Eur J Vasc Endovasc Surg (xxxx) xxx, xxx

EJVES Open Access

SYSTEMATIC REVIEW

Timing of Carotid Intervention in Symptomatic Carotid Artery Stenosis: A Systematic Review and Meta-Analysis

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WHAT THIS PAPER ADDS

The evidence from this systematic review and meta-analysis suggests that (at present) carotid endarterectomy (CEA) is safer than carotid artery stenting (CAS) when performed within two or seven days of the index event. Also, considering absolute rates of 30 day stroke, mortality, and death/stroke, CEA performed within two days of the index event complies with the accepted thresholds in international guidelines. The findings of this analysis will guide clinical practice when deciding on the type of intervention in the symptomatic patient with severe carotid stenosis. The ideal timing for performing CAS (when indicated against CEA) is not yet defined.

Objective: This review aimed to analyse the timing of carotid endarterectomy (CEA) and carotid artery stenting (CAS) after the index event as well as 30 day outcomes at varying time periods within 14 days of symptom onset.
Methods: A systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-analysis statement, comprising an online search of the Medline and Cochrane databases. Methodical quality assessment of the included studies was performed. Endpoints included procedural stroke and/or death stratified by delay from the index event and surgical technique (CEA/CAS).
Results: Seventy-one studies with 232 952 symptomatic patients were included. Overall, 34 retrospective analyses of prospective databases, nine prospective, three RCT, three case control, and 22 retrospective studies were included. Compared with CEA, CAS was associated with higher 30 day stroke (OR 0.70; 95% CI 0.58 — 0.85) and mortality rates (OR 0.41; 95% CI 0.31 — 0.53) when performed $\leq$ 2 days of symptom onset. Patients undergoing CEA/CAS were analysed in different time frames ($\leq$ 2 *vs.* 3 — 14 and $\leq$ 7 *vs.* 8 — 14 days). Expedited CEA (*vs.* 3 — 14 days) presented a sampled 30 day stroke rate of 1.4%; 95% CI 0.9 — 1.8 *vs.* 1.8%; 95% CI 1.8 — 2.0, with no statistically significant difference. Expedited CAS (*vs.* 3 — 14 days) was associated with no difference in stroke rate but statistically significantly higher mortality rate (OR 2.76; 95% CI 1.39 — 5.50).
Conclusion: At present, CEA is safer than transfemoral CAS within 2/7 days of symptom onset. Also, considering absolute rates, expedited CEA complies with the accepted thresholds in international guidelines. The ideal timing for performing CAS (when indicated against CEA) is not yet defined. Additional granular data and standard reporting of timing of intervention will facilitate future monitoring.

Keywords: Carotid stenosis, Death, Endarterectomy, carotid, Stent, Stroke
Article history: Received 24 February 2021, Accepted 13 August 2021, Available online XXX
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INTRODUCTION

Carotid revascularisation improves long term stroke free survival in patients with recent ischaemic stroke or transient ischaemic attack (TIA). Recency of the index event has been recognised as a key determinant of the effectiveness of revascularisation, balancing the natural history risk of a

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https://doi.org/10.1016/j.ejvs.2021.08.021

Please cite this article as: Coelho A et al., Timing of Carotid Intervention in Symptomatic Carotid Artery Stenosis: A Systematic Review and Meta-Analysis, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.08.021

second (more severe) event against the potential for a higher peri-procedural risk when carotid interventions are performed very early after the onset of symptoms.

The optimal timing for carotid revascularisation, by either carotid endarterectomy (CEA) or carotid artery stenting (CAS), remains a matter for debate. The 2017 European Society for Vascular Surgery (ESVS) guidelines advise that CEA should be performed within 14 days of the index neurological event, as this was the highest risk time period for recurrent stroke.[1] This is particularly true for neurologically stable patients presenting with TIA or minor stroke. However, it remains unclear as to the optimal timing of either CEA or CAS within this 14 day time period (i.e., Is it better for the carotid intervention to be performed $<$ 2 days, $<$ 7 days, or perhaps 8 — 14 days after symptom onset?).

A recent systematic review reported that the risk of recurrent stroke can vary from 6% within 2 — 3 days of the index event, to 20% within 7 days, and up to 26% within 14 days of the index event.[2] Conversely, a meta-analysis of published studies comparing expedited carotid interventions (2 days) *vs.* early (3 — 14 days) found a significantly higher risk of procedural stroke when CEA was performed within 2 days of the index event.[3] However, this systematic review did not include two large national CEA registries ($>$ 70 000 CEAs), which confounds meaningful interpretation of their data. In the case of CAS, the available data on safety very early after the onset of symptoms appears limited.[4]

The lack of high quality evidence and consensus definitions for what constitutes "early" or "urgent" carotid interventions has contributed to conflicting results in the literature. Heterogeneity regarding patient symptoms, medical therapy, and varying surgical approaches have also led to polarised debates about the timing of CEA in patients who present with neurological symptoms.[5]

The aims of the current systematic review and meta-analysis were to analyse temporal changes in the timing of carotid interventions after symptom onset and to determine 30 day outcomes following CEA and CAS when performed at varying time periods in the first 14 days after onset of symptoms, to define the optimal timing and carotid intervention (CEA *vs.* CAS) in recently symptomatic patients.

