Washington State Health Care Authority

Health Technology Assessment

Stenting for Treatment of Atherosclerotic Stenosis of the Extracranial Carotid Arteries or Intracranial Arteries

Final Evidence Report: Appendices

August 13, 2013

Health Technology Assessment Program (HTA)
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126
hta.hca.wa.gov

shtap@hca.wa.gov

Stenting for Treatment of Atherosclerotic Stenosis of the Extracranial Carotid Arteries or Intracranial Arteries

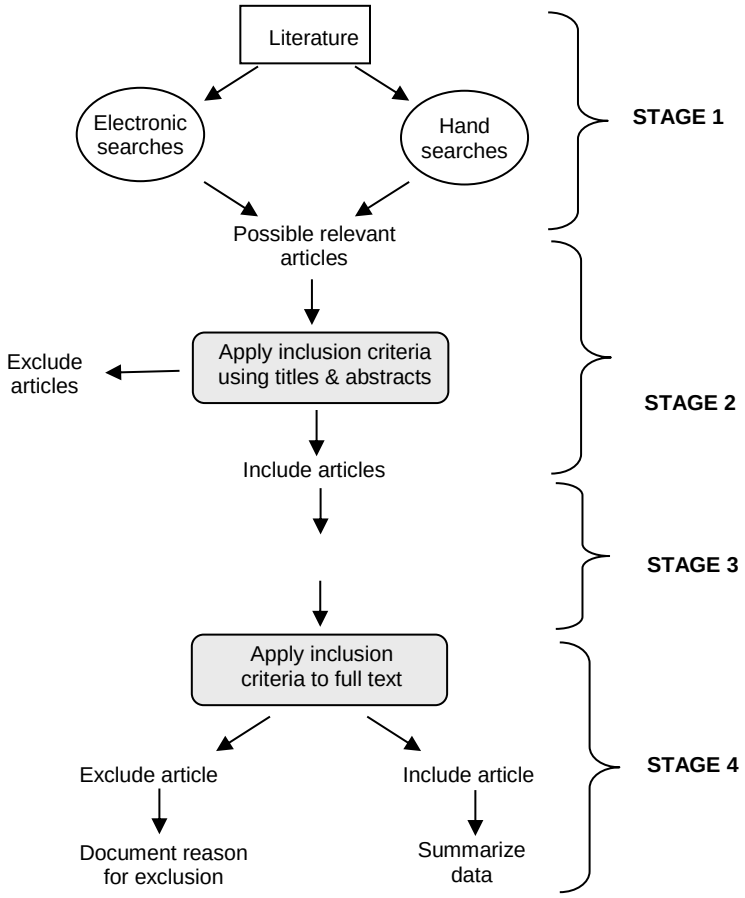
Provided by:

Spectrum Research, Inc.

August 13, 2013

APPENDICES

APPENDIX A. ALGORITHM FOR ARTICLE SELECTION



APPENDIX B. SEARCH STRATEGIES

Below is the search strategy for PubMed. Parallel strategies were used to search other electronic databases listed below. Key word searches were conducted in the other listed resources.

Carotid artery stenosis:
PubMed search performed through 02/28/2013
Limits Activated: Humans; English

Symptomatic and Asymptomatic

	Search terms	No. of articles
1.	Angioplasty OR "Angioplasty, balloon"[Mesh] OR stent OR "stenting" OR endovascular OR "Endovascular Procedures"[Mesh] OR intraluminal	113,426
2.	"carotid artery" OR carotid artery, common[Mesh] OR carotid artery, external[Mesh] OR carotid artery, internal[Mesh]	33,775
3.	"carotid artery disease" OR "carotid artery thrombosis" OR thrombosis OR carotid stenosis OR constriction[Mesh]	140,533
4.	endarterectomy OR "Endarterectomy, Carotid"[Mesh] OR medical OR "medical therapy" OR conservative	1,846,836
5.	#1 AND #2 AND #3 AND #4	1,929
6.	#5 AND Filter: Randomized Controlled Trial	71
7.	#5 AND Filter: Comparative Study	367
8.	#5 AND Filter: Clinical Trial	216
9.	#5 AND #6 AND #7 AND #8	503
10.	#9 AND ("asymptomatic disease"[MeSH] OR asymptomatic OR "no symptoms" OR "symptomatic disease" OR symptom*)	297
11.	#10 AND (safety OR adverse events OR complications OR "periprocedural" OR efficacy, treatment[MeSH] OR restenosis OR "quality of life" OR "health-related quality of life" OR function OR "Treatment Outcome"[Mesh] OR "effectiveness")	281
12.	#9 AND (safety OR adverse events OR complications OR "periprocedural" OR efficacy, treatment[MeSH] OR restenosis OR "quality of life" OR "health-related quality of life" OR function OR "Treatment Outcome"[Mesh] OR "effectiveness")	454
	Additional studies identified through hand searching, bibliography cross-referencing and searching PubMed for related literature	40
	Final number of studies identified to assess for inclusion	494

Carotid artery stenosis:
EMBASE search performed through 01/30/2013
Limits Activated: Humans; English

Search code:

'common carotid artery'/exp OR 'external carotid artery'/exp OR 'internal carotid artery'/exp AND ('angioplasty'/exp OR 'percutaneous transluminal angioplasty'/exp OR stent* OR endovascular OR intraluminal) AND ('endarterectomy'/exp OR medical OR conservative) AND ('carotid artery disease'/exp OR 'carotid artery thrombosis'/exp OR 'carotid artery obstruction'/exp OR 'ligation'/exp) AND ('symptomatic disease' OR symptom* OR 'asymptomatic disease'/exp OR 'asymptomatic' OR 'no symptoms') AND ('therapy'/exp OR 'restenosis'/exp OR 'quality of life'/exp OR 'health-related quality of life'/exp OR function OR 'cognition'/exp OR 'safety'/exp OR 'adverse events' OR complications OR periprocedural OR 'cost benefit analysis'/exp OR 'cost effectiveness'/exp) AND [humans]/lim AND [english]/lim

No. articles retrieved: 440
Duplicates: 62
Total for abstract/full text review: 378

Economics:
PubMed search performed through 03/27/2013
Limits Activated: Humans; English

	Search terms	No. of articles
1	cost carotid stenting	128
2	("Carotid Artery Diseases"[Mesh]) OR "Carotid Stenosis"[Mesh]	35,233
3	"Stents"[Mesh]	47,782
4	#2 AND #3	3,341
5	#4 AND (cost OR economic OR cost-effectiveness OR cost-utility OR cost-benefit)	109
6	("Angioplasty/economics"[Mesh]) OR "Stents/economics"[Mesh]	1,336
7	#2 AND #6	53
8	#2 AND #6 Filters: Abstract available	32
9	#49 AND #13 Filters: Abstract available; English	32
	Additional studies identified through a Centers for Reviews and Dissemination search using: Carotid AND Cost. There were 103 returns, 27 were selected for abstract review based on title	2
	Final number of studies identified to assess for inclusion	34

APPENDIX C. EXCLUDED STUDIES

Table C1. Articles excluded as primary studies after full text review for Key Questions 1, 3, 4, 5 evaluating carotid artery stenosis.

	Citation	Reason for Exclusion
1.	Abou-Chebl A, Yadav JS, Reginelli JP, Bajzer C, Bhatt D, Krieger DW. Intracranial hemorrhage and hyperperfusion syndrome following carotid artery stenting: risk factors, prevention, and treatment. J Am Coll Cardiol. May 5 2004;43(9):1596-1601	Mixed population – data not stratified by symptom status
2.	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 Nov;34(5):831-8.	Mixed population – data not stratified by symptom status
3.	Alberts MJ. Results of a multicentre prospective randomized trial of carotid artery stenting vs carotid endarterectomy. Stroke 2001;32:325.	Meeting abstract only
4.	Alvaerz B, Ribo M, Maeso J, et al. Transcervical carotid stenting with flow reversal is safe in octogenarians: A preliminary safety study. J Vasc Surg 2008;47:96-100.	Mixed population – data not stratified by symptom status
5.	Anderson HV, Rosenfield KA, White CJ, et al. Clinical Features and Outcomes of Carotid Artery Stenting by Clinical Expert Consensus Criteria: A Report From the CARE Registry. Catheterization and Cardiovascular Interventions 2010;75:519–525.	Mixed population – data not stratified by symptom status
6.	Aronow HD, Gray WA, Ramee SR, Mishkel GJ, Schreiber TJ, Wang H. Predictors of neurological events associated with carotid artery stenting in high-surgical-risk patients: insights from the Cordis Carotid Stent Collaborative. Circ Cardiovasc Interv. Dec 2010;3(6):577-584.	Not comparative
7.	Becquemin JP, Ben El Kadi H, Desgranges P, Kobeiter H. Carotid stenting versus carotid surgery: a prospective cohort study. J Endovasc Ther. 2003;10(4):687-694.	Not stratified by symptom status; no subgroup analysis
8.	Bergeron, P., J. P. Becquemin, et al. (1999). "Percutaneous stenting of the internal carotid artery: The European CAST I study." Journal of Endovascular Surgery 6(2): 155-159.	Mixed population – data not stratified by symptom status
9.	Blackshear JL, Cutlip DE, Roubin GS, et al. Myocardial infarction after carotid stenting and endarterectomy: results from the carotid revascularization endarterectomy versus stenting trial. Circulation. Jun 7 2011;123(22):2571-2578.	Not stratified by symptom status; no subgroup analysis
10.	Brewster LP, Beaulieu R, Kasirajan K, 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. Nov 2012;56(5):1291-1294; discussion 1294-1295.	CEA group has < 30 patients (n = 18)
11.	Brewster LP, Kasirajan KP, Beaulieu 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. 2011;54(6):1854.	CEA group has < 30 patients (n = 20); duplicate study with 2012?
12.	Brewster LP, Beaulieu R, Corriere MA, et al. Carotid revascularization outcomes comparing distal filters, flow reversal, and endarterectomy. J Vasc Surg. Oct 2011;54(4):1000-1004; discussion 1004-1005.	Not stratified by symptom status; comparison not of interest (CEA vs. CAS with different types of EPD)
13.	Bush RL, Kougias P, Guerrero MA, et al. A comparison of carotid artery stenting with neuroprotection versus carotid endarterectomy under local anesthesia. Am J Surg 2005;190(5):696-700.	Mixed population – data not stratified by symptom status
14.	Bosiers M, Peeters P, Deloose K, Verbist J, Sievert H, Sugita J, et al. Does carotid artery stenting work on the long run: 5-year results in high-volume centers (ELOCAS Registry). J Cardiovasc Surg (Torino) 2005;46:241-7.	Not comparative (case-series)
15.	Cao P, De Rango P, Verzini F, Maselli A, Norgiolini L, Giordano G. Outcome of carotid stenting versus endarterectomy: a case-control study. Stroke. May 2006;37(5):1221-1226.	Mixed population – data not stratified by symptom status
16.	Capoccia L, Speziale F, Gazzetti M, et al. Comparative study on carotid revascularization (endarterectomy vs stenting) using markers of cellular brain injury, neuropsychometric tests, and diffusion-weighted magnetic resonance imaging. J Vasc Surg 2010; 51(3):584-92.	Overlap with Capoccia 2012 included in report
17.	CaRESS Steering Committee. Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) phase I clinical trial: 1-year results. Journal of Vascular Surgery 2005 Aug;42(2):213-19.	Mixed population – data not stratified by symptom status
18.	Carotid revascularization using endarterectomy or stenting systems (CARESS): phase I clinical trial. J Endovasc Ther. 2003; 10(6):1021-1030.	Mixed population – data not stratified by symptom status

	Citation	Reason for Exclusion
19.	CAVATAS investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet. Jun 2 2001;357(9270):1729-1737.	< 80% of patients underwent stenting
20.	Chaturvedi S, Matsumura JS, Gray W, et al. Carotid Artery Stenting in Octogenarians Periprocedural Stroke Risk Predictor Analysis From the Multicenter Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events (CAPTURE 2) Clinical Trial. Stroke 2010;41:757-764.	Not comparative
21.	Chung J, Kim BM, Paik HK, et al. Effects of carotid artery stenosis treatment on blood pressure. J Neurosurg 2012 117(4):755-60.	Mixed population – data not stratified by symptom status
22.	Chang CK, Huded CP, Nolan BW, Powell RJ. Prevalence and clinical significance of stent fracture and deformation following carotid artery stenting. J Vasc Surg. Sep 2011;54(3):685-690.	Mixed population – data not stratified by symptom status
23.	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. Oct 4 2011;58(15):1557-1565.	Not stratified by symptom status; no subgroup analysis
24.	Coppi G, Moratto R, Silingardi R et al. (2005). PRIAMUS—proximal flow blockage cerebral protection during carotid stenting: results from a multicenter Italian registry. J Cardiovasc Surg (Torino), 46(3):219-27.	Mixed population – data not stratified by symptom status
25.	Dieter RS, Ikram S, Satler LF et al. (2006) Perforation complicating carotid artery stenting: the use of a covered stent. Catheterization & Cardiovascular Interventions 67: 972–5.	Not comparative, case-report
26.	Ecker RD, Lay T, Levy EI, et al. Thirty-day morbidity and mortality rates for carotid artery intervention by surgeons who perform both carotid endarterectomy and carotid artery angioplasty and stent placement. J Neurosurg 106:217–221, 2007	Mixed population – data not stratified by symptom status
27.	Endo S, Kuwayama N, Hirashima Y. Japan Carotid Atherosclerosis Study: JCAS. Neurol Med Chir (Tokyo). 2004;44(4):215-217.	Mixed population – data not stratified by symptom status
28.	Ederle J, Bonati LH, Dobson J, 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. Oct 2009;8(10):898-907.	< 80% of patients underwent stenting
29.	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. Feb 2011;53(2):307-315.	No subgroup analysis for CAS vs CEA.
30.	Felli MM, Alunno A, Castiglione A, et al. CEA versus CAS: short-term and mid-term results. Int Angiol. 2012 Oct; 31(5):420-6	Mixed population – data not stratified by symptom status
31.	Fiehler J, Jansen O, Berger J, Eckstein HH, Ringleb PA, Stingele R. Differences in complication rates among the centres in the SPACE study. Neuroradiology. Dec 2008;50(12):1049-1053.	Subgroup not of interest (number of treated patients per center for CAS vs. CEA)
32.	Friedman JA, Kallmes DF, Wijdicks EF (2004) Thalamic hemorrhage following carotid angioplasty and stenting. Neuroradiology 46: 399–403.	Not comparative, case-report
33.	Gadoth A, Auriel E, Shaim H, Bornstein NM. Periprocedural complication rate of carotid endarterectomy versus carotid angioplasty and stenting: a retrospective study and review of the literature. Isr Med Assoc J. Oct 2011;13(10):601-604.	Mixed population – data not stratified by symptom status
34.	Goode SD, Cleveland TJ, Gaines PA; on behalf of the British Society of Interventional Radiology. First BSIR Carotid Stent Registry Report 2011.	Not comparative
35.	Gray WA, Rosenfield KA, Jaff MR, et al. Influence of site and operator characteristics on carotid artery stent outcomes: analysis of the CAPTURE 2 (Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events) clinical study. JACC Cardiovasc Interv. Feb 2011;4(2):235-246.	Not comparative
36.	Gray WA, Chaturvedi S, Verta P on behalf of the Investigators and the Executive Committees. (2009). Thirty-Day Outcomes for Carotid Artery Stenting in 6320 Patients From 2 Prospective, Multicenter, High-Surgical- Risk Registries. Circ Cardiovasc Intervent 2009;2;159-166; originally published online Mar 6, 2009.	Not comparative
37.	Gray WA, Hopkins LN, Yadav S et al. (2006a). Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. J Vasc Surg, 44(2):258-68.	Not comparative
38.	Gray WA, Yadav JS, Verta P et al. (2006b). The CAPTURE registry: Results of carotid stenting with embolic protection in the post approval setting. Catheter Cardiovasc	Not comparative

	Citation	Reason for Exclusion
	Interv, 69(3):341-348.	
39.	Gray WA, White HJ Jr, Barrett DM, Chandran G, Turner R, Reisman M. Carotid stenting and endarterectomy: a clinical and cost comparison of revascularization strategies. Stroke. 2002;33:1063-70.	Mixed population – data not stratified by symptom status
40.	Gupta N, Corriere MA, Dodson TF, et al. The incidence of microemboli to the brain is less with endarterectomy than with percutaneous revascularization with distal filters or flow reversal. J Vasc Surg. Feb 2011;53(2):316-322.	Mixed population – data not stratified by symptom status
41.	Hammer FD, Lacroix V, Duprez T, et al. Cerebral microembolization after protected carotid artery stenting in surgical high-risk patients: results of a 2-year prospective study. J Vasc Surg. Nov 2005;42(5):847-853; discussion 853.	Mixed population – data not stratified by symptom status
42.	Higashida RT, Popma JJ, Apruzzese P et al. (2010). Evaluation of the medtronic exponent self-expanding carotid stent system with the medtronic guardwire temporary occlusion and aspiration system in the treatment of carotid stenosis: combined from the MAVErIC (Medtronic AVE Self-expanding CaRotid Stent System with distal protection In the treatment of Carotid stenosis) I and MAVErIC II trials. Stroke, 41(2):e102-9.	Not comparative
43. 44.	Hill MD, Morrish W, Soulez G, et al. Multicenter evaluation of a self-expanding carotid stent system with distal protection in the treatment of carotid stenosis. AJNR Am J Neuroradiol. 2006;27: 759–765.	Mixed population – data not stratified by symptom status
45.	Hirschberg K, Dosa E, Huttl K, et al. Early restenosis after eversion carotid endarterectomy versus carotid stenting: a single-centre retrospective study. J Cardiovasc Surg (Torino). Oct 2009;50(5):655-663.	Mixed population – data not stratified by symptom status
46.	Hobson RW II, Goldstein JE, Jamil Z, Lee BC, Padberg FT Jr, Hanna AK, et al. Carotid restenosis: operative and endovascular management. J Vasc Surg 1999;29:228-38.	Mixed population – data not stratified by symptom status
47.	Hobson RW, 2nd, Howard VJ, Roubin GS, 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. Dec 2004;40(6):1106-1111.	CAS only, no comparator group; interim data from CREST lead-in phase
48.	Hopkins LN, Myla S, Grube E et al. (2008). 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, 71(7):950-60.	Not comparative
49. 50.	Howard VJ, Voeks JH, Lutsep HL, et al. Does sex matter? Thirty-day stroke and death rates after carotid artery stenting in women versus men: results from the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) lead-in phase. Stroke. Apr 2009;40(4):1140-1147.	CAS only, no comparator group; patients treated as part of institution application to be in CREST, so treated prior to randomization (lead-in phase).
51.	Iyer SS, White CJ, Hopkins LN et al. (2008). 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, 51(4):427-34.	Not comparative
52.	Jansen O, Fiehler J, Hartmann M, Bruckmann H. Protection or nonprotection in carotid stent angioplasty: the influence of interventional techniques on outcome data from the SPACE Trial. Stroke. Mar 2009;40(3):841-846.	No comparator group, CAS only
53.	Jeyabalan G, Golla S, Makaroun M et al. (2009) Recurrent laryngeal nerve injury following uncomplicated carotid angioplasty and stenting. Journal of Endovascular Therapy: Official Journal of the International Society of Endovascular Specialists 16: 345–8.	Case report; 2-stage procedure
54.	Jordan WD Jr, Voellinger DC, Fisher WS, Redden D, McDowell HA. A comparison of carotid angioplasty with stenting versus endarterectomy with regional anesthesia. J Vasc Surg. 1998 Sep;28(3):397-402; discussion 402-3.	Mixed population – data not stratified by symptom status
55.	Jordan WD, Schroeder P, Fisher WS, McDowell HA. A comparison of angioplasty with stenting versus endarterectomy for the treatment of carotid artery stenosis. Annals of Vascular Surgery, 1997; 11:2-8.	Mixed population – data not stratified by symptom status
56.	Kang, H. S., M. H. Han, et al. (2007). "Intracranial hemorrhage after carotid angioplasty: A pooled analysis." Journal of Endovascular Therapy 14(1): 77-85.	Mixed population – data not stratified by symptom status
57.	Kasirajan K, Matteson B, Marek JM, Langsfeld M. Comparison of nonneurological events in high-risk patients treated by carotid angioplasty versus endarterectomy. Am J Surg. Apr 2003;185(4):301-304.	Mixed population – data not stratified by symptom status
58.	Katzen BT, Criado FJ, Ramee SR et al. (2007). Carotid artery stenting with emboli protection surveillance study: thirty-day results of the CASES-PMS study. Catheter Cardiovasc Interv, 70(2):316-23.	Not comparative

	Citation	Reason for Exclusion
59.	Khan AA, Chaudhry SA, Sivagnanam K, Hassan AE, Suri MF, Qureshi AI. Cost-effectiveness of carotid artery stent placement versus endarterectomy in patients with carotid artery stenosis. J Neurosurg. Jul 2012;117(1):89-93.	Not separated by symptom status
60.	Kilaru S, Korn P, Kasirajan K, et al. Is carotid angioplasty and stenting more cost effective than carotid endarterectomy? Journal of vascular surgery. Feb 2003;37(2):331-339.	Not separated by symptom status
61.	Kojuri J, Ostovan MA, Zamiri N, Farshchizarabi S, Varavipoor B. Hemodynamic instability following carotid artery stenting. Neurosurg Focus. Jun 2011;30(6):E12.	Not comparative; indirect outcome; hemodynamics
62.	Kovacic S, Kovacevic M, Strenja-Linic I, Budiselic B, Knezevic S. Comparison between carotid stenting and carotid endarterectomy in early outcome. Coll Antropol. Sep 2011;35 Suppl 2:271-274.	Mixed population – data not stratified by symptom status
63.	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. Sep 2012;11(9):755-763.	Not stratified by symptom status
64.	Ling F, Jiao LQ. Preliminary report of trial of endarterectomy versus stenting for the treatment of carotid atherosclerotic stenosis in China (TESCAS-C). Chinese Journal of Cerebrovascular Diseases 2006;3(1):4–8.	Not in English; info from website and abstract
65.	Liu CW, Liu B, Ye W, et al. [Carotid endarterectomy versus carotid stenting: a prospective randomized trial]. Zhonghua Wai Ke Za Zhi. Feb 15 2009;47(4):267-270.	Not in English
66.	Madyoon H, Braunstein E, Callcott F, Oshtory M, Gurnsey L, Croushore L, et al. Unprotected carotid artery stenting compared to carotid endarterectomy in a community setting. J Endovasc Ther 2002; 9:803-9.	Mixed population – data not stratified by symptom status
67.	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. Oct 2010;41(10 Suppl):S31-34.	Age categories for CAS vs CEA not stratified by symptomatic status; duplicate report
68.	Massop D, Dave R, Metzger C et al. (2009). Stenting and angioplasty with protection in patients at high-risk for endarterectomy: SAPPHIRE Worldwide Registry first 2,001 patients. Catheter Cardiovasc Interv, 73(2):129-36	Not comparative
69.	Matsumura JS, Gray W, Chaturvedi S, Gao X, Cheng J, Verta P. CAPTURE 2 risk-adjusted stroke outcome benchmarks for carotid artery stenting with distal embolic protection. J Vasc Surg. Sep 2010;52(3):576-583, 583 e571-583 e572.	Not comparative
70.	Naggara O, Touze E, Beyssen B, et al. Anatomical and technical factors associated with stroke or death during carotid angioplasty and stenting: results from the endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis (EVA-3S) trial and systematic review. Stroke. Feb 2011;42(2):380-388.	No comparator group, CAS only
71.	Park S-H, Lee CY (2008) Contralateral cerebral infarction after stent placement in carotid artery: an unexpected complication. Journal of Korean Neurosurgical Society 44: 159–62.	Not comparative, Case-report
72.	Park B, Mavanur A, Dahn M, Menzoian J. Clinical outcomes and cost comparison of carotid artery angioplasty with stenting versus carotid endarterectomy. J Vasc Surg. Aug 2006;44(2):270-276.	Mixed population – data not stratified by symptom status
73.	Parlani G, De Rango P, Cieri E, et al. Diabetes is not a predictor of outcome for carotid revascularization with stenting as it may be for carotid endarterectomy. J Vasc Surg. Jan 2012;55(1):79-89; discussion 88-79.	Not stratified by symptom status
74.	Protack CD, Bakken AM, Xu J, Saad WA, Lumsden AB, Davies MG. Metabolic syndrome: A predictor of adverse outcomes after carotid revascularization. J Vasc Surg. May 2009;49(5):1172-1180 e1171; discussion 1180.	Not stratified by symptom status
75.	Reimers B, Sievert H, Schuler GC et al. (2005). Proximal endovascular flow blockage for cerebral protection during carotid artery stenting: results from a prospective multicenter registry. J Endovasc Ther, 12(2):156-65.	Not comparative
76.	Reimers B, Schluter M, Castriota F, et al. Routine use of cerebral protection during carotid artery stenting: results of a multicenter registry of 753 patients. Am J Med 2004;116(4):217-22.	Not comparative
77.	Robbs JV, Mulaudzi T, Paruk N, et al. Carotid intervention: stent or surgery? A prospective audit. Cardiovasc J Africa 2009;20:336-339	Mixed population – data not stratified by symptom status
78.	Roh HG, Byun HS, Ryoo JW, et al. Prospective analysis of cerebral infarction after carotid endarterectomy and carotid artery stent placement by using diffusion-weighted imaging. AJNR Am J Neuroradiol. 2005;26(2):376-384.	Mixed population – data not stratified by symptom status

	Citation	Reason for Exclusion
79.	Sadek M, Hynecek RL, Sambol EB, et al. Carotid angioplasty and stenting, success relies on appropriate patient selection. J Vasc Surg 2008; 47(5): 946-51 .	Mixed population – data not stratified by symptom status
80.	Safian RD, Bresnahan JF, Jaff MR et al. (2006). Protected carotid stenting in high-risk patients with severe carotid artery stenosis. J Am Coll Cardiol, 47(12):2384-9.	Not comparative
81.	Setacci, C., G. Pula, et al. (2003). "Determinants of in-stent restenosis after carotid angioplasty: a case-control study." J Endovasc Ther 10(6): 1031-1038.	Mixed population – data not stratified by symptom status
82.	Shenoy AU, Aljutaili M, Stollenwerk B. Limited economic evidence of carotid artery stenosis diagnosis and treatment: a systematic review. Eur J Vasc Endovasc Surg. Nov 2012;44(5):505-513.	Systematic review of broader topic
83.	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. Oct 2009;50(4):762-767; discussion 767-768.	No comparator group, CAS only
84.	Shobha N, Almekhlafi MA, Pandya A, et al. Carotid angioplasty and stenting is safe in women. Can Assoc Radiol J. Aug 2012;63(3 Suppl):S18-22.	Mixed population – data not stratified by symptom status
85.	Skjelland M, Krohg-Sorensen K, Tennoe B, et al. Cerebral Microemboli and Brain Injury During Carotid Artery Endarterectomy and stenting. Stroke. 2009;40:230-234	Mixed population – data not stratified by symptom status
86.	Stabile E, Garg P, Cremonesi A, et al. European Registry of Carotid Artery Stenting: results from a prospective registry of eight high volume EUROPEAN institutions. Catheter Cardiovasc Interv. Aug 1 2012;80(2):329-334.	Mixed population – data not stratified by symptom status
87.	Stanziale SF, Marone LK, Boules TN, et al. Carotid artery stenting in octogenarians is associated with increased adverse outcomes. J Vasc Surg. Feb 2006;43(2):297-304.	Mixed population – data not stratified by symptom status
88.	Sternbergh WC, 3rd, Crenshaw GD, Bazan HA, Smith TA. Carotid endarterectomy is more cost-effective than carotid artery stenting. Journal of vascular surgery. Jun 2012;55(6):1623-1628.	Not separated by symptom status
89.	Stolker JM, Mahoney EM, Safley DM, Pomposelli FB, Jr., Yadav JS, Cohen DJ. Health-related quality of life following carotid stenting versus endarterectomy: results from the SAPPHIRE (Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy) trial. JACC. Cardiovascular interventions. May 2010;3(5):515-523.	Not stratified by symptom status
90.	Surdell D, Shaibani A, Bendok B et al. (2007) Fracture of a nitinol carotid artery stent that caused restenosis. Journal of Vascular & Interventional Radiology 18: 1297–9.	Not comparative, case-report
91.	Tang GL, Matsumura JS, Morasch MD, et al. Carotid Angioplasty and Stenting vs Carotid Endarterectomy for Treatment of Asymptomatic Disease Single-Center Experience. Arch Surg 2008; 143(7): 653-658.	Prior CEA in 20% of CAS arm (vs. 2.9 of CEA); neck surgery or irradiation 9.2% (vs. 0%)
92.	Theiss W, Hermanek P, Mathia K, et al. Predictors of Death and Stroke After Carotid Angioplasty and Stenting : A Subgroup Analysis of the Pro-CAS Data. Stroke. 2008;39:2325-2330.	Mixed population – data not stratified by symptom status
93.	Timaran CH, Mantese VA, Malas M, et al. Differential outcomes of carotid stenting and endarterectomy performed exclusively by vascular surgeons in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). J Vasc Surg. Feb 2013;57(2):303-308.	Subgroup (vascular surgeon vs other specialists) not of interest. (Note: results stratified by symptomatic vs. asymptomatic patients)
94.	Tsukahara T, Fukuda S, Nakakuki T, et al. Indication for surgical treatment of carotid arterial stenosis in high risk patients. Acta Neurochirurgica 2011; Vol 112:21-4	Mixed population – data not stratified by symptom status
95.	Varcoe RL, Mah J , Young N, et al. Prevalence of Carotid Stent Fractures in a Single-Center Experience. J Endovasc Ther 2008;15:485–489	Mixed population – data not stratified by symptom status
96.	Voeks JH, Howard G, Roubin GS, et al. Age and outcomes after carotid stenting and endarterectomy: the carotid revascularization endarterectomy versus stenting trial. Stroke. Dec 2011;42(12):3484-3490.	Age subgroups for CAS vs CEA not stratified by symptomatic status.
97.	Vogel TR, Dombrovskiy VY, Graham A M. Carotid Artery Stenting in the Nation: The Influence of Hospital and Physician Volume on Outcomes. Vascular and Endovascular Surgery 2010;44(2):89-94	Mixed population – data not stratified by symptom status
98.	Vogel TR, Dombrovskiy VY, Haser PB, Graham AM. Carotid artery stenting: Impact of practitioner specialty and volume on outcomes and resource utilization. J Vasc Surg. May 2009;49(5):1166-1171.	No comparator group, CAS only
99.	Vouyouka AG, Egorova NN, Sosunov EA, 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	Incomplete subgroup analysis for all subgroups, as data reported for: sex (females but

	Citation	Reason for Exclusion
	with carotid endarterectomy. J Vasc Surg 2012;56(2): 334-42.	not males), renal disease (present but not absent), diabetes (present but not absent), age (80+ but not under the age of 80), race (blacks but not other races), and artery disease (present but not absent).
100.	White CJ, Iyer SS, Hopkins LN et al. (2006). Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. Catheter Cardiovasc Interv, 67(4):503-12.	Mixed population – data not stratified by symptom status
101.	Wholey MH, Al-Mubarek N, Wholey MH. Updated review of the global carotid artery stent registry. Catheter Cardiovasc Interv 2003; 60:259-66.	Not comparative
102.	Xia ZY, Yang H, Xu JX, et al. Effect of stenting on patients with chronic internal carotid artery occlusion. Int Angiol 2012;31:356-60.	CAS n < 30; totally occluded vessels
103.	Yamagami H, Sakai N, Matsumaru Y, et al. Periprocedural cilostazol treatment and restenosis after carotid artery stenting: the Retrospective Study of In-Stent Restenosis after Carotid Artery Stenting (ReSISteR-CAS). J Stroke Cerebrovasc Dis. Apr 2012;21(3):193-199.	Mixed population – data not stratified by symptom status
104.	Yuo TH, Goodney PP, Powell RJ, Cronenwett JL. "Medical high risk" designation is not associated with survival after carotid artery stenting. J Vasc Surg. Feb 2008;47(2):356-362.	Mixed population – data not stratified by symptom status
105.	Zhao, XL, Jia JP, Ji XM, et al. A follow-up : stroke in patients with bilateral severe carotid stenosis after intervention treatment. Chinese Journal of Clinical Rehabilitation. 2003; 7(19): 2714-2715.	Bilateral carotid stenosis
106.	Zhou W, Dinishak D, Lane B, et al. Long-term radiographic outcomes of microemboli following carotid interventions. J Vasc Surg 2009; 50:1314-9.	Mixed population – data not stratified by symptom status
107.	Zhu L, Wintermark M, Saloner D, Fandel M, Pan XM, Rapp JH. The distribution and size of ischemic lesions after carotid artery angioplasty and stenting: evidence for microembolization to terminal arteries. J Vasc Surg. Apr 2011;53(4):971-975; discussion 975-976.	Mixed population – data not stratified by symptom status

Table C2. Articles excluded as primary studies <u>after full text review</u> for Key Question 2 evaluating intracranial artery stenosis.

	Citation	Reason for exclusion
1.	Abou-Chebl A, Bashir Q, Yadav J. Drug-eluting stents for the treatment of intracranial anterosclerosis. Stroke. 36:e165-e168.	N < 50
2.	Ahlhelm F, Ulmer S, Ahlhelm D, et al. Periprocedural thrombembolic events associated with angioplasty and stenting of the extra- and intracranial carotid artery assessed by neurological status and diffusion weighted magnetic resonance imaging (DWI). Clinical Neuroradiology. 2011;21(3):187.	N < 50
3.	Al-Ali F, Cree T, Hall S, et al. Predictors of unfavorable outcome in intracranial angioplasty and stenting in a single-center comparison: results from the Borgess Medical Center-Intracranial Revascularization Registry. AJNR. American journal of neuroradiology. Aug 2011;32(7):1221-1226.	Retrospective case-series
4.	Castano C, Garcia-Bermejo P, Garcia MR. A single center experience of stenting in symptomatic intracranial atherosclerosis. Neuroradiology Journal. 2012;25(5):548-562.	N < 50
5.	Costalat V, Maldonado IL, Vendrell JF, et al. Endovascular treatment of symptomatic intracranial stenosis with the Wingspan stent system and Gateway PTA balloon: a multicenter series of 60 patients with acute and midterm results. J Neurosurg. Oct 2011;115(4):686-693.	Retrospective case-series
6.	Fiorella D, Levy EI, Turk AS, et al. US multicenter experience with the wingspan stent system for the treatment of intracranial atheromatous disease: periprocedural results. Stroke. Mar 2007;38(3):881-887.	Mixed population – data not stratified by symptom status
7.	Fiorella DJ, Levy EI, Turk AS, et al. Target lesion revascularization after wingspan: assessment of safety and durability. Stroke. Jan 2009;40(1):106-110.	Not a population of interest; target lesion revascularization

	Citation	Reason for exclusion
		after instent restenosis
8.	Guo XB, Ma N, Hu XB, Guan S, Fan YM. Wingspan stent for symptomatic M1 stenosis of middle cerebral artery. European journal of radiology. Dec 2011;80(3):e356-360.	Retrospective case-series
9.	Jiang WJ, Xu XT, Du B, et al. Comparison of elective stenting of severe vs moderate intracranial atherosclerotic stenosis. Neurology. Feb 6 2007;68(6):420-426.	Not FDA approved stenting devices for intracranial
10.	Jiang WJ, Yu W, Du B, Wong EH, Gao F. Wingspan experience at Beijing Tiantan Hospital: new insights into the mechanisms of procedural complication from viewing intraoperative transient ischemic attacks during awake stenting for vertebrobasilar stenosis. J Neurointerv Surg. Jun 2010;2(2):99-103.	Subset of Jiang 2011 which is more complete
11.	Kurre W, Berkefeld J, Brassel F, et al. In-hospital complication rates after stent treatment of 388 symptomatic intracranial stenoses: results from the INTRASTENT multicentric registry. Stroke; a journal of cerebral circulation. Mar 2010;41(3):494-498.	Not FDA approved stenting devices for intracranial
12.	Lawson MF, Fautheree GL, Waters MF, Decker DA, Mocco JD, Hoh BL. Acute intraprocedural thrombus formation during wingspan intracranial stent placement for intracranial atherosclerotic disease. Neurosurgery. Sep 2010;67(3 Suppl Operative):ons166-170; discussion ons170.	Retrospective case-series
13.	Levy EI, Turk AS, Albuquerque FC, et al. Wingspan in-stent restenosis and thrombosis: incidence, clinical presentation, and management. Neurosurgery. Sep 2007;61(3):644-650; discussion 650-641	Albuquerque 2008 (included) reports same outcomes in larger population with more follow-up
14.	Lylyk P, Vila JF, Miranda C, et al. Endovascular reconstruction by means of stent placement in symptomatic intracranial atherosclerotic stenosis. Neurol Res. 2005;27 Suppl 1:S84-88.	Not FDA approved stenting devices for intracranial
15.	Nahab F, Lynn MJ, Kasner SE, et al. Risk factors associated with major cerebrovascular complications after intracranial stenting. Neurology. Jun 9 2009;72(23):2014-2019.	Prognostic
16.	Nakahara, T., S. Sakamoto, et al. (2002). "Stent-assisted angioplasty for intracranial atherosclerosis." Neuroradiology 44(8): 706-710.	N < 50
17.	Povedano G, Zuberbuhler P, Lylyk P, Ameriso SF. Management strategies in posterior circulation intracranial atherosclerotic disease. J Endovasc Ther. Jun 2010;17(3):308-313.	Not FDA approved stenting devices for intracranial
18.	Samaniego EA, Hetzel S, Thirunarayanan S, Aagaard-Kienitz B, Turk AS, Levine R. Outcome of symptomatic intracranial atherosclerotic disease. Stroke; a journal of cerebral circulation. Sep 2009;40(9):2983-2987.	Not FDA approved stenting devices for intracranial
19.	Suh DC, Kim JK, Choi JW, et al. Intracranial stenting of severe symptomatic intracranial stenosis: results of 100 consecutive patients. AJNR Am J Neuroradiol. Apr 2008;29(4):781-785.	Not FDA approved stenting devices for intracranial
20.	Tang CW, Chang FC, Chern CM, Lee YC, Hu HH, Lee IH. Stenting versus medical treatment for severe symptomatic intracranial stenosis. AJNR. American journal of neuroradiology. May 2011;32(5):911-916.	Not FDA approved stenting devices for intracranial
21.	Tarlov N, Jahan R, Saver JL, et al. Treatment of high risk symptomatic intracranial atherosclerosis with balloon mounted coronary stents and Wingspan stents: single center experience over a 10 year period. J Neurointerv Surg. Jan 1 2012;4(1):34-39.	Not FDA approved stenting devices for intracranial
22.	Turk AS, Levy EI, Albuquerque FC, et al. Influence of patient age and stenosis location on wingspan in-stent restenosis. AJNR Am J Neuroradiol. Jan 2008;29(1):23-27.	Prognostic; age and location of lesion and effect on instent restenosis
23.	Vajda Z, Aguilar M, Gohringer T, Horvath-Rizea D, Bazner H, Henkes H. Treatment of intracranial atherosclerotic disease with a balloon-expandable paclitaxel eluting stent procedural safety, efficacy and mid-term patency. Clinical Neuroradiology. 2012;22(3):227-233.	Mixed population – data not stratified by symptom status
24.	Wolfe TJ, Fitzsimmons BF, Hussain SI, Lynch JR, Zaidat OO. Long term clinical and angiographic outcomes with the Wingspan stent for treatment of symptomatic 50-99% intracranial atherosclerosis: single center experience in 51 cases. J Neurointerv Surg. Jul 2009;1(1):40-43.	Substantial overlap with Zaidat 2008 (~35%) which is included
25.	Zhang L, Huang Q, Zhang Y, et al. Wingspan stents for the treatment of symptomatic atherosclerotic stenosis in small intracranial vessels: safety and efficacy evaluation. AJNR. American journal of neuroradiology. Feb 2012;33(2):343-347.	Retrospective case-series

APPENDIX D. CRITICAL APPRASIAL, RISK OF BIAS AND OVERALL STUDY QUALITY DETERMINATION

Each study was critically appraised based on a set of general pre-set criteria listed in the Tables below as an initial starting point for identify risk of bias. The resulting worksheets provide insight into overall quality of individual studies.

