroke risk in patients with severe stenosis (≥70%), indicating that a more aggressive approach may be warranted in this subset of patients.[3,20]

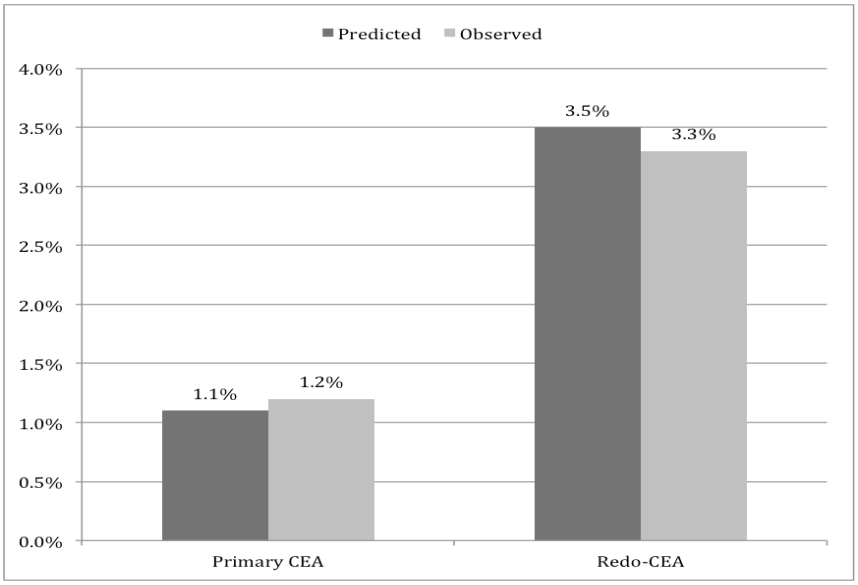
Few studies have reported an increased stroke risk after redo-CEA compared to primary CEA.[9,10] Aburahma et al.'s study yielded an ipsilateral stroke rate of 4.8% (6/124) after redo-CEA, compared to 0.8% (2/265) following primary intervention with five of six strokes in the redo group happening in symptomatic patients.[9] In contrast, more recent studies did not detect a difference in stroke rate compared to primary surgery, and concluded that redo-CEA was as safe as primary CEA.[21-23] However, small sample size limited the ability to detect statistical differences or to stratify patients by symptom status in most of these series. Others have reported on outcome after redo-CEA in single center cohorts without a control group.[24-30] While most of these studies

reported 'acceptable' perioperative stroke/death rates (0 – 4.6%, all patients), several groups have reported increased risk for local complications such as nerve injury (4.6% – 21%) and wound hematoma (4.2%)[7,8,20,30,31]. We did not identify an increased risk for CNI compared to primary CEA, nor did we note an increased risk for other local complications with redo-surgery in a much larger population. As illustrated by a greater predicted stroke or death rate than was actually observed in the redo-group, the increased risk for re-intervention was therefore indicative of a high-risk population rather than a high-risk procedure.

Under the assumption that surgical risk with redo-CEA was increased, CMS approved reimbursement for CAS in patients with symptomatic, severe (>70%) restenosis after CEA. This policy was mainly based on the results of the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, designed to compare CAS vs CEA in a high-risk population.[32,33] In SAPPHIRE, the 30-day stroke, death, MI rate in the CEA arm was as high as 9.8% (vs 4.8% CAS, P=.09). The MI rate of 6.6% strongly influenced this composite endpoint. Moreover, the generalizability of this cohort may be limited as approximately 70% of the study population was asymptomatic and the study design lacked stratification within the various high-risk groups (only 22% had recurrent stenosis after CEA). Despite controversy over the applicability of the SAPPHIRE results and the classification of 'high-risk'[7,34], CAS was increasingly performed and evaluated in patients with restenotic lesions. The SVS Vascular Registry (VR) data indicated a protective effect of CAS in restenotic lesions compared to primary CAS and this observation was supported by a sub-analysis in the current study.[12,35] A combination of a higher risk population in the primary CAS group and a supposedly more stable plaque in restenotic lesions caused by intimal hyperplasia[36] may explain these findings. This hypothesis is further supported by the lower risk of procedural bradycardia in CAS after prior CEA, which has also been previously shown.[37] Our results suggested that patients undergoing CAS after redo-CEA were treated for intimal hyperplasia rather than 'late' restenosis (>24 Months) through progression of atherosclerotic restenosis. Yet, the reported risk for 30-day stroke/death/MI after CAS in restenotic lesions is still relatively high in both asymptomatic (SVS VR: 3.5% and VSGNE: 3.3% [current analysis]) and symptomatic patients (SVS VR: 6.7% and VSGNE: 5.8% [current analysis]) and not superior to redo-CEA.[35] Long-term results after CAS have not been thoroughly discussed in the current literature.[13,38] Our findings indicate that rate of restenosis ≥70% after one year is similar after CAS and CEA (3.0% vs 5.2%, NS). The vast majority lesions remained asymptomatic without a need for re-intervention.

Few other groups have attempted to compare CAS and CEA directly in patients with restenosis after prior CEA. In a series of 83 patients, Aburahma et al.[31] reported increased 30-day stroke rates after CAS compared to CEA (16% vs 2.4%) and >50% in stent restenosis at 6 months, as defined by duplex ultrasound. In a later report comprising 192 patients (72 redo-CEA and 120 CAS), the same group did not detect any differences in 30-day stroke rate between redo-CEA and CAS (3% vs 1%, P=0.6), while the increased risk for restenosis after CAS (mean time of follow-up 2 yr) persisted.[15] Several studies have however shown elevated sonographic velocities after stenting in the absence of angiographically proven restenosis, which might have caused increased rates of restenosis greater than 50% after CAS.[39] Two other groups showed equivalent outcome between CAS and CEA albeit with smaller numbers.[14,16] Nolan et al. using VSGNE data sought to compare real world outcomes of CAS and CEA and found that a history of prior ipsilateral CEA was an

Figure 2 Predicted and observed stroke or death rate of patients undergoing primary CEA and redo-CEA



Both predicted and observed rates were significantly different between primary CEA and Redo-CEA (P<.01).

independent risk factor for stroke or death in a model including all patients undergoing CAS and CEA.[17] This observation prompted us to further stratify this cohort using a larger number of patients. While primary CEA in symptomatic patients has proven to be beneficial over CAS, patients with symptomatic recurrent stenosis do equally well with CAS. Similar predictors for adverse outcome were previously shown in the SVGNE.[17,40] While age >80 year was associated with stroke and death, female gender and congestive heart failure were predictive for stroke/death/MI. Preoperative antiplatelet therapy was protective for stroke and death, but was not associated with stroke/death/MI.

The results of this study must be interpreted in the context of its design including the limitations of the dataset. The VSGNE does not record the duration from primary CEA to secondary intervention, however, we were able to identify this time interval for several patients who also underwent their primary CEA procedure in the VSGNE. We are also not aware of the reasons for intervention in patients with asymptomatic lesions <70%. Reporting bias is inherent to any registry-based study and potentially leads to under-reporting of events. The low stroke rate in the VSGNE compared to RCTs such as CREST is likely in part caused by the absence of a routine postoperative evaluation by a neurologist. However, it seems unlikely that there was bias in the reporting of events between CAS and CEA, patients with and without prior CEA or symptomatic and asymptomatic patients. Furthermore, we used the Social Security Death Index to ensure that all deaths were

captured in our dataset. The lack of a standard protocol to identify postoperative MI might have lead to lower rates compared to the randomized controlled trials. Furthermore, the relatively low event rate after revascularization procedures, particularly in the re-intervention groups, may have resulted in a type II error limiting our ability to identify significant differences. However, this is the largest comparison to date of CAS versus redo-CEA in patients with restenosis after prior CEA, and we were able to quantify the potential effect size and direction among these patients, stratified for symptom status. Also, follow-up length was limited at a median of one year. Lastly, the duplex criteria were determined at each individual center and are thus not uniform across the VSGNE. Nonetheless, all the vascular laboratories in the VSGNE centers are certified by the Intersocietal Commission for the Accreditation of Vascular Laboratories.[1] These factors should be considered while interpreting our results on restenosis.

In conclusion, we found that in a large regional quality improvement registry reflecting real world outcome, patients undergoing re-intervention after prior CEA are at increased risk for adverse events, regardless of procedure. For patients presenting with symptomatic recurrent carotid artery stenosis, both CAS and CEA are suitable options. For asymptomatic patients, the risk and benefits of intervention should be carefully weighed for individual patients. Future work should focus on identifying those asymptomatic lesions that will eventually become symptomatic, and which asymptomatic patients have increased risk for perioperative adverse outcome.

References

1. Goodney PP, Nolan BW, Eldrup-Jorgensen J, Likosky DS, Cronenwett JL. Restenosis after carotid endarterectomy in a multicenter regional registry. *J Vasc Surg* 2010;52:897-904, 5 e1-2; discussion -5.
2. van Lammeren GW, Peeters W, de Vries JP, de Kleijn DP, De Borst GJ, Pasterkamp G, et al. Restenosis after carotid surgery: the importance of clinical presentation and preoperative timing. *Stroke* 2011;42:965-71.
3. Lal BK, Beach KW, Roubin GS, Lutsep HL, Moore WS, Malas MB, et al. Restenosis after carotid artery stenting and endarterectomy: a secondary analysis of CREST, a randomised controlled trial. *Lancet Neurol* 2012;11:755-63.
4. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery Developed in Collaboration With the American Academy of Neurology and Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2011;57:e16-94.
5. Vidale S. Restenosis after carotid endarterectomy and stenting. *Lancet Neurol* 2012.
6. Lal BK. Recurrent carotid stenosis after CEA and CAS: diagnosis and management. *Semin Vasc Surg* 2007;20:259-66.
7. Mozes G, Sullivan TM, Torres-Russotto DR, Bower TC, Hoskin TL, Sampaio SM, et al. Carotid endarterectomy in SAPPHIRE-eligible high-risk patients: implications for selecting patients for carotid angioplasty and stenting. *J Vasc Surg* 2004;39:958-65; discussion 65-6.
8. AbuRahma AF, Choueiri MA. Cranial and cervical nerve injuries after repeat carotid endarterectomy. *J Vasc Surg* 2000;32:649-54.
9. AbuRahma AF, Jennings TG, Wulu JT, Tarakji L, Robinson PA. Redo carotid endarterectomy versus primary carotid endarterectomy. *Stroke* 2001;32:2787-92.
10. Meyer FB, Piepgras DG, Fode NC. Surgical treatment of recurrent carotid artery stenosis. *J Neurosurg* 1994;80:781-7.
11. Hobson RW, 2nd, Lal BK, Chakhtoura E, Goldstein J, Haser PB, Kubicka R, et al. Carotid artery stenting: analysis of data for 105 patients at high risk. *J Vasc Surg* 2003;37:1234-9.
12. White RA, Sicard GA, Zwolak RM, Sidawy AN, Schermerhorn ML, Shackelton RJ, et al. Society of Vascular Surgery Vascular Registry® comparison of carotid artery stenting outcomes for atherosclerotic vs nonatherosclerotic carotid artery disease. *J Vasc Surg*;51:1116-23.
13. Leger AR, Neale M, Harris JP. Poor durability of carotid angioplasty and stenting for treatment of recurrent artery stenosis after carotid endarterectomy: an institutional experience. *J Vasc Surg* 2001;33:1008-14.
14. Attigah N, Kulkens S, Deyle C, Ringleb P, Hartmann M, Geisbusch P, et al. Redo surgery or carotid stenting for restenosis after carotid endarterectomy: results of two different treatment strategies. *Ann Vasc Surg* 2010;24:190-5.
15. AbuRahma AF, Abu-Halimah S, Hass SM, Nanjundappa A, Stone PA, Mousa A, et al. Carotid artery stenting outcomes are equivalent to carotid endarterectomy outcomes for patients with post-carotid endarterectomy stenosis. *J Vasc Surg* 2010;52:1180-7.
16. Hobson RW, 2nd, Goldstein JE, Jamil Z, Lee BC, Padberg FT, Jr., Hanna AK, et al. Carotid restenosis: operative and endovascular management. *J Vasc Surg* 1999;29:228-35; discussion 35-

8.
17. Nolan BW, De Martino RR, Goodney PP, Schanzer A, Stone DH, Butzel D, et al. Comparison of carotid endarterectomy and stenting in real world practice using a regional quality improvement registry. *J Vasc Surg* 2012;56:990-6.
18. Cronenwett JL, Likosky DS, Russell MT, Eldrup-Jorgensen J, Stanley AC, Nolan BW. A regional registry for quality assurance and improvement: the Vascular Study Group of Northern New England (VSGNNE). *J Vasc Surg* 2007;46:1093-101; discussion 101-2.
19. Ricotta JJ, O'Brien MS, DeWeese JA. Natural history of recurrent and residual stenosis after carotid endarterectomy: implications for postoperative surveillance and surgical management. *Surgery* 1992;112:656-61; discussion 62-3.
20. O'Donnell TF, Jr., Rodriguez AA, Fortunato JE, Welch HJ, Mackey WC. Management of recurrent carotid stenosis: should asymptomatic lesions be treated surgically? *J Vasc Surg* 1996;24:207-12.
21. Coyle KA, Smith RB, 3rd, Gray BC, Salam AA, Dodson TF, Chaikof EL, et al. Treatment of recurrent cerebrovascular disease. Review of a 10-year experience. *Ann Surg* 1995;221:517-21; discussion 21-4.
22. Domenig C, Hamdan AD, Belfield AK, Campbell DR, Skillman JJ, LoGerfo FW, et al. Recurrent stenosis and contralateral occlusion: high-risk situations in carotid endarterectomy? *Ann Vasc Surg* 2003;17:622-8.
23. Hill BB, Olcott Ct, Dalman RL, Harris EJ, Jr., Zarins CK. Reoperation for carotid stenosis is as safe as primary carotid endarterectomy. *J Vasc Surg* 1999;30:26-35.
24. de Borst GJ, Zanen P, de Vries JP, van de Pavoordt ED, Ackerstaff RG, Moll FL. Durability of surgery for restenosis after carotid endarterectomy. *J Vasc Surg* 2008;47:363-71.
25. O'Hara PJ, Hertzer NR, Karafa MT, Mascha EJ, Krajewski LP, Beven EG. Reoperation for recurrent carotid stenosis: early results and late outcome in 199 patients. *J Vasc Surg* 2001;34:5-12.
26. Stoner MC, Cambria RP, Brewster DC, Juhola KL, Watkins MT, Kwolek CJ, et al. Safety and efficacy of reoperative carotid endarterectomy: a 14-year experience. *J Vasc Surg* 2005;41:942-9.
27. Cho JS, Pandurangi K, Conrad MF, Shepard AS, Carr JA, Nypaver TJ, et al. Safety and durability of redo carotid operation: an 11-year experience. *J Vasc Surg* 2004;39:155-61.
28. Rockman CB, Riles TS, Landis R, Lamparello PJ, Giangola G, Adelman MA, et al. Redo carotid surgery: An analysis of materials and configurations used in carotid reoperations and their influence on perioperative stroke and subsequent recurrent stenosis. *J Vasc Surg* 1999;29:72-80; discussion -1.
29. Coscas R, Rhissassi B, Gruet-Coquet N, Couture T, de Tymowski C, Chiche L, et al. Open surgery remains a valid option for the treatment of recurrent carotid stenosis. *J Vasc Surg* 2010;51:1124-32.
30. Das MB, Hertzer NR, Ratliff NB, O'Hara PJ, Beven EG. Recurrent carotid stenosis. A five-year series of 65 reoperations. *Ann Surg* 1985;202:28-35.
31. Aburahma AF, Bates MC, Stone PA, Wulu JT. Comparative study of operative treatment and percutaneous transluminal angioplasty/stenting for recurrent carotid disease. *J Vasc Surg* 2001;34:831-8.
32. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2004;351:1493-501.
33. Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, et al. Long-Term Results of Carotid Stenting versus Endarterectomy in High-Risk Patients. *N Engl J Med* 2008;358:1572-9.
34. Gasparis AP, Ricotta L, Cuadra SA, Char DJ, Purtill WA, Van Bemmelen PS, et al. High-risk carotid endarterectomy: fact or fiction. *J Vasc Surg* 2003;37:40-6.
35. Schermerhorn ML, Fokkema M, Goodney P, Dillavou ED, Jim J, Kenwood CT, et al. The impact of Centers for Medicaid and Medicare Services high-risk criteria on outcome after carotid endarterectomy and carotid artery stenting in the SVS Vascular Registry. *J Vasc Surg* 2013.
36. Hellings WE, Moll FL, de Vries JP, de Bruin P, de Kleijn DP, Pasterkamp G. Histological characterization of restenotic carotid plaques in relation to recurrence interval and clinical

presentation: a cohort study. *Stroke* 2008;39:1029-32.
37. Mylonas SN, Moulakakis KG, Antonopoulos CN, Kakisis JD, Liapis CD. Carotid artery stenting-induced hemodynamic instability. *J Endovasc Ther* 2013;20:48-60.
38. AbuRahma AF, Abu-Halimah S, Bensenhaver J, Nanjundappa A, Stone PA, Dean LS, et al. Primary carotid artery stenting versus carotid artery stenting for postcarotid endarterectomy stenosis. *J Vasc Surg* 2009;50:1031-9.
39. Lal BK, Hobson Ii RW, Tofighi B, Kapadia I, Cuadra S, Jamil Z. Duplex ultrasound velocity criteria for the stented carotid artery. *J Vasc Surg* 2008;47:63-73.
40. Goodney PP, Likosky DS, Cronenwett JL. Factors associated with stroke or death after carotid endarterectomy in Northern New England. *J Vasc Surg* 2008;48:1139-45.

CHAPTER FOUR

Carotid stenting versus endarterectomy in patients with restenosis following prior endarterectomy: an individual patient data meta-analysis

Manuscript submitted

Authors

Margriet Fokkema, MD[1,2*], Joyce E.P. Vrijenhoek, MD[1,3,4*], Hester M. Den Ruijter, PhD[3,5], Rolf H.H. Groenwold, MD PhD[5], Marc L. Schermerhorn, MD PhD[2], Michiel L. Bots, MD PhD[5], Gerard Pasterkamp, MD PhD[3], Frans L. Moll, MD PhD[1], Gert Jan De Borst, MD PhD [1], on behalf of the TREAT CARE Study Group†

** Shared first authorship*

Affiliations

[1] Department of Vascular Surgery, University Medical Center Utrecht, The Netherlands, [2] Department of Vascular and Endovascular Surgery, Beth Israel Medical Center, Boston, MA, USA , [3] Experimental Cardiology Laboratory, University Medical Center, Utrecht, the Netherlands, [4] Interuniversity Cardiology Institute of the Netherlands, Utrecht, the Netherlands, [5] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands

† Collaborating authors of the TREAT CARE Study Group

Pierre Alric[a], Nicolas Attigah[b], Rafael Beyar[c], Dittmar Böckler[b], Pascal Branchereau[a], Walter Dorigo[d], Christoph Domenig[e], Mark L. Eskandari[f], Krishna M. Jain[g], Shikha Jain[g], Milu Ju[f], Yasha Kadkhodayan[h], Ashraf Mansour[i], Eugenia Nikolsky[c], Frank B. Pomposelli[e], Raffaele Pulli[d], Djordje Radak[j], Robert H. Rosenwasser[k], Slobodan Tanaskovic[j], Stavropoula I. Tjoumakaris[k], Jan Albert Vos[l], Justin Whisenant[m].

[a] Department of Vascular Surgery, University of Montpellier, Montpellier, France. [b] Department of Vascular and Endovascular Surgery, University of Heidelberg, Heidelberg, Germany. [c] Division of Invasive Cardiology & Cardiovascular Research Unit, Rambam Medical Center, Haifa, Israel. [d] Department of Vascular Surgery, University of Florence, Florence, Italy. [e] Division of Vascular Surgery, Beth Israel Deaconess Medical Center, Boston, MA, USA. [f] Division of Vascular Surgery, Northwestern University, Chicago, IL, USA. [g] Michigan State University, Kalamazoo Center for Medical Studies, MI, United States. [h] Interventional Neuroradiology, Abbott Northwestern Hospital Neuroscience Institute, Consulting Radiologists Ltd, Minneapolis, MN, USA. [i] Michigan State University College of Human Medicine, Spectrum Health Medical Group, MI, USA. [j] Vascular Surgery Clinic, School of Medicine, Belgrade University "Dedinje" Cardiovascular Institute, Belgrade, Serbia. [k] Division of Neurovascular and Endovascular Surgery, Thomas Jefferson University Hospital, Philadelphia, PA, USA. [l] Department of Radiology, St. Antonius Hospital, Nieuwegein, The Netherlands. [m] Interventional Neuroradiology, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO, USA.

ABSTRACT

Background. The optimal treatment strategy for patients with restenosis after carotid endarterectomy (CEA) remains unknown. Furthermore, restenosis has been considered as a high-risk condition for redo-CEA, suggesting that these patients might be better treated with carotid artery stenting (CAS). We aimed to study perioperative results and restenosis during follow-up of CAS versus CEA for restenosis after prior ipsilateral CEA in an individual patient data (IPD) meta-analysis.

Methods. A comprehensive search of electronic databases (Medline, Embase) until July 1, 2013 was performed, supplemented by a review of references. Studies were considered for inclusion if they reported procedural outcome of CAS or CEA after prior ipsilateral CEA of a minimum of five patients. IPD were combined into one dataset and an IPD meta-analysis was performed. The primary endpoint was perioperative stroke or death and the secondary endpoint was restenosis >50%, comparing CAS and CEA.

Results. In total, 13 studies contributing to 1132 unique patients, treated by CAS (10 studies, n=653) or CEA (7 studies; n=479) were included. Among CAS and CEA patients, 30% versus 40% were symptomatic, respectively (P<.01). After adjustment for potential confounding, the primary endpoint did not differ between CAS and CEA groups (2.3% respectively 2.9%, adjusted OR 0.8, 95% CI 0.4-1.7). Also, no difference between the groups was identified for symptomatic (3.1% vs. 3.7%, unadjusted OR 0.8, 95% CI 0.3-2.5) or asymptomatic patients (2.0% vs. 2.4%, OR 0.8, 95% CI 0.3-2.2).

Conclusion. In patients with restenosis after previous ipsilateral CEA, CAS does not appear to be superior to redo-CEA in terms of procedural stroke and death, indicating that this cannot be confirmed as a high-risk condition for redo-CEA.

INTRODUCTION

Restenosis after carotid endarterectomy (CEA) hampers the long-term durability in terms of stroke free survival.[1,2] The reported incidence of restenosis is variable according to its definition, the duration of follow-up and its measurement methods. Duplex ultrasound derived > 50% restenosis has been reported varying between 6-14% at two years.[3,4] Restenotic lesions have been shown to be clinically important, since recurrent lesions >70% have been related to an increased risk for ipsilateral stroke.[5] However, the optimal treatment strategy of significant restenotic lesions remains unclear.[6-8] Redo-CEA potentially leads to a more challenging procedure[9,10], and therefore restenosis following prior CEA has been adapted among the "high-risk" criteria within several registries and trials comparing outcome after carotid artery stenting (CAS) versus CEA.[11,12] In extension, CAS has been suggested and applied as an alternative for CEA in these deemed high-risk cases.[13] Yet, there is no evidence suggesting that the (peri)procedural risk for stroke in these patients is lower for CAS when compared to CEA. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial (SAPPHIRE) is the only randomized controlled trial comparing CAS versus CEA that included a subgroup of patients with restenosis after prior ipsilateral CEA, however no subgroup analysis was performed in these patients.[11] Numerous single centers and several larger registries have reported on outcome of patients treated for restenosis after prior ipsilateral CEA through CAS or CEA[14-16]. Only few (non-randomized) studies reported on outcome of both treatment modalities.[16-22] Generally, small numbers limit the current evidence on the treatment strategy for restenosis. Most studies were underpowered to stratify patients in different risk categories or to adjust for patient factors in association with outcome, such as symptomatic presentation. While a randomized control trial is beyond perspective, accurate outcome analysis with the use of individual patient data (IPD) seems the highest retrievable level of evidence at present.

Therefore, we used IPD and pooled all the publically available evidence regarding the surgical or endovascular treatment of patients with restenosis after prior CEA. The aim of this study was to compare CEA and CAS, hypothesizing that both techniques show similar results regarding perioperative results and outcome during follow-up.

METHODS

The study protocol defining the process for obtaining patient level data and the pre-planned analyses was designed by the core study group (MF, JV, HR, FM, GJB) and approved by all collaborating authors of the TREAT CARE (optimal TREATment of CArotid REstenosis) study group.

Search strategy and study selection

A systematic search was performed on Pubmed and Embase databases until July 1, 2013. Synonyms for 'recurrent carotid stenosis' and 'carotid endarterectomy' and/or 'carotid angioplasty and stenting' were used to identify relevant studies. No filters or restrictions were applied (see table 1 for search query). References of relevant articles were screened for additional useful studies. Two independent researchers (MF and JV) screened all publications on the following predefined inclusion criteria: 1) patients who underwent CEA or CAS for restenosis after prior

Table I Search strategy

Recurrent stenosis OR Recurrent carotid stenosis OR Restenosis OR Post-CEA stenosis OR Post carotid endarterectomy stenosis OR Post endarterectomy stenosis AND CEA OR carotid endarterectomy OR carotid surgery OR Carotid revascularization OR OCS OR Open surgical repair OR Redo surgery OR Endarterectomy OR CAS OR Carotid artery stenting OR Carotid angioplasty OR Carotid stenting

ipsilateral CEA, 2) data on the primary endpoint reported, 3) publications in English, Dutch, German, French or Spanish, 4) original data. Studies were excluded if there was no full text version available or if the number of patients treated was less than five. Duplicates were removed manually. All citations that met the inclusion criteria were read full-text and thoroughly assessed for final inclusion.

Our search resulted in 1334 articles on Pubmed and 1207 on Embase (figure 1). After removing duplicates, 1521 articles remained, of which 1424 were excluded after screening citations. Of the remaining 93 articles, 14 were excluded for different reasons (figure 1). Reference check of these 93 articles yielded 5 relevant studies, resulting in a final total of 84 eligible articles.

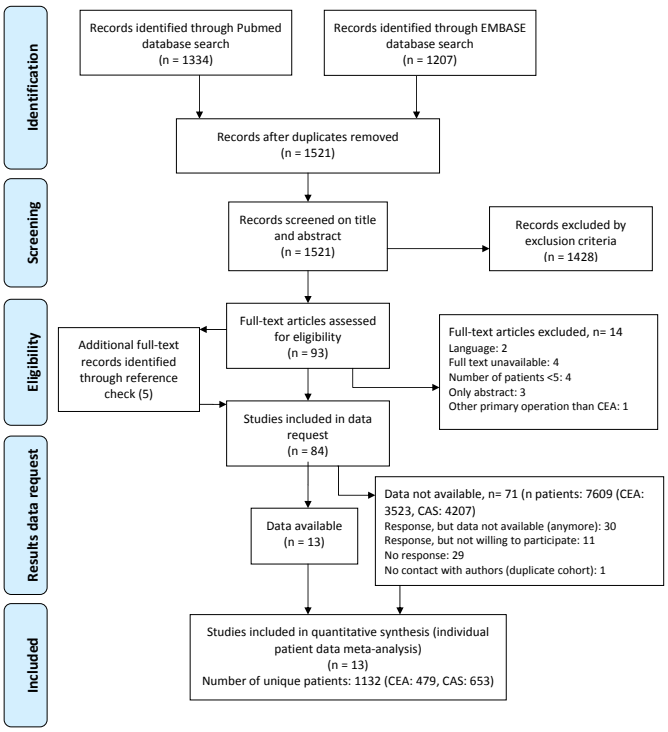
Table II Overview of included studies

Article	Type of study	Years of inclusion	N CEA	N CAS
Alric et al., 2002	Singlecenter	1997-2000	0	15
Attigah et al., 2010	Singlecenter	1989-2007	28	41
Benitez et al., 1998	Singlecenter	1996-1997	0	5
Bettendorf et al., 2007	Singlecenter	1998-2006	28	29
Domenig et al., 2003	Singlecenter	1990-2001	82	0
Dorigo et al., 2013	Singlecenter	2005-2011	37	58
Eskandari et al., 2010	Singlecenter	2001-2009	0	70
Fokkema et al., 2013	Multicenter	2003-2012	212	220
Halabi et al., 2006	Singlecenter	1998-2004	0	72
Jain et al., 2007	Singlecenter	1988-2005	80	0
Kadkhodayan et al., 2007	Singlecenter	1996-2005	0	73
Radak et al. 2012	Multicenter (2 centers)	2000-2008	12	0
Vos et al., 2009	Singlecenter	1997-2006	0	70
Total			479	653

Individual patient data acquisition

Authors of eligible articles were contacted per email or per post with a request for joining the TREAT CARE initiative. We obtained the contact details of any author listed on the article (sequence of contact: corresponding author, first author, senior author, other co-authors). If we did not receive a response after one week, the authors were contacted again, with a maximum of four attempts within a timeframe of three months. From the 84 eligible articles (7609 patients, possibly including duplicate patients and interventions others than CEA/CAS), we received IPD from 13 studies. From the remaining 71 studies, IPD could not be retrieved because 29 authors did not respond, 30 did respond that the data was not available (reported reasons: no access to the data anymore because of change of institution or retirement and institutional review board restrictions), and 11 respond that they were not willing to participate (unknown reasons). One study[23] was not contacted because we had recognized that this cohort was a duplicate with another study,[24] though these were different publications. Of the studies that provided IPD, some included a subset of patients treated with interposition grafting (n=43), carotid bypass (n=24), or angioplasty only (n=2), and these subsets were excluded from our database. Furthermore, 32 bilateral or tertiary procedures were excluded, resulting in a total of 1132 unique patients (479 CEA, 653 CAS). Figure 1 and table II show an overview of data acquisition and the 13 included articles, respectively.

Figure 1: Flow Diagram TREAT CARE study



Data extraction and outcome

Demographics, patient related risk factors, procedural details, perioperative outcome and follow-up data were extracted from the received IPD files. The data was aggregated to one database, after we carefully checked the received data with the original manuscript. The primary endpoint of the current study was any perioperative stroke or death. The secondary endpoint was recurrent carotid restenosis (>50%) during follow-up. Other procedural complications such as cranial nerve injury (CNI), neck hematoma, wound infection (following CEA) and residual stenosis (>30%), technical failure and access site complications (following CAS) were also extracted.

Statistical analysis

Baseline characteristics between CEA and CAS patients were compared using Fisher's exact test for categorical variables, and parametric (Student t-test) or non-parametric test (Mann-Whitney U-test) for continuous variables, where applicable.

The primary endpoint (any perioperative stroke or death) was compared between CEA and CAS with the Fisher's exact test. For adjusted analyses, potential confounders were previously determined based on availability (<75% missing values) and clinical relevance by four members of the core study group (MF, JV, HR, GB). These variables were age, gender, smoking, hypertension, degree of ipsilateral stenosis, symptom status, diabetes and coronary artery disease. To prevent bias due to exclusion of observations because of missing values in these variables, we used single imputation (using the multivariate imputation by chained equations algorithm in R with one imputation).[25,26] Predictors in the imputation model included all variables to be imputed, including the primary endpoint, as recommended previously.[26] Because of the low event rate of stroke or death, a propensity score including the above listed variables and obtained considerable balance between treatment group was constructed. The primary endpoint comparing CEA and CAS was subsequently analyzed by a logistic regression model, adjusted for the propensity score. Odds ratios (OR) and 95% confidence intervals (CI) are reported.

The secondary endpoint (restenosis during follow-up) was analyzed using a multivariable Cox proportional hazard model to allow time to event analyses, adjusted for the same propensity score as above. Hazard ratios (HR) and 95% CI are reported.

SPSS version 20.0 (IBM Corp, IBM SPSS Statistics for Windows, Armonk, NY) and R Statistical software[27] were used for statistical analyses (R packages "mice" and "survival"). P-values <.05 were considered significant in all statistical analyses.

RESULTS

Baseline characteristics

Baseline characteristics of patients undergoing CEA (n=479) compared to CAS (n=653) for restenosis after prior ipsilateral CEA are shown in table 3. While CAS patients were more likely to be older (mean age 70 year vs. 68 year, P<.01). CEA patients were more often symptomatic (40% vs. 30%, P<.01) and a greater proportion of CEA patients suffered from severe ipsilateral stenosis >70% (94% vs. 85%, P<.01). Data on time to restenosis from the initial CEA was available for 56% (n=639) of patients. Median time from primary CEA to re-intervention was significantly shorter for CAS compared to CEA patients (14 months vs. 52 months, P<0.01), and also shorter

for asymptomatic versus symptomatic patients (18 months vs. 33 months, P<0.01). Of all 639 patients, 50.5% of patients (29% CEA and 61% CAS) had early restenosis (<24 months after primary CEA) and 49.5% (71% CEA vs. 39% CAS) were treated for late restenosis (>24 months after primary CEA).

Table III Baseline characteristics

	CEA (n = 479)		CAS (n = 653)		
	N / Total	%	N / Total	%	P - value
Age yr, mean ± SD	67.9 ± 9.3		69.7 ± 8.7		<.01
Gender (male)	238/479	49.7	345/653	52.8	0.31
Time to re-intervention Mo, median (IQR)	52 (77)		14 (39)		<.01
Patch (vs primary) closure during primary CEA	30/37	81.1	68/87	78.2	0.81
Side (right)	182/399	45.6	241/504	47.8	0.55
Symptomatic	190/479	39.5	193/653	29.6	<.01
Degree of ipsilateral stenosis					<.01
50-69%	30/459	6.5	86/589	14.6	
>70%	429/459	93.5	503/589	85.4	
Hypertension	400/479	83.5	505/573	88.0	0.04
Diabetes mellitus	147/479	30.7	175/570	30.7	1.0
Coronary artery disease	201/479	42.0	220/592	37.2	0.12
Renal failure	18/295	6.1	45/428	10.5	0.04
Hypercholesterolaemia	170/209	81.3	209/341	61.3	0.07
Smoking (prior or current)	388/468	82.9	332/570	58.2	<.01
Antiplatelet therapy	354/414	85.5	444/457	97.2	<.01
Statin use	270/360	75.0	284/364	78.0	0.38
Contralateral occlusion	30/318	9.4	58/566	10.2	0.72

CEA: carotid endarterectomy; CAS: carotid angioplasty and stenting; SD:standard deviation;
Mo: months; IQR: interquartile range.

Primary endpoint

Perioperative stroke or death rate did not differ between CAS and CEA (2.3% vs. 2.9%, OR 0.8, 95% CI 0.4 – 1.6). After adjusting for potential confounders (age, gender, smoking, hypertension, degree of ipsilateral stenosis, symptom status, diabetes and coronary artery disease, combined in a propensity score), still no difference was observed in the primary endpoint between CAS compared to CEA (adjusted OR 0.8, 95% CI 0.4-1.7).

Also unadjusted myocardial infarction, any stroke, and mortality (separately) were similar between the two treatment modalities (Table 4). Similarly, no differences in stroke or death rate were identified between CAS and CEA among both symptomatic (3.1% vs. 3.7%, unadjusted OR 0.8, 95% CI 0.3-2.5) and asymptomatic patients (2.0% vs. 2.4%, unadjusted OR 0.8, 95% CI 0.3-2.2). While patients treated for early restenosis tended to have lower stroke or death rates

with CAS compared to CEA (1.1% vs. 2.9%, unadjusted OR 0.4, 95% CI 0.1-2.1), the difference did not reach significance. Among all patients with late restenosis, stroke or death rate after CAS was 2.4% and after CEA 2.7% (unadjusted OR 0.9, 95% CI 0.2 – 3.5).