METHODS

A systematic review was conducted according to the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement.[6]

The literature search was from January 1995 to January 2021. Using the Medline and Cochrane databases, the following query ((("Carotid Stenosis"[Mesh]) AND "Stents"[Mesh]) OR "Endarterectomy, Carotid"[Mesh]) AND ("Stroke"[Mesh] OR Symptomatic OR timing of intervention) was used for online search.

Eligibility criteria included any publication regarding the revascularisation of symptomatic carotid artery stenosis by either CAS or CEA. Timing of intervention and impact of delay on procedural risks were documented. Only atherosclerotic stenotic carotid disease was considered, with exclusion of procedures performed for non-atherosclerotic pathologies.

Exclusion criteria were (1) articles published in a language other than English; and (2) case reports and literature reviews.

Endpoints included any stroke and/or death within 30 days of intervention stratified by delay of intervention after the index event and by intervention technique (CEA and

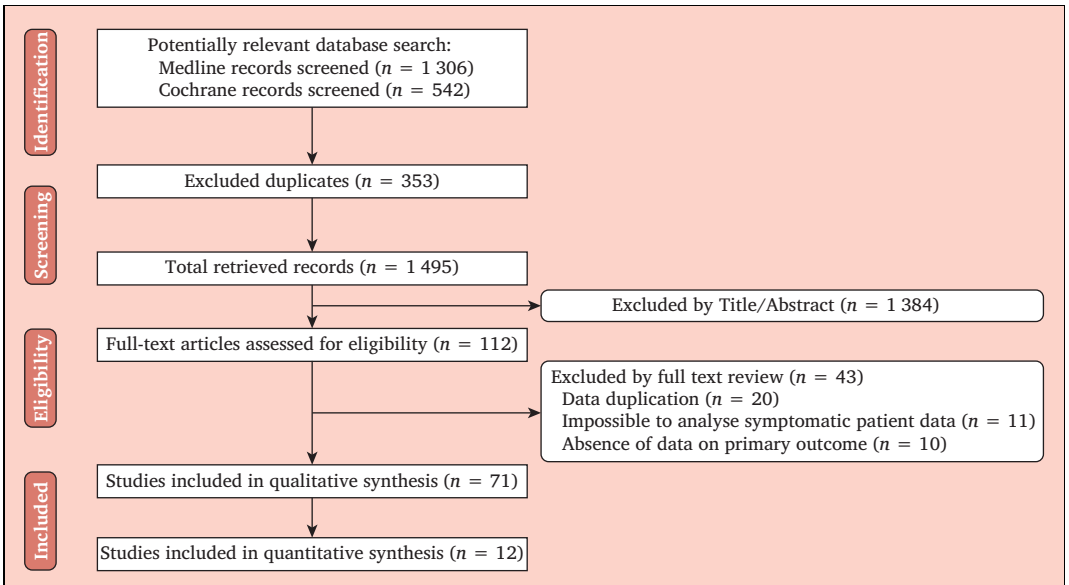

Figure 1. Preferred reporting items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram summarising literature screening process for studies of timing after index event and outcome after carotid endarterectomy (CEA) or carotid artery stenting (CAS).

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Table 1. Analysis of study characteristics and intervention delay for carotid endarterectomy (CEA) or carotid artery stenting (CAS) after index event