Table D1. Definition of the class of evidence and risk of bias for studies on therapy

		Studies of Therapy	
Class	**Bias Risk**	**Study design**	**Criteria**
I	**Low risk:** Study adheres to commonly held tenets of high quality design, execution and avoidance of bias	Good quality RCT	• Random sequence generation • Allocation concealment • Intent-to-treat analysis • Blind or independent assessment for important outcomes • Co-interventions applied equally • F/U rate of 80%+ • Adequate sample size
II	**Moderately low risk:** Study has potential for some bias; study does not meet all criteria for class I, but deficiencies not likely to invalidate results or introduce significant bias	Moderate or poor quality RCT	• Violation of one of the criteria for good quality RCT
		Good quality cohort	• Blind or independent assessment in a prospective study, or use of reliable data* in a retrospective study • Co-interventions applied equally • F/U rate of 80%+ • Adequate sample size • Controlling for possible confounding†
III	**Moderately High risk:** Study has significant flaws in design and/or execution that increase potential for bias that may invalidate study results	Moderate or poor quality cohort	• Violation of any of the criteria for good quality cohort
		Case-control	• Any case-control design
IV	**High risk:** Study has significant potential for bias; lack of comparison group precludes direct assessment of important outcomes	Case series	• Any case series design

* Outcome assessment is independent of healthcare personnel judgment. Reliable data are data such as mortality or re-operation.
† Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Table D2. Definition of the class of evidence and risk of bias for registry studies

		Registry Studies	
Class	**Risk of Bias**	**Study design**	**Criteria**
II	**Moderately low risk:** Study has potential for some bias; does not meet all criteria for class I but deficiencies not likely to invalidate results or introduce significant bias	Good quality registry	• Designed specifically for conditions evaluated • Includes prospective data only • Validation of completeness and quality of data • Patients followed long enough for outcomes to occur • Independent outcome assessment* • Complete follow-up of > 85% • Controlling for possible confounding† • Accounting for time at risk‡
III	**Moderately high risk:** Study has flaws in design and/or execution that increase potential for bias that may invalidate study results	Moderate quality registry	• Prospective data from registry designed specifically for conditions evaluated with violation of 2 of the rest of the criteria in level I
IV	**High risk:** Study has significant potential for bias; does not include design features geared toward minimizing bias and/or does not have a comparison group	Poor quality registry	• Prospective data from registry designed specifically for conditions evaluated with violation of 3 or more of the rest of the criteria in level I • Retrospective data or data from a registry not designed specifically for conditions evaluated

* Outcome assessment is independent of healthcare personnel judgment. Some examples include patient reported outcomes, death, and reoperation.
† Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.
‡ Equal follow-up times or for unequal follow-up times, accounting for time at risk.

Methods for critical appraisal and level of evidence assessment

The method used for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of rating scheme developed by the Oxford Centre for Evidence-based Medicine, [Phillips 2001- Oxford Centre for Evidence-based Medicine Levels of Evidence] precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group, [Atkins 2004] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[West 2002] Taking into account features of methodological quality and important sources of bias combines epidemiologic principles with characteristics of study design.

Determination of Overall Strength of Evidence (Overall quality of evidence)

After individual article evaluation, the overall body of evidence with respect to each outcome is determined based on precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group [Atkins 2004] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ). [West 2002, 2012 AHRQ

GUIDE] Qualitative analysis is performed considering AHRQ required and additional domains [OWENS].

The initial strength of the overall body of evidence was considered HIGH for RCTs and LOW for observational studies. The body of evidence may be downgraded one or two levels based on the following criteria: (1) risk of bias (study limitations), (2) inconsistency of results, (3) indirectness of evidence, (4) imprecision of the effect estimates (e.g., wide confidence intervals) or (4) failure to provide am *a priori* statement of subgroup analyses. The body of evidence may be upgraded one or two levels based on the following criteria: (1) large magnitude of effect or (2) dose-response gradient (3) if all plausible biases would decrease the magnitude of an apparent effect. The final overall strength of the body of literature expresses our confidence in the estimate of effect and the impact that further research may have on the results. Interpretation of the strength of evidence categories, based on the AHRQ Methods Guide are as follows:

High -Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable

Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains

Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or the estimate is close to the true effect

Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; No available evidence or the body of evidence has unacceptable deficiencies precluding judgment.

Similar methods for determining the overall quality (strength) of evidence related to economic studies or administrative studies have not been reported.

Assessment of Economic Studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists (Canadian, BMJ, AMA) [Henrikson 2013] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman, et al. [Ofman 2003] QHES embodies the primary components relevant for critical appraisal of economic studies [Ofman 2003, Chiou 2003] It also incorporates a weighted

scoring process and which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (eg, with respect to age, gender, medical conditions, etc)? To what extent are the populations for each intervention comparable and are differences considered or accounted for? To what extent are population characteristics consistent with "real world" applications of the comparators?
- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?
- What types of studies form the basis for the data used in the analyses? Data (eg, complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.
- Were the interventions applied in a comparable manner (eg, similar protocols, follow-up procedures, evaluation of outcomes, etc)?
- How were the data and/or patients selected or sampled (eg, a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?
- Were the outcomes and consequences of the interventions being compared comparable for each? (eg, were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?)

Assessment of the overall strength of evidence for formal economic analyses does not appear to be documented in the literature. For the purposes of this HTA, overall strength was determined by:

- Quality of the individual studies: Where the majority of quality indicators described in the QHES met and were the methods related to patient/claim selection, patient population considerations and other factors listed above consistent with a high quality design?
- Number of formal analyses (3 or more)
- Consistency of findings and conclusions from analyses across studies.

QHES Instrument[Ofman 2003] **Study**_____

Questions	Points	Yes	No
1. Was the study objective presented in a clear, specific, and measurable manner?	7		
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4		
3. Were variable estimates used in the analysis from the best available source (i.e., randomized controlled trial - best, expert opinion - worst)?	8		
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1		
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9		
6. Was incremental analysis performed between alternatives for resources and costs?	6		
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5		
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7		
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8		
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	6		
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7		
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8		
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7		
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	6		
15. Were the conclusions/recommendations of the study justified and based on the study results?	8		
16. Was there a statement disclosing the source of funding for the study?	3		
TOTAL POINTS	100		

Administrative Database Study evaluation

What constitutes a high quality administrative database study? What criteria?

Although the precise guidelines that should govern high quality administrative database studies are still under development, [Langan 2013] a number of criteria that should be met in a high quality administrative database study have been suggested.[Langan 2013, van Walraven 2012] The checklist below highlights many of these qualities as was used to provide an initial assessment of administrative data studies. Individual report topics may have unique aspects of coding, requirements for developing algorithms for subject identification and potential for misclassification that need to be considered as part of an assessment of bias risk and study limitations.

Table D3. Checklist for evaluating the quality of administrative database studies.

Methodological Principle	Author 1 (2004)	Author 2 (2006)	Author (2008)
Study design Administrative database comparative study Administrative database case-control study Administrative database case series			
Why database created clearly stated			
Description of database's inclusion/exclusion criteria			
Description of methods for reducing bias in database			
Codes and search algorithms reported			
Rationale for coding algorithm reported			
Code accuracy reported			
Code validity reported			
Clinical significance assessed			
Is the period of data consistent with the outcome data?			
Statement regarding whether data stems from single or multiple hospital admissions			
Statement regarding whether data stems from single or multiple procedures			
Accounting for clustering			
Number of criteria met (maximum: 12)			

Below is a description of criteria used to evaluate administrative database studies.

Robust descriptions of the data set

High quality administrative database studies will include clear descriptions of the data set used for the study.[Langan 2013, van Walraven 2012]

- Why the database was created should be clearly stated.
- How the administrative database was created should be clearly stated, including:
    - Description of the database's inclusion and exclusion criteria.
    - Description of the methods by which the data sets are created so that the potential for biased or missing information can be assessed.[van Walraven 2012]

Code accuracy

- The diagnostic and/or procedural codes used in the search algorithm should be clearly stated.
- The rationale for coding algorithm reported.
- Code accuracy should be clearly reported. Code accuracy allows one to estimate the percentage of misclassified data as well as the degree of resulting bias. There are several different types of studies used to measure code accuracy, and the design will affect the reliability of the results.
    - "Ecological" studies compare outcomes measured by the code to those from another more reliable method. Because these studies do not evaluate

accuracy at the patient level, they are at risk for "ecological bias" and should be considered to be a relatively crude measure of code accuracy.[van Walraven 2012]

- "Reabstraction" studies reabstract a set of individual medical records and check them against the code(s) entered into the database for that patient. The reliability of statistics from reabstraction studies can be affected by missed cases (due to incorrect diagnosis or unrecorded information in the chart) as well as by misinterpreted cases (diagnosed and recorded correctly but misinterpreted by the person translating that information into code in the database).
- "Gold standard" studies are the most reliable type of validation studies and compare the code to some gold standard, such as a set of standard clinical or laboratory criteria required for diagnosis or an accurate population-based disease registry.[van Walraven 2012]

  - The validity of the codes should be clearly stated as it provides information as to whether the code or combination of used actually represent the diagnosis or outcome of interest The validity of the database study is dependent on a statistically significant association between degree to which the diagnostic or procedural code is associated with the actual diagnosis or procedure, so that the reader has confidence that the code actually represents the diagnosis or procedure under study. Note that code validity statistics are commonly reported in one of two ways:

- PPV (positive predictive value) is most frequently used, and reflects the percentage of patients identified by the code that are "true positives", or actually have the condition (or underwent the procedure) of interest. However, this statistic bears a major drawback: its accuracy decreases with decreasing disease prevalence. While validation studies are typically done on a population of patients with the code, and thus have a high prevalence of disease, the prevalence of the disease within the database population is typically going to be much lower. Thus, the probability of a patient in the database study having the disease represented by the code is likely to be lower than the PPV reported in the validation study suggests.[van Walraven 2012]
- Sensitivity and specificity may be used, and tend to be more accurate measures of code accuracy than PPV as they don't vary as much with disease prevalence.
- Positive likelihood ratio can be calculated from sensitivity and specificity. Positive likelihood ratio can also be combined with the baseline odds of disease to determine the likelihood that a patient identified by the code actually has the disease. Disease prevalence within the study population must be estimated in order to perform such a calculation, and is best done using data from a gold standard validation study.[van Walraven 2012]

Clinical significance

- Results should not solely be based on p-values, but should be interpreted based on clinical relevance.
    - This is because in large database studies, very small differences between groups can result in statistically significant differences, but these differences may not be clinically relevant.[van Walraven 2012]
    - Remember that additional zeroes in a p-value does not imply a more meaningful result.
    - Instead, the significance of the results should be interpreted by evaluating the absolute and relative differences between treatment groups.
    - Determining whether there is overlap in the 95% confidence intervals between groups can help the reader determine whether a result may be clinically significant, as they highlight the differences in results between the treatment groups.[van Walraven 2012]

Time-dependent bias

- Is the period of data consistent with the outcome data? That is, if looking at hospital discharge data (like NIS), then is the reported follow-up period for outcomes of interest reflective of that?
- Does the data set specify whether it includes data from the initial hospital admission only, or were data from repeat admissions included?
- Does the data set specify whether it includes data from the first procedure only, or were data from repeat procedures included?

Clustering

- The administrative database study should properly account for clustering that may be present in the data set.
    - Patient populations in health administrative data sets are often clustered (ie., within a health care provider), and outcomes for those within the same cluster tend to be more similar than those patients in a different cluster even after adjusting for potentially confounding variables using conventional regression analysis. Multilevel (or hierarchical, random effects, or mixed effects) regression models allow the user to account for patient clustering (e.g., within health care providers and facilities) when evaluating clustered data. Inaccurate conclusions may result if the appropriate methods to account for clustering are not used.[van Walraven 2012]

APPENDIX E. CLASS OF EVIDENCE EVALUATION

Randomized controlled trials (RCTs):
Methodological quality of therapeutic studies evaluating efficacy (long-term outcomes) and safety (periprocedural, 30-day) outcomes following CAS compared with CEA for the treatment of symptomatic and asymptomatic carotid artery stenosis (Key Questions 1 and 3).

Table E1. Class of evidence worksheet for include RCTs

Methodological Principle	CREST				BACASS	EVA-3S			ICSS		
	Brott 2010	Silver 2011	Howard 2011	Hill 2012	Hoffman 2008	Mas 2006	Mas 2008	Arquizan 2011	Ederle 2010	Altinbas(a) 2011	Altinbas(b) 2011
Study design											
Randomized controlled trial	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prospective cohort study											
Retrospective cohort study											
Case-control											
Case-series											
Random sequence generation*	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Statement of concealed allocation*	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Intention to treat*	✓	✓	✓		✓		✓		✓		
Independent or blind assessment	✓	✓		✓	✓	✓	✓		✓		
Co-interventions applied equally	✓	✓	✓	✓					✓	✓	✓
Complete follow-up of ≥80%	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adequate sample size	‡	‡	‡	‡		‡	‡	‡	✓		✓
Controlling for possible confounding†	✓	✓	✓	✓	✓				✓	✓	✓
Evidence Level	**II**	**II**	**II**	**II**	**II**	**II**	**II**	**II**	**I**	**II**	**II**

Blank cells indicate that the criterion was either not met or that it could not be determined
*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding presented
‡These studies state that they did not have adequate power based on their sample size

Table E1 cont.

Methodological Principle	Kentucky	Kentucky	Leicester	Regensburg	SPACE		SAPPHIRE	
	Brooks 2001	Brooks 2004	Naylor 1998	Steinbauer 2008	Eckstein 2008	Stingele 2008	Yadav 2004	Gurm 2008
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	✓	✓	✓	✓	✓	✓	✓	✓
Random sequence generation*			✓		✓	✓	✓	✓
Statement of concealed allocation*			✓		✓	✓		
Intention to treat*				✓	✓	✓	✓	✓
Independent or blind assessment	✓	✓	✓	✓	✓	✓	✓	✓
Co-interventions applied equally	✓	✓	✓	✓			✓	✓
Complete follow-up of ≥80%			✓	✓	✓	✓	✓	✓
Adequate sample size					‡	‡		
Controlling for possible confounding†	✓			✓	✓	✓		
Evidence Level	**II**	**II**	**II**	**II**	**II**	**II**	**II**	**II**

Blank cells indicate that the criterion was either not met or that it could not be determined
*Applies only to randomized controlled trials
†Groups must be comparable on baseline characteristics or evidence of control for confounding presented
‡These studies state that they did not have adequate power based on their sample size.

Critical Appraisal of Randomized Controlled Trials (RCTs)

The ICSS study primary report [Ederele] was well reported and appears to be the highest quality RCT, based on the above worksheet. Aside from sample size concerns noted by the authors of these studies, primary reports of from the CREST trial [Brott, Silver] were also considered highest quality for RCTs. For some outcomes in these reports, statically significant results were reported. The lowest quality RCTs were the BACASS[Hoffman 2008], Regensberg [Steinbauer 2008] and both Kentucky trials[Brooks 2001, Brooks 2004], based on failure to report randomization sequence generation, concealment of allocation and small sample size.

Random sequence generation and statement of concealed allocation

All RCTs indicated that allocation of treatment was randomized. All of the large, multicenter trials (CREST, EVA-3S[Mas 2008], ICSS and SPACE[Eckstein 2008]) involved centralized

randomization, either computerized (EVA, SPACE) or automated telephone response systems (CREST, ICSS), that also allowed for concealment of allocation. In addition, one single center RCT (Leicester) [Naylor 1998] use randomly generated treatment assignments in opaque, sealed envelopes. For these RCTs, random sequence generation and allocation concealment were judged to be adequate. An additional four small, single center RCTs (BACASS, Kentucky 2001, Kentucky 2004 and Regensburg) did not provide detailed information regarding methods of randomization and concealment; thus, there is a potential for bias in these studies.

Intention-to-treat analysis

Intent to treat analysis was used for all four multicenter RCT's [Brott 2010, Silver 2011, Mas 2008, ICSS 2010]. One additional report from the EVA-3S RCT [Mas 2006] reported ITT analyses; however, individuals who were randomized but did not receive their assigned treatment were excluded from analyses. In addition, several small trials [Kentucky 2001, Kentucky 2004, Leicester, Altibinas (both)] there was no information available to determine whether intent to treat analyses were conducted.

Independent or blind assessment of primary outcomes

Due to the nature of treatments involved in these trials, it was not possible to blind patients, physicians or other members of the health care team to treatment status. However, the majority of RCTs reported independent assessment of outcomes by clinicians not involved in the trial procedures [CREST (Brott 2010, Silver 2011), BACASS (Hoffman 2008), EVA-3S (Mas 2008), ICSS (Ederle 2010), Leicester(Naylor 1998), Space (Eckstein 2008)], and all of the large multicenter RCTs reported centralized adjudication of outcomes by an independent team of clinicians.[EVA-3S (Mas 2006), ICSS (Ederle 2010), SPACE (Mas 2008), CREST (Brott 2010)]. In three follow-up studies [Altinbas 2011 blood pressure, Altinbas 2011 cognition] from large multicenter RCTs, no information was available to determine whether follow-up or assessment of the primary outcomes was independent or blinded; therefore, there is a potential for bias in these studies.

Co-interventions applied equally between treatment groups

The majority of studies (CREST, ICSS, Kentucky 2001, Kentucky 2004, Leicester, Regensburg) reported that the same care, aside from the differences inherent to treatment group, was provided to all patients; therefore, risk of bias on this criterion was judged to be low. There is a potential risk of bias for two large RCTs [EVA-3S, SPACE], which explicitly state that CAS and CEA received different co-interventions. For example, in the SPACE trial, CAS received 100 mg aspirin plus 75 mg clopidogrel daily for at least 3 days before and 30 days after the intervention, whereas CEA received only 100 mg aspirin "before, during and after surgery". It is not clear to what extent this may bias results. One additional small RCT provided no information on co-interventions; thus, the risk of bias on this criterion for this study is unclear.

Loss to follow-up

The majority of studies (CREST, ICSS, SPACE, EVA-3S, Leicester, Regensburg, BACASS) report follow-up that is 80% or greater; therefore, the risk of bias from incomplete follow-up is lower in these studies. Two smaller RCTs (Kentucky 2001, Kentucky 2004) no information was available to determine whether follow-up was complete; thus, there is a potential for bias in these studies.

Adequate sample size

Only one large RCT was adequately powered to detect statistically significant differences in risks between CAS and CEA, based on information reported by the authors.[ICSS (Ederle 2010)] The other three large RCTs stated that they were underpowered to detect statistically significant differences in risks between CAS and CEA, however, for some outcomes, statically significant results were reported. In these three trials, recruitment was terminated early and their sample sizes did not meet those needed to provide adequate power. Nevertheless, in each of these studies did report clinically significant differences between CAS and CEA. For all of the smaller single center RCTs (N<110) [BACASS, Kentucky 2001, Kentucky 2004, Leicester, Regensburg] no information was available to determine whether sample size was adequate; although it is unlikely given that these studies had smaller sample sizes than the multicenter RCTs that were not adequately powered, and none of these studies reported significant differences between CAS and CEA.

Controlling for possible confounding

Three of the four multicenter RCTs (CREST, ICSS, SPACE) and one additional small RCT[Kentucky 2001] were adequately controlled for confounding, either by balanced randomization or multivariate analyses. One additional multicenter RCT (EVA-3S) had a slightly unbalanced randomization, and none of the primary analyses appeared to be adjusted for potential confounders and no statement was made regarding exploring the potential influence of the small imbalances. For two smaller RCTs, no information was available to determine whether confounding was adequately controlled.

For Key Question 4, differential efficacy, effectiveness and safety were evaluated. Patient-level data were available for age and sex for up to six trials (Leicester, EVA-3S, SPACE, BACASS, ICSS, and CREST) as reported in the Bonati systematic review.[Bonati 2012] Otherwise, six studies[Hill 2012, Howard 2011, Stingele 2008, Eckstein 2008, Ederle 2010, Mas 2008] from four trials (EVA-3S, SPACE, ICSS, and CREST) were included, five of which were considered to be at moderately low risk of bias[Hill 2012, Howard 2011, Stingele 2008, Eckstein 2008, Mas 2008], and one of which was considered to be at low risk of bias.[Ederle 2010] Of the individual RCTs, four studies prespecified subgroups analyses [Howard 2011, Stingele 2008, Eckstein 2008, Ederle 2010], while two did not[Hill 2012, Mas 2008].

Other considerations:

Funding sources
Funding sources varied across studies. No RCTs report 100% of funding from public, i.e. the National Institutes of Health; however, two large RCTs (CREST, ICSS) reported a combination of public and private funds, and other studies report funding from private funds only [Kentucky 2001, EVA-3S, Regensburg, Leicester]. Other studies report either funding from both public and private or funding sources are not reported (SPACE, BACASS).

Provider experience (CREST)
The majority of studies (CREST, BACASS, EVA-3S, ICSS, Leicester) indicated that some degree of training or provider certification was required for this trial; however, there is substantial heterogeneity in the exact requirements. For example, for the CREST trial, providers were required to perform >=12 procedures per year with a <= 5% rate, while in the ICSS trial, providers are required to perform >= 50 carotid or stenting operations (>=10 per year).

Early study termination
Four RCTs were terminated early early [BACASS, EVA-3S(Mas 2006), Regensburg, SPACE (Eckstein 2008)] due to the initiation of a larger trial with similar aims [BACASS, Regensburg], or adverse events, therefore, these studies were underpowered.

Nonrandomized comparative studies:
Methodological quality of therapeutic studies evaluating effectiveness (long-term outcomes) and safety (periprocedural, 30-day) outcomes following CAS compared with CEA for the treatment of symptomatic and asymptomatic carotid artery stenosis (Key Questions 1 and 3).

Studies included in the AHRQ report

Table E2. Class of Evidence worksheet for clinical cohort studies that were included in the AHRQ report

Methodological Principle	Bosiers 2005	De Rango 2011	Marine 2006	Sherif 2005	Zarins 2009
Study design					
Randomized controlled trial					
Prospective cohort study		✓			✓
Retrospective cohort study	✓		✓	✓	
Case-control					
Case-series					
Random sequence generation*					
Statement of concealed allocation*					
Intention to treat*					
Independent or blind assessment		✓		✓	✓
Co-interventions applied equally		✓			
Complete follow-up of ≥80%	✓		✓	✓	
Adequate sample size		✓		✓	✓
Controlling for possible confounding†				✓	
Evidence class	III	III	III	III	III

*Applies only to randomized controlled trials

†Groups must be comparable on baseline characteristics or evidence of control for confounding presented

Blank cells indicate that the criterion was either not met or that it could not be determined

Table E3. Class of Evidence for registries studies that were included in the AHRQ report

Methodological principle	Bangalore 2010 REACH registry	Lindstrom 2012 Swedvasc registry
Designed specifically for conditions evaluated	✓	✓
Includes prospective data only	✓	✓
Validation of completeness and quality of data	✓	✓
Patients followed long enough for outcomes to occur	✓	✓
Independent outcome assessment*	✓	
Complete follow-up of ≥ 85%	✓	
Controlling for possible confounding†	✓	
Accounting for time at risk‡	✓	✓
Evidence class	**II**	**IV**

*Outcome assessment is independent of healthcare personnel judgment. Some examples include patient reported outcomes, death, and reoperation.

†Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

‡Equal follow-up times or for unequal follow-up times, accounting for time at risk.

Blank cells indicate that the criterion was either not met or that it could not be determined

Studies not included in the AHRQ report

Table E4. Class of Evidence for clinical cohort studies that were not included in the AHRQ report

Methodological Principle	Brown 2008	Capoccia 2012	Feliziani 2010	Iihara 2006	Kastrup 2003	Kastrup 2004	Lal 2011
Study design							
Randomized controlled trial							
Prospective cohort study		✓	✓	✓			✓
Retrospective cohort study	✓				✓	✓	
Case-control							
Case-series							
Random sequence generation*							
Statement of concealed allocation*							
Intention to treat*							
Independent or blind assessment			✓		✓	✓	
Co-interventions applied equally							
Complete follow-up of ≥80%	✓	✓	✓	✓	✓	✓	✓
Adequate sample size		✓					✓
Controlling for possible confounding†					✓		✓
Evidence class	III	III	III	III	III	III	III

*Applies only to randomized controlled trials

†Groups must be comparable on baseline characteristics or evidence of control for confounding presented

Blank cells indicate that the criterion was either not met or that it could not be determined

Table E5. Class of Evidence for registries studies that were included in the AHRQ report

Methodological principle	Jim 2012 SVS-VR registry	Nolan 2012 VSGNE registry
Designed specifically for conditions evaluated	✓	✓
Includes prospective data only	✓	✓
Validation of completeness and quality of data	✓	✓
Patients followed long enough for outcomes to occur	✓	✓
Independent outcome assessment*		✓
Complete follow-up of ≥ 85%		✓
Controlling for possible confounding†	✓	✓
Accounting for time at risk‡	✓	✓
Evidence class	**III**	**II**

*Outcome assessment is independent of healthcare personnel judgment. Some examples include patient reported outcomes, death, anreoperation.

†Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

‡Equal follow-up times or for unequal follow-up times, accounting for time at risk.

Blank cells indicate that the criterion was either not met or that it could not be determined

Critical Appraisal of Nonrandomized Comparative Studies

All 12 cohort studies were considered to be at moderately high risk of bias. Study designs were prospective in six studies and retrospective in six. Only half of the studies reported independent or blind assessment of primary outcomes. In all but one study, co-interventions, in this case primarily concomitant medical/drug therapy, were not applied equally between the treatment groups or not adequately described. It is unclear to what degree the medical therapy given represented the standard of care for each type of treatment. Sample sizes were small across the majority of studies, especially in the three studies relating to cognition (< 30 in each group). Only three studies controlled for possible confounding factors, specifically baseline characteristics that were unequally distributed between groups. Most studies did have a complete follow-up of at least 80% of patients.

The four registries varied in their risk of bias, two fulfilled all the required criteria for a good quality registry and were considered to be at a moderately low risk of bias. A third registry was considered to be at moderately high risk of bias due to the lack of independent outcome assessment and complete follow-up of less than 85%. The fourth registry was a poor quality registry with a high risk of bias attributable to the lack of independent outcome assessment, complete follow-up of less than 85%, and failure to control for possible confounding factors.

Administrative database studies

Quality of Administrative database studies used to provide supporting evidence for effectiveness (long-term outcomes) and safety (periprocedural, 30-day) outcomes following CAS compared with CEA for the treatment of symptomatic and asymptomatic carotid artery stenosis (Key Questions 1 and 3) and for differential effectiveness or safety for special population (Key Question 4). There is no universally accepted method of critically appraising administrative database studies. Wide variation in the diagnostic codes used and algorithms (use of primary and/or secondary diagnosis codes) for identifying patients across studies make it challenging to compare results and there are concerns regarding misclassification of patients based on symptom status. These factors combine with consideration of the extent to which the included studies had characteristics that have been described as attributes of high quality administrative studies led us to conclude that overall, these studies were at high risk of bias and should not be part of the graded evidence base for this HTA.

Table E6. Quality of Administrative database studies

Methodological Principle	Bisdas (2012)	Giacovelli (2010)	Giles (2010)	Khatri (2012)	McDonald (2011)	McPhee (2007)
Study design Administrative database comparative study Administrative database case-control study Administrative database case series	✓	✓	✓	✓	✓	✓
Why database created clearly stated	✓			✓		✓
Description of database's inclusion/exclusion criteria	✓			✓		✓
Description of methods for reducing bias in database	✓	✓				✓
Codes and search algorithms reported	✓	✓	✓	✓	✓	✓
Rationale for coding algorithm reported	✓	✓	✓	✓	✓	✓
Code accuracy reported						
Code validity reported						
Clinical significance assessed						
Is the period of data consistent with the outcome data?	✓	✓	✓	✓	✓	✓
Statement regarding whether data stems from single or multiple hospital admissions						
Statement regarding whether data stems from single or multiple procedures						
Accounting for clustering	✓	✓	✓	✓	✓	✓
Number of criteria met (maximum: 12)	7	5	4	6	4	7

Table E6. continued

Methodological Principle	McPhee (2008)	Rockman (2011)	Timaran (2009)	Wang (2011)	Young (2011)
Study design Administrative database comparative study Administrative database case-control study Administrative database case series	✓	✓	✓	✓	✓
Why database created clearly stated	✓	✓	✓		
Description of database's inclusion/exclusion criteria	✓	✓	✓		
Description of methods for reducing bias in database	✓		✓		
Codes and search algorithms reported	✓			✓	✓
Rationale for coding algorithm reported	✓		✓	✓	✓
Code accuracy reported					
Code validity reported					
Clinical significance assessed					
Is the period of data consistent with the outcome data?	✓	✓	✓	✓	✓
Statement regarding whether data stems from single or multiple hospital admissions					
Statement regarding whether data stems from single or multiple procedures				✓	
Accounting for clustering	✓	✓	✓	✓	✓
Number of criteria met (maximum: 12)	7	4	6	5	4

Economic studies
QHES evaluations for included full economic studies (Mean: 94 Range: 84-100)

Study: Janssen 2008	Points	Yes	No	*Notes:*
1. Was the study objective presented in a clear, specific, and measurable manner?	**7**	**Y**		*Use ICER to evaluate CE of CAS vs CEA using SAPPHIRE trial data*
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	**4**		**N**	*Not stated in article*
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	**8**	**Y**		*Used ECST Cochrane, Wholey, Treatment cost based on successful procedures*
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	**1**	**Y**		*2 different studies – Cochran and Wholey/ECST*
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	**9**	**Y**		*Used one-way sensitivity analysis to measure impact of data sources and other important variables*
6. Was incremental analysis performed between alternatives for resources and costs?	**6**	**Y**		*Performed the analysis but arrived at inconclusive results*
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	**5**	**Y**		*Derived from literature review.*
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	**7**	**Y**		*Used a 10-year time horizon. Discounted at 4%.*
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	**8**	**Y**		*Procedural and complication costs presented and rationale given. Cost breakdown also given.*
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	**6**	**Y**		*They did use relevant outcomes.*
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	**7**	**Y**		*Evaluated different data sources*
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	**8**	**Y**		*Markov decision model and structure clearly defined.*
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	**7**	**Y**		*Assumptions given, and limitations discussed (p.71). Minimal justifications were provided*
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	**6**	**Y**		*Discussed with limitations*
15. Were the conclusions/recommendations of the study justified and based on the study results?	**8**	**Y**		*Conclusion more evidence is necessary*

Study: Janssen 2008	Points	Yes	No	*Notes:*
16. Was there a statement disclosing the source of funding for the study?	**3**	**Y**		*Netherland Organization for Health Research* *Authors- 1 Sanofi, 1 Medtronic*
TOTAL POINTS	**100**	**96**		

Study: Mahoney 2011	Points	Yes	No	*Notes:*
1. Was the study objective presented in a clear, specific, and measurable manner?	**7**	**Y**		*Compare CE of CAS and CEA using simulation*
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	**4**	**Y**		*States societal perspective*
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	**8**	**Y**		*SAPPHIRE trial data used which was a RCT*
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	**1**		**N**	*Examined both asymptomatic and symptomatic patients however, not prespecified*
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	**9**	**Y**		*Used one-way sensitivity and multivariate to simulate possible parameters.*
6. Was incremental analysis performed between alternatives for resources and costs?	**6**	**Y**		*Base case results gave costs and QALY. AAD treatment of dominated.*
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	**5**	**Y**		*Derived from literature review. Provided reasons for inclusion and exclusion.*
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	**7**	**Y**		*Used a life long time horizon. Discounted at 3%*
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	**8**	**Y**		*Cos Procedural cost estimates obtained from hospital accounting, complication cost estimates obtained from literature*
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	**6**	**Y**		*Given in Table IV*
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	**7**	**Y**		*Actual measure at multiple time points, derived from EQ5D*
12. Were the economic model (including structure), study	**8**	**Y**		*Used bootstrap simulation*

Study: Mahoney 2011	Points	Yes	No	*Notes:*
methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?				
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	**7**	**Y**		*Assumptions given, and limitations discussed Minimal justifications were provided*
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	**6**	**Y**		*Discusses limitations and makes comparisons to other studies*
15. Were the conclusions/recommendations of the study justified and based on the study results?	**8**	**Y**		*Conclusions tied closely to results and in line with similar studies.*
16. Was there a statement disclosing the source of funding for the study?	**3**	**Y**		*Bottom of first page – Cordis*
TOTAL POINTS	**100**	**99**		

Study: Maud 2010	Points	Yes	No	*Notes:*
1. Was the study objective presented in a clear, specific, and measurable manner?	**7**	**Y**		*Assess the CE of CAS vs CEA for patients at high surgical risk*
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	**4**	**Y**		*Societal cost*
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	**8**	**Y**		*Relies on SAPPHIRE trial data*
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	**1**	**Y**		*Not applicable*
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	**9**	**Y**		*Limited sensitivity analysis presented. Does give 95% CIs*
6. Was incremental analysis performed between alternatives for resources and costs?	**6**	**Y**		*Base case results gave costs and QALY. Compared with a ICER*
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	**5**	**Y**		*Derived from SAPPHIRE*
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	**7**		**N**	*Only 1-year time horizon*
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	**8**	**Y**		*Cost obtained from the Healthcare Cost and Utilization Project*
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	**6**		**N**	*Results clearly given, no short/long-term or negative outcomes*

Study: Maud 2010	Points	Yes	No	*Notes:*
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	**7**	**Y**		*Justified simulations of SAPPHIRE trial*
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	**8**	**Y**		*Used Monte Carlo simulations*
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	**7**	**Y**		*Main assumptions addressed and limitations discussed*
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	**6**	**Y**		*Mentioned along with limitations*
15. Were the conclusions/recommendations of the study justified and based on the study results?	**8**	**Y**		*Conclusions discussed and compared with similar studies*
16. Was there a statement disclosing the source of funding for the study?	**3**		**N**	*none*
TOTAL POINTS	**100**	**84**		

Study: Vilain 2012	Points	Yes	No	*Notes:*
1. Was the study objective presented in a clear, specific, and measurable manner?	**7**	**Y**		*Investigate the relative cost and effectiveness of CAS and CEA*
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	**4**	**Y**		*US Healthcare perspective*
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	**8**	**Y**		*CREST trial data*
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	**1**	**Y**		*Separate analysis for symptomatic status*
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	**9**	**Y**		*All parameters resampled likelihood of cost-effectiveness results were given*
6. Was incremental analysis performed between alternatives for resources and costs?	**6**	**Y**		*Base case results given in $/QALY*
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	**5**	**Y**		*Derived from CREST and used SF-36 for utilities*
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	**7**	**Y**		*10-year times horizon discounted at 3%*

Study: Vilain 2012	Points	Yes	No	*Notes:*
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	**8**	**Y**		*Resource data and hospital billing records were used to estimate costs over the first year*
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	**6**		**N**	*Given in table 5. No short/long-term or negative outcomes discussed.*
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	**7**	**Y**		*Simulated from CREST trial*
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	**8**	**Y**		*Markov decision model and structure clearly defined and illustrated (figures in appendix)*
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	**7**	**Y**		*Structure and assumptions justified. Limitations discussed*
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	**6**	**Y**		*Limitations discussed and comparison to published studies given*
15. Were the conclusions/recommendations of the study justified and based on the study results?	**8**	**Y**		*Conclusions tied closely to results and comparable with similar studies.*
16. Was there a statement disclosing the source of funding for the study?	**3**	**Y**		*Funding National Institute of Neurological Disorders and Stroke and the National Institutes of Health*
TOTAL POINTS	**100**	**94**		

Study: Young 2010	Points	Yes	No	*Notes:*
1. Was the study objective presented in a clear, specific, and measurable manner?	**7**	**Y**		*Evaluate the cost effectiveness of CAS and CEA in symptomatic patients*
2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	**4**	**Y**		*US Medicare costs perspective*
3. Were variable estimates used in the analysis from the best available source (ie, randomized controlled trial - best, expert opinion - worst)?	**8**	**Y**		*Compiled several data sources. SAPCE, SAPPHIRE, and EVA-3S*
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	**1**	**Y**		*Symptomatic patients*
5. Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	**9**	**Y**		*Thorough sensitivity analysis was given looking at many key input variables. 0ne-way, Two-way and uncertainty analysis conducted*

Study: Young 2010	Points	Yes	No	*Notes:*
6. Was incremental analysis performed between alternatives for resources and costs?	**6**	**Y**		*Base case results given in $/QALY. CAS dominated by CEA*
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	**5**	**Y**		*In detail.*
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	**7**	**Y**		*Lifetime horizon discounted at 3%*
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	**8**	**Y**		*Only direct costs used. Sources referenced*
10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included?	**6**	**Y**		*Outcomes measures clearly cited. Time range tested*
11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	**7**	**Y**		*Health outcomes came from with literature review.*
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	**8**	**Y**		*Markov decision model and structure clearly defined.*
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	**7**	**Y**		*All stated and clear. Minimal justification*
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	**6**	**Y**		*Given with potential limitations*
15. Were the conclusions/recommendations of the study justified and based on the study results?	**8**	**Y**		*Conclusions tied closely to results and comparable with similar studies.*
16. Was there a statement disclosing the source of funding for the study?	**3**	**Y**		*National Center for Research Resources and NIC Roadmap*
TOTAL POINTS	**100**	**100**		

APPENDIX F. EVIDENCE TABLES FOR INCLUDED STUDIES FOR KEY QUESTIONS 1, 2, 3 AND 5

****Evidence tables for included studies for Key Question 4 are in a separate Appendix (Appendix G)**

CAROTID ARTERY STENOSIS

Randomized Controlled Trials (Key Questions 1 and 3)

Table F1. Study characteristic of RCTs comparing CAS with CEA for asymptomatic carotid artery disease (Key Questions 1 and 3)

Study (year)/ Location/ No. of centers	Inclusion criteria	Exclusion criteria	Definition of asymptomatic disease	Stent Device/ EPD (%)	Co-intervention	Primary outcome	Follow-up (% followed)	Provider certification	Funding	Comments
Kentucky Brooks 2004 USA Single center	• No symptoms plus stenosis > 80% as determined by NASCET criteria • Anticipated life expectancy of 5 years • Willingness to complete treatment within 1 month • Ability to sign an informed consent	• Allergy or sensitivity to aspirin, heparin, or clopidogrel • History of bleeding diathesis • Coagulopathy • Cardiac arrhythmia	No symptoms (no other details)	10 x 20-mm Wallstent (% NR) or a 10 x 38-mm Dynalink (% NR) stent Distal protection devices were not used	325 mg Aspirin and 75 mg Clopidogrel pre-procedural	Post-procedural stenosis, complications, length of hospital stay, perception of pain, return to activity, cost of procedure	**48 months** (100%)	NR	No conflicts of interest	
CREST Brott 2010 Silver 2011 USA/Canada 117 centers	• Symptomatic patients: stenosis of 50% or more on angiography, 70% or more on ultrasonography, or 70% or more on computed tomographic angiography or magnetic resonance angiography if the stenosis on ultrasonography was 50 to 69% • Asymptomatic patients: 60% stenosis by	• Previous stroke that was sufficiently severe to confound the assessment of end points • Chronic atrial fibrillation, paroxysmal atrial fibrillation that had occurred within the preceding 6 months or that necessitated anticoagulation therapy • Myocardial	Symptomatic: Transient ischemic attack, amaurosis fugax, or minor nondisabling stroke involving the study carotid artery within 180 days before randomization Asymptomatic: NR	RX Acculink stent and whenever feasible (% NR) RX Accunet embolic-protection device	2x daily 325 mg Aspirin and either 1x daily 75 mg Clopidogrel or 250 mg 2x daily Ticlopidine	Stroke, myocardial infarction (MI), or death in the periprocedural period or ipsilateral stroke thereafter up to 4 years	**90 months** (NR)	Surgeons had to perform >12 CEAs annually. Interventionalists had to demonstrate experience in CAS, receive hands-on experience with the devices	Supplemental funding was received from Abbott Vascular Solutions, Inc	Initially symptomatic only, later extended to asymptomatic

Study (year)/ Location/ No. of centers	Inclusion criteria	Exclusion criteria	Definition of asymptomatic disease	Stent Device/ EPD (%)	Co-intervention	Primary outcome	Follow-up (% followed)	Provider certification	Funding	Comments
	angiography, 70% by ultrasound, or 80% by CT angiography or MR angiography if the stenosis on ultrasonography was 50% to 69% (Not NASCET)	infarction within the previous 30 days • Unstable angina **Silver 2011** • See above								

AMA = American Heart Association; EPD = embolic protection device; NASCET = North American Symptomatic Carotid Endarterectomy Trial; MI = myocardial infarction; SAPPHIRE = Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy;
*i.e. congestive heart failure, abnormal stress test, or need for open-heart surgery.