Secondary endpoint

Data on restenosis during follow-up was available for 716 patients from 10 studies[14,16,18,19,24,28-32], with a median follow-up time of 13 months (interquartile range 8.5-26). Of these 716, 97 patients developed restenosis >50% (14%, 51% CAS patients) and 45 had restenosis >70% (6%, 36% CAS patients). In an unadjusted analysis comparing restenosis >50% following CAS versus CEA, HR was 1.3, 95% CI: 0.8-1.9. After adjustment for predefined variables we also found no difference between the treatments groups regarding restenosis >50% in CAS patients (HR 1.4, 95% CI 0.7-2.2). Symptom status was not an effect modifier in this analysis (P of interaction=0.40), thus, this risk was similar for both symptomatic (HR 1.8, 95% CI 0.6-3.9) and asymptomatic patients (HR 1.3, 95% CI 0.8-2.3). Regarding clinical outcome during follow-up, there were 6 strokes (1 in the CAS group, 5 in the CEA group) and 8 cardiovascular deaths (3 in the CAS group, 5 in the CEA group) during follow-up. These limited numbers did not allow for a reliable comparison between treatments or (multivariable) analysis.

Table IV Perioperative outcome in all patients undergoing CEA or CAS

	CEA N/total	%	CAS N /total	%	OR (95% CI)
Primary outcome					
Any stroke or death	14/479	2.9	15/653	2.3	0.8 (0.4 – 1.6)
Any stroke	12/479	2.5	13/653	2.0	0.8 (0.4 – 1.7)
Death	4/479	0.8	4/653	0.8	0.7 (0.2 – 3.0)
Myocardial infarction	9/479	2.2	8/653	1.2	0.5 (0.2 – 1.4)
CEA					
Cranial nerve injury	26/474	5.4	na	na	na
Bleeding	13/474	2.7	na	na	na
Wound infections	1/462	0.2	na	na	na
CAS					
Technical failure	na	na	8/640	1.3	na
Residual stenosis	na	na	2/640	0.3	na
Access site complication	na	na	11/580	1.7	na

CEA: carotid endarterectomy; CAS: carotid angioplasty and stenting; OR: odds ratio; na: not applicable. Odds ratios for CAS compared to CEA are shown.

Minor complications

Following CEA, CNI was identified in 5.4%, bleeding in 2.7% and wound infections in 0.2%. After CAS, technical failure rate was 1.3%, residual stenosis was seen in 0.3% and access site complications were identified in 1.7% of cases.

Sensitivity analysis

Table 5 shows an overview of all event rates per included study separately, showing percentages from 0 to 5.5% for CAS and 0 to 7.1% for CEA. A sensitivity analysis was performed by excluding patients from the largest study.[16] In these subset analysis, a similar effect size and direction was identified for both primary and secondary endpoints compared to the entire cohort (1132 patients, OR stroke/death: 0.9, 95% CI 0.3-2.6 and HR restenosis: 1.1, 95% CI 0.6-2.0). In addition, we analyzed outcome in the 4 studies with both treatments to be able to differentiate treatment effect and study effects and found similar results (data not shown).

Table V Procedural stroke and death rates reported in 13 included studies

	CEA	CAS
Alric et al., 2002		0%
Attigah et al., 2010	7.1%	0%
Benitez et al.,* 1998		0%
Bettendorf et al.,* 2007	7.1%	3.4%
Domenig et al., 2003	2.4%	
Dorigo et al., 2013	0%	0%
Eskandari et al., 2010		1.4%
Fokkema et al., 2013	3.3%	3.2%
Halabi et al., 2006		2.8%
Jain et al., 2007	1.2%	
Kadkhodayan et al., 2007		5.5%
Radak et al. 2012	0%	
Vos et al.,† 2009		0%

CEA: carotid endarterectomy; CAS: carotid angioplasty and stenting.
All percentages are stroke and death rate adapted from individual patient data. All rates are 30-day postoperative event rates, unless indicated otherwise. * Postoperative event timeframe not specified. † 7 day postoperative event rate.

DISCUSSION

This meta-analysis of individual patients' data from thirteen studies shows that in symptomatic and asymptomatic patients with restenosis after prior ipsilateral CEA, perioperative stroke and death rate and restenosis during follow-up were comparable following CAS and CEA. These results indicate that restenosis after CEA is not a strict 'high-risk' criterion for redo-CEA when revascularization is considered indicated. As a consequence, both CAS and CEA seem suitable options to treat restenosis after prior ipsilateral CEA. It suggests that choice of treatment should

probably be based on patient characteristics (use of a shunt at the primary operation, severe co-morbidities, poor anatomical accessibility e.g. due to excessive subcutaneous fat or a short neck) and physician experience.

'High-risk' criteria for CEA have been a matter of debate for a long time.[13,33] It remains undefined whether these patients are considered at increased risk for stroke, death or other periprocedural complications after CEA. While the Centers for Medicare & Medicaid approved reimbursement for CAS in patients with severe, symptomatic restenosis, no evidence exists that the results with stenting are better than with CEA in these patients. Our study proved that the absolute stroke rates were considerably low among both symptomatic and asymptomatic patients undergoing CEA or CAS. However, the indication for revascularization of asymptomatic patients with restenosis after prior CEA is still under debate, since a great proportion of lesions will potentially remain asymptomatic. In these patients, the procedural risk for either intervention should be carefully balanced against the natural risk for stroke during follow-up.[34]

We also found that the durability of both procedures at follow-up was comparable, regardless of symptom status at baseline. However, the 50% cut-of point to determine restenosis after CAS is questionable, because stent tortuosity in CAS patients may lead to higher velocity patterns and subsequent increased degree of reported stenosis.[35,36] Therefore, the rate of restenosis in CAS patients may be overestimated when compared to CEA patients. This was illustrated by a prior study, that reported an increased incidence of restenosis >50% in CAS compared to CEA, while this difference was absent when looking at restenosis >80%.[21] Unfortunately, we were not able to look at severe restenosis greater than 70% or 80%, because most of the received IPD only reported on restenosis >50%. Besides the possible apparent in-stent restenosis in CAS patients, patients were followed for a median of 13 months in this study, possibly indicating that some restenosis cases have represented residual stenosis, instead of new, recurrent stenotic lesions. Yet it is important to consider that restenosis is usually asymptomatic.[37]

An increased risk for cranial nerve injury in patients undergoing redo-CEA has been reported previously.[10,21] Our pooled CNI rate of 5.4% was comparable with CNI rate in primary CEA procedures (4.7% - 8.6%) as shown in prior large trials[12,38,39], suggesting that the impact of redo-CEA on nerve injury is limited. However, the uses of objective measurement methods play an important role in the detection of CNI and therefore, direct comparisons on CNI rates difficult. In general, the clinical relevance of nerve palsies seems limited due to its transient nature and minor impact on health related outcomes.[40]

The strength of this study is a relatively high number of patients in both CEA and CAS groups. We have acquired data of more than 1100 patients out of a possible 7609. This last number is probably an overestimation because seven groups reported about similar or overlapping cohorts in a total of 20 articles. In addition, studies sometimes exclusively reported about different types of re-interventions than CEA or CAS, such as carotid bypass and interposition grafts or angioplasty without stent, which we excluded for this study.

While a selection bias could have occurred based on the response rate and availability of data, this effort has still resulted in the largest comparison of CEA and CAS in patients with restenosis after prior CEA currently available. In addition, we were able to adjust for various risk factors, that may have a significant impact outcome after carotid intervention. While in most comparative analyses CAS patients generally have increased risk factors compared to CEA patients,[13] in this

study we found that comorbidities between CEA and CAS patients were overall quite balanced. This was also indicated by the finding that adjustment for risk factors did not substantially change the risk of the primary endpoint.

This study has some limitations. Although we have made an effort to include all eligible data that were available in the current literature, the number of events was considerably low, particularly during follow-up. Therefore, we were not able to adjust for potential confounders in subgroup analysis (e.g. stratified by symptom status) and to perform comparative analyses on clinical events (stroke or death) during follow-up. While the response rate on our IPD data request was acceptable, we could not acquire data of numerous studies. However, we cannot make inferences regarding the possible influence of excluded data, because analyzing aggregate data from these studies would be less reliable than IPD.[41] In addition, publication bias could be an issue, but unfortunately this is inherent in meta-analyses, because positive results of treatments are more likely to get published. Another concern with IPD data is that certain studies may have a greater impact on outcome than others. Therefore, we conducted a sensitivity analysis by excluding the largest study.[16] This did not change the results, indicating that the reported outcomes are not driven by this study only. Finally, we could not reliably adjust for confounding due to clustering of patients within studies. Ideally, in IPD meta-analysis, this is taken into account by analyzing the data using a random effects model. However, for a number of studies included in our analysis, all patients in the particular studies were treated with the same treatment modality. Consequently, our analysis could not differentiate between study effects (i.e., differences between studies) and the actual treatment effect.

Nonetheless, this is the best (available) evidence to date, and a randomized controlled trial in this small group of patients, accompanied by low event rates after the intervention, would not be feasible.

Conclusions. In patients with restenosis after previous ipsilateral CEA, CAS does not appear to be superior to redo-CEA in terms of procedural stroke and death, indicating that this cannot be confirmed as a high-risk condition for redo-CEA.

References

1. de Borst GJ, Zanen P, de Vries J-PP, et al. Durability of surgery for restenosis after carotid endarterectomy. J Vasc Surg 2008;47:363-71.
2. Bekelis K, Moses Z, Missios S, et al. Indications for treatment of recurrent carotid stenosis. Br J Surg 2013;100:440-7.
3. Goodney PP, Nolan BW, Eldrup-Jorgensen J, et al. Restenosis after carotid endarterectomy in a multicenter regional registry. J Vasc Surg 2010;52:897-904, 5 e1-2; discussion -5.
4. van Lammeren GW, Peeters W, de Vries JP, et al. Restenosis after carotid surgery: the importance of clinical presentation and preoperative timing. Stroke 2011;42:965-71.
5. Lal BK, Beach KW, Roubin GS, et al. Restenosis after carotid artery stenting and endarterectomy: a secondary analysis of CREST, a randomised controlled trial. Lancet Neurol 2012;11:755-63.
6. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery Developed in Collaboration With the American Academy of Neurology and Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2011;57:e16-94.
7. Vidale S. Restenosis after carotid endarterectomy and stenting. Lancet Neurol 2013;12:130.
8. Lal BK. Recurrent carotid stenosis after CEA and CAS: diagnosis and management. Semin Vasc Surg 2007;20:259-66.
9. Piepgras DG, Sundt TM, Jr., Marsh WR, et al. Recurrent carotid stenosis. Results and complications of 57 operations. Ann Surg 1986;203:205-13.
10. Das MB, Hertzer NR, Ratliff NB, et al. Recurrent carotid stenosis. A five-year series of 65 reoperations. Ann Surg 1985;202:28-35.
11. Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493-501.
12. Brott TG, Hobson RW, 2nd, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363:11-23.
13. Schermerhorn ML, Fokkema M, Goodney P, et al. The impact of Centers for Medicare and Medicaid Services high-risk criteria on outcome after carotid endarterectomy and carotid artery stenting in the SVS Vascular Registry. J Vasc Surg 2013;57:1318-24.
14. de Borst GJ, Ackerstaff RG, de Vries JP, et al. Carotid angioplasty and stenting for postendarterectomy stenosis: long-term follow-up. J Vasc Surg 2007;45:118-23.
15. Domenig C, Hamdan AD, Belfield AK, et al. Recurrent stenosis and contralateral occlusion: high-risk situations in carotid endarterectomy? Ann Vasc Surg 2003;17:622-8.
16. Fokkema M, de Borst GJ, Nolan BW, et al. Carotid Stenting versus Endarterectomy in Patients undergoing Re-intervention after Prior Carotid Endarterectomy. J Vasc Surg 2013;Epub ahead of print.
17. Bowser AN, Bandyk DF, Evans A, et al. Outcome of carotid stent-assisted angioplasty versus open surgical repair of recurrent carotid stenosis. J Vasc Surg 2003;38:432-8.
18. Bettendorf MJ, Mansour MA, Davis AT, et al. Carotid angioplasty and stenting versus redo endarterectomy for recurrent stenosis. Am J Surg 2007;193:356-9; discussion 9.
19. Attigah N, Kulkens S, Deyle C, et al. Redo surgery or carotid stenting for restenosis after carotid endarterectomy: results of two different treatment strategies. Ann Vasc Surg 2010;24:190-5.
20. Aburahma AF, Bates MC, Stone PA, et al. Comparative study of operative treatment and percutaneous transluminal angioplasty/stenting for recurrent carotid disease. J Vasc Surg

2001;34:831-8.
21. AbuRahma AF, Abu-Halimah S, Hass SM, et al. Carotid artery stenting outcomes are equivalent to carotid endarterectomy outcomes for patients with post-carotid endarterectomy stenosis. J Vasc Surg 2010;52:1180-7.
22. Hobson RW, 2nd, Goldstein JE, Jamil Z, et al. Carotid restenosis: operative and endovascular management. J Vasc Surg 1999;29:228-35; discussion 35-8.
23. Munn JS, Jain KM, Simoni EJ. Reoperation for recurrent carotid stenosis: a ten-year experience. Vasc Surg 1998;32:425-32.
24. Jain S, Jain KM, Kumar SD, et al. Operative intervention for carotid restenosis is safe and effective. Eur J Vasc Endovasc Surg 2007;34:561-8.
25. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J Stat Soft 2011;45.
26. Moons KG, Donders RA, Stijnen T, et al. Using the outcome for imputation of missing predictor values was preferred. J Clin Epidemiol 2006;59:1092-101.
27. R: A language and environment for statistical computing. R Foundation for Statistical Computing. In. Vienna, Austria: http://www.R-project.org; 2012.
28. Dorigo W, Pulli R, Fargion A, et al. Comparison of open and endovascular treatments of post-carotid endarterectomy restenosis. Eur J Vasc Endovasc Surg 2013;45:437-42.
29. Kadkhodayan Y, Moran CJ, Derdeyn CP, et al. Carotid angioplasty and stent placement for restenosis after endarterectomy. Neuroradiology 2007;49:357-64.
30. Radak D, Davidovic L, Tanaskovic S, et al. Surgical treatment of carotid restenosis after eversion endarterectomy--Serbian bicentric prospective study. Ann Vasc Surg 2012;26:783-9.
31. Halabi M, Gruberg L, Pitchersky S, et al. Carotid artery stenting in surgical high-risk patients. Catheter Cardiovasc Interv 2006;67:513-8.
32. Alric P, Branchereau P, Berthet JP, et al. Carotid artery stenting for stenosis following revascularization or cervical irradiation. J Endovasc Ther 2002;9:14-9.
33. Gasparis AP, Ricotta L, Cuadra SA, et al. High-risk carotid endarterectomy: fact or fiction. J Vasc Surg 2003;37:40-6.
34. Ricotta JJ, O'Brien MS, DeWeese JA. Natural history of recurrent and residual stenosis after carotid endarterectomy: implications for postoperative surveillance and surgical management. Surgery 1992;112:656-61; discussion 62-3.
35. Lal BK, Hobson Ii RW, Tofighi B, et al. Duplex ultrasound velocity criteria for the stented carotid artery. J Vasc Surg 2008;47:63-73.
36. Reichmann BL, Hellings WE, van der Worp HB, et al. Interprocedural comparison of changes in natural flow velocity patterns in the internal carotid artery following CAS or CEA. Eur J Vasc Endovasc Surg 2013;45:554-61.
37. Yadav JS, Roubin GS, Iyer S, et al. Elective stenting of the extracranial carotid arteries. Circula tion 1997;95:376-81.
38. Cunningham EJ, Bond R, Mayberg MR, et al. Risk of persistent cranial nerve injury after carotid endarterectomy. J Neurosurg 2004;101:445-8.
39. Ferguson GG, Eliasziw M, Barr HW, et al. The North American Symptomatic Carotid Endarterectomy Trial : surgical results in 1415 patients. Stroke 1999;30:1751-8.
40. Cohen DJ, Stolker JM, Wang K, et al. Health-Related Quality of Life After Carotid Stenting Versus Carotid Endarterectomy: Results From CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial). J Am Coll Cardiol 2011;58:1557-65.
41. Debray TP, Moons KG, Abo-Zaid GM, et al. Individual participant data meta-analysis for a binary outcome: one-stage or two-stage? PLoS One 2013;8:e60650.

PART ②

The identification of the ‘high risk’ patient

CHAPTER FIVE

The impact of Centers for Medicaid and Medicare Services high risk criteria on outcome after carotid endarterectomy and carotid artery stenting in the SVS Vascular Registry

Journal of Vascular Surgery
May 2013; Vol 57 Pages: 1318-24

Authors
Schermerhorn M.L[1], Fokkema M[1], Goodney P[2], Dillavou E.D[3], Jim J[4], Kenwood C.T[5], Siami F.S[5], White R.A[6]; SVS Outcome Committee

Affiliations
[1]Beth Israel Deaconess Medical Center, Boston, [2]Dartmouth-Hitchcock Medical Center, Lebabon, NH, [3]University of Pittsburgh Medical Center, Pittsburgh, Pa, [4]Washington University School of Medicine, St. Louis, Mo, [5]New England Reserach Insitute, Inc, Watertown, Mass, [6]Harbor-UCLA Medical Center, Los Angelas, Ca

ABSTRACT

Objectives. CMS requires high-risk (HR) criteria for carotid stent (CAS) reimbursement. The impact of these criteria on outcomes after carotid endarterectomy (CEA) and CAS remains uncertain. Additionally, if these HR criteria are associated with more adverse events after CAS, then existing comparative effectiveness analysis of CEA vs CAS may be biased. We sought to elucidate this using data from the SVS Vascular Registry™.

Methods. We analyzed 10,107 patients undergoing CEA (6,370) and CAS (3,737), stratified by CMS HR criteria. The primary endpoint was composite death, stroke and MI (MACE) at 30 days. We compared baseline characteristics and outcomes using univariate and multivariable analyses.

Results. CAS patients were more likely to have preoperative stroke (26% vs 21%) or TIA (23% vs 19%) than CEA. While age ≥ 80 years was similar, CAS patients were more likely to have all other HR criteria. For CEA, HR patients had higher MACE than normal risk in both symptomatic (7.3% vs 4.6%, $p<0.01$) and asymptomatic patients (5% vs 2.2%, $p<0.0001$). For CAS, HR status was not associated with a significant increase in MACE for symptomatic (9.1% vs 6.2%, $p=0.24$) or asymptomatic patients (5.4% vs 4.2%, $p=0.61$). All CAS patients had MACE rates similar to HR CEA. After multivariable risk adjustment, CAS had higher rates than CEA for MACE (OR 1.2, 95% CI 1.0-1.5), death (1.5, 1.0-2.2) and stroke (1.3, 1.0-1.7), while there was no difference in MI (OR 0.8, 0.6-1.3). Among CEA patients, age ≥ 80 (OR 1.4, 1.02-1.8), CHF (OR 1.7, 1.03-2.8), EF<30% (OR 3.5, 1.6-7.7), angina (OR 3.9, 1.6-9.9), contralateral occlusion (OR 3.2, 2.1-4.7), and high anatomic lesion (OR 2.7, 1.33-5.6) predicted MACE. Among CAS patients, recent MI (OR 3.2, 1.5-7.0) was predictive and radiation (OR 0.6, 0.4-0.8) and restenosis (OR 0.5, 0.3-0.96) were protective for MACE.

Conclusions. While CMS HR criteria can successfully discriminate a group of patients at HR for adverse events after CEA, certain CMS HR criteria are more important than others. However, CEA appears safer for the majority of patients with carotid disease. Among patients undergoing CAS, non-HR status may be limited to restenosis and radiation.

INTRODUCTION

Over the last two decades, carotid artery stenting (CAS) has emerged as an alternative to carotid endarterectomy (CEA) to reduce the risk of stroke in patients with severe carotid artery stenosis. Meanwhile, subsequent trials have shown conflicting results with failure to meet non-inferiority between the two revascularization procedures in average risk patients.[1-4] The Centers for Medicare and Medicaid Services (CMS) have approved reimbursement for CAS in patients who are at 'high risk' for CEA with symptomatic ≥70% stenosis unless enrolled in a clinical trial.[5] High risk (HR) criteria include several medical and anatomic conditions; criteria that many presume are associated with increased operative risk.

As a result of these HR criteria proposed by CMS, there may be over representation of HR and/or symptomatic patients selected for CAS, which may introduce bias into the comparisons of CAS and CEA. Additionally, there is no clear evidence suggesting that the risk with CAS is lower in these HR patients when compared to CEA. The HR criteria used by CMS were developed years ago, based on outcomes from a randomized trial including mainly asymptomatic patients[6] and several prospective – still ongoing at that time – CAS registries.[7-9] The validity of these HR criteria was called into question by several authors.[10-13] However, the results of these studies cannot be justified since they are limited by low numbers of patients or the inability to adequately stratify patients into HR groups using only administrative data.

The Vascular Registry (VR) is the largest published database of CAS in the United States, designed to capture real-world practices. It therefore allows stratification of patients undergoing CAS or CEA by symptom status as well as the predefined HR criteria of CMS. In this study, we aimed to assess the validity and the impact the impact of these HR criteria on 30-day outcomes following CAS and CEA and to identify patient factors associated with increased procedural risk.

METHODS

VR data are reported by providers through web-based electronic data capture. The measurement schedule includes baseline (preoperative) demographics, medical history, carotid symptom status, pre-procedural diagnostic imaging and laboratory studies, procedural (CAS or CEA) information including clinical utility, intraoperative and pre-discharge complications, and follow-up information such as postoperative mortality, stroke, myocardial infarction and other morbidity. Specifically, the VR include all individual HR criteria outlined by CMS. The VR does not use inclusion or exclusion criteria for patient eligibility and is reliant on site entry of patients in whom CAS or CEA is performed. All data entered into the VR are fully compliant with the Health Insurance Portability and Accountability Act (HIPAA) regulations and are auditable. All data reports and analyses performed include only de-identified and aggregated data. New England Research Institutes, Inc (NERI, Watertown, MA) maintains the online database and funding for the administration and database management of the VR has been provided by the Society for Vascular Surgery.

Outcomes. The primary endpoint was a major adverse cardiovascular event (MACE) diagnosed within 30 days of treatment, defined as a composite of death, stroke, and myocardial infarction (MI). Secondary outcomes were combined stroke and death, death, stroke, and MI at 30-days

following CAS and CEA. Stroke is defined as any non-convulsive, focal neurological deficit of abrupt onset persisting more than 24 hours. The ischemic event must correspond to a vascular territory. An MI is classified as either Q wave MI in which one of the following criteria is required: (1) chest pain or other acute symptoms consistent with myocardial ischemia and new pathological Q waves in two or more contiguous ECG leads, or (2) new pathologic Q waves in two or more contiguous ECG leads and elevation of cardiac enzymes; or non-Q wave MI, defined as CK ratio >2, and CK-MB >1 in the absence of new, pathological Q waves. Analysis of 30-day outcomes was based on only those patients who had at least a 30-day post procedure visit or who experienced a MACE within 30 days of treatment.

Statistical methods. Tests of statistical significance were conducted with χ^2 or Fisher's exact tests for categorical variables and two-tailed t test for continuous variable age. Descriptive statistics are listed as percent (frequency) for categorical variables and mean (range) for continuous variable age. Subset analyses were performed using the χ^2 or Fisher's exact test, as necessary, for discrete/categorical data. The event rates are calculated per-patient. Unadjusted and adjusted odds ratios were used to compare the primary outcomes across treatment groups. Odds ratios were adjusted for symptomatic status and HR status in the overall comparison of CEA and CAS. Differences were considered significant if $P < .05$. All statistical analyses were performed by NERI using SAS Statistical Software (Cary, NC).

RESULTS

Data collected in the VR from November 2001 – September 2011 from 81 institutions (community-based, university-based, private practice, and non-university teaching hospitals) were analyzed. 10,107 patients who underwent CEA (n=6,370; 37.5% symptomatic) and CAS (n=3,737; 45.5% symptomatic) with data on 30-day outcomes were identified. The majority of the procedures (71% CAS; 93% CEA) were performed by vascular surgeons. Baseline demographics, patient characteristics, CMS HR status and individual HR factors are presented in Table I and II. Mean age was 71 years, and approximately 59% were male and 92% were white. CAS patients were more likely to have a preoperative stroke (25.5% vs. 21.0% CEA, $P = <0.001$) or TIA (23.1% vs. 19.1% CEA, $P = <0.001$) compared to CEA patients. CAS patients also had a significantly higher prevalence of cardiac comorbidities (coronary artery disease [57.8% vs. 48.1%], MI [22% vs. 16.3%], chronic heart failure [14.1% vs. 7.8%]), and non-atherosclerotic disease (recurrent or radiation induced stenosis [31.5% vs. 1.8%]). All individual CMS qualifying high risk factors were more prevalent in CAS patients, except for age ≥80 (19.3% CAS vs. 20.7% CEA, P =NS). Only 37% of CEA patients met any of the HR factors compared to 90.5% of CAS patients (P <0.001).

CEA outcomes. In symptomatic patients, the 30-day rate of MACE was 7.3% in HR patients versus 4.6% ($P = 0.008$) in non-HR patients. Combined stroke/death and death rates were significantly higher in HR patients compared to non-HR patients (6.4% vs. 3.9%, P =0.006 and 1.8% vs. 0.6%, $P = 0.008$, respectively). Stroke alone did not show significant differences between HR and non-HR symptomatic patients (4.9% vs. 3.5%, P =0.09).

Table I Demographics and clinical characteristics of 10,107 patients undergoing CEA or CAS in SVS VR

	CEA (n =6370)	CAS (n = 3737)	P-value
Age (year, mean, range)	70.9 (18 - 96)	70.9 (34 - 98)	0.98
Gender (male)	58.6%	60.4%	0.08
White - Caucasian	92.8%	91.9%	0.13
Symptom status	38.0%	41.0%	<0.01
Preoperative Symptoms			
Stroke	21.0%	25.5%	<0.001
TIA	19.1%	23.1%	<0.001
TMB	5.4%	7.4%	<0.001
Etiology of lesion			<0.001
Atherosclerosis	98.2%	68.5%	
Radiation	0.1%	5.2%	
Restenosis	1.3%	24.0%	
Diabetes	31.4%	34.0%	<0.01
Hypertension	84.3%	83.0%	0.08
Current or Past Smoker	60.8%	61.3%	0.65
Coronary Artery Disease	48.1%	57.8%	<0.001
Myocardial Infarction	16.3%	22.0%	<0.001
Valvular Heart Disease	7.9%	6.0%	<0.001
Cardiac Arrhythmia	12.9%	14.4%	0.03
Congestive Heart Failure	7.8%	14.1%	<0.001
COPD	17.7%	20.3%	<0.01
Chronic Renal Failure	3.4%	3.8%	0.28
Peripheral Vascular Disease	43.7%	37.2%	<0.001
GI Ulcer/Bleeding	3.0%	4.8%	<0.001
Cancer	13.0%	19.8%	<0.001
Coagulopathy	1.4%	1.1%	0.2
NY Heart Association Scale			
Class I or II	95.4%	89.1%	<0.001
Class III or IV	4.6%	10.9%	

TIA, transient ischemic attack; TMB, transient monocular blindness; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; NY, New York

The rate of MI was similar between HR and non-HR patients (1.4% vs. 1.1%, *P* =0.57). (Table III)
In asymptomatic patients, the 30-day rate of MACE was 5.0% in HR patients versus 2.2% in non-HR patients (*P* <0.001). Combined stroke/death, death, and stroke rates were all significantly higher in HR patients compared to non-HR patients. There was no difference in the rate of MI between HR and non-HR asymptomatic patients (1.6% vs. 1.1%, *P* =0.30). (Table IV)
In univariate analysis, patients with contralateral occlusion had significantly higher risks of MACE (symptomatic 16.1%, asymptomatic 8.8%), stroke/death (symptomatic 16.1%, asymptomatic 7.2%), death (symptomatic and asymptomatic 2.2%), and stroke (symptomatic 15.1%, asymptomatic 5.0%) compared to patients without contralateral occlusion. A multivariable model showed that symptomatic status, age ≥80, CHF Class III/IV, LVEF<30%, angina, contralateral occlusion and high anatomic lesion were independent predictors for MACE (Table V). The same factors were identified as predictors for stroke/death with the exception of age ≥ 80. CHF, angina, restenosis, and contralateral occlusion were risk factors for death. For stroke alone, symptomatic status, contralateral occlusion, and a high anatomic lesion were predictive. Angina was the only risk factor identified for MI.

Table II CMS Qualifying High Risk Factors

	CEA (n = 6370)	CAS (n = 3737)	P-value
Age ≥ 80 years	19.3%	20.7%	0.1
NYHA CHF Class III/IV	3.5%	10.4%	<0.001
LVEF < 30%	0.9%	4.1%	<0.001
Unstable Angina	0.6%	3.6%	<0.001
Recent MI (within 30 days)	0.5%	1.2%	<0.001
Restenosis	2.5%	29.5%	<0.001
Radical neck dissection	0.1%	4.0%	<0.001
Contralateral occlusion	4.3%	13.4%	<0.001
Prior radiation to neck	0.3%	8.4%	<0.001
Contralateral laryngeal nerve injury	0.1%	0.9%	<0.001
High anatomic lesion	1.2%	9.4%	<0.001
At Least One High Risk Factor	37.0%	90.5%	<0.001

NYHA, New York Heart Association; LVEF, left ventricle ejection fraction; MI, myocardial infarction

CAS outcomes. In both symptomatic and asymptomatic CAS patients, no significant difference was detected in MACE between HR and non-HR patients (9.1% vs. 6.2%, p=0.25 symptomatic, 5.4% vs. 4.2%, *P* =0.6 asymptomatic) (Table III and IV). Stroke/death, mortality, stroke, and MI rates were similar in both groups for both symptomatic and asymptomatic patients.
In a multivariable model, symptom status (OR 1.6, 95%CI 1.3-2.2) and recent MI (OR 3.4, 95%CI 1.7-7.0) were independent predictors for MACE, while restenosis (MACE rate: 3.5%, OR 0.6,

95%CI 0.4 – 0.8) and previous cervical radiation therapy (MACE rate: 4.6%, OR 0.4, 95%CI 0.2-0.8) were protective (Table VI). The same predictors were identified for combined stroke/death. Angina (OR 2.4, 95%CI 1.1-5.6), previous MI (OR 8.0, 95%CI 3.4 – 18.9) and contralateral occlusion (OR 1.9, 95%CI 1.1-3.4) were risk factors for mortality. Independent predictors for stroke alone were symptom status and age ≥80 years. Age ≥80 was the only predictor for MI (OR 2.1, 95% CI 1.1-3.8).

Anatomical high-risk factors. In symptomatic patients with contralateral occlusion, 30-day MACE rate was 16.1% after CEA and 9.3% after CAS (*P* = 0.13). In asymptomatic patients, MACE rates were 8.8% after CEA versus 6.9% after CAS (*P* = 0.58). Risk for MACE in patients with symptomatic restenosis was 7.9% after CEA versus 6.7% (*P*= 0.79) after CAS and 7.1% versus 3.5% (*P* = 0.10) in asymptomatic patients. Patients with prior neck radiation undergoing CAS (n=315) had MACE risk of 4.5% (symptomatic patients) and 2.5% (asymptomatic patients). Only 19 patients with prior neck irradiation had CEA, without any adverse events. For patients with a high anatomical lesion (C2 or higher), symptomatic patients had a risk for MACE of 11.9% after CEA versus 13.2% after CAS (*P* = 1.0). In asymptomatic patients, MACE rate was 12.2% after CEA versus 4.52% after CAS (*P* = 0.13).

Table III 30-Day event rates for symptomatic patients undergoing CEA and CAS stratified by risk group

CEA Patients			
	HR (n = 936)	Non-HR (n = 1470)	P-value
MACE	7.3%	4.6%	<0.01
Stroke, Death	6.4%	3.9%	<0.01
Mortality	1.8%	0.6%	<0.01
Stroke	4.9%	3.5%	0.09
MI	1.4%	1.1%	0.57
CAS Patients			
	HR (n = 1538)	Non-HR (n = 162)	P-value
MACE	9.1%	6.2%	0.25
Stroke, Death	7.9%	4.9%	0.21
Mortality	2.4%	1.9%	1
Stroke	6.7%	3.7%	0.18
MI	1.4%	1.2%	1

HR, high risk; MACE, major adverse cardiovascular events; MI, myocardial infarction

CAS versus CEA outcome. No significant differences in MACE were identified between CAS and CEA within the strata of non-HR and HR group. Symptomatic HR patients had 9.1% MACE risk following CAS versus 7.3% after CEA (OR 1.3, 95%CI 0.95 – 1.73, *P* = 0.11). MACE risk in asymptomatic HR patients was 5.4% after CAS versus 5.0% after CEA (OR 1.1, 95%CI 0.79 – 1.47, *P* = 0.65). In non-HR group, symptomatic patients undergoing CAS had a MACE risk of 6.2% versus 4.6% in patients undergoing CEA (OR 1.4, 95%CI 0.69 – 2.69, *P* = 0.38). For asymptomatic non-HR patients, MACE risk was 4.2% after CAS versus 2.2% after CEA (OR 1.92, 95%CI 0.90 – 4.09, *P* = 0.09). In unadjusted models assessing outcome across treatment groups, CAS patients had higher odds ratios for MACE (1.7, 95% CI 1.4 - 2.0), combined stroke and death (1.9, 95% CI 1.6 - 2.3), mortality (2.3, 95% CI 1.6 - 3.2) and stroke (1.9, 95% CI 1.5 - 2.4), but not for MI (0.9, 95% CI 0.7 - 1.4). After adjusting for symptom and HR status, CAS patients had still higher odds ratios for MACE (1.2, 95% CI 1.0-1.5), mortality (1.5 95% CI 1.0-2.2) and stroke (1.4 95% CI 1.0-1.7), while there was no difference in stroke/death and MI. (Table VII)

Table IV 30-Day event rates for asymptomatic patients undergoing CEA and CAS stratified by risk group

CEA Patients			
	HR (n = 1418)	Non-HR (n = 2546)	P-value
MACE	5.0%	2.2%	<.001
Stroke, Death	3.7%	1.4%	<.001
Mortality	1.3%	0.5%	<0.01
Stroke	2.7%	1.1%	<0.001
MI	1.6%	1.1%	0.3
CAS Patients			
	HR (n = 1844)	Non-HR (n = 193)	P-value
MACE	5.4%	4.2%	0.61
Stroke, Death	4.8%	3.6%	0.59
Mortality	1.7%	1.6%	1
Stroke	3.4%	2.6%	0.68
MI	1.1%	1.0%	1

HR, high risk; MACE, major adverse cardiovascular events; MI, myocardial infarction

Table V Predictors for 30-day outcomes of CEA

	MACE		Stroke/Death		Stroke		Death		MI	
Risk Factors	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Symptomatic	1.8	1.4 - 2.4	2.3	1.7 - 3.1	2.5	1.8 - 3.5	-	-	-	-
Age ≥ 80	1.4	1.0 - 1.8	-	-	-	-	-	-	-	-
CHF Class (III/IV)	1.7	1.0 - 2.8	1.8	1.0 - 3.2	-	-	3.5	1.5 -7.8	-	-
LVEF < 30%	3.5	1.6 - 7.7	3.2	1.3 - 7.6	-	-	-	-	-	-
Angina	3.9	1.6 - 9.9	3.2	1.1 - 9.6	-	-	5.9	1.6 - 21.4	6.8	2.0 – 22.5
Contralateral Occlusion	3.2	2.1 - 4.7	3.7	2.4 - 5.8	4.1	2.6 - 6.6	2.5	1.0 - 5.9	-	-
High Anatomic Lesion	2.7	1.3 - 5.6	3	1.4 - 6.5	3.4	1.5 - 7.6	-	-	-	-
Restenosis	-	-	-	-	-	-	3.6	1.4 - 9.3	-	-

MACE, major adverse cardiovascular event; MI, myocardial infarction; OR, odds ratio; CI, confidence interval; CHF, congestive heart failure, left ventricle ejection fraction

Table VI Predictors for 30-day outcomes of CAS

	MACE		Stroke/Death		Stroke		Death		MI	
Risk Factors	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Symptomatic	2	1.5 - 2.6	1.6	1.2 - 2.1	2	1.5 - 2.7	-	-	-	-
Age ≥ 80	-	-	-	-	1.5	1.1 - 2.1	-	-	2.1	1.1 - 3.8
Recent MI	3.2	1.5 - 7.0	4	2.0 - 8.3	-	-	8	3.4 - 18.9	-	-
Angina	-	-	-	-	-	-	2.4	1.1 - 5.6	-	-
Contralateral Occlusion	-	-	-	-	-	-	1.9	1.1 - 3.4	-	-
Restenosis	0.6	0.4 - 0.8	0.6	0.5 - 0.9	-	-	-	-	-	-
Prior Radiation to Neck	0.5	0.3 - 0.9	0.5	0.3 - 0.9	-	-	-	-	-	-

MACE, major adverse cardiovascular event; MI, myocardial infarction; OR, odds ratio; CI, confidence interval

Table VII 30-day outcome of CAS versus CEA, unadjusted and adjusted for HR and symptomatic patients

	Unadjusted CAS vs. CEA			Adjusted CAS vs. CEA		
	OR	95% CI	P-value	OR	95% CI	P-value
MACE	1.7	1.4 - 2.0	<0.001	1.2	1.0 - 1.5	0.04
Stroke, Death	1.9	1.6 - 2.3	<0.001	1.3	1.1 - 1.7	0.01
Death	2.3	1.6 - 3.2	<0.001	1.5	1.0 - 2.2	0.04
Stroke	1.9	1.5 - 2.4	<0.001	1.4	1.1 - 1.7	0.02
MI	0.9	0.7 - 1.4	0.91	0.9	0.6 - 1.3	0.46

OR, odd ratio; CI, confidence interval; MACE, major adverse cardiovascular event; MI, myocardial infarction

DISCUSSION

Patients with symptomatic or asymptomatic severe carotid stenosis and HR status have an increased risk for MACE following CEA compared to non-HR patients undergoing CEA. Of the CMS HR criteria, age ≥80, CHF, angina, contralateral occlusion and high anatomic lesion predict MACE after CEA. For CAS, 30-day outcomes between HR and non-HR patients were similar. Prior MI predicted MACE after CAS, while previous radiation and restenosis proved to be protective conditions. By comparing CAS and CEA after adjusting for symptoms and HR status, CAS patients had significantly higher rates than CEA for MACE, combined stroke/death, mortality, and stroke, while there was no difference in MI.