Article (Year) Journal	Type of article	CEA/ CAS	Patients	Symptomatic	Definition delay (days)	Timing of intervention	Mean delay ± SD − d
Kashyap[34] (2020) *Stroke*	Prosp; Multicentre	CAS	632	164 (26)	NR	NR	NR
Karpenko[35] (2020) *J Stroke Cerebrovasc Dis*	Retrosp; Single centre	CEA/CAS	1 791 CEA: 1215 (57); CAS: 917 (43)	160 (8.9)	NR	NR	NR
Jankowitz[13] (2020) *Neurosurgery*	Retrosp analysis of prosp data; Single centre	CEA/CAS	120 CEA: 59 (49.2); CAS: 61 (59.8)	120 (100)	Urgent (0−2)	0−2 d: 120 (100)	CEA: 1.6 ± 0.8; CAS: 1.0 ± 0.7; *p* <.001
Roussopoulo[9] (2019) *Eur J Neurol*	Prosp; Multicentre	CEA	311	311 (100)	Urgent (0−2); Early (3−14)	0−2 d: 63 (20.3); 3−14 d: 248 (79.7)	NR
Howie[36] (2019) *World Neurosurg*	Retrosp; Single centre	CEA/CAS	314 CEA: 204 (64.9); CAS: 110 (35.1)	265 (84.5)	NR	NR	NR
Vang[37] (2019) *Surgery*	Retrosp; Single centre	CEA	1233	509 (41.3)	NR	NR	NR
Lee[38] (2018) *Ann Vasc Surg*	Retrosp; Multicentre	CEA/CAS	677 CEA: 331 (48.9); CAS: 346 (51.1)	677 (100)	NR	NR	NR
Huang[14] (2018) *J Vasc Surg*	Retrosp; Single centre	CEA	238	238 (100)	Early (0−14); (0 −2); (3−7); (8−14); Delayed (15−180)	0−2 d: 11 (4.6); 3−7 d: 23 (9.7); 8−14 d: 23 (9.7); 15−180 d: 181 (76.1)	NR
Rocco[20] (2018) *J Vasc Interv Radiol*	Retrosp analysis of prosp data; Single centre	CEA/CAS	110 CEA: 48 (43.6); CAS: 62 (56.4)	110 (100)	NR	NR	CEA: 1.7 ± 2.4; CAS: 2.8 ± 2.1
Seguchi[10] (2017) *J Stroke CerebrovascDis*	Retrosp; Single centre	CAS	105	105 (100)	Early (0−2); Delayed (3−180)	0−2 d: 40 (38.1); 3−180 d: 65 (61.9)	NR
Rantner[44] (2017) *Stroke* EVA-3S, SPACE, ICSS, CREST	Retrosp analysis of prosp data; Multicentre	CEA *vs.* CAS	4 138	4 138 (100)	Early (0−7); Delayed (8−180)	0−7 d: 513 (12.4); 8−180 d: 3625 (87.6)	
		CEA	2 045 (49.4)	2 045 (100)	Early (0−7); Delayed (8−180)	0−7 d: 226 (11); 8−180 d: 1819 (89)	34.5 ± 15.6
		CAS	2 093 (50.6)	2 093 (100)	Early (0−7); Delayed (8−180)	0−7 d: 287 (14); 8−180 d: 1806 (86)	31 ± 14.4
Hobeanu[42] (2017) *Stroke*	Nested case control study	CEA/CAS *vs.* BMT	561 CEA/CAS: 187 (33.3) BMT: 374 (66.7)	187 (100)	NR	NR	12.8 ± 4.9
Nordanstig[8] (2017) *Eur J Vasc Endovasc Surg*	Prosp; Multicentre	CEA	418	418 (100)	Early (0−2); Delayed (3−14)	0−2 d: 46 (11); 3−14 d: 372 (89)	Early: 1.3 ± 0.69 Delayed: 6.7 ± 2.9
Kazandjian[46] (2016) *J Vasc Surg*	Retrosp analysis of prosp data; Single centre	CEA	114	114 (100)	Early (0−14); Delayed (15−180)	0−14 d: 32 (28); 15−180 d: 82 (72)	22 ± 33
Tsantilas[23] (2016) *J Vasc Surg*	Retrosp analysis of prosp data; Single centre	CEA	401	401 (100)	Early (0−14); (0 −2); (3−7); (8−14); Delayed (15−180)	0−2 d: 60 (15); 3−7 d: 110 (27.4); 8−14 d: 65 (16.2); 15−180 d: 166 (41.4)	NR
Charbonneau[17] (2016) *J Vasc Surg*	Retrosp; Single centre	CEA	103	103 (100)	(0−14); (15−90); (91−180)	0−14 d: 40 (38.8); 15−90 d: 37 (35.9); 91−180 d: 26 (25.2)	36.5 ± 21.4
Chisci[19] (2015) *Ann Vasc Surg*	Retrosp; Single centre	CEA	322	322 (100)	Early (0−14); Delayed (15−30);	0−14 d: 100 (31.1); 15−30 d: 222 (68.9)	16.8 ± 9.2 4.6 ± 3.1 22.3 ± 4.6
Kretz[26] (2015) *Ann Vasc Surg*	Retrosp analysis of prosp data; Single centre	CEA	417	417 (100)	Early (0−15); Deferred (16−45); Delayed (46−180)	0−15 d: 158 (37.9); 16−45 d: 79 (18.9); 46−180 d: 180 (43.2)	7.7 ± 3.8 28.3 ± 8.6 89.4 ± 36.7
Charmoille[47] (2014) *Ann Vasc Surg*	Retrosp; Single centre	CEA	149	149 (100)	Early (0−14); Late (15−180)	0−14 d: 62 (41.6); 15−180 d: 87 (58.4)	NR
Rantner[85] (2014) *Eur J Vasc Endovasc Surg*	Retrosp; Single centre	CEA	761	761 (100)	Early (0−14); (0 −2); (3−7); (8−14); Delayed (15−180)	0−2 d: 206 (27.1); 3−7 d: 219 (28.8); 8−14 d: 136 (17.9); 15−180 d: 200 (26.3)	NR
Tsivgoulis[49] (2014) *Eur J Neurol*	Prosp; Multicentre	CEA	165	165 (100)	Ultra-Early (0−2); Early (3−14)	0−2 d: 20 (12); 3−14 d: 145 (88)	6 ± 1.7
Mo[51] (2014) *J NeuroIntervent Surg*	Retrosp analysis of prosp data; Single centre	CAS	402	169 (42.0)	NR	NR	NR
Shahidi[53] (2013) *Stroke*	Prosp; Single centre	CEA	115	115 (100)	Early (0−14); Deferred (15−30); Delayed (31−180)	NR	36.3 ± 25.1