Table F2. Baseline characteristics of patients from included RCTs comparing CAS with CEA for asymptomatic carotid artery disease (Key Questions 1 and 3).

	KENTUCKY		CREST	
	Brooks 2004		Silver 2011	
	CAS	CEA	CAS	CEA
Demographics				
N	43	42	594	587
% Male	NR	NR	63.8	67.5
Mean age, years	66.6	69.9	69.0	69.6
% Smokers (define)	93.0*	88.1*	26.1†	22.2†
Comorbidities				
% HTN	81.4	97.6	88.2	87.9
% AFib/Aflutter	NR	NR	NR	NR
% Hyperlipidemia	NR	NR	NR	NR
% DM	16.3	11.9	32.6	33.7
% Prior MI	NR	NR	NR	NR
% CAD	81.4	47.6	NR	NR
% PVD	NR	NR	NR	NR
Qualifying Events				
% Stroke	NR	NR	NR	NR
% TIA	NR	NR	NR	NR
% Amaurosis fugax	NR	NR	NR	NR
Previous Symptoms				
% Contralateral occlusion	7.0	9.5	2.3	2.7
Mean % stenosis	NR (>80%)	NR (>80%)	92.8	91.8

*Current smokers; †Current or ex-smokers.
AFib= atrial fibrillation; AFlutter = atrial flutter; CAD = coronary artery disease; CAS = carotid artery stenting; CEA = carotid endarterectomy; DM = diabetes mellitus; HTN = hypertension; ND = not defined; NR = not reported; PVD = peripheral vascular disease; TIA = transient ischemic attack.

We reported qualifying events: stroke, TIA, amaurosis fugax, one author, Mas 2008, reported prior history of vascular disease as well as qualifying events. Exclusion criteria for many studies is that <20% of patients have prior revascularization, so percent previous carotid artery stenting, or endarterectomy are not reported.

Table F3. Detailed results of RCTs comparing CAS with CEA for the treatment of asymptomatic carotid artery disease (Key Questions 1 and 3).

Study	Primary Outcomes	Secondary Outcomes	Cognition/Function/Pain/Other	Comments
CREST				
Brott 2010	***Periprocedural*** **Death**[γ] NR **Any Stroke**[γ] • CAS: 2.5% ± 0.6 (15/594) • CEA: 1.4% ± 0.5 (8/587) AR: 1.2 (−0.4, 2.7) HR: 1.88 (0.79, 4.42) *P* = 0.15 **Stroke or Death**[γ] • CAS: 2.5% ± 0.6 (15/594) • CEA: 1.4% ± 0.5 (8/587) AR: 1.2 (−0.4, 2.7) HR: 1.88 (0.79, 4.42) *P* = 0.15 **MI**[γ] • CAS: 1.2% ± 0.4 (7/594) • CEA: 2.2% ± 0.6 (13/587) AR: −1.0 (−2.5, 0.4) HR: 0.55 (0.22, 1.38) *P* = 0.20 ***48 month (including periprocedural)*** **Ipsilateral stroke**[γ] • CAS: 4.5 ± 0.9 (24/533) • CEA: 2.7% ± 0.8 (13/481) AR: 1.9 (−0.5, 4.3) HR: 1.86 (0.95, 3.66) *P* = 0.07	NR	NR	Kaplan-Meier analysis of periprocedural stroke, MI, or death or 4 year ipsilateral stroke. Analyses based on superiority. Intent-to-treat analysis used. NIH funded.

Study	Primary Outcomes	Secondary Outcomes	Cognition/Function/Pain/Other	Comments
	Ipsilateral stroke or Death[γ] • CAS: 4.5% ± 0.9 (24/533) • CEA: 2.7% ± 0.8 (13/481) AR: 1.9 (−0.5, 4.3) HR: 1.86 (0.95, 3.66) *P* = 0.07 **MI**[γ] NR			
Silver 2011	***Periprocedural*** **Death** NR **Any Stroke** • CAS: 2.5% ± 0.6 (15/594) • CEA: 1.4% ± 0.5 (8/587) AR: 1.2 (-0.4, 2.7) HR: 1.88 (0.79, 4.42) *P* = 0.15 **Major Stroke** • CAS: 0.5% ± 0.3 (3/594) • CEA: 0.3% ± 0.2 (2/587) AR: 0.2 (-0.6, 0.9) HR: 1.50 (0.25, 9.95) *P* = 0.66 **Minor Stroke** • CAS: 2.0% ± 0.6 (12/594) • CEA: 1.0% ± 0.4 (6/587) AR: 1.0 (-0.4, 2.4) HR: 2.06 (0.77, 5.51) *P* = 0.15 **MI** • CAS: 1.2% ± 0.4 (7/594) • CEA: 2.2% ± 0.6 (13/587) AR: -1.0 (-2.5, 0.4) HR: 0.55 (0.22, 1.38) *P* = 0.20	***Periprocedural*** **Hematoma** • CAS: 0% (0/594) • CEA: 1.9% (11/587) **Cranial nerve palsy** • CAS: 0.17% (1/594) • CEA: 4.2% (25/587) **Hypertension** • CAS: 1.5% (9/594) • CEA: 3.9% (23/587) **Bradycardia** • CAS: 3.5% (21/594) • CEA: 0.34% (2/587) **Hypotension‡** • CAS: 3.9% (23/594) • CEA: 1.9% (11/587) **Femoral artery complications, nonhemorrhagic** • CAS: 0.67% (4/594) • CEA: 0.17% 1/587)	NR	Intent-to-treat analysis used. Secondary outcome percentages calculated to fit data.

Study	Primary Outcomes	Secondary Outcomes	Cognition/Function/Pain/Other	Comments
	Death or Stroke • CAS: 2.5% ± 0.6 (15/594) • CEA: 1.4% ± 0.5 (8/587) AR: 1.2 (-0.4, 2.7) HR: 1.88 (0.79, 4.42) *P* = 0.15			
KENTUCKY				
Brooks 2004	***Periprocedural*** **Death** • CAS: 0% (0/43) • CEA: 0% (0/42) **Stroke** • CAS: 0% (0/43) • CEA: 0% (0/42) **TIA** • CAS: 0% (0/43) • CEA: 0% (0.42) **MI** NR ***48 months*** **Death** • CAS: 0% (0/43) • CEA: 0% (0/42) **Stroke** • CAS: 0% (0/43) • CEA: 0% (0/42) **TIA** • CAS: 0% (0/43) • CEA: 0% (0/42) **MI** NR	***Periprocedural*** **Bradycardia or hypotension** • CAS: 11.6% (5/43) • CEA: 0% (0/42) **Cranial nerve injury** NR **Cervical nerve injury** • CAS: NA • CEA: 7.1% (3/42)	**Pain scale (0-10), mean (range)** *24 hours* • CAS: 1.1 (0-4) • CEA: 2.0 (0-5) *1 month* • CAS: < 1.0 (0-3) • CEA: < 1.0 (0-3) **Return to full activity, mean ± SD no. days** *Without complications* • CAS: 6.5 ± 2.8 (3-14) • CEA: 8.3 ± 3.5 (4-14) *With complications* • CAS: 8.6 ± 5.9 (6-15) • CEA: 9.8 ± 6.1 (4-18) **Length of hospital stay, mean ± SD no. days** *All patients* • CAS: 5.2 ± 11.4 • CEA: 3.7 ± 3.1 *Without complications* • CAS: 1.8 ± 0.58 • CEA: 2.7 ± 1.2 *With complications* • CAS: 13.3 ± 21 • CEA: 3.8 ± 3.5 **Costs/charges, mean ± SD $** *Total costs* • CAS: 3600 ± 422 • CEA: 3969 ± 557 *Nursing costs* • CAS: 400 ± 86 • CEA: 1059 ± 89 *Cath/OR Lab* • CAS: 3550 ± 286 • CEA: 1159 ± 359 *Pharmacy costs* • CAS: 66 ± 16 • CEA: 470 ± 229 *Lab costs*	

Study	Primary Outcomes	Secondary Outcomes	Cognition/Function/Pain/Other	Comments
			• CAS: 55 ± 6 • CEA: 70 ± 4 *Radiology costs* • CAS: 92 ± 4 • CEA: 109 ± 16 *Charges (excluding physician fees)* • CAS: 6447 ± 325 • CEA: 5371 ± 112	

γ Patients could have had more than one event (e.g., fatal stroke was counted as both a death and a stroke, and patients may have had an ipsilateral stroke followed by a nonipsilateral stroke).

Table F4. Study characteristics of RCTs comparing CAS with CEA for symptomatic carotid artery disease (Key Questions 1 and 3)

Study (year)/ Location/ No. of centers	Inclusion criteria	Exclusion criteria	Definition of symptomatic disease	EPD (%) Stent device	Co-intervention	Primary outcome	Follow-up (% followed)	Provider certification	Funding	Comments
BACASS Hoffmann 2008 Switzerland 1 center	• Symptomatic high grade internal carotid artery (ICA) stenosis ≥70% on ultrasonography • Symptomatic within last 3 months • Neurological examination by stroke neurologist	• Unwillingness to participate • Unavailability for follow-up visits for ≥2 years • ICA occlusion • Free-floating • Carotid thrombus • Recurrent ICA stenosis status after neck irradiation. • History of intracranial haemorrhage within 2 months prior to intervention • Intracranial mass lesions • Vascular malformations • Life expectancy <2 years • Allergy to contrast media	NR	Carotid Easy Wallstent and FilterWire with Angioguard RX protection device (100%)	Aspirin and clopidogrel	Periprocedural stroke, death or MI	**1 month** (NR) **6 months** (NR) **12 months** (NR) **2 years** (CAS: 80% CEA: 90%)	CEA performed since 1970 with ~50 CEA per year, CAS performed since 1997 with ~15 patients per year during last couple years	NR	
CREST Brott 2010 Silver 2011 USA/Canada 108 centers	• Stenosis of ≥50% on angiography, ≥70%on ultrasonography, or ≥70% on computed tomographic angiography or magnetic resonance angiography if the stenosis on ultrasonography was 50 to 69%. • Clinical and anatomical	• Previous stroke that was sufficiently severe to confound the assessment of endpoints. • Chronic atrial fibrillation. • Paroxysmal atrial fibrillation that had occurred within the preceding 6 months or that necessitated anticoagulation therapy.	Transient ischemic attack, amaurosis fugax, or minor nondisabling stroke involving the study carotid artery within 180 days before randomization	RX Acculink stent and whenever feasible (% NR) RX Accunet embolic-protection device	325mg aspirin and 75mg clopidogrel twice daily. When stenting was scheduled for within 48 hours after randomization, 650mg aspirin and 450mg clopidogrel given ≥4 hours before	Stroke, MI, or death	**30 days after treatment** (NR) **4 years** (NR)	≥12 procedures per year, complication/death rates ≤5%.	National Institute of Neurological Disorders and Stroke (NINDS) and the NIH, Abbott Vascular Solutions. Multiple authors have potential conflicts of	

Study (year)/ Location/ No. of centers	Inclusion criteria	Exclusion criteria	Definition of symptomatic disease	EPD (%) Stent device	Co-intervention	Primary outcome	Follow-up (% followed)	Provider certification	Funding	Comments
	suitability, before randomization, for management by means of either of the study revascularization techniques **Silver 2011** • See above	• MI within the previous 30 days. • Unstable angina. **Silver 2011** • See above			procedure, and one or two 325-mg doses of daily aspirin for 30 days with either 75mg daily clopidogrel, or 250mg twice daily ticlopidine for 4 weeks				interest.	
EVA-3S Mas 2006 Mas 2008 Arquizan 2011 France 30 centers	**Mas 2006** • ≥18 yrs • Had had a hemispheric or TIA or nondisabling stroke (or retinal infarct) within 120 days before enrollment • Stenosis of ≥60% in symptomatic carotid artery, as determined by NASCET **Mas 2008** • See above **Arquizan 2011** • See above	**Mas 2006** • Modified Rankin score of ≥3 (disabling stroke) • Nonatherosclerotic carotid disease • Severe tandem lesions (stenosis of proximal common carotid artery or intracranial artery more severe than cervical lesion) • Previous revascularization of symptomatic stenosis • History of bleeding disorder • Uncontrolled hypertension or diabetes • Unstable angina • Contraindication to heparin, iclopidine, or clopidogrel • Life expectancy of <2 years • Percutaneous or surgical intervention within 30 days before or	NR	Carotid Wallstent, Acculink, Precise RC, Carotid Wallstent OTW, Zilver 91.9% had EPD (n = 227/247)	Daily use of aspirin (100 to 300 mg) and clopidogrel (75 mg) or ticlopidine (500 mg) for 3 days before and 30 days after stenting was recommended	Composite of any stroke or death occurring within 30 days after treatment	**48 hours** (NR) **30 days** (NR) **6 months** (NR) **Every 6 months thereafter** (NR)	Vascular surgeon had to have performed ≥25 endarterectomies in year before enrollment. Interventional physician Had to have performed ≥12 carotid-stenting procedures or ≥35 stenting procedures in supraaortic trunks, of which ≥5 were in carotid artery.	Programme Hospitalier de Recherche Clinique of the French Ministry of Health. Multiple authors report having potential conflicts of interest.	

Study (year)/ Location/ No. of centers	Inclusion criteria	Exclusion criteria	Definition of symptomatic disease	EPD (%) Stent device	Co-intervention	Primary outcome	Follow-up (% followed)	Provider certification	Funding	Comments
		after study procedure **Mas 2008** • See above **Arquizan 2011** • See above								
ICSS ICSS Investigators 2010 Altinbas 2011a (Cognition) Altinbas 2011b (Blood Pressure) Europe/ Australia/New Zealand/ Canada	**ICSS Investigators 2010** • >40 years of age • Symptomatic atheromatous carotid artery stenosis measured as >50% by the NASCET criteria (or non-invasive equivalent) • Symptoms attributable to the randomized artery needed to have occurred within 12 months before randomisation. • Non-invasive imaging of the carotid artery, including duplex ultrasound **Altinbas 2011a** • See above **Altinbas 2011b** • See above	**ICSS Investigators 2010** • Major stroke without useful recovery of function • Previous carotid endarterectomy or stenting in the randomised artery • Contraindications for either treatment • Planned coronary artery bypass grafting • Other major surgery **Altinbas 2011a** • See above **Altinbas 2011b** • Patients with missing blood pressure records	Symptomatic atheromatous carotid artery stenosis measured as >50% by the NASCET criteria (or non-invasive equivalent)	Chosen at discretion of interventionist but had to have CE mark **≥10% patients:** Carotid Wallstent, Precision, and Protégé **≤10% patients:** Acculink, Xact, Smart, Cristallo Ideale, Exponent, Next Stent. **EPD** 593/828 (72%) patients **≥10% patients:** FilterWire EZ, Angioguard, Spider FX, and Emboshield **≤5% patients** Other EPD In 27 patients,	Combinatio of aspirin and clopidogrel was recommended	3-year rate of fatal or disabling stroke in any territory, (not yet analysed), 120-day rate of stroke, death, or procedural MI	**30 days after treatment** (NR) **120 days after randomization** (>85%)	Centre had to have surgeon who had done ≥50 carotid operations (≥10 cases per year) and physician or surgeon who had done ≥50 stenting procedures, with ≥10 cases in the carotid artery	Medical Research Council, The Stroke Association, Sanofi - Synthélabo, and the European Union, Reta Lila Weston Trust for Medical Research, Swiss National Science Foundation, University of Basel, Department of Health's National Institute for Health Research Biomedical Research Centres, Gore Medical. Multiple authors have potential conflicts of interest.	

Study (year)/ Location/ No. of centers	Inclusion criteria	Exclusion criteria	Definition of symptomatic disease	EPD (%) Stent device	Co-intervention	Primary outcome	Follow-up (% followed)	Provider certification	Funding	Comments
				it was not clear whether or not a protection device was used						
KENTUCKY Brooks 2001 USA Single center	• Events confined to carotid circulation within three months of evaluation • >70% stenosis of ipsilateral carotid bifurcation as determined by NASCET • Anticipated life expectancy of five years • Willingness to complete treatment within two weeks • Ability to sign informed consent	• Symptoms of vertebral-basilar insufficiency or intracranial occlusive disease shown by cerebral angiography • NIH stroke scale of >4 • Cardiac arrhythmia • Allergy and/or sensitivity to aspirin, heparin, ticlopidine or clopidogrel; • History of bleeding diathesis or coagulopathy • History of intracranial hemorrhage within two months of randomization.	NR	Wallstent (100%), no protection device used.	100µg/kg heparin, 325 mg aspirin and 75 mg clopidrogel .25mg/kg ReoPro for 20min followed by continuous .125 µg/kg/min for 12 hours to maximum of 10µg/min for individuals with cerebral vascular accidents	NR	2 years (NR)	NR	NR	
LEICESTER Naylor 1998 UK Single center	• Carotid territory symptoms • Evidence of ≥70% internal carotid artery stenosis	• Asymptomatic disease • <70% stenosis • TIA or stroke in evolution • Vertebrobasilar or nonhemispheric symptoms • Refusal to give informed consent	NR	Wallstent, EPD NR	5000 IU heparin, 600µg atropine, dextran-40	Death or stroke within 30 days	**30 days** (100%)	Radiologist with experience in >4000 peripheral artery angioplasties	UK Stroke Association, Schneider UK Ltd	
REGENSBURG Steinbauer 2008 Germany Single center	• >70% symptomatic carotid artery stenosis as defined by NASCET	• NR	NR	Carotid Wallstent, no protection device used.	75 mg of clopidogrel and 100 mg of aspirin daily for 1 month; thereafter 300	Long-term stroke recurrence, restenosis, and death	**3 month** (NR) **6 month** (NR) **1 year** (NR)	NR	Bristol Myers Squibb and Boston Scientific Multiple	

Study (year)/ Location/ No. of centers	Inclusion criteria	Exclusion criteria	Definition of symptomatic disease	EPD (%) Stent device	Co-intervention	Primary outcome	Follow-up (% followed)	Provider certification	Funding	Comments
					mg of aspirin daily				authors have potential conflicts of interest.	
SPACE SPACE Collaborative Group 2006 Germany, Austria, Switzerland 35 centers	**SPACE 2006** • Symptomatic stenosis (amaurosis, transient ischaemic attack, or stroke) of carotid bifurcation or internal-carotid artery within past 180 days • Modified Rankin scale score of ≤3 • ≥50 yrs • Negative pregnancy test for women with childbearing potential • Possibility for follow up examinations • Written informed consent provided • Stenosis of carotid bifurcation or internal-carotid artery of ≥70% proven by duplex ultrasound or angiography corresponding to stenosis level of ≥70% according to European Carotid Surgery Trial criteria or ≥50% according NASCET **Eckstein 2008**	**SPACE 2006** • Intracranial bleeding in past 90 days • Uncontrolled arterial hypertension • Known intracranial arteriovenous malformation or aneurysm • Severe concomitant disease with poor prognosis (life expectance <2 years) • Uncorrectable coagulation abnormality • Contraindications for heparin, aspirin, or clopidogrel • Contraindications for contrast media • Planned simultaneous surgical procedures • Condition that could impose hazards to patient if study therapy is iniated (left to discretion of investigator) • Occlusion of common-carotid or internal-carotid artery • Stenosis due to	Amaurosis, TIA, or stroke	Carotid Wallstent, Precise, or Acculink with PercuSurge GuardWire, FilterWire EX, AngioGuard, NeuroShield, or Carotid Trap EPD (% of patients treated with each system NR)	100 mg aspirin plus 75 mg clopidogrel daily for at least 3 days before and 30 days after the intervention	Ipsilateral stroke (ischaemic stroke or intracerebral bleeding or both, with symptoms lasting more than 24 h) or death of any cause between randomisation and 30 days after treatment	**7 days** (NR) **30 days** (CAS: >94% CEA: >93%) **6 months** (NR) **1 year** (NR) **2 years** (NR)	NR	NR Multiple authors have potential conflicts of interest	

Study (year)/ Location/ No. of centers	Inclusion criteria	Exclusion criteria	Definition of symptomatic disease	EPD (%) Stent device	Co-intervention	Primary outcome	Follow-up (% followed)	Provider certification	Funding	Comments
	• See above	external compression • Stenosis due to dissection • Recurrent stenosis after surgery or stenting • Radiation-induced stenosis • Stenosis due to fibromuscular dysplasia • Floating thrombus • Additional intracranial stenosis with higher grade **Eckstein 2008** • See above								

EPD = embolic protection device; MI = myocardial infarction; NASCET = North American Symptomatic Carotid Endarterectomy Trial; NIH = National Institutes of Health; NR = not reported; TIA = transient ischemic attack.

Table F5. Baseline characteristics of patients from included RCTs comparing CAS with CEA for symptomatic carotid artery disease (Key Questions 1 and 3).

	BACASS		CREST		EVA-3S		ICSS		KENTUCKY		LEICESTER		REGENSBURG		SPACE	
	Hoffman 2008		Silver 2011		Mas 2008		ICSS Investigators 2010		Brooks 2001		Naylor 1998		Steinbauer 2008		Eckstein 2008	
	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA
Demographics																
N	10	10	668	653	265	262	853	857	53	51	7	10	43	44	607	589
% Male	80	90	63.9	66.4	73	78	70	71	NR	NR	71	40	NR	NR	72	72
Mean age, years	69	71	68.9	69.2	69.1	70.2	70	70	66.4	69.6	68	66.7	67.9	68.4	68.1	68.7
% Smokers	50*	60*	26.4*	26.1*	25*	23*	24* 48 †	23* 49 †	38*	40*	NR	NR	19‡	18‡	71‡	70‡
Comorbidities																
% HTN	70	80	85.8	86.1	72	72	69	69	45	48	NR	NR	34	34	75	76

	BACASS		CREST		EVA-3S		ICSS		KENTUCKY		LEICESTER		REGENSBURG		SPACE	
	Hoffman 2008		Silver 2011		Mas 2008		ICSS Investigators 2010		Brooks 2001		Naylor 1998		Steinbauer 2008		Eckstein 2008	
	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA	CAS	CEA
% AFib/ Aflutter	NR	NR	0	0	NR	NR	7	7	NR	NR	NR	NR	NR	NR	NR	NR
% Hyper-lipidemia	70	60	NR	NR	58	56	61	66	NR	NR	NR	NR	22	23	NR	NR
% DM	30	30	30.6	30.4	22	26	22	22	19	12	NR	NR	19	15	26	29
% Prior MI	NR	NR	NR	NR	11	13	18	18	NR	NR	NR	NR	NR	NR	NR	NR
% CAD	20	40	NR	NR	NR	NR	NR	NR	39	31	NR	NR	18	20	21	24
% PVD	NR	NR	NR	NR	15	11	16	16	NR	NR	NR	NR	8	8	NR	NR
Qualifying Events																
% Stroke	90	40	NR	NR	48	54	46	44	NR	NR	57.1	40	27.9	36.4	44.5	42.8
% TIA	10	10	NR	NR	50	44	32	35	NR	NR	28.6	30	53.5	40.9	29.7	31.1
% Amaurosis fugax	0	50	NR	NR	NR§	NR§	17**	17	23	20	14.3	30	18.6	29.5	15.7	15.3
Previous Symptoms																
% Contra-lateral occlusion	10	0	2.7	3.2	13	14	6	4	NR	NR	NR	NR	NR	NR	7	8
Mean % stenosis	84.5	82	NR	NR	NR	NR	<50%: 66	<50%: 65	NR (>80%)	NR (>80%)	NR (70-90%)	NR (70-90%)	84.7	85.1	NR	NR

*Current smokers; †Ex-smoker; ‡Current or ex-smokers; §2% in each arm report Retinal infarction; **reported as "most recent ipsilateral event"
AFib = atrial fibrillation; AFlutter = atrial flutter; CAD = coronary artery disease; CAS = carotid artery stenting; CEA = carotid endarterectomy; DM = diabetes mellitus; HTN = hypertension; MI = myocardial infarction; ND = not defined; NR = not reported; PVD = peripheral vascular disease; TIA = transient ischemic attack.

We reported qualifying events: stroke, TIA, amaurosis fugax, one author reported prior history of vascular disease as well as qualifying events (Mas 2008). Exclusion criteria for many studies is that <20% of patients have prior revascularization, so percent previous carotid artery stenting, or endarterectomy are not reported.

Table F6. Detailed results of RCTs comparing CAS with CEA for the treatment of symptomatic carotid artery disease (Key Questions 1 and 3).

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
BACASS				
Hoffmann 2008	***Periprocedural*** **Death** • CAS: 0% (0/10) • CEA: 0% (0/10) **Ipsilateral major stroke** • CAS: 0% (0/10) • CEA: 10% (1/10) **MI** • CAS: 0% (0/10) • CEA: 0% (0/10) **TIA** • CAS: 0% (0/10) • CEA: 0% (0/10) **Stroke or death**** • CAS: 0% (0/10) • CEA: 10% (1/10) ***48 month (including periprocedural)*** **Stroke** • CAS: 0% (0/10) • CEA: 0% (1/10) **Death** • CAS: 0% (1/10) • CEA: 0% (2/10)	***Periprocedural*** **Hematoma** • CAS: 0% (0/10) • CEA: 0% (0/10) **Cranial nerve paralysis** • CAS: 0% (0/10) • CEA: 0% (0/10)	**Length of Hospital stay, mean ± SD no. of days** • CAS: 3.5 ± 1.8 • CEA: 7.8 ± 3.3 ***48 months*** **Patency** 30-49% • CAS: 12.5% (1/8) • CEA: 11.1% (1/9) 50-69% • CAS: 0% (0/8) • CEA: 11.1% (1/9) 70-99% • CAS: 0% (0/8) • CEA: 0% (0/9) **Restenosis ≥ 70%** • CAS: 0% (0/8) • CEA: 0% (0/9)	Analyses based on non-inferiority of CAS TRIAL STOPPED due to start of ICSS Low power
CREST				
Brott 2010	***Periprocedural*** **Any Stroke** • CAS: 5.5% ± 0.9 (37/668) • CEA: 3.2% ± 0.7 (21/653) AR: 2.3 (0.1, 4.5) HR: 1.74 (1.02, 2.98) *P* = 0.04	NR	NR	Kaplan-Meier analysis of periprocedural stroke, MI, or death or 4 year ipsilateral stroke.

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	Stroke or Death • CAS: 6.0% ± 0.9 (40/668) • CEA: 3.2% ± 0.7 (21/653) AR: 2.8 (0.5, 5.0) HR: 1.89 (1.11, 3.21) *P* = 0.02 **MI** • CAS: 1.0% ± 0.4 (7/668) • CEA: 2.3% ± 0.6 (15/653) AR: −1.2 (−2.6, 0.1) HR: 0.45 (0.18, 1.11) *P* = 0.08 ***48 month (including periprocedural)*** **Any periprocedural stroke or postprocedural ipsilateral stroke** • CAS: 7.6 ± 1.1 (48/668) • CEA: 6.4% ± 1.1 (37/653) AR: 1.2 (−1.8, 4.1) HR: 1.29 (0.84, 1.98) *P* = 0.25 **Any periprocedural stroke or death or postprocedrual ipsilateral stroke** • CAS: 8.0% ± 1.1 (51/668) • CEA: 6.4% ± 1.1 (37/653) AR: 1.6 (−1.4, 4.6) HR: 1.37 (0.90, 2.09) *P* = 0.14 **MI** NR			Analyses based on superiority. Intent-to-treat analysis used.
Silver 2011	***Periprocedural*** **Death** NR	***Periprocedural*** **Hematoma** • CAS: 0% (0/668)	NR	Intent-to-treat analysis used.

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	Any Stroke • CAS: 5.5% ± 0.9 (37/668) • CEA: 3.2% ± 0.7 (21/653) AR: 2.3 (0.1, 4.5) HR: 1.74 (1.02, 2.98) *P* = 0.043 **Major Stroke** • CAS: 1.2% ± 0.4 (8/668) • CEA: 0.9% ± 0.4 (6/653) AR: 0.3 (-0.8, 1.4) HR: 1.32 (0.46, 3.80) *P* = 0.61 **Minor Stroke** • CAS: 4.3% ± 0.8 (29/668) • CEA: 2.3% ± 0.6 (15/653) AR: 2.0 (0.1, 4.0) HR: 1.91 (1.03, 3.57) *P* = 0.042 **Stroke or Death** • CAS: 6.0% ± 0.9 (33/668) • CEA: 3.1% ± 0.7 (21/653) AR: 2.8 (0.5, 5.0) HR: 1.89 (1.11, 3.21) *P* = 0.019 **MI** • CAS: 1.0% ± 0.4 (7/668) • CEA: 2.3% ± 0.6 (15/653) AR: -1.2 (-2.6, 0.1) HR: 0.45 (0.18, 1.11) *P* = 0.083	• CEA: 1.2% (8/653) **Cranial nerve palsy** • CAS: 0.4% (3/668) • CEA: 5.1% (33/653) **Hypertension** • CAS: 1.1% (8/668) • CEA: 4.9% (32/653) **Bradycardia** • CAS: 2.99% (20/668) • CEA: 0.61% (4/653) **Hypotension‡** • CAS: 4.49% (30/668) • CEA: 1.99% (13/653) **Femoral artery complications, nonhemorrhagic** • CAS: 0.90% (6/668) • CEA: 0.31%% (2/653)		

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
EVA-3S				
Mas 2006	***Periprocedural*** **Death** *All death* • CAS: 0.8% (2/261) • CEA: 1.2% (3/259) RR: 0.7 (0.1, 3.9) *P* = 0.68 *Fatal stroke* • CAS: 0.4% (1/261) • CEA: 0.8% (2/259) *Other cause* • CAS: 0.4% (1/261) • CEA: 0.4% (1/259) **Stroke** *Nonfatal stroke* • CAS: 8.8% (23/261) • CEA: 2.7% (7/259) RR: 3.3 (1.4, 7.5) *P* = 0.004 *Stroke with symptoms lasting ≥7 days* • CAS: 7.7% (20/261) • CEA: 2.3% (6/259) *Nondisabling stroke* • CAS: 6.1% (16/261) • CEA: 2.3% (6/259) *Disabling stroke*[β] • CAS: 2.7% (7/261) • CEA: 0.4% (1/259)	***Periprocedural*** **Bradycardia or hypotension requiring treatment** • CAS: 4.2% (11/261) • CEA: 0% (0/259) RR: NR *P* <0.001 **Cranial nerve injury** • CAS: 1.1% (3/261) • CEA: 7.7% (20/259) RR: 0.15 (0.04, 0.49) *P* <0.001 **Cervical or groin hematoma requiring treatment** • CAS: 0.4% (1/261) • CEA: 0.8% (2/259) **Infection requiring treatment** • CAS: 0.4% (1/261) • CEA: 0.4% (1/259)	NR	Intent-to-treat analysis used. Analysis based on non-inferiority. Terminated early due to excess strokes in stent group; planned n =900

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	MI[α] • CAS: 0.4% (1/261) • CEA: 0.8% (2/259) *P* = 0.62 **Stroke or death** • CAS: 9.6% (25/261) • CEA: 3.9% (10/259) RR: 0.5 (0.04, 0.54) *P* = 0.01 **Any disabling stroke or death** • CAS: 3.4% (9/261) • CEA: 1.5% (4/259) RR: 2.2 (0.7, 7.2) *P* = 0.26 **TIA** • CAS: 2.3% (6/261) • CEA: 0.8% (2/259) RR: 3.0 (0.6, 14.6) *P* = 0.28 ***6 month (including periprocedural)*** **Any stroke or death** • CAS: 11.7% (31/262) • CEA: 6.1% (16/265) *P* = 0.02 **Any periprocedural stroke or death plus any stroke up to 6 months** • CAS: 10.9% (29/262) • CEA: 4.6% (12/265) *P* = 0.007 **Any periprocedural stroke or death plus ipsilateral stroke up to 6 months**			

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	• CAS: 10.2% (27/262) • CEA: 4.2% (11/265) *P* = 0.008			
Mas 2008	***Periprocedural*** **Any stroke or death** • CAS: 9.4% (25/265) • CEA: 3.8% (10/262) **Any stroke** • CAS: 9.1% (24/265) • CEA: 3.4% (9/262) **Non-stroke deaths** • CAS: 0.4 (1/265) • CEA: 0.4% (1/262) **MI** • CAS: 0.38% (1/265) • CEA: 0.76% (2/262) ***48 month (excluding periprocedural)*** **Deaths** *Any death* • CAS: 13.6% (36/265) • CEA: 13.0% (34/262) *Ipsilateral stroke* • CAS: 0.4% (1/265) • CEA: 0.4% (1/262) *Non-ipsilateral stroke* • CAS: 0.75% (2/265) • CEA: 0% (0/262) *Other vascular* • CAS: 4.9% (13/265) • CEA: 2.3% (6/262) *Non-vascular* • CAS: 7.5% (20/265) • CEA: 10.3% (27/262) **Stroke**	NR	NR	Kaplan-Meier analysis of 4 year stroke risk probability. Analysis based on non-inferiority. Effect modification data for sex, age, stenosis severity, hypertension, diabetes, smoking, prior stroke, qualifying event, contralateral stenosis, event-to-treatment delay

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	Any stroke • CAS: 3.8% (10/265) • CEA: 3.8% (10/262) KM Cumulative probability • CAS: 14.2% • CEA: 9.1% HR: 1.77 (1.03, 3.02) *P* = 0.04 *Ipsilateral stroke* • CAS: 1.5% (4/265) • CEA: 1.5% (4/262) KM Cumulative probability • CAS: 11.1% • CEA: 6.2% HR: 1.97 (1.06, 3.67) *P* = 0.03 *Non-Ipsilateral stroke* • CAS: 2.3% (6/265) • CEA: 2.3% (6/262) *Fatal or disabling ipsilateral stroke* KM Cumulative Probability • CAS: 4.9% • CEA: 2.4% HR: 2.00 (0.75, 5.33) *P* = 0.17 *Fatal or disabling stroke* KM Cumulative Probability • CAS: 6.3% • CEA: 4.0% HR: 1.68 (0.74, 3.84) *P* = 0.22 **MI** NR			

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	Any stroke or death NR KM Cumulative Probability • CAS: 26.9% • CEA: 21.6% HR: 1.39 (0.96, 2.00) *P* = 0.08 *Disabling stroke or death* KM Cumulative Probability • CAS: 19.6% • CEA: 17.0% HR: 1.20 (0.78, 1.85) *P* = 0.41			
Arquizan 2011	NR	NR	***6 month*** **50-69% Restenosis** NR KM Cumulative Probability • CAS: 4.5% • CEA: 1.2% **70-99% Restenosis** NR KM Cumulative Probability • CAS: 1.4% • CEA: 2.8% **50-99% Restenosis or Occlusion** NR KM Cumulative Probability • CAS: 5.9% • CEA: 3.5% ***12 month*** **50-69% Restenosis** KM Cumulative Probability • CAS: 9.1%	Analysis based on non-inferiority. Effect modification for sex, age, hypertension, diabetes, smoking, antiplatelet therapy, lipid-lowering drug, closed vs. open cell stent

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
			• CEA: 1.2% **70-99% Restenosis** KM Cumulative Probability • CAS: 1.4% • CEA: 2.8% **50-99% Restenosis or Occlusion** NR KM Cumulative Probability • CAS: 10.4% • CEA: 4.9% ***24 month*** **50-69% Restenosis** NR KM Cumulative Probability • CAS: 9.1% • CEA: 2.2% **70-99% Restenosis** NR KM Cumulative Probability • CAS: 1.8% • CEA: 2.8% **50-99% Restenosis or Occlusion** NR KM Cumulative Probability • CAS: 10.4% • CEA: 5.0% ***36 month*** **50-69% Restenosis** NR KM Cumulative Probability • CAS: 10.5% • CEA: 2.2%	