Our results emphasize that some, but not all, CMS HR criteria identify patients at increased risk for MACE after CEA. However, these patients do not per se seem to benefit from CAS. CMS reimbursement for CAS covers HR symptomatic patients, as long as stenting is performed using FDA-approved systems with embolic-protection devices and at CMS-approved facilities. This policy was mainly based on favorable endovascular results of the SAPPHIRE trial, designed to compare CAS versus CEA in a HR population.[14, 15] The applicability of the results was however questioned by several others. In SAPPHIRE, the 30-day stroke, death, and MI rates in the CEA arm were as high as 9.8% (vs. 4.8% CAS, P =.09). The MI rate of 6.6% strongly influenced this combined endpoint. Also, approximately 70% of the study population was asymptomatic. Outcomes of our VR real world data looking at the same HR population consequently do not compare with the SAPPHIRE trial, with a MACE rate of 5.0% (MI rate: 1.6%) after CEA in asymptomatic patients and 7.3% in symptomatic patients. Noteworthy, the primary end point in SAPPHIRE did not differ significantly in symptomatic patients at 30-days and at 1 year (16.8% CAS vs. 16.5% CEA, P = 0.95), one of the major reimbursement criteria from CMS.

Several other studies have retrospectively sought to evaluate medical,[10, 13] anatomical,[16-18] or a combination of HR criteria[11, 12, 19, 20] outlined by CMS. Most of these studies analyzed risk factors against a non-HR group in only one treatment arm (CAS or CEA). Our prior analysis[10] using the Nationwide Inpatient Sample identified significantly lower stroke/death rates after CEA compared to CAS with a stratified analysis by symptom status and HR status, questioning

the validity of the HR criteria. In that analysis, medical HR status was associated with worse outcome (stroke/death, mortality) following CEA compared to non-HR patients undergoing CEA. Outcomes with CAS, however, were not improved in these high risk patients (combined stroke/death CAS vs. CEA in symptomatic patients: 14.4% vs. 6.9%, $P<0.001$). However, anatomic HR could not be determined and medical HR could not be precisely quantified due to the limitations of administrative data. Additionally, outcome events other than death may not be reliably documented with administrative data.

We undertook the current analysis to perform a thorough identification of HR factors and better discrimination of pre- and postoperative outcomes. We found that recent angina was a predictor for all major outcomes after CEA except for stroke alone, and also a predictor for death after CAS. We also found that those patients aged ≥80 years had an increased risk for MACE after CEA, and for stroke and MI after CAS. A differential effect of advancing age on outcome was also observed in the CREST lead in and the randomized trial, where older patients had significantly better outcomes after CEA and younger patients had a non-significant trend toward better outcomes after CAS.[21-23]

Considering anatomical HR factors, we found that patients with contralateral occlusion were at high risk for adverse outcomes following CEA and CAS. Controversy regarding the benefit of CEA exists in patients with contralateral occlusion, with some studies reporting similar outcome after CEA,[18, 24] while others showing increased risk of adverse events.[25, 26] However, little data exist to evaluate the impact on CAS outcomes.[27] Our data suggest that the risk for adverse outcome after both CEA and CAS was increased in patients with contralateral occlusion, in both symptomatic and asymptomatic patients. We were not able to assess shunt use during CEA, which might impact perioperative outcome. For patients with restenosis, this was not true. With an odds ratio of 3.6 (95%CI, 1.4-9.3), restenosis was predictive for death after CEA, but proved to be a protective condition for MACE and stroke/death after CAS. However, MACE rates were similarly high between symptomatic patients undergoing CAS and CEA, but for asymptomatic patients the MACE rate with CAS was half that of CEA (3.5% vs. 7.1%, P = NS). This expands the evidence of a prior report of the VR, were no differences in stroke/death/MI rate between CAS patients with atherosclerotic disease compared to non-atherosclerotic disease (e.g. restenosis and prior radiation therapy) were identified.[16] These findings suggest that asymptomatic patients with restenosis or prior radiation therapy might be considered as the only 'low' risk group in CAS. Differences in histology may explain this observation, since intimal hyperplasia and radiation-induced plaque have been shown to be more stable compared to atherosclerotic plaque.[28, 29] Additionally, patients with high anatomical lesions suffered from high MACE risks after both procedures (>10% in symptomatic patients), far beyond the accepted complication rates after carotid revascularization and thus questioning the benefit of revascularization over medical treatment in these patients. No such trials exist today and accepted rates are however based on trials in which these patients were specifically excluded, such as CREST.[30]

Results of the CREST trial showed that both symptomatic and asymptomatic patients had equal low risks after CAS and CEA for combined stroke/death/MI.[23] Stroke rates alone were lower following CEA while an increased risk for MI was seen compared to CAS. Symptomatic patients had lower stroke and death rates with CEA compared to CAS.[31] As stated above, most HR criteria outlined by CMS (except for age≥80 years and contralateral occlusion) were exclusion criteria

in this trial. The study also required that interventionalists have documented prior performance of at least 35 CAS procedures, emphasizing that CAS might be a safe procedure under specific conditions in selected patients treated by selected physicians. Unadjusted data from a regional quality improvement registry (VSGNE) showed increased in-hospital risk for stroke/death/MI in symptomatic patients undergoing CAS (5.8%) compared to CEA (2.7%), but equal results in asymptomatic patients.[32] In the real world data from the VR, the vast majority (90.5%) of the CAS patients meet CMS HR criteria and had more comorbid conditions than CEA patients where only 37% were HR, making unadjusted comparison difficult to interpret and likely biased.

This study has several limitations. Self-reporting bias by treating physicians and institutions is inherent to any registry-based study and the potential effect of reporting bias within the Vascular Registry has been investigated and discussed. Given that 90% of CAS patients were HR there were a relatively small number of patients in the non-HR group available for stratified analysis. It is possible that a type II error prevented finding a significant difference in subgroup comparisons stratified by symptom status and non-HR status. It is also possible that some of the patients considered non-HR were in fact HR and were mislabeled. Given that CMS reimbursement and site approval for performance of CAS in Medicare patients is dependent upon this documentation, we feel that this is unlikely. Non-HR patients may be entered into clinical trials and have CMS re-imbursement. Because the VR data is capturing real world data, it is reliant on site entry of patients without predefined exclusion or inclusion criteria. Therefore, differences in patient selection may have occurred for both CAS and CEA. Lastly, the combined outcome of MACE is flawed in that it equates death, stroke, and MI. While there has been considerable debate about the relative importance of stroke versus MI,[33, 34] we do not think this impacts our findings as we had similar findings using the stroke/death outcome that had previously been considered the standard.

In conclusion we find that certain CMS HR criteria are associated with adverse outcomes after CEA. However, outcomes in HR patients are not improved after CAS, and patients treated with CEA fare better than CAS after adjustment for symptom status and HR status. Therefore, our study finds little advantage for CAS over CEA in patients at HR for perioperative complications, and suggests that the strongest advantage of CAS over CEA lies in patients with restenosis or prior neck radiation, as compared to those patients with HR medical conditions.

References

1. Featherstone RL, Brown MM, Coward LJ. International carotid stenting study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. Cerebrovasc Dis 2004;18:69-74.
2. Mas J-L, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin J-P, et al. Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis. N Engl J Med 2006;355:1660-71.
3. Brott TG, Hobson RW, 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363:11-23.
4. Naylor AR, Bolia A, Abbott RJ, Pye IF, Smith J, Lennard N, et al. Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. J Vasc Surg 1998;28:326-34.
5. 100-03 P. Medicare National Coverage Determinations. 2010.
6. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493-501.
7. White CJ, Iyer SS, Hopkins LN, Katzen BT, Russell ME. Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. Catheter Cardiovasc Interv 2006;67:503-12.
8. Gray WA, Hopkins LN, Yadav S, Davis T, Wholey M, Atkinson R, et al. Protected carotid stenting in high-surgical-risk patients: The ARCHeR results. J Vasc Surg 2006;44:258-68.
9. Iyer SS, White CJ, Hopkins LN, Katzen BT, Safian R, Wholey MH, et al. Carotid Artery Revascularization in High-Surgical-Risk Patients Using the Carotid WALLSTENT and FilterWire EX/EZ: 1-Year Outcomes in the BEACH Pivotal Group. J Am Coll Cardiol 2008;51:427-34.
10. Giles KA, Hamdan AD, Pomposelli FB, Wyers MC, Schermerhorn ML. Stroke and death after carotid endarterectomy and carotid artery stenting with and without high risk criteria. J Vasc Surg 2010;52:1497-504.
11. Gasparis AP, Ricotta L, Cuadra SA, Char DJ, Purtill WA, Van Bemmelen PS, et al. High-risk carotid endarterectomy: fact or fiction. J Vasc Surg 2003;37:40-6.
12. Kang JL, Chung TK, Lancaster RT, LaMuraglia GM, Conrad MF, Cambria RP. Outcomes after carotid endarterectomy: Is there a high-risk population? A National Surgical Quality Improvement Program report. J Vasc Surg 2009;49:331-9.e1.
13. Yuo TH, Goodney PP, Powell RJ, Cronenwett JL. "Medical high risk" designation is not associated with survival after carotid artery stenting. J Vasc Surg 2008;47:356-62.
14. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected Carotid-Artery Stenting versus Endarterectomy in High-Risk Patients. N Engl J Med 2004;351:1493-501.
15. Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, et al. Long-Term Results of Carotid Stenting versus Endarterectomy in High-Risk Patients. N Engl J Med 2008;358:1572-9.
16. White RA, Sicard GA, Zwolak RM, Sidawy AN, Schermerhorn ML, Shackelton RJ, et al. Society of vascular surgery vascular registry comparison of carotid artery stenting outcomes for atherosclerotic vs nonatherosclerotic carotid artery disease. J Vasc Surg 2010;51:1116-23.
17. Fokkema M, den Hartog AG, Bots ML, van der Tweel I, Moll FL, de Borst GJ. Stenting versus surgery in patients with carotid stenosis after previous cervical radiation therapy: systematic

review and meta-analysis. Stroke 2012;43:793-801.
18. Rockman CB, Su W, Lamparello PJ, Adelman MA, Jacobowitz GR, Gagne PJ, et al. A reassessment of carotid endarterectomy in the face of contralateral carotid occlusion: Surgical results in symptomatic and asymptomatic patients. J Vasc Surg 2002;36:668-73.
19. Reed AB, Gaccione P, Belkin M, Donaldson MC, Mannick JA, Whittemore AD, et al. Preoperative risk factors for carotid endarterectomy: defining the patient at high risk. J Vasc Surg 2003;37:1191-9.
20. Mozes G, Sullivan TM, Torres-Russotto DR, Bower TC, Hoskin TL, Sampaio SM, et al. Carotid endarterectomy in SAPPHIRE-eligible high-risk patients: implications for selecting patients for carotid angioplasty and stenting. J Vasc Surg 2004;39:958-65; discussion 65-6.
21. Hobson RW, 2nd, Howard VJ, Roubin GS, Brott TG, Ferguson RD, Popma JJ, et al. Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. J Vasc Surg 2004;40:1106-11.
22. Voeks JH, Howard G, Roubin GS, Malas MB, Cohen DJ, Sternbergh WC, 3rd, et al. Age and outcomes after carotid stenting and endarterectomy: the carotid revascularization endarterectomy versus stenting trial. Stroke 2011;42:3484-90.
23. Mantese VA, Timaran CH, Chiu D, Begg RJ, Brott TG. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): stenting versus carotid endarterectomy for carotid disease. Stroke 2010;41:S31-4.
24. AbuRahma AF, Robinson P, Holt SM, Herzog TA, Mowery NT. Perioperative and Late Stroke Rates of Carotid Endarterectomy Contralateral to Carotid Artery Occlusion : Results From a Randomized Trial. Stroke 2000;31:1566-71.
25. Goodney PP, Likosky DS, Cronenwett JL. Factors associated with stroke or death after carotid endarterectomy in Northern New England. J Vasc Surg 2008;48:1139-45.
26. Gasecki AP, Eliasziw M, Ferguson GG, Hachinski V, Barnett HJM. Long-term prognosis and effect of endarterectomy in patients with symptomatic severe carotid stenosis and contralateral carotid stenosis or occlusion: results from NASCET. J Neurosurg 1995;83:778-82.
27. Sabeti S, Schillinger M, Mlekusch W, Nachtmann T, Lang W, Ahmadi R, et al. Contralateral High-Grade Carotid Artery Stenosis or Occlusion Is Not Associated with Increased Risk for Poor Neurologic Outcome after Elective Carotid Stent Placement1. Radiology 2004;230:70-6.
28. Hellings WE, Moll FL, de Vries JP, de Bruin P, de Kleijn DP, Pasterkamp G. Histological characterization of restenotic carotid plaques in relation to recurrence interval and clinical presentation: a cohort study. Stroke 2008;39:1029-32.
29. Fokkema M, den Hartog AG, van Lammeren GW, Bots ML, Pasterkamp G, Vink A, et al. Radiation-induced Carotid Stenotic Lesions have a more Stable Phenotype than De Novo Atherosclerotic Plaques. Eur J Vasc Endovasc Surg 2012.
30. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. Stroke 2011;42:e420-63.
31. Silver FL, Mackey A, Clark WM, Brooks W, Timaran CH, Chiu D, et al. Safety of Stenting and Endarterectomy by Symptomatic Status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). Stroke 2011;42:675-80.
32. Nolan BW, De Martino RR, Goodney PP, Schanzer A, Stone DH, Butzel D, et al. Comparison of

carotid endarterectomy and stenting in real world practice using a regional quality improvement registry. J Vasc Surg 2012.
33. Sidawy AN, Zwolak RM, White RA, Siami FS, Schermerhorn ML, Sicard GA, et al. Risk-adjusted 30-day outcomes of carotid stenting and endarterectomy: Results from the SVS Vascular Registry. J Vasc Surg 2009;49(1):71-9.
34. Naylor AR. Hearts and Minds. Eur J Vasc Endovasc Surg 2012;43:1-3.
35. Blackshear JL, Cutlip DE, Roubin GS, Hill MD, Leimgruber PP, Begg RJ, et al. Myocardial Infarction After Carotid Stenting and Endarterectomy / Clinical Perspective. Circulation 2011;123:2571-8.

CHAPTER SIX

The impact of contralateral carotid stenosis or occlusion on outcome following carotid endarterectomy and stenting

Manuscript submitted

Authors

Margriet Fokkema, Philip P. Goodney, Thomas Curran, Viranda I. Patel, April E. Nedeau, Frans L. Moll, Gert Jan de Borst, Marc L. Schermerhorn for the Vascular Study Group of New England

Affiliations

Department of Vascular and Endovascular Surgery, [1]Beth Israel Deaconess Medical Center, Boston, MA, [2]University Medical Center Utrecht, Utrecht, the Netherlands, [3]Dartmouth-Hitchcock Medical Center, Lebanon, MA, Massachusetts General Hospital, Boston, MA, Central Maine Medical Center, ME

ABSTRACT

Objectives. The impact of degree of contralateral stenosis on clinical outcome following carotid angioplasty and stenting (CAS) and endarterectomy (CEA) remains unknown. We aimed to identify those patients at increased procedural risk due to contralateral carotid stenosis or occlusion.

Methods. From 2003-2012, all patients undergoing CEA or CAS in the Vascular Study Group of New England were identified. Patients were stratified by preoperative symptom status and degree of ipsilateral stenosis (50-79% or 80-99% as assessed by duplex ultrasound). The primary endpoint was any stroke or death at 30 days postoperatively. Bivariate and multivariable analyses (adjusted for age, gender and procedure) were performed to assess the impact of the degree of contralateral stenosis.

Results. In total 8925 CEA patients (33% symptomatic) and 614 CAS patients (34% symptomatic) were included. In asymptomatic patients with ipsilateral 80-99% stenosis, stroke/death rate was 0.9% (n=45). Of those, patients with contralateral occlusion had significantly increased stroke/death rate (3.4%, OR 4.5, 95% CI 2.1 – 9.9 [vs. <50%]). In symptomatic patients with 50-79% ipsilateral stenosis, stroke/death rate was 2% (n=22). Of those, patients with 80-99% contralateral stenosis had the highest stroke/death rate (6.9%, OR 5.1, 95% CI 1.1 – 24.7 [vs. <50%]), followed by patients with CCO although this was not significant (5.1%, OR 2.7, 95% CI 0.7 – 11.5 [vs. <50%]). Contralateral disease or occlusion did not impact outcome in asymptomatic patients with 50-79% ipsilateral stenosis and in symptomatic patients with 80-99% ipsilateral stenosis.

Conclusions. The impact of contralateral disease on outcome after carotid revascularization is different for asymptomatic versus symptomatic patients. CCO increases the risk for asymptomatic patients with 80-99% ipsilateral stenosis, while 80-99% contralateral stenosis increases the risk for symptomatic patients with 50-79% ipsilateral stenosis.

INTRODUCTION

Stroke is the leading cause of disability in the western world with a significant proportion attributable to carotid artery disease.[1] Among an average risk population with severe symptomatic or asymptomatic carotid artery stenosis, carotid endarterectomy (CEA) reduces the risk for future stroke significantly, despite the risk of stroke associated with surgery.[2,3] Yet, several patient related factors have been suggested to increase the perioperative stroke risk with CEA, and for some of those patients, carotid angioplasty and stenting (CAS) has been proposed as an alternative revascularization procedure.[4]

Occlusion of the contralateral artery is one factor that potentially increases surgical stroke risk, however, the evidence to support this hypothesis is conflicting. While some studies, including the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS) demonstrated increased rates of stroke or death among patients with contralateral carotid occlusion (CCO) undergoing CEA,[5-10] others found no difference or a marginally higher risk in patients with CCO compared to patients without CCO.[11-14] The risk associated with CAS in CCO patients may also be increased, because CAS does not offer shunting in the presence of a diminished collateral circulation.[15] Previous comparative analyses between CAS and CEA showed equivalent outcome between CAS and CEA in patients with CCO.[16,17]

While several prior studies have reported on the outcome of patients with CCO, limited evidence is available on the impact of non-occlusive contralateral carotid stenosis.[18] Patients with severe contralateral stenosis (eg 80-99%), likely have many of the same risk factors as those patients with CCO including reduced collateral circulation, advanced cerebrovascular disease and increased risk for cerebral hyperperfusion following revascularization.

In the present study, we hypothesized that the severity of the contralateral artery stenosis might influence outcome after revascularization, regardless of the type revascularization procedure. Therefore, we stratified patients by symptom status and degree of ipsilateral carotid stenosis to study the impact of contralateral carotid disease on perioperative outcome after carotid revascularization procedures.

METHODS

Database. Prospectively collected data from the Vascular Study Group of New England (VSGNE) were used for this analysis. The VSGNE is a regional quality improvement initiative developed in 2002, which currently includes over 180 physicians at 30 centers (14 academic, 16 community centers). Preoperative clinical characteristics, imaging studies, operative outcome and follow-up data are collected and entered in the registry by trained nurses or clinical data abstractors. Operative details are entered by surgeons. Research analysts are blinded to patient, surgeon, and hospital identity. Further details on this registry have been published previously and are available at http://www.vascularweb.org/regionalgroups/vsgne.[19]

VSGNE data have been validated for completeness using audits of discharge claims data from each participating institution.[20] Additionally, no mortality bias was seen in an audit of cases not initially captured.[19]

Table I Preoperative characteristics of 9539 patients undergoing carotid revascularization

	N	%
Procedure		
CAS	614	6.4
CEA	8925	93.6
Age, yr (median, IQR)	70	14
Age >80 yr	1460	15.3
Gender		
Male	5732	60.1
Female	3806	39.9
Race (non-white)	162	1.7
Any ipsilateral symptoms		
TIA	1338	14
Stroke	865	9.1
Ocular	971	10.2
Degree of ICA stenosis		
50-79%	2677	28.1
80-99%	6862	71.9
Degree of contralateral ICA		
<50%	5378	56.4
50-79%	2942	30.8
80-99%	580	6.1
Occluded	639	6.7
Any Smoke (prior or current)	7633	80
Hypertension (>=140/90 or history)	8375	78.8
Diabetes Mellitus	2938	31
Coronary artery disease	3083	32.3
CABG/PCI	3056	32
Congestive heart failure	796	8.3
COPD	2185	22.9
Antiplatelets	8659	90.8
Statin	7415	77.7
Stress test abnormal (MI or ischemia)	998	10.5
Creatinine (>1.78 mg/dL)	503	5.3
ASA 3 and 4	3790	39.7
Prior ipsilateral CEA	396	4.2
Urgency		
Elective	8471	88.8
Urgent	1068	11.2

IQR, interquartile range, TIA, transient ischemic attack, ICA, internal carotid artery, CABG, coronary artery bypass grafting, PCI, percutaneous coronary intervention, COPD, chronic obstructive pulmonary disease, ASA, American Society of Anesthesiology

Patients. Our initial study sample included all patients (n = 10246) in the VSGNE database who underwent CEA (January 2003 - December 2011) and all patients who underwent CAS (July 2005 and March 2012). Patients undergoing CEA with a concomitant coronary bypass procedure were

excluded (n = 221, 2.2%). In addition, 486 (4.7%) patients with missing values for preoperative evaluation of degree of stenosis of the ipsilateral (92, 0.9%) or contralateral carotid artery (372, 3.6%) or both (22, 0.2%) were excluded. This resulted in a total population of 9539 patients undergoing 8925 CEAs and 614 CAS procedures.

Endpoints and Measurements. The main exposure variable was contralateral degree of stenosis of the internal carotid artery (ICA), defined as <50% stenosis, 50-79% stenosis, 80-99% stenosis, or CCO. Degree of stenosis was defined by one or more of the following imaging modalities: duplex ultrasound, computed tomography angiography, magnetic resonance angiography, or arteriogram. Our primary endpoint was a composite of any stroke or death at 30-days postoperatively. Secondary endpoints were a composite of any stroke, death, and myocardial infarction (MI), its individual component endpoints at 30-days and postoperative hyperperfusion symptoms (seizure or hemorrhage) at discharge.

The definition of stroke included ipsilateral or contralateral major stroke (cortical, vertebrobasilar, or ocular disability resulting in non independent living status, or blindness) and ipsilateral or contralateral minor stroke (other strokes not defined as major). Neurologists did not routinely examine patients postoperatively. Myocardial infarction included clinical, electrocardiogram, and troponin-only MI. Indications for obtaining postoperative troponin were variable, and not recorded.

Patients were stratified by preoperative symptom status, in combination with degree of ipsilateral stenosis (50-79% or 80-99%). This resulted in four major groups of patients: symptomatic patients with ipsilateral degree of stenosis 50-79% (1) or 80-99% (2), or asymptomatic patients with ipsilateral degree of stenosis 50-79% (3) or 80-99% (4). Symptomatic patients were defined as having an ipsilateral neurologic event preceding the intervention, including any hemispheric or ocular transient ischemic attack, major or minor stroke preceding the intervention. No absolute time frame is captured through the VSGNE.[20]

Statistical Analysis. Bivariate analysis using chi-square test was performed to assess whether the status of the contralateral carotid artery was associated with our endpoints following revascularization in one of the four aforementioned patient groups. Subsequently, associations were independently tested in a multivariable model for stroke or death among symptomatic and asymptomatic patients. We choose to use these two different models because it was previously shown that symptom status has a strong impact on outcome.[20] The models were derived through step-wise logistic regression using candidate variables from bivariate analyses (P-value <.01). (Appendix A and B, available online.) Both models were adjusted for age and gender. Associations with a P-value <.05 were considered significant. SPSS version 20.0 statistical software (IBM, SPSS Inc., Chicago Illinois, USA) was used for statistical analyses.

RESULTS

Of 9539 patients, 60% were male, median age was 70 years and a third of patients were symptomatic. (Table I) In total, 72% had severe, 80-99% ipsilateral ICA stenosis, while the remainder had moderate, 50-79% ipsilateral stenosis. Of all revascularization procedures, 43.6% had contralateral disease (CCO: 7%, 80-99% stenosis: 6%, 50-79% stenosis: 31%).

Table II shows the same preoperative patient characteristics, stratified by symptom status

(symptomatic vs asymptomatic) and degree of ipsilateral stenosis (moderate 50-79% or severe 80-99% stenosis), resulting in the previously defined four groups. In asymptomatic patients, severe stenosis was relatively more common than moderate stenosis (ratio 3:1) compared to symptomatic patients (ratio of 2:1). The four groups of patients differed in several ways. Asymptomatic patients with 50-79% ipsilateral ICA stenosis most frequently underwent CEA. Symptomatic patients with 80-99% ipsilateral stenosis were more likely to be older than 80 years and smokers, and had the greatest proportion of patients with contralateral disease between 80-99%. Asymptomatic patients with 80-99% ipsilateral stenosis were more likely to be female, hypertensive and to have a history of coronary artery disease, while they were less likely to undergo emergent procedures.

CAS versus CEA. We identified a similar effect, both in magnitude and direction, for the primary outcome for patients undergoing CAS and CEA (data not shown), and therefore the results were not further stratified by type of procedure. Previous work using the VSGNE database did not show differences between procedures in asymptomatic patients, while symptomatic patients treated with CAS had increased stroke or death rates compared to CEA.[20] The CEA vs CAS difference in these symptomatic patients was mainly driven by a higher rate of ipsilateral stroke or death (1.3% vs 5.6%, P<.001). Therefore, we adjusted for procedure type in the multivariable model for symptomatic patients only.

Symptomatic patients with 50-79% ipsilateral stenosis. Among symptomatic patients with moderate degree of ipsilateral stenosis (50-79%), the stroke/death rate was 2% (n=22), stroke/death/MI rate 3% (n=33), stroke rate 1.8% (n=20), death rate 0.5% (n=5) and MI rate 1.5% (n=16). (Table III) Most strokes (75%) were ipsilateral (7 major, 8 minor), while 5 strokes were contralateral (3 major and 2 minor). One patient who had a major and one patient who had a minor ipsilateral stroke experienced hyperperfusion symptoms. One patient had hyperperfusion symptoms in the absence of stroke. On bivariate analyses, stroke/death rates were increased, but not statistically different, among patients with 80-99% contralateral stenosis (6.9%, n=2) and patients with CCO (5.1%, n=3), compared to patients with a contralateral stenosis <50% (1.4%, n=10) and 50-79% (2.4%, n=7). (Table III) Of the two stroke/death events that occurred in the 29 patients with 80-99% contralateral stenosis, one was a non-fatal major ipsilateral stroke and one a non-fatal contralateral minor stroke. Death risk was significantly higher among patients with CCO (3.4%, P<.05). On multivariable analyses, contralateral stenosis of 80-99% (vs <50%) was an independent predictor for stroke/death (OR 5.1, 95%CI 1.1 – 24.7, P = 0.04), while CCO did not reach a statistically significant difference (OR 2.7, 95% CI 0.7 – 11.5, P = 0.2). Procedure type was also not significantly different (CAS vs CEA, OR 2.4, 95%CI 0.6 – 9.3, P=0.2). (Table IV)

Symptomatic patients with 80-99% ipsilateral stenosis. Among symptomatic patients with 80-99% ipsilateral stenosis, stroke/death rate was 2.1% (n=44), stroke rate was 1.8% (n=38), death rate was 0.5% (n=10), MI rate was 1.3% (n=27) and stroke/death/MI rate was 3.2% (n=67). While patients with 80-99% contralateral stenosis had the highest stroke/death rate (3.5%), no significant differences in outcome were identified based on the status of the contralateral artery. (Table III)

Table II Indication for 9539 patients undergoing CEA (n=8925) or CAS (n=614), stratified by symptoms status and degree of stenosis of the ipsilateral internal carotid artery

	Symptomatic				Asymptomatic				
	50 - 79% *N=1082*		80 – 99% *N=2093*		50 - 79% *N=1595*		80 – 99% *N=4769*		
	N	%	N	%	N	%	N	%	P-value
Procedure									<.05
CAS	55	5.1	150	7.6	67	4.2	333	7	
CEA	1027	94.9	1934	92.4	1528	95.8	4436	93	
Age >80 yr	189	17.5	374	17.9	198	12.4	699	14.7	<.01
Male gender	693	64	1308	62.5	959	60.1	2772	58.1	<.01
Non-white race	17	1.6	36	1.7	28	1.8	81	1.8	
Contralateral									<.05
<50%	698	64.5	1173	56	961	60.3	2546	53.4	
50 - 79%	296	27.4	630	30.1	498	31.2	1518	31.8	
80 - 99%	29	2.7	173	8.3	26	1.6	352	7.4	
CCO	59	5.5	117	5.6	110	6.9	353	7.4	
Smoking	655	79	1685	80.6	1283	80.5	3810	80	0.73
Hypertension	911	84.3	1815	86.7	1403	88	4246	89.1	<.01
Diabetes	359	33.2	596	28.5	525	32.9	1476	30.9	0.01
CAD	300	27.8	683	32.6	489	30.7	1611	33.8	<.01
CABG/PCI	293	27.1	567	27.1	548	34.4	1648	34.6	<.01
CHF	99	9.1	170	8.1	110	6.9	417	8.7	0.09
COPD	276	25.5	479	22.9	351	22	1079	22.6	0.17
Antiplatelet	983	90.9	1888	90.2	1464	91.8	4324	90.7	0.42
Statin	823	67.1	1499	71.7	1296	81.3	3797	79.6	<.01
Stress test abnormal	74	23.7	195	31.9	156	27.9	573	29.3	0.07
Renal failure	67	6.4	88	4.4	82	5.3	266	5.8	0.06
ASA 3 and 4	450	88.6	744	90	704	86.3	1892	86.1	0.02
Prior ipsilateral CEA	35	3.2	99	4.7	48	3	214	4.5	0.01
Urgency									<.01
Elective	827	76.4	1543	73.7	1505	94.4	4596	96.4	
Urgent	255	23.6	550	26.3	90	5.6	173	3.6	

CAD, coronary artery disease, CABG, coronary artery bypass grafting, PCI, percutaneous coronary intervention, CHF, congestive heart failure, COPD, chronic obstructive pulmonary disease, ASA, American Society of Anesthesiology

Asymptomatic patients with 50-79% ipsilateral stenosis. In asymptomatic patients with a moderate degree of ipsilateral stenosis (50-79%), a low complication rate was seen. Stroke/death rate was 0.8% (n=13), stroke rate 0.8% (n =12), death rate 0.1% (n=2), MI rate 1.1% (n=17) and stroke/death/MI rate was 1.8% (n=28). No differences were identified based on the status of the contralateral artery. (Table V) Stroke/death was 0.9% in patients with contralateral occlusion and 0% in patients with contralateral stenosis 80-99%.

Asymptomatic patients with 80-99% ipsilateral stenosis. In asymptomatic patients with ipsilateral stenosis 80-99%, overall adverse outcome was also low, with a stroke/death rate of 0.9% (n = 45), stroke rate of 0.9% (n=41), death rate of 0.2% (n=9), MI rate of 0.9% (n=45) and stroke/death/MI rate of 1.8% (n=84). Approximately a third of strokes happened on the contralateral side (20 major, 6 minor), while the remainder were ipsilateral (11 major, 20 minor). Patients with CCO had a significantly higher stroke/death rate (3.4%, n=12) compared to patients without CCO (P<.01). (Table V) Of these 12 patients, one patient died after a major contralateral stroke and one following ipsilateral stroke. Other strokes were non-fatal ipsilateral major (n=3), minor (n=4), contralateral major (n=2) and contralateral minor (n=1). For MI, no differences were identified based on status of the contralateral artery. In asymptomatic patients with 80-99% ipsilateral stenosis, contralateral occlusion was an independent predictor for stroke or death (OR 4.6, 95% CI 2.1-9.9, P<.001). Other predictors on multivariable analyses were age>80 year and a history of ipsilateral CEA. Antiplatelet therapy proved to be protective. (Table VI)

Table III 30-day outcome in symptomatic patients undergoing carotid revascularization, stratified by degree of stenosis of the ipsilateral artery

	CS < 50%		CS 50-79%		CS 80-99%		CCO			Total	
	N	%	N	%	N	%	N	%	P-value	N	%
50-79% ipsilateral stenosis (N=1082)											
Stroke	8	1.1	7	2.4	2	6.9	3	5.1	0.02	20	1.8
Death	3	0.4	0	0	0	0	2	3.4	0.006	5	0.5
MI	10	1.2	2	0.7	2	6.9	2	3.4	0.03	16	1.5
Stroke/Death	10	1.4	7	2.4	2	6.9	3	5.1	0.05	22	2
Stroke/Death/MI	17	2.4	9	3	3	10.3	4	6.8	0.03	33	3
80-99% ipsilateral stenosis (N=2093)											
Stroke	22	1.9	10	1.6	5	2.9	1	0.9	0.59	38	1.8
Death	5	0.4	2	0.3	2	1.2	1	0.9	0.49	10	0.5
MI	15	1.3	6	1	3	1.7	3	2.6	0.5	27	1.3
Stroke/Death	25	2.1	11	1.7	6	3.5	2	1.7	0.56	44	2.1
Stroke/Death/MI	38	3.2	15	2.4	9	5.2	5	4.3	0.26	67	3.2

CS, contralateral stenosis; CCO, carotid contralateral occlusion, MI, myocardial infarction

Table IV Multivariable model for stroke or death at 30-days after carotid revascularization in symptomatic patients with 50-79% ipsilateral carotid stenosis

	Odds Ratio	95% CI		P-value
		Lower	Upper	
Age > 80 y	0.8	0.2	2.6	0.66
Female gender	1.2	0.5	2.8	0.72
Procedure (CAS vs. CEA)	2.4	0.6	9.3	0.22
CS 50-79%*	1.7	0.6	4.4	0.3
CS 80-99% *	5.1	1.07	24.7	**0.04**
CCO *	2.7	0.7	11.5	0.17

CI, confidence interval, * vs. <50%; CS, contralateral stenosis; CCO, carotid contralateral occlusion; bold, variable significant associated with outcome P<.05

DISCUSSION

In a large regional quality improvement database, we evaluated the impact of contralateral carotid artery disease on outcome after carotid revascularization procedures. We found that the influence of contralateral stenosis or occlusion on outcome is different for asymptomatic versus symptomatic patients, and is dependent on the degree of ipsilateral carotid artery stenosis.