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Table 1-*continued*

Article (Year) Journal	Type of article	CEA/ CAS	Patients	Symptomatic	Definition delay (days)	Timing of intervention	Mean delay ± SD − d
Sharpe[15] (2013) *Eur J Vasc Endovasc Surg*	Retrosp; Single centre	CEA	475	475 (100)	Early (0−14); Hyperacute (0−2); (3−7); (8−14); Delayed (15−180)	0−2 d: 41 (8.6); 3−7 d: 167 (35.2); 8−14 d: 133 (28.0); 15−180 d: 134 (28.2)	NR
Faggioli[54] (2013) *Ann Vasc Surg*	Retrosp analysis of prosp data; Single centre	CEA	610	162 (27)	Early (0−14); Deferred (15−30); Delayed (31−180)	0−14 d: 60 (37.0); 15−30 d: 18 (11.1); 31−180 d: 84 (51.9)	NR
Hartog[5] (2013) *Eur J Vasc Endovasc Surg*	Retrosp; Single centre	CEA	555	555 (100)	Early (0−14); Delayed (15−180)	0−14 d: 105 (18.9); 15−180 d: 450 (81.1)	40.3 ± 15.9
Tas[52] (2013) *Adv Ther*	Retrosp; Single centre	CEA/CAS	65 CEA 32 (49.2); CAS 33 (50.8)	65 (100)	NR	NR	NR
Annambhotla[59] (2012) *J Vasc Surg*	Retrosp; Single centre	CEA	312	312 (100)	Early (0−30); (0 −7); (8−14); (15 −21); (22−30); Delayed (31−180)	0−7 d: 27 (8.7); 8−14 d: 17 (5.4); 15−21 d: 12 (3.8); 22−30 d: 12 (3.8); 31−180 d: 243 (77.9)	NR
Kessler[56] (2012) *J Neuroradiol*	Retrosp; Single centre	CAS	55	55 (100)	NR	NR	NR
Kimiagar[57] (2012) *Vasc Endovascular Surg*	Retrosp; Single centre	CEA/CAS	116	116 (100)	NR	NR	NR
Lin[61] (2009) *J NeuroIntervent Surg*	Retrosp; Single centre	CAS	224	224 (100)	Early (0−30); Ultra-Early (0−14); Delayed (31−180)	0−30 d: 122 (54.5); 31−180 d: 102 (45.5)	NR
Gray[64] (2009) *Circ Cardiovasc Intervent* EXACT CAPTURE-2	Prosp; Multicentre	CAS	6320	759 (12.0)	NR	NR	NR
Ballotta[68] (2008) *J Vasc Surg*	Retrosp; Single centre	CEA	102	102 (100)	Early (0−14)	0−14 d: 102 (100)	6.3 ± 3.2
Setacci[69] (2008) *Eur J Vasc Endovasc Surg*	Prosp; Multicentre	CAS	57	57 (100)	Deferred for TIA (1 −2); Deferred for Stroke (14−30)	1−2 d (TIA): 24 (42); 14−30 (Stroke): 33 (58)	NR
Massop[67] (2008) *Catheter Cardiovasc Interv*	SAPPHIRE Registry	CEA/CAS	2001	555 (27.7)	NR	NR	NR
Steinbauer[70] (2008) *J Vasc Surg*	RCT	CEA/CAS	87 CEA: 44 (50.6); CAS: 43 (49.4)	87 (100)	NR	NR	NR
Topakian[73] (2007) *Eur J Neurol*	Retrosp; Single centre	CAS	77	77 (100)	Early (0−14)	0−14 d: 23 (29.9); 15−180 d: 54 (70.1)	NR
Suzue[74] (2007) *J Vasc Surg*	Retrosp; Single centre	CEA	72	72 (100)	Early (0−30); Delayed (31−180)	0−30 d: 15 (20.8); 31−180 d: 57 (79.2)	NR
Dellagrammaticas[71] (2007) *Clin Med* GALA TRIAL	RCT	CEA	1 001	867 (86.6)	NR	NR	86 ± 30.0
Flanigan[72] (2007) *J Vasc Surg*	Retrosp analysis of prosp data; Single centre	CEA	442	170 (38.5)	NR	NR	NR
Sbarigia[76] (2006) *Eur J Vasc Endovasc Surg*	Prosp; Multicentre	CEA	96	96 (100)	NR	NR	1.5 ± 2
Imai[77] (2005) *Am J Neuroradiol*	Retrosp; Single centre	CAS	17	17 (100)	NR	NR	2.3 ± 2.4
Rantner[78] (2005) *Eur J Vasc Endovasc Surg*	Retrosp; Single centre	CEA	104	104 (100)	Acute (0−24 hours); Ultra-Early (0−6 hours); (0−27); (28 −180)	0 d: 7 (6.7); <28 d: 29 (27.9); ≥28 d: 62 (59.6)	
Ecker[80] (2004) *J Neurosurg*	Case Control	CEA/CAS	436 CEA: 391 (89.7) CAS: 45 (10.3)	436 (100)	NR	NR	NR
Kastrup[83] (2003) *Cerebrovasc Dis*	Case Control	CEA/CAS	242 CEA: 142 (58.7); CAS: 100 (41.3)	155 (64.0)	NR	NR	NR
Welsh[81] (2003) *Cerebrovasc Dis*	Prosp; Multicentre	CEA	40	40 (100)	Early (0−1); Delayed (60−180)	0−1 d: 19 (47.5); 60−180 d: 21 (52.5)	NR
ECST[84] (1988) *Lancet*	RCT	CEA *vs.* BMT	1 807	1 807 (100)	NR	NR	NR