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
			70-99% Restenosis NR KM Cumulative Probability • CAS: 3.3% • CEA: 2.8% **50-99% Restenosis or Occlusion** NR KM Cumulative Probability • CAS: 12.5% • CEA: 5.0% ***36 month (including periprocedural)*** **≥50% Restenosis** • CAS: 10.1% (27/265) • CEA: 4.6% (12/262) **50-69% Restenosis** • CAS: 8.7% (23/265) • CEA: 1.9% (5/262) **≥70% Restenosis** • CAS: 1.9% (5/265) • CEA: 2.7% (7/262)	
ICSS				
ICSS Investigators 2010	***Periprocedural*** **Death** *PP* *Procedural death* • CAS: 1.3% (11/828) • CEA: 0.5% (4/821) *Death unrelated to stroke or MI* • CAS: 0.12% (1/828) • CEA: 0.12% (1/821) **Stroke**	***Periprocedural*** **Cranial nerve palsy** *PP* *Any cranial nerve palsy* • CAS: 0.01% (1/828) • CEA: 5.5% (45/821) *Disabling cranial nerve palsy* • CAS: 0.01% (1/828) • CEA: 0.01% (1/821) **Hematoma**	NR	Per-protocol (PP) analyses used for periprocedural outcomes. Intent-to-treat (ITT) analyses used for long-term outcomes

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	PP *Any stroke* • CAS: 7.0% (58/828) • CEA: 3.3% (27/821) RR: 2.13 (1.36, 3.33) AR: 3.7% (1.6, 5.8) *P* = 0.001 *Ipsilateral stroke* • CAS: 6.3% (52/828) • CEA: 3.0% (25/821) *Ischaemic stroke* • CAS: 6.8% (56/828) • CEA: 2.6% (21/821) *Haemorrhagic stroke* • CAS: 2.4% (2/828) • CEA: 0.61% (5/821) *Uncertain cause stroke* • CAS: 0% (0/828) • CEA: 0.12% (1/821) *Non-disabling stroke* • CAS: 4.3% (36/828) • CEA: 13.4% (11/821) *Non-disabling stroke lasting <7 days* • CAS: 0.10% (8/828) • CEA: 0.61% (5/821) *Non-disabling stroke lasting >7 days* • CAS: 3.5% (29/828) • CEA: 0.73% (6/821)	*PP* *Any hematoma* • CAS: 3.6% (30/828) • CEA: 6.1% (50/821) *Severe hematoma (requiring treatment)* • CAS: 1.0% (8/828) • CEA: 3.4% (8/821) ***4 months (including periprocedural)*** **Cranial nerve palsy** *ITT* *Any cranial nerve palsy* • CAS: 0.01% (1/853) • CEA: 5.3% (45/857) *Disabling cranial nerve palsy* • CAS: 0.01% (1/853) • CEA: 0.01% (1/857) **Hematoma** *ITT* *Any hematoma* • CAS: 3.6% (31/853) • CEA: 5.8% (50/857) *Severe hematoma (requiring treatment)* • CAS: 0.01% (9/853) • CEA: 3.3% (28/857)		

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	Disabling stroke • CAS: 1.7% (14/828) • CEA: 1.7% (14/821) *Fatal stroke* • CAS: 0.10% (8/828) • CEA: 0.37% (3/821) **Stroke or death** *PP* • CAS: 7.4% (61/828) • CEA: 3.4% (28/821) RR: 2.16 (1.40, 3.34) AR: 4.0% (1.8, 6.1) *P* = 0.004 **Disabling stroke or death** *PP* • CAS: 3.1% (26/828) • CEA: 2.2% (18/821) RR: 1.43 (0.79, 2.59) AR: 0.9% (-0.6, 2.5) *P* = 0.23 **MI** *PP* *Any MI* • CAS: 0.36% (3/828) • CEA: 0.61% (5/821) *Non-fatal MI* • CAS: 0% (0/828) • CEA: 0.61% (5/821) *Fatal MI* • CAS: 0.36% (3/828)			

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	• CEA: 0% (0/821) ***<u>4 months (periprocedural included)</u>*** **Death** *ITT* *All cause death* • CAS: 2.3% (19/853) • CEA: 0.8% (7/857) HR: 2.76 (1.16, 6.56) AR: 1.4% (0.3, 2.6) *P* = 0.017 *Death unrelated to stroke or MI* • CAS: 0.82% (7/853) • CEA: 0.61% (5/857) **Stroke** *ITT* *Any stroke* • CAS: 7.7% (65/853) • CEA: 4.1% (35/857) HR: 1.92 (1.27, 2.89) AR: 3.5% (1.3, 5.8) *P* = 0.002 *Ipsilateral stroke* • CAS: 6.8% (58/853) • CEA: 3.5% (30/857) *Ischaemic stroke* • CAS: 7.4% (63/853) • CEA: 3.5% (30/857) *Haemorrhagic stroke* • CAS: 3.5% (3/853) • CEA: 0.58% (5/857)			

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	Uncertain cause stroke • CAS: 0% (0/853) • CEA: 2.3% (2/857) *Non-disabling stroke* • CAS: 4.6% (39/853) • CEA: 1.6% (14/857) *Non-disabling stroke lasting <7 days* • CAS: 1.1% (9/853) • CEA: 0.58% (5/857) *Non-disabling stroke lasting >7 days* • CAS: 3.6% (31/853) • CEA: 1.1% (9/857) *Disabling stroke* • CAS: 2.0% (17/853) • CEA: 2.3% (20/857) *Fatal stroke* • CAS: 1.1% (9/853) • CEA: 0.23% (2/857) **Stroke or death** *ITT* *Any stroke or death* • CAS: 8.5% (72/853) • CEA: 4.7% (40/857) HR: 1.86 (1.26, 2.74) AR: 3.8% (1.4, 6.1) *P* = 0.001 *Any stroke or procedural death* • CAS: 8.0% (68/853)			

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	• CEA: 4.2% (36/857) HR: 1.95 (1.30, 2.92) AR: 3.8% (1.5, 6.0) *P* = 0.001 *Disabling stroke or death* • CAS: 4.0% (32/853) • CEA: 3.2% (27/857) HR: 1.28 (0.77, 2.11) AR: 0.8% (-0.9, 2.6) *P* = 0.34 **MI** *ITT* *Any MI* • CAS: 0.35% (3/853) • CEA: 0.47% (4/857) *Non-fatal MI* • CAS: 0% (0/853) • CEA: 0.35% (3/857) *Fatal MI* • CAS: 0.35% (3/853) • CEA: 0% (0/857)			
Altinbas 2011a	NR	NR	***6 months*** **Change in cognitive sum z score**[λ] • CAS: -0.19 (0.38) • CEA: -0.02 (0.71) MD[§]: -0.17 (-0.38, 0.03) **Change in cognition domain z scores** *Abstract reasoning* • CAS: -0.17 (0.48)	This was a per protocol analyses and excluded patients that were randomized but did not get treatment. Adjusted for age, sex, and education

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
			• CEA: 0.04 (0.45) MD: -0.22 (-0.44, 0.00) *Attention* • CAS: -0.09 (1.05) • CEA: -0.13 (1.60) MD: 0.04 (-0.46, 0.53) *Executive functioning* • CAS: 0.13 (0.36) • CEA: 0.17 (0.48) MD: -0.05 (-0.21, 0.12) *Language* • CAS: -0.25 (0.68) • CEA: -0.18 (0.70) MD: -0.07 (-0.32, 0.18) *Verbal memory* • CAS: -0.16 (0.76) • CEA: -0.09 (1.00) MD: -0.07 (-0.39, 0.26) *Visual memory* • CAS: 0.24 (0.72) • CEA: 0.24 (0.66) MD: 0.00 (-0.27, 0.26) *Visual perception* • CAS: -0.14 (0.54) • CEA: -0.17 (0.73) MD: -0.04 (-0.21, 0.28) *Neglect* • CAS: -1.75 (1.70) • CEA: -0.61 (3.57)	

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
			MD: -1.13 (-2.27, 0.01)	
Altinbas 2011b	NR	NR	***Mean 3-day*** **Change in systolic blood pressure (SBP)** • CAS: -19.1 (-21.3, 16.9) • CEA: -8.8 (-10.9, -6.8) MD: -10.3 (-13.3, -7.3) *P*: <0.0001 **Change in diastolic blood pressure (DBP)** • CAS: -9.0 (-10.2, -7.9) • CEA: -5.0 (-6.1, -3.8) MD: -4.1 (-5.7, -2.4) *P*: <0.0001 ***1 month*** **Change in SBP** • CAS: -0.4 (-2.4, 1.7) • CEA: -1.6 (-3.4, 0.2) MD: -1.3 (-1.5, 4.0) *P*: <0.370 **Change in DBP** • CAS: -1.1 (0.0, 2.1) • CEA: 0.8 (-0.2, 1.9) MD: 0.2 (-1.3, 1.7) *P* = 0.775 **Antihypertensive use** • CAS: 57% • CEA: 67% RR: 0.86 (0.79, 0.93) *P* = 0.0002 ***6 month***	Per protocol analysis Adjusted for age, sex, and cardiac failure

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
			Change in SBP • CAS: -2.5 (-4.7, -0.4) • CEA: -3.0 (-5.0, -0.9) MD: -0.4 (-2.5, 3.4) *P* = 0.772 **Change in DBP** • CAS: -0.9 (-2.1, 0.2) • CEA: -0.3 (-1.4, 0.9) MD: -0.7 (-2.3, 1.0) *P* = 0.430 **Antihypertensive use** • CAS: 67% • CEA: 71% RR: 0.93 (0.86, 1.00) *P* = 0.0472 ***12 month*** **Change in SBP** • CAS: -2.1 (-4.3, 0.2) • CEA: -4.4 (-6.5, 2.2) MD: 2.3 (-0.8, 5.4) *P* = 0.147 **Change in DBP** • CAS: -0.5 (-1.7, 0.6) • CEA: -0.7 (-1.9, 0.4) MD: 0.2 (-1.4, 1.8) *P* = 0.793 **Antihypertensive use** • CAS: 67% • CEA: 74% RR: 0.91 (0.85, 0.97) *P* = 0.0073	

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
KENTUCKY				
Brooks 2001	***Periprocedural***** **TIA** • CAS: 1.9% (1/53) • CEA: 0% (0/51) **Stroke** • CAS: 0% (0/53) • CEA: 0% (0/51) **Death** • CAS: 0% (0/53) • CEA: 2.0% (1/51) **MI** • CAS: 0% (0/53) • CEA: 2.0% (1/51) **Stroke or Death** • CAS: 0% (0/53) • CEA: 2.0% (1/51) ***24 Months (including periprocedural)*** **TIA** • CAS: 1.9% (1/53) • CEA: 0% (0/51) **Stroke** • CAS: 0% (0/53) • CEA: 0% (0/51) **Death** • CAS: 0% (0/53) • CEA: 2.0% (1/51) **MI**	***Periprocedural*** **Bradycardia** • CAS: 13.2% (7/53) • CEA: 0% (0/51) **Hypotension** • CAS: 22.6% (12/53) • CEA: 5.9% (3/51) **Cranial or cervical nerve injury** • CAS: 0% (0/53) • CEA: 7.8% (4/51) **Arterial thrombosis/amputation** • CAS: 1.9% (1/53) • CEA: 0% (0/51) **Hematoma requiring treatment** • CAS: 5.7% (3/53) • CEA: 2.0% (1/51)	**Pain scale (0-10), mean (range)** *24 hours* • CAS: 1.2 (0-5) • CEA: 2.7 (0-5) *1 month* • CAS: < 1.0 (0-4) • CEA: < 1.0 (0-4) **Return to full activity, mean ± SD no. days** *Without complications* • CAS: 12 (2-30) • CEA: 16 (7-30) *With complications* • CAS: 120 (57-140) • CEA: 21 (9-30) **Length of hospital stay, mean ± SD no. days** *All patients* • CAS: 5.2 ± 11.4 • CEA: 3.7 ± 3.1 *Without complications* • CAS: 1.8 ± 0.58 • CEA: 2.7 ± 1.2 *With complications* • CAS: 13.3 ± 21 • CEA: 3.8 ± 3.5 **Costs/charges, mean ± SD $** *Total* • CAS: 4077 ± 460 • CEA: 3415 ± 1289 *Nursing costs* • CAS: 327 ± 39	

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	• CAS: 0% (0/53) • CEA: 2.0% (1/51) **Stroke or Death** • CAS: 0% (0/53) • CEA: 2.0% (1/51)		• CEA: 1187 ± 101 *Cath/OR Lab* • CAS: 3550 ± 286 • CEA: 1159 ± 359 *Pharmacy costs* • CAS: 66 ± 16 • CEA: 470 ± 229 *Lab costs* • CAS: 81 ± 26 • CEA: 79 ± 41 *Radiology costs* • CAS: 105 ± 111 • CEA: 108 ± 58 *Charges (excluding doctor fees)* • CAS: 6653 ± 367 • CEA: 5594 ± 166	
LEICESTER				
Naylor 1998	***Periprocedural*** **Death** • CAS: 0% (0/7) • CEA: 0% (0/10) **Stroke** *Any stroke* • CAS: 71.4% (5/7) • CEA: 0% (0/10) *Ipsilateral stroke* • CAS: 71.4% (5/7) • CEA: 0% (0/10) *Disabling stroke* • CAS: 42.9% (3/7) • CEA: 0% (0/10) **MI**	***Periprocedural*** **Cranial nerve injury** • CAS: 0% (0/7) • CEA: 0% (0/10) **Cerebral emboli (median; range)** • CAS: (284; 151-379) • CEA: (12; 0-26) *P* = 0.0015	NR	Single center. Mean stenosis 82%. Stopped early due to harm.; mean stenosis was 82%

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	NR **Any Stroke or Death**** • CAS: 71.4% (5/7) • CEA: 0% (0/10)			
REGENSBURG				
Steinbauer 2008	***12 months*** **Stroke (nonfatal)** • CAS: 2.3% (1/43) • CEA: 0% (0/44) **TIA** • CAS: 7.0% (3/43) • CEA: 4.5% (2/44) **Death** • CAS: 0% (0/43) • CEA: 0% (0/44) **MI** • CAS: 0% (0/43) • CEA: 2.3% (1/44) ***Median 65 ± 13 months*** **Death** *All causes** • CAS: 23.3% (10/43) • CEA: 29.5% (13/44) *Due to ipsilateral stroke* • CAS: 2.3% (1/43) • CEA: 0% (0/44) *Due to MI/cardiac failure* • CAS: 9.3% (4/43) • CEA: 6.8% (3/44) *Other*$^{\psi}$	***12 months*** **Hematoma** • CAS: 2.3% (1/43) • CEA: 13.6% (6/44) **Infection** • CAS: 0% (0/43) • CEA: 2.3% (1/44) **Cranial nerve injury** • CAS: 0% (0/43) • CEA: 2.3% (1/44) **Restenosis > 70%** • CAS: 4.7% (2/43) • CEA: 0% (0/44) ***Median 65 ± 13 months*** **Re-intervention rate** • CAS: 15.6% (5/32) CEA: 0% (0/29) *P* < .027 **Disease progression to a high-grade stenosis of the contralateral carotid artery** • CAS: 15.6% (5/32) • CEA: 10.3% (3/29) *P*> 0.05	***Median 65 ± 13 months*** **Restenosis > 70%/occlusion** • CAS: 18.8% (6/32) • CEA: 0% (0/29) *P* < .023 *Medium-grade restenosis(<70%)* • CAS: 25.0% (8/32) • CEA: 3.4% (1/29) • *P*: NR *High-grade restenosis due to kinking* • CAS: 9.4% (3/32) • CEA: 0% (0/29) • *P*: NR	Hematoma, infection, and cranial nerve injury should be considered periprocedural Kaplan-Meier analysis of survival rates, freedom from ipsilateral stroke, freedom from all neurologic events, freedom from restenosis/occlusion, and freedom from reintervention. RANDOMIZATION STOPPED – Initiation of SPACE Low power

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	• CAS: 9.4% (5/43) • CEA: 22.7% (10/44) **Ipsilateral stroke** • CAS: 9.5% (4/42) • CEA: 0% (0/42) *P* < .041 **Stroke and TIA** • CAS: 11.9% (5/42) • CEA: 7.1% (3/42) *P* = .092			
SPACE				
SPACE Collaborative Group 2006	***Periprocedural*** **Death** • CAS: 0.7% (4/599) • CEA: 0.9% (5/584) OR: 0.75 (0.15-3.64) **Stroke** *Any stroke* • CAS: 7.7% (45/599) • CEA: 6.5% (36/584) OR: 1.24 (0.79, 1.95) *Ipsilateral ischaemic stroke* • CAS: 6.51% (39/599) • CEA: 5.14% (30/584) OR: 1.26 (0.77, 2.18) *Disabling ipsilateral stroke* • CAS: 4.01% (24/599) • CEA: 2.91% (17/584) OR: 1.39 (0.74, 2.62) **MI**	***Periprocedural*** **Ipsilateral intracerebral bleeding** • CAS: 0.17% (1/599) • CEA: 0.86% (5/584) OR: 0.19 (0.004, 1.74) **Procedural failure** • CAS: 3.17% (19/599) • CEA: 2.05% (12/584) OR: 1.56 (0.71, 3.56)	NR	Analysis based on non-inferiority. Kaplan-Meier analysis of event occurrence. Intent-to-treat analysis used. Stopped early for harm/futility; planned n = 1900 Procedure failure including inability to treat the allocated technique, remaining stenosis of 50% or more measured with ultrasound at one of the follow-up visits, or vessel occlusion

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	• CAS: 0% (0/599) • CEA: 0% (0/584) **Death or Stroke** *Any death or stroke* • CAS: 7.68% (46/599) • CEA: 6.51% (38/584) OR: 1.19 (0.75, 1.92) *Ipsilateral death or stroke* • CAS: 6.84% (41/599) • CEA: 6.34% (37/584) OR: 1.09 (0.69, 1.72) AR: 0.51 (-1.89, 2.91) *Disabling ipsilateral stroke or death* • CAS: 4.67% (28/599) • CEA: 3.77% (22/584) OR: 1.25 (0.71, 2.22)			assessed up to 30 days after treatment.
Eckstein 2008	***Periprocedural*** **Death** *ITT* • CAS: 1.0% (6/607) • CEA: 0.85% (5/589) HR: 1.16 (0.38, 3.56) *PP* • CAS: 0.66%% (4/573) • CEA: 0.51% (3/563) HR: 1.31 (0.33, 5.21) **Stroke** *Any stroke* *ITT* • CAS: 7.2% (44/607) • CEA: 6.3% (37/589)	***Periprocedural*** **Ipsilateral cerebral bleeding** *ITT* • CAS: 0.33% (2/607) • CEA: 0.85% (5/589) HR: 0.39 (0.09, 1.73) *PP* • CAS: 0.35% (2/573) • CEA: 0.71% (4/563) HR: 0.49 (0.11, 2.29) **Procedural failure** *ITT* • CAS: 3.5% (21/607) • CEA: 2.6% (15/589) HR: 1.36 (0.72, 2.58)	**Restenosis ≥ 70%** *ITT* • CAS: 10.7% (64/607) • CEA 4.6% (26/589) *PP* • CAS: 11.1% (64/573) • CEA 4.6% (26/563)	Analysis based on non-inferiority of CAS. Intent-to-treat and per-protocol analyses used. Kaplan-Meier analysis of number at risk for outcomes. 24 month Ns calculated to fit data. Periprocedural percentages adjusted

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	HR: 1.15 (0.76, 1.76) *PP* • CAS: 7.2% (44/573) • CEA: 6.3% (37/563) HR: 1.15 (0.76, 1.76) *Ipsilateral ischaemic stroke* *ITT* • CAS: 6.4% (39/607) • CEA: 5.3% (31/589) HR: 1.22 (0.77, 1.92) *PP* • CAS: 6.3% (36/573) • CEA: 4.6% (26/563) HR: 1.36 (0.84, 2.21) *Any disabling stroke* *ITT* • CAS: 4.1% (25/607) • CEA: 2.9% (17/589) HR: 1.43 (0.79, 2.59) *PP* • CAS: 4.2% (24/573) • CEA: 2.5% (14/563) HR: 1.68 (0.89, 3.19) **MI** NR **Stroke or death** *Any stroke or death* *ITT* • CAS: 7.4% (45/607)	*PP* NR		to fit data.

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	• CEA: 6.6% (39/589) HR: 1.12 (0.74, 1.69) *PP* • CAS: 7.3% (42/573) • CEA: 5.7% (32/563) HR: 1.29 (0.83, 2.01) *Ipsilateral stroke or death* *ITT* • CAS: 6.9% (42/607) • CEA: 6.5% (38/589) HR: 1.07 (0.70, 1.63) *PP* • CAS: 6.8% (39/573) • CEA: 5.5% (31/563) HR: 1.24 (0.78, 1.95) *Any disabling stroke or death* *ITT* • CAS: 5.1% (31/607) • CEA: 3.9% (23/589) HR: 1.31 (0.78, 2.21) *PP* • CAS: 4.9% (28/573) • CEA: 3.2% (18/563) HR: 1.53 (0.82, 2.93) *Ipsilateral disabling stroke or death* *ITT* • CAS: 4.9% (30/607) • CEA: 3.7% (22/589) HR: 1.32 (0.78, 2.25)			

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	PP • CAS: 4.7% (27/573) • CEA: 3.0% (17/563) HR: 1.56 (0.87, 2.81) ***24 month (including periprocedural)*** **Death** *ITT* • CAS: 5.3% (32/607) • CEA: 4.8% (28/589) HR: 1.11 (0.67, 1.85) *PP* • CAS: 5.1% (29/573) • CEA: 4.4% (25/563) HR: 1.14 (0.67, 1.94) **Any stroke** *ITT* • CAS: 10.5% (64/607) • CEA: 9.7% (57/589) HR: 1.10 (0.77, 1.57) *PP* • CAS: 10.6% (61/573) • CEA: 9.1% (51/563) HR: 1.19 (0.83, 1.73) **MI** NR **Stroke or death** *Ipsilateral ischaemic strokes including periprocedural strokes or deaths* *ITT* • CAS: 9.2% (56/607)			

Study	Primary Outcomes for HTA	Secondary Outcomes for HTA	Cognition/Function/Pain/Other Outcomes	Comments
	• CEA: 8.5% (50/589) HR: 1.10 (0.75, 1.61) *PP* • CAS: 9.2% (53/573) • CEA: 7.6% (43/563) HR: 1.23 (0.82, 1.83) *Ipsilateral disabling strokes including periprocedural disabling strokes or deaths* *ITT* • CAS: 5.6% (34/607) • CEA: 4.6% (27/589) HR: 1.24 (0.75, 2.05) *PP* • CAS: 5.4% (31/573) • CEA: 3.9% (22/563) HR: 1.41 (0.82, 2.41) *Ipsilateral ischaemic stroke or vascular death* *ITT* • CAS: 10.0% (61/607) • CEA: 9.2% (54/589) HR: 1.11 (0.77, 1.60) *PP* • CAS: 9.9% (57/573) • CEA: 8.5% (48/563) HR: 1.18 (0.81, 1.74)			

***** Causes other than ones listed, in the CAS and CEA groups, respectively, included malignancy (n = 2, n = 3), liver failure (n = 0, n = 1), lung embolism (n = 0, n = 1), diabetic coma (n = 1, n = 0), GI ischemia/bleeding (n = 1, n = 1), Parkinson's disease (n = 0, n = 1), and unknown (n = 1, n = 3).
‡ Hypotension defined as systolic blood pressure ≤80 mm Hg or pressors administered ≥24 hours.

λ Change measured as the cognitive sum z score at follow-up minus the sum z score at baseline (negative values indicate a decrease in z score). After adjustment for age, sex, and education, these results did not change essentially.
α Myocardial infarction was defined by at least two of the following criteria: typical chest pain lasting 20 minutes or more; serum levels of creatine kinase, creatine kinase MB, or troponin at least twice the upper limit of the normal range; and new Q wave on at least two adjacent derivations or predominant R waves in V1 (R wave ≥1 mm >S wave in V1).
β Stroke was defined as disabling if the modified Rankin score (on a scale of 0 to 5, with higher scores indicating more severe disability) was 3 or more for at least 30 days after the event, with an increase of 2 points or more over the prestroke score.
Ψ Other causes of death include malignancy, liver failure, lung embolism, diabetic coma, GI ischemia/bleeding, Parkinson's disease, and unknown cause.
§ Mean difference calculated by change of the cognitive sum z score between baseline and follow-up between the 2 groups with corresponding 95% confidence intervals.

Nonrandomized Comparative Studies (Key Questions 1 and 3)

Table F7. Detailed results of NRCS comparing CAS and medical therapy with medical therapy alone for the treatment of asymptomatic carotid artery disease that were included in the AHRQ report (Key Questions 1 and 3).

Author/ Study design	CAS	Medical	Follow-up	Outcomes – *CAS vs. MT (95% CI)*	Comments
Sherif 2005 Retrospective cohort* Single-center	N = 421 Male: 68% Age: 72 years Total population: Asymptomatic (100%)	N = 525 Male: 68% Age: 73 years Total population: Asymptomatic (100%)	Median 25 months	***5-year Kaplan Meier rates:*** **Stroke-free survival rates (95% CI)** 1 year: 94% (92%-96%) vs. 97% (96%-98%) 3 years: 93% (91%-95%) vs. 93% (91%-95%) 5 years: 91% (88%-94%) vs. 89% (86%-92%) *P* = .56 between rates over time HR = 0.47; 95% CI, 0.24-0.90; *P* = .023† **Survival rates** 1 year: 97% vs. 89% 3 years: 94% vs. 79% 5 years: 80% vs. 68% *P* < .001 HR = 0.67; 95% CI, 0.46-0.97; *P* = .035† **Stroke/death-free rates** 1 year: 91% vs. 87% 3 years: 80% vs. 74% 5 years: 71% vs. 62%	Conducted a propensity score-adjusted analysis‡ Infrequent use of embolic protection devices; only used in the last 22 patients

Author/ Study design	CAS	Medical	Follow-up	Outcomes – *CAS vs. MT (95% CI)*	Comments
				P < .004 HR = 0.66; 95% CI, 0.49-0.91; *P* = .012†	
Bosiers 2005 Retrospective cohort Single-center	Asymptomatic N = 59 Male: NR Age: NR	Asymptomatic N = 16 Male: NR Age: NR	30 days	**Stroke/death rate** 30 days: 1.7% (n = 1) vs. 0% HR = not estimable†	Cannot compare CAS to medical therapy within symptomatic groups because no symptomatic patient received MT only Embolic protection device use unclear

*Single center registry; AHRQ calls this study a nonrandomized comparative study.
†As reported by the AHRQ.
‡Following baseline clinical characteristics were entered into a multivariate probit model to define a propensity score: age, gender, body mass index, degree of carotid stenosis, diabetes, hypertension, hyperlipidemia, smoking, congestive heart failure, coronary artery disease, history of myocardial infarction, peripheral artery disease, concomitant malignancy, American Society of Anesthesiologists classification (I to IV), Asymptomatic Carotid Atherosclerosis Study eligibility, and the date of CAS to account for temporal trends during the study period.)

Table F8. Detailed results of NRCS comparing CAS and medical therapy with CEA and medical therapy for the treatment of symptomatic and asymptomatic carotid artery disease that were included in the AHRQ report (Key Questions 1 and 3).

Author/ Study Design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
Clinical or registry data					
Zarins 2009, CaRESS Steering Committee 2005 Prospective, cohort Multicenter (14 sites)	Total N = 143 Male: 60% Age: 71.2 years Asymptomatic N = 99 Male: NR Mean age: NR Symptomatic N = 44 Male: NR Mean age: NR	Total N = 254 Male: 63% Age: 71.4 years Asymptomatic N = 170 Male: NR Mean age: NR Symptomatic N = 84 Male: NR Mean age: NR	30 days 4 years	**ASYMPTOMATIC** **Any stroke** 30 days: 1.0 % (n = 1) vs. 1.8% (n = 3); *P* = .61 RR = 0.57; 95% CI, 0.06-5.42; *P* = .63† 4 years: 9.2% (n = 7) vs. 5.7% (n = 9); *P* = .12 RR = 1.34; 95% CI, 0.51-3.47; *P* = .55† **Death** 30 days: 0% vs. 0% RR = not estimable 4 years: 22.2% (n = 19) vs. 19.7% (n = 24); *P* = .38 RR = 1.36; 95% CI, 0.78-2.35; *P* = .27† **MI** 30 days: 0% vs. 1.2% (n = 2); P = .28 RR = 0.43; 95% CI, 0.01-9.42; *P* = .59† 4 years: 7.9% (n = 6) vs. 10.1% (n = 12); *P* = .69 **Any stroke or death** 30 days: 1.0% (n = 1) vs. 1.8% (n = 3); *P* = .61 RR = 0.57; 95% CI, 0.06-5.42; *P* = .63† 4 years: 25.8% (n = 22) vs. 23.2% (n = 30); *P* = .55 RR = 1.26; 95% CI, 0.77-2.05; *P* = .36† **Any stroke or death or MI** 30 days: 1.0% (n = 1) vs. 3.0% (n = 5): *P* = .29 4 years: 25.6% (n = 22) vs. 24.0% (n = 32); *P* = .73 RR = 1.18; 95% CI, 0.72-1.91; *P* = .50† **SYMPTOMATIC** **Any stroke** 30 days: 4.7% (n = 2) vs. 7.2% (n = 6); *P* = .571 4 years: 7.2% (n = 3) vs. 17.8% (n = 13); *P* = .124	100% EPD

Author/ Study Design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
				Death 30 days: 0% vs. 1.3% (n = 1); *P* = .476 4 years: 10.4% (n = 4) vs. 24.9% (n = 15); *P* = .093 **MI** 30 days: 0% vs. 0% 4 years: 7.1% (n = 2) vs. 12.6% (n = 7); *P* = .236 **Any stroke or death** 30 days: 4.7% (n = 2) vs. 7.2% (n = 6); *P* = .571 4 years: 12.4% (n = 5) vs. 33.5% (n = 23); *P* = .019 **Any stroke or death or MI** 30 days: 4.7% (n = 2) vs. 7.2% (n = 6): *P* = .571 4 years: 12.4% (n = 5) vs. 33.5% (n = 23); *P* = .571	
De Rango 2011 Prospective cohort Single center	Total N = 1084 Male: 71.1% Mean age: 71.5 ± 7.5 Asymptomatic N = 816 Male: NR Age: NR Symptomatic N = 268 Male: NR Age: NR	Total N = 1118 Male: 70.9% Mean age: 71.1 ± 7.7 Asymptomatic N = 702 Male: NR Age: NR Symptomatic N = 416 Male: NR Age: NR	Mean 2.8 years	**ASYMPTOMATIC** **Stroke or death** 30 days: 2.3% (n = 19) vs. 1.6% (n = 11) OR = 1.5; 95% CI, 0.71-3.17; P = .36 **Any periprocedural (30 day) stroke or death or postprocedural ipsilateral stroke (Kaplan-Meier composite endpoint rates)** 2.8 years: 3.3% vs. 2.5%; *P* = .20 RR = 0.83; 95% CI, 0.49-1.39; *P* = .48† **SYMPTOMATIC** **Stroke or death** 30 days: 4.5% (n = 12) vs. 2.9% (n = 12) OR = 1.6; 95% CI, 0.69-3.57; P = .29 **Any periprocedural (30 day) stroke or death or postprocedural ipsilateral stroke (Kaplan-Meier composite endpoint rates)** 2.8 years: 4.9% vs. 8.7%; *P* = .67	Various embolic protection devices used in 100% of CAS Patients enrolled/ reviewed were treated after a training phase Cox regression analysis and propensity matching – for whole population not for stratified (symptom status) populations

Author/ Study Design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
Bangalore 2010 Prospective registry Multicenter	N = 836 Male: 68.1% Age: 70 years Total population: Asymptomatic (80% after propensity matching)	N = 836 Male: 66.6% Age: 69 years Total population: Asymptomatic (80% after propensity matching)	1.5 years	**Any stroke** 1.5 years: 3.8% (n = 27) vs. 2.6% (n = 20) HR = 1.41; 95% CI, 0.79-2.51; *P* = .25 **Death** 1.5 years: 7.4% (n = 40) vs. 7.4% (n = 57) HR = 0.73; 95% CI, 0.49-1.09; *P* = .13 **MI** 1.5 years: 3.2% (n = 23) vs. 4.8% (n = 37) HR = 0.64; 95% CI, 0.38-1.08; *P* = .10 **Any stroke or TIA** 1.5 years: 5.5 (n = 40) vs. 5.0% (n = 38) HR = 1.10; 95% CI, 0.71-1.72; *P* = .67 **Any stroke or death** 1.5 years: 9.9% (n = 58) vs. 8.9% (n = 68) HR = 0.89; 95% CI, 0.63-1.27; *P* = .53 **Any stroke or death or MI** 1.5 years: 11.7% (n = 72) vs. 12.2 (n = 94) HR = 0.79; 95% CI, 0.58-1.08; *P* = .14	Embolic protection devices used in 100% of CAS Authors conducted a propensity-score matched analysis AHRQ appeared to treat the whole population as Asx (after propensity matching ~ 79.5% Asx; whole population = 70%) They took their info from table 2, population "matched".
Marine 2006 Retrospective cohort Single-center	N = 93 Male: 63.4% Age: 69.8 years Total population: Asymptomatic (100%)	N = 145 Male: 61.4% Age: 69.6 years Total population: Asymptomatic (100%)	30 days	**Any stroke** 30 days: 1.1% (n = 1) vs. 2.1% (n = 3); *P* = .99 RR = 0.52; 95% CI, 0.05-4.92; *P* = .57† **Death** 30 days: 1.1% (n = 1) vs. 0.7% (n = 1); *P* = .99 RR = 1.56; 95% CI, 0.09-24.6; *P* = .75† **MI** 30 days: 1.1% (n = 1) vs. 1.4% (n = 2); *P* = .99 RR = 0.78; 95% CI, 0.07-8.47; *P* = .84† **Any stroke or death** 30 days: 2.2% (n = 2) vs. 2.1% (n = 3); *P* = .99	Embolic protection devices were used in 91.4% of CAS CAS in high-risk pts vs. CEA in standard risk (potential bias, groups different; 28% restenosis and 15% hostile neck in CAS group) They break down stroke into hemispheric and occipital

Author/ Study Design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
				RR = 1.04; 95% CI, 0.17-6.10; *P* = .97† **Cranial nerve palsy** 30 days: 0% vs. 2.8% (n = 4); *P* = .16 RR = 0.17; 95% CI, 0.00-3.18; *P* = .24† **Hematoma** 30 days: 5.4% (n = 5) vs. 4.1% (n = 6); *P* = .75 RR = 1.30; 95% CI, 0.40-4.13; *P* = .66†	Also report on various other postprocedure morbidity outcomes
Bosiers 2005 Retrospective cohort Single-center	Total N = 212 Male: NR Age: NR Asymptomatic N = 59 Male: NR Age: NR Symptomatic N = 153 Male: NR Age: NR	Total N = 80 Male: NR Age: NR Asymptomatic N = 20 Male: NR Age: NR Symptomatic N = 60 Male: NR Age: NR	30 days	**ASYMPTOMATIC** **Any stroke or death** 30 days: 1.7% (n = 1) vs. 0% RR = 1.02; 95% CI, 0.04-23.9; *P* = .99† **SYMPTOMATIC** **Any stroke or death** 30 days: 2.6% (n = 4) vs. 3.3% (n = 2)	Embolic protection device use unclear
Lindstrom 2012 Prospective registry (Swedvasc Registry) Multicenter	Total N = 243 Male: NR Age: NR Asymptomatic N = 101 Male: NR Age: NR Symptomatic N = 142 Male: NR Age: NR	Total N = 6322 Male: NR Age: NR Asymptomatic N = 1315 Male: NR Age: NR Symptomatic N = 5007 Male: NR Age: NR	30 days	**ASYMPTOMATIC** **Any stroke or death** 30 days: 10.9% (n = 11) vs. 4.0% (n = 53) RR = 2.70; 95% CI, 1.46-5.01; *P* = .002† **SYMPTOMATIC** 30 days: 4.9% (n = 7) vs. 4.4% (n = 220)	Tables 3 (CAS) and 4 (CEA) for Swedvasc only High risk vs. average risk in CAS arm AHRQ only report Swedish national data – embolic protection device use unclear

Author/ Study Design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
Sidawy 2009 Prospective registry (SVS-VR) Multicenter	Total N = 1450 Male: 59.5% Mean age: 70.8 ± 10 Asymptomatic N = 805 Male: NR Age: NR Symptomatic N = 645 Male: NR Age: NR	Total N = 1368 Male: 59.7% Mean age: 71.2 ± 9.4 Asymptomatic N = 862 Male: NR Age: NR Symptomatic N = 506 Male: NR Age: NR	30 days	**ASYMPTOMATIC** **Any stroke** 30 days: 2.1% (n = 17) vs. 1.3% (n = 11) RR = 1.65; 95% CI, 0.77-3.51; *P* = .19† **TIA** 30 days: 1.2% (n = 10) vs. 0.46% (n = 4) RR = 3.21; 95% CI, 1.04-9.91; *P* = .042† **Death** 30 days: 2.0% (n = 16) vs. 0.70% (n = 6) RR = 2.86; 95% CI, 1.12-7.26; *P* = .028† **MI** 30 days: 1.4% (n = 11) vs. 0.58% (n = 5) RR = 2.36; 95% CI, 0.82-6.75; *P* = .11† **Any stroke, death or MI** 30 days: 4.6% (n = 37) vs. 2.0% (n = 17) RR = 2.33; 95% CI, 1.32-4.10; *P* = .003† **SYMPTOMATIC** **Any stroke** 30 days: 5.3% (n = 34) vs. 2.4% (n = 12) **TIA** 30 days: 2.0% (n = 13) vs. 1.4% (n = 7) **Death** 30 days: 2.2% (n = 14) vs. 0.79% (n = 4) **MI** 30 days: .93% (n = 6) vs. 0.59% (n = 3) **Any stroke, death or MI** 30 days: 7.1% (n = 46) vs. 3.8% (n = 19)	Embolic protection devices used in 94.9% of CAS 70.7% of CAS performed for atherosclerotic disease vs. 98% in CEA; total population = 85.5% Potential for bias due to baseline differences in groups Also report transient monocular blindness/ amaurosis fugax

Author/ Study Design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
				Transient Monocular blindness/Amaurosis fugax 30 days: .16% (n = 1) vs. 0%	
Administrative data					
McPhee 2008 Administrative data National Inpatient Sample, 2005	Total N = 12,914 Male: 62.3% Age: 70.9 years Asymptomatic N = 11,302 Male: 62.9% Age: 71.6 years Symptomatic N = 1116 Male: 60.9% Age: 68.9 years	Total N = 122,786 Male: 57.4% Age: 71.0 years Asymptomatic N = 111,684 Male: 57.2% Age: 71.1 years Symptomatic N = 9380 Male: 58.1% Age: 69.5 years	In-hospital	**ASYMPTOMATIC** **Any stroke** In-hospital (< 30 days): 1.6% vs. 0.88%; *P* = .001 RR = 1.82; 95% CI, 1.55-2.12; *P* < .0001† **Death** In-hospital (< 30 days): 0.57% vs. 0.38%; *P* = .18 RR = 1.49; 95% CI, 1.14-1.93; *P* = .003† **SYMPTOMATIC** **Any stroke** In-hospital (< 30 days): 4.1% vs. 2.5%; *P* = .15 **Death** In-hospital (< 30 days): 4.6% vs. 1.4%; *P* = .0002	
McPhee 2007 Administrative data National Inpatient Sample, 2003 and 2004	Total N = 14,035 Male: NR Age: NR Asymptomatic N = 12,278 Male: 59.3% Age: 70.5 years Symptomatic N = 1757 Male: 55.8% Age: 68.6 years	Total N = 245,045 Male: NR Age: NR Asymptomatic N = 226,111 Male: 56.9% Age: 71.2 years Symptomatic N = 18,934 Male: 61.1% Age: 70.1 years	In-hospital	**ASYMPTOMATIC** **Any stroke** In-hospital (< 30 days): 1.8% vs. 0.86%; *P* < .0001 RR = 2.09; 95% CI, 1.82-2.40; *P* < .0001† **Death** In-hospital (< 30 days): 0.44% vs. 0.34%; *P* = .36 RR = 1.29; 95% CI, 0.98-1.70; *P* = .07† **MI** In-hospital (< 30 days): 2.0% vs. 1.7%; *P* = .31 RR = 1.18; 95% CI, 1.04-1.35; *P* = .01† **SYMPTOMATIC** **Any stroke** In-hospital (< 30 days): 4.2% vs. 1.1%; *P* < .0001 **Death** In-hospital (< 30 days): 7.5% vs. 1.0%; *P* < .0001	Table III – outcomes by sx status Table IV. Multivariate analysis of CAS vs. CEA for inhosp mortality and stroke – not stratified by sx status

Author/ Study Design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
				MI In-hospital (< 30 days): 2.2% vs. 2.0%; *P* = .73	
Giacovelli 2010 Administrative data Discharge data sets from NY and CA states, 2005-2007	Total N = 4919 Male: 60.7% Age: 71.3 years Asymptomatic N = 4353 Male: 59.9% Age: 71.4 years Symptomatic N = 543 Male: 59.5% Age: 70.1 years	Total N = 4919 Male: 57.1% Age: 72.6 years Asymptomatic N = 4353 Male: 60.2% Age: 72.0 years Symptomatic N = 543 Male: 60.4% Age: 72.7 years	In-hospital	**ASYMPTOMATIC** **Any stroke** In-hospital (< 30 days): 2.0% vs.1.8%; *P* = .30 RR = 1.17; 95% CI, 0.86-1.58; *P* = .31†‡ **Death** In-hospital (< 30 days): 0.55% vs. 0.39%; *P* = .27 RR = 1.41; 95% CI, 0.75-2.62; *P* = .28†‡ **Any stroke or death** In-hospital (< 30 days): 2.4% vs. 1.9%; *P* = .16 RR = 1.23; 95% CI, 0.92-1.63; *P* = .16†‡ **Cranial nerve palsy** In-hospital (< 30 days): 0.18% vs. 0.44%; *P* = .03 RR = 0.47; 95% CI, 0.21-1.04; *P* = .064 **Bleeding** In-hospital (< 30 days): 3.4% vs. 3.8%; P = .36 RR = 0.90 (0.72-1.12) **Cardiac complications** In-hospital (< 30 days): 4.9% vs. 4.1%; P = .08 **Transient cerebral ischemia** In-hospital (< 30 days): 0.32% vs. 0.30%; P = .84 **SYMPTOMATIC** **Any stroke** In-hospital (< 30 days): 5.7% vs. 4.1%; *P* = .22 **Death** In-hospital (< 30 days): 3.7% vs. 1.3%; *P* = .01	Matched pairs by propensity score (propensity-score matched analysis) Report other postop complications (bleeding, VTE, etc.), unspecified cardiac complications, not reported by AHRQ

Author/ Study Design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
				Any stroke or death In-hospital (< 30 days): 8.3% vs. 4.6%; *P* = .01 **Transient cerebral ischemia** In-hospital (< 30 days): .41% vs. .26%; *P* = .22 **Cranial nerve palsy** In-hospital (< 30 days): .14% vs. .39%; *P* = .02 **Bleeding** In-hospital (< 30 days): 3.4% vs. 3.4%; *P* = .96 **Cardiac complications** In-hospital (< 30 days): 5.0% vs. 4.3%; *P* = .13 **Venuous thromboembolism** In-hospital (< 30 days): .10% vs. .10%; *P* = .56 ***Other complications:*** **Device malfunction** In-hospital (< 30 days): .41% vs. .12%; *P* = .006 **Nonvascular neurologic complications** In-hospital (< 30 days): .87% vs. .85%; *P* = .91 **Respiratory complications** In-hospital (< 30 days): 1.7% vs. 2.7%; *P* = .0004 **Respiratory infection** In-hospital (< 30 days): .51% vs. .59%; *P* = .59 **Urinary infection** In-hospital (< 30 days): .98% vs. .77%; *P* = .27 **Procedure-relaed infection** In-hospital (< 30 days): .02% vs. .02%; *P* > .99	

Author/ Study Design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
				Shock In-hospital (< 30 days): .02% vs. .02%; *P* > .99 **Renal complications** In-hospital (< 30 days): 1.8% vs. 1.6%; *P* = .53 **Urinary catheter complications** In-hospital (< 30 days): 0.53% vs. 1.3%; *P* < .0001	

†Calculated from raw data by AHRQ.
‡Adjusted for age, sex, hospital teaching type, year of procedure, payer status, coronary artery disease/previous MI, congestive heart failure, valvular heart disease, diabetes mellitus, chronic lung disease, hypertension, renal failure, and obesity

Table F9. Detailed results of nonrandomized comparative studies comparing CAS and medical therapy with CEA and medical therapy for the treatment of symptomatic and asymptomatic carotid artery disease that were not included in the AHRQ report (Key Questions 1 and 3).