Our results indicate that in asymptomatic patients with ipsilateral stenosis between 80-99%, CCO significantly increased stroke or death risk. For symptomatic patients with moderate 50-79% ipsilateral stenosis, high-grade contralateral stenosis had a significant adverse impact on perioperative stroke/death, while CCO had increased (but not significantly) risk of stroke/death. These results were not influenced by procedure, suggesting that contralateral disease should not be used to select patients preferentially for CAS. This was consistent with the results from the SVS Vascular Registry that showed no statistical difference between CAS and CEA in both symptomatic and asymptomatic patients with CCO.[9,16] Yet, despite the risk of intervention in symptomatic patients with contralateral disease, revascularization still proves beneficial compared to medical management as the natural history of medically treated patients is poor with two-year stroke risk ranging from 26% in patients with mild-to-moderate contralateral lesions to 70% in patients with CCO.[5]

The natural history of asymptomatic patients remains uncertain, and for those patients with high-grade stenosis and CCO the stroke/death risk (3.4%) was above the upper limit (3%) considered acceptable for asymptomatic lesions in a recent inter-societal consensus guideline document.[15]

The increased stroke risk in patients with contralateral high-grade disease could be related to a diminished collateral blood flow. However, this would not account for the fact that symptomatic patients with severe stenosis were not impacted by contralateral disease, nor was there increased risk for those with severe ipsilateral disease compared to moderate disease in either symptomatic or asymptomatic patients. As such, the exact mechanisms of stroke are not fully understood. Cerebral hyperperfusion could be more common among patients with a low cerebral flow state, causing secondary hemorrhagic strokes. However, despite our large series, our sample size

remains too small to evaluate this hypothesis.

Previous studies have shown different results regarding the perioperative risk in patients with CCO after both CAS and CEA.[7,10,21,22] The controversy among prior studies can be explained in several ways. First, analyzing rare events such as stroke or death after revascularization can be challenging, particularly since the incidence of patients with CCO is also low.[23] Therefore, most studies are limited by small, retrospective cohorts, which are often underpowered to detect differences or stratify for symptom status. Finally, differences in patient population may explain the disparities in outcome of prior studies. Yet, the results of our study indicate that contralateral disease is only important for certain patient populations, and cannot be generalized among all patients undergoing revascularization.

Table V 30-day outcome in asymptomatic patients undergoing carotid revascularization, stratified by degree of stenosis of the ipsilateral artery

	CS <50%		CS 50-79%		CS 80-99%		CCO			Total	
	N	%	N	%	N	%	N	%	P-value	N	%
50-79% ipsilateral stenosis (N=1595)											
Stroke	8	0.8	3	0.6	0	0	1	0.9	0.93	12	0.8
Death	2	0.2	0	0	0	0	0	0	0.72	2	0.1
MI	8	0.8	8	1.6	0	0	1	0.9	0.54	17	1.1
Stroke/Death	9	0.9	3	0.6	0	0	1	0.9	0.88	13	0.8
Stroke/Death/MI	16	1.7	10	2	0	0	2	1.8	0.87	28	1.8
80-99% ipsilateral stenosis (N=4769)											
Stroke	17	0.7	11	0.7	1	0.3	12	3.4	<.001	41	0.9
Death	2	0.1	5	0.3	0	0	2	0.6	0.09	9	0.2
MI	21	0.8	18	1.2	4	1.1	2	0.6	0.57	45	0.9
Stroke/Death	18	0.7	14	0.9	1	0.3	12	3.4	<.001	45	0.9
Stroke/Death/MI	36	1.4	29	1.9	5	1.4	14	4	0.007	84	1.8

CS, contralateral stenosis; CCO, carotid contralateral occlusion, MI, myocardial infarction

While most prior work focuses on CCO, few studies have investigated symptom status in combination with ipsilateral degree of stenosis to assess the impact of contralateral stenosis or occlusion. In a subset-analysis of NASCET, patients (n=659) with severe (>70%), symptomatic carotid stenosis were stratified by severity of the contralateral stenosis. Compared to patients with severe (>80%), symptomatic stenosis in the VSGNE (n = 2093), the incidence of patients with CCO and severe contralateral stenosis was very similar (6.5% vs. 5.6% and 8.6% vs. 8.3% respectively). Contrary to our findings in patients with severe ipsilateral stenosis, the risk of perioperative stroke or death in patients with an occluded contralateral carotid artery raised sharply (14.3%) compared to mild-to-moderate (5.1%) and severe contralateral stenosis (4%).[5] However, our results showed a similar impact of the contralateral artery in symptomatic patients with moderate ipsilateral stenosis (50-79%). In a population-based study of more than 9000 Medicare beneficiaries, Halm et al. identified 50-99% contralateral stenosis (not CCO) as an independent predictor for complications following CEA, adjusted for several other factors

including symptom status.[18] Although these results were similar to our findings for symptomatic patients, no relation with the ipsilateral degree of stenosis was described.

The results of this study must be interpreted within the context of its design. Several limitations are inherent to this dataset, such as the inability to look at mechanism of stroke. In addition, stroke rate at 30-days may be underreported, since the number of stroke is based on both the procedural and the long-term follow-up record. However, prior audits of the VSGNE data identified no missed strokes based on claims data, indicating that few, if any strokes were missed.[20] We were also not able to compare CAS versus CEA directly, based on the small number of patients in the different contralateral stenosis 'severity' groups in combination with low adverse event rates. When we analyzed these outcomes separately, we identified a similar effect size and direction between the two procedures among both symptomatic and symptomatic patients that prompted us to merge these patients and further adjust for procedure in multivariable models. Although we were able to identify >1000 patients in each subgroup, the relatively low event rate after revascularization may have resulted in a type II error limiting our ability to identify significant differences, particularly in symptomatic patients with ipsilateral 80-99% stenosis and asymptomatic patients with ipsilateral 50-79% stenosis. In the current analysis, we did not focus on shunt use in the setting of CCO, because prior results of VSGNE data showed that among patients with CCO, shunt use was not associated with 30-day stroke or death. However, surgeons who routinely used shunts in all of their CEAs had a significantly lower stroke rate than the surgeons who selectively placed shunts (1.5% vs. 5.6%).[7]

In summary, we found that the impact of contralateral disease on outcome after carotid revascularization is different for asymptomatic versus symptomatic patients. Regardless of procedure type, CCO increases the risk for asymptomatic patients with 80-99% ipsilateral stenosis, while 80-99% contralateral stenosis increases the risk for symptomatic patients with 50-79% ipsilateral stenosis. These findings may have implications on patient selection and risk stratification for patients with severe carotid disease undergoing revascularization procedures.

Table VI Multivariable model for stroke and death at 30-days after carotid revascularization in asymptomatic patients with 80-99% ipsilateral carotid stenosis.

	Odds Ratio	95% CI		P – value
		Lower	Upper	
Age > 80 y	2.3	1.2	4.5	**0.02**
Female gender	1.4	0.8	2.6	0.26
Prior ipsilateral CEA	3.1	1.3	7.7	**0.01**
Hypertension	5.5	0.8	40.5	0.09
Preoperative antiplatelet	0.3	0.2	0.7	**0.002**
Urgency	1.9	0.7	5.6	0.23
CS 50-79%[a]	1.3	0.6	2.6	0.46
CS 80-99% [a]	0.4	0.1	3.1	0.39
CCO [a]	4.6	2.1	9.9	**<.001**

CI, confidence interval, CEA, carotid endarterectomy[a] versus <50%; CS, contralateral stenosis; CCO, carotid contralateral occlusion; bold, variable significant associated with outcome P<.05

Appendix A Bivariate association of patient characteristics with 30-day stroke or death in symptomatic and asymptomatic patients undergoing revascularization

	Symptomatic		Asymptomatic	
	OR	P	OR	P
Age > 80 yr	1.5	0.2	2.3	<.01
Female gender	1	0.9	1.2	0.43
Non white race	1	0.63	1	1
Procedure (CAS vs. CEA)	3.5	<.001	1.1	0.78
Prior ipsilateral CEA	1.9	0.2	2.7	0.03
Any Smoke (prior or current)	0.7	0.27	1.4	0.51
Hypertension (>=140/90 or history)	1.7	0.29	7.2	0.02
Diabetes Mellitus	1.2	0.59	0.6	0.16
Coronary artery disease	1.1	0.5	0.7	0.27
CABG/PCI	1.2	0.58	0.7	0.21
Congestive heart failure	1.7	0.17	1.2	0.58
COPD	1.4	0.24	1.4	0.21
Aspirin/clopidogrel	0.9	0.68	0.4	<.01
Stress test abnormal (MI or ischemia)	1.2	0.73		0.95
Creatinine (>1.78 mg/dL)	1.2	0.56	0.3	0.38
ASA 3 and 4	1.1	1	1.1	1
Urgency	1.6	0.09	3.8	<.001
Ipsilateral stenosis 80-99% (vs 50-79%)	1	1	1.2	0.76

OR, odds ratio, CABG, coronary artery bypass grafting, PCI, percutaneous coronary intervention, COPD, chronic obstructive pulmonary disease, ASA, American Society of Anesthesiology

Appendix B Independent factors associated with 30-day stroke or death in asymptomatic patients

	OR	95% CI		P-value
		Lower	Upper	
Age >80 year	2.2	1.2	3.9	0.008
History of ipsilateral CEA	2.8	1.2	6.5	0.021
Aspirin/clopidogrel	0.4	0.2	0.7	0.004
Hypertension	7.4	1.03	54	0.047
Urgency	3.4	1.6	7.3	0.002

OR, odds ratio; CI, confidence interval

References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation* 2013;127:143-52.
2. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1991;325:445-53.
3. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995;273:1421-8.
4. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2004;351:1493-501.
5. Gasecki AP, Eliasziw M, Ferguson GG, Hachinski V, Barnett HJ. Long-term prognosis and effect of endarterectomy in patients with symptomatic severe carotid stenosis and contralateral carotid stenosis or occlusion: results from NASCET. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. *J Neurosurg* 1995;83:778-82.
6. Baker WH, Howard VJ, Howard G, Toole JF. Effect of contralateral occlusion on long-term efficacy of endarterectomy in the asymptomatic carotid atherosclerosis study (ACAS). ACAS Investigators. *Stroke* 2000;31:2330-4.
7. Goodney PP, Wallaert JB, Scali ST, Stone DH, Patel V, Shaw P, et al. Impact of practice patterns in shunt use during carotid endarterectomy with contralateral carotid occlusion. *J Vasc Surg* 2012;55:61-71 e1.
8. Fluri F, Hatz F, Voss B, Lyrer PA, Engelter ST. Etiology of late cerebrovascular events after carotid endarterectomy. *Eur J Neurol* 2011;18:343-6.
9. Ricotta JJ, Upchurch GR, Landis GS, Kenwood CT, Siami FS, Ricotta JJ, et al. The influence of contralateral occlusion on results of carotid interventions from the Society of Vascular Surgery (SVS) Vascular Registry. *J Vasc Surg* 2012;55(Suppl).
10. Antoniou GA, Kuhan G, Sfyroeras GS, Georgiadis GS, Antoniou SA, Murray D, et al. Contralateral occlusion of the internal carotid artery increases the risk of patients undergoing carotid endarterectomy. *J Vasc Surg* 2013;57:1134-45.
11. Coyle KA, Smith RB, 3rd, Salam AA, Dodson TF, Chaikof EL, Lumsden AB. Carotid endarterectomy in patients with contralateral carotid occlusion: review of a 10-year experience. *Cardiovasc Surg* 1996;4:71-5.
12. AbuRahma AF, Robinson P, Holt SM, Herzog TA, Mowery NT. Perioperative and late stroke rates of carotid endarterectomy contralateral to carotid artery occlusion : results from a randomized trial. *Stroke* 2000;31:1566-71.
13. Dalainas I, Nano G, Bianchi P, Casana R, Malacrida G, Tealdi DG. Carotid endarterectomy in patients with contralateral carotid artery occlusion. *Ann Vasc Surg* 2007;21:16-22.
14. Rockman CB, Su W, Lamparello PJ, Adelman MA, Jacobowitz GR, Gagne PJ, et al. A reassessment of carotid endarterectomy in the face of contralateral carotid occlusion: surgical results in symptomatic and asymptomatic patients. *J Vasc Surg* 2002;36:668-73.
15. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery DiseaseA Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery Developed in Collaboration With the American Academy of Neurology and Society of Cardiovascular Computed Tomography. *Journal of the American College of*

Cardiology;57:e16.
16. Schermerhorn ML, Fokkema M, Goodney P, Dillavou ED, Jim J, Kenwood CT, et al. The impact of Centers for Medicaid and Medicare Services high-risk criteria on outcome after carotid endarterectomy and carotid artery stenting in the SVS Vascular Registry. *J Vasc Surg* 2013.
17. Brewster LP, Kasirajan KP, Beaulieu R, Reeves JP, Corriere MA, Rajani R, et al. Contralateral Occlusion is not a Clinically Important Reason for Choosing Carotid Artery Stenting for Patients with Significant Carotid Artery Stenosis. *J Vasc Surg* 2012;54:1854.
18. Halm EA, Tuhrim S, Wang JJ, Rockman C, Riles TS, Chassin MR. Risk factors for perioperative death and stroke after carotid endarterectomy: results of the new york carotid artery surgery study. *Stroke* 2009;40:221-9.
19. Cronenwett JL, Likosky DS, Russell MT, Eldrup-Jorgensen J, Stanley AC, Nolan BW. A regional registry for quality assurance and improvement: the Vascular Study Group of Northern New England (VSGNNE). *J Vasc Surg* 2007;46:1093-101; discussion 101-2.
20. Nolan BW, De Martino RR, Goodney PP, Schanzer A, Stone DH, Butzel D, et al. Comparison of carotid endarterectomy and stenting in real world practice using a regional quality improvement registry. *J Vasc Surg* 2012;56:990-6.
21. Mehta RH, Zahn R, Hochadel M, Mudra H, Ischinger T, Hauptmann KE, et al. Effectiveness and safety of carotid artery stenting for significant carotid stenosis in patients with contralateral occlusion (from the German ALKK-CAS Registry experience). *Am J Cardiol* 2009;104:725-31.
22. Gonzalez A, Gonzalez-Marcos JR, Martinez E, Boza F, Cayuela A, Mayol A, et al. Safety and security of carotid artery stenting for severe stenosis with contralateral occlusion. *Cerebrovasc Dis* 2005;20 Suppl 2:123-8.
23. Rockman C. Carotid endarterectomy in patients with contralateral carotid occlusion. *Semin Vasc Surg* 2004;17:224-9.

PART II

CHAPTER SEVEN

Clinical relevance of cranial nerve injury following carotid endarterectomy

European Journal of Vascular and Endovascular Surgery
September 2013; Accepted for publication

Authors
M. Fokkema[1,2], G.J. de Borst[2], B.W. Nolan[3], J. Indes[4], D.B. Buck[1,2], R.C. Lo[1], F.L. Moll[2], M.L. Schermerhorn[1] on behalf of the Vascular Study Group of New England

Affiliations
Department of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center, Boston, MA, USA[1], University Medical Center Utrecht, Utrecht, The Netherlands[2], Dartmouth Hitchcock Medical Center, Lebanon, NH, USA[3], Yale Medical Center, New Haven, CT, USA[4]

ABSTRACT

Objectives. The benefit of carotid endarterectomy (CEA) may be diminished by cranial nerve injury (CNI). Using a quality improvement registry, we aimed to identify the nerves affected, duration of symptoms (transient vs. persistent) and clinical predictors of CNI.

Materials and Methods. We identified all patients undergoing CEA in the Vascular Study Group of New England between 2003-2011. Surgeon observed CNI rate was determined at discharge (postoperative CNI) and at follow-up to determine persistent CNI (CNI's that persisted at routine follow-up visit). Hierarchical multivariable model controlling for surgeon and hospital was used to assess independent predictors for postoperative CNI.

Results. 6878 patients (33.8% symptomatic) were included for analyses. CNI rate at discharge was 5.6% (n=382). Sixty patients (0.7%) had more than one nerve affected. The hypoglossal nerve was most frequently involved (n=185, 2.7%), followed by the facial (n=128, 1.9%), the vagus (n=49, 0.7%) and the glossopharyngeal (n=33, 0.5%) nerve. The vast majority of these CNI's were transient; only 47 patients (0.7%) had a persistent CNI at their follow-up visit (median 10.0 months, range 0.3 – 15.6). Patients with perioperative stroke (0.9%, n=64) had significantly higher risk of CNI (n=15, CNI risk: 23.4% P<0.01). Predictors for CNI were urgent procedures (OR 1.6, 95% CI 1.2-2.1, P<0.01), immediate re-exploration after closure under the same anaesthetic (OR 2.0, 95% CI 1.3-3.0, P<0.01) and return to the operating room for a neurologic event or bleeding (OR 2.3, 95% CI 1.4-3.8, P<0.01), but not redo-CEA (OR 1.0, 95% CI 0.5-1.9, P=0.90) or prior cervical radiation (OR 0.9, 95% CI 0.3-2.5, P=0.80).

Conclusions. As patients are currently selected in the VSGNE, persistent CNI after CEA is rare. While conditions of urgency and (sub) acute re-intervention carried increased risk for postoperative CNI, a history of prior ipsilateral CEA or cervical radiation were not associated with increased CNI rate.

INTRODUCTION

Carotid endarterectomy (CEA) has been established as the standard of care for long-term stroke prevention in patients with severe carotid stenosis in an average risk population.[1,2] Carotid artery stenting (CAS) has emerged as an alternative to CEA, but the comparative effectiveness of these modalities remains controversial.

The advantage of a lower perioperative stroke rate with CEA compared to CAS may be somewhat offset by the added risk of postoperative myocardial infarction (MI) and cranial nerve injury (CNI) after surgery.[3-5] However, the clinical importance of CNI as a relevant safety endpoint is debatable.[3,6-8] Although most postoperative nerve lesions seem transient, the actual rate of persistent CNI following CEA remains unclear.[8-11] Postoperative CNI rates vary between 3 – 27%, depending on the observer, definition of CNI, and study design.[11,12] Prior studies have been limited to single institution observations with small sample size and highly selected surgeons or patients participating in randomized controlled trials. Very few studies commented on the patient characteristics or operative conditions associated with increased risk for CNI.[11,13] Higher rates are often reported after redo-CEA and prior radiation, but most of these studies were not designed to identify independent predictors for CNI given its low event rate. [14-16] Using a large quality improvement registry reflective of real world vascular surgery practice, we aimed to 1) establish rates of surgeon observed postoperative and persistent CNI after CEA, 2) identify the specific nerves at risk for injury, and 3) identify clinical predictors for postoperative CNI.

MATERIALS AND METHODS

Database. We used prospective data collected by the Vascular Study Group of New England (VSGNE). The VSGNE is a regional quality improvement initiative developed by vascular surgeons in 2001, and currently involves over 180 physicians, (vascular surgeons, radiologists and cardiologists) at 30 centers (14 academic, 16 community). The goal of this cooperative group of clinicians, hospital administrators and research personnel is to continuously improve the quality, safety, effectiveness, and cost of caring for patients with vascular disease. Preoperative clinical characteristics, imaging studies, perioperative outcome noted at discharge and follow-up data are collected from eight vascular procedures (including CEA), and entered in the registry by trained nurses or clinical data abstractors. Surgeons enter operative details including complications. Research analysts are blinded to patient, surgeon, and hospital identity. Further details on this registry have been published previously and are available at http://www.vascularweb.org/regionalgroups/vsgne. VSGNE data have been validated for completeness using audits of discharge claims data from each participating institution to ensure entry of all patients.[17,18]

Patients. Our study sample included all patients in the VSGNE who underwent CEA between January 2003 and December 2011 for whom information on CNI was available at time of discharge and at one later time point after discharge (nerve injury recorded during surgical follow-up visit). This was done to obtain a valid sample to determine CNI rate at discharge and to assess the proportion of CNI's that resolved or persisted after discharge.

Table I Bivariate associations of preoperative patient characteristics with CNI of 6878 patients undergoing CEA

	Total		CNI				
	N	%	N	%	P-value	OR	95% CI
Age >80 year	972	14.1	59	6.1	.45	1.1	0.8 – 1.5
Gender (male)	4141	60.2	288	5.5	.83	1.0	0.8 – 1.3
Race (white)	6778	98.6	376	5.5	.82	0.9	0.4 – 2.1
Ipsilateral symptoms	2325	33.8	148	6.4	.03	1.3	1.02 – 1.6
Smoking (prior or current)	5481	79.8	311	5.7	.39	1.1	0.9 – 1.5
Hypertension	6034	87.8	354	5.9	<.01	1.8	1.3 – 2.7
Diabetes	2090	30.4	106	5.1	.30	0.9	0.7 – 1.1
BMI					.12		
<18.5	205	3.1	13	6.3			
18.5-24.9	1822	27.4	123	6.8			
25-29.9	2591	39.0	138	5.3			
30-34.9	1346	20.2	67	5.0			
35-40	472	7.1	23	4.9			
>40	214	3.2	7	3.3			
Contralateral occlusion	417	6.1	28	6.7	.30	1.2	0.8 – 1.8
Previous radiation	88	1.3	4	4.5	1	0.8	0.3 – 2.2
Previous ipsilateral CEA	152	2.2	8	5.3	1	0.9	0.5 – 1.9

CNI, cranial nerve injury, OR, odds ratio, CI, confidence interval, BMI, body mass index;

Endpoints and Measurements. Primary endpoints were any CNI at discharge and the rate of persistent CNI at follow-up for both symptomatic and asymptomatic patients. The surgeon identified the clinical manifestation of the nerve injury after surgery. A CNI will be reported to the VSGNE if there was no palsy present before surgery. Injury to the following nerves are distinguished: facial nerve (VII) - facial droop, glossopharyngeal nerve (IX) - swallowing difficulty unless other diagnosis confirmed, vagus nerve (X) - hoarseness unless laryngoscopy normal, hypoglossal nerve (XII) - any tongue deviation or dis-coordination. The VSGNE also records other 'non-specified' cranial nerve injuries (e.g. accessory nerve [XI], trigeminal nerve [V], or injuries to one of the above mentioned cranial nerves that were not further specified during data entry). The real world nature of our database does not allow routine examination of patients postoperatively by a neurologist or otolaryngologist to identify CNI. Therefore, objective tests such as laryngoscopy for vocal cord function were not used routinely and their use was not recorded. Persistent CNI was identified by the vascular surgeon and defined as a CNI at discharge that was not resolved at the time of the surgical follow-up visit. In the VSGNE, the status of the CNI has to be entered in the registry as a categorical variable during regular follow-up visit, specifying 'no CNI' versus 'resolved CNI' versus 'persistent CNI'. Because no exact time to event is calculated for CNI at follow-up, the median time with corresponding interquartile ranges (IQR)

to follow-up was calculated. Although the VSGNE aims to collect follow-up data at one year after the procedure, the time to follow-up in the database varies between patients reflecting real world practice. Symptomatic patients were defined as having preoperative ipsilateral cortical neurological symptoms prior to surgery.[17] 'Immediate reoperation' included surgical revision after closure of the artery in the operating room (OR). Reasons for immediate re-operation may include intimal flap, debris or residual plaque on completion imaging studies.[19] 'Return to the OR' included reoperations after a patient had left the operating room. Causes for return to the OR included neurologic events or bleeding that required re-intervention. The surgeon performing the CEA made the designation of urgent cases versus elective cases. Urgent cases may include patients with stroke in evolution or crescendo TIA's. This was reflected by the fact that the vast majority of urgent cases were symptomatic and admitted to the hospital preoperatively (as opposed to same day admissions). (Appendix, online)

Statistical Analysis. Associations of preoperative patient characteristics, operative details and perioperative outcome with postoperative CNI were examined using χ^2 test and Fisher's exact test for categorical variables. To gain insight into factors independently associated with CNI, all variables with values of P <.2 in the previously described bivariate analyses were used to develop a multivariable regression model. A multilevel hierarchical model (data structure: patient, surgeon, center) was used to adjust for surgeon and centers within the VSGNE.[20] This type of modelling uses a random intercept that accounts for all variable factors between hospitals and surgeons in the VSGNE, including surgeon and hospital volume.
Associations were calculated using manual elimination procedure, in which all candidate variables were entered in the first step and removed stepwise based on the highest non-significant P-value. P-values < .05 were considered significant. Odds ratios (OR) and corresponding 95% Confidence Interval (CI) were reported. SPSS version 20.0 statistical software (IBM, SPSS Inc, Chicago Illinois, USA) was used for statistical analyses.

RESULTS

Of all 9362 patients undergoing isolated CEAs, 2484 (26.5%) had missing data for CNI and were therefore excluded from this analysis. Of those, 1% died (n=24) during hospital admission and 14.9% (n=370) after discharge. For the remaining missing patients (84.1%), CNI information was not available at one later time point after discharge due to lack of follow-up. We performed a subgroup analysis of these excluded patients confirming that no important information on CNI was lost for the purpose of this study. In particular, CNI rate at discharge in these excluded patients was similar to CNI rate in our final study sample (n= 136, 5.5%). This had also no impact on the predictors for CNI.
In total, 6878 CEAs (33.8% symptomatic) from 23 centers performed by 104 surgeons were included. Median caseload per center and surgeon were 85 and 27 respectively. The mean age was 69 year (SD ± 9.3) and 60.2% were men. 152 (2.2%) patients underwent redo-surgery following prior ipsilateral CEA and 88 (1.3%) had a history of previous cervical radiation therapy. (Table I) 10% of patients were operated under loco-regional anesthesia and 10% were urgent procedures (as opposed to elective procedures). In 217 (3.2%) patients, immediate re-exploration after closure was performed. Another 111 patients (1.6%) were taken back to the OR

for neurologic events (TIA or stroke, n=26), bleeding (n=62) or unknown (n=23) complications after awakening from anesthesia. Median length of stay was 1.5 days (IQR 0). At 30-days, the stroke rate was 0.9% (n=64) (symptomatic 1.2% [n=29] and asymptomatic 0.8% [n=35]) and MI rate was 0.9% (n=63).

Table II Bivariate associations of procedural variables and outcome with CNI of 6878 patients undergoing CEA

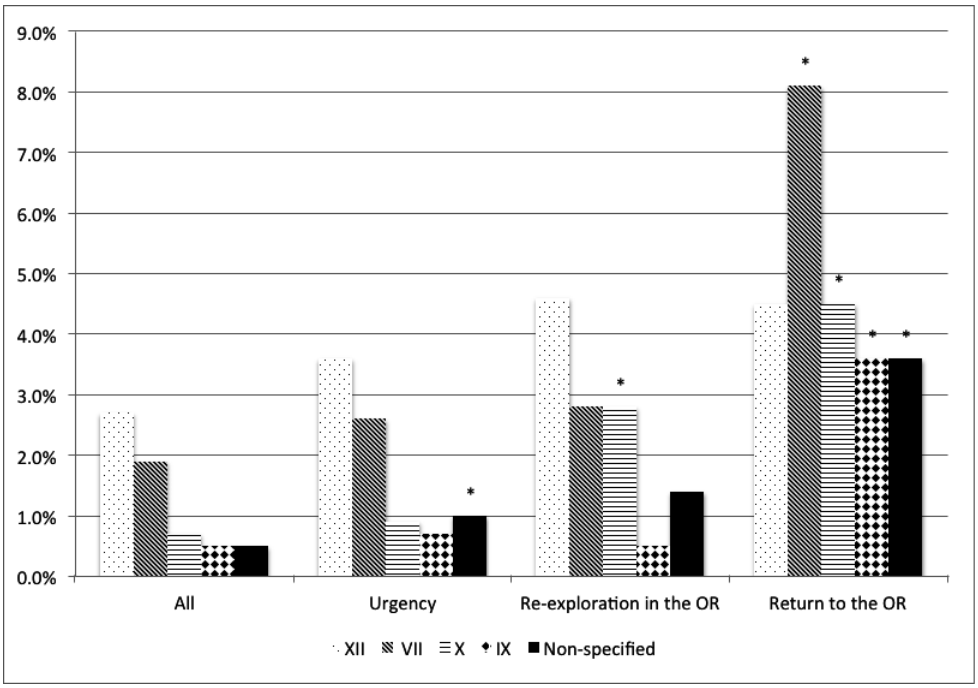
	Total		CNI		P-value	OR	95% CI
	N	%	N	%			
Anesthesia					.60	0.9	0.6 – 1.3
General	6189	90.0	347	5.6			
Loco-regional	689	10.0	35	5.1			
Urgency					.02	1.4	1.1 – 2.0
Elective	6186	89.9	330	5.3			
Urgent	692	10.1	42	7.5			
CEA type					.37	1.2	0.8 – 1.6
Longitudinal endarterectomy	6226	90.5	341	5.5			
Eversion technique	651	9.5	41	6.3			
Shunt use					.37	0.9	0.7 – 1.1
No	3641	52.9	211	5.8			
Yes	3237	46.8	171	5.3			
Patch use					.32	0.8	0.5 – 1.2
No (primary closure of longitudinal endarterectomy)	327	5.3	22	6.7			
Yes	5899	94.4	319	5.4			
Drain					.33	0.5	0.1– 1.7
No	655	79.6	23	3.5			
Yes	168	20.4	3	1.8			
Re-exploration after closure	217	3.2	21	9.7	.01	1.9	1.2– 3.0
Return to the operating room	111	1.6	16	14.4	<.001	2.9	1.7– 5.1

CNI, cranial nerve injury, OR, odds ratio, CI, confidence interval

Cranial nerve injury. Overall, 382 patients had any CNI at discharge (5.6%). Symptomatic patients had higher rates (6.4%) than asymptomatic patients (5.1%, P<0.05). The hypoglossal nerve (injured in 185 [2.7%]) and the facial nerve (injured in 128 [1.9%]) were most frequently involved, followed by the vagus nerve (injured in 49 [0.7%]) and the glossopharyngeal nerve (injured in 33 [0.5%]). Another 0.5% (n=31) involved unspecified cranial nerves. Of all patients, 296 (4.3%) had a single deficit, 42 had two nerves (0.6%) and 13 patients (0.1%) had three or more nerves affected. Of the 382 patients who had a nerve injury at discharge, the deficit resolved

over time in 88% (n=335). Only 47 patients (0.7%) had a persistent injury at their follow-up visit (median 10.0 months, range 0.3 – 15.6). Median time to follow-up for all patients was 12.1 months (range 0.3 – 57.6). Lesions of the hypoglossal (n=7, 0.1%) and the facial nerve (n=6, 0.1%) were the most persistent, followed by the vagus (n=3, 0.1%) and the glossopharyngeal nerves (n=1, 0.02%). Length of hospital stay was prolonged in patients with CNI compared to those without (2 days vs. 1.5 day, P<0.01).

Figure Cranial nerve injury per predictor



Predictors for postoperative nerve injury. On bivariate analyses of preoperative patient characteristics with CNI, no clinical relevant associations were identified for CNI. (Table I) Urgent procedures, immediate re-exploration and return to the OR were associated with increased risk for CNI. (Table II) Type of procedure (eversion versus longitudinal), shunt use, patch use (versus primary closure of longitudinal endarterectomy) and type of anaesthesia (loco-regional versus general) did not influence CNI. Patients with a perioperative stroke within 30 days (n=64, 0.9%) had increased CNI (23.4% vs. no stroke 5.4%, P<0.01). On multivariable regression, urgent procedures (OR 1.6, 95% CI, 1.2-2.1, P=0.006), re-exploration (OR 2.0, 95% CI 1.3-3.0, P=0.004) and return to the operating room (OR 2.3, 95% CI 1.4-3.8, P=0.004) were independent risk factors for CNI. (Table III) Specifically, return to the OR for stroke or TIA was predictive of CNI (OR 4.8, 95% CI 2.1-11.2, P=0.002), while return to the OR for bleeding did not reach significance (OR 1.6, 95% CI 0.8-3.3, P=0.3). In a subgroup analyses among urgent cases, symptomatic patients had increased CNI compared to asymptomatic patients

(8.5% vs. 4.0%, OR 2.3, 95% CI 0.9-5.4, P=0.08). Among elective cases, CNI rate between symptomatic and asymptomatic patients was comparable (5.7% vs. 5.2%, OR 1.1, 95% CI 0.9 – 1.4, P=0.4). Because others have previously reported that prior radiation therapy and redo-CEA can be predictive conditions for CNI, we forced them into our prediction model.[15,16,21] However, no impact on CNI was identified among these variables (prior radiation therapy: OR 0.9, 95% CI 0.3-2.5, P=0.8 and redo-CEA (OR 1.0, 95% CI 0.5-2.1, P=0.9).

Nerves at risk. In the situation of immediate re-intervention after closure, a significant increased risk for vagus injury (n=6, 2.8%) was identified. Patients who had to returned to the OR after surgery were at increased risk for facial (n=9, 8.1%), glossopharyngeal (n=4, 3.6%), vagus (n=5, 4.5%), and other non-specified nerves (n=4, 3.6%), but not for hypoglossal nerve (n=5, 4.5%) injury. (Figure) Urgent procedures were not associated with specific nerve injuries.

Table III Independent predictors for cranial nerve injury following CEA

	Odds ratio	95% CI	*P*-value [a]
Urgent cases [b]	1.6	1.2 – 2.1	0.006
Immediate re-exploration	2.0	1.3 – 3.0	0.004
Return to the operating room	2.3	1.4 – 3.8	0.004

[a] Based on a hierarchical multilevel regression model accounting for surgeon and centers within the VSGNE
[b] vs. elective procedures

DISCUSSION

The postoperative risk for any CNI was 5.6% among patients undergoing CEA in the Vascular Study Group of New England. While most lesions were transient, 0.7% of patients had a persistent lesion at their follow-up consultation. Independent risk factors for postoperative cranial nerve injury were urgent cases, immediate re-exploration after closure and return to the operating room.

The reported frequency of CNI in the published literature ranges from 3 to 27%.[11,12] Variable study design (prospective vs. retrospective), the use of objective measurements (e.g. otolaryngeal examinations), the observer, and variation in the definition of CNI (sensory deficits vs. purely motor injuries) contribute to this wide variability. Yet, cranial (motor) nerve injury at discharge in the VSGNE (5.6%) was similar to prior large studies, such as the New York Carotid Artery Surgery study (NYCAS, 5.5%)[22], the European Carotid Surgery Trial (ECST, 5.1%),[13] the North American Symptomatic Carotid Endarterectomy Trial (8.6%)[23] and the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST, 4.7%)[5]. In the randomized trials, CNI was identified by an independent stroke neurologist that was not involved in the performance of the CEA itself, as opposed to surgeon observed CNI in the large registries such as the NYCAS and the VSGNE. We found that symptomatic patients had higher rates of postoperative CNI than asymptomatic

patients (6.4% vs. 5.1%), which was also seen in CREST (5.1% vs. 4.3%). This can be explained by a high CNI risk among symptomatic patients who underwent urgent procedures (8.5%), which proved to be independent predictor for CNI in our study.