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Table 1-*continued*

Article (Year) Journal	Type of article	CEA/ CAS	Patients	Symptomatic	Definition delay (days)	Timing of intervention	Mean delay ± SD − d
National Registry							
Kuhrij[21] (2019) *Eur J Vasc Endovasc Surg* Dutch Audit for Carotid Intervention	Retrosp analysis of prosp data; Multicentre	CEA	8 620	8 620 (100)	Early (0−14)	0−14 d: 6645 (78)	11 ± 1.7
Faateh[39] (2018) *J Vasc Surg* National Quality Improvement	Retrosp analysis of prosp data; Multicentre	CEA	9 271	9 271 (100)	Emergency: Performed within the same hospitalisation OR reported as emergency by the team	Emergency: 546 (5.9); Non-emergency: 8725 (94.1)	NR
Tsantilas[40] (2018) *J Am Heart Assoc* German Statutory Quality Assurance	Retrosp analysis of prosp data; Multicentre	CAS	4 717	4 717 (100)	Early (0−14); (0 −2); (3−7); (8−14); Delayed (15−180)	0−2 d: 550 (11.6); 3−7 d: 1579 (33.4); 8−14 d: 1244 (26.3); 15−180 d: 1344 (28.4)	NR
Blay[41] (2018) *Ann Vasc Surg* ACS-NSQIP	Retrosp analysis of prosp data; Multicentre	CEA	3 427	3 427 (100)	Early (0−7); Delayed (8−180)	0−7 d: 3247 (94.7); 8−180 d: 180 (5.3)	NR
Avgerinos[43] (2017) *J Vasc Surg* VSGNE Database	Retrosp analysis of prosp data; Multicentre	CEA	989	989 (100)		0 d: 96 (9.8); 1−2 d: 322 (32.6) 3−5 d: 94 (9.1); 6−180 d: 477 (48.2)	NR
Venermo[45] (2017) *Eur J Vasc Endovasc Surg* VQI/Vascunet	Retrosp analysis of prosp data; Multicentre	CEA/CAS	58 607 CEA: 52 434 (89.5); CAS: 6 173 (10.5)	30 520 (52.1)	NR	NR	NR
Kjorstad[18] (2017) *Eur J Vasc Endovasc Surg* National Norwegian Carotid Study	Retrosp analysis of prosp data; Multicentre	CEA	368	368 (100)	Early (0−14)	0−14 d: 227 (61.7); 15−180 d: 141 (36.8)	12.75 ± 4.3
Loftus[24] (2016) *Eur J Vasc Endovasc Surg* UK National Vascular Registry	Retrosp analysis of prosp data; Multicentre	CEA	33 194	23 235 (70.0)	Early (0−14); (0 −2); (3−7); (8−14); (15−21); Delayed (22−180)	0−2 d: 780 (3.4); 3−7 d: 5126 (22.1); 8−14 d: 6292 (27.1); 15−21 d: 2765 (11.9); 22−180 d: 8272 (35.6)	2009: 9.3 ± 4.9; 2010: 7.0 ± 4.1; 2011: 5.5 ± 2.90; 2012: 5.0 ± 2.3; 2013: 4.5 ± 2.3; 2014: 5.75 ± 6.7
Jonsson[16] (2015) *Eur J Vasc Endovasc Surg* Swedvasc Registry	Retrosp analysis of prosp data; Multicentre	CAS	323	323 (100)	Early (0−14); (0 −2); (3−7); (8−14); Delayed (15−180)	0−2 d: 13 (4.0); 3−7 d: 85 (26.3); 8−14 d: 80 (24.8); 15−180 d: 145 (44.9)	NR
Geraghty[50] (2014) *J Vasc Surg* SVS Vascular Registry	Retrosp analysis of prosp data; Multicentre	CEA/CAS	8 640 CEA: 5 758 (66.6); CAS: 2 882 (33.3)	2 904 (33.6)	Symptomatic: Neurologic events in the previous 12 months	NR	NR
Villwock[12] (2014) *J Stroke Cerebrovasc Dis* Nationwide Inpatient Sample	Retrosp analysis of prosp data; Multicentre	CEA *vs.* CAS	72 797 CEA: 62 327 (85.6); CAS: 13 470 (18.4)	72 797 (100)	Ultra-Early (0−2); Early (3−14)	0−2 d: 41008 (56.3); 3−14 d: 31789 (43.7)	NR
Witt[25] (2013) *Stroke* Danish Stroke Registry/Danish Vascular Registry	Retrosp analysis of prosp data; Multicentre	CEA	813	813 (100)	Early (0−14)	NR	Decrease in the delay to CEA with time: 13% underwent CEA in two weeks in 2007, 33% in 2008, 37% in 2009, 47% in 2010 (OR 5.8, 95% CI 4.3−10.1)
Schermerhorn[55] (2013) *J Vasc Surg* CMS	Retrosp analysis of prosp data; Multicentre	CEA/CAS	10 107 CEA: 6 370 (63.0); CAS: 3 737 (37.0)	3 916 (38.7)	NR	NR	NR
Nolan[58] (2012) *J Vasc Surg* VSGNE 2003−2010	Retrosp analysis of prosp data; Multicentre	CEA/CAS	8 079 CEA: 7 649 (94.6); CAS: 430 (5.4)	2 763 (34.2)	NR	NR	NR