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
Clinical data or registry studies					
Iihara 2006 Prospective cohort Single-center	Total N = 92 Male: 90.2% Mean age: 71.3 ± 6.0 years Asymptomatic N = 59 Male: NR Mean age: NR Symptomatic N = 30 Male: NR Mean age: NR	Total N = 139 Male: 92.0% Mean age: 68.1 ± 6.9 years Asymptomatic N = 47 Male: NR Mean age: NR Symptomatic N = 73 Male: NR Mean age: NR	Peri-procedural/ 30 days	**ASYMPTOMATIC** **Incidence of ischemic neurological complications (i.e. non-disabling stroke)** Total: 8.5% (n = 5) vs. 2.1% (n = 1) Grade I: 4.8% (1/21) vs. 0% (0/26), P = .37 Grade II: 14.3% (1/7) vs. 0% (0/4), P = 1.0 Grade III: 9.7% (3/31) vs. 5.9% (1/17), P = 1.0 **Incidence of new abnormalities on DW MR imaging** Total: 32.2% (n = 19) vs. 4.3% (n = 2) Grade I: 9.5% (2/21) vs. 0% (0/26), P = .19 Grade II: 42.9% (3/7) vs. 0% (0/4), P = .51 Grade III: 45.2% (14/31) vs. 11.8% (2/17), P = .03 **SYMPTOMATIC** **Incidence of ischemic neurological complications (i.e. non-disabling stroke)** Total: 6.7% (n = 2) vs. 4.1% (n = 3) Grade I: 0% (0/11) vs. 0% (0/37), P = .229 Grade II: 0% (0/3) vs. 0% (0/11), P = NR Grade III: 12.5% (2/16) vs. 4.0% (1/25), P = .550 **Incidence of new abnormalities on DW MR imaging** Total: 24.2% (n = 8) vs. 16.3% (n = 15) Grade I: 36.4% (4/11) vs. 5.4% (2/37), P = .019 Grade II: 33.3% (1/3) vs. 0% (0/11), P = .214 Grade III: 50.0% (8/16) vs. 4.0% (1/25), P = .001	All of the ischemic complications were **nondisabling stroke** as noted in table 4 Distal balloon embolic protection devices used in 100% of CAS (some patients with a different, newer system) Selection bias in assigning patients to the CEA and CAP groups based on the CEA risk grades
Brown 2008 Retrospective	Total N = 113 Male: 98%	Total N = 91 Male: 98%	Peri-procedural/ 30 days	**ASYMPTOMATIC** **TIA** 2.5% (n = 2) vs. 0%; P = ns	Veteran population Embolic protection devices used in 98.2% of CAS (n =

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
cohort Single-center	Mean age: 70 ± 8 years <u>Asymptomatic</u> N = 79 Male: NR Mean age: NR <u>Symptomatic</u> N = 34 Male: NR Mean age: NR	Mean age: 67 ± 10 years <u>Asymptomatic</u> N = 50 Male: NR Mean age: NR <u>Symptomatic</u> N = 41 Male: NR Mean age: NR		**Any stroke** 3.8% (n = 3) vs. 2.0% (n = 1); P = ns **Death** 0% vs. 2.0% (n = 1); P = ns **Any stroke or death** 3.8% (n = 3) vs. 4.0% (n = 2); P = ns **<u>SYMPTOMATIC</u>** **TIA** 2.9% (n = 1) vs. 2.4% (n = 1); P = ns **Any stroke** 2.9% (n = 1) vs. 2.4% (n = 1); P = ns **Death** 0% vs. 0%; P = ns **Any stroke or death** 2.9% (n = 1) vs. 2.4% (n = 1); P = ns	111) In-stent stenosis, not by sx status AHRQ tracking sheet says they included this study but cannot find it in report
Kastrup 2003 Retrospective cohort Single-center	<u>Total</u> N = 100 Male: 75% Mean age: 70 ± 9 years <u>Asymptomatic</u> N = 37 Male: NR Mean age: NR <u>Symptomatic</u> N = 63 Male: NR	<u>Total</u> N = 142 Male: 74% Age: 70 ± 8 years <u>Asymptomatic</u> N = 50 Male: NR Mean age: NR <u>Symptomatic</u> N = 92 Male: NR Mean age: NR	Peri-procedural/ 30 days	**<u>ASYMPTOMATIC</u>** **Any stroke** 0% vs. 2.0% (n = 1); P = ns **Minor stroke** 0% vs. 2.0% (n = 1); P = ns **Major stroke** 0% vs. 0% **MI** 0% vs. 0% **Death** 0% vs. 0%	No mention of EPD use

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
	Mean age: NR			**Any stroke or death** 0% vs. 2.0% (n = 1); P = ns **Hematoma (requiring surgery)** 8.0% (n = 3) vs. 4.0% (n = 2) **Cranial nerve palsy*** 0% vs. 13.0% (n = 6); P < .05 *mild and rapidly reversible **SYMPTOMATIC** **Any stroke** 6% (n = 4) vs. 6% (n = 6); P = ns **Minor stroke** 3% (n = 2) vs. 3% (n = 3) **Major stroke** 3% (n = 2) vs. 3% (n = 3) **MI** 0% vs. 0% **Death** 2% (n = 1) vs. 0% **Any stroke or death** 8% (n = 5) vs. 6.5% (n = 6); P = ns **Hematoma (requiring surgery)** 0% vs. 1% (n = 1) **Cranial nerve palsy*** 0% vs. 13.0% (n = 12); P < .01 *mild and rapidly reversible	
Kastrup 2004 Retrospective	Total N = 53 Male: 68%	Total N = 110 Male: 64%	30 day	**ASYMPTOMATIC – N/A** **SYMPTOMATIC**	ASYMPTOMATIC group excluded from report due to sample size, n = 23 in CAS

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
cohort Single-center	Median age: 78 years (75-90) <u>Symptomatic</u> N = 30 Male: NR Mean age: NR	Median age: 78 years (75-91) <u>Symptomatic</u> N = 69 Male: NR Mean age: NR		**Any stroke** 30 days: 10% (n = 3) vs. 2.9% (n = 2); *P* = .2 **Major stroke** 30 days: 3.3% (n = 1) vs. 2.9% (n = 2); *P* = 1.0 **Minor stroke** 30 days: 6.6% (n = 2) vs. 0%; *P* = .09 **Fatal stroke** 30 days: 0% vs. 0%	group (needs to be ≥30 in each group) Filter-type embolic protection devices were used in 100% of CAS All patients aged 75 or older = elderly population CAS patients were prospectively enrolled; CEA patients were retrospectively evaluated
Nolan 2012 Prospective registry Vascular Study Group of New England (VSGNE) registry Multicenter (17 sites)	<u>Total</u> N = 430 Male: 66% Mean age: 69 years <u>Asymptomatic</u> N = 273 Male: NR Mean age: NR <u>Symptomatic</u> N = 156 Male: NR Mean age: NR	<u>Total</u> N = 7649 Male: 60% Mean age: 70 years <u>Asymptomatic</u> N = 5043 Male: NR Mean age: NR <u>Symptomatic</u> N = 2605 Male: NR Mean age: NR	In-hospital	**<u>ASYMPTOMATIC</u>** **Any stroke or death** 0.73% vs. 0.89%; P = .78 **Ipsilateral stroke** 0.4% vs. 0.6%; P = .58 **Major stroke** 0.4% vs. 0.3%; P = .90 **Minor stroke** 0.5% vs. 0.4%; P = .74 **TIA** 0.5% vs. 0.3%; P = .77 **MI** 0.7% vs. 1.0%; P = .69 **Death** 0.4% vs. 0.2%; P = .42	Embolic protection devices used in 97% of CAS

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
				Cranial nerve injury* 0% vs. 0.9%; P = .11 *permanent/persistent **SYMPTOMATIC** **Any stroke or death** 5.1% vs. 1.6%; P = .001 **Ipsilateral stroke** 3.8% vs. 1.2%; P = .004 **Major stroke** 2.6% vs. 0.6%; P = .005 **Minor stroke** 2.6% vs. 0.8%; P = .019 **TIA** 0.7% vs. 0.6%; P = .99 **MI** 1.3% vs. 1.3%; P = .99 **Death** 1.3% vs. 0.2%; P = .20 **Cranial nerve injury*** 0% vs. 1.1%; P = .19 *permanent/persistent	
Jim 2012 Prospective registry (SVS-VR) Multicenter	Total N = 3397 Male: 59.8% Mean age: 70.9 years Asymptomatic	Total N = 5516 Male: 58.7% Mean age: 71.0 years Asymptomatic	Peri-procedural/ 30 days	**ASYMPTOMATIC** **Death** 1.6% (n = 29) vs. 0.7% (n = 25) **Stroke** 3.2% (n = 59) vs. 1.7% (n = 58)	Stratified by Medicare age; were able to calculated data for asymptomatic and symptomatic populations as a whole Update to Sidawy 2009

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
	N = 1850 Male: NR Mean age: NR <u>Symptomatic</u> N = 1547 Male: NR Mean age: NR	N = 3418 Male: NR Mean age: NR <u>Symptomatic</u> N = 2098 Male: NR Mean age: NR		**MI** 1.1 % (n = 20) vs. 1.0% (n = 35) **<u>SYMPTOMATIC</u>** **Death** 2.0% (n = 31) vs. 1.1% (n = 23) **Stroke** 6.1% (n = 95) vs. 4.1% (n = 85) **MI** 1.4% (n = 21) vs. 1.3% (n = 27)	(SVS-VR) registry included in AHRQ. This report includes 2891 more patients No mention of embolic protection devices
Capoccia 2012 Prospective cohort Single-center	N = 28 Male: 57% Age: 71.7 ± 7.2 years <u>Total population: Asymptomatic (100%)</u>	N = 32 Male: 68% Age: 70.1 ± 7.2 years <u>Total population: Asymptomatic (100%)</u>	12 months (f/u 96.6% at 12 months; n = 58/60) Postop, 6 and 12 months	**<u>MMSE scores (mean ± SD)</u>** **Preop** 25.6 ± 4.46 vs. 26.1 ± 3.46 **Postop (24 hours)** 22.9 ± 4.54 vs. 25.6 ± 3.27 **Change score (pre-post)** -2.7 vs. -0.5; P = .045 for CAS and .67 for CEA **> 5 point decrease in postop scores** 25% (n = 7) vs. 3% (n = 1); P = .03 **6 months** 23.7 ± 4.58 vs. 25.9 ± 3.43; P = ns for within and between group analysis **12 months*** 24.1 vs. 25.7 *estimated from figure provided in article **Preop and 12-month score comparison** CAS: P = .045 CAS: P = ns	Filter-type embolic protection devices used in 100% of CAS Correlate presence of new ischemic lesion on DW-MRI with MMSE scores
Feliziani 2010	N = 24 Male: 54%	N = 22 Male: 82%	12 months	***Global cognition*** **<u>MMSE</u>**	Various types of embolic protection devices used in

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
Prospective cohort Single-center	Age: 75.6 ± 5.7 years Total population: Asymptomatic (100%)	Age: 71.9 ± 5.7 years Total population: Asymptomatic (100%)	1, 3, and 12 months	*Pre-op:* 27.2 ± 1.9 vs. 27.8 ± 2.3 *3 months:* 26.5 ± 2.8 vs. 27.4 ± 2.4 *12 months*: 27.7 ± 2.1 vs. 27.6 ± 3.0 *Change score 3 months-pre-op:* –0.53 ± 3.1 vs. –0.52 ± 2.5 *Change score 12 months-pre-op:* 0.13 ± 2.7 vs. –0.03 ± 2.5 ***Functional Scales*** **ADL** *Pre-op:* 5.7 ± 0.5 vs. 5.9 ± 0.4 *3 months:* 5.4 ± 0.5 vs. 5.7 ± 0.6 *12 months*: 5.6 ± 0.5 vs. 5.7 ± 0.5 *Change score 3 months-pre-op:* –0.16 ± 0.51 vs. –0.15 ± 0.60 *Change score 12 months-pre-op:* –0.06 ± 0.5 vs. –0.10 ± 0.47 **IADL** *Pre-op:* 5.9 ± 2.1 vs. 5.6 ± 1.7 *3 months:* 6.2 ± 1.4 vs. 5.6 ± 2.0 *12 months*: 6.2 ± 2.0 vs. 6.0 ± 1.7 *Change score 3 months-pre-op:* 0.38 ± 2.1 vs. –0.15 ± 2.2 *Change score 12 months-pre-op:* 0.06 ± 2.0 vs. 0.37 ± 2.0 ***Mood*** **GDS** *Pre-op:* 4.4 ± 2.4 vs. 3.0 ± 1.5 *3 months:* 2.9 ± 1.9 vs. 2.3 ± 1.9 *12 months*: 4.1 ± 3.9 vs. 2.2 ± 1.7 *Change score 3 months-pre-op:* –1.0 ± 2.1 vs. –0.6 ± 2.0 *Change score 12 months-pre-op:* –0.2 ± 3.9 vs. –0.8 ± 1.7	100% of CAS

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
				Memory **Babcock SR** *Pre-op:* 9.0 ± 3.1 vs. 9.1 ± 3.1 *3 months:* 8.5 ± 3.6 vs. 10.6 ± 3.0 *12 months*: 9.5 ± 2.4 vs. 9.7 ± 4.0 *Change score 3 months-pre-op:* –0.2 ± 4.5 vs. 1.4 ± 3.9 *Change score 12 months-pre-op:* –0.4 ± 3.3 vs. 0.3 ± 5.0 **Rey-IR** *Pre-op:* 35.5 ± 8.9 vs. 33.5 ± 7.0 *3 months:* 34.7 ± 10.2 vs. 33.9 ± 7.8 *12 months*: 34.6 ± 6.1 vs. 35.2 ± 6.7 *Change score 3 months-pre-op:* –0.5 ± 12.0 vs. –1.5 ± 6.3 *Change score 12 months-pre-op:* –1.5 ± 9.2 vs. 1.6 ± 6.2 **Rey-DR** *Pre-op:* 7.4 ± 4.0 vs. 8.7 ± 3.8 *3 months:* 6.9 ± 2.1 vs. 7.3 ± 2.4 *12 months*: 7.7 ± 1.9 vs. 7.8 ± 3.0 *Change score 3 months-pre-op:* –0.1 ± 2.6 vs. –1.9 ± 4.8 *Change score 12 months-pre-op:* –0.6 ± 2.4 vs. –0.9 ± 4.6 **CNT** *Pre-op:* 14.3 ± 4.0 vs. 14.3 ± 4.7 *3 months:* 15.2 ± 4.7 vs. 16.0 ± 5.6 *12 months*: 13.6 ± 4.0 vs. 13.1 ± 4.5 *Change score 3 months-pre-op:* 0.8 ± 5.8 vs. 1.2 ± 7.1 *Change score 12 months-pre-op:* –1.9 ± 3.5 vs. –1.4 ± 4.5 ***Attention and cognitive functioning*** **TMT-A, s**	

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
				Pre-op: 74.1 ± 37.7 vs. 52.9 ± 24.4 *3 months:* 109.2 ± 74.4 vs. 63.2 ± 50.0; P < .05 *12 months*: 97.2 ± 51.0 vs. 55.6 ± 22.5; P < .01 *Change score 3 months-pre-op:* 30.7 ± 65.2 vs. 12.7 ± 57.5 *Change score 12 months-pre-op:* 21.5 ± 59.1 vs. –0.1 ± 28.2 **TMT-B, s** *Pre-op:* 135.4 ± 78.5 vs. 162.5 ± 108.5 *3 months:* 123.7 ± 99.6 vs. 154.9 ± 127.5 *12 months*: 118.3 ± 145.2 vs. 134.6 ± 92.3 *Change score 3 months-pre-op:* –3.0 ± 122.0 vs. –3.2 ± 98.3 *Change score 12 months-pre-op:* –56.7 ± 72.5 vs. –49.3 ± 88.6 **COWA** *Pre-op:* 22.7 ± 7.8 vs. 22.4 ± 9.1 *3 months:* 25.3 ± 7.9 vs. 25.7 ± 11.8 *12 months*: 24.0 ± 8.7 vs. 28.0 ± 12.2 *Change score 3 months-pre-op:* 0.9 ± 8.5 vs. 1.9 ± 10.8 *Change score 12 months-pre-op:* 3.6 ± 8.8 vs. 5.0 ± 8.1 ***Visuospatial and constructional abilities*** **CD** *Pre-op:* 12.5 ± 2.0 vs. 12.5 ± 1.7 *3 months:* 13.1 ± 1.4 vs. 12.1 ± 1.6 *12 months*: 12.0 ± 1.9 vs. 11.5 ± 2.4 *Change score 3 months-pre-op:* 0.8 ± 2.0 vs. –0.5 ± 1.7 *Change score 12 months-pre-op:* –0.7 ± 2.9 vs. –1.3 ± 2.3	
Lal 2011 Prospective	N = 21 Male: 62% Age: NR*	N = 25 Male: 68% Age NR*	Mean 5.2 months (range, 4-6)	**Trail Making Test A & B (motor speed/coordination and executive function)** ***Change score (postop-preop)***	Primary endpoint was standardized cognitive change scores (follow-up

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
cohort Single-center	*state the 2 groups were comparable <u>Total population: Asymptomatic (100%)</u>	*state the 2 groups were comparable <u>Total population: Asymptomatic (100%)</u>		0.63 vs. 0.74; P = ns ***Raw scores*** *Pre-op*: 121 ± 22 vs. 138 ± 26 *Post-op*: 120 ± 19 vs. 129 ± 21 P = .04 for CEA, ns for CAS **<u>Processing Speed Index (psychomotor speed)</u>** ***Change score (postop-preop)*** – 0.32 vs. 0.58; P = .001 ***Raw scores*** *Pre-op*: 107 ± 16 vs. 106 ± 13 *Post-op*: 102 ± 16 vs. 144 ± 14 P = ns for both CAS and CEA **<u>Boston Naming Test (language)</u>** ***Change score (postop-preop)*** 0.59 *vs*. 0.66; P = ns ***Raw scores*** *Pre-op:* 52 ± 8 vs. 56 ± 10 *Post-op:* 57 ± 9 vs. 63 ± 7 *P = ns* for both CAS and CEA **<u>Working Memory Index (memory/concentration)</u>** ***Change score (postop-preop)*** 0.46 *vs*. –0.41; P = .001 ***Raw scores*** *Pre-op:* 100 ± 16 vs. 103 ± 15 *Post-op:* 108 ± 12 vs. 97 ± 12 *P = ns* for both CAS and CEA **<u>Controlled Oral Word Association Test (verbal fluency)</u>** ***Change score (postop-preop)*** 0.69 *vs*. 0.61; P = ns ***Raw scores*** *Pre-op:* 38 ± 9 vs. 39 ± 11 *Post-op:* 44 ± 9 vs. 46 ± 11	vs. baseline) – see stats methods for calculation + change score indicates improvement in cog. function after procedure, – score indicates deterioration Embolic protection devices used in 100% of CAS See Limitations section

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
				P = *ns* for both CAS and CEA **<u>Hopkins Verbal Learning Test (learning/memory)</u>** ***Change score (postop-preop)*** 0.77 *vs*. 0.86; P = ns ***Raw scores*** *Pre-op:* 7.9 ± 2.0 vs. 8.1 ± 1.7 *Post-op:* 9.4 ± 1.9 vs. 9.6 ± 2.1 *P* = .05 for both CAS and CEA **<u>Composite for all tests</u>** ***Change score (postop-preop)*** 0.47 *vs*. 0.51; P = ns ***Raw scores*** NR	
Administrative data					
Timaran 2009 Administrative data National Inpatient Sample, 2005	N = 13,093 Male: 62.2% Age (median): 72 years **For ICH** <u>Total population:</u> <u>Asymptomatic (>90%)</u> **For stroke and death** <u>Asymptomatic</u> N = 11,836 Male: NR Mean age: NR <u>Symptomatic</u> N = 1257	N = 122,984 Male: 57.4% Age (median): 72 years **For ICH** <u>Total population:</u> <u>Asymptomatic (>90%)</u> **For stroke and death** <u>Asymptomatic</u> N = 113,514 Male: NR Mean age: NR <u>Symptomatic</u> N = 9470	In-hospital	**<u>INTRACRANIAL HEMORRHAGE</u>** **Acute Intracranial hemorrhage:** 0.15% (n = 19) vs. 0.02% (n = 20); P < .001 **Leading to death:** 26% (n = 5/19) vs. 0% (n = 0/20) **Mortality among patients developing ICH:** 12.5% (OR = 23.2; 95% CI, 9.1-54.4; P < .001) **Risk of ICH – CAS vs. CEA*:** Adjusted OR = 5.9; 95% CI, 3.1-11.1; P < .001 *adjusted for age, sex, sx status, comorbidity index, admission, hospital type All 19 instances of ICH after CAS occurred in ***Asymptomatic*** patients vs. 15 (75%) cases in the CEA group ICH was identified as an independent predictor for in-hospital mortality by multivariate regression analysis (OR = 4.01; 95% CI, 1.5-10.9; *P* < .001).	Primary outcome of this study is ICH – Secondarily report stroke and mortality data too.

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
	Male: NR Mean age: NR	Male: NR Mean age: NR		**STROKE AND DEATH** ***Asymptomatic only*** **Stroke** 1.8% vs. 1.0; P < .001 **Death** 0.7% vs. 0.5%; P = .002 ***Symptomatic only*** **Stroke** 5.0% vs. 2.6%; P < .001 **Death** 4.6% vs. 1.4%; P < .001	
McDonald 2011 Administrative data National Inpatient Sample, 2001-2008	Total N = 13,884 Male: Mean age: Asymptomatic N = 12,633 Male: 60.7% Mean age: 72 years Symptomatic N = 1251 Male: 54.2% Mean age: 65 years	Total N = 215,012 Male: Mean age: Asymptomatic N = 204,963 Male: 57.4% Mean age: 72 years Symptomatic N = 10,049 Male: 60.0% Mean age: 72 years	In-hospital	**ASYMPTOMATIC** **Subarachnoid hemorrhage** 0.2% (n = 25) vs. 0.02% (n = 42) • In-hospital mortality: 28% (n = 7) vs. 14% (n = 6) **Intracranial hemorrhage** 0.2% (n = 31) vs. 0.04% (n = 87) • In-hospital mortality: 52% (n = 16) vs. 31% (n = 27) **Nontraumatic extradural hemorrhage** 0% vs. 0.0005% (n = 1) • In-hospital mortality: none **Unspecified intracranial hemorrhage** 0.04% (n = 3) vs. 0.002 (n = 4) • In-hospital mortality: 33% (n = 1) vs. 0% **Any ICH** 0.5% (n = 59) vs. 0.06% (n = 134); P < .0001 **Mortality** 0.6% vs. 0.5%; P = .083	

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
				SYMPTOMATIC **Subarachnoid hemorrhage** 2.8% (n = 35) vs. 0.3% (n = 34) • In-hospital mortality: 17% (n = 6) vs. 11% (n = 4) **Intracranial hemorrhage** 4.0% (n = 21) vs. 0.4% (n = 44) • In-hospital mortality: 82% (n = 12) vs. 31% (n = 15) **Nontraumatic extradural hemorrhage** 0% vs. 0% • In-hospital mortality: none **Unspecified intracranial hemorrhage** 0.1% (n = 1) vs. 0.03 (n = 3) • In-hospital mortality: 100% (n = 1) vs. 0% **Any ICH** 4.4% (n = 55) vs. 0.8% (n = 81); P < .0001 **Mortality** 6.2% vs. 4.0%; P < .0001	
Giles 2010 Administrative data National Inpatient Sample, 2004-2007	Total N = 56,564 Male: 60.2% Mean age: 69.8 ± 11.3 years Asymptomatic N = 49,126 Male: NR Mean age: NR Symptomatic N = 7438	Total N = 482,394 Male: 57.5% Mean age: 71.1 ± 9.5 years Asymptomatic N = 436,895 Male: NR Mean age: NR Symptomatic N = 45,499	In-hospital	**ASYMPTOMATIC** **Stroke or death** 1.6% (n = 807) vs. 0.9% (n = 3973); *P* < .001 **Mortality** 0.8% (n = 398) vs. 0.4% (n = 1618); *P* < .001 **Stroke** 1.0% (n = 490) vs. 0.6% (n = 2628); *P* < .001 **SYMPTOMATIC** **Stroke or death** 13.1% (n = 973) vs. 5.9% (n = 2698); *P* < .001	Multivariate analysis with OR adjusted for age & sex done for risk of stroke or death= for symptomatic pts only, p. 1499

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
	Male: NR Mean age: NR	Male: NR Mean age: NR		Adjusted OR = 2.6 (95% CI, 2.1-3.2); P< .001 **Mortality** 6.0% (n = 448) vs. 1.8% (n = 814); *P* < .001 **Stroke** 8.1% (n = 603) vs. 4.6% (n = 2099); *P* < .001	
Rockman 2011 Administrative data National Inpatient Sample, 2004-2005	Total N = 3091 Male: 61.2% Age: NR Asymptomatic N = 2733 Male: 62.1% Mean age: NR Symptomatic N = 358 Male: 54.7% Mean age: NR	Total N = 50,783 Male: 57.4% Age: NR Asymptomatic N = 48,297 Male: 57.4% Mean age: NR Symptomatic N = 2486 Male: 58.3% Mean age: NR	In-hospital	**ASYMPTOMATIC** **Stroke** 1.9% (n = 52) vs. 0.9% (n = 444) **Mortality** 0.5% (n = 14) vs. 0.4% (n = 200) **SYMPTOMATIC** **Stroke** 5.0% (n = 18) vs. 2.6% (n = 65) **Mortality** 6.1% (n = 22) vs. 2.5% (n = 61)	
Bisdas 2012 Administrative data NY State Department of Health, 2000-2009	Total N = 4012 Male: 50% Age: NR Asymptomatic N = 3546 Male: 50% Mean age: NR Symptomatic N = 466 Male: 50% Mean age: NR	Total N = 53,410 Male: 50% Age: NR Asymptomatic N = 49,042 Male: 50% Mean age: NR Symptomatic N = 4368 Male: 50% Mean age: NR	In-hospital	**ASYMPTOMATIC** **Mortality** 0.79% (n = 28) vs. 0.48% (n = 233) **Stroke** 2.06% (n = 73) vs. 1.27% (n = 622) **Stroke or death** 2.54% (n = 90) vs. 1.65% (n = 810) **Acute MI** 0.62% (n = 22) vs. 0.63% (n = 309) **SYMPTOMATIC** **Mortality**	Data from Table 4 for asymptomatic and Table 5 for symptomatic – propensity-score matched by sex; calculated n's from % and N given

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
				4.08% (n = 19) vs. 0.89% (n = 39) **Stroke** 6.87% (n = 32) vs. 3.81% (n = 167) **Stroke or death** 9.66% (n = 45) vs. 4.28% (n = 187) **Acute MI** 2.15% (n = 10) vs. 1.13% (n = 49)	
Wang 2011 Administrative data Centers for Medicare and Medicaid Services 5% Medicare Provider Analysis Review and Denominator files, 2004-2006	N = 1323 Male: 57.5% Age: 77 ± 6 years Total population: Asymptomatic (87.5%)	N = 9635 Male: 57.3% Age: 76 ± 6 years Total population: Asymptomatic (87.5%)	In-hospital 1-year (f/u%: CAS, 55.7% [n = 737]; CEA, 69.8% [n = 6724])	**AYMPTOMATIC** **In-hospital** **Death** 0.9% (n = 12) (95% CI, 0.4-1.4) vs. 0.6% (n = 58) (95% CI, 0.5-0.8); P = .20 **Stroke** 1.9% (n = 25) (95% CI, 1.2-2.6) vs. 1.4% (n = 132) (95% CI, 1.1-1.6); P = .14 **1 year (CAS, n = 737; CEA, n = 6724)** **Death** 9.9% (n = 73) (95% CI, 8.0-12.3) vs. 6.1% (n = 412) (95% CI, 5.6-6.7); P < .001 *Unadjusted model CAS (vs. CEA):* HR = 1.65; 95% CI, 1.29-2.12 *Adjusted propensity model CAS (vs. CEA):* HR = 1.30; 95% CI, 1.01-1.69 **Stroke** 5.3% (n = 39) (95% CI, 3.9-7.2) vs. 4.1% (n = 277) (95% CI, 3.7-4.6); P = .12 *Unadjusted model CAS (vs. CEA):*	87.5% of population was asymptomatic Propensity score-adjusted analysis for 1 year outcomes Sensitivity analysis

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
				HR = 1.30; 95% CI, 0.93-1.82 *Adjusted propensity model CAS (vs. CEA):* HR = 1.26; 95% CI, 0.89-1.78 **Acute MI** 4.8% (n = 35) (95% CI, 3.5-6.7) vs. 2.5% (n = 165) (95% CI, 2.1-2.9); P < .001 *Unadjusted model CAS (vs. CEA):* HR = 1.97; 95% CI, 1.37-2.84 *Adjusted propensity model CAS (vs. CEA):* HR = 1.56; 95% 1.07-2.27 **SYMPTOMATIC – N/A**	
Young 2011 Administrative data National Inpatient Sample, 2006-2007	N = 31,197 Male: 60.0% Age: 71.2 ± 0.12 years Total population: Asymptomatic (100%)	N = 218,395 Male: 57.2% Age: 71.2 ± 0.04 years Total population: Asymptomatic (100%)	In-hospital	**ASYMPTOMATIC** **Stroke or death** 1.69% (n = 527) vs. 1.16% (n = 2533) OR = 1.46 (95% CI, 1.18-1.80) Adjusted OR = 1.28 (95% CI, 1.03–1.58); P = .03 **Stroke** 1.31% (n = 409) vs. 0.88% (n = 1922) OR = 1.5 (95% CI, 1.18-1.90) **Death** 0.57% (n = 178) vs. 0.39% (n = 852) OR = 1.46 (95% CI, 1.02-2.09) **Cardiac complications** 2.15% (n = 671) vs. 1.86% (n = 4062) OR = 1.16 (95% CI, 0.96-1.39) **SYMPTOMATIC – N/A**	N's calculated from % given ICD-9 code used for cardiac complications was 997.1 (cardiac complications, not elsewhere classified) ORs are unadjusted unless otherwise stated Some economic data

Author/study design	CAS	CEA	Follow-up	Outcomes – *CAS vs. CEA*	Comments
Khatri 2012 Administrative data National Inpatient Sample, 2005-2008	N = 57,626 Male: 60.3% Age: 70.8 years Total population: Asymptomatic (95.7%)	N = 437,705 Male: 57.7% Age: 71.1 years Total population: Asymptomatic (95.7%)	In-hospital	**ASYMPTOMATIC** **Mortality** 0.61% (n = 354) vs. 0.40% (n = 1756) **Stroke** 1.72% (n = 989) vs. 0.98% (n = 4289) **Cardiac complications** 2.26% (n = 1303) vs. 1.89% (n = 8268) **SYMPTOMATIC – N/A**	95.7% of population is asymptomatic Calculated total population by adding incidences in both age groups within procedure group

INTRACRANIAL ARTERIAL STENOSIS (Key Question 2)

Table F10. Study characteristics and inclusion/exclusion criteria of the from SAMMPRIS trial evaluating stenting versus aggressive medical therapy for the treatment of intracranial arterial stenosis (Key Question 2).