Among the aforementioned studies, only the ECST reported CNI rates beyond hospital discharge. The ECST showed a persistent CNI rate of 0.5% at 4 months and one year.[13] We found a comparable persistent CNI rate of 0.7% at a median interval of 10 months, confirming that most lesions are transient.[8,9] The transient nature of most lesions suggests that the majority of CNIs are related to traction or cautery rather than transections.[12,24] In CREST, CNI was not associated with a sustained impact on quality of life at one year, but at two weeks, CAS patients reported less difficulty eating or swallowing as compared with CEA patients.[6] However, some have suggested that the effects from a CNI can be likened to having a minor stroke.[3,7,8]

Our results indicate that patients are at greatest risk for CNI during times of surgeon stress and that surgeons should take particular care to protect specific nerves in conditions of urgency, re-exploration, and return to OR. In particular, the vagus nerve was at greatest risk in re-exploration cases, while all nerves but the facial nerve were at risk in patients who were taken back to the OR. Patients who returned to the OR for stroke had greater risk for CNI than patients who were taken back for bleeding. The relation of local complications (e.g. CNI) with stroke was previously shown.[22]

Only one prior study with preoperative and postoperative examinations by an otolaryngologist, reported on associations of specific nerves with patients or operative factors.[11] They showed an overall CNI risk of 27% (51/ 190) at 2 days after surgery and found that plaque extension >2cm was related to lesions of the vagus nerve (OR=3.5; CI 1.09-12.3, P=0.03). The ESCT analysed a limited number of risk factors to identify predictors for all nerve injuries. Operation longer than two hours was found to be the only predictive factor (HR 1.56, 95% CI 1.31–1.81 per 30-minute increment).[13] While others have previously reported an increased risk for CNI after redo-CEA and prior radiation,[14,15,25] in this study we did not. Theoretically, these conditions can lead to more complex CEA procedures and therefore, CNI's may be more frequent.[26] Reported causative factors include absent tissue planes in the diseased vessel wall and (radiation-induced) fibrosis.[27] The condition of the preoperative tissue in the cervical area could have result in differences in patient selection (CAS vs. CEA), and may possibly explain the difference with prior reports.

In reports prior to 1995, CAS was not readily available and accepted for patients with a hostile neck due to extensive radiation or prior neck surgery.[21,25] In the current era of carotid stenting, it is likely that those with the most hostile necks are no longer selected for redo-CEA.[28]

While the strength of the VGSNE database is its large size and detailed clinical data, reporting bias is inherent to any registry-based study and potentially leads to under-reporting of events. Yet, the lack of follow-up data on CNI for several patients in the VSGNE is most likely rather a data collection issue then reporting bias, since the postoperative rate of CNI in patients with and without follow-up data was similar (5.5% vs. 5.6%). Our subgroup analysis also affirmed that there was no impact on the identification of predictors. Therefore, it is very unlikely that the subset of excluded patients due to lack of follow-up will change the results of this study. The exact time to recovery remains unknown due to the lack of follow-up at set time points in the VSGNE. Our analysis was also limited by the lack of a formal protocol including objective CNI measurement at set time points. Therefore, it seems reasonable that subtle nerve lesions may have

been missed and our rate of 5.6% could be underestimating CNI.[24] Some hoarseness may have been incorrectly ascribed to trauma from endotracheal intubation rather than CNI due to the lack of routine otolaryngoscopic evaluation. Since the rate of CNI was similar for those undergoing loco-regional and general anaesthesia, this is not very likely. The clinical assessment of persistent injury to the vagus nerve seems also difficult, since patients are often able to compensate deficits resulting in a 'normal' voice. On the other hand, it has also been suggested that the use of objective methods may lead to the inclusion of several asymptomatic deficits with minor clinical relevance.[13,24] Therefore, we believe that the majority of clinically relevant injuries are captured in the VSGNE and that these rates of CNI could serve as a benchmark for every-day practice.

As patients are currently selected in the VSGNE, persistent CNI after CEA is rare. CNI is more likely in urgent procedures and after re-exploration in the OR, or return to the OR; while redo-CEA and a history of prior cervical radiation were not associated with increased CNI rate.

References

1. Beneficial Effect of Carotid Endarterectomy in Symptomatic Patients with High-Grade Carotid Stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991;325:445-53.
2. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995;273:1421-8.
3. Meier P, Knapp G, Tamhane U, Chaturvedi S, Gurm HS. Short term and intermediate term comparison of endarterectomy versus stenting for carotid artery stenosis: systematic review and meta-analysis of randomised controlled clinical trials. BMJ 2010;340:c467.
4. Economopoulos KP, Sergentanis TN, Tsivgoulis G, Mariolis AD, Stefanadis C. Carotid artery stenting versus carotid endarterectomy: a comprehensive meta-analysis of short-term and long-term outcomes. Stroke 2011;42:687-92.
5. Brott TG, Hobson RW, 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363:11-23.
6. Cohen DJ, Stolker JM, Wang K, Magnuson EA, Clark WM, Demaerschalk BM, et al. Health-Related Quality of Life After Carotid Stenting Versus Carotid Endarterectomy: Results From CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial). J Am Coll Cardiol 2011;58:1557-65.
7. Bangalore S, Kumar S, Wetterslev J, Bavry AA, Gluud C, Cutlip DE, et al. Carotid artery stenting vs carotid endarterectomy: meta-analysis and diversity-adjusted trial sequential analysis of randomized trials. Arch Neurol 2011;68:172-84.
8. Schauber MD, Fontenelle LJ, Solomon JW, Hanson TL. Cranial/cervical nerve dysfunction after carotid endarterectomy. J Vasc Surg 1997;25:481-7.
9. Ballotta E, Da Giau G, Renon L, Narne S, Saladini M, Abbruzzese E, et al. Cranial and cervical nerve injuries after carotid endarterectomy: a prospective study. Surgery 1999;125:85-91.
10. Forssell C, Takolander R, Bergqvist D, Bergentz SE, Gramming P, Kitzing P. Cranial nerve injuries associated with carotid endarterectomy. A prospective study. Acta Chir Scand 1985;151:595-8.
11. Zannetti S, Parente B, De Rango P, Giordano G, Serafini G, Rossetti M, et al. Role of surgical techniques and operative findings in cranial and cervical nerve injuries during carotid endarterectomy. Eur J Vasc Endovasc Surg 1998;15:528-31.
12. Regina G, Angiletta D, Impedovo G, De Robertis G, Fiorella M, Carratu MR. Dexamethasone minimizes the risk of cranial nerve injury during CEA. J Vasc Surg 2009;49:99-102; discussion 3.
13. Cunningham EJ, Bond R, Mayberg MR, Warlow CP, Rothwell PM. Risk of persistent cranial nerve injury after carotid endarterectomy. J Neurosurg 2004;101:445-8.
14. AbuRahma AF, Abu-Halimah S, Hass SM, Nanjundappa A, Stone PA, Mousa A, et al. Carotid artery stenting outcomes are equivalent to carotid endarterectomy outcomes for patients with post-carotid endarterectomy stenosis. J Vasc Surg 2010;52:1180-7.
15. Fokkema M, den Hartog AG, Bots ML, van der Tweel I, Moll FL, de Borst GJ. Stenting versus surgery in patients with carotid stenosis after previous cervical radiation therapy: systematic review and meta-analysis. Stroke 2012;43:793-801.
16. AbuRahma AF, Choueiri MA. Cranial and cervical nerve injuries after repeat carotid endarterectomy. J Vasc Surg 2000;32:649-54.
17. Nolan BW, De Martino RR, Goodney PP, Schanzer A, Stone DH, Butzel D, et al. Comparison of carotid endarterectomy and stenting in real world practice using a regional quality improvement registry. J Vasc Surg 2012;56:990-6.
18. Goodney PP, Wallaert JB, Scali ST, Stone DH, Patel V, Shaw P, et al. Impact of practice patterns in shunt use during carotid endarterectomy with contralateral carotid occlusion. J Vasc Surg 2012;55:61-71 e1.
19. Wallaert JB, Goodney PP, Vignati JJ, Stone DH, Nolan BW, Bertges DJ, et al. Completion imaging after carotid endarterectomy in the Vascular Study Group of New England. J Vasc Surg 2011;54:376-85, 85 e1-3.

20. Douglas L. Multilevel Modeling. Thousand Oaks, CA: Sage; 2004.
21. Das MB, Hertzer NR, Ratliff NB, O'Hara PJ, Beven EG. Recurrent carotid stenosis. A five-year series of 65 reoperations. Ann Surg 1985;202:28-35.
22. Greenstein AJ, Chassin MR, Wang J, Rockman CB, Riles TS, Tuhrim S, et al. Association between minor and major surgical complications after carotid endarterectomy: results of the New York Carotid Artery Surgery study. J Vasc Surg 2007;46:1138-44; discussion 45-6.
23. Ferguson GG, Eliasziw M, Barr HW, Clagett GP, Barnes RW, Wallace MC, et al. The North American Symptomatic Carotid Endarterectomy Trial : surgical results in 1415 patients. Stroke 1999;30:1751-8.
24. Hertzer NR, Feldman BJ, Beven EG, Tucker HM. A prospective study of the incidence of injury to the cranial nerves during carotid endarterectomy. Surg Gynecol Obstet 1980;151:781-4.
25. Meyer FB, Piepgras DG, Fode NC. Surgical treatment of recurrent carotid artery stenosis. J Neurosurg 1994;80:781-7.
26. Frego M, Bridda A, Ruffolo C, Scarpa M, Polese L, Bianchera G. The hostile neck does not increase the risk of carotid endarterectomy. J Vasc Surg 2009;50:40-7.
27. Friedell ML, Joseph BP, Cohen MJ, Horowitz JD. Surgery for carotid artery stenosis following neck irradiation. Ann Vasc Surg 2001;15:13-8.
28. Fokkema M, de Borst GJ, Nolan BW, Lo RC, Cambria RA, Powell RJ, et al. Carotid stenting versus endarterectomy in patients undergoing reintervention after prior carotid endarterectomy. J Vasc Surg 2013.

PART II

7

PART ③

Consequences of comparative outcome analyses between carotid stenting and surgery

CHAPTER EIGHT

In-hospital versus postdischarge adverse events following carotid endarterectomy

Journal of Vascular Surgery
June 2013; Vol 57 Pages:1568-1575

Authors
Fokkema M[1,2], Bensley RP[1], Lo RC[1], Hamden AD[1], Wyers MC[1], Moll FL[2], GJ de Borst[2], ML Schermerhorn[1]

Affiliations
Department of Vascular Surgery, [1]Beth Israel Deaciness Medical Center, Boston, MA
[2]University Medical Center Utrecht, the Netherlands

ABSTRACT

Introduction and objectives. Most studies based on state and nation-wide registries evaluating perioperative outcome after carotid endarterectomy (CEA) rely on hospital discharge data only. Therefore, the true 30-day complication risk after carotid revascularization may be underestimated.

Methods. We used the National Surgical Quality Improvement Program (NSQIP) database 2005-2010 to assess the in-hospital and post discharge rate of any stroke, death, cardiac event (new Q-wave MI or cardiac arrest), combined stroke/death and combined adverse outcome (S/D/CE) at 30 days following CEA. Multivariable analyses were used to identify predictors for in-hospital and post discharge events separately, and in particular, those that predict post discharge events distinctly.

Results. A total of 35,916 patients who underwent CEA during 2005-2010 were identified in the NSQIP database. 59% were male (median age 72 years) and 44% had a previous neurologic event. Thirty-day stroke rate was 1.6% (n=591), death rate was 0.8% (n=272), cardiac event rate was 1.0% (n=350), stroke or death rate was 2.2% (n=794) and combined S/D/CE rate was 2.9% (n=1043). 33% of strokes, 53% of deaths, 32% of cardiac events, 40% of combined stroke/death and 38% of combined S/D/CE took place after hospital discharge. Patients with a prior stroke or TIA had similar proportions of post discharge events as compared to patients without prior symptoms. Independent predictors for post discharge events, but not for in-hospital events were female gender (stroke [OR 1.6, 95% CI 1.2-2.1] and stroke/death [OR 1.4, 95% CI 1.1-1.7]), renal failure (stroke [OR 3.0, 95% CI 1.4-6.2]) and COPD (stroke/death [OR 1.8, 95% CI 1.4-2.4] and S/D/CE [OR 1.8, 95% CI 1.4-2.3]).

Conclusions. With 38% of perioperative adverse events after CEA happening post hospitalization, regardless of symptoms status, we need to be alert to the ongoing risks after discharge particularly in women, patients with renal failure, or a history of COPD. This emphasizes the need for reporting and comparing 30-day adverse event rates when evaluating outcomes for CEA, or comparing carotid stenting to CEA.

INTRODUCTION

The benefit of carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS) is highly influenced by the rate of perioperative adverse events, defined as stroke, myocardial infarction (MI), or mortality up to 30-days after the procedure. Many studies reporting and comparing perioperative complication rates following carotid revascularization rely on state and nation-wide registries, which only include in-hospital data.[1-3] However, procedure related complications and mortality after revascularization procedures might also take place after hospital discharge. Results from the Society for Vascular Surgery Vascular Registry suggest that in-hospital events do not reflect the full procedural event rate after CAS and CEA, as an additional 31% and 22% of combined adverse events, respectively, occurred after discharge from the hospital.[4] However, in that analysis less than 50% of the total patients completed 30-day follow up, and thus these estimates may under- or overestimate the true event rates. Others have suggested that 10-37% of strokes took place after discharge, but these studies are limited by small study size or incomplete follow-up.[5, 6] Also, these analyses did not include adverse outcomes after CEA other than stroke. In order to compare and evaluate outcomes of CEA and CAS, it seems crucial to report 30-day outcome. For patients, it is important to understand the true operative risk they are facing when deciding whether to undergo CEA. Those patients who are at high risk to develop procedural related events after discharge might benefit from closer surveillance after discharge and possibly changes in management. Different preoperative patient characteristics may be related to the timing of events. Our objective was to assess the in-hospital and post discharge rate of adverse events following CEA in a 100% follow-up cohort at 30 days and to identify independent predictors for the timing of these events.

METHODS

Database. Data were obtained from medical records of patients undergoing CEA between 2005-2010 in the American College of Surgeon's (ACS) National Surgical Quality Improvement Program (NSQIP) database. The NSQIP is a multicenter, prospective quality-improvement registry that includes academic and private U.S. hospitals. In 2005, 37 institutions participated in the program, and the number has increased to 258 by 2010. Demographics, preoperative risk factors, intraoperative variables, and 30-day postoperative mortality and morbidity outcomes are collected, validated, and submitted by a trained and audited surgical clinical nurse-reviewer designated by the ACS. No specific procedural information on CEA (such as reconstruction technique, shunt use, type of artery closure or neurologic monitoring) is captured by the current iteration of NSQIP. Postsurgical data are obtained for the entire 30-day time period, regardless of whether the patient is discharged to the outpatient setting before this time. A detailed description of the NSQIP study methods has been previously published and validated.[7] The NSQIP data are subject to annual auditing and the reliability of accurate data acquisition has improved with each year.[8]

Patient selection. The NSQIP database was queried to identify patients undergoing CEA between 2005 and 2010 using the Current Procedural Terminology (CPT) codes 35301 and 35390. Cases were selected in which CEA was the primary procedure. Patients undergoing concurrent cardiac surgery were excluded. The remaining procedure data were searched to ensure that no other

major procedure was included. Indication for surgery (symptom status and degree of stenosis) is not available in the database. Therefore, we were not able to formally stratify patients by symptom status. However, NSQIP captures a history of a previous neurologic event (stroke, TIA) and hemiplegia, without the timing and laterality of these events. This variable was used to distinguish patients who were clearly asymptomatic (ASX) from those who had previous neurological symptoms (SXS). Recent work from our group showed that those with prior SXS were most likely to be symptomatic.[9]

Endpoints and Measurements. Our primary endpoint was the development of stroke, death, or a cardiac event within 30 days after CEA. Stroke was defined as the development of an embolic, thrombotic, or hemorrhagic vascular accident or stroke with motor, sensory, or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory) that persists for 24 or more hours. A cardiac event was defined as a new Q-wave myocardial infarction on ECG or cardiac arrest that necessitated cardiopulmonary resuscitation. Our secondary endpoint was wound infection, defined as either involving the carotid artery, deep (involving deep soft tissues e.g., fascia and muscle layers of the incision) or a superficial surgical site infection (limited to skin and subcutaneous).
Results were stratified for the in-hospital period (intra-operative or pre-discharge) and the post discharge period through 30-days after surgery. Timing to adverse event was recorded per day, starting from the day of surgery (day 0). The proportion of post discharge events was analyzed for both patients with a history of neurologic symptoms and patients without a history of neurologic symptoms. For in-hospital analysis, patients with post discharge events were excluded. Likewise, for post discharge events, patients with in-hospital events were excluded. If patients suffered both in hospital and post discharge events, the in-hospital event was counted for analysis. Predictor variables for the primary outcome included demographics and preoperative variables. Continuous variables were categorized for the purpose of this study. Detailed definitions of these variables are listed in the Appendix.

Statistical Analysis. Bivariate analysis was carried out to assess the relation of the preoperative variables with the primary outcome (stroke, death, cardiac event or a composite of stroke/death and S/D/CE) at the different time points (in-hospital, post-discharge, 30-day) using Pearson $\chi 2$ test and Fisher's exact test. Initial bivariate analysis included 29 preoperative demographic and comorbidity variables. Multivariable logistic regression was used to assess independent risk factors for outcome events at each of the above specified time points. Demographics and preoperative variables were entered into the multivariable regression analysis if $P < .2$ in bivariate analysis. Associations were calculated using backward elimination procedure, in which all variables were entered in the first step and removed stepwise based on the highest non-significant P-value ($P \geq 0.05$). After carrying out this iterative process, covariates were included in the final model if predictive of primary outcome events in any of the three specified clinical time intervals with this model demonstrating the contribution of each covariate to timing of events. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Hosmer and Lemeshow test was used to test the goodness of fit in each model. Statistical analysis was performed using SPSS version 19.0 statistical software (SPSS Inc, Chicago Illinois, USA).

Table I Demographics and clinical characteristics of 35,916 patients undergoing carotid endarterectomy

	N or Median	% or (IQR)		N or Median	% or (IQR)
Demographics			Alcohol use > 2 eh/day	1557	4.3
Age, y	72	(13)	BMI		
Age			< 18.5	537	1.5
< 60 y	5123	14.4	18.5 – 24.9	9507	26.5
60 – 69 y	11283	31.8	25 – 29.9	13814	38.5
70 – 80 y	13226	37.3	30 – 34.9	7470	20.8
> 80 y	5871	16.5	35 – 40	2687	7.5
Gender			≥ 40	1154	3.2
Male	21184	59.1	Height		
Female	14657	40.9	< 64 inch	12040	34
Race, non-white	3046	8.5	64 – 70 inch	14750	41.6
Clinical characteristics			> 70 inch	8636	24.4
Redo CEA	82	0.2	Renal failure	476	1.3
Hx stroke/ hemiplegia	8936	24.9	Hx of COPD	3792	10.6
Hx of TIA	9954	27.7	Dyspnea	6847	19.1
Hx of Angina or MI	1364	3.8	Steroid use	747	2.1
Congestive Heart Failure	371	1	Hx of revascularization for PVD	3499	9.7
Previous PCI	6710	18.7	Restpain/gangrene	344	1
Previous Cardiac Surgery	8196	22.8	Functional status		
Diabetes Mellitus	9984	27.8	Independent	33952	94.5
Hypertension	30658	85.4	Dependent	1961	5.5
Current smoker	10033	27.9	Emergency procedure	614	1.7
Hx of smoking			ASA class > 3	4753	13.2
<10 pack-y	11161	32.3	General anesthesia	30184	84.1
10 – 29 pack-y	4939	13.8	Vascular surgeon	34019	94.7
30 – 49 pack-y	3726	10.4	PGY level ≤ 3	4152	11.6
50 – 70 pack-y	3517	9.8			
> 70 pack-y	2921	8.1			

Hx, history, TIA, transient ischemic attack, MI, myocardial infarction, PCI, percutaneous coronary intervention, BMI, Body Mass Index; COPD, chronic obstructive pulmonary disease, PVD, peripheral vascular disease, ASA, American Society of Anesthesiologists; PGY, post-graduate year of resident

Table II Outcome and timing of in-hospital, post discharge and 30-day events of 35,916 patients undergoing carotid endarterectomy

	Time to event, days		In-hospital event rate	Post discharge event rate	30-Day event rate	Proportion of events that occurred after discharge
	Median, IQR	Mean ± SD	N (%)	N (%)	N (%)	
All patients						
Stroke	1, 6	4.5 ± 6.6	396 (1.1)	195 (0.5)	591 (1.6)	33%
Death	8.5, 14	11.2 ± 8.6	128 (0.4)	144 (0.4)	272 (0.8)	53%
Cardiac event	NA	NA	238 (0.7)	112 (0.3)	350 (1.0)	32%
Stroke/Death	NA	NA	480 (1.3)	320 (0.9) [a]	794 (2.2)	40%
Stroke/Death/Cardiac event	NA	NA	656 (1.8)	399 (1.1) [b]	1043 (2.9)	38%
Patients with a prior neurological event						
Stroke	2, 6	4.6 ± 6.4	249 (1.6)	127 (0.8)	376 (2.4)	34%
Death	9, 15	11.8 ± 8.7	81 (0.5)	86 (0.5)	167 (1.1)	52%
Cardiac event	NA	NA	126 (0.8)	56 (0.4)	182 (1.1)	31%
Stroke/Death	NA	NA	302 (1.9)	201 (1.3)	497 (3.1)	40%
Stroke/Death/Cardiac event	NA	NA	387 (2.4)	238 (1.5)	616 (3.9)	39%
Asymptomatic patients						
Stroke	1, 6	4.5 ± 6.9	147 (0.7)	68 (0.3)	215 (1.1)	32%
Death	8, 8	10.5 ±8.2	47 (0.2)	58 (0.3)	105 (0.5)	55%
Cardiac event	NA	NA	112 (0.6)	56 (0.3)	168 (0.8)	33%
Stroke/Death	NA	NA	178 (0.9)	119 (0.6)	297 (1.5)	40%
Stroke/Death/Cardiac event	NA	NA	269 (1.3)	161 (0.8)	427 (2.1)	38%

IQR, Interquartile range, SD, Standard deviation, N, Number of patients experiencing the events, Na, data not available
[a] 6 patient died post discharge after having an in-hospital stroke [b]12 patients experienced a secondary post discharge event, after having an in-hospital stroke (N=6) or cardiac event (N=6)

Table III Independent preoperative predictors for in-hospital, post discharge and 30-day stroke

	In-hospital			Post discharge			30 – Day		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Female	1.0	0.8 – 1.3	0.9	1.6	1.2 – 2.1	<.01	1.2	0.99 – 1.4	0.06
Age <60 years [a]	1.2	0.9 – 1.7	0.1	1.5	0.99 – 2.2	0.07	1.3	1.04 – 1.7	0.03
Redo CEA	3.3	1.03 – 10.6	0.05	2.4	0.3 – 17.2	0.4	3.0	1.1 – 8.2	0.04
Hx of stroke/hemiplegia	1.9	1.5 – 2.3	<.001	2.3	1.7 – 3.1	<.001	2.0	1.7 – 2.4	<.001
Hx of TIA	1.4	1.2 – 1.8	<.01	1.5	1.1 – 2.1	<.01	1.5	1.2 – 1.7	<.001
Hx of angina/MI	1.6	1.04 – 2.4	0.03	1.7	1.0 – 3.1	0.06	1.6	1.2 – 2.3	<.01
Renal failure	1.0	0.4 – 2.2	0.9	3.0	1.4 – 6.2	<.01	1.5	0.9 – 2.7	0.1
Underweight [b]	2.3	1.3 – 4.1	<.01	0.9	0.3 – 2.9	0.8	1.8	1.1 – 3.0	0.03
Obesity class II [b]	1.5	1.01 – 2.1	0.05	0.9	0.5 – 2.0	0.6	1.3	0.9 – 1.7	0.2
Functional status, dependent [c]	1.6	1.2 – 3.2	<.01	1.4	0.9 – 2.3	0.2	1.7	1.3 – 2.2	<.001
Emergency procedure	1.9	1.1 – 3.2	0.01	0.9	0.3 – 2.4	0.8	1.5	0.99 – 2.5	0.05
ASA class > 3	1.4	1.1 – 1.8	0.02	1.2	0.8 – 1.7	0.4	1.3	1.1 – 1.6	0.02

OR, Odds Ratio, CI, Confidence Interval, CEA, carotid endarterectomy, Hx, history, TIA, transient ischemic attack, MI, myocardial infarction, ASA, American Society of Anesthesiology [a] vs. 60-70 yr [b] vs. normal weight [c] vs. independent

RESULTS

A total of 35,916 patients undergoing CEA between 2005 and 2010 in the NSQIP database were identified and included for analysis. The median age was 72 years (Interquartile Range [IQR] 13), 59.1% were men, and 44.1% had a history of stroke, TIA or hemiplegia. Demographics, clinical characteristics and operative details are shown in Table I.

Stroke rate at 30-days was 1.6% (n=591, prior neurologic SXS: 2.4%, ASX 1.1%, P <.001, OR 2.25 95% CI 1.89-2.66), death rate was 0.8% (n=272, prior neurologic SXS 1.1%, ASX 0.5%, P<.001, OR 2.03 95% CI 1.59-2.59) and cardiac event rate was 1.0% (n=350, prior neurologic SXS 1.1%, ASX 0.8%, P = .003, OR 1.38 95% CI 1.12-1.70). Combined stroke/death rate was 2.2% (n= 794, prior neurologic SXS: 3.1% vs. ASX 1.5%, P<.001, OR 2.16 95% CI 1.87-2.50) and combined S/D/CE rate was 2.9% (n=1043, prior neurologic SXS 3.9%, ASX 2.1%, P <.001, OR 1.86, 95% CI 1.64-2.11). The median length of hospital stay was 1 day (IQR 1).

Timing of events. In-hospital S/D/CE occurred in 656 patients (1.8%). After discharge, an additional 38% of S/D/CE (n=399, 1.1%) occurred: 33% of strokes (n=195, 0.5%), 53% of deaths (n=144, 0.4%), 32% of cardiac events (n=122, 0.3%) and 40% of stroke/death (n=320, 0.9%) occurred after discharge. The proportion of combined S/D/CE after discharge was similar in patients with prior neurological symptoms versus those without (39% and 38%, respectively). Post discharge, stroke happened in 34% of patients with prior neurologic symptoms, and in 32% of ASX patients. 52% of deaths, 31% of cardiac events and 40% of stroke/death occurred after discharge in patients with prior neurologic symptoms, versus 55% of deaths, 33% of cardiac events and 40% of stroke/death in ASX patients. (Table II) In-hospital adverse events happened at a median of 1 day (IQR 1). These patients were discharged from the hospital at a median of 7 days (IQR 8) postoperatively. Patients who experienced post discharge events were discharged at day one (median) post operatively (IQR 1). Post discharge stroke occurred at a median of 8 days after the operation (IQR 11). (Figure) MI or cardiac arrest (cardiac events) after discharge took place at a median of 6 days (IQR 17) and 11 days (IQR 19), respectively. Patients who survived to discharge but did not survive the post discharge period, died at a median interval of 11 days (IQR 15).

Thirty-day wound infection rate was 0.5% (N=197). The majority of wound infections took place after discharge; 94% of superficial wound infection (N=141, 0.4%), 94% of deep wound infection (N=47, 0.1%) and 89% of carotid infection (N=9, 0.03%).

Predictors for stroke. *In-hospital.* Independent predictors for in-hospital stroke were redo-CEA, a history of stroke/hemiplegia, history of TIA, history of angina/MI, underweight (versus normal weight) and obesity class II (versus normal weight) , functional dependent status (versus independent), emergency procedures and ASA class >3. (Table III)

Post discharge. History of stoke/hemiplegia, history of TIA, renal failure and female gender were associated with increased risk of post discharge stroke on multivariable analyses. (Table III) Women were more likely to have a post discharge stroke than men (38.1% vs. 29.0%, OR 1.57, 95% CI 1.18 – 2.09, P =0.002). In patients with a previous neurological event, a significantly higher stroke rate was seen in women compared to men (1.0% vs. 0.7% P = 0.02, OR 1.5, 95% CI 1.1 – 2.1). In ASX patients, the stroke rate was again higher in women with a similar odds

ratio, however this did not reach statistical significance (0.4% vs. 0.3%, P=0.08, OR 1.6, 95% CI 0.97 – 2.5). Stroke in woman took place at a median of 2 days (IQR 6), compared to 1 day (IQR 6) in men (P =0.4). Stroke in patients with renal failure took place at a median of 7 days (IQR 9) after discharge, compared to 1 day (IQR 6) in patients without renal failure (P<.001). Female gender and renal failure were both predictive for post discharge stroke in multivariable analysis, but not for in-hospital stroke. (Table III)

Predictors for stroke or death. *In-hospital*. In multivariable analysis, age>80 year, history of stroke/hemiplegia, history of TIA, history of angina/MI, renal failure, history of revascularization for peripheral vascular disease (PVD), dependent functional status, emergency procedures and ASA class >3 were independent predictors for stroke or death. (Table IV)
Post discharge. Female gender, history of stroke/hemiplegia, history of angina/MI, renal failure, COPD and dependent functional status were independently associated with post discharge stroke or death. Female gender and COPD were predictive for post discharge stroke/death, but not for in-hospital events. (Table IV)

Predictors for other adverse events. A history of COPD or dyspnea was predictive for post discharge and 30-day death, but not for in-hospital death. (Table V, available online) For cardiac events, no differential predictors were identified in the post discharge time period compared to in-hospital time frame. (Table VI, available online) As was seen with death and stroke/death, patients with a history of COPD were at increased risk for post discharge and 30-day combined S/D/CE, but not for in-hospital adverse events. (Table VII, available online). Although the risk factors identified for post discharge events (but not for in-hospital outcome) predicted different endpoints, the cumulative effect of these risk factors (female gender, renal failure and COPD) is shown in table VIII (online appendix) for all different time points. Patients undergoing emergency procedures were at increased risk for all in-hospital events, but not for post discharge events. All independent predictors for death (Table V), cardiac events (Table VI) and combined S/D/CE (Table VII) with respect to the different time intervals are available as an online supplement.

DISCUSSION

In a large number of patients among both community and academic institutions in the United States, carotid endarterectomy was performed with very low complication rates for stroke, death or cardiac events (MI or cardiac arrest). Approximately one third of procedural related events occur after discharge from the hospital. This was true for both patients with prior neurologic symptoms and for those who were asymptomatic. In this study we identified predictors for post discharge events, which have not previously been reported. We found that independent predictors for post discharge events, but not for in-hospital events were female gender (stroke and stroke/death), renal failure (stroke) and COPD (death, stroke/death and S/D/CE).
Previously, Sidawy et al.[4] described the occurrence of adverse events happening after discharge but within 30-days of revascularization. For CAS they found that 31% of combined strokes/deaths or MI's were not captured during hospital admission; for CEA 28% of events were missed when only analyzing in-hospital data. Although less than half of patients in that analysis had 30-day

follow-up, our results confirm these estimates in a 100% follow-up cohort. Most administrative vascular registries do not include post discharge events. The results of this study indicate that this may be a confounding feature for many studies based on such datasets.[1-3, 10] It is well known that that hospital administrative data are not reliable to estimate non-fatal operative complication rates for surgical procedures in general.[11] Recently, the reliability of administrative data to determine outcomes specifically for carotid revascularization procedures was questioned.[9, 12]

Consistent entry of data beyond the in-hospital period seems to be not only important for true perioperative event risk estimation, but also to identify patients at risk for adverse perioperative events. Registries such as the NSQIP are critical to evaluate rare events such as postoperative stroke after CEA since single surgeon or single center experience are typically underpowered to evaluate procedures with low event rates. Our results demonstrate that in a subgroup of patients adverse events are more likely to happen after discharge, possibly influencing preoperative counseling and perioperative management. The timing of strokes suggests that some may be due to hyperperfusion and subsequent intracerebral hemorrhage.[13, 14] Intracerebral hemorrhage occurs at unpredictable intervals in the postoperative course and its mechanism remains unclear. Previous analyses identified high-grade stenosis and severe intra- or postoperative hypertension as possible risk factors.[13] Better blood pressure control and perhaps selective transcranial Doppler monitoring might benefit these patients.[15] 'Late' stroke might also occur due to thrombo-embolism[13] in patients who do not respond to anti-platelet therapy. Preoperative testing for antiplatelet responsiveness may identify subgroups at risk that may benefit from additional antiplatelet medication. Unfortunately, the type and laterality of post-operative stroke is not captured in the NSQIP. Future research efforts should evaluate the mechanism of post-operative stroke to guide further changes in perioperative management.

In our study we found that stroke in women seems to happen more frequently after discharge. Studies based on in-hospital results did not find differences in stroke and death rates after CAS and CEA in relation to gender.[10, 16] However, several others have also identified women as a subgroup of patients at higher risk for 30-day adverse outcome after CEA.[6, 17] Especially for asymptomatic women, the benefit of surgery may be less than that for men.[18, 19] In our analyses, the difference between men and woman in post discharge events was identified for both those with, and without a previous neurological event, although this did not quite reach statistical significance for asymptomatic patients. Gender differences in outcome of CEA are still not well understood and merit further investigation.[20, 21] Renal failure was also an independent predictor for post discharge stroke, but not for in-hospital or 30-day stroke. Two studies based on NSQIP data[6, 22] found that impaired renal function was an independent risk factor for mortality and cardiac and pulmonary morbidity after CEA, but was not associated with increased risk of neurologic complications at 30-days, which was consistent with our results. Also other reports have suggested that renal failure is a risk factor for increased stroke risk and a marker for advanced atherosclerotic disease causing morbidity and mortality.[23-25]

Several authors have reported risk factors associated with adverse outcome after CEA in order to identify high-risk groups and optimize management of patients with carotid artery disease.[5, 6, 18, 26, 27] Similar to prior reports we found that symptom status was a consistent predictor for adverse events (both in-hospital and post discharge), and that a history of preoperative stroke was more predictive than a history of TIA.[27, 28] Among other risk factors for only in-hospital

or both in-hospital and post discharge outcome, we identified several patient characteristics previously described by others, including diabetes[26, 27] and age >80 [27, 29]. Interestingly, we found that patients with redo-CEA had increased risk for in-hospital stroke, whereas others did not[30, 31] or only identified increased risk for local complications such as cranial nerve injury.[32] However, these studies might not have detected a difference due to low event rates and small sample sizes. Adequately powered studies are needed to define optimal treatment in these patients. Under- and overweight patients had increased risk for stroke, suggesting that obesity is not only a risk factor for mortality,[33, 34] but also for morbidity after CEA. This obesity paradox has been previously identified with vascular surgery procedures with a reverse J-shaped relation of BMI and adverse outcome, with the highest risk in the underweight and morbidly obese extremes, and the lowest rates in the overweight and mildly obese patients.[33-36] Not surprisingly and consistent with previous literature,[5, 27, 37] emergent procedures were predictive for all in-hospital adverse outcomes. This increased risk was, however, not persistent after discharge. This is understandable as most emergent procedures would be presumed to be performed for either stroke-in-evolution or crescendo TIA.[28, 38]

This study has several limitations. NSQIP does not define preoperative symptom status in the same manner as most clinical trials.[6] Although a recent report from our group showed that NSQIP does identify symptomatic patients with a high sensitivity, the number of false positives was about 25% (due to stroke or TIA occurring > 6 months prior to surgery or contralateral to the CEA).[9] Therefore, we were only able to stratify the analysis regarding timing of events for patients with and without a previous neurological event and accounted for these symptoms individually in multivariable prediction models. However, importantly, we did not find a difference in the occurrence of post-discharge stroke in those who were clearly asymptomatic compared to a group who had pre-operative neurologic events, the vast majority of which were likely within 6 months of and ipsilateral to their CEA. Another limitation inherent to this database is the lack of anatomical preoperative factors such as history of previous neck radiation, degree of stenosis, or radical neck dissection. Also, the retrospective nature of the data may introduce a selection bias, which might have influenced the results. Because non-fatal cardiac events proved to have a strong effect on patient survival, we included cardiac events as one of our primary outcome measures. Our definition of a cardiac event will capture both cardiac arrest and new Q-wave MI on ECG, but is somewhat limited by the NSQIP database because patients with ST-elevation MI (troponin leak) will be missed. Lastly, CAS procedures are not yet included in the NSQIP, but will be in the future allowing comparison of the two procedures.