Continued

Table 1-*continued*

Article (Year) Journal	Type of article	CEA/ CAS	Patients	Symptomatic	Definition delay (days)	Timing of intervention	Mean delay ± SD − d
Stromberg[27] (2012) *Stroke* Swedvasc Registry	Retrosp analysis of prosp data; Multicentre	CEA	2 596	2 596 (100)		0−2 d: 148 (5.7); 3−7 d: 804 (31.0); 8−14 d: 677 (26.1); 15−180 d: 967 (37.2)	NR
Garg[60] (2011) *Ann Vasc Surg* National Surgery Quality Improvement	Retrosp analysis of prosp data; Multicentre	CEA	17 388	8 103 (46.6)	NR	NR	NR
Palombo[62] (2009) *J Cardiovasc Surg* Italian Vascular Registry	Retrosp analysis of prosp data; Multicentre	CEA	5 809	1 894 (32.6)	NR	NR	NR
Halliday[86] (2009) *BMJ* UK Surgeons undertaking CEA	Retrosp analysis of prosp data; Multicentre	CEA	5 513	4 576 (83)	Early (0−12); (0 −2); (2−4); (5−12); Delayed (13−180);	0−2 d: 944 (20.0); 3−4 d: 654 (14); 5−12 d: 1621 (34); 13−180 d: 1372 (30)	45.3 ± 19.4
Vogel[65] (2009) *J Vasc Surg* Nationwide Inpatient Sample (2005)	Retrosp analysis of prosp data; Multicentre	CEA/CAS	80 498 CEA: 73 929 (91.8); CAS 6 569 (8.2)	2 237 (2.8)	NR	NR	NR
Gladstone[63] (2009) *Stroke* Canadian Stroke Network	Retrosp analysis of prosp data; Multicentre	CEA	105	105 (100)	Early (0−14); Deferred (15−30); Delayed (31−180)	0−14 d: 38 (36.2); 15−30 d: 53 (50.5); 31−180 d: 26 (24.8)	37.8 ± 20.5
Goodney[66] (2008) *J Vasc Surg* VSGNE 2003 −2007	Retrosp analysis of prosp data; Multicentree	CEA	3 092	1 360 (44)	Emergency (0−6 h); Urgent (0−24 h)	0−1 d: 309 (10)	NR
McPhee[75] (2007) *J Vasc Surg* Nationwide Inpatient Sample	Retrosp analysis of prosp data; Multicentre	CEA/CAS	259 080 CEA: 245 045 (94.6); CAS 14 035 (5.4)	20 750 (8)	NR	NR	NR
Pell[79] (2004) *Scott Med J* National Prospective Survey Scotland	Retrosp analysis of prosp data; Multicentre	CEA	877	855 (97.5)	Early (0−30); Deferred (31−60)	0−30 d: 103 (27); 31−60 d: 222 (58)	NR
Tu[82] (2003) *Stroke* Ontario Carotid Endarterectomy Registry	Retrosp analysis of prosp data; Multicentre	CEA	6 038	4 192 (69.4)	NR	NR	NR

Data are presented as *n* (%) unless stated otherwise. NR = not reported; Retrosp = retrospective; Prosp = prospective.