	SAMMPRIS Chimowitz 2011
Study (year)/ location/ no. of centers	• SAMMPRIS (2011) • 50 sites, United States
Inclusion criteria	• TIA or stroke within 30 days before enrollment attributed to stenosis of 70-99% by angiogram of a major carotid artery • Modified Rankin score of ≤ 3 • Target area of stenosis in an intracranial artery that has a normal diameter of 2.00mm to 4.50mm • Target area of stenosis is ≤ 14mm in length • Age 30-80 years • Patients 30-49 years must have an additional criteria of: o Insulin dependent diabetes for at least 15 years o Two of the following: ▪ Hypertension, dyslipidemia, smoking, non-insulin dependent diabetes or insulin dependent diabetes of less than 15 years duration, family history of any of the following: myocardial infarction, coronary artery bypass, coronary angioplasty or stenting, stroke, carotid endarterectomy or stenting, peripheral vascular surgery in parent or sibling who was <55 years of age for men or <65 for women at the time of the event o History of myocardial infarction, coronary artery bypass, coronary angioplasty or stenting, carotid endarterectomy or stenting, or peripheral vascular surgery for atherosclerotic disease o Any stenosis of an extracranial carotid or vertebral artery, another intracranial artery, subclavian artery, coronary artery, iliac or femoral artery, other lower or upper extremity artery, mesenteric artery, or renal artery that was documented by non-invasive vascular imaging or catheter angiography and is considered atherosclerotic o Aortic arch atheroma documented by non-invasive vascular imaging or catheter angiography o Any aortic aneurism documented by non-invasive vascular imaging or catheter angiography that is considered atherosclerotic • Negative pregnancy test in a female who has had any menses in the last 18 months • Patient is willing and able to return for all follow-up visits required by the protocol • Patient is available by phone • Patient understands the purpose and requirements of the study, can make him/herself understood, and has provided informed consent
Exclusion criteria	• Tandem extracranial or intracranial stenosis (70%–99%) or occlusion that is proximal or distal to the target intracranial lesion (NOTE: an exception is allowed if the occlusion involves a single vertebral artery proximal to a symptomatic basilar artery stenosis and the contralateral vertebral artery is

	SAMMPRIS Chimowitz 2011
	supplying the basilar artery) • Bilateral intracranial vertebral artery stenosis of 70%–99% and uncertainty about which artery is symptomatic (e.g. if patient has pontine, midbrain, or temporal – occipital symptoms) • Stenting, angioplasty, or endarterectomy of an extracranial (carotid or vertebral artery) or intracranial artery within 30 days prior to expected enrollment date • Previous treatment of target lesion with a stent, angioplasty, or other mechanical device, or plan to perform staged angioplasty followed by stenting of target lesion • Plan to perform concomitant angioplasty or stenting of an extracranial vessel tandem to an intracranial stenosis • Presence of intraluminal thrombus proximal to or at the target lesion • Any aneurysm proximal to or distal to stenotic intracranial artery • Intracranial tumor (except meningioma) or any intracranial vascular malformation • CT or angiographic evidence of severe calcification at target lesion • Thrombolytic therapy within 24 hours prior to enrollment • Progressive neurological signs within 24 hours prior to enrollment • Brain infarct within previous 30 days of enrollment that is of sufficient size (> 5 cms) to be at risk of hemorrhagic conversion during or after stenting • Any hemorrhagic infarct within 14 days prior to enrollment • Any hemorrhagic infarct within 15 – 30 days that is associated with mass effect • Any history of a primary intracerebral (parenchymal) hemorrhage (ICH) • Any other intracranial hemorrhage (subarachnoid, subdural, epidural) within 30 days • Any untreated chronic subdural hematoma of greater than 5 mm in thickness • Intracranial arterial stenosis due to arterial dissection, Moya Moya disease; any known vasculitic disease; herpes zoster, varicella zoster or other viral vasculopathy; neurosyphilis; any other intracranial infection; any intracranial stenosis associated with CSF pleocytosis; radiation induced vasculopathy; fibromuscular dysplasia; sickle cell disease; neurofibromatosis; benign angiopathy of central nervous system; post-partum angiopathy; suspected vasospastic process, suspected recanalized embolus • Presence of any of the following unequivocal cardiac sources of embolism: chronic or paroxysmal atrial fibrillation, mitral stenosis, mechanical valve, endocarditis, intracardiac clot or vegetation, myocardial infarction within three months, dilated cardiomyopathy, left atrial spontaneous echo contrast, ejection fraction less than 30% • Known allergy or contraindication to aspirin, clopidogrel, heparin, nitinol, local or general anesthesia • History of life-threatening allergy to contrast dye. If not life threatening and can be effectively pretreated, patient can be enrolled atphysician's discretion • Active peptic ulcer disease, major systemic hemorrhage within 30 days, active bleeding diathesis, platelets < 100,000, hematocrit < 30, • INR > 1.5, clotting factor abnormality that increases the risk of bleeding,

	SAMMPRIS Chimowitz 2011
	current alcohol or substance abuse, uncontrolled severe hypertension (systolic pressure > 180 mm Hg or diastolic pressure > 115 mm Hg), severe liver impairment (AST or ALT > 3 x normal, cirrhosis), creatinine > 3.0 (unless on dialysis) • Major surgery (including open femoral, aortic, or carotid surgery) within previous 30 days or planned in the next 90 days after enrollment • Indication for warfarin or heparin beyond enrollment (NOTE: exceptions allowed for use of systemic heparin during stenting procedure or subcutaneous heparin for deep vein thrombosis (DVT) prophylaxis while hospitalized) • Severe neurological deficit that renders the patient incapable of living independently • Dementia or psychiatric problem that prevents the patient from following an outpatient program reliably • Co-morbid conditions that may limit survival to less than 3 years • Pregnancy or of childbearing potential and unwilling to use contraception for the duration of this study • Enrollment in another study that would conflict with the current study.
Definition of asymptomatic disease	Asymptomatic brain hemorrhage was defined as a parenchymal, subarachnoid, or intraventricular hemorrhage that was asymptomatic or associated with symptoms or signs that lasted less than 24 hours
Stent device/ **EPD (%)**	Gateway PTA Balloon Catheter and Wingspan stent system; EPD (%) NR
Co-intervention	• Enteric coated aspirin (325mg per day for the entire follow-up) • Clopidogrel (75mg per day for 90 days after enrollment) • Intensive management of the primary risk factors
Primary outcome	• Stroke or death within 30 days after enrollment • Any stroke or death within 30 days after a revascularization procedure of the qualifying lesion during follow-up • Ischemic stroke in the territory of the qualifying artery beyond 30 days
Follow-up (% followed)	

Provider certification	• Interventionists must submit procedure and discharge or follow-up notes from the 20 most recent consecutive intracranial stent or angioplasty cases in which they were the primary operator (not during fellowship or as an assistant)
	• Accepted cases include:
	  ○ The Wingspan stent for intracranial atherosclerosis
	  ○ A balloon-mounted coronary stent for intracranial atherosclerosis
	  ○ A self-expanding stent for aneurysm
	  ○ Angioplasty alone for intracranial atherosclerosis if the interventionist did not have 20 stenting cases
	• Experience of interventionists was reviewed by a credentialing committee

Funding	Research grant from the US National Institute of Neurological Disorders and Stroke, other institutions supported by Clinical and Translational Science Awards funded by the NIH include: Medical University of South Carolina (UL1RR029882), University of Florida (UL1RR029889), University of Cincinnati (UL1RR029890), and University of California, San Francisco (UL1RR024131). Corporate support from Stryker Neurocascular, Vendor support from Nationwide Better Health - INTERVENT

	SAMMPRIS Chimowitz 2011
Comments	This study was terminated early because of the difference in 30-day death rates between the two groups.

Table F11. Baseline characteristics of patients from SAMMPRIS trial evaluating stenting versus aggressive medical therapy for the treatment of intracranial arterial stenosis (Key Question 2).

SAMMPRIS trial		
Baseline demographics & characteristics	**Treatment groups % (n)**	
	CAS + medical therapy (N =224)	**Medical therapy only (N = 227)**
Demographics		
Male	56.7	63.9
Mean age ± SD (years)	61.0 ± 10.7	59.5 ± 11.8
Current Smoker	24.2	30.4
Mean % stenosis (± SD)	80 ± 7	81 ± 7
Comorbidities		
Hypertension	89.7	89.4
Diabetes	47.3	45.4
Lipid disorder	86.6	89.4
History of coronary artery disease	21.0	26.0
History of stroke other than qualifying event	26.8	25.6
Already receiving antithrombotic therapy at time of qualifying event	64.7	62.1
Qualifying event		
Stroke	63.4	67.0
TIA	36.6	33.0

AFib = atrial fibrillation; AFlutter = atrial flutter; CAD = coronary artery disease; CAS = carotid artery stenting; CEA = carotid endarterectomy; DM = diabetes mellitus; HTN = hypertension; MI = myocardial infarction; ND = not defined; NR = not reported; PVD = peripheral vascular disease; TIA = transient ischemic attack.

Table F12. Detailed result of the SAMMPRIS trial evaluating stenting versus aggressive medical therapy for the treatment of intracranial arterial stenosis (Key Question 2).

Author/study design	CAS	MT	Follow-up	Outcomes – *CAS vs. MT**	Comments
Chimowitz 2011 SAMMPRIS Trial RCT, multicenter (50 sites in US) Wingspan stent system	N = 224 Age: 61.0 ± 10.7 years Male: 56.7%	N = 227 Age: 59.5 ± 11.8 years Male: 63.9%	30 days, 1 year	**PRIMARY OUTCOME – Stroke or death within 30 days after enrollment or after a revascularization procedure for the qualifying lesion during the follow-up period or stroke in the territory of the qualifying artery beyond 30 days** *Probability at 30 days* 14.7% (n = 33) (95% CI, 10.7-20.1) vs. 5.8% (n = 13) (95% CI, 3.4-9.7); *P* = .002 *Death* 2.2% (n = 5; all stroke-related) vs. 0.4% (n = 1; non-stroke related) • 10 (30.3%) of the 33 strokes in the CAS group were symptomatic brain hemorrhages compared with 0 of the 12 in the MT group; *P* = .04 *Probability at 1 year* 20.0% (n = 26) (95% CI, 15.2-26.0) vs. 12.2% (n = 46) (95% CI, 8.4-17.6); *P* = .009 **SECONDARY OUTCOMES** **Any stroke or death** *Probability at 30 days*: 14.7% (95% CI, 10.7-20.1) vs. 5.8% (95% CI, 3.4-9.7) *Probability at 1 year*: 23.4% (95% CI, 18.1-29.8) vs. 17.5% (95% CI, 12.8-23.6); P = .06 **Death** *Probability at 30 days*: 2.2% (95% CI, 0.9-5.3) vs. 0.4% (95% CI, 0.1-3.1) *Probability at 1 year*: 3.4% (95% CI, 1.6-7.2) vs. 4.1% (95% CI, 2.0-8.5); P = .95	Enrollment was stopped after 451 patients underwent randomization due to the high 30-day rate of stroke or death in the CAS group compared with CEA 100% symptomatic Angiographic stenosis of 70%-99% Outcomes broken down further into subcategories, see summary tables in report

Author/study design	CAS	MT	Follow-up	Outcomes – *CAS vs. MT**	Comments
				Any stroke *Probability at 30 days*: 14.7% (95% CI, 10.7-20.1) vs. 5.3% (95% CI, 3.1-9.2) *Probability at 1 year*: 22.3% (95% CI, 17.2-28.7) vs. 14.9% (95% CI, 10.6-20.7); P = .03 **Disabling or fatal stroke** *Probability at 30 days*: 7.0% (95% CI, 4.3-11.4) vs. 1.8% (95% CI, 0.7-4.8) *Probability at 1 year*: 9.0% (95% CI, 5.7-13.9) vs. 6.4% (95% CI, 3.7-11.1); P = .21 **MI** *Probability at 30 days*: 0.5% (95% CI, 0.1-3.2) vs. 1.3% (95% CI, 0.4-4.1) *Probability at 1 year*: 2.2% (95% CI, 0.8-5.8) vs. 4.0% (95% CI, 1.9-8.4); P = .60 **Major non-stroke-related hemorrhage** *Probability at 30 days*: 2.7% (95% CI, 1.2-5.9) vs. 0.9% (95% CI, 0.2-3.5) *Probability at 1 year*: 3.6% (95% CI, 1.8-7.1) vs. 1.4% (95% CI, 0.4-4.2); P = .10 **Any major hemorrhage** *Probability at 30 days*: 8.0% (95% CI, 5.1-12.5) vs. 0.9% (95% CI, 0.2-3.5) *Probability at 1 year*: 9.0% (95% CI, 5.9-13.5) vs. 1.8% (95% CI, 0.7-4.8); P < .001	

Table F13. Detailed result of prospective case-series evaluating stenting for the treatment of intracranial arterial stenosis (Key Question 2).

Author/study design	CAS	Follow-up	Outcomes	Comments
Bose (2007)/FDA Summary of Safety and Probable Benefit (2004) Boston Scientific: Wingspan Stent System with Gateway PTA Balloon Catheter Prospective, multicenter (12 international sites)	N = 45 Mean age: 66 ± 8 years Male: 73.3%	30-day (97.8%, n = 44) 6 months (93.3%; n = 42)	**Stent delivery success** 97.8% (n = 44/45) ***30 days*** **Death or ipsilateral stroke** 4.5% (n = 2/44) **Major ipsilateral stroke** 4.5% (n = 2/44) **Death** 2.3% (n = 1/44) **Parent vessel dissections** None **Stent migration** None **Access site complications** 11.4% (n = 5/44, 7 events) requiring treatment: 9.1% (n = 4/44) ***6 months*** **Death or ipsilateral stroke** 7.1% (n = 3/42) **Ipsilateral stroke** Total: 7.1% (n = 3/42) Major: 4.8% (n = 2/42) Minor: 2.4% (n = 1/42)	50%-99% stenosis MCA 22% Carotid 29% Vertebral 29% Basilar 20 Each patient received clopidogrel (75 mg PO QD for 3 days before the procedure or 225 mg PO on the day before treatment) and aspirin (300 or 325 mg PO QD for 3 days before procedure or 300 to 650 mg PO on the day before treatment). A bolus and continuous intravenous infusion of heparin were given before the procedure. Heparin infusion was continued for 24 hours to maintain the activated clotting time. Each patient received clopidogrel (75 mg PO QD) for 30 days and aspirin (300 or 325 mg PO QD) for life *1 year data as reported in the Bose 2007 article from a non-adjudicated, physician-reported follow-up of 43 patients with an average of 13 months follow-up (range, 7-22) conducted outside the study protocol.

Author/study design	CAS	Follow-up	Outcomes	Comments
			Contralateral stroke Total: 2.4% (n = 1/42) Major: 2.4% (n = 1/42) Minor: 0% **Death** 2.4% (n = 1/42) **All-cause stroke** Total: 9.5% (n = 4/42) Major: 7.1% (n = 3/42) Minor: 2.4% (n = 1/42) **Parent vessel dissections** None **Stent migration** None ***1 year**** **Ispilateral stroke** 2.3% (1/43) **Death** None	
Zaidat 2008 NIH registry for Wingspan (Phase I trial prior to SAMMPRIS) Prospective, multicenter	N = 129 Mean age: 64.2 ± 12.4 years Male: 55%	Periprocedural/ 30 days; up to 6 months	**Any stroke (ischemic or hemorrhagic) or death at 30 days:** n = 12; 9.6% (95% CI, 5.6%-16.3%) • 8 occurred w/in 24 hours: 6.2% (95% CI, 3.2%-12.0%) **Any stroke (ischemic or hemorrhagic) at 30 days:** n = 11; 8.5% **Death at 30 days:** n = 4; 3.1%	70-99% stenosis MCA 33% Carotid 26% Vertebral 24% Basilar 17% All patients were treated with aspirin (81 to 325 mg daily) and clopidogrel 75 mg daily at least 3 days prior to the procedure or loaded with 300 mg of clopidogrel and 81 to 325 mg aspirin within 24 hours of the

Author/study design	CAS	Follow-up	Outcomes	Comments
			Any stroke or death <u>within 30 days</u> or stroke in the territory of the stented artery <u>after 30 days</u> At 6 months: 14.0% (95% CI = 8.7-22.1) • 4 additional ischemic strokes in the territory of the stented artery occurred after 30 days **Restenosis (narrowing ≥ 50%) at <u>4.8 ± 2.1 months</u>** 25.0% (n = 13/52) (2 symptomatic [stroke]) **Other neurological complications (during the periprocedural period)** • Stent thrombosis: n = 4 • Cerebral infarct on MRI with neurological signs lasting < 24 hours: n = 2 • TIA: n = 2 • Somnolence for 3 days with no infarct on MRI: n = 1 • Asymptomatic vessel dissection: n = 2 • Transient vasospasm: n = 2	procedure. Intraprocedure unfractionated heparin was administered at approximately 70 units/kg as an IV bolus to achieve an activated clotting time of 250 to 300 seconds. The heparin was not reversed post procedure. Patients were admitted to a neurointensive or general critical care unit for 24 hours for hemodynamic and neurologic monitoring. Aspirin 81 to 325 mg was recommended throughout follow-up and clopidogrel 75 mg daily was recommended for 4 to 12 weeks after stenting.
The SSYLVIA Study Investigators 2004 Prospective, multicenter, international Neurolink stent system	N = 43 Mean age: 63.6 years* Male: 82%* Mean % stenosis: 69.9% ± 12.4% *entire population (including extracranial, n = 18)	Periprocedural, 1 year	**Death** **30 days:** 0% (n = 0) **Stroke** **30 days:** 7.0% (n = 3) **1 year:** 14.0% (n = 6) **Subarachnoid hemorrhage** **30 days:** 2.3% (n = 1) **Restenosis (narrowing > 50%)** **6 months:** 32.4% (12/37)	50%-99% stenosis MCA: 12% Carotid: 35% Vertebral: 12% Basilar: 40% Posterior cerebral: 2% Aspirin (minimum 100 mg, twice daily) and clopidogrel (minimum 75 mg twice daily) were given at least 48 hours before the procedure. After the procedure, aspirin (minimum 100 mg daily) was prescribed for a minimum of 1 year and clopidogrel (75 mg daily) for at least 4 weeks. Heparin

Author/study design	CAS	Follow-up	Outcomes	Comments
				was administered to maintain an activated clotting time of 200 to 300 seconds throughout the procedure. Adjunctive drugs such as IIb/IIIa inhibitors were only allowed in patients at high risk for subsequent thromboembolic complications.
Fiorella 2011 Prospective, multicenter (US) US Wingspan Registry	N = 158 (168 lesions) Average age: 62.7 years Male: 60.1%	Average 14.2 months 12 mo f/u, n = 110	**Periprocedural** **Stroke:** 5.7% (n = 9) **Death:** 2.5% (n = 4) **Any stroke or death:** 5.7% (n = 9) **1 year** Any stroke or death within 30 days or any ipsilateral stroke after 30 days: 15.7%	See Fiorella 2007 for minor complications – can report these for this smaller group since there are some important complications
Albuquerque 2008 Prospective, multicenter (US) US Wingspan Registry	N = 127 (pts with follow-up imaging) Mean age: NR Male: NR	Mean 8.5 months (3.3-15.5)	**In-stent restenosis**: 28.3% (n = 36/127) • Symptomatic: n = 13 **Stent occlusion:** 3.9% (n = 5/127) • Symptomatic: n = 2	
Fiorella 2007 Prospective, multicenter (US) US Wingspan Registry	N = 78 (82 lesions) Mean age: 63.6 years Male: 57.7%	Periprocedural	**Stent delivery success** 98.8% (n = 81/82) **Major procedural complications (morbidity and mortality)** Overall (stroke or death): 6.1% (n = 5/82) • device related, vessel perforation (death): 2.4% (n = 2/82) • multiple posterior circulation strokes (death): 1.2% (n = 1/82) • contralateral embolic infarction (death): 1.2% (n = 1/82) Death: 4.9% (n = 4/82) Aphasia and hemiparesis (pt with reperfusion hemorrhage): 1.2% (n = 1/82)	Postop DW-MRI imaging 77 (98.7%) symptomatic; 1 (1.3%) asymptomatic In the Limitations section they say "any major procedural morbidity (periprocedural stroke or death)" 50-99% stenosis MCA: 27% Carotid: 39% Vertebral: 17%

Author/study design	CAS	Follow-up	Outcomes	Comments
			Minor complications • Transient visual symptoms (completely resolved within 36 hours of procedure): 1.2% (n = 1/82); • Flowing limiting intracranial dissection requiring stenting: 1.2% (1/82), no neurological morbidity; • Extracranial parent-vessel dissection related to guide catheter manipulation: 6.1% (5/82); 2 were flow-limiting and required stenting	Basilar: 17% All patients were pretreated with antiplatelet agents (typically, both aspirin and clopidogrel) and were typically discharged on both aspirin (325 mg daily) and clopidogrel (75 mg daily). Heparinization was instituted during the procedure. The dual antiplatelet regimen was maintained for a minimum of 4 weeks after the procedure, after which time patients remained on aspirin therapy (325 mg daily).
Jiang 2011 Prospective, single center (Beijing, China)	N = 100 (105 lesions) Mean age: 53.2 ± 9.2 Male: 87%	Mean 1.8 years	**Stent-delivery success:** (n = 99/100) **<u>Periprocedural</u>** **Any stroke:** 5% (n = 5) (3 ischemic strokes and 2 ICHs) **Death:** 0% **Any stroke or death:** 5% (n = 5) **TIA:** 7% (n = 7) (5 posterior circulation, 2 anterior) **Other complications:** • 2 emergency cerebral artery revascularizations **<u>2 year follow-up (i.e. after 30 days)</u>** **Ipsilateral stroke:** 4% (= 4) (1 was fatal, and one was disabling) **Death:** • After 30 days: 1% (n = 1) (ipsilateral stroke) • Cumulative: 1% (n = 1) **TIA in the territory of the stented artery:** • After 30 days: 6% (n = 6) • Cumulative (to include periprocedural): 13%	Stenosis 70%-99%

Author/study design	CAS	Follow-up	Outcomes	Comments
			(n = 13) **Cumulative probability of the primary end point (any stroke or death within 30 days and ipsilateral ischemic stroke afterward):** • at 1 year: 7.3% (95% CI, 2.0-12.5) • at 2 years: 9.6% (95% CI, 0.0-19.2) **In-stent restenosis (n = 45 lesion in 44 patients; mean 8.6 months):** 26.7% (n = 12/45) • Symptomatic restenosis: 11.1% (n = 5/45)	

ECONOMIC STUDIES

Table F14. Data Summary Table of Included Cost-Utility Analysis Studies

Author (year) Country Funding	Population Treatments Methods	Effectiveness Estimates	Cost Estimates	Results Sensitivity Analysis

Janssen 2008[Janssen]
 	
Netherlands
 	
Funding: Netherlands Organization for Health Research and Development
 	
Two authors serve advisory roles for industry companies and have received research grants for other work.
	Population:
	• Symptomatic patients
	• Data source:
	  • ECST (n=309)
	  • Cochrane (CEA n=919)
	  • Wholey (n=2111)
	  • Cochrane (CAS n=938)
	
	Treatments:
	• CAS
	• CEA
	
	Methods:
	• Cost utility analysis
	• Outcome measures:
	  • Expected cost
	  • Quality adjusted life years (QALY)
		• Effectiveness measures: derived from literature review:
		  • Complication Rates
		  ▪ Technical failure during CAS: 1.11%[Wholey]
		  ▪ Reoperation rate (per year): 0.68%[Bosiers]
		  ▪ Reoperation rate CEA (per year): 0.09%[ECST]
		  ▪ Post operative major stroke rate (per year): 0.43%[ECST]
		  ▪ Post operative minor stroke rate (per year): 0.66%[ECST]
		  ▪ MI rate (per year): 1.59%[ECST]
		  • Survival Parameters[ECST]
		  ▪ Death HR given stroke: 2.07
		  ▪ Death HR given disabling stroke: 6.05
		  ▪ Death HR given MI: 2.09
		  ▪ Death HR given MI + stroke: 3.09
		  ▪ Risk of death after peri-operative disabling stroke: 9.3%[ECST]
		  ▪ Risk of death after disabling stroke:
			• Treatment cost based on actual costs of successful procedure
			• CAS procedure: $6,510
			• CEA procedure: $4,749
			• Cost of complications derived from published literature.
			• MIs: $17,757[Legrand]
			• Acute major stroke: $30,505[Huijsman]
			• Major stroke follow up (1st 6 months): $22,242
			• Major stroke on follow up (after 6 months): $9,490[Bergman]
			• Major stroke on death (1st 6 months): $9,208
				Base-case analysis:
				• CAS procedural cost: $6,510
				• CEA procedural cost: $4,749
				• ICER not reported due to variability
				
				One-way sensitivity analysis:
				• Marginal costs and effects of 1% increase in complications:
				  • Re-intervention CAS:
				  ▪ Cost: $427
				  ▪ QALY: -0.010
				  • Peri-operative minor stroke rate:
				  ▪ Cost: $69
				  ▪ QALY: -0.028
				  • Peri-operative major stroke rate:
				  ▪ Cost: $1,244
				  ▪ QALY: -0.059
				  • Peri-operative death rate
				  ▪ Cost: $-49

Author (year) Country Funding	Population Treatments Methods	Effectiveness Estimates	Cost Estimates	Results Sensitivity Analysis
	• Incremental cost-effectiveness ratio (ICER) • Perspective: Provider • Model used: Markov decision analysis • Time horizon: 10 years	30.8%[ECST] ▪ Risk of death after MI: 22.6%[ECST] • Utility measures (QALYs per year): derived from literature review: • MI: 0.88[Tsevat] • Minor stroke: 0.65[Post] • Major stroke 0.15[Post] • Death: 0.00	• Minor stroke on follow up (1st 6 months): $6,577[Huijsman] • Minor stroke on follow up (after 6 months): $4,908[Huijsman] • Discounted at 4% to 2003 price level. • Converted to USD from Euros using 2003 purchasing power parities.[OECD]	▪ QALY: -0.068 • Reducing hospital stay by 3-days reduces cost of CEA by $876 and further reduces the cost-effectiveness of CAS One-way uncertainty analysis: • Tests peri-operative incidence rates from multiple data sources (1-ECST70+, 2-Cochrane, 3-Wholey, 4-Cochrane) • Simulating the Wholey vs ECST data authors finds CAS to be cost-effective 93.3% of the time with a ICER of $29,595
Maud 2010[Maud] United States Funding: NR States that authors have no commercial, proprietary or financial interest in any of the products or companies described in the study.	Population: • Patients with severe carotid stenosis considered to be at high risk for CEA • Primary data source: SAPPHIRE CAS n=167, CEA n=167 • Avg. Age = 72 • Avg. Male = 67% Treatments: • CAS • CEA Methods: • Cost utility analysis • Outcome measures: • Expected cost • Quality adjusted life years (QALY) • Incremental cost-effectiveness ratio (ICER) • Perspective: societal cost • Monte Carlo simulation • Time horizon: 1 year	• Clinical outcome rates (as specified in SAPPHIRE): • CAS complications: ▪ Minor stroke: 4% ▪ Major stroke 1% ▪ MI: 2% ▪ Death: 7% • CEA complications: ▪ Minor stroke: 2% ▪ Major stroke 4% ▪ MI: 5% ▪ Death: 13% • Utility weights (specified in SAPPHIRE): • Good health: 0.815 • MI: 0.744 • Stroke: 0.718 • Death: 0.0	• Cost obtained from the Healthcare Cost and Utilization Project • CAS procedure: $11,220 • CEA procedure: $6,802 • Minor Stroke: $2,808 • Major Stroke: $4,200 • MI: $4,200 • Death: $5,000[Gage] • Costs are given in 2006 USD	Base-case analysis: • CAS cost = $12,782, QALY = 0.712 • CEA cost = $8,916, QALY = 0.753 • CAS vs. CEA ICER: $67,891 Uncertainty: • Intervals for the results of the simulation were presented: • CAS cost 95%CI: $12,205-$13,563 • CEA cost 95%CI: $8,267-$9,766 • CAS QALY 95%CI: 0.715- 0.779 • CEA QALY 95%CI: 0.654- 0.738 • CAS vs. CEA ICER 95%CI: $-129,372-$379,661
Young 2010[Young] United States Funding: National	Population: • Symptomatic patients • 70-year-old cohort • Primary data sources: SPACE, SAPPHIRE, and EVA-3S Treatments:	• Clinical outcome rates: • CAS complication incidence rate (30-day)[Gurm]: ▪ Minor stroke: 0.0381 ▪ Major stroke: 0.0321 ▪ MI: 0.0064 ▪ Death: 0.0062 • CEA complication incidence rate (total):	• All costs are direct medical cost; no indirect costs included • CAS procedure: $10,400[Brooks;Kilaru] • CEA procedure: $9,170[Brooks;Kilaru]	Base-case analysis: • CAS: cost = $52,900, QALY = 8.97 • CEA: net cost = $35,200, QALY = 9.64 • CAS dominated by CEA One-way uncertainty analysis: • Tripling the long-term stroke rate to 6.3% caused CEA to be

Author (year) Country Funding	Population Treatments Methods	Effectiveness Estimates	Cost Estimates	Results Sensitivity Analysis

Center for Research Resources and NIC Roadmap for Medical Research.
 	
Authors report potential conflict of interest as partial salary from the NIH and also a clinical research grant ACT-1.
	• CAS
	• CEA
	
	Methods:
	• Cost utility analysis
	• Outcome measures:
	  • Expected cost
	  • Quality adjusted life years (QALY)
	  • Incremental cost-effectiveness ratio (ICER)
	• Perspective: US Medicare costs
	• Model used: Markov decision analysis
	• Time horizon: lifetime of cohort with one month cycles
		▪ Minor stroke: 0.0266[ECST;Eckstein;Gurm;Mas]
		▪ Major stroke: 0.0303[Eckstein;Gurm;Mas]
		▪ MI: 0.0131[ECST;Gurm]
		▪ Death: 0.126[Eckstein;ECST;Gurm;Mas]
		• Utility weights:
		▪ Minor stroke: 0.65[Post;Tengs]
		▪ Major stroke: 0.15[Post;Tengs]
		▪ MI: 0.88[Mahoney;Tsevat]
		▪ Death: 0
			• Complication Costs:
			  • Minor stroke hospitalization: $9,800[Holloway;Lee;O'Brien;Kuntz]
			  • Major stroke hospitalization: $10,500[Holloway;Kuntz;Lee;O'Brien]
			  • MI (per year): $4,500[Tsevat]
			  • Minor stroke (per year): $7,500[Cronenwett;Kilaru;Kuntz;Oster;Post;Yin]
			  • Major stroke (1st year): $66,500[Cronenwett;Kilaru;Kuntz]
			  • Major stroke (per year): $33,900[Cronenwett;Kilaru;Kuntz;Post]
			• Future costs and utilities discounted at 3% to 2007 values
				dominated.
				• Varying the proportion starting well or minor stroke did not affect the dominance of CEA Nor did changing the peri-operative risks
				Two-way uncertainty analysis:
				• Explored impact of long-term stroke rates and showed CEA to dominate CAS
				
				Uncertainty:
				• Probabilistic sensitivity analysis showed CEA remained dominant 59% of the time for range of QALYs.

Mahoney 2011[Mahoney]
 	
United States
 	
Funding source not disclosed, though funding agreement stipulated that the authors reserved the right to publish regardless of their findings.
 	
Authors disclose
	Population:
	• Asymptomatic patients
	• Primary data source: SAPPHIRE CAS n=167, CEA n=167
	  • Avg. Age = 72
	  • Avg. Male = 67%
	
	Treatments:
	• CAS
	• CEA
	
	Methods:
	• Cost utility analysis
	• Outcome measures:
	  • Expected cost
	  • Quality adjusted life years
		• Clinical outcome rates (as specified in SAPPHIRE):
		  • CAS complications:
		  ▪ Minor stroke: 4%
		  ▪ Major stroke 1%
		  ▪ MI: 2%
		  ▪ Death: 7%
		  • CEA complications:
		  ▪ Minor stroke: 2%
		  ▪ Major stroke 4%
		  ▪ MI: 5%
		  ▪ Death: 13%
		• Initial hospital outcome rates:
		  • CAS complications:
		  ▪ Stroke: 3.1%
		  ▪ MI: 1.9%
		  ▪ Death: 0%
			• Procedural cost estimates obtained from hospital accounting
			• Complication cost estimates obtained from literature
			• CAS procedure: $7,084
			• CAS total hospital cost: $11,835
			• CEA procedure: $3,003
			• CEA total hospital cost: $11,295
			• Complication Costs:
			  • Minor stroke: $5,817
			  • Major stroke: $18,515
			  • MI: $10,176
				Symptomatic Results:
				• CAS: cost = $61,131
				• CEA: cost = $5,141
				• Incremental QALY (CAS-CEA): 0.03
				• CAS vs. CEA ICER: $204,229/QALY
				
				Asymptomatic Results:
				• CAS: cost = $60,700
				• CEA: cost = $58,798
				• Incremental QALY (CAS-CEA): 0.71
				• CAS vs. CEA ICER: $2,667/QALY
				
				Sensitivity analysis:
				• Changing the discount rate from 0% to 5% resulted in an an ICER of $6,290 and $6,744 respectively.

Author (year) Country Funding	Population Treatments Methods	Effectiveness Estimates	Cost Estimates	Results Sensitivity Analysis
various industry ties.	(QALY) • Incremental cost-effectiveness ratio (ICER) • Perspective: Health care system • Model used: Bootstrap simulations • Time horizon: lifetime	• CEA complications: ▪ Stroke: 2.6% ▪ MI: 5.3% ▪ Death: 0.7% • Multiplicative utility weights (obtained from the EQ-5D): • No event: 0.841 • MI: 0.737 • Minor stroke: 0.729 • Major stroke: 0.436 • Death: 0	• Future costs and utilities discounted to at 3% 2002 values	• If the cost of stents and embolic protection devices are cut in half the ICER becomes $2,373/QALY • A 50% increase in device cost produces a ICER or $10,735/QALY • If mortality associated with death risk, MI and stroke are cut in half the ICER becomes $10,623 • Assuming a constant utility of the ICER becomes $5,575/QALY • If no long-term benefits are assumed the ICER is $49,514
Vilain 2012[Vilain] United States Funding National Institute of Neurological Disorders and Stroke and the National Institutes of Health Authors disclose various industry ties.	Population: • Separate analysis for symptomatic and asymptomatic patients • Uses CREST trial data Treatments: • CAS • CEA Methods: • Cost utility analysis • Outcome measures: • Expected cost • Quality adjusted life years (QALY) • Incremental cost-effectiveness ratio (ICER) • Perspective: US Health care system • Model used: Markov Model • Time horizon: 10 year	• Clinical outcome rates (as specified in CREST): • CAS complications: ▪ Minor stroke: 2.5% ▪ Major stroke 0.5% ▪ MI: 1.5% ▪ Death: 0.3% • CEA complications: ▪ Minor stroke: 1.0% ▪ Major stroke 0.3% ▪ MI: 2.9% ▪ Death: 0.2% • Multiplicative utility weights (obtained from the SF-36 data): • Major stroke: 0.1 (1-month) and 0.06 (after 1-month) • Minor stroke: 0.02 (1-month) and 0.03 (after 1-month)	• Resource data and hospital billing records were used to estimate costs over the first year • CAS procedure: $15,055 • CAS 1-year total cost: $16,375 • CEA procedure: $14,816 • CEA 1-year total cost: $16,108 • Future costs and utilities discounted to at 3% 2008 values	Symptomatic Results: • CAS: cost = $79,988 QALY = 4.823 • CEA: cost = $79,540 QALY = 4.840 • CAS is dominated by CEA Asymptomatic Results: • CAS: cost = $80,314 QALY = 4.862 • CEA: cost = $79,705 QALY = 4.859 • ICER: $277,249/QALY Sensitivity analysis: • Assuming a willingness to pay of $50,000, and resampling all parameters from there appropriate distributions showed that CEA was the economically preferred treatment 54% of the time for asymptomatic patients and 57% of the time for symptomatic patients.

CAS: Carotid Angioplasty and Stenting; CEA: Carotid Endarterectomy; CREST: Carotid Revascularization Endarterectomy versus Stenting Trial; HR: Hazard Ratio; ICER: Incremental Cost Effectiveness Ratio defined to be the difference in cost divided by the difference in QALY. A generalized measure of cost per unit of improvement; MI: myocardial infarction; QALY: Quality Adjusted Life Years. A utility weighted measure of patients' duration and quality of life; QHES: Quality of Health Economics Score; QoL: Quality of Life; SAPPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy.

APPENDIX G. EVIDENCE TABLES FOR INCLUDED STUDIES FOR KEY QUESTION 4

Table G1. Cohort studies: Asymptomatic patients. Outcomes according to demographic characteristics (CAS versus medical therapy).

Study Study type CoE	Outcome	Subgroup	CAS aHR (95% CI)	Medical therapy aHR (95% CI)
		Ipsilateral stenosis (IS)		
Sherif 2005* Retrospective cohort study CoE III	25 months (median) (range, 6-72 months) Stroke	IS: 70-79% (n = 307)	aHR: 1.32 (0.43)	aHR: 1.0
		IS: 80-89% (n = 366)	aHR: 0.91 (0.33, 2.49)	aHR: 2.36 (1.02, 5.44)
		IS: 90-99% (n = 273)	aHR: 0.98 (0.27, 3.61)	aHR: 3.17 (1.15, 4.11)

aHR: adjusted hazard ratio (adjusted for factors that were disproportionate ($P < .20$) between CAS and medical therapy treatment groups, also adjusted for established risk factors for stroke)
*Raw data not reported.

Table G2. RCTs: Asymptomatic patients. Outcomes according to demographic characteristics.

Trial (Study) Study type CoE	Outcome	Subgroup*	CAS	CEA	RD (95% CI) (p-value)	Interaction p-value	RR (95% CI) (p-value)	Interaction p-value	HR (95% CI)	Interaction p-value
RCTs										
		Sex								
CREST (Howard 2011) RCT	Periprocedural Any stroke, death, or MI	Female	n = NR (9 events)	n = NR (7 events)	-	-	-	-	1.18 (0.44, 3.16) P=0.75	0.72
CoE II		Male	n = NR (12 events)	n = NR (14 events)	-		-		0.93 (0.43, 2.01) P=0.85	
	Periprocedural Any stroke	Female	n = NR (7 events)	n = NR (3 events)	-	-	-	-	2.11 (0.55, 8.15) P=0.28	0.82

Trial (Study) Study type CoE	Outcome	Subgroup*	CAS	CEA	RD (95% CI) (p-value)	Interaction p-value	RR (95% CI) (p-value)	Interaction p-value	HR (95% CI)	Interaction p-value
		Male	n = NR (8 events)	n = NR (5 events)	-		-		1.75 (0.57, 5.37) P=0.33	
	Periprocedural Any stroke or death	Female	n = NR (7 events)	n = NR (3 events)	-	-	-	-	2.11 (0.55, 8.15) P=0.28	0.82
		Male	n = NR (8 events)	n = NR (5 events)	-		-		1.75 (0.57, 5.37) P=0.33	
	Periprocedural MI	Female	n = NR (3 events)	n = NR (4 events)					0.67 (0.15, 3.01) P=0.60	0.74
		Male	n = NR (4 events)	n = NR (9 events)					0.48 (0.15, 1.56) P=0.22	
	4 year Ipsilateral stroke (including any stroke, death, or MI during the periprocedural period)	Female	n = NR (11 events)	n = NR (9 events)	-	-	-	-	1.08 (0.45, 2.62) P=0.86	0.83
		Male	n = NR (19 events)	n = NR (17 events)	-		-		1.24 (0.65, 2.39) P=0.52	
	4 year Ipsilateral stroke (including any stroke during the periprocedural period)	Female	n = NR (9 events)	n = NR (5 events)	-	-	-	-	1.59 (0.53, 4.75) P=0.40	0.71
		Male	n = NR (15 events)	n = NR (8 events)	-		-		2.16 (0.91, 5.10) P=0.08	
	4 year Any stroke or death (including any stroke or death during the periprocedural period)	Female	n = NR (9 events)	n = NR (5 events)	-	-	-	-	1.59 (0.53, 4.75) P=0.40	0.71
		Male	n = NR (15 events)	n = NR (8 events)	-		-		2.16 (0.91, 5.10) P=0.08	

Table G3. Cohort studies and registries: Asymptomatic patients. Outcomes according to demographic characteristics and carotid stenosis characteristics

Study Study type CoE	Outcome	Subgroup	CAS	CEA	RR (95% CI) (p-value)	Interaction p-value	Adjusted OR* (95% CI) (p-value)
		Age					
Jim 2012 Registry CoE III	30d Death	Age: < 65 years	1.4% (6/428)	0.8% (6/762)	1.78 (0.58, 5.49) P=0.32	(P = 0.71)	OR (adjusted): 0.445 (0.090, 2.192) *P* = .3194
		Age: ≥65 years	1.6% (23/1422)	0.7% (19/2656)	2.26 (1.24, 4.14) P=0.008		OR (adjusted): 0.546 (0.265, 1.124)
	30d Stroke	Age: < 65 years	2.3% (10/428)	1.3% (10/762)	1.78 (0.75, 4.24) P=0.19	(P = 0.89)	OR (adjusted): 0.695 (0.206, 2.339) *P* = .5567
		Age: ≥65 years	3.5% (49/1422)	1.8% (48/2656)	1.91 (1.29, 2.82) P=0.001		OR (adjusted): 0.474 (0.292, 0.767) *P* = .0024
	30d MI	Age: < 65 years	1.2% (5/428)	0.4% (3/762)	2.97 (0.71, 12.36) P=0.14	(P = 0.12)	OR (adjusted): 0.189 (0.035, 1.025) *P* = .0534
		Age: ≥65 years	1.1% (15/1422)	1.2% (32/2656)	0.88 (0.48, 1.61) P=0.67		OR (adjusted): 1.379 (0.629, 3.020) *P* = .4224

Study Study type CoE	Outcome	Subgroup	CAS	CEA	RR (95% CI) (p-value)	Interaction p-value	Adjusted OR* (95% CI) (p-value)
	30d Death, stroke, or MI	Age: < 65 years	4.4% (19/428)	2.1% (16/762)	2.11 (1.10, 4.07) P=0.02	(P = 0.44)	OR (adjusted): 0.501 (0.208, 1.208) *P* = .1236
		Age: ≥65 years	5.3% (75/1422)	3.3% (88/2656)	1.59 (1.18, 2.15) P=0.002		OR (adjusted): 0.649 (0.443, 0.953) *P* = .0273

*reported by the study; adjusted ORs calculated after adjusting for atherosclerosis, presence of coronary artery disease, recent MI, congestive heart failure, stroke, stenosis > 80% on ultrasound imaging, and use of antiplatelet agents.