Conclusion. With 38% of perioperative adverse events after CEA happening post hospitalization, regardless of symptom status, surgeons should be alert to the ongoing risks after discharge particularly in women and patients with renal failure or a history of COPD. For research and quality improvement purposes, the full 30-day adverse event rates should be reported and compared when evaluating CEA or comparing CAS and CEA.

Table IV Independent preoperative predictors for in-hospital, post discharge and 30-day stroke or death

	In-hospital			Post discharge			30 – Day		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Female	1.1	0.9 – 1.3	0.4	1.4	1.1 – 1.7	<.01	1.2	1.03 – 1.4	0.02
Age < 60 [a]	1.1	0.9 – 1.6	0.2	1.4	0.96 - 1.9	0.09	1.3	1.01 – 1.6	0.05
Age > 80 [a]	1.4	1.1 – 1.8	0.01	1.3	0.9 – 1.9	0.09	1.4	1.1 – 1.7	<.01
Hx of stroke/hemiplegia	1.8	1.5 – 2.2	<.001	2.0	1.5 – 2.5	<.001	1.9	1.6 – 2.2	<.001
Hx of TIA	1.3	1.04 – 1.5	0.02	1.3	0.99 – 1.6	0.05	1.3	1.1 – 1.5	<.01
Hx of Angina/MI	1.9	1.4 – 2.7	<.001	1.6	1.1 – 2.6	0.03	1.8	1.4 – 2.4	<.001
Renal failure	2.1	1.3 – 3.4	<.01	3.2	1.9 – 5.5	<.001	2.5	1.7 – 3.6	<.001
Hx of COPD	1.2	0.9 – 1.5	0.3	1.8	1.4 – 2.4	<.001	1.4	1.2 – 1.7	<.01
Hx of PVD	1.5	1.1 – 2.0	<.01	1.3	0.9 – 1.9	0.1	1.4	1.2 – 1.8	<.001
Functional status, dependent [b]	2.2	1.7 – 2.9	<.001	1.6	1.2 – 2.4	<.01	2.0	1.6 - 2.5	<.001
Emergency procedure	2.7	1.8 – 3.9	<.001	0.6	0.2 – 1.5	0.3	1.9	1.3 – 2.7	<.01
ASA class > 3	1.6	1.3 – 2.0	<.001	1.3	0.99 – 1.8	0.06	1.5	1.3 – 1.8	<.001

OR, Odds Ratio, CI, Confidence Interval, Hx, history, TIA, transient ischemic attack, MI, myocardial infarction, COPD, chronic obstructive pulmonary disease, PVD, peripheral vascular disease, ASA, American Society of Anesthesiology [a] vs. 60-70 yr [b] vs. independent

Table V Independent preoperative predictors for in-hospital, post discharge and 30-day death

	In-hospital			Post discharge			30 – Day		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Female	1.1	0.8 – 1.6	0.7	1.2	0.8 – 1.7	0.3	1.1	0.9 – 1.5	0.3
Age > 80 [a]	2.5	1.5 – 4.2	<.001	2.4	1.5 – 3.8	<.001	2.4	1.7 – 3.5	<.001
Hx of stroke/hemiplegia	1.7	1.1 – 2.5	.01	1.7	1.2 – 2.5	<.01	1.7	1.3 – 2.2	<.001
Hx of Angina/MI	2.8	1.6 – 4.7	<.001	1.1	0.5 – 2.2	0.8	1.9	1.2 – 2.9	<.01
Renal failure	5.7	3.1 – 10.3	<.001	3.0	1.4 – 6.4	<.01	4.3	2.7 – 6.9	<.001
Hx of CHF	1.7	0.8 – 3.6	0.2	2.0	0.9 – 4.5	0.1	1.9	1.02 – 3.2	0.04
Dyspneu	1.3	0.9 – 2.1	0.2	1.7	1.1 – 2.5	<.01	1.5	1.2 – 2.0	<.01
Hx of COPD	1.4	0.9 – 2.3	0.1	2.5	1.6 – 3.7	<.001	1.9	1.4 – 2.6	<.001
Hx of PVD	1.9	1.1 – 3.0	.01	1.8	1.2 – 2.8	.01	1.8	1.3 – 2.5	<.001
Functional status, dependent [b]	3.6	2.4 – 5.6	<.001	2.0	1.2 – 3.3	<.01	2.8	2.0 – 3.8	<.001
Emergency procedure	5.4	3.0 – 9.5	<.001	0.4	0.1 – 2.5	0.3	2.9	1.7 – 4.8	<.001
ASA class > 3	2.8	1.8 – 4.1	<.0001	1.4	0.9 – 2.1	<.01	1.9	1.4 – 2.5	<.001

OR, Odds Ratio, CI, Confidence Interval, Hx, history, MI, myocardial infarction, CHF, congestive heart failure, COPD, chronic obstructive pulmonary disease, PVD, peripheral vascular disease, ASA, American Society of Anesthesiology [a] vs. 60-70 yr [b] vs. independent

Table VI Independent preoperative predictors for in-hospital, post discharge and 30-day cardiac events

	Inhospital			postdischarge			30 – Day		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Female	1.1	0.8 – 1.4	0.5	0.9	0.6 – 1.4	0.7	1.0	0.8 – 1.3	0.7
Race non-white[a]	1.6	1.1 – 2.4	0.01	1.2	0.6 – 2.2	0.6	1.5	1.1 – 2.1	0.02
Age > 80[b]	2.7	1.8 – 3.8	<.001	2.0	1.2 – 3.3	<.01	2.4	1.8 – 3.3	<.001
Hx of stroke/hemiplegia	1.5	1.1 – 2.0	<.01	1.2	0.8 – 1.8	0.3	1.4	1.1 – 1.8	<.01
Hx of angina/MI	3.4	2.3 – 5.0	<.001	1.9	0.9 – 3.6	0.07	2.8	2.0 – 4.0	<.001
Diabetes	1.7	1.3 – 2.3	<.001	1.2	0.8 – 1.8	0.4	1.5	1.2 – 1.9	<.001
Renal failure	2.1	1.1 – 4.1	0.03	2.7	1.2 – 6.4	0.02	2.3	1.3 – 3.9	<.01
Dyspnea	1.4	1.04 – 1.9	0.02	1.6	1.02 – 2.4	0.04	1.5	1.1 – 1.9	<.01
Hx of PVD	1.8	1.3 – 2.5	<.01	1.6	0.97 – 2.7	0.07	1.7	1.3 – 2.3	<.001
ASA > 3	1.6	1.2 – 2.2	<.01	2.2	1.4 – 3.3	<.001	1.8	1.4 – 2.3	<.001
Emergency	2.5	1.4 – 4.7	<.01	0.9	0.2 – 3.7	0.9	2.0	1.1 – 3.5	0.02

Adjusted for gender. OR, Odds Ratio, CI, Confidence Interval, Hx, history, MI, myocardial infarction, PVD, peripheral vascular disease, ASA, American Society of Anesthesiology [a] vs. white [b] vs. 60-70 yr

Table VII Independent preoperative predictors for in-hospital, post discharge and 30-day stroke, death or cardiac events

	In-hospital			Post Discharge			30 – Day		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Female	1.1	0.9 – 1.3	0.2	1.2	0.97 – 1.5	0.08	1.1	1.01 – 1.3	0.05
Age > 80[a]	1.7	1.3 – 2.1	<.001	1.6	1.2 – 2.1	<.01	1.6	1.4 – 2.0	<.001
Redo CEA	3.2	1.3 – 8.0	.02	1.2	0.2 – 8.5	0.9	2.4	1.04 – 5.7	0.04
Hx of stroke/hemiplegia	1.7	1.4 – 2.0	<.001	1.7	1.4 – 2.2	<.001	1.7	1.5 – 1.9	<.001
Hx of TIA	1.2	0.9 – 1.4	0.06	1.3	1.01 – 1.6	0.04	1.2	1.1 – 1.4	<.01
Diabetes	1.2	1.03 – 1.4	0.02	1.0	0.8 – 1.3	0.7	1.2	1.01 – 1.3	0.04
Hx of angina/MI	2.3	1.8 – 3.0	<.001	1.7	1.2 – 2.6	<.01	2.1	1.7 – 2.6	<.001
Renal failure	1.8	1.2 – 2.9	<.01	3.0	1.8 – 5.0	<.001	2.5	1.7 – 3.6	<.001
Hx of COPD	1.1	0.9 – 1.4	0.4	1.8	1.4 – 2.3	<.001	1.3	1.1 – 1.6	<.01
Hx of PVD	1.5	1.2 – 1.9	<.01	1.3	0.98 – 1.8	0.06	1.4	1.2 – 1.7	<.001
Functional status, dependent[b]	1.9	1.5 – 2.4	<.001	1.6	1.1 – 2.2	<.01	1.8	1.3 – 2.5	<.001
Emergency procedure	2.5	1.8 – 3.6	<.001	0.6	0.2 – 1.5	0.3	1.8	1.3 – 2.5	<.001
ASA class > 3	1.5	1.3 – 1.9	<.001	1.5	1.2 – 1.9	<.01	1.5	1.3 – 1.8	<.001

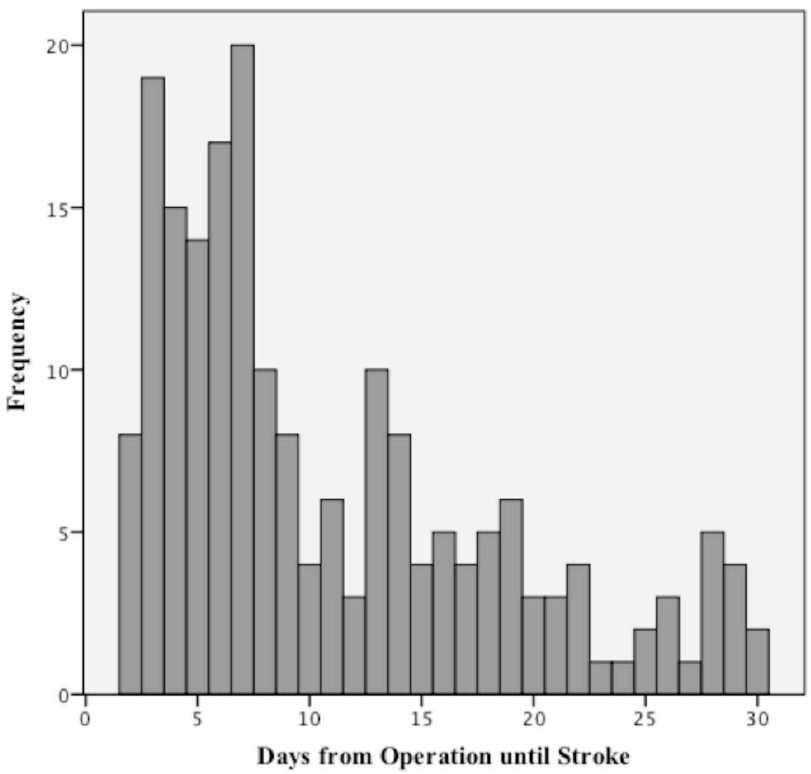
OR, Odds Ratio, CI, Confidence Interval, CEA, carotid endarterectomy, Hx, history, TIA, transient ischemic attack, MI, myocardial infarction, COPD, chronic obstructive pulmonary disease, PVD, peripheral vascular disease, ASA, American Society of Anesthesiology [a] vs. 60-70 yr [b] vs. independent

Table VIII Cumulative risk for stroke and stroke or death in the high risk groups (female gender, renal failure and COPD)* for post discharge events

	Stroke			Stroke/Death		
# of risk factors	In-hospital	Post Discharge	30-Day	In-hospital	Post Discharge	30-Day
0	1.0%	0.4%	1.4%	1.2%	0.7%	1.8%
1	1.2%	0.7%	1.9%	1.5%	1.1%	2.6%
2	0%	2.5%	2.5%	3.5%	5.0%	8.5%
3[a]	0%	0%	0%	4.3%	4.3%	8.7%

*High risk group based on the independent predictors identified for post discharge events by multivariable models. [a] 23 patients with all three risk factors present

Figure Days from operation until post discharge stroke after carotid endarterectomy



References

1. Nolan BW, De Martino RR, Goodney PP, Schanzer A, Stone DH, Butzel D, et al. Comparison of carotid endarterectomy and stenting in real world practice using a regional quality improvement registry. *J Vasc Surg*. 2012;epub.
2. Eslami MH, McPhee JT, Simons JP, Schanzer A, Messina LM. National trends in utilization and postprocedure outcomes for carotid artery revascularization 2005 to 2007. *J Vasc Surg*. 2011;53:307-15.
3. Vogel TR, Dombrovskiy VY, Haser PB, Scheirer JC, Graham AM. Outcomes of carotid artery stenting and endarterectomy in the United States. *J Vasc Surg*. 2009;49:325-30.
4. Sidawy AN, Zwolak RM, White RA, Siami FS, Schermerhorn ML, Sicard GA. Risk-adjusted 30-day outcomes of carotid stenting and endarterectomy: Results from the SVS Vascular Registry. *J Vasc Surg*. 2009;49:71-9.
5. Goodney PP, Likosky DS, Cronenwett JL. Factors associated with stroke or death after carotid endarterectomy in Northern New England. *J Vasc Surg*. 2008;48:1139-45.
6. Kang JL, Chung TK, Lancaster RT, Lamuraglia GM, Conrad MF, Cambria RP. Outcomes after carotid endarterectomy: is there a high-risk population? A National Surgical Quality Improvement Program report. *J Vasc Surg*. 2009;49:331-8.
7. Fink AS, Campbell DA, Jr., Mentzer RM, Jr., Henderson WG, Daley J, Bannister J, et al. The National Surgical Quality Improvement Program in non-veterans administration hospitals: initial demonstration of feasibility. *Ann Surg*. 2002;236:344-53.
8. Shiloach M, Frencher Jr SK, Steeger JE, Rowell KS, Bartzokis K, Tomeh MG, et al. Toward Robust Information: Data Quality and Inter-Rater Reliability in the American College of Surgeons National Surgical Quality Improvement Program. *J Am Coll Surg*. 2009;210:6-16.
9. Bensley RP, Yoshida S, Lo RC, Fokkema M, Darling JD, Handam AD, et al. Accuracy of administrative versus clinical data to evaluate carotid endarterectomy and caritid stenting. *Manuscript under revision J Vasc Surg*. 2012.
10. Rockman CB, Garg K, Jacobowitz GR, Berger JS, Mussa FF, Cayne NS, et al. Outcome of carotid artery interventions among female patients, 2004 to 2005. *J Vasc Surg*. 2011;53:1457-64.
11. Best WR, Khuri SF, Phelan M, Hur K, Henderson WG, Demakis JG, et al. Identifying patient preoperative risk factors and postoperative adverse events in administrative databases: results from the department of veterans affairs national surgical quality improvement program. *J Am Coll Surg*. 2002;194:257-66.
12. Hertzer NR. The Nationwide Inpatient Sample may contain inaccurate data for carotid endarterectomy and carotid stenting. *J Vasc Surg*. 2011;55:263-6.
13. Riles TS, Imparato AM, Jacobowitz GR, Lamparello PJ, Giangola G, Adelman MA, et al. The cause of perioperative stroke after carotid endarterectomy. *J Vasc Surg*. 1994;19:206-16.
14. de Borst GJ, Moll FL, van de Pavoordt HD, Mauser HW, Kelder JC, Ackerstaf RG. Stroke from carotid endarterectomy: when and how to reduce perioperative stroke rate? *Eur J Vasc Endovasc Surg* 2001;21:484-9.
15. Pennekamp CW, Tromp SC, Ackerstaff RG, Bots ML, Immink RV, Spiering W, et al. Prediction of cerebral hyperperfusion after carotid endarterectomy with transcranial Doppler. *Eur J Vasc Endovasc Surg*. 2012;43:371-6.
16. Akbari CM, Pulling MC, Pomposelli Jr FB, Gibbons GW, Campbell DR, LoGerfo FW. Gender and carotid endarterectomy: Does it matter? *J Vasc Surg*. 2000;31:1103-9.
17. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJM. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *The Lancet*. 2004;363:915-24.
18. Calvillo-King L, Xuan L, Zhang S, Tuhrim S, Halm EA. Predicting Risk of Perioperative Death and Stroke After Carotid Endarterectomy in Asymptomatic Patients. *Stroke*. 2010;41:2786-94.
19. Rothwell PM, Goldstein LB. Carotid Endarterectomy for Asymptomatic Carotid Stenosis. *Stroke*.

2004;35:2425-7.
20. den Hartog AG, Algra A, Moll FL, de Borst GJ. Mechanisms of gender-related outcome differences after carotid endarterectomy. *J Vasc Surg*. 2010;52:1062-71.e6.
21. Bensley RP, Lo RC, Hurks R, Chaikof EL, Hamdan AD, Wyers MC, et al. Gender differences in presentation of patients undergoing CEA and CAS in VSGNE. *Manuscript in progress*. 2012.
22. Sidawy AN, Aidinian G, Johnson Iii ON, White PW, DeZee KJ, Henderson WG. Effect of chronic renal insufficiency on outcomes of carotid endarterectomy. *J Vasc Surg*. 2008;48:1423-30.
23. Kretz B, Abello N, Brenot R, Steinmetz E. The impact of renal insufficiency on the outcome of carotid surgery is influenced by the definition used. *J Vasc Surg*. 2010;51:43-50.
24. Hamdan AD, Pomposelli FB, Jr., Gibbons GW, Campbell DR, LoGerfo FW. Renal insufficiency and altered postoperative risk in carotid endarterectomy. *J Vasc Surg*. 1999;29:1006-11.
25. Stoner MC, Abbott WM, Wong DR, Hua HT, Lamuraglia GM, Kwolek CJ, et al. Defining the high-risk patient for carotid endarterectomy: an analysis of the prospective National Surgical Quality Improvement Program database. *J Vasc Surg*. 2006;43:285-95.
26. Tu JV, Wang H, Bowyer B, Green L, Fang J, Kucey D, et al. Risk Factors for Death or Stroke After Carotid Endarterectomy. *Stroke*. 2003;34:2568-73.
27. Halm EA, Tuhrim S, Wang JJ, Rockman C, Riles TS, Chassin MR. Risk Factors for Perioperative Death and Stroke After Carotid Endarterectomy. *Stroke*. 2009;40:221-9.
28. Bond R, Rerkasem K, Rothwell PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke*. 2003;34:2290-301.
29. Voeks JH, Howard G, Roubin GS, Malas MB, Cohen DJ, Sternbergh WC, et al. Age and Outcomes After Carotid Stenting and Endarterectomy. *Stroke*. 2011;42:3484-90.
30. de Borst GJ, Zanen P, de Vries J-PP, van de Pavoordt ED, Ackerstaff RG, Moll FL. Durability of surgery for restenosis after carotid endarterectomy. *J Vasc Surg*. 2008;47:363-71.
31. Hobson RW, 2nd, Goldstein JE, Jamil Z, Lee BC, Padberg FT, Jr., Hanna AK, et al. Carotid restenosis: operative and endovascular management. *J Vasc Surg*. 1999;29:228-35; discussion 35-8.
32. AbuRahma AF, Abu-Halimah S, Bensenhaver J, Nanjundappa A, Stone PA, Dean LS, et al. Primary carotid artery stenting versus carotid artery stenting for postcarotid endarterectomy stenosis. *J Vasc Surg*. 2009;50:1031-9.
33. Davenport DL, Xenos ES, Hosokawa P, Radford J, Henderson WG, Endean ED. The influence of body mass index obesity status on vascular surgery 30-day morbidity and mortality. *J Vasc Surg*. 2009;49:140-7.e1.
34. Mullen JT, Moorman DW, Davenport DL. The Obesity Paradox: Body Mass Index and Outcomes in Patients Undergoing Nonbariatric General Surgery. *Ann Surg*. 2009;250:166-72.
35. Reeves JG, Kasirajan K, Veeraswamy RK, Ricotta Ii JJ, Salam AA, Dodson TF, et al. Characterization of resident surgeon participation during carotid endarterectomy and impact on perioperative outcomes. *J Vasc Surg*. 2011;55:268-73.
36. Giles KA, Wyers MC, Pomposelli FB, Hamdan AD, Ching YA, Schermerhorn ML. The impact of body mass index on perioperative outcomes of open and endovascular abdominal aortic aneurysm repair from the National Surgical Quality Improvement Program, 2005-2007. *J Vasc Surg*. 2010;52:1471-7.
37. Musser DJ, Nicholas GG, Reed JF, 3rd. Death and adverse cardiac events after carotid endarterectomy. *J Vasc Surg*. 1994;19:615-22.
38. Rerkasem K, Rothwell PM. Systematic Review of the Operative Risks of Carotid Endarterectomyfor Recently Symptomatic Stenosis in Relation to the Timing of Surgery. *Stroke*. 2009;40:e564-e72.

CHAPTER NINE

The impact of the present on admission indicator on the accuracy of administrative data for carotid endarterectomy and stenting

Journal of Vascular Surgery
August 2013; Epub ahead of print

Authors
Margriet Fokkema[1], Rob Hurks[2], Rodney P. Bensley[1], Thomas Curran[1], Allen D. Hamdan[1], Mark C. Wyers[1], Frans L. Moll[2], Marc L. Schermerhorn[1]

Affiliations
Department of Surgery, Division of Vascular and Endovascular Surgery, [1]Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, [2]University Medical Center Utrecht, The Netherlands

ABSTRACT

Introduction. Administrative data are often hampered by coding errors, absent data, and the difficulty of distinguishing pre-existing conditions from perioperative complications. We evaluated whether the introduction of the present on admission (POA) indicator improved outcome analysis of carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS) using administrative data.

Methods. State inpatient databases from CA (2005-2008), NY (2008) and NJ (2008) were used to identify patients undergoing CAS and CEA. We first analyzed morbidity data without the POA indicator, using ICD-9 complication codes (eg 997.02, iatrogenic cerebrovascular infarction or hemorrhage, postoperative stroke) and diagnosis codes (eg 433.11, occlusion and stenosis of the carotid artery with cerebral infarction). Then we applied the POA indicator to both diagnosis and complication codes and calculated the proportion of events that were labeled POA. Symptom status and perioperative stroke rate were compared using these coding approaches.

Results. We identified 21,639 patients who underwent CEA and 3,688 patients who underwent CAS. Without the POA indicator, the complication code for stroke indicated a postoperative stroke rate of 1.4% for CEA and 2.4% for CAS. After applying the POA indicator, 54% (CEA) and 62% (CAS) of these strokes were labeled POA. These POA strokes were either preoperative or intraoperative events. Proportion of symptomatic patients ranged from 7 – 16% for CEA and from 5 – 22% for CAS. Perioperative stroke rate was the lowest in the POA method (1.1% CEA, 1.8% CAS) compared to two other methods without POA information (1.4% and 9.5% CEA and 2.4% and 16.4% CAS). Kappa indicated a poor (0.2) to fair (0.7) agreement between these approaches.

Conclusions. Administrative data has known limitations for assignment of symptom status and non-fatal perioperative outcomes. Given the uncertain timing of POA events as preoperative versus intraoperative and its apparent underestimation of the perioperative stroke rate, the use of administrative data even with the POA indicator for symptom status and non-fatal outcomes after CEA and CAS is hazardous.

INTRODUCTION

The use of administrative data to analyze population-based outcomes after carotid revascularization has recently been called into question.[1,2] Despite the benefit of large patient samples, administrative data are often hampered by coding errors, absent data, and the difficulty of distinguishing pre-existing conditions from post-operative complications. More specifically, stroke may be either the indication for revascularization of a symptomatic carotid stenosis, or an adverse event after carotid angioplasty and stenting (CAS) or carotid endarterectomy (CEA). Such misclassification may lead to under- or overestimating both the proportion of symptomatic patients and the number of perioperative complications. Previous comparisons of CAS and CEA utilizing administrative data have been further limited by a lack of standardized outcome definitions. While some reports considered only complication codes (eg 997.02 iatrogenic cerebral infarction or hemorrhage - postoperative stroke) to identify postoperative strokes, others included diagnosis codes (eg 434.11 cerebral embolism with cerebral infarction) as well.[3-5] A present on admission (POA) indicator has been developed to improve coding accuracy beyond the standard International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) diagnosis and complication codes. When the Centers for Medicare and Medicaid Services (CMS) implemented a new pay-for-performance policy in 2008, they mandated that all pre-existing diagnoses or conditions be identified as POA in patient discharge abstracts. Whereas hospitals would not be penalized for pre-existing conditions designated as POA, management of ten pre-specified hospital acquired conditions (stroke not included), those without a POA identifier, would be non-reimbursable and ineligible for contribution to higher reimbursement diagnosis related groups (DRG).[6] The refinement of administrative claims data through the addition of a POA indicator has been shown to improve the validity of surgical outcome measures, as investigated by prior studies.[7-10] However, the impact of the new POA methodology has not yet been evaluated for carotid interventions. Therefore we utilized the State Inpatient Databases (SID), which consist of inpatient hospital discharge abstracts in participating states (about 90% of all U.S. hospital discharges) translated into a uniform format containing a core set of clinical and nonclinical information on all patients, regardless of payer. Our aim was to investigate the impact of the POA indicator on administrative data in order to evaluate outcomes of CAS and CEA.

METHODS

Database. The SID from three states (California 2005-2008, New York 2008 and New Jersey 2008) was used to identify patients undergoing CEA and CAS. Database selection was made based upon data availability and sample size. Our inclusion criteria generated a study population >25,000 patients, which is comparable to other population based studies in the field.[11,12] The SID is a component of the Healthcare Cost and Utilization Project (HCUP) produced by the Agency for Healthcare Research and Quality (AHRQ) and captures all hospitalizations that occur in community and academic hospitals in the participating states.[13] Quality and comparison reports of the data are available online (http://www.hcup-us.ahrq.gov). Effective October 1, 2007, the Hospital Uniform Bill was enacted which set forth specific data requirements for hospital claims including a POA indicator for each diagnosis field. However, pioneering the practice in the

1990s, New York and California were early adopters of the POA indicator and required to report POA information in all in hospital discharge data as of that time. Thus, the POA indicator was a requirement for all included states during the study period. For the purposes of the POA indicator, hospitals code (using a uniform format across all states) any conditions the patient has at the time of inpatient admission as POA. Medical record documentation from any provider involved in the care and treatment of the patient may be used to support the determination of whether a condition was present on admission. Hospitals and other facilities are required to use a standardized set of requirements and definitions to report the POA indicator as delineated in the *Official UB-04 Data Specifications Manual and the ICD-9-CM Official Guidelines for Coding and Reporting*.

Data retrieval. The SID was queried for patient selection using both ICD-9-CM procedure and diagnosis codes. Patients undergoing CEA (38.12) and CAS (00.61, 00.63) were identified. Patients undergoing cardiac procedures during the same hospital stay were excluded (coronary artery bypass, cardiac valve repair, percutaneous coronary artery intervention or a diagnostic cardiac catheterization). To ensure accurate coding on POA information, patients were selected with at least one diagnosis listed as POA. ICD-9 diagnosis codes include a separate set of codes for *'Complications of surgical and medical care, not elsewhere classified'*. For the purpose of this manuscript we will refer to these codes as 'complication codes', as others have done previously.[1] We used all diagnosis and complication codes (in each diagnosis field) that potentially represent comorbidities or outcome following carotid revascularization, as specified in the Appendix A. Codes were obtained by a thorough review of the coding literature and include all codes that were previously used for carotid interventions.

Present on Admission (POA) Defined. Present on admission is defined as any condition present at the time the inpatient admission order is placed. For carotid revascularization procedures, POA codes can refer to different events depending on the specific order of events for a particular patient. If the patient is admitted to the hospital prior to carotid revascularization, a POA event refers to a preoperative, pre-hospital condition, e.g. a complication stroke coded as POA will refer to a symptomatic patient. However, when the inpatient order is written after the procedure (e.g. same day admission patients scheduled for elective procedures), a POA event most likely refers to an intraoperative event. In the latter scenario, it is unclear which event or condition was present before the operation and which events were complications during procedures.

Data analyses. For all patients undergoing CAS or CEA, frequencies and event rates for potential preadmission comorbidities and perioperative outcomes were calculated using diagnosis and complication codes without the application of the POA information. We then analyzed these rates in the presence of the POA information, which was applied on those same diagnosis and complication codes. The proportion of events that were POA and revised rates for each event were calculated, distinguishing the rate of 'POA event rate' from 'non-POA event rate'. Subsequently, the proportion of symptomatic patients and postoperative stroke rate in symptomatic and asymptomatic patients was evaluated using three different previously described methodologies.[3-5,14] While the first method (A) uses the complication code for stroke to identify perioperative

stroke, the second method (B) uses diagnosis codes for stroke together with the complication code for stroke to identify perioperative stroke. (Table I) In administrative data that contains POA information, a third methodology (POA) was used.[11] Under the assumption that a complication code of stroke with a POA label refers to a pre-procedural condition, preoperative symptom status could be identified using both diagnosis and complication codes for neurologic symptoms (stroke, TIA, amaurosis fugax)[5] with the POA flag. (Appendix B) Patients without any diagnosis codes for neurological symptoms are considered asymptomatic. Perioperative outcomes include both diagnosis codes and the complication code for stroke in the absence of POA flags. We calculated Cohen's Kappa (K) to measure agreement of Method A and B with the POA Method to identify symptom status and perioperative stroke rate. Kappa values > 0.75 indicate excellent agreement between methodologies, 0.4 to 0.75 indicate fair to good agreement, and values < 0.4 indicate poor agreement. In addition, mortality rates and stroke to death ratios were investigated. Queries of the SID data were performed with SAS version 9.2. (SAS Institute, Cary, NC). IBM SPSS version 19.0 (IBM Corp., Armonk, NY) was used for all statistical analyses.

Table I Different methodologies to identify symptom status and perioperative stroke rate using administrative data

	Symptom status	Perioperative stroke
Method A	Diagnosis codes for stroke, TIA and amaurosis fugax	Complication code for stroke
Method B	Diagnosis codes for TIA and amaurosis fugax	Diagnosis codes and the complication code for stroke
Method POA	Diagnosis codes for stroke, TIA and amaurosis fugax and the complication code for stroke with POA label	Diagnosis codes and complication code without POA label

TIA, transient ischemic infarction, POA, present on admission

RESULTS

A total of 41,684 patients were identified who underwent CEA (n=36,002; 86.4%) or CAS (n=5,682; 13.6%). 60.7% of those patients had at least one diagnosis listed as POA, resulting in a final study sample of 25,327 patients including 21,639 (85.4%) undergoing CEA and 3688 (14.6%) undergoing CAS.

The proportions of comorbidities and adverse events that were POA. Without POA information, diagnosis codes for stroke were found in 9.1% (n=1960) of those undergoing CEA and 15.6% (n=574) of those undergoing CAS. After applying the POA information, 90.3% (CEA) and 91.3% (CAS) of these strokes were labeled POA. (Table II and III) The complication code for stroke was present in 1.4% (n=296) of patients undergoing CEA and 2.4% (n=87) of patients who underwent CAS. In 54% of CEA and in 62% of CAS patients, these strokes were labeled as POA. The vast majority of diagnosis codes for other neurologic or acute cardiac diagnoses such as TIA, amaurosis fugax and acute myocardial infarction (MI) were POA. The cardiac complication code was designated POA in 58% of CEA and 62% of CAS. Conditions that are infrequently encountered after carotid interventions, but are more likely to represent a postoperative

complication than a pre-existing condition, were most impacted by the POA indicator: between 40 – 61% of peripheral vascular complications, respiratory complications, pneumonia and acute renal failure diagnosis were labeled POA for both CEA and CAS. Conditions that are regularly pre-existing conditions were correctly designated as being POA in more than 88% of diagnoses.

Defining preoperative symptom status using administrative data. 15.9% (n=3436) of CEA patients were considered symptomatic using Method A (no POA information) and 7.1% (n=1540) using Method B (no POA information). In Method POA, 15.4% (n=3324) of CEA patients were considered symptomatic. (Table IV). Kappa indicated an excellent agreement between Method A compared to Method POA (0.96), while a fair agreement (0.57) was seen between Method B and Method POA.

Among CAS patients, 21.7% (n=801) of patients were symptomatic using Method A, 4.6% (n=243) using Method B and 21.0% (n=776) using Method POA. Similar to CEA, kappa indicated an excellent agreement between Method A and Method POA (0.95) and a fair agreement (0.40) between Method B and Method POA.

Defining perioperative stroke and mortality using administrative data. Following CEA, the perioperative stroke rate was 1.4% (5.9% symptomatic and 0.5% asymptomatic) using Method A. Using Method B, the perioperative stroke rate was 9.5% (4.8% symptomatic and 9.9% asymptomatic). Using Method POA, the perioperative stroke rate was 1.1% (2.5% symptomatic and 0.9% asymptomatic). (Table V) Between Method A and Method POA, kappa indicated a fair agreement in the identification of postoperative strokes (kappa 0.7). Although the stroke rate in Method A (1.4%, n=296) and Method POA (1.1%, n=247) was fairly similar, 23.9% (n=59) of strokes that were designated as perioperative events with the POA Method were not picked up as perioperative strokes with Method A. Similarly, Method A designated 36.5% (n=108) of strokes as perioperative events, while these strokes were pre-existing with the POA methodology. Method B clearly identifies all strokes that were found using Method POA, but 88% (n=1817) of these strokes were designated as being POA with the POA Method. A kappa of 0.2 showed poor agreement between Method B and Method POA. Mortality for all patients was 0.5% and varied between symptomatic and asymptomatic patients according to the different methodologies that were applied. (Table V) Using the POA Method, death rate was 1.3% and stroke to death ratio was 1.9:1 for symptomatic patients, while death rate in asymptomatic patients was 0.4% and stroke to death ratio 2.5:1.

Following CAS, the perioperative stroke rate was 2.4% (7.5% symptomatic and 0.9% asymptomatic) using Method A. Using Method B, the perioperative stroke rate was 16.4% (8.4% symptomatic patients and 11.4% asymptomatic). Using Method POA, the perioperative stroke rate was 1.8% (3.4% symptomatic and 1.6% asymptomatic patients). (Table V). Similar inaccuracies and agreements between the three methodologies were identified as after CEA, illustrated by kappa values of 0.6 (Method A and Method POA) and 0.2 (Method B and Method POA).