CAS). An analysis of reporting of timing of CEA and CAS after the index event was also performed.

Stroke was defined as a rapidly developing clinical syndrome of focal disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin. Stroke was considered procedural if the event occurred at any time between the revascularisation procedure (day 0) and day 30 after revascularisation.

Stroke was classified as disabling if there was an increase in the modified Rankin score (mRS) to $\geq$ 3, attributable to the event 30 days after the procedure. Neurological symptomatic status was defined as a transient ischaemic attack or minor disabling ischaemic stroke in the previous six months attributable to the ipsilateral carotid artery territory.

For the purpose of this meta-analysis, "expedited intervention" was used to define any intervention performed within two days of the index event. Index event was defined as the symptom that led the patient to seek medical advice as suggested in the ESVS guidelines.[1]

Two reviewers (AC and JP) screened the identified studies independently and were also responsible for data extraction (Fig. 1). Collected data included type of study, year of publication, number of patients and consecutiveness, adjudication of events by a clinical event committee (CEC), age, gender, and criteria for carotid revascularisation (presence and type of neurological symptoms and their timing). The definition of intervention delay regarding the index event was registered in different studies. Neurological events after the index event and before intervention were registered as well as procedural (30 day) events: stroke, myocardial infarction (MI), and death. Comparative data between early and delayed intervention were analysed, especially for interventions performed $\leq$ 2 days *vs.* between 3 and 14 days and for interventions performed $\leq$ 7 days *vs.* between 8 and 14 days of the index event.

When duplicates were identified, the most recent study was included unless the earlier version reported more data on specific parameters included in the analysis.

Please cite this article as: Coelho A et al., Timing of Carotid Intervention in Symptomatic Carotid Artery Stenosis: A Systematic Review and Meta-Analysis, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.08.021

Table 2. Analysis of patient characteristics including the type of neurological symptoms undergoing carotid endarterectomy (CEA) or carotid artery stenting (CAS) after index event