Table G4. Administrative database studies: Asymptomatic patients. Outcomes according to demographic characteristics.

Study Study type	Outcome	Subgroup	CAS	CEA	RR (95% CI) (p-value)	Interaction p-value
		Age				
Khatri 2012* Admin	In-hospital Death	Age: < 70 years	0.7% (184/24063)	0.2% (529/180827)	2.61 (2.21, 3.09) P<0.0001	(P < 0.0001)
		Age: ≥70 years	0.5% (170/33563)	0.4% (1227/256878)	1.06 (0.90, 1.24) P=0.47	
	In-hospital Stroke	Age: < 70 years	1.3% 326/24063	1.0% (1846/180827)	1.33 (1.18, 1.49) P<0.0001	(P < 0.0001)
		Age: ≥70 years	1.9% (663/33563)	1.0% (2443/256878)	2.08 (1.91, 2.26) P<0.0001	
	In-hospital Cardiac complications	Age: < 70 years	1.9% (468/24063)	1.3% (2494/180827)	1.41 (1.28, 1.56) P<0.0001	(P < 0.0001)
		Age: ≥70 years	2.4% (835/33563)	2.2% (5774/256878)	3.57 (3.31, 3.86) P<0.0001	
	In-hospital Death, stroke, or cardiac complications	Age: < 70 years	3.7% (900/24063)	2.4% (4515/180827)	1.50 (1.40, 1.61) P<0.0001	(P = 0.005)
		Age: ≥70 years	4.5% (1513/33563)	3.4% (8768/256878)	1.32 (1.25, 1.39) P<0.0001	
McDonald 2011 Admin	In-hospital Intracerebral hemorrhage	Age: < 70 years	0.4% (21/5158)	0.1% (50/82683)	6.73 (4.05, 11.20) P<0.0001	(P = 0.89)
		Age: ≥70 years	0.5% (37/7475)	0.1% (86/122280)	7.04 (4.79, 10.34) P<0.0001	
	In-hospital Death	Age: < 70 years	0.4% (21/5158)	0.3% (248/82683)	1.36 (0.87, 2.12) P=0.18	(P = 0.56)
		Age: ≥70 years	0.7% (52/7475)	0.6% (734/122280)	1.16 (0.88, 1.53) P=0.30	
Young 2011 Admin	In-hospital Death, stroke, or cardiac complications	Age: ≤ 79 years	3.3% (809/24,521)	2.7% (4706/174,279)	1.22 (1.14, 1.31) P<0.0001	(P = 0.44)
		Age: ≥80 years	4.9% (327/6676)	3.8% (1676/44116)	1.29 (1.15, 1.45) P<0.0001	
		Sex				
Bisdas 2012† Admin	In-hospital Death	Female	0.8% (14/1773)	0.5% (114/24521)	1.70 (0.98, 2.95) P=0.06	(P = 0.93)
		Male	0.8% (14/1773)	0.5% (118/24521)	1.64 (0.94, 2.85) P=0.08	
	In-hospital	Female	2.1%	1.4%	1.55 (1.12, 2.17)	(P = 0.71)

Study Study type	Outcome	Subgroup	CAS	CEA	RR (95% CI) (p-value)	Interaction p-value
	Stroke		38/1773)	(338/24521)	P=0.009	
		Male	2.0% (35/1773)	1.2% (284/24521)	1.70 (1.20, 2.41) P=0.003	
	In-hospital Stroke or death	Female	2.7% (47/1773)	1.7% (405/24521)	1.60 (1.19, 2.16) P=0.002	(P = 0.69)
		Male	2.4% (43/1773)	1.7% (405/24521)	1.47 (1.08, 2.00) P=0.02	
	In-hospital Acute MI	Female	1.0% (17/1773)	0.5% (184/24251)	1.28 (0.78, 2.10) P=0.33	(P = 0.11)
		Male	0.3% (5/1773)	0.5% (124/24251)	0.56 (0.23, 1.36) P=0.20	
Rockman 2011 Admin	In-hospital Death	Female	0.7% (7/1037)	0.4% (77/20584)	1.80 (0.83, 3.90) P=0.13	(P = 0.23)
		Male	0.4% (7/1696)	0.4% (123/27713)	0.93 (0.43, 1.99) P=0.85	
	Postoperative Stroke	Female	2.1% (22/1037)	0.9% (183/20584)	2.39 (1.54, 3.70) P<0.0001	(P = 0.42)
		Male	1.8% (30/1696)	0.9% (261/27713)	1.88 (1.29, 2.73) P=0.001	

* 93% (CAS) and 96% (CEA) were asymptomatic.
†Asymptomatic patients propensity-matched by sex. CAS: out of 4763 asymptomatic patients (2939 males vs. 1824 females), 1773 males (60%) and 1773 (97%) females were matched. CEA: out of 58,971 asymptomatic patients (33,356 males vs. 25,615 females), 24,251 males (73%) and 24,251 (95%) females were matched.

Table G5. Cohort studies and registries: Asymptomatic patients. Outcomes according to surgical risk.

Study Study type CoE	Outcome	Subgroup	CAS	CEA	RR (95% CI) (p-value)	Interaction p-value
		CEA Risk Grade*				
(Ilhara 2006) Prospective cohort study CoE III	30d Stroke (non-disabling)	CEA Risk Grade I*	5% (1/21)	0% (0/26)	3.68 (0.16, 85.98) P=0.42	(P < 0.72)
		CEA Risk Grade II*	14% (1/7)	0% (0/4)	1.88 (0.09, 37.63) P=0.68	
		CEA Risk Grade III*	10% (3/31)	6% (1/17)	1.65 (0.19, 14.62) P=0.66	

* CEA Risk Grades: I, neurologically stable patients with no major medical or angiographically defined risks but with unilateral or bilateral ulcerative/stenotic CA disease; II, neurologically stable patients with no major medical risks but with significant angiographically defined risks; III, neurologically stable patients with no major medical risks and with or without significant angiographically defined risks.

Table G6. Administrative database studies: Asymptomatic patients. Outcomes according to surgical risk.

Study Study type	Outcome	Subgroup	CAS	CEA	RR (95% CI) (p-value)	Interaction p-value
		Surgical risk*				
Giles (2010) Admin	In-hospital Death	High surgical risk*	0.7% (~173/24809)†	0.6% (~1332/221943)†	1.16 (0.99, 1.36) P=0.06	(P < 0.0001)
		Low surgical risk*	0.9% (~218/24317)†	0.1% (~215/214952)†	8.96 (7.43, 10.82) P<0.0001	
	In-hospital Stroke	High surgical risk*	1.0% (~247/24809)†	0.7% (~1554/221943)†	1.42 (1.24, 1.63) P<0.0001	(P = 0.0005)
		Low surgical risk*	1.0% (~243/24317)†	0.5% (~1074/214952)†	2.00 (1.74, 2.30) P<0.0001	
	In-hospital Death or stroke	High surgical risk*	1.5% (~371/24809)†	1.2% (~2663/221943)†	1.25 (1.12, 1.39) P<0.0001	(P < 0.0001)
		Low surgical risk*	1.8% (~436/24317)†	0.6% (~1290/214952)†	2.99 (2.68, 3.33) P<0.0001	

* High surgical risk defined as CMS criteria: Age > 80, renal failure, severe lung disease, recent myocardial infarction, LV ejection fraction <30%, requirement for aortocoronary bypass or cardiac valve within 30 days, unstable angina, Class III, IV congestive heart failure.
† Only the percentages, rather than the actual patient numbers for symptomatic and asymptomatic high-risk CAS patients, symptomatic and asymptomatic non-high-risk CAS patients, symptomatic and asymptomatic high-risk CEA patients, and symptomatic and asymptomatic non-high-risk CEA patients were not reported. We calculated the patient numbers based on the assumption that that 50.5% of both symptomatic and asymptomatic CAS patients were high-risk (the study reported that 50.5% of CAS patients were high-risk), and that 50.8% of symptomatic and asymptomatic CEA patients were high-risk, (the study reported that 50.8% of CEA patients were high-risk). This was done as the reported percentages were consistent with this assumption. For example: 973 symptomatic CAS patients had stroke or death, which was reported to be 13.1% of all symptomatic CAS patients (7438 patients). The total of high risk plus non-high risk pts with stroke or death must be 973. The study reported that 14.4% of symptomatic high-risk CAS patients and 11.8% of symptomatic high-risk CAS patients had stroke or death. Because the average of these percentages, 14.4% and 11.8%, equals that of the total symptomatic CAS population (13.1%), we can assume that approximately half of the total symptomatic CAS population was high-risk and the other half was non-high-risk. We thus feel justified in making the assumption stated above, that 50.5% of both symptomatic and asymptomatic CAS patients were high-risk.

Table G7. RCTs: Asymptomatic patients. Outcomes according to surgical risk.

Trial (Study) Study type CoE	Outcome	Subgroup	CAS	CEA	RD (95% CI) (p-value)	RR (95% CI) (p-value)
		Surgical risk				
SAPPHIRE* (Yadav 2004) CoE II	30 days Death, Stroke, or MI	High risk	5.4% (6/117)	10.2% (12/120)	-0.05 (-0.12, 0.02) p=0.15	0.51 (0.20, 1.32) p=0.17
	1 year Ipsilateral stroke or death (including periprocedural death, stroke, or MI)	High risk	9.9% (12/117)	21.5% (26/120)	-0.11 (-0.21, -0.02) p=0.02	0.47 (0.25, 0.89) p=0.02
SAPPHIRE* (Grum 2008) CoE II	3 years Stroke	High risk	10.3% (12/117)	9.2% (11/120)	-0.02 (-0.09, 0.04) p=0.46	0.74 (0.34, 1.62) p=0.45
	3 years Ipsilateral stroke or death (including 30-day death, stroke, or MI).	High risk	21.4% (25/117)	29.2% (35/120)	-0.08 (-0.19, 0.03) p=0.17	0.73 (0.47, 1.14) p=0.17

***** SAPPHIRE enrolled only patients considered to be at high surgical risk.

Table G8. Cohort studies and registries: Symptomatic patients. Outcomes according to demographic characteristics.

Study Study type CoE	Outcome	Subgroup	CAS	CEA	RR (95% CI) (p-value)	Interaction p-value
		Age				
Jim 2012 Registry CoE III	30d Death	Age: < 65 years	0.9% (4/443)	0.7% (4/585)	1.32 (0.33,5.25) P=0.69	(P = 0.62)
		Age: ≥65 years	2.4% (27/1114)	1.3% (19/1513)	1.93 (1.08,3.45) P=0.03	
	30d Stroke	Age: < 65 years	4.6% (20/443)	4.8% (28/585)	0.94 (0.54, 1.65) P=0.84	(P = 0.06)
		Age: ≥65 years	6.7% (75/1114)	3.8% (57/1513)	0.94 (0.54, 1.65) P=0.001	
	30d MI	Age: < 65 years	0.7% (3/443)	0.2% (1/585)	3.96 (0.41, 37.96) 0.23	(P = 0.23)
		Age: ≥65 years	1.6% (18/1114)	1.7% (26/1513)	0.94 (0.52, 1.71) P=0.84	
	30d Death, stroke, or MI	Age: < 65 years	6.0% (26/443)	5.5% (32/585)	1.07 (0.65, 1.77) P=0.78	(P = 0.17)
		Age: ≥65 years	9.5% (106/1114)	6.0% (90/1513)	1.60 (1.22, 2.10) P=0.0007	

Table G9. Administrative database studies: Symptomatic patients. Outcomes according to demographic characteristics.

Study Study type	Outcome	Subgroup	CAS	CEA	RR (95% CI) (p-value)	Interaction p-value
		Age (years)				
McDonald 2011 Admin	In-hospital Intracerebral hemorrhage	Age: < 70	5.0% (39/788)	0.9% (38/4276)	5.57 (3.59, 8.65) P<0.0001	(P = 0.64)
		Age: ≥70	3.3% (15/463)	0.7% (40/5773)	4.68 (2.60, 8.40) P<0.0001	
	In-hospital Death	Age: < 70	5.8% (46/788)	2.3% (98/4276)	2.55 (1.81,3.59) P<0.0001	(P = 0.005)
		Age: ≥70	6.7% (31/463)	5.3% (306/5773)	1.26 (0.88,1.81) P=0.20	
		Sex				
Bisdas 2012* Admin	In-hospital Death	Female	4.3% (10/233)	0.7% (162/2184)	0.58 (0.31,1.08) P=0.09	(P = 0.0002)
		Male	3.9% (9/233)	1.1% (23/2184)	3.67 (1.72, 7.83) P<0.0001	
	In-hospital Stroke	Female	8.2% (19/233)	4.0% (88/2184)	2.02 (1.26, 3.26) P=0.004	(P < 0.0001)
		Male	5.6% (13/233)	3.6% (79/2184)	15.63 (8.22, 29.69) P=<0.0001	
	In-hospital Stroke or death	Female	10.7% (25/233)	4.4% (97/2184)	2.42 (1.59, 3.67) <0.0001	(P = 0.64)
		Male	8.6% (20/233)	4.1% (90/2184)	2.08 (1.31, 3.32) P=0.002	
	In-hospital Acute MI	Female	1.7% (4/233)	1.3% (38/2184)	0.99 (0.36, 2.74) P=0.98	(P = 0.15)
		Male	2.6% (6/233)	1.0% (21/2184)	2.68 (1.09, 6.57) P=0.03	
Rockman 2011 Admin	In-hospital Death	Female	3.7% (6/162)	2.1% (22/1037)	1.75 (0.72, 4.24) P=0.22	(P = 0.08)
		Male	8.2% (16/196)	2.7% (39/1449)	4.66 (2.50, 8.67) P<0.0001	
	Postoperative Stroke	Female	6.2% (10/162)	3.4% (35/1037)	2.56 (1.29, 5.06) P=0.007	(P = 0.62)
		Male	4.1% (8/196)	2.1% (30/1449)	1.97 (0.92, 4.24) P=0.08	

* Symptomatic patients propensity-matched by sex. CAS: out of 637 symptomatic patients (387 males vs. 250 females), 233 males (60%) and 233 (93%) females were matched. CEA: out of 5317 symptomatic patients (3089 males vs. 2228 females), 2184 males (70%) and 2184 (97%) females were matched.

Table G10. RCTs: Symptomatic patients. Outcomes according to demographic characteristics.

Trial (Study) Study type CoE	Outcome	Subgroup*	CAS	CEA	RD (95% CI) (p-value)	Interaction p-value	RR (95% CI) (p-value)	Interaction p-value	HR (95% CI)	Interaction p-value
RCTs										
		Age								
ICSS 2010 (Ederle 2010) RCT CoE I	120d Death, stroke, or MI	Age: < 70 years	n = NR (21 events)	n = NR (15 events)	NC	NC	NC	NC	1.46 (0.75, 2.84)	*P* = 0.62
		Age: ≥ 70 years	n = NR (51 events)	n = NR (29 events)	NC		NC		1.79 (1.14, 2.83)	
SPACE (Eckstein 08) RCT CoE II	2 yr (inc 30d) Ipsilateral stroke or death	Age: < 68 years	5.0% (14/293)	9.0% (25/284)	-0.04 (-0.08, 0.00) p=0.05	P=0.005	0.54 (0.29, 1.02) P=0.06	P=0.006	-	-
		Age: ≥ 68 years	13.7% (42/314)	8.6% (25/305)	0.05 (0.00, 0.10) p=0.04		1.63 (1.02, 2.61) P=0.04		-	-
EVA-3S 2006 (Mas 2008) RCT CoE II	4yr Ipsilateral stroke (inc. 30-d stroke or death)	Age: < 70 years (n = 233)	NR	NR	NC	NC	NC	NC	~1.10 (0.45, 2.70)†	*P* = .08
		Age: ≥ 70 years (n = 294)	NR	NR	NC		NC		~3.40 (1.40, 8.10)†	
		Sex								
ICSS 2010 (Ederle 2010) RCT CoE I	120d Death, stroke, or MI	Sex: Female	n = NR (20 events)	n = NR (19 events)	NC	NC	NC	NC	2.17 (1.35, 3.50)	*P* = .071
		Sex: Male	n = NR (52 events)	n = NR (25 events)	NC		NC		1.05 (0.56, 1.97)	
SPACE (Eckstein 08) RCT CoE II	2 yr (inc 30d) Ipsilateral stroke or death	Sex: Female	8.3% (14/171)	6.7% (11/167)	0.02 (-0.04, 0.07) p=0.57	P=0.73	1.24 (0.58, 2.66) p=0.58	P=0.69	-	-
		Sex: Male	9.9% (42/436)	9.6% (39/422)	0.0 (-0.04, 0.04) p=0.84		1.04 (0.69, 1.58) p=0.84		-	
EVA-3S 2006 (Mas 2008) RCT	4yr Ipsilateral stroke (inc. 30-d stroke or death)	Sex: Female (n = 130)	NR	NR	NC	NC	NC	NC	~0.65 (0.25, 2.10)†	*P* = .03

Trial (Study) Study type CoE	Outcome	Subgroup*	CAS	CEA	RD (95% CI) (p-value)	Interaction p-value	RR (95% CI) (p-value)	Interaction p-value	HR (95% CI)	Interaction p-value
CoE II		Sex: Male (n = 397)	NR	NR	NC		NC		~3.30 (1.50, 7.40)†	
CREST (Howard 2011) RCT CoE II	Periprocedural Any stroke, death, or MI	Female	n = NR (22 events)	n = NR (9 events)	-	-	-	-	2.33 (1.07, 5.07) P=0.033	0.04
		Male	n = NR (23 events)	n = NR (26 events)	-		-		0.88 (0.50, 1.55) P=0.66	
	Periprocedural Any stroke	Female	n = NR (18 events)	n = NR (6 events)	-	-	-	-	2.80 (1.11, 7.07) P=0.030	0.17
		Male	n = NR (19 events)	n = NR (15 events)	-		-		1.28 (0.65, 2.52) P=0.47	
	Periprocedural MI	Female	n = NR (4 events)	n = NR (3 events)	-	-	-	-	1.26 (0.28, 5.63) P=0.76	0.11
		Male	n = NR (3 events)	n = NR (12 events)	-		-		0.25 (0.07, 0.88) P=0.030	
	4 year Ipsilateral stroke (including any stroke, death, or MI during the periprocedural period)	Female	n = NR (26 events)	n = NR (17 events)	-	-	-	-	1.49 (0.81, 2.74) P=0.20	0.19
		Male	n = NR (29 events)	n = NR (33 events)	-		-		0.87 (0.53, 1.44) P=0.59	
	4 year Ipsilateral stroke (including any stroke during the periprocedural period)	Female	n = NR (23 events)	n = NR (14 events)	-	-	-	-	1.58 (0.81, 3.08) P=0.18	0.41
		Male	n = NR (25 events)	n = NR (23 events)	-		-		1.10 (0.62, 1.94) P=0.74	
	4 year Any stroke or death (including any stroke or	Female	n = NR (23 events)	n = NR (14 events)	-	-	-	-	1.58 (0.81, 3.08) P=0.18	0.56

Trial (Study) Study type CoE	Outcome	Subgroup*	CAS	CEA	RD (95% CI) (p-value)	Interaction p-value	RR (95% CI) (p-value)	Interaction p-value	HR (95% CI)	Interaction p-value
	death during the periprocedural period)									
		Male	n = NR (28 events)	n = NR (23 events)	-		-		1.23 (0.71, 2.14) P=0.46	
		Diabetes?								
ICSS 2010 (Ederle 2010) RCT CoE I	120d Death, stroke, or MI	Diabetes*: Yes	n = NR (19 events)	n = NR (12 events)	NC	NC	NC	NC	1.67 (0.81, 3.43)	*P* = .97
		Diabetes*: No	n = NR (51 events)	n = NR (32 events)	NC		NC		1.64 (1.05, 2.55)	
EVA-3S 2006 (Mas 2008) RCT CoE II	4yr Ipsilateral stroke (inc. 30-d stroke or death)	Diabetes: No (n = 401)	NR	NR	NC	NC	NC	NC	~1.20 (0.30, 3.75)†	*P* = .27
		Diabetes: Yes (n = 126)	NR	NR	NC		NC		~2.60 (1.20, 5.60)†	
		Hypertension?								
ICSS 2010 (Ederle 2010) CoE I	120d Death, stroke, or MI	Treated hypertension*: Yes	n = NR (45 events)	n = NR (36 events)	NC	NC	NC	NC	1.29 (0.83, 2.00)	*P* = .039
		Treated hypertension*: No	n = NR (25 events)	n = NR (8 events)	NC		NC		3.25 (1.46, 7.20)	
EVA-3S 2006 (Mas 2008) CoE II	4yr Ipsilateral stroke (inc. 30-d stroke or death)	Hypertension: Yes (n = 383)	NR	NR	NC	NC	NC	NC	~1.80 (0.85, 3.65)†	*P* = .62
		Hypertension: No (n = 144)	NR	NR	NC	NC	NC	NC	~2.90 (0.75, ≥8)†	
		Smoker?								
EVA-3S 2006 (Mas 2008) CoE II	4yr Ipsilateral stroke (inc. 30-d stroke or death)	Smoker: Yes (n = 126)	NR	NR	NC	NC	NC	NC	~1.75 (0.5, 6.1)†	*P* = .81
		Smoker: No (n = 401)	NR	NR	NC	NC	NC	NC	~2.10 (1.00, 4.40)†	
		Qualifying event (QE):								

Trial (Study) Study type CoE	Outcome	Subgroup*	CAS	CEA	RD (95% CI) (p-value)	Interaction p-value	RR (95% CI) (p-value)	Interaction p-value	HR (95% CI)	Interaction p-value
CREST (Hill) RCT CoE II	30d Stroke (any)	QE: Stroke	6.2% (16/257)	1.9% (5/262)	0.04 (0.01, 0.08) *P* = 0.01	*P* = 0.46	3.26 (1.21, 8.77) *P* = 0.02	*P* = 0.53	-	-
		QE: TIA	6.0% (15/252)	2.8% (7/250)	0.03 (-0.00, 0.07) *P* = 0.08		2.13 (0.88, 5.12) *P* = 0.09		-	-
		QE: AF/ Ocular	3% (3/87)	3.0% (3/100)	0.00 (-0.05, 0.06) *P* = 0.86		1.15 (0.24, 5.55) *P* = 0.86		-	-
SPACE (Stingele 08) RCT CoE II	30d Ipsilateral stroke or death	QE*: Stroke	7.0% (19/270)	8.3% (21/252)	-0.01 (-0.06, 0.03) *P* = 0.58	*P* = 0.48	0.84 (0.47, 1.53) *P* = 0.58	*P* = 0.55	-	-
		QE*: TIA	8.3% (15/180)	6.6% (12/183)	0.02 (-0.04, 0.07) *P* = 0.52		1.27 (0.61, 2.64) *P* = 0.52		-	-
		QE*: AF/ Ocular	3% (3/95)	4% (4/90)	-0.01 (-0.07, 0.04) *P* = 0.65		0.71 (0.16, 3.09) *P* = 0.65		-	-
		QE*: Multiple events	9% (4/47)	2% (1/56)	0.07 (-0.02, 0.15) *P* = 0.13		4.77 (0.55, 41.19) *P* = 0.16		-	-
		QE*: Other	7% (1/15)	0% (0/8)	0.07 (-0.14, 0.27) *P* = 0.53		1.69 (0.08, 37.26) *P* = 0.74		-	-
SPACE (Eckstein 08) RCT CoE II	2 yr (inc 30d) Ipsilateral stroke or death	QE*: Stroke	8.7% (23/270)	11.0% (27/252)	0.04 (-0.02, 0.09) *P* = 0.17	*P* = 0.13	1.56 (0.84, 2.93) *P* = 0.16	*P* = 0.25	-	-
		QE*: TIA	9.6% (19/180)	10.8% (17/183)	0.01 (-0.05, 0.07) *P* = 0.69		1.14 (0.61, 2.11) *P* = 0.69		-	-
		QE*: AF/ Ocular OR other	5.5% (6/110)	5% (5/98)	0.00 (-0.06, 0.06) *P* = 0.91		1.07 (0.34, 3.39) *P* = 0.91		-	-
		QE*: Multiple events	19% (8/47)	2% (1/56)	0.15 (0.04, 0.27) *P* = 0.008		9.53 (1.24, 73.48) *P* = 0.03		-	-
EVA-3S 2006 (Mas 2008) RCT	4yr Ipsilateral stroke (inc. 30-d stroke or death)	QE: Stroke (n = 269)	NR	NR	NC	NC	NC	NC	~3.00 (1.60, 6.80)†	*P* = .16
CoE II		QE: TIA (n = 176)	NR	NR	NC	NC	NC	NC	~1.50 (0.45, 5.15)†	*P* = .52

Trial (Study) Study type CoE	Outcome	Subgroup*	CAS	CEA	RD (95% CI) (p-value)	Interaction p-value	RR (95% CI) (p-value)	Interaction p-value	HR (95% CI)	Interaction p-value
		QE: Ocular (n = 82)	NR	NR	NC	NC	NC	NC	~2.00 (0.10, 4.30)†	
		Ipsilateral stenosis (IS)								
ICSS 2010 (Ederle 2010) RCT CoE I	120d Death, stroke, or MI	IS*: 50-69%	n = NR (4 events)	n = NR (3 events)	NC	NC	NC	NC	1.13 (0.25, 5.04)	*P* = .584
		IS*: 70-99%	n = NR (68 events)	n = NR (41 events)	NC		NC		1.75 (1.19, 2.58)	
SPACE (Eckstein 08) RCT CoE II	2 yr (inc 30d) Ipsilateral stroke or death	IS*: < 70%	8.2% (18/225)	6.3% (14/230)	0.02 (-0.03, 0.07) p=0.43	P=0.54	1.31 (0.67, 2.58) p=0.43	P=0.49	-	-
		IS*: 70-99%	10.2% (38/382)	10.3% (36/359)	-0.00 (-0.04, 0.04) p=0.96		0.99 (0.64, 1.52) p=0.96		-	
EVA-3S 2006 (Mas 2008) CoE II	4yr Ipsilateral stroke (inc. 30-d stroke or death)	IS: < 90% (n = 315)	NR	NR	NC	NC	NC	NC	~2.30 (1.00, 5.40)†	*P* = .61
		IS: ≥ 90% (n = 212)	NR	NR	NC		NC		~1.65 (0.60, 4.30)†	
		Contralateral stenosis (CS)								
ICSS 2010 (Ederle 2010) RCT CoE I	120d Death, stroke, or MI	CS*: 0-49%	n = NR (45/565)	n = NR (27/561)	NC	NC	NC	NC	1.70 (1.05, 2.73)	*P* = .741
		CS*: 50-69%	n = NR (14/128)	n = NR (8/142)	NC		NC		2.04 (0.85, 4.85)	
		CS*: 70-99%	n = NR (9/105)	n = NR (7/110)	NC		NC		1.37 (0.51, 3.68)	
		CS*: 100%	n = NR (2/49)	n = NR (1/37)	NC		NC		1.51 (0.14, 16.61)	
SPACE (Stingele 08) RCT CoE II	30d Ipsilateral stroke or death	CS*: < 70%	7.1% (40/567)	5.9% (32/543)	0.01 (-0.02, 0.04) *P* = 0.43	*P* = 0.14	1.20 (0.76, 1.88) *P* = 0.43	*P* = 0.16	-	-
		CS*: 70-99%	5% (2/40)	13% (6/46)	-0.08 (-0.20, 0.04) *P* = 0.18		0.38 (0.08, 1.79) *P* = 0.22		-	-
SPACE	2 yr (inc 30d)	CS*: < 70%	9.4%	16.2%	-0.07 (-0.12, -0.02)		0.57 (0.39, 0.83)		-	-

Trial (Study) Study type CoE	Outcome	Subgroup*	CAS	CEA	RD (95% CI) (p-value)	Interaction p-value	RR (95% CI) (p-value)	Interaction p-value	HR (95% CI)	Interaction p-value
(Eckstein 08) RCT CoE II	Ipsilateral stroke or death		(52/567)	(41/253)	*P* = 0.007		*P* = 0.003			
		CS*: 70-99%	9% (2/22)	22% (6/27)	-0.13 (-0.33, 0.07) *P* = 0.19	*P* = 0.82	0.41 (0.09, 1.83) *P* = 0.24	*P* = 0.89	-	-
		CS*: 100%	11% (2/18)	16% (3/19)	-0.05 (-0.27, 0.17) *P* = 0.68		0.70 (0.13, 3.73) *P* = 0.68		-	-
EVA-3S 2006 (Mas 2008) CoE II	4yr Ipsilateral stroke (inc. 30-d stroke or death)	CS: < 70% (n = 458)	NR	NR	NC	NC	NC	NC	~2.20 (1.10, 4.30)†	*P* = .65
		CS: 70-100% (n = 69)	NR	NR	NC		NC		~1.45 (0.30, 6.50)†	
Time to treatment		**Time to treatment (TT)**								
ICSS 2010 (Ederle 2010) CoE I	120d Death, stroke, or MI	TT*: < 14 days	n = NR (15 events)	n = NR (5 events)	NC	NC	NC	NC	2.21 (0.82, 5.95)	*P* = .68
		TT*: ≥ 14 days	n = NR (46 events)	n = NR (28 events)	NC		NC		1.76 (1.12, 2.78)	
EVA-3S 2006 (Mas 2008) CoE II	4yr Ipsilateral stroke (inc. 30-d stroke or death)	TT: < 14 days (n = 94)	NR	NR	NC	NC	NC	NC	~6.75 (0.80, ≥8)†	*P* = .40
		TT: ≥ 14 days (n = 426)	NR	NR	NC		NC		~1.70 (0.80, 3.45)†	

AF: Amaurosis Fugax; CS: contralateral stenosis; HR: hazard ratio (reported here only if that is the only data reported in the study); IS: ipsilateral stenosis; NC: not calculable; NR: not reported; RD: risk difference; RR: relative risk; TIA: transient ischemic attack; TT: time to treatment

* indicates that a given sstudy prespecified this subgroup analysis

† Hazard ratios approximated from a forest plot; hazard ratios < 1 favor CAS, hazard ratios > 1 favor CEA.

Table G11. RCTs: Symptomatic patients. Outcomes according to surgical risk.

Trial (Study) Study type CoE	Outcome	Subgroup	CAS	CEA	RD (95% CI) (p-value)	RR (95% CI) (p-value)
		Surgical risk				
SAPPHIRE* (Yadav 2004) CoE II	30 days Death, Stroke, or MI	High risk	2.1% (1/50)	9.3% (4/46)	-0.07 (-0.16, 0.02) p=0.15	0.23 (0.03, 1.98) p=0.18
	1 year Ipsilateral stroke or death (including periprocedural death, stroke, or MI)	High risk	16.8% (8/50)	16.5% (8/46)	-0.01 (-0.16, 0.14) p=0.86	0.92 (0.38, 2.25) p=0.86
SAPPHIRE* (Grum 2008) CoE II	3 years Stroke	High risk	6% (3/50)	9% (4/46)	-0.03 (-0.13, 0.08) p=0.61	0.69 (0.16, 2.92) p=0.61
	3 years Ipsilateral stroke or death (including 30-day death, stroke, or MI).	High risk	32% (16/50)	22% (10/46)	0.10 (-0.07, 0.28) p=0.25	1.47 (0.74, 2.91) p=0.27

***** SAPPHIRE enrolled only patients considered to be at high surgical risk.

Table G12. Cohort studies and registries: Symptomatic patients. Outcomes according to surgical risk.

Study Study type CoE	Outcome	Subgroup	CAS	CEA	RR (95% CI) (p-value)	Interaction p-value
		CEA Risk Grade*				
(IIhara 2006) Prospective cohort study CoE III	30d Ischemic neurological complications	CEA Risk Grade I*	0% (0/11)	0% (0/37)	Not Estimable	Not Estimable
		CEA Risk Grade II*	0% (0/3)	0% (0/11)	Not Estimable	
		CEA Risk Grade III*	13% (2/16)	4% (1/25)	3.43 (0.28, 41.32) P=0.33	

* CEA Risk Grades: I, neurologically stable patients with no major medical or angiographically defined risks but with unilateral or bilateral ulcerative/stenotic CA disease; II, neurologically stable patients with no major medical risks but with significant angiographically defined risks; III, neurologically stable patients with no major medical risks and with or without significant angiographically defined risks.

Table G13. Administrative database studies: Symptomatic patients. Outcomes according to surgical risk.

Study Study type	Outcome	Subgroup	CAS	CEA	RR (95% CI) (p-value)	Interaction p-value
		Surgical risk*				
Giles 2010 Admin	In-hospital Death	High surgical risk*	6.8% (~254/3756)†	2.5% (~577/23113)†	2.71 (2.35, 3.13) P<0.0001	(P < 0.0001)
		Low surgical risk*	5.3% (~194/3682)†	1.0% (~224/22386)†	5.27 (4.36, 6.36) P<0.0001	
	In-hospital Stroke	High surgical risk*	8.8% (~328/3756)†	5.0% (~1156/23113)†	1.75 (1.55, 1.96) P<0.0001	(P = 0.84)
		Low surgical risk*	7.5% (~275/3682)†	4.2% (~940/22386)†	1.78 (1.56, 2.03) P<0.0001	
	In-hospital Death or stroke	High surgical risk*	14.4% (~540/3756)†	6.9% (~1595/23113)†	2.08 (1.90, 2.28) P<0.0001	(P = 0.05)
		Low surgical risk*	11.8% (~433/3682)†	4.9% (~1097/22386)†	2.40 (2.16, 2.67) P<0.0001	

* High surgical risk defined as CMS criteria: Age > 80, renal failure, severe lung disease, recent myocardial infarction, LV ejection fraction <30%, requirement for aortocoronary bypass or cardiac valve within 30 days, unstable angina, Class III, IV congestive heart failure.

† Only the percentages, rather than the actual patient numbers for symptomatic and asymptomatic high-risk CAS patients, symptomatic and asymptomatic non-high-risk CAS patients, symptomatic and asymptomatic high-risk CEA patients, and symptomatic and asymptomatic non-high-risk CEA patients were not reported. We calculated the patient numbers based on the assumption that that 50.5% of both symptomatic and asymptomatic CAS patients were high-risk (the study reported that 50.5% of CAS patients were high-risk), and that 50.8% of symptomatic and asymptomatic CEA patients were high-risk, (the study reported that 50.8% of CEA patients were high-risk). This was done as the reported percentages were consistent with this assumption. For example: 973 symptomatic CAS patients had stroke or death, which was reported to be 13.1% of all symptomatic CAS patients (7438 patients). The total of high risk plus non-high risk pts with stroke or death must be 973. The study reported that 14.4% of symptomatic high-risk CAS patients and 11.8% of symptomatic high-risk CAS patients had stroke or death. Because the average of these percentages, 14.4% and 11.8%, equals that of the total symptomatic CAS population (13.1%), we can assume that approximately half of the total symptomatic CAS population was high-risk and the other half was non-high-risk. We thus feel justified in making the assumption stated above, that 50.5% of both symptomatic and asymptomatic CAS patients were high-risk.

APPENDIX H. ASSESSMENT AND OUTCOMES MEASURES USED IN COMPARATIVE STUDIES

Structured Instruments:

Studies that reported functional and activity scores from disease specific clinician-based or patient-reported outcomes, generic quality of life and pain are described below, Table 1.

- One patient-reported disease specific outcomes measures was used, TIA Stroke Questionnaire. The TIA Stroke Questionnaire assesses the patient's history of stroke and TIA and any sudden onset of any various focal neurologic symptoms
- Fifteen different clinician based outcomes, the National Institutes of Health Stroke Scale (NIHSS), the Barthel Index, the modified Rankin Scale (mRS), and the Oxfordshire Handicap Scale (OHS), Oxfordshire Handicap Scale (OHS), Mini-Mental State Examination (MMSE), Rey's auditory verbal learning test (RAVLT), Babcock Story Recall (SR), Category Naming Test (CNT), Trail-Making Test (TMT), Copy Drawing (CD), Processing Speed Index (PSI), Boston Naming Test (BNT), Working Memory Index (WMI), Hopkins Verbal Learning Test (HVLT-revised), Basic activities of daily living (ADL), Instrumental activities of daily living (IADL) were used. The mRS and NIHSS were most frequently used. All fifteen scales combined a component of patient symptoms with physician assessment.
- Two quality of life measures were used: the SF-36 outcomes and GDS measures. The SF-36 include 8 subscales that assess physical function, role limitations due to physical health problems, pain, general health, vitality, limitations due to emotional problems, and mental health. One study specified the physical functioning component of the SF-36. The GDS included 3 subscales assessing distractibility, vigilance, and delay.
- One pain measure was assessed by two studies although it is unclear if a visual analog scale or numeric rating scale was used.
- The Barthel Index established MCID (1.85) in stroke patients in one study [1]
- Five studies established validity/reliability in stroke patients for the NIHSS [2-6]
- Nine studies established validity/reliability in stroke patients for the Barthel Index [7-15]
- Four studies established validity/reliability in stroke patients for the mRS [16-19]
- Two studies established validity/reliability in stroke patients for the SF-36, and one for the physical component [20-22]
- Four studies established validity/reliability in stroke patients for the MMSE [23-26]
- One study established validity/reliability in stroke patients for the IADL [27]

ADL: Activities of daily living; BNT: Boston Naming Test; CD: Copy Drawing Test; CNT: Category Naming Test; GDS: Geriatric Depression Scale; HVLT: Hopkins Verbal Learning Test; IADL: Instrumental activities of daily living; MCID: Minimal clinically important difference; MMSE: Mini-Mental State Examination; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; OHS: Oxfordshire Handicap Scale; PSI: Processing Speed Index; RAVLT: Rey's Auditory Verbal Learning Test; SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey; SR: Babcock's Story Recall; TIA: Transient Ischemic Attack; TMT: Trail-Making Test; WMI: Working Memory Index.