Table II Frequencies of diagnosis and complication codes used in the State Inpatient Databases of CA, NY and NJ in 21,639 patients undergoing CEA and the impact of the POA indicator on preoperative conditions and perioperative outcome

		Rates identified w/o POA indicator		Proportion POA[a]		Revised rates with POA indicator	
		%	n	%	n	POA rate [b] (%)	Non-POA rate [c] (%)
Major neurological or acute cardiac diagnoses that may represent either pre-existing conditions or complications after intervention							
Stroke	Diagnosis code	9.1	1960	90.3	1770	8.2	0.9
	Complication code	1.4	296	53.7	159	0.7	0.6
Transient ischemic attack		3.1	665	94.9	631	2.9	0.2
Amaurosis fugax		4.2	905	98.0	887	4.1	0.1
Cardiac complication		2.8	609	58.3	355	1.6	1.2
Acute myocardial infarction		2.4	509	70.3	358	1.7	0.7
Conditions that are infrequently encountered after intervention							
Peripheral vascular complication		0.1	18	61.1	11	0.1	0.0
Respiratory complication		0.7	151	45.0	68	0.3	0.4
Pneumonia		1.6	337	54.6	184	0.9	0.7
Acute renal failure		2.4	527	60.0	316	1.5	1.0
Conditions that are regularly pre-existing comorbidities							
Coronary artery disease		29.4	6369	97.3	6195	28.6	0.8
Angina		1.4	313	88.2	276	1.3	0.2
Congestive heart failure		11.2	2414	91.3	2203	10.2	1.0
Chronic obstructive pulmonary disease		27.3	5918	96.6	5719	26.4	3.4
Chronic kidney disease		11.5	2495	96.7	2412	11.1	0.4
Diabetes		49.9	10801	97.5	10526	48.6	1.3

[a] Of the rates that were identified w/o the use of the present on admission (POA) indicator, [b] Condition flagged POA, [c] Condition not flagged POA

Table III Frequencies of diagnosis and complication codes used in the State Inpatient Databases of CA, NY and NJ in 3,688 patients undergoing CAS

and the impact of the POA indicator on preoperative conditions and perioperative outcome

		Rates identified w/o POA indicator		Proportion POA[a]		Revised rates with POA indicator	
		%	n	%	n	POA rate [b] (%)	Non-POA rate [c] (%)
Major neurological or acute cardiac diagnoses that may represent either pre-existing conditions or complications after intervention							
Stroke	Diagnosis code	15.6	574	91.3	524	14.2	1.4
	Complication code	2.4	87	62.1	54	1.5	0.9
Transient ischemic attack		3.4	125	93.6	117	3.2	0.2
Amaurosis fugax		3.4	126	95.2	120	3.3	0.2
Cardiac complication		3.4	125	61.6	77	2.1	1.3
Acute myocardial infarction		2.8	103	73.8	76	2.1	0.7
Conditions that are infrequently encountered after intervention							
Peripheral vascular complication		0.3	12	58.3	7	0.2	0.1
Respiratory complication		0.4	15	40.0	6	0.2	0.2
Pneumonia		1.8	67	58.2	39	1.1	0.8
Acute renal failure		2.9	108	56.5	61	1.7	1.3
Conditions that are regularly pre-existing comorbidities							
Coronary artery disease		33.4	1230	96.3	1185	32.1	1.2
Angina		2.2	81	91.6	76	2.1	0.1
Congestive heart failure		15.6	575	93.9	540	14.6	0.9
Chronic obstructive pulmonary disease		23.1	853	96.2	821	22.3	0.9
Chronic kidney disease		12.0	441	97.3	429	11.6	0.3
Diabetes		47.9	1766	98.2	1735	47.0	0.8

Of the rates that were identified w/o the use of the present on admission (POA) indicator, [b] Condition flagged POA, [c] Condition not flagged POA

DISCUSSION

In this study we examined the impact of the POA indicator on the accuracy of administrative data in order to evaluate outcome after CAS and CEA. While the majority of diagnosis codes represented conditions that were POA, we found that nearly half of complication codes were coded as POA. Our evaluation of the POA indicator identified several flaws with the use of this method as well as the others, indicating that the use of administrative data for carotid outcome analysis is limited.

A major limitation of the POA indicator is its variable designation of intraoperative strokes as either pre-existing or perioperative complications depending on the timing of admission order placement. Most elective carotid procedures will be scheduled as same day admissions with admission order placed only after the procedure. Following the coding guidelines, an intraoperative stroke during carotid intervention should then be coded as a complication code of stroke with a POA label. While the goal of the CMS pay-for-performance policy was to differentiate pre-admission conditions (unrelated to hospital stay) from conditions or complications that develop during the hospital stay (and can be thus attributed to medical or surgical management), this interpretation is not applicable to a large proportion of carotid procedures. Therefore, the coding of such intraoperative strokes is confusing and potentially subject to error. This is reflected by an inconsistency in the proportion of strokes that would have occurred intraoperative in the SID (54% of all CEA strokes and 62% of all CAS strokes) compared to the proportion of intraoperative stroke identified in the SVS Vascular Registry (16% of all CEA and 33% of all CAS strokes)[12] and in a large institutional review (15% of all CEA strokes).[15]

While it is unclear what proportion of patients are admitted before or after their procedure, many will interpret POA events as preoperative comorbidities and conditions without a POA label as periprocedural events.[11] Although the POA indicator was never validated by physician chart review, this POA methodology has the potential to improve outcome analyses based on administrative data compared to traditional methodologies. However, in all methodologies that were examined in this study, we identified serious shortcomings. The most important limitation of the POA method is that the POA indicator eliminates the ability to detect a second (perioperative) stroke in those patients who have a stroke complication code labeled POA. Under the assumption that this stroke represents a symptomatic patient, all perioperative events in this exceptionally high-risk group of patients would be missed. This also translates to a reduced apparent perioperative stroke rate for the Method POA even in comparison to Methods A and B, of which Method A is known to underestimate perioperative strokes. [3-5,14]

The low stroke rate in combination with an unexpectedly high proportion of asymptomatic patients in the NIS was recently criticized.[1,2] The reported periprocedural stroke rate in these studies was lower than in major randomized controlled trials (RCT) such as the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST).[16] This is unexpected, because these RCT's were executed in ideal circumstances with highly selected patients, surgeons and interventionalists. Using administrative data, mortality rate following CEA was higher in non-trial hospitals compared to death rates in a trial setting.[17] We found that the ratio of stroke to death after CEA and CAS in SID was half that or less compared to the combined stroke to death ratio's of three major RCT's among symptomatic patients ([CEA 1.9:1 in SID versus 3.8:1 in RCT's]; [CAS 0.6:1 in SID versus 4.3:1 in RCT's]).[18] However, the NIS and SID capture only in-hospital outcome while the RCT's were based on 30-day outcome. A recent report from our

group found that over 30% of strokes happen after discharge but within 30 days of surgery.[19] These findings indicate that the non-fatal outcome of stroke is underreported in administrative databases particularly in comparison to mortality, which is a more readily definable endpoint.

Similarly, symptom status is unreliable in administrative data.[3,20] Using the POA method, we calculated that 15% of CEA's and 21% of CAS procedures were performed in symptomatic patients. In other large vascular registries such as the VSGNE, one third of patients were reported as being symptomatic.[21] The SVS vascular registry reported even higher rates between 40-50%.[12,16] The low rates found with the POA methodology thus do not ameliorate concerns regarding the use of administrative data to assign symptom status to patients undergoing carotid revascularization. Although it is highly unlikely that the NIS data represents the true proportion of symptomatic patients undergoing carotid revascularization in the US, certain societal guidelines still draw heavily on data derived from these administrative studies.[22] Though the inclusion of administrative data to determine societal guidelines is well intentioned, it may be relying on inaccurate data.[23] Hopefully future studies and the improvement of administrative data accuracy may confirm the generalizability of RCT's to a broad spectrum of healthcare centers.

In our opinion, the only way to improve the reliability of administrative data for carotid interventions is to use diagnosis codes strictly for pre-existing conditions and complication codes strictly for postoperative outcome. In the ICD-10 coding system (goal implementation by October 2014), the current ICD-9 'complication' code for stroke will be converted to a new code that will further define whether a complication of stroke occurred intra-operatively or postoperatively, with the addition of stroke laterality. Under this system, if the diagnosis codes for stroke were used for preoperative symptoms, the POA indicator would not be needed for carotid interventions. This methodology will also take away the possibility of miscoding an intraoperative event as a preoperative condition. Until the ICD-10 is implemented, the NIS and SID are inappropriate for analysis of stroke risk outcomes. However, the POA indicator is still of general interest for hospital and/or surgeon quality improvement programs and for pay-for-performance initiatives as this assists in appropriately categorizing DRGs and calculating hospital reimbursements.

This study must be interpreted in the context of its design including the inherent limitations of administrative data as discussed in this manuscript. The POA indicator is subject to coding error with improved accuracy for chronic conditions as compared to acute conditions.[24] Although no evidence was found of systematic undercoding of POA, we limited our analyses to those patients with at least one diagnosis listed as POA to minimize coding errors on POA information. Finally, administrative data do not capture anatomic risk factors such as severity of carotid stenosis nor do they provide detailed information regarding preoperative symptoms such as laterality, frequency or severity. However, it is unlikely that these limitations of administrative data had a significant effect on our overall findings.

In conclusion, we found that the vast majority of diagnosis codes and nearly half of complication codes for stroke were coded POA. Whether with the POA indicator or previously described methods for assignment of symptom status or perioperative strokes, administrative data appears to significantly underestimate the proportion of symptomatic patients undergoing carotid revascularization and the proportion of patients suffering perioperative strokes in comparison to RCT's and other clinical registries of vascular surgery. This demonstrates a persistent concern

about the validity of administrative data in defining symptom status and perioperative outcome after CEA and CAS. The primary benefit of this analysis is that it provides further evidence that administrative data have limited usefulness for non-fatal outcome analysis after CEA and CAS.

Table IV Symptom status of patients undergoing CEA or CAS using different methodologies (A, POA and B)

	Method A		Method POA		Method B	
	n	%	n	%	n	%
CEA						
Symptomatic	3436	15.9	3324	15.4	1540	7.1
Asymptomatic	18203	84.1	18315	84.6	20099	92.9
CAS						
Symptomatic	801	21.7	776	21.0	243	4.6
Asymptomatic	2887	78.3	2912	79.0	3445	95.4

POA, present on admission

Table V Stroke and death rate in patients undergoing CEA or CAS using different methodologies (A, POA and B)

	Method A			Method POA			Method B		
	Stroke (%)	Death (%)	Stroke: Death	Stroke (%)	Death (%)	Stroke: Death	Stroke (%)	Death (%)	Stroke: Death
CEA									
All patients	1.4	0.5	2.8:1	1.1	0.5	2.2:1	9.5	0.5	19:1
Symptomatic	5.9	1.4	4.2:1	2.5	1.3	1.9:1	4.8	0.5	9.6:1
Asymptomatic	0.5	0.4	1.3:1	0.9	0.4	2.3:1	9.9	0.5	19.8:1
CAS									
All patients	2.4	1.5	1.6:1	1.8	1.5	1.2:1	16.4	1.5	9.4:1
Symptomatic	7.5	5.6	1.3:1	3.4	5.3	0.6:1	7.4	0.8	10.5:1
Asymptomatic	0.9	0.4	2.3:1	1.4	0.5	2.8:1	17.0	1.6	9.5:1

POA, present on admission

Appendix A: ICD-9 Codes used throughout the manuscript to evaluate comorbidities with and without POA information

Symptom	ICD-9 Code
Angina	4111
Acute myocardial infarction	410, 41000, 41001, 41010, 41011, 41020, 41021, 41030, 41031, 41040, 41041, 41050, 41051, 41060, 41061, 41070, 41071, 41080, 41081, 41090, 41091
Coronary artery disease	4110, 4111, 4118, 41181, 4119, 4130, 4131, 4139, V4581, V4582
Congestive heart failure	4280, 4281, 42820, 42821, 42822, 42823, 42830, 42831, 42832, 42833, 42840, 42841, 42842, 42843, 4289, 40201, 40211, 40291, 40401, 40403, 40411, 40413, 40491, 40493
COPD	490, 4910, 4911, 49120, 49121, 49122, 4918, 4919, 4920, 4928, 4930, 4931, 49320, 49321, 49322, 4940, 4941, 4950, 4951, 4952, 4953, 4954, 4955, 4956, 4957, 4958, 4959, 496
Pneumonia	4801, 4803, 4808, 4809, 481, 4820, 4821, 4822, 48230, 48231, 48232, 48239, 48240, 48241, 48242, 48249, 4828, 48281, 48282, 48283, 48284,48289, 4829, 4830, 4831, 4838, 484, 4841, 4843, 4845, 4846, 4847, 4848,485,486, 4870, 4871,4878,488
Chronic kidney disease	5853, 5854, 5855, 5856, 5859, 586, V420, V451, V4511, V4512,V560,V561, V562, V563m V5631, V5632
Acute renal failure	584, 5845, 5846, 5847, 5848, 5849
Diabetes	25000, 25001, 25002, 25010, 25011, 25012, 25013, 25020, 25021, 25022, 25023, 25030, 25031, 25032, 25033, 25040, 25041, 25042, 25043, 25050, 25051, 25052, 25053, 25060, 25061, 25062, 25063, 25070, 25071, 25072, 25073, 25080, 25081, 25082, 25083, 25090, 25091, 25092, 25093

ICD-9, International Classification of Diseases, Ninth Revision; COPD, chronic obstructive pulmonary disease

Appendix B: ICD-9 Codes used throughout the manuscript to evaluate symptom status and perioperative complications with and without POA information

Symptom	ICD-9 Code	Description
Stroke	99702[a]	Iatrogenic cerebrovascular infarction or hemorrhage
	43301	Occlusion and stenosis of basilar artery with cerebral infarction
	43311	Occlusion and stenosis of carotid artery with cerebral infarction
	43321	Occlusion and stenosis of vertebral artery with cerebral infarctic
	43331	Occlusion and stenosis of multiple and bilateral precerebral arte
	43381	Occlusion and stenosis of other specified precerebral artery with
	43391	Occlusion and stenosis of unspecified precerebral artery with ce
	43401	Cerebral thrombosis with infarction
	43411	Cerebral embolism with infarction
43491		Cerebral artery occlusion, unspecified with infarction
	431	Intracerebral hemorrhage
	3429	Hemiplegia, unspecified, affecting unspecified side
	36231	Central retinal artery occlusion
	36232	Retinal arterial branch occlusion
	4371	Other generalized ischemic cerebrovascular disease
Transient ischemic attack	4350	Basilar artery syndrome
	4351	Vertebral artery syndrome
	4352	Subclavian steal syndrome
	4353	Vertebrobasilar artery syndrome
	4358	Other specified transient cerebral ischemias
	4359	Unspecified transient cerebral ischemia
	7814	Transient paralysis of limb
Amaurosis fugax	36234	Transient retinal arterial occlusion
	36812	Transient visual loss
	36284	Retinal ischemia

ICD-9, International Classification of Diseases, Ninth Revision
[a]The 'complication code' for stroke

References

1. Hertzer NR. The Nationwide Inpatient Sample may contain inaccurate data for carotid endarterectomy and carotid stenting. *J Vasc Surg* 2012;55:263-6.
2. Bensley RP, Yoshida S, Lo RC, Fokkema M, Hamdan AD, Wyers MC, et al. Accuracy of administrative data versus clinical data to evaluate carotid endarterectomy and carotid stenting. *J Vasc Surg* 2013.
3. Eslami MH, McPhee JT, Simons JP, Schanzer A, Messina LM. National trends in utilization and postprocedure outcomes for carotid artery revascularization 2005 to 2007. *J Vasc Surg* 2011;53:307-15.
4. Vogel TR, Dombrovskiy VY, Haser PB, Scheirer JC, Graham AM. Outcomes of carotid artery stenting and endarterectomy in the United States. *J Vasc Surg* 2009;49:325-30; discussion 30.
5. Giles KA, Hamdan AD, Pomposelli FB, Wyers MC, Schermerhorn ML. Stroke and death after carotid endarterectomy and carotid artery stenting with and without high risk criteria. *J Vasc Surg* 2010;52:1497-504.
6. Hospital-Acquired Conditions (Present on Admission Indicator). (Accessed at http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalAcqCond/index.html?redirect=/HospitalAcqCond.)
7. Houchens RL, Elixhauser A, Romano PS. How often are potential patient safety events present on admission? *Jt Comm J Qual Patient Saf* 2008;34:154-63.
8. Fry DE, Pine M, Jordan HS, Elixhauser A, Hoaglin DC, Jones B, et al. Combining administrative and clinical data to stratify surgical risk. *Ann Surg* 2007;246:875-85.
9. Pine M, Jordan HS, Elixhauser A, Fry DE, Hoaglin DC, Jones B, et al. Modifying ICD-9-CM Coding of Secondary Diagnoses to Improve Risk-Adjustment of Inpatient Mortality Rates. *Med Decis Making* 2009;29:69-81.
10. Kim H, Capezuti E, Kovner C, Zhao Z, Boockvar K. Prevalence and predictors of adverse events in older surgical patients: impact of the present on admission indicator. *Gerontologist* 2010;50:810-20.
11. Vouyouka AG, Egorova NN, Sosunov EA, Moskowitz AJ, Gelijns A, Marin M, et al. Analysis of Florida and New York state hospital discharges suggests that carotid stenting in symptomatic women is associated with significant increase in mortality and perioperative morbidity compared with carotid endarterectomy. *J Vasc Surg* 2012;56:334-42.
12. Sidawy AN, Zwolak RM, White RA, Siami FS, Schermerhorn ML, Sicard GA. Risk-adjusted 30-day outcomes of carotid stenting and endarterectomy: results from the SVS Vascular Registry. *J Vasc Surg* 2009;49:71-9.
13. HCUP State Inpatient Databases (SID). Healthcare Cost and Utilization Project (HCUP). (Accessed at http://www.hcup-us.ahrq.gov/sidoverview.jsp.)
14. McPhee JT, Hill JS, Ciocca RG, Messina LM, Eslami MH. Carotid endarterectomy was performed with lower stroke and death rates than carotid artery stenting in the United States in 2003 and 2004. *J Vasc Surg* 2007;46:1112-8.
15. Riles TS, Imparato AM, Jacobowitz GR, Lamparello PJ, Giangola G, Adelman MA, et al. The cause of perioperative stroke after carotid endarterectomy. *J Vasc Surg* 1994;19:206-14; discussion 15-6.
16. Silver FL, Mackey A, Clark WM, Brooks W, Timaran CH, Chiu D, et al. Safety of Stenting and Endarterectomy by Symptomatic Status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke* 2011;42:675-80.
17. Wennberg DE, Lucas FL, Birkmeyer JD, Bredenberg CE, Fisher ES. Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume, and patient characteristics. *JAMA* 1998;279:1278-81.
18. Bonati LH, Dobson J, Algra A, Branchereau A, Chatellier G, Fraedrich G, et al. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *Lancet* 2010;376:1062-73.

19. Fokkema M, Bensley RP, Lo RC, Hamden AD, Wyers MC, Moll FL, et al. In-hospital versus postdischarge adverse events following carotid endarterectomy. *J Vasc Surg* 2013;57:1568-75 e3.
20. McDonald RJ, Cloft HJ, Kallmes DF. Intracranial hemorrhage is much more common after carotid stenting than after endarterectomy: evidence from the National Inpatient Sample. *Stroke* 2011;42:2782-7.
21. Nolan BW, De Martino RR, Goodney PP, Schanzer A, Stone DH, Butzel D, et al. Comparison of carotid endarterectomy and stenting in real world practice using a regional quality improvement registry. *J Vasc Surg* 2012;epub.
22. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. *J Neurointerv Surg* 2011;3:100-30.
23. Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease: executive summary. *J Vasc Surg* 2011;54:832-6.
24. Goldman LE, Chu PW, Osmond D, Bindman A. The accuracy of present-on-admission reporting in administrative data. *Health Serv Res*;46:1946-62.

General discussion

Since DeBakey performed the first successful carotid endarterectomy (CEA) in 1953, the precise role of carotid revascularization procedures in the prevention of stroke has been the subject of much literature and controversy. While four landmark randomized trials have clearly validated the use of CEA for the management of asymptomatic and symptomatic significant carotid artery stenosis, its risk-to-benefit ratio is variable for different patients.[1-4] With the advent of carotid artery stenting (CAS) and the recent improvements in medical therapy, an added degree of complexity has emerged in the effort to optimize management for patients with carotid artery disease. While insight toward this clinical dilemma has come from a number of study designs, (comparative) outcome analyses of CAS and CEA form the cornerstone of the evidence presented in this thesis.

In 1902, Boston surgeon Codman was pioneering the 'End Result Idea', and he developed the first registry on bone sarcoma.[5,6] Though this was considered curious at the time, he advocated transparency to promote quality improvement, patient selection, and physician education. Nowadays, this systematic approach to evaluate postoperative outcomes is just as crucial and informative as it was a century ago. High quality clinical outcome research has impacted healthcare tremendously and will continue to do so. Following Iezzoni's 'Algebra of Effectiveness' theory, health care outcome is a function of clinical patient factors, quality of care and random events.[7] In this thesis we investigated how these three aspects influenced outcome of patients with high-risk comorbid conditions undergoing CEA or CAS, ultimately enabling optimal decision making for the individual patient. In this final chapter I will outline our main findings within the context of the current literature. I will also discuss future directions for further investigation in this area.

Consequences of the high-risk stratification

Patients with unfavorable anatomical features or medical comorbidities are generally considered a 'high-risk group' for CEA.[8] Based on this potential increased surgical risk, patients were excluded from the large randomized controlled trials (RCT) that compare the effectiveness of CAS versus CEA.[9-11] The consequences of these exclusions were two-fold. First, RCT's were executed in circumstances with highly selected patients, surgeons and interventionalists, leading to an 'ideal' setting among 'average' or even 'low' risk patients. While the results of such studies serve as a benchmark for many vascular practices, they cannot simply be applied to all patients with carotid artery disease. This phenomenon was illustrated by increased mortality rates following CEA in non-trial hospitals compared to death rates in the trial setting.[12] Although the composite outcome of stroke, death, myocardial infarction (MI) was similar between endovascular and surgical treatment, literature suggests that CEA has a lower stroke or death rate at 30-days than CAS.[9,11,13,14] This benefit of CEA is generally counterbalanced by a greater risk of cranial nerve injury (CNI) and MI as compared to CAS. While this evidence indicates that CAS may be a safe procedure under specific conditions in selected patients treated by selected physicians, the generalizability of these results remains unknown. CEA remains the standard of care for treating patients with severe carotid disease in the absence of high-risk factors.

Second, the effectiveness of CAS in these 'high-risk' patients for CEA was assessed in various CAS trials and registries.[15-17] While most suggested 30-day safety, the SAPPHIRE trial is the only RCT

designed to compare CAS and CEA in a high-risk population.[18,19] In this non-inferiority study, the 30-day stroke, death, and MI rates in the CEA arm were as high as 9.8% (vs. 4.8% CAS). The MI rate of 6.6% strongly influenced this composite endpoint. The generalizability of this cohort may be limited as approximately 70% of the study population was asymptomatic and the study design lacked stratification within the various high-risk groups. Despite this limited evidence, the Centers for Medicare and Medicaid Services (CMS) have approved reimbursement for CAS in patients meeting high-risk criteria with symptomatic ≥70% stenosis.[20] This led to a significant increase in CAS use among these patients, particularly in the United States.[21] Since that time, the debate as to what precisely defines 'high-risk' and as to whether the CMS criteria correctly identify high-risk patients has emerged.[22-25] Is the risk of undergoing CAS in these patients decreased, equal to, or even increased as compared to CEA?

The concept of high-risk

Increased surgical risk is a relatively nebulous concept encompassing patients at increased risk for several adverse events after CEA including 'major' complications such as stroke, MI or death, as well as 'minor' complications such as CNI, bleeding or infection. The incidence of these events are often used as measures of effectiveness, but the risk of these procedures may vary only minimally between CAS and CEA, if the quality of care is considered equal.[9,26] Following Iezzoni's theory, ultimate outcome is determined by clinical patient factors associated with the risks of either procedure (CAS or CEA). The likelihood of complications during an intervention generally increases with increasing baseline patient risk. Comorbid conditions impact the relative safety of both CAS and CEA, but often to a different extent. This point is emphasized in several chapters of this thesis.

The results of **chapter 5** indicate that some, but not all, CMS high-risk criteria identified patients at increased risk for 30-day stroke or death after CEA. For both treatment modalities, symptom status was a significant predictor of adverse outcome. Of the high-risk criteria, congestive heart failure class III/IV, left ventricle ejection fraction <30%, angina, contralateral occlusion and high anatomic lesion predicted stroke or death after CEA. For CAS, only recent MI was predictive of stroke or death. Despite this, 30-day CAS outcomes between high-risk patients and patients who did not meet any of the high-risk criteria were statistically similar for both symptomatic (7.9% vs. 4.9%, P=NS) and asymptomatic (4.8% vs. 3.6%, P=NS) patients. On the other hand, all CEA patients with a high-risk status had an increased risk for adverse events compared to non high-risk patients (symptomatic: 6.3% vs. 3.9%, P<.01, asymptomatic: 3.7% vs. 1.4%, P<.01). These results indicate several things: 1) That 'high-risk status' only includes certain patient-related characteristics; 2) That these criteria are different for CAS and for CEA; 3) That outcomes in high-risk CEA patients are not improved with CAS; and 4) That CAS and CEA may be complementary procedures in patients with certain high-risk factors. These general implications (Figure) were confirmed in chapters 1, 3, 4 and 6 where we assessed the outcome of CAS and CEA per anatomic high-risk factor.

In **chapter 1** we concluded that CAS and CEA were equally effective in patients with prior cervical radiation therapy. We performed a systematic literature review to overcome the limitations related to study of rare events with small sample size cohort studies. Even in chapter 5, the number of patients with prior radiation therapy who underwent CEA was too small to draw any conclusions

on outcome (n=19, no events). However, combined stroke, death, MI rate after CAS in this study (4.5% in symptomatic patients, 2.5% in asymptomatic patients) compared favorably to the rate of 3.9% that we identified in our pooled analysis in the first chapter. Due to heterogeneity among the included studies, we were unfortunately not able to stratify for symptom status in this meta-analysis. In chapter 5, we identified a protective effect for major adverse events after CAS (OR 0.5, 95% CI 0.3 – 0.9) among patients with a history of prior radiation compared to patients without prior radiation. The protective effect among patients treated with CAS may be attributed to a more stable, less vulnerable lesion[27], as shown in **chapter 2**. Despite a more stable plaque, patients with prior radiation therapy seem to have an increased risk for symptomatic carotid stenosis. The mechanism for these apparently contradictory findings remains unclear and may be the subject of future projects. Possibly, factors other than plaque rupture or thrombus formation may contribute to neurological symptoms, such as progressive stenosis through intima-media thickening.[28] Unfortunately, neither chapter informs us on the exact condition of the preoperative tissue in the neck that may influence outcome.[29] Therefore, we believe that choice of treatment for patients with a history of prior radiation therapy should be individualized taking into consideration other patient factors (e.g. the status of the cervical area, life expectancy or age) that could impact outcome. Future work should focus on the identification of these other factors and to the long-term benefit of CAS and CEA in this population.

In agreement with the results chapter 5, **chapters 3 and 4** demonstrated that CEA and CAS yielded similar results in both symptomatic and asymptomatic patients with restenosis after prior CEA. In chapter 3 we found that the risk associated with CEA in these patients was increased compared to patients undergoing primary CEA, while the risk with CAS was lower in patients with restenosis after prior CEA compared to patients without restenosis. Similar to our findings in the previously irradiated patients, the combination of a higher risk population in the primary CAS group and a supposedly more stable plaque in restenotic lesions may explain these results. For symptomatic patients, both CAS and CEA are suitable options for carotid revascularization in the setting of restenosis. For asymptomatic patients, the benefit of intervention for restenosis is less clear with stroke/death rate of 2.9% after CEA, generally the upper limit of acceptable risk cited in societal guidelines. Future work should focus on identifying those asymptomatic lesions that will eventually become symptomatic, and which asymptomatic patients have increased risk for perioperative events.

Both radiation and restenosis have historically been thought to confer increased risk of intraoperative CNI. While others have reported an increased risk of CNI after redo-CEA and prior radiation therapy,[30,31] our data did not demonstrate this finding. Because the clinical importance of CNI as a relevant safety endpoint remains debatable,[14,32-34] we undertook a thorough analysis identifying transient and persistent CNI in **chapter 7.** In this chapter we confirmed that cranial nerve risk is not necessarily higher in patients with an impaired neck due to prior radiation or redo-surgery. On the contrary, we identified several operative factors such as urgency and (sub) acute re-operation as independent predictors of CNI. Although these results were based on standard of care and quality in the New England region and CNI was not evaluated by objective methods, our results were comparable to previous large studies and major RCTs (4.7 – 8.6%).[9,35-37] This chapter also emphasized the value of a large database to determine the true effects of patient related variables on outcome.

In chapter 6 we assessed contralateral occlusion, another anatomical criterion thought to confer 'high risk' after CEA. Based on our findings in chapter 5, we designed our study to assess the impact of the status of the contralateral artery, stratified for different degrees of severity. Our results indicated that the influence was different for different subgroups, depending on symptom status and degree of stenosis of the ipsilateral artery. The increased stroke risk in patients with contralateral high-grade disease could be related to diminished collateral blood flow. However, this would not account for the fact that symptomatic patients with severe stenosis were not impacted by contralateral disease. As such, the exact mechanism of stroke is not fully understood. It would be very interesting to unravel these mechanisms and relate patient characteristics to different types of stroke, leading to better risk stratification. This would be also of importance to better explain our findings in **chapter 8,** where we identified that women, patients with renal failure and patients with COPD were at increased risk for ongoing stroke after discharge (until 30-days after the procedure). The timing of post-discharge strokes suggests that some may be due to hyperperfusion and subsequent intracerebral hemorrhage.[38,39]

Pitfalls of outcome analyses in carotid revascularization

In this thesis, we used data from prior literature, institutional data and registry data to help select the optimal mode of revascularization therapy for 'high-risk' patients. While one might prefer randomized data to select the optimal procedure for a particular patient, this is likely many years away and as discussed previously, the ideal circumstances of RCT's limit the generalizability of the results to the real world setting. In addition, the large sample size and 'real world' setting of registry data favor its use for the purpose of this thesis. However, some serious difficulties must be addressed and discussed. For example, in the real world data from the SVS Vascular Registry (VR) in chapter 5, the vast majority (90.5%) of CAS patients meet Centers for Medicare & Medicaid (CMS) high-risk criteria and had more comorbid conditions than CEA patients, where only 37% met criteria for one or more high-risk factors, making unadjusted comparison difficult to interpret. As a result of the high-risk criteria proposed by CMS, there may be over-representation of high-risk and/or symptomatic patients selected for CAS. However, after multivariable risk adjustment, CAS had higher rates than CEA for major adverse events (OR 1.2, 95% CI 1.01-1.5), death (OR 1.5, 95% CI 1.01-2.2) and stroke (OR 1.3, 95% CI 1.01-1.7), while there was no difference in MI (OR 0.8, 95% CI 0.6-1.3).[21] Although these results compare favorably to the outcomes of the large RCT's, the resulting imbalance in the underlying risk profile between CAS and CEA patients can generate biased results. In all our chapters, we carefully adjusted for differences in patient characteristics. By looking at anatomic high-risk factors separately, patient characteristics were reasonably well balanced across treatment arms. In chapter 4, the CEA group had even 'worse' comorbid conditions than the CAS group. However, unknown factors could be missed that made the surgeon decide CEA such as the physician's experience or patient's preference.

In **chapter 8** we identified another issue limiting the comparison of CAS and CEA in many studies. Many reports that are based on institutional, registry and administrative data do not include post discharge events. In the (NSQIP) Surgical Quality Improvement Database we found that approximately a third of adverse events occurred after hospital discharge. These results suggest that the lack of post-discharge follow up may represent a serious limitation in the many studies

based on such datasets.[40-43] Consistent entry of data beyond the in-hospital period seems to be not only important for true perioperative event risk estimation, but also to identify patients at risk for adverse perioperative events. Our results demonstrate that in a subgroup of patients adverse events are more likely to happen after discharge, possibly influencing preoperative counseling, perioperative management, post-hospital disposition and follow up.

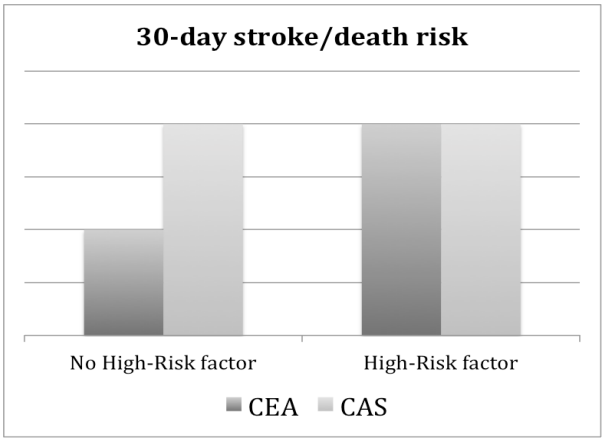
The last major issue in outcomes analyses with large databases is the source of the data. It is well known that hospital administrative data are generally not reliable for estimation of non-fatal perioperative complication rates.[44] While others have questioned the reliability of administrative data to determine outcomes specifically for carotid revascularization procedures,[45,46] we proved that the Nationwide Inpatient Sample, data predominantly used for billing purposes, contain inaccurate data for the purposes of outcome analyses after CEA and CAS **(chapter 9)**. It seems highly unlikely that these datasets represent the true proportion of symptomatic patients undergoing carotid revascularization in the United States and accordingly, the postoperative stroke rate is likely grossly underestimated. The present on admission indicator did not improve these inaccuracies. However, certain societal guidelines still draw heavily on data derived from these administrative studies.[47] Hopefully future studies and the improvement of administrative data accuracy may confirm the generalizability of RCT's to a broad spectrum of healthcare centers. While administrative data have many limitations, registries developed for quality improvement purposes (in contrast to billing purposes) such as the NSQIP, SVS-VR and the Vascular Study Group of New England are critical to evaluate rare events such as postoperative stroke after CEA and CAS. Single surgeon or single center experiences are typically underpowered to evaluate procedures with low event rates such as these. It would be very interesting to introduce such quality improvement auditing for specific vascular procedures to Europe to systematically track outcomes and subsequently improve vascular care on patient-, surgeon- and population levels. As part of the Dutch Institute for Clinical Auditing, the recently started (July 1, 2013) Dutch Audit for Carotid Interventions does have this potential for The Netherlands.

Future directions

The goal of this thesis was to evaluate the concept of risk in relation to both CEA and CAS in an attempt to help guide present-day clinical decision-making and to highlight gaps in knowledge that may serve as areas of further investigation. This thesis proved that anatomical and physiologic conditions could affect the anticipated outcome of each treatment modality. We found that high-risk patients, when included in the risk-to-benefit analysis of a given therapeutic modality, often have a greater impact on safety and efficacy analysis than the remainder of the study group. We also found that the initially 'high-risk' patient for CEA does not seem to benefit from CAS per se, but that the role of CAS is rather complementary to CEA than competitive. Ultimately, a tailored approach to each patient's clinical situation is likely to result in the best outcome following treatment. Outcome is not determined by one high-risk factor, but relies on a combination patient' factors. Ideally, clinicians should be able to estimate the outcome of individual patients, expressed in risks and benefits (stroke-free survival) for intervention and best medical therapy. In order to reach this goal, the unanswered questions discussed in this chapter should be explored in future endeavors. Furthermore, future work should focus on the identification of those asymptomatic patients that are likely to become symptomatic.

These patients will benefit from carotid intervention. Because 'high-risk' conditions increase the likelihood of adverse events during CAS and CEA, in patients who remain asymptomatic, revascularization will be hazardous.