Table H1. Summary of outcomes measures in stenting for treatment of atherosclerotic stenosis

Outcome measure	Study (year)	Clinician or patient reported	Instrument type	Components	Score range	Interpretation	Validity and reliability	MCID
Randomized controlled trials								
National Institutes of Health Stroke Scale (NIHSS)	Brooks (2001) Brott (2010) Eckstein (2008) Ringleb (2006)	CBO	Disease specific	11 subscales (13 items): • Level of consciousness • Horizontal eye movement • Visual field test • Facial palsy • Motor arm • Motor leg • Limb ataxia • Sensory • Language • Dysarthria • Extinction and inattention	0-42	0 = No stroke symptoms 1-4 = Minor stroke 5-15 = Moderate stroke 16-20 = Moderate to severe stroke 21-42 = Severe stroke	5 studies [2-6] Intraclass correlation coefficient .93 and .95[3]	NR
Barthel Index	Brooks (2001) Brooks (2004)	CBO	Disease specific	5 subscales (10 items): • Self-care • Walking • Transfers • Controlling bowels and bladder • Feeding	0-100	Lower score = greater disability	9 studies [7-15] Reliability coefficient .4±.2[10] Validity rho .89 (week 1) .95 (week 3) and .98 (week 6)[11] Spearman correlation coefficient median .96[12] Overall reliability kappa = .46[13] Internal consistency reliability coefficient .9[15]	1.85 in stroke patients
Pain Scale	Brooks (2001) Brooks (2004)	PRO	Pain	1 subscale (1 item): • Pain	0-10	Higher score = greater pain	NR	NR
Modified Rankin Scale (mRS)	Brooks (2001) Brott (2010) CAVATAS (2001) Eckstein (2008)	CBO	Disease specific	1 subscale (1 item): • Degree of disability or dependence in daily activities	0-6	0 = No symptoms 1 = No significant disability 2 = Slight disability	4 studies [16-19] Intraclass correlation coefficient .947 (neurologists) and .963	NR

Outcome measure	Study (year)	Clinician or patient reported	Instrument type	Components	Score range	Interpretation	Validity and reliability	MCID
	Ederle (2010) Mas (2006) Mas (2008) Ringleb (2006)					3 = Moderate disability 4 = Moderately severe disability 5 = Severe disability 6 = Dead	(nurses/physiotherapists)[16] Unweighted kappa .44, weighted kappa .78[17] Unweighted kappa .25, weighted kappa .71[18] Intraclass correlation coefficient .675[19]	
Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)	Brott (2010)	PRO	General health	8 subscales (36 items): • Physical functioning • Bodily pain • Physical role limitations • General health • Vitality • Social functioning • Emotional role limitations • Mental health	0-100	Lower score = greater disability	2 studies [20, 22] Cronbach's alpha >.7[20] Intraclass correlation coefficient .28[22]	NR
Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) Physical component	Brott (2010)	PRO	Physical health	• None	0-100	Lower score = greater disability	1 study [21]	NR
Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) Mental component	Brott (2010)	PRO	Mental health	• None	0-100	Lower score = greater disability	NR	NR
Transient Ischemic Attack (TIA) Stroke Questionnaire	Brott (2010)	PRO	Disease specific	3 subscales (8 items): • History of TIA • History of stroke • Sudden onset of any various focal neurologic symptoms consistent	NA	NA	NR	NR

Outcome measure	Study (year)	Clinician or patient reported	Instrument type	Components	Score range	Interpretation	Validity and reliability	MCID
				with TIA or stroke				
Oxfordshire Handicap Scale (OHS)	Naylor (1998)	CBO	Disease specific	1 subscale • Post-operative stroke	0-6	Lower score = less disability	NR	NR
Nonrandomized controlled trials								
Mini-Mental State Examination (MMSE)	Capoccia (2012), Feliziani (2010)	CBO	Cognitive	7 subscales • Temporal orientation index • Physical orientation index • Total orientation index • Language index • Memory index • Attention/Concentration (working memory index • Motor index	30	Lower score = greater disability	4 studies [23-26] Kappa = .57, intraclass correlation coefficient = .57[24]	NR
Rey's auditory verbal learning test (RAVLT)	Feliziani (2010)	CBO	Cognitive	2 subscales • Immediate recall (Rey-IR) • Delayed recall (Rey-DR	0-45	Lower score = greater disability	NR	NR
Babcock Story Recall (SR)	Feliziani (2010)	CBO	Cognitive	2 subscales • Immediate recall • Delayed recall	16	Lower score = greater disability	NR	NR
Category Naming Test (CNT)	Feliziani (2010)	CBO	Cognitive	None	0-20	Lower score = greater disability	NR	NR
Trail-Making Test (TMT)	Feliziani (2010), Lal (2011)	CBO	Cognitive	2 subscales • Part A (TMT-A; numbers) • Part B (TMT-B; numbers and letters)	NA (score is time to completion)	Lower score = less disability	NR	NR
Copy Drawing (CD)	Feliziani (2010)	CBO	Cognitive	4 subscales • Speed and accuracy • Incidental learning • Visual-motor dexterity • Non-verbal short-term memory	0-1	Lower score = greater disability	NR	NR

Outcome measure	Study (year)	Clinician or patient reported	Instrument type	Components	Score range	Interpretation	Validity and reliability	MCID
Processing Speed Index (PSI)	Lal (2011)	CBO	Cognitive	None	NA	Lower score = greater disability	NR	NR
Boston Naming Test (BNT)	Lal (2011)	CBO	Cognitive	None	0-60	Lower score = greater disability	NR	NR
Working Memory Index (WMI)	Lal (2011)	CBO	Cognitive	None	NA	Lower score = greater disability	NR	NR
Hopkins Verbal Learning Test (HVLT-revised)	Lal (2011)	CBO	Cognitive	6 subscales • Delayed recall • Delayed recognition • Learning • Retention • Discrimination index • Recognition bias	0-36	Lower score = greater disability	NR	NR
Geriatric Depression Scale (GDS)	Feliziani (2010)	PRO	QoL and Function	3 subscales • Distractability • Vigilance • Delay	0-30	Lower score = less disability	NR	NR
Basic activities of daily living (ADL)	Feliziani (2010)	CBO	QoL and Function	None	0-6	Lower score = greater disability	NR	NR
Instrumental activities of daily living (IADL)	Feliziani (2010)	CBO	QoL and Function	None	0-8	Lower score = greater disability	1 study [27] Validity rho = .6[27]	NR

CBO: clinician-based outcome; MCID: Minimal clinically important difference; NA: not applicable; NR: not reported; PRO: patient-reported outcome; QoL: quality of life; TIA: transient ischemic attack.

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Table H2. Definitions for primary outcomes reported in included RCTs

	ICSS 2010	EVA-3S (Mas 2006)	EVA-3S (Mas 2008)	BACASS	CREST	REGENSBURG	SPACE	LEICESTER (Naylor)	Kentucky (Brooks 2001)
Periprocedural:									
	Within 30 days of treatment	Within 30 days of treatment	Within 30 days of treatment	Within 30 days of treatment (implied but not explicitly stated)	Within 30 days of treatment	NA	Within 30 days of randomization	Within 30 days of treatment	Within 30 days of treatment
Stroke:									
	Acute disturbance of focal neurological function with symptoms lasting more than 24 h resulting from intracranial vascular disturbance; it must be established whether the cause is infarction or haemorrhage (primary intracranial or subarachnoid); visual loss resulting from embolic or haemodynamic retinal ischaemia lasting more than 24 h will be included within the category of stroke	Not defined (need access to protocol (ref 11 on 2006)	Not defined (need access to protocol (ref 11 on 2006)	Not defined	Acute neurological event lasting ≥ 24 hours with focal symptoms and signs	Neurologic symptoms > 24 hours	Ischaemic stroke or intracerebral bleeding or both, with symptoms lasting > 24 hours	New neurologic deficit persisting for > 24 hours	Not defined
Disabling stroke:									
	Increase in Rankin score to 3 or more, attributable to the event at 30 days after onset.	Modified Rankin score of 3 or more for ≥ 30 days post treatment	Modified Rankin score of 3 or more for ≥ 30 days post treatment, with an increase of ≥ 2 from baseline				Disabling ipsilateral stroke: modified Rankin score ≥3, or death from any cause	Score of 3-6 on Oxfordshire Handicap Stroke score	
Myocardial infarction (MI):									
	Presence of two or more of the following (specific cardiac enzymes >2x ULN, history of chest discomfort of ≥30 min, development of specific abnormalities (eg. Q waves) on standard 12-lead ECG).	Presence of two or more of the following (serum creatine kinase, creatine kinase MB, or troponin >2x ULN, history of chest discomfort of ≥20 min, development of new Q wave on ≥ 2 adjacent	Presence of two or more of the following (serum creatine kinase, creatine kinase MB, or troponin >2x ULN, history of chest discomfort of ≥20 min, development of new Q wave on ≥ 2 adjacent	Not defined	Elevation of cardiac markers (CK-MB or troponin) to a value ≥ 2x ULN AND any one of the following: chest pain or equivalent symptoms consistent with MI; ECG	Not defined			Not defined

	ICSS 2010	EVA-3S (Mas 2006)	EVA-3S (Mas 2008)	BACASS	CREST	REGENSBURG	SPACE	LEICESTER (Naylor)	Kentucky (Brooks 2001)
		derivations or predominant R waves in V1).	derivations or predominant R waves in V1).		evidence of ischemia (new ST segment depression or elevation > 1mm in 2 or more contiguous leads)				
Transient ischemic attack (TIA):									
	An acute disturbance of focal neurological function with symptoms lasting less than 24 h attributed to cerebrovascular disease	Not defined		Focal ischaemic neurological deficit of abrupt onset resolving completely within 24 hours		Not defined			Not defined
Hematoma									
	Bleeding attributed to the treatment of carotid narrowing requiring new surgery, transfusion or prolonging hospital stay			Not defined					
Cranial nerve injuries									
	Evaluated using the modified Rankin scale; weakness or sensory impairment in the distribution of one of the cranial nerves attributed to treatment	Not defined (need access to protocol (ref 11 on 2006)	Not defined (need access to protocol (ref 11 on 2006)	Not defined	Not defined (even checked protocol/design paper)			Not defined	Cervical nerve injury: manifested as diminished sensation in the mandible or neck.

APPENDIX I. FDA APPROVED STENTS, ACCREDITATION

ACCREDITATION
Details of Private Organization that Provide Carotid Stenting Facility Accreditation

Intersocietal Commission for the Accreditation of Carotid Stenting Facilities (ICACSF) SVS Registry	http://www.intersocietal.org/carotid/ **Sponsoring Organizations** • American Academy of Neurology (AAN) • American Association of Neurological Surgeons/Congress of Neurological Surgeons Cerebrovascular Section (AANS/CNS) • American Association of Physicists in Medicine (AAPM) • American Society of Neuroradiology (ASNR) • Neurocritical Care Society (NCS) • Society for Vascular Medicine (SVM) • Society for Vascular Surgery (SVS) • Society of Interventional Radiology (SIR) • Society of NeuroInterventional Surgery (SNIS) • Society of Vascular and Interventional Neurology (SVIN) **Brief Overview of Standards** • *Eligible applicants*: "Facilities that perform extracranial carotid stenting." • *Facility standards***:** Various specific requirements for examination areas, interpretation areas, equipment and instrumentation; must have at least one designated fluoroscopy system; must implement a Quality Improvement program for maintenance of equipment and instrumentation • *Personnel standards:* Various specific requirements for the Physicians, Medical Director, Medical Staff, Interventional Technologist Technical/Administrative Director, Interventional Nurse Technical/Administrative Director, Technical Staff (Interventional Technologists and Nurses), Neurological Assessment Examiners, Ancillary Personnel, and Medical Physicist. • *Physician training*: "Must meet one of the published national society training standards pertaining to cervical/extracranial carotid angioplasty and stenting and be credentialed by the health care facility to perform cervical/extracranial carotid angioplasty and stenting." [Connors 2004, Rosenfield 2005, Qureshi 2008] • *Physician criteria*: "Must be privileged by clear and concise requirements as outlined by their hospital privileging committee that include periodic review and documentation of credentialed staff." (other criteria not specified) • *Case volume*: "At least 25 carotid stent procedures over the preceding three-year period" OR "At least one operator must have performed 15 carotid stent cases (either in training or during post training experience as the primary operator) preferably with an embolic protection device in the past three years with adequate outcomes." • *Quality assurance*: "<6% all stroke and death within 30 days of the procedure" for symptomatic and "<3% all stroke and death within 30 days of the procedure" for asymptomatic patients. Other complication threshold N/A. • *Renewal*: Every 3 years. **Accredited Facilities** • Avera Heart Hospital of South Dakota (Sioux Falls, SD) • Forsyth Medical Center (Winston-Salem, NC) • Iowa Methodist Medical Center (Des Moines, IA)

	• Northwestern Memorial Hospital (Chicago, IL) • William Beaumont Hospital (Royal Oak, MI)
Accreditation for Cardiovascular Excellence (ACE) ACC Registry	http://www.cvexcel.org/cas.aspx **Sponsoring Organizations** • Society for Cardiovascular Angiography and Interventions (SCAI) • American College of Cardiology (ACC) **Brief Overview of Standards** • *Eligible applicants*: "Any facility where cardiologists, radiologists, vascular surgeons, and others practice." • *Facility standards*: "Each hospital department or section performing CAS must document that they have the resources [and equipment] to perform the procedure in a safe manner." (Various specifics outlined) • *Personnel standards*: Each department must have a licenced, ABMS board-certified physician as a Medical Director; a Technical Director with 5 years specialized experience; designated individual for quality assurance activities; NIH certified provider to conduct independent neurological stroke evaluations for monitoring of periprocedural/30 day outcomes; other pertinent skilled health care professionals. • *Physician training*: "Each department within the institution mush have a clearly delineated program for the initial granting of carotid stent privileges with physician operators meeting one of the peer-reviewed national societal training standards regarding carotid stent placement." [Barr 2003, Rosenfield K 2005] • *Physician criteria*: "Must obtain 20 hours of Category 1 continuing medical education credits over a 3-year period in the field of endovascular therapy of peripheral or cerebrovascular diseases (i.e. non-coronary, non-cardiac vascular diseases). At least 10 of these hours must be in the field of cervico-cerebral vascular disease management including carotid, vertebral, and intracranial endovascular therapy." • *Case volume*: Not specified. • *Quality assurance*: Threshold complication rate determined by oversight committee, "major events such as death and major stroke rate should not exceed 3% for asymptomatic and should not exceed 6% for symptomatic patients." • *Renewal*: Annual, via online survey; for provisional status required "more frequently." **Accredited Facilities** • Northeast Georgia Medical Center (Gainesville, GA)

Connors III JJ, Sacks D, Furlan AJ, et al. Training, Competency and Credentialing Standards for Diagnostic Cervicocerebral Angiography, Carotid Stenting and Cerebrovascular Intervention: A Joint Statement from the American Academy of Neurology, American Association of Neurological Surgeons, American Society of Interventional and Therapeutic Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, AANS/CNS Cerebrovascular Section and Society of Interventional Radiology. *J Vasc Interv Radiol*, 2004; 15:1347–1356. www.sirweb.org/clinical/cpg/Carotid_Standard_2004.pdf

Rosenfield K, Cowley MJ, Jaff MR, et al. Clinical Competence Statement on Carotid Stenting: Training and Credentialing for Carotid Stenting — Multispecialty Consensus Recommendations: A Report of the SCAI/SVMB/SVS Writing Committee to develop a clinical competence statement on carotid interventions. *J Vasc Surg*, 2005; 41:160-8. www.vascularweb.org/professionals/Practice_Issues/PDF_Doc_JPEG/Competence_statement_carotid_stenting_JVS_2005.pdf

Qureshi AI, Abou-Chebl A, Jovin TG, et al. Qualification Requirements for Pperforming Neurointerventional Procedures: A Report of the Practice Guidelines Committee of the American Society of Neuroimaging and the Society of Vascular and Interventional Neurology. *J Neuroimaging*, 2008 Oct; 18(4):433-47.

Barr, J. D. et al (2003). Quality Improvement Guidelines for the Performance of Cervical Carotid Angioplasty and Stent Placement. J Vasc Interv Radiol , 14:S321-S335.

Centers for Medicare and Medicaid

The following is an exerpt taken directly from the 2013 CMS National Coverage Determination for Percutaneous Transluminal Angioplasty (PTA) with and without stenting and describes the minimum standards all facilities must meet in order to receive coverage for carotid artery stenting for high risk patients:

- Facilities must have necessary imaging equipment, device inventory, staffing, and infrastructure to support a dedicated carotid stent program. Specifically, high-quality x-ray imaging equipment is a critical component of any carotid interventional suite, such as high resolution digital imaging systems with the capability of subtraction, magnification, road mapping, and orthogonal angulation.
- Advanced physiologic monitoring must be available in the interventional suite. This includes real time and archived physiologic, hemodynamic, and cardiac rhythm monitoring equipment, as well as support staff who are capable of interpreting the findings and responding appropriately.
- Emergency management equipment and systems must be readily available in the interventional suite such as resuscitation equipment, a defibrillator, vasoactive and antiarrhythmic drugs, endotracheal intubation capability, and anesthesia support.
- Each institution shall have a clearly delineated program for granting carotid stent privileges and for monitoring the quality of the individual interventionalists and the program as a whole. The oversight committee for this program shall be empowered to identify the minimum case volume for an operator to maintain privileges, as well as the (risk-adjusted) threshold for complications that the institution will allow before suspending privileges or instituting measures for remediation. Committees are encouraged to apply published standards from national specialty societies recognized by the American Board of Medical Specialties to determine appropriate physician qualifications. Examples of standards and clinical competence guidelines include those published in the December 2004 edition of the American Journal of Neuroradiology, and those published in the August 18, 2004 Journal of the American College of Cardiology.
- To continue to receive Medicare payment for CAS under this decision, the facility or a contractor to the facility must collect data on all CAS procedures done at that particular facility. This data must be analyzed routinely to ensure patient safety. This data must be

made available to CMS upon request. The interval for data analysis will be determined by the facility but shall not be less frequent than every 6 months.

Since there currently is no recognized entity that evaluates CAS facilities, CMS has established a mechanism for evaluating facilities. Facilities must provide written documentation to CMS that the facility meets one of the following:

1. The facility was an FDA -approved site that enrolled patients in prior CAS IDE trials, such as SAPPHIRE, and ARCHER;
2. The facility is an FDA -approved site that is participating and enrolling patients in ongoing CAS IDE trials, such as CREST;
3. The facility is an FDA -approved site for one or more FDA post approval studies; or
4. The facility has provided a written affidavit to CMS attesting that the facility has met the minimum facility standards. This should be sent to:

Director, Coverage and Analysis Group
7500 Security Boulevard, Mailstop **S3-02-01**
Baltimore, MD 21244

The letter must include the following information:

- Facility's name and complete address;
- Facility's national provider identifier (formerly referred to as the Medicare provider number);
- Point-of-contact for questions with telephone number;
- Discussion of how each standard has been met by the hospital;
- Mechanism of data collection of CAS procedures; and
- Signature of a senior facility administrative official.

A list of certified facilities will be made available and viewable at: http://www.cms.gov/coverage/carotid-stent-facilities.asp. In addition, CMS will publish a list of approved facilities in the Federal Register.

Facilities must recertify every two (2) years in order to maintain Medicare coverage of CAS procedures. Recertification will occur when the facility documents that and describes how it continues to meet the CMS standards.

Approved facilities in Washington State

CMS Approval Requirements

- High-resolution digital imaging systems with the capability of subtraction, magnification, road mapping, and orthogonal angulation.
- Image storage, retrieval, and archiving capability.
- Real-time and archived physiologic, hemodynamic, and cardiac rhythm monitoring equipment, and support staff capable of interpreting the findings and responding appropriately.
- The ability to measure activated clotting time on-site is highly desirable.
- Supplies including but not limited to:
    - Guidewires (0.035", 0.018", and 0.014");
    - Balloon dilation catheters (coronary and noncoronary balloons in diameters ranging from 2 to 14 mm; balloon lengths from 10 to 40 mm with sufficient useable catheter length);
    - Self-expanding (4-10 mm diameter, 20-60 mm length)
    - Balloon-expandable (2-12 mm diameter) stents with sufficient useable catheter length;
    - Coronary guide catheters (6-9 Fr)
    - Long arterial sheaths ranging from 6 to 8 Fr in size and at least 85 cm in length;
    - Temporary pacemakers;
    - Emboli protection devices.
    - Covered stents, coils, snares, and vascular access closure devices.
- Resuscitation equipment, a defibrillator, vasoactive and antiarrhythmic drugs, endotracheal intubation capability, and anesthesia support.
- Procedure staff should be familiar with rapid response to hemodynamic and rhythm instability.
- Skilled allied health professionals in the laboratory (nurses and technicians) must be trained and experienced in evaluating patients before and after catheter-based interventional procedures and in the recognition and management of acute neurological syndromes.
- Clearly delineated program for granting carotid stent privileges and for monitoring the quality of the individual interventionalists and the program as a whole. Oversight committee must be empowered to identify the minimum case volume for an operator to maintain privileges, as well as the (risk-adjusted) threshold for complications that the institution will allow before suspending privileges or instituting measures for remediation.

Approved Hospitals

Hospital	Approval Date
Deaconess Medical Center	5/10/05
Evergreen Hospital Medical Center	12/14/10
Franciscan Health System d/b/a St. Joseph Medical Center	7/31/06
Grays Harbor Community Hospital	12/11/09
Harborview Medical Center	10/14/05
Harrison Medical Center	8/22/06
Kadlec Medical Center	8/22/05
King County Public Hospital District #1	11/21/05
Overlake Hospital Medical Center	6/20/05

Hospital	Approval Date
Providence Everett Medical Center	12/19/05
Providence St. Peter Hospital	6/20/05
Sacred Heart Medical Center	7/15/05
Southwest Washington Medical Center	5/26/05
St. Joseph Hospital	9/28/05
Swedish Medical Center-First Hill Campus	5/17/05
Swedish Medical Center-Providence Campus	5/23/05
Tacoma General Hospital Multicare Health System	8/18/06
University of Washington Medical Center	2/28/07
UW Medicine - Northwest Hospital	8/4/11
Virginia Mason Medical Center	6/27/05
Yakima Regional Medical and Cardiac Center	7/27/05

FDA approved devices for stenting of the extracranial carotid and intracranial arteries.

Carotid stent systems are medical devices used to treat Stroke due to Atherosclerotic disease, also known as Carotid Artery Stenosis (CAS). All currently available FDA-approved devices are bare-metal; no drug-eluting stents have thus far been approved. Most of these devices are used in conjunction with an embolic protection device (EPD). CAS can be symptomatic or asymptomatic, with higher levels of stenosis typically corresponding to asymptomatic disease, and different devices are manufactured for each type (though some are indicated for both). Devices are also used either intra- or extra-cranially based on the stenosis.

RX Acculink Carotid Stent System (Abbott Vascular)

i. Bare-metal stent
ii. Symptomatic and Asymptomatic patients (based on use of CREST study)
iii. EPD required
iv. Extracranial placement

Carotid WALLSTENT Monorail Endoprosthesis (Boston Scientific Corporation)

i. Bare-metal
ii. Symptomatic and asymptomatic patients (based on use of BEACH study)
iii. EPD required
iv. Extracranial placement

ACCULINK Carotid Stent System (Guidant Corporation)

i. Bare-metal stent
ii. Symptomatic (≥50% stenosis) and asymptomatic (≥80% stenosis) patients
iii. EPD required
iv. Extracranial placement

Protégé GPS Carotid Stent System Protégé RX Carotid Stent System (ev3 Inc.)

i. Bare-metal stent
ii. Symptomatic (≥50% stenosis) and asymptomatic (≥80% stenosis) patients
iii. EPD required
iv. Extracranial placement

Exponent Self-Expanding Carotid Stent System (Medtronic Vascular, Inc.)

i. Bare-metal stent
ii. Symptomatic (≥50% stenosis) and asymptomatic (≥80% stenosis) patients
iii. EPD required
v. Extracranial placement

Xact Rapid Exchange Carotid Stent System (Abbott Vascular Devices)

i. Bare-metal stent
ii. Symptomatic (≥50% stenosis) and asymptomatic (≥80% stenosis) patients
iii. EPD required
iv. Extracranial placement

PRECISE Nitinol Stent System (Cordis Corporation)

i. Bare-metal stent
ii. Symptomatic (≥50% stenosis) and asymptomatic (≥80% stenosis) patients (based on use of SAPPHIRE study)
iii. EPD required
iv. Extracranial placement

Nexstent Carotid Stent System (Endotex Interventional Systems, Inc.)

i. Bare-metal stent
ii. Symptomatic (≥50% stenosis) and asymptomatic (≥80% stenosis) patients
iii. EPD required
iv. Extracranial placement

Wingspan Stent System (Boston Scientific SMART)*

i. Bare-metal stent
ii. Symptomatic patients (based on use of SSYLVIA study)
iii. No EPD required
iv. Intracranial placement

NEUROLINK System (Guidant Corporation)*

i. Bare-metal stent
ii. Symptomatic (≥50% stenosis) patients
iii. No EPD required
iv. Intracranial placement

***Humanitarian Use Device approval**

Humanitarian Use Devices (HUDs) are approved for treating conditions which are manifested in fewer than 4,000 individuals per year, and thus the manufacturer's research and development costs could exceed the revenue for the device. As incentive, HUDs are approved through application for Humanitarian Device Exemption (HDEs) which is similar to a Premarket Approval (PMA) application but without the effectiveness requirements. However, as a result, use of HUDs in facilities must be approved by a local Institutional Review Board (IRB) and the devices is labeled as not having been demonstrated as effective for the particular condition.

(U.S. Food and Drug Administration, 2010)

References

U.S. Food and Drug Administration. (2010, August 30). *Humanitarian Device Exemption*. Retrieved from U.S. Food and Drug Administration: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/default.htm

Table 1. FDA indications of two devices to treat symptomatic ischemic disease in patients with de novo lesions in native carotid arteries

Device (Manufacturer)	Date of FDA approval	Lesion length	Target vessel diameter	No. of lesions (stents)	Specific indications	Specific contraindications
Extracranial stents						
RX Acculink Carotid Stent System (Abbott Vascular)	08/30/04	NR	4.0–9.0 mm	NR	• High likelihood of complications due to other medical problems or body abnormalities if they had surgical alternative (carotid endarterectomy), AND: ○ recent stroke and at least a moderate (≥ 50%) blockage in blood vessels of neck, OR ○ no recent stroke but has very tight (≥80%) blockage in vessels of neck • Normal likelihood of complications if they had the surgical alternative (carotid endarterectomy), AND: ○ recent stroke and at least moderately tight (≥70% or ≥50% depending on technique physician	• Narrowed area in neck artery located beyond sharply curved vessels (tortuous anatomy), making it difficult to place stent and embolic protection device. • Anticoagulant and/or antiplatelet therapy is contraindicated • Allergic to nickel-titanium (Nitinol) or contrast dye • Uncorrected bleeding disorders • Blockages (lesions) at opening/beginning of neck artery

Device (Manufacturer)	Date of FDA approval	Lesion length	Target vessel diameter	No. of lesions (stents)	Specific indications	Specific contraindications
					uses to look at blocked vessel) blockage in blood vessels of neck, OR ○ no recent stroke but has at least moderately tight blockage (≥70% or ≥60% depending on technique physician uses to quantify blockage) in vessels of neck.	
Carotid WALLSTENT Monorail Endoprosthesis (Boston Scientific Corporation)	10/03/08	≤36mm	4.0–9.0 mm	NR	• History of stroke, OR • Very tight (≥80%) blockage in vessels of neck, AND • Medical problems or body abnormalities that would put the patient at too high risk to have surgical alternative (carotid endarterectomy).	• Anticoagulant and/ or antiplatelet therapy is contraindicated. • Uncontrolled bleeding disorders • Allergy to stent metal/material. • Blockages (lesions) at beginning of neck artery • Anatomical problems preventing catheter from getting to the blockage
ACCULINK Carotid Stent System (Guidant Corporation)	03/15/04	≤40 mm	4.0–9.0 mm	1 (2)	• High risk for adverse events from carotid endarterectomy who require carotid revascularization and • 1. neurological symptoms and ≥50% stenosis of the common or internal carotid artery by ultrasound or angiogram OR patients without neurological symptoms and ≥80% stenosis of the common or internal carotid artery by ultrasound or angiogram, AND • 2. Patients must have a reference vessel diameter within the range of 4.0 mm and 9.0 mm at the target lesion.	• Anti-coagulant and/or anti-platelet therapy is contraindicated • Severe vascular tortuosity or anatomy that would preclude the safe introduction of a guide catheter, sheath, embolic protection system, or stent system. • Known hypersensitivity to nickel-titanium (Nitinol). • Uncorrected bleeding disorders • Lesions in the ostium of the common carotid artery.
Protégé GPS Carotid Stent System Protégé RX Carotid Stent System (ev3 Inc.)	01/09/06	≤60 mm	4.5–9.5 mm	NR	• High risk for adverse events from carotid endarterectorny who require percutaneous carotid revascularization and • 1. Patients with carotid artery stenosis (≥ 50% for symptomatic patients by	• Anticoagulant, antiplatelet therapy or thrombolytic drugs is contraindicated • Vascular tortuosity or anatomy, which precludes the safe introduction of the sheath, guide catheter, embolic protection system, or stent system

Device (Manufacturer)	Date of FDA approval	Lesion length	Target vessel diameter	No. of lesions (stents)	Specific indications	Specific contraindications
					ultrasound or angiography or ≥80% for asymptomatic patients by ultrasound or angiography) of the common or internal carotid artery, AND • Reference vessel diameter within the range of 4.5 mm and 9.5 mm at the target lesion.	• Known hypersensitivity to nickel-titanium (Nitinol) • Uncorrected bleeding disorders • Lesions in the ostium of the common carotid artery
Exponent Self-Expanding Carotid Stent System (Medtronic Vascular, Inc.)	04/30/07	≤40 mm	4.5–9.5 mm	NR	• High risk for adverse events from carotid endarterectomy who require carotid revascularization and • 1. Patients with neurological symptoms and ≥50 % stenosis of the common or internal carotid artery by either ultrasound or angiogram OR patients without neurological symptoms and ≥80 % stenosis of the common or internal carotid artery by either ultrasound or angiogram, AND • 2. Patients having a vessel with reference diameters between 4.5 mm and 9.5 mm at the target lesion.	• Anticoagulant and/ or antiplatelet therapy is contraindicated • Severe vascular tortuosity or anatomy that would preclude the safe introduction of a guide catheter, sheath, embolic protection device, or stent delivery system • Known hypersensitivity to nickel-titanium (Nitinol) • Uncorrected bleeding disorders • Lesions in the ostium of the common carotid artery
Xact Rapid Exchange Carotid Stent System (Abbott Vascular Devices)	09/03/04	NR	4.8–9.1 mm	NR	• Considered at high risk for adverse events from carotid endarterectomy who require percutaneous carotid angioplasty and stenting for occlusive artery disease and • Carotid artery stenosis (≥ 50% for symptomatic patients by ultrasound or angiography or ≥ 80% for asymptomatic patients by ultrasound or angiography), located between the origin of the common carotid artery and the intra-cranial segment of the internal carotid artery AND • Must have a reference vessel diameter ranging between 4.8 mm and 9.1 mm at the target lesion.	• Anticoagulant and/or antiplatelet therapy is contraindicated. • Severe vascular tortuosity or anatomy that would preclude the safe introduction of the Guiding Catheter/ Introducer Sheath RX BareWireTM , Emboshield Delivery Catheter, Filtration Element, and/or Retrieval Catheter. • Hypersensitivity to nickel-titanium (Nitinol) • Uncorrected bleeding disorders • Lesions in the ostium of the common carotid artery

Device (Manufacturer)	Date of FDA approval	Lesion length	Target vessel diameter	No. of lesions (stents)	Specific indications	Specific contraindications
PRECISE Nitinol Stent System (Cordis Corporation)	10/08/03	≤40 mm	4.0–9.0 mm	NR	• High risk for adverse events from carotid endarterectomy who require carotid revascularization • Patients with neurological symptoms and ≥50 % stenosis of the common or internal carotid artery by either ultrasound or angiogram OR patients without neurological symptoms and ≥80 % stenosis of the common or internal carotid artery by either ultrasound or angiogram, AND • 2. Patients having a vessel with reference diameters between 4.0 mm and 9.0 mm at the target lesion. The vessel distal to the target lesion must be within the range of 3.0 and 7.5 mm to allow for placement of the ANGIOGUARD XP Emboli Capture Guidewire.	• Anticoagulant and/or antiplatelet therapy is contraindicated • Severe vascular tortuosity or anatomy that would preclude the safe introduction of a guide catheter, sheath, embolic protection system, or device catheter, and/or retrieval catheter. • Uncorrected bleeding disorders • Known allergies to nickel-titanium (Nitinol) • Lesions in the ostium of the common carotid artery
Nexstent Carotid Stent System (Endotex Interventional Systems, Inc.)	07/14/05	<30mm	4.0–9.0 mm	NR	• High risk for adverse events from carotid endarterectomy who require carotid revascularization and • 1. Patients with neurological symptoms and ≥50 % stenosis of the common or internal carotid artery by either ultrasound or angiogram OR patients without neurological symptoms and ≥80 % stenosis of the common or internal carotid artery by either ultrasound or angiogram, AND • 2. Patients having a vessel with reference diameters between 4.0 mm and 9.0 mm at the target lesion and a stenosis <30 mm in length.	• Anti-coagulant and/or anti-platelet therapy is contraindicated. • Severe vascular tortuosity or anatomy that would preclude the safe introduction of a guide catheter, sheath, embolic protection system, or device catheter, and/or retrieval catheter. • Known hypersensitivity to nickel-titanium. • Uncorrected bleeding disorders. • Lesions in the ostium of the common carotid artery.
Intracranial stents						
Wingspan Stent System (Boston	01/28/05	≤14mm	2.5–4.5 mm	NR	• Intracranial	• Anticoagulant and/or

Device (Manufacturer)	Date of FDA approval	Lesion length	Target vessel diameter	No. of lesions (stents)	Specific indications	Specific contraindications
Scientific SMART)	Humanitarian Device Exemption (HDE)				atherosclerotic disease, refractory to medical therapy, in intracranial vessels with ≥50% stenosis that are accessible to the system	antiplatelet therapy is contraindicated. • Lesions that are highly calcified or otherwise could prevent access or appropriate expansion of the stent • Treatment of: ○ stroke with an onset of symptoms within seven days or less of treatment ○ transient ischemic attacks (TIAs)
NEUROLINK System (Guidant Corporation)	10/31/01 Humanitarian Device Exemption (HDE)	NR	2.5–4.5 mm	NR	• Treatment of recurrent intracranial stroke attributable to atherosclerotic disease refractory to medical therapy in intracranial vessels with ≥50% stenosis and that are accessible to the Stent system	• Anticoagulant and/or antiplatelet therapy is contraindicated. • Known hypersensitivity to heparin, stainless steel, anesthesia, or x-ray contrast media • Lesions that are highly calcified or otherwise could prevent access or appropriate expansion of the stent.

APPENDIX J. CLINICAL PEER REVIEWERS

Invited Peer Reviewers

Individual	Experience
R. Eugene Zierler, MD Professor of Surgery, Division of Vascular Surgery, University of Washington Medical Director, D. E. Strandness, Jr. Vascular Laboratory University of Washington	• M.D. Johns Hopkins University, School of Medicine (1976) • Certificate of Special Qualifications in General Vascular Surgery American Board of Surgery (Certificate #616); Recertified 1993 and 2004 • Assistant professorships in surgery (UCLA, UW); former chief of vascular surgery at Seattle VAMC • Non-invasive vascular testing • Previously on Board of Directors, Intersocietal Commission for the Accreditation of Vascular '/ Laboratories • Current Editorial Board service: International Angiology, Vascular and Endovascular Surgery, Vascular Specialist
Danial K. Hallam, M.D., M.Sc. Associate Professor of Radiology Joint Associate Professor of Neurological Surgery University of Washington	• M.D. Stanford Medical School (1989) • Diplomate of the American Board of Radiology, 1994 • Diplomate of the National Board of Medical Examiners, 1990. • American Board of Radiology Certificate of Added Qualifications in Neuroradiology, 1997-2007 • Treatment of stroke • Endovascular Treatment of the Acute Ischemic Stroke Patient • Co-investigator for START Trial: Clinical Outcome in Acute Stroke Treatment After Image Guided Patient Selection for Interventional Revascularization Therapy
Rita Redberg, MD, M.Sc UCSF Division of Cardiology, Professor of Clinical Medicine Director, Women's Cardiovascular Services, San Francisco, CA Adjunct Associate, Center for Health Policy/Center for Primary Care and Outcomes Research (CHP/PCOR), Stanford University	• MD, University of Pennsylvania; • ABIM-Internal medicine and Cardiovascular specialty • MSc, London School of Economics • Over 30 years of research-related and clinical experience. • Research areas include cardiovascular disease in women, cardiovascular imaging, health policy and technology assessment, evidence based-practice • Reviewer/consultation for AHRQ, USPSTF, MCAC, CDRH • Congressional testimonies on medical devices, regulation an approval processes • Core Faculty Member, Philip R. Lee Institute for Health Policy Studies, San Francisco, CA • Editor, Archives of Internal Medicine • Fellow: American College of Cardiology, American Heart Association
Robert M. Bersin, MD, MPH Swedish Medical Center Heart and Vascular Seattle, Washington	• MD, University of California, Los Angeles • MPH, University of California, Los Angeles • Over 30years research related and clinical experience • Research areas include carotid and coronary stenting and stenting of other vessels; cardiac catherization, metabolic and hemodynamic effects of sodium bicarbonate and carbicarb, intravascular ultrasound

Individual	Experience
Medical Director, North End Cardiology Operations	• Editorial review board service for various peer-reviewed journals including the Journal of the American College of Cardiology • Scientific Council Advisor –FDA Orphan Drug Division • Medical advisory board for various companies including Boston Scientific, Cordis Endovascular, Genentech, ReVascular Therapeutics • Board or committee service: Society for Cardiac Angiography and Intervention, Swedish Heart and Vascular Institute, American College of Cardiology Interventional Cardiology Task Force
Stephen J. Monteith, MD Swedish Neuroscience Institute Seattle Washington Endovascular and cerebrovascular neurosurgeon	• MBChB (Bachelor of Medicine and Bachelor of Surgery) with Distinction, The University of Auckland School of Medicine, Auckland, New Zealand; ECFMG Certification – MD equivalency certification process • American Board of Neurological Surgeons Written Board Examination for credit • 10 years of clinical and research related experience • Clinical and research areas include treatment of intracerebral haemorrhage, vascular malformations and tumors, MRI-guided focused ultrasound surgery, gamma knife surgery. • Memberships: American Association of Neurological Surgeons, Congress of Neurological Surgeons, New Zealand Medical Council.

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