Figure General patterns of the impact of high-risk factors on outcome after CEA or CAS



References

1. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. Lancet 1991;337:1235-43.
2. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991;325:445-53.
3. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004;363:1491-502.
4. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995;273:1421-8.
5. Mallon WJ. Ernest Amory Codman: The End Result of a Life in Medicine. Philidelphia: Saunders; 2000.
6. Codman EA. The product of a hospital. 1914. Arch Pathol Lab Med 1990;114:1106-11.
7. Iezzoni LI. Risk adjustment for measuring health care outcomes. Ann Arbor, MI: Health Administration Press; 1994.
8. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493-501.
9. Brott TG, Hobson RW, 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363:11-23.
10. Ederle J, Bonati LH, Dobson J, Featherstone RL, Gaines PA, Beard JD, et al. Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. Lancet Neurol 2009;8:898-907.
11. Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet 2010;375:985-97.
12. Wennberg DE, Lucas FL, Birkmeyer JD, Bredenberg CE, Fisher ES. Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume, and patient characteristics. JAMA 1998;279:1278-81.
13. Economopoulos KP, Sergentanis TN, Tsivgoulis G, Mariolis AD, Stefanadis C. Carotid artery stenting versus carotid endarterectomy: a comprehensive meta-analysis of short-term and long-term outcomes. Stroke 2011;42:687-92.
14. Meier P, Knapp G, Tamhane U, Chaturvedi S, Gurm HS. Short term and intermediate term comparison of endarterectomy versus stenting for carotid artery stenosis: systematic review and meta-analysis of randomised controlled clinical trials. BMJ 2010;340:c467.
15. White CJ, Iyer SS, Hopkins LN, Katzen BT, Russell ME. Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. Catheter Cardiovasc Interv 2006;67:503-12.
16. Gray WA, Hopkins LN, Yadav S, Davis T, Wholey M, Atkinson R, et al. Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. J Vasc Surg 2006;44:258-68.
17. Hopkins LN, Myla S, Grube E, Wehman JC, Levy EI, Bersin RM, et al. Carotid artery revascularization in high surgical risk patients with the NexStent and the Filterwire EX/EZ: 1-year results in the CABERNET trial. Catheter Cardiovasc Interv 2008;71:950-60.
18. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected Carotid-Artery Stenting versus Endarterectomy in High-Risk Patients. N Engl J Med 2004;351:1493-501.
19. Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, et al. Long-Term Results of Carotid Stenting versus Endarterectomy in High-Risk Patients. N Engl J Med 2008;358:1572-9.
20. 100-03 P. Medicare National Coverage Determinations. 2010.

21. Schermerhorn ML, Fokkema M, Goodney P, Dillavou ED, Jim J, Kenwood CT, et al. The impact of Centers for Medicaid and Medicare Services high-risk criteria on outcome after carotid endarterectomy and carotid artery stenting in the SVS Vascular Registry. J Vasc Surg 2013.
22. Giles KA, Hamdan AD, Pomposelli FB, Wyers MC, Schermerhorn ML. Stroke and death after carotid endarterectomy and carotid artery stenting with and without high risk criteria. J Vasc Surg;52:1497-504.
23. Gasparis AP, Ricotta L, Cuadra SA, Char DJ, Purtill WA, Van Bemmelen PS, et al. High-risk carotid endarterectomy: fact or fiction. J Vasc Surg 2003;37:40-6.
24. Kang JL, Chung TK, Lancaster RT, LaMuraglia GM, Conrad MF, Cambria RP. Outcomes after carotid endarterectomy: Is there a high-risk population? A National Surgical Quality Improvement Program report. J Vasc Surg 2009;49:331-9.e1.
25. Yuo TH, Goodney PP, Powell RJ, Cronenwett JL. "Medical high risk" designation is not associated with survival after carotid artery stenting. J Vasc Surg 2008;47:356-62.
26. Nolan BW, De Martino RR, Goodney PP, Schanzer A, Stone DH, Butzel D, et al. Comparison of carotid endarterectomy and stenting in real world practice using a regional quality improvement registry. J Vasc Surg 2012;56:990-6.
27. Verhoeven B, Hellings WE, Moll FL, de Vries JP, de Kleijn DP, de Bruin P, et al. Carotid atherosclerotic plaques in patients with transient ischemic attacks and stroke have unstable characteristics compared with plaques in asymptomatic and amaurosis fugax patients. J Vasc Surg 2005;42:1075-81.
28. Gianicolo ME, Gianicolo EA, Tramacere F, Andreassi MG, Portaluri M. Effects of external irradiation of the neck region on intima media thickness of the common carotid artery. Cardiovasc Ultrasound 2010;8:8.
29. Tallarita T, Oderich GS, Lanzino G, Cloft H, Kallmes D, Bower TC, et al. Outcomes of carotid artery stenting versus historical surgical controls for radiation-induced carotid stenosis. J Vasc Surg 2011;53:629-36 e1-5.
30. AbuRahma AF, Abu-Halimah S, Hass SM, Nanjundappa A, Stone PA, Mousa A, et al. Carotid artery stenting outcomes are equivalent to carotid endarterectomy outcomes for patients with post-carotid endarterectomy stenosis. Journal of Vascular Surgery;52:1180-7.
31. Fokkema M, den Hartog AG, Bots ML, van der Tweel I, Moll FL, de Borst GJ. Stenting versus surgery in patients with carotid stenosis after previous cervical radiation therapy: systematic review and meta-analysis. Stroke 2012;43:793-801.
32. Cohen DJ, Stolker JM, Wang K, Magnuson EA, Clark WM, Demaerschalk BM, et al. Health-Related Quality of Life After Carotid Stenting Versus Carotid Endarterectomy: Results From CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial). Journal of the American College of Cardiology;58:1557-65.
33. Bangalore S, Kumar S, Wetterslev J, Bavry AA, Gluud C, Cutlip DE, et al. Carotid artery stenting vs carotid endarterectomy: meta-analysis and diversity-adjusted trial sequential analysis of randomized trials. Arch Neurol;68:172-84.
34. Schauber MD, Fontenelle LJ, Solomon JW, Hanson TL. Cranial/cervical nerve dysfunction after carotid endarterectomy. J Vasc Surg 1997;25:481-7.
35. Ferguson GG, Eliasziw M, Barr HW, Clagett GP, Barnes RW, Wallace MC, et al. The North American Symptomatic Carotid Endarterectomy Trial : surgical results in 1415 patients. Stroke 1999;30:1751-8.
36. Greenstein AJ, Chassin MR, Wang J, Rockman CB, Riles TS, Tuhrim S, et al. Association between minor and major surgical complications after carotid endarterectomy: results of the New York Carotid Artery Surgery study. J Vasc Surg 2007;46:1138-44; discussion 45-6.
37. Cunningham EJ, Bond R, Mayberg MR, Warlow CP, Rothwell PM. Risk of persistent cranial nerve injury after carotid endarterectomy. J Neurosurg 2004;101:445-8.
38. Riles TS, Imparato AM, Jacobowitz GR, Lamparello PJ, Giangola G, Adelman MA, et al. The cause of perioperative stroke after carotid endarterectomy. J Vasc Surg 1994;19:206-16.

39. de Borst GJ, Moll FL, van de Pavoordt HD, Mauser HW, Kelder JC, Ackerstaf RG. Stroke from carotid endarterectomy: when and how to reduce perioperative stroke rate? Eur J Vasc Endovasc Surg 2001;21:484-9.
40. Rockman CB, Garg K, Jacobowitz GR, Berger JS, Mussa FF, Cayne NS, et al. Outcome of carotid artery interventions among female patients, 2004 to 2005. J Vasc Surg 2011;53:1457-64.
41. Vogel TR, Dombrovskiy VY, Haser PB, Scheirer JC, Graham AM. Outcomes of carotid artery stenting and endarterectomy in the United States. J Vasc Surg 2009;49:325-30.
42. Eslami MH, McPhee JT, Simons JP, Schanzer A, Messina LM. National trends in utilization and postprocedure outcomes for carotid artery revascularization 2005 to 2007. J Vasc Surg 2011;53:307-15.
43. Nolan BW, De Martino RR, Goodney PP, Schanzer A, Stone DH, Butzel D, et al. Comparison of carotid endarterectomy and stenting in real world practice using a regional quality improvement registry. J Vasc Surg 2012;epub.
44. Best WR, Khuri SF, Phelan M, Hur K, Henderson WG, Demakis JG, et al. Identifying patient preoperative risk factors and postoperative adverse events in administrative databases: results from the department of veterans affairs national surgical quality improvement program. J Am Coll Surg 2002;194:257-66.
45. Bensley RP, Yoshida S, Lo RC, Fokkema M, Darling JD, Handam AD, et al. Accuracy of administrative versus clinical data to evaluate carotid endarterectomy and caritid stenting. Manuscript under revision J Vasc Surg 2012.
46. Hertzer NR. The Nationwide Inpatient Sample may contain inaccurate data for carotid endarterectomy and carotid stenting. J Vasc Surg 2011;55:263-6.
47. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. J Neurointerv Surg 2011;3:100-30.

Nederlandse samenvatting - Summary in Dutch

Een cerebrovasculair accident (CVA) is de meest voorkomende oorzaak van invaliditeit in de westerse wereld. 80% van de CVA's berust op een kortdurende, of langere ischemische periode van een deel van het brein. Dit lijdt tot voorbijgaande (transient ischemic attack, TIA) of blijvende uitvalsverschijnselen (herseninfarct of stroke). Een vernauwing van de diameter van de de arteriae carotides (halsslagaders) is een belangrijke oorzaak van deze symptomen. Atherosclerose (aderverkalking) ligt meestal ten grondslag aan deze vernauwing. Atherosclerose wordt omschreven als een ontstekingsproces van de vaatwand, dat begint met een opeenstapeling van vetten. Als deze zogenaamde 'plaque' langzaam groter wordt, wordt de diameter van het vat nauwer en spreekt men van een stenose. Dit proces kan jaren duren. De plaque belemmert de bloedtoevoer naar de hersenen, maar kan ook deels of volledig afscheuren. Beide situaties lijden tot ischemie (zuurstoftekort) van de hersenen en de daarbij behorende (invaliderende) symptomen zoals hierboven beschreven. Dit proefschrift richt zich op de optimale behandeling van patiënten met een carotis stenose, om zo een CVA of een recidief CVA in de toekomst te voorkomen.

Revascularisatie mogelijkheden

De behandeling van een carotis stenose is gericht op twee pijlers. De eerste is de medicamenteuze behandeling, waarbij het bloed dun gehouden wordt en het atherosclerotisch proces wordt geremd door middel van medicijnen. De tweede pijler bestaat uit het revasculariseren van de arterie carotis, ofwel het herstellen van de vascularisatie (doorbloeding). De eerste, en oudste methode hiervoor is de carotis endarteriëctomie (CEA). Deze operatie werd vanaf de jaren '50 in toenemende mate uitgevoerd. Jaarlijks worden er ongeveer 100.000 carotisoperaties in de VS verricht. De plaque, die meestal ter plaatse van de carotis bifurcatie zit (daar waar de carotis communis zich splitst in de carotis interna en externa), wordt hierbij operatief verwijderd.

De resultaten van enkele belangrijke studies hebben de toegevoegde waarde van de CEA bij een symptomatische (doorgemaakte TIA of stroke) stenose ≥70% bewezen ten opzichte van medicamenteuze behandeling alleen. Een gunstig effect van een CEA bij een asymptomatische stenose (nog geen TIA of stroke doorgemaakt) lijkt alleen stand te houden als de incidentie van complicaties gedurende de operatie laag is. Omdat de operatie als inherente complicatie soms juist datgene veroorzaakt (een CVA), wat het beoogt te voorkomen, is een zorgvuldige risicoafweging noodzakelijk. Als alternatief voor de conventionele CEA is in de afgelopen twee decennia de endovasculaire methode middels stentplaatsing (CAS) ontstaan. CAS heeft de potentiële voordelen van een minimaal invasieve revascularisatie procedure, zoals het vermijden van lokale chirurgische complicaties, geen risico's van algemene anesthesie en een korter ziekenhuisverblijf. Echter, CAS verwijdert niet de atherosclerotische plaque, en zou daarom potentieel minder duurzaam kunnen zijn dan CEA.

Behandel strategie

Een aantal belangrijke gerandomiseerde trials hebben de resultaten van CAS en CEA met elkaar vergeleken. Hieruit blijkt dat CAS mogelijk een iets hoger risico op een stroke geeft gedurende de procedure in vergelijking met CEA. De verschillen op lange termijn zijn miniem. Deze vergelijkende onderzoeken zijn destijds uitgevoerd in de 'normale' patiëntpopulatie met een

'gemiddeld' risico op complicaties tijdens de procedure. Een belangrijke groep patiënten zijn voor deze trials uitgesloten, omdat zij een potentieel hoger risico zouden hebben op complicaties tijdens de CEA. Deze groep omvat patiënten met uiteenlopende kenmerken, gecategoriseerd in anatomische en fysiologische karakteristieken (zie tabel). Voor deze patiëntengroep wordt vaak CAS voorgesteld als alternatieve, minimaal invasieve behandeling voor CEA. CAS wordt in de VS zelfs alleen vergoed indien patiënten aan deze bepaalde karakteristieken voldoen. Dit heeft ertoe geleid dat CAS in toenemende mate wordt uitgevoerd onder deze patiënten. De absolute risico's met CAS zijn echter onbekend en er is onvoldoende bewijs dat de behandeling daadwerkelijk beter is dan CEA.

Dit proefschrift

In dit proefschrift zijn de risico's van zowel CAS als CEA in de verschillende hoog-risico patiënten naast elkaar gezet en met elkaar vergeleken. We zien dat er in geen van alle specifieke hoog-risico groepen een duidelijke voorkeur voor een procedure is. In de meeste gevallen zien we dat het stroke risico's in ieder geval niet lager is na CAS dan na CEA.

In het eerste deel hebben we de resultaten van CAS en CEA vergeleken in twee hoog-risico patiënt categorieën, namelijk 1) patiënten met eerdere radiotherapeutische bestraling in de hals regio (hoofdstuk 1 en 2) en 2) patiënten met een restenose na een eerdere operatie aan dezelfde arterie carotis (hoofdstuk 3 en 4). Deze twee factoren maken de hals regio een minder aantrekkelijk operatiegebied, doordat het weefsel is aangetast door eerdere therapie. Een endovasculaire procedure geeft hier mogelijk minder lokale problemen, zoals hersenzenuwletsel en wondinfecties. We zien inderdaad dat er iets meer zenuwletsel is bij CEA, maar dat het stroke risico gelijk is bij CEA en CAS. In hoofdstuk 7 tonen we echter aan dat het risico van hersenzenuwletsel niet verhoogd is onder deze groep patiënten in vergelijking met de 'normaal-risico' patiënt. Ook zijn de meeste hersenzenuwletsels van voorbijgaande aard en deze complicatie zal daarom niet als doorslaggevend criterium gebruikt moeten worden om te kiezen voor CAS boven een CEA. Ook in patiënten met een contralaterale occlusie zagen we geen duidelijk verschil in uitkomst tussen CAS en CEA (hoofdstuk 5). Daarom hebben we de procedures samengenomen en gekeken welke patiënten er een groter risico hebben op een complicatie na de ingreep door de aanwezigheid van een carotis stenose of occlusie (volledige afsluiting) aan de contralaterale zijde. We vonden dat een contralaterale occlusie in een symptomatische patiënt geen hoger risico op complicaties geeft dan een symptomatische patiënt zonder contralaterale occlusie. Een asymptomatische patiënt met een hooggradige stenose en een contralaterale occlusie heeft echter wel een significant hoger stroke risico. De manier van revascularisatie (CAS of CEA) is hier niet op van invloed. De laatst genoemde patiëntengroep zou mogelijk in aanmerking komen voor medicamenteuze therapie alleen, zonder interventie.

In de verschillende hoofdstukken in dit proefschrift tonen we aan dat er vele, vaak uiteenlopende, factoren samenhangen met het uiteindelijke behandelresultaat. Andere factoren dan de genoemde anatomische 'hoog-risico' factoren die het risico op stroke of overlijden met CEA verhogen zijn bijvoorbeeld geslacht (vrouwen), nierfalen, COPD, spoedoperatie, een 'zorgbehoevende' status en perifeer vaatlijden. De juiste behandeling kiezen voor de individuele patiënt met een carotis stenose blijft dus een uitdaging. Het is echter onmogelijk om de therapiekeus af te laten hangen van één hoog-risico factor. De besproken anatomische hoog-risico factoren mogen dan ook

zeker niet het enige argument zijn om een stentplaatsing te doen, maar deze beslissing zal verder onderbouwd moeten worden. In het algemeen zijn de procedurele risico's van zowel CAS en CEA echter laag en lijken beide behandelingen elkaar eerder aan te vullen dan dat ze concurrenten van elkaar zijn.

In dit proefschrift zijn niet alleen de risico's van CAS versus CEA met elkaar vergeleken, maar is ook kritisch gekeken naar de bron van de gepresenteerde data. Grote databases zijn populair om uitkomsten van grote groepen mensen te objectiveren en te vergelijken. De registraties die erop gericht zijn om de kwaliteit van het onderzoek te verbeteren zijn hier uitermate geschikt voor. Er wordt op deze manier op vlotte wijze grote aantallen data verzameld, waardoor er met een relatief hoge zekerheid een statistisch verschil kan worden aangetoond, ondanks dat de complicatie (bijvoorbeeld stroke) zelf niet vaak voorkomt. Het voordeel is dat men 'real world' data kan analyseren en het directe effect van een (kwaliteits-) verandering of maatregel kan meten, om hier vervolgens op te kunnen anticiperen. Ondanks dat er vaak onafhankelijke personen zijn aangenomen om de gegevens in de database in te voeren, blijven het zogenaamde 'zelfgeraporteerde' data. Als de resultaten geanonimiseerd blijven voor derden lijkt dit geen probleem. Echter als de data (ook) voor andere, met name financiële, doeluiteinden gebruikt worden blijken de data zeer onbetrouwbaar. Wij concluderen dat de grootste database in the USA (Nationwide Inpatient Sample) uiterst ongeschikt is om CAS en CEA met elkaar te vergelijken. Alle conclusies die uit eerder onderzoek in deze database volgen zijn hierdoor ook onbetrouwbaar en zullen niet gebruikt moeten worden om aanbevelingen te doen in de (internationale) richtlijnen voor de behandeling van de carotis stenose.

Tabel: Definitie van hoog-risico door de Centers for Medicare & Medicaid Services

Patiënten met een hoog-risico voor CEA worden gedefinieerd als patiënten met comorbiditeiten of anatomische risicofactoren, waardoor zij als 'slechte' kandidaten voor CEA worden gezien door de behandelend chirurg.

Fysiologische risicofactoren

- Hartfalen klasse III/IV;
- Linker ventrikel ejectie fractie <30%;
- Onstabiele angina pectoris;
- Recent myocard infarct;

Anatomische risicofactoren

- Contralaterale occlusie van de arterie carotis.
- Eerdere ipsilaterale CEA met restenose;
- Eerdere radiotherapie in de cervicale regio; en

Overige condities die eerder gebruikt zijn in grote vergelijkende onderzoeken tussen CAS en CEA om patiënten met een hoog-risico voor CEA uit te sluiten.

Review committee

Prof. dr. M.L. Bots
Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht, Utrecht, The Netherlands

Prof. dr. L.J. Kappelle
Department of Neurology and Neurosurgery
University Medical Center Utrecht, Utrecht, The Netherlands

Prof. dr. P.A.F.M. Doevedans
Department of Cardiology
University Medical Center Utrecht, Utrecht, The Netherlands

Prof. dr. C.J. Kalkman
Department of Anesthesiology
University Medical Center Utrecht, Utrecht, The Netherlands

Acknowledgement/ Dankwoord

I would like to thank several people who were, in some way, involved in my 'PhD years'
for a wealth of new experiences
for being a source of inspiration
for being part of a great team
for being friends, colleagues and family
for making this thesis worthwhile

In particular, this thesis would not have existed without the help and support of many great people. Some words of thankfulness…

Prof. dr. F.L. Moll, beste professor, uw voorstel om te solliciteren voor een research plek in Boston kon ik niet afslaan. Een half jaar later was u op bezoek als 'visiting professor'. Als groot vaatchirurg sprak u op 'mijn' grand rounds. Ik was trots en mijn aanzien steeg aanzienlijk onder de BIDMCers. Ik ben ontzettend blij en dankbaar voor het vertrouwen dat u me gaf, ook in moeilijker tijden en tegenslag. Altijd op het juiste moment zat er een mailtje in m'n inbox met een relativerende en verhelderende boodschap. Ik bewonder uw wetenschappelijke expertise, geduld en vakmanschap. Heel veel dank voor alles, het is een eer en een genoegen om onder u te mogen promoveren.

Dr. de Borst, beste GJ, wat ben ik blij dat ik als vierdejaars student bij jou en Anne in het team mocht! Mij ging zo'n review veel te langzaam, maar jij inspireerde, motiveerde en hield immer vertrouwen. Vanaf vele (lucht)havens mailden we over en weer, ik kan me echt geen betere begeleider wensen dan jij. Altijd had je ideëen voor nieuwe projecten, of 'nog wat patiëntennummers' op een briefje gekrabbeld. 'Of ik dat wilde opschrijven.' Veel van jouw hypotheses hebben geresulteerd in dit boekje. Tijdens mijn ASAS telde de patiënt, maar namen we na de visite snel de revisies door. En zelfs dan was er tijd voor gezelligheid. Ik zie je als een groot voorbeeld als mens, vaatchirurg en wetenschapper. Voor nu heel veel dank voor alles waar onze projecten toe hebben geleid! Op naar de toekomst.

Dear Dr. Schermerhorn, I would like to thank you for the opportunity to work with you at the BI Deaconess. This scientific year was amazing to me. It took me some time to feel comfortable with all the numbers and databases that were available to me. You taught me how to interpret the numbers and how to blow up the figures in my PowerPoint. This resulted in a productive year including several presentations at different vascular conferences. While you schedule was incredibly busy, you always managed to take care of your patients and your employees. Maybe that's why everyone likes you. Thank you for taking me on this one-year trip of (American) experiences, the introduction to outcome research in vascular surgery, the amazing diners and the collaboration on many projects. A lifelong present. It's very special to have you and Jill come over on November 28th.

Leden van de Leescommissie, Prof. dr. M.L. Bots, Prof. dr. L.J. Kappelle, Prof. dr. P.A.F.M Doevedans, Prof. dr. C.J. Kalkman. Heel hartelijk dank voor het kritisch beoordelen mijn proefschrift.

Leden van de Oppositie, Dr. P.C.M. Verbeek (chirurg en opleider Heelkunde Flevoziekenhuis), Dr. R.J. Toorop (vaatchirurg, UMC Utrecht), Dr. J.A. Vos (interventie-radioloog, St. Antonius Ziekenhuis Nieuwegein); veel dank voor jullie tijd en interesse om zitting te nemen in de oppositie tijdens de verdediging van mijn proefschrift. Ik hoop dat ik jullie allen zal blijven tegenkomen in de steeds veranderende medische wereld, waarin de vraag naar kritische blikken en innovatieve oplossingen van groot belang is.

All my collaborating authors of the SVS Outcome Committee and the Vascular Study Group of New England, and in particular Phil Goodney, Brian Nolen, Jeff Indes, Robert Cambria, Richard Powell, Viranda Patel and April Nedeau. You have a great organization with numerous great vascular surgeons delivering high-level research projects. Thank you for your collaboration!

My colleagues and the collaborating authors of the Beth Israel Deaconess Medical Center, including the staff of the Department of Vascular and Endovascular Surgery: Frank Logerfo, Elliot Chaikof, Allan Hamdan, Mark Wyers, Raoul Guzman, Michelle, Matth, Carla, Mary and Patty. Thanks a lot for your hospitality, your input in our manuscripts and the fun (waiting) time in the hybrid OR.

Rodney, Ruby, Tommy, Jeremy; I am a lucky person that I got the chance to work with you. From English edits to learn about swass... Thanks a million for the great year in the Schermerhorn research group. Rob en Do, wat heerlijk om deze ervaring met jullie te kunnen delen, dank voor jullie enthousiasme en hulp. Hopefully we'll all meet at many SVS meetings in the future!

Alle co-auteurs in het UMC Utrecht: Michel Bots, Ingeborg van der Tweel, Gerard Pasterkamp, Arjen Vink, Hester den Ruijter, Anne den Hartog, Guus van Lammeren, Bo Reichmann en Joyce Vrijenhoek. Geweldig hoe je door een fijne samenwerking iets moois neer kan zetten! Heel veel dank voor jullie kritische blik, harde werk en altijd waardevolle input.

Chirurgen en arts-assistenten heelkunde in het UMC Utrecht. Veel dank voor de mooie en leerzame tijd in het UMC!

Susan en Cobie, heel veel dank voor jullie interesse, hulp en gezelligheid in de stafgang.

Collega arts-onderzoekers heelkunde; Lutske Lodewijk, Guido van Bogerijen, Wouter Hoogendoorn, Herman Zantvoort, Martin Teraa, Klaas Govaert, Benjamin Emmink, Okan Bastian, Marjolijn Heeres, Peter Paul Wisman, Bas Nelissen, Leonie Haverkamp, Amy Gunning, Stephanie Peeters Weem en Quirina de Ruiter.

De Toren; lieve kamergenoten, Jakob Kist, Laurien Waaijer, Claire Pennekamp en Sjoerd Nell, ik heb van jullie genoten afgelopen half jaar! Door jullie reisde ik (bijna) elke dag vol energie naar de mooiste plek op de Uithof. Jullie zijn te gek, en daar kan geen nespresso-apparaat tegenop! Dankjulliewel.

AD6ers Carmen van de Pol, Emily Postma, Pieter Leliefeld, Kari Trumpi, Loek Loozen en Thomas Vellinga; wat geweldig om met jullie de uitdaging aan te zijn gegaan! De tochtjes naar Den Haag vond ik net zo leuk als de Alpe d'HuZes, waarvoor heel veel dank.

Chirurgen en arts-assistenten heelkunde in het Flevoziekenhuis; wat ben ik super blij dat ik jullie als nieuwe collega's heb getroffen. Dank voor jullie interesse en begrip bij de afronding van dit boekje. Vanaf nu alle focus op de kliniek.

Lieve clubvriendinnetjes (trouble in the tunnel/ op t IJ...), allerleukste huis van Utrecht (freaky fridays...), de echte Boston in Damsko (zonder jullie had ik het nooit overleefd!), LMAML en vele vele anderen; DANK dat jullie er altijd voor me zijn. Vanaf nu geen deadlines meer. Ik hoop op nog vele jaren vriendschap.

Lieve Mariek, een groot deel van mijn promotie maakte jij mee zonder dat we beiden wisten dat het zou leiden tot dit boekje. Er telde namelijk maar 1 ding; de NED 6 moest winnen! Uren klussen, hangen op

vliegvelden, gymsessies in Club Sportive, McDreamy 1 en 2, (te) gekke Ozzies, wiervelden in China en shoppen in Miami hebben geleid tot onvergetelijke jaren en resultaten op het water. Je bent de beste bemanning ooit en je gaat goud halen in Rio! Jouw talent en drive is ongekend lieverd. Dank voor alles.

Mijn paranimfen,
Lieve Sjaakie, wat ben ik ongelofelijk trots op jou! Van de fijne momenten op de Schroeder van de Kolk tot de vele vroege ritjes over de A2 naar het UMC (met Nick en Simon op repeat); wat is het een feest om bij jou in de buurt te zijn. Je bent echt een geweldige vriendin, dokter en straks chirurg. Jouw wijsheid, doorzettingsvermogen en harde werken zullen je alles brengen wat je wil. En ik, ik gun je de wereld en hoop ooit nog eens samen op de OK te staan. Dankjewel dat je mijn paranimf bent!

Lieve Juul, ik ben super blij, trots en dankbaar dat jij vandaag naast me staat. Jou leerde ik kennen in een tent, een vriendschap die uitgroeide tot op de Riemstraat samen met Fred en Eek. Je bent echt een heel bijzonder mens Juul. Staat altijd klaar voor iedereen, begripvol maar nuchter en met de juiste woorden. Toen jij en Eek vorig jaar uit de Fung Wah bus stapten in Boston, was ik gelukkiger dan ooit. Zo ver weg is het zo fijn om te voelen dat er mensen zijn bij wie je je thuis voelt. Ik hoop dat we nog ontzettend veel samen mee gaan maken, je bent een topper!

Esther Vinke, door jouw professionele blik en creatieve brein hadden we binnen no-time een geweldige omslag. Gordijnen uit het SLAZ...ach ja, why not? Dank voor je harde werk en mooie cover. Gert, Fred en zus; dankjulliewel voor je (mentale) ondersteuning bij het design van dit boekje.

Lieve familie van Bart, wat bof ik met jullie. Dank voor jullie interesse, steun en gezelligheid!

Lieve oma, ik zwaai via de maan! Je bent een geweldige oma, ik hou van je en dank je voor je wijsheid, liefde en interesse in mij en in alle mensen om me heen.

Lieve zusjes, lieve Tjerk en Wien. Jullie zijn echt de liefste zusjes die ik me maar kan wensen. En ik ben super trots op jullie. Dankjulliewel dat jullie me altijd gesteund hebben, promotie of niet, buitenland of niet, zeilen of niet...en ga zo maar door. Zoals jullie er voor mij zijn, zal ik er ook altijd voor jullie zijn. Op nog vele knusse momenten aan wal of op ‘t Nieuw Getij.

Lieve papamama, heb geen woorden voor alles wat ik van jullie geleerd heb, voor jullie onvoorwaardelijke liefde en ongekende vertrouwen in alles wat ik doe. Met z’n tweeën kunnen jullie denk ik letterlijk de wereld aan, en daar word ik een heel blij en trots meisje van. Hou van jullie!

Bart, ik hou zo veel van jou!! Samen lachen, samen leven, samen delen. Straks twee boeken in misschien wel een kast. En als niet dan toch, geniet ik van elke seconde met jou...! Dank voor je zijn piefie. Heb zoveel zin in alle dingen die het leven voor ons in gedachten heeft!

Publications

Fokkema M, de Borst GJ, Nolan BW, Indes J, Buck DB, Lo RC, Moll FL, Schermerhorn ML, on behalf of the Vascular Study Group of New England. *Clinical Relevance of Cranial Nerve Injury following Carotid Endarterectomy.*
Eur J Vasc Endovasc Surg. 2013 Sept. Accepted for publication

Fokkema M, Hurks R, Curran T, Bensley RP, Hamdan AD, Wyers MC, Moll FL, Schermerhorn ML. *The impact of the present on admission indicator on the accuracy of administrative data for carotid endarterectomy and stenting.*
J Vasc Surg. 2013 Aug 27. [Epub ahead of print]

Fokkema M, de Borst GJ, Nolan BW, Lo RC, Cambria RA, Powell RJ, Moll FL, Schermerhorn ML; the Vascular Study Group of New England. *Carotid stenting versus endarterectomy in patients undergoing reintervention after prior carotid endarterectomy.*
J Vasc Surg. 2013 Aug 21. [Epub ahead of print]

Fokkema M, Reichmann BL, den Hartog AG, Klijn CJ, Schermerhorn ML, Moll FL, de Borst GJ. *Selective external endarterectomy in patients with ipsilateral symptomatic internal carotid artery occlusion.*
J Vasc Surg. 2013 Jul;58(1):145-51.e1.

Bensley RP, Yoshida S, Lo RC, **Fokkema M**, Hamdan AD, Wyers MC, Chaikof EL, Schermerhorn ML. *Accuracy of administrative data versus clinical data to evaluate carotid endarterectomy and carotid stenting.*
J Vasc Surg. 2013 Aug;58(2):412-9.

Schermerhorn ML, **Fokkema M**, Goodney P, Dillavou ED, Jim J, Kenwood CT, Siami FS, White RA; SVS Outcomes Committee. *The impact of Centers for Medicare and Medicaid Services high-risk criteria on outcome after carotid endarterectomy and carotid artery stenting in the SVS Vascular Registry.*
J Vasc Surg. 2013 May;57(5):1318-24.

Fokkema M, Bensley RP, Lo RC, Hamden AD, Wyers MC, Moll FL, de Borst GJ, Schermerhorn ML. *In-hospital versus postdischarge adverse events following carotid endarterectomy.*
J Vasc Surg. 2013 Jun;57(6):1568-75, 1575.e1-3.

Fokkema M, den Hartog AG, van Lammeren GW, Bots ML, Pasterkamp G, Vink A, Moll FL, de Borst GJ. *Radiation-induced carotid stenotic lesions have a more stable phenotype than de novo atherosclerotic plaques.*
Eur J Vasc Endovasc Surg. 2012 Jun;43(6):643-8.

Fokkema M, den Hartog AG, Bots ML, van der Tweel I, Moll FL, de Borst GJ. *Stenting versus surgery in patients with carotid stenosis after previous cervical radiation therapy: systematic review and meta-analysis*. Stroke. 2012 Mar;43(3):793-801.

Pending publications

Fokkema M, Goodney PP, Curran T, Patel VI, Nedeau AE, Moll FL, de Borst GJ, Schermerhorn ML, for the Vascular Study Group of New England. T*he impact of contralateral carotid stenosis or occlusion on outcome following carotid endarterectomy and stenting.*

Fokkema M*, Vrijenhoek JEP*, Den Ruijter HM, Groenwold RHH, Schermerhorn ML, Bots ML, Pasterkamp G, Moll FL, De Borst GJ, on behalf of the TREAT CARE Study Group. *Carotid Stenting versus endarterectomy in patients with restenosis following prior endarterectomy: an individual patient data meta-analysis*

Lo RC, Lu B, **Fokkema M**, Fillinger M, Conrad M, Patel VI, Matyal R, Schermerhorn ML. *Relative importance of aneurysm diameter and body size for predicting AAA rupture in men and women.*

Lo RC, **Fokkema M**, Curran T, Hamdan AD, Wyers M, Guzman RJ, Chaikof EL, Schermerhorn ML. *The decline of mesenteric ischemia-related mortality in the last decade.*

Herrmann J*, Lo RC*, **Fokkema M**, Hamdan A, Wyers M, Patel VI, Fillinger M, Schermerhorn ML. *Preoperative risk factors and consequences of type II endoleaks.*

Lo RC, **Fokkema M**, Curran T, Darling J, Hamdan AD, Wyers M, Chaikof EL, Schermerhorn ML. *Predictors of access-site related complications after lower extremity percutaneous revascularization.*

Botta R, Schlosser F, Nolan B, Goodney P, **Fokkema M**, Schermerhorn ML, Bertges D, Indes J. *Characteristics that define high risk in carotid endarterectomy from the Vascular Study Group of New England (VSGNE).*

Curran T, Lo RC, **Fokkema M,** Wyers MC, Hamdan AD, Chaikof EL, Schermerhorn ML. *Predictors of 30-day readmission and post-discharge mortality following carotid endarterectomy in the ACS-NSQIP*

Curran T, **Fokkema M,** Lo RC, Wyers MC, Hamdan AD, Chaikof EL, Schermerhorn ML. *Predictors of 30-day readmission and post-discharge mortality following lower extremity amputation the ACS-NSQIP*

Fockens MM, **Fokkema M**, Alves M, Nelson RC, Hayman NS, Friedman DJ, Danziger J. *Vitamin K deficiency in patients with known peripheral artery disease*

Curriculum Vitae

Talje Margriet Fokkema was born on August 18th, 1986 in Rosmalen. She was the second child of Willem Fokkema and Tallien Fokkema-Zylker, and the sister of Tjerkje (1985) and later Lidwien (1987). The family Fokkema lived in Douala (Camaroon) during the first years of Margriet's life, where Willem used to work for an international beer brewery. After four years, the family moved back to The Netherlands, where Margriet finished primary school in Haren and started to become a fervent sailor in the optimist. She graduated high school at the Stedelijk Gymnasium in Arnhem and started her medical study at the University of Utrecht in 2004. She became an active member of the student sorority. During this period, she competed in numerous international sailing regatta's in the 470 class. Together with Marieke Jongens (crew), they qualified for the Dutch Sailing Team. Margriet took a break from her medical internships, while she started to combine medical research with professional sailing. She became involved and enthusiastic in vascular surgery under the supervision of Gert Jan de Borst and Frans Moll. After she finished her final internship at the Department of Vascular Surgery in the UMC Utrecht, she graduated from medical school in December 2011. Margriet was given the opportunity to work as a PhD research fellow for Dr. Schermerhorn in Boston to proceed to work on projects that involve the carotid artery. The results of her projects are presented in this thesis. Currently, Margriet works as a surgical resident (not in training) at the Flevoziekenhuis in Almere (The Netherlands).