Article (Year)	CEA / CAS	Time periods	Symptomatic CEA / CAS	Age	Male sex	Type of event				New events before intervention
						TIA	Crescendo TIA / stroke in evolution	Afx	Minor / major stroke	
Jankowitz[13] (2020)	CEA *vs.* CAS	All (0–2 d)	120 (100)							
	CEA		59 (49.2)	68.4 ± 11.3	38 (64)	NR	NR	NR	NR	NR
	CAS		61 (50.8)	71.5 ± 12.9	42 (71)	NR	NR	NR	NR	NR
Roussopoulo[9] (2019)	CEA	All (0–14 d)	311 (100)	69 ± 11	230 (74)	128 (41)	28 (9)	–	183 (59)	NR
		0–2 d	63 (20.3)	67 ± 15	45 (71)	31 (49)	13 (21)	–	32 (51)	NR
		3–14 d	248 (79.7)	69 ± 10	186 (75)	99 (40)	17 (7)	–	124 (50)	NR
Huang[14] (2018)	CEA	All (0–180 d)	238 (100)	72 ± 9.1	158 (68)	176 (74)	–	71 (30)	62 (26)	NR
		Group 1 (0–14 d)	57 (23.9)	72 ± 10	34 (60.7)	48 (84)	–	18 (32)	9 (16)	NR
		0–2 d	11 (4.6)							
		3–7 d	23 (9.7)							
		8–14 d	23 (9.7)							
		Group 2 (14–180 d)	181 (76.1)	72 ± 8.8	124 (70)	128 (71)	–	53 (29)	53 (29)	NR
Seguchi[10] (2017)	CAS	All (0–180 d)	105 (100)							
		0–2 d	40 (38.1)	74.8 ± 2.5	37 (92.5)	9 (22.5)	25 (62.5)	–	31 (77.5)	NR
		3–180 d	65 (61.9)	77.0 ± 3.5	59 (90.8)	NR	0 (0)	NR	NR	NR
Rantner[44] (2017) EVA-3S, SPACE, ICSS, CREST	CEA *vs.* CAS	All (0–180 d)	4138 (100)							
	CEA *vs.* CAS	0–7 d	513 (12.4)		355 (8.6)	258 (6.2)	–	258 (6.2)	67 (1.6)	NR
	CEA		226 (11)	69.2 ± 8.9	157 (3.8)	112 (2.7)	–	112 (2.7)	30 (0.7)	NR
	CAS		287 (14)	68.3 ± 9.0	198 (4.9)	146 (3.5)	–	146 (3.5)	37 (0.9)	NR
	CEA *vs.* CAS	8–180 d	3625 (87.6)		2536 (61.3)	1277 (30.9)	–	1277 (30.9)	643 (15.5)	NR
	CEA		1819 (89)	69.6 ± 9.4	1285 (31.1)	649 (15.7)	–	649 (15.7)	317 (7.7)	NR
	CAS		1806 (86)	69.6 ± 9.2	1251 (30.2)	628 (15.2)	–	628 (15.2)	326 (7.9)	NR
Nordanstig[8] (2017)	CEA	0–2 d*	75 (18)	73.0 ± 8.5	55 (73)	28 (37)	14 (19)	18 (24)	15 (20)	NA
		3–14 d*	343 (82)	73.7 ± 8.5	237 (69)	106 (31)	17 (5)	12 (24)	138 (40)	NA
Tsantilas[23] (2016)	CEA	All (0–180 d)	401 (100)	69.8 ± 3.7	273 (68.1)	174 (43.4)	–	102 (25.4)	125 (31.1)	NR
		0–2 d	60 (15)	70.8 ± 10.1	44 (72)	32 (53)	–	13 (22)	15 (3.7)	NR
		3–7 d	110 (27.4)	70.8 ± 14.1	75 (68)	46 (42)	–	29 (26)	35 (8.7)	NR
		8–14 d	65 (16.2)	70.8 ± 18.8	41 (63.1)	25 (39)	–	9 (14)	31 (7.7)	NR
		14–180 d	166 (41.4)	68.5 ± 3.5	113 (68.1)	71 (43)	–	51 (31)	44 (10.9)	NR
Charbonneau[17] (2016)	CEA	All (0–180 d)	103 (100)	68.5 ± 13.3	71 (68.9)	42 (40.8)	–	21 (20.4)	40 (38.8)	43 (42)
		0–14 d	40 (38.8)		26 (36.6)	12 (28.6)	–	5 (23.8)	23 (57.5)	NR
		15–90 d	37 (35.9)		26 (36.6)	18 (42.9)	–	7 (33.3)	12 (30.0)	NR
		91–180 d	26 (25.2)		19 (26.8)	12 (28.6)	–	9 (42.9)	5 (12.5)	NR
Chisci[19] (2015)	CEA	All (0–30 d)	322 (100)	73.2 ± 9	235 (73)	166 (51)	43 (13)	27 (9)	129 (40)	NR
		0–14 d	100 (31.1)	72.5 ± 9.1	75 (75)	52 (52)	17 (17)	5 (5)	43 (43)	NR
		15–30 d	222 (68.9)	73.5 ± 8.9	160 (72)	114 (51)	26 (12)	22 (10)	86 (39)	NR
				$p = .35$	$p = .68$					
Kretz[26] (2015)	CEA	All (0–180 d)	417 (100)							
		0–15	158 (37.9)	73.8 ± 10	116 (73.4)	58 (36.7)	–	20 (12.7)	56 (35.4)	NR
		16–45	79 (18.9)	73.8 ± 11	53 (67.1)	33 (41.8)	–	9 (11.4)	24 (30.4)	NR
		46–180	180 (43.2)	73.1 ± 9.6	136 (75.6)	55 (30.6)	–	21 (11.7)	77 (42.8)	NR
Jonsson[16] (2015)	CAS	All (0–180 d)	323 (100)							
		0–2 d	13 (4.0)	69 ± 6.4	10 (76.9)	2 (15.4)	0 (0)	2 (15.4)	9 (69.2)	NR
		3–7 d	85 (26.3)	71 ± 8.7	58 (68.2)	37 (43.5)	0 (0)	15 (17.6)	33 (38.9)	NR
		8–14 d	80 (24.8)	72 ± 9.3	60 (74.1)	37 (46.3)	1 (1.3)	9 (11.1	34 (30)	NR
		15–180 d	145 (44.9)	70 ± 8.7	98 (67.6)	62 (42.8)	0 (0)	35 (24.1)	38 (33.1)	NR
Charmoille[47] (2014)	CEA	All (0–180 d)	149 (100)	71.5	119 (79.9)	60 (40.3)	19 (12.7)	14 (9.4)	75 (50.3)	NR
		0–14 d	62 (41.6)	69.7 ± 10.9	68 (78.2)	29 (46.8)	11 (17.7)	6 (9.7)	27 (43.5)	NR
		15–180 d	87 (58.4)	71.2 ± 13.3	51 (82.3)	31 (35.6)	8 (21.8)	8 (9.2)	48 (55.2)	NR
Rantner[48] (2014)	CEA	All (0–180 d)	761 (100)	70.1 ± 9.7	559 (73.5)	305 (40.1)	–	162 (21.3)	294 (38.6)	NR
		0–2 d	206 (27.1)	70.1 ± 10.3	152 (73.8)	115 (55.8)	–	37 (18)	54 (26.2)	NR
		3–7 d	219 (28.8)	70.9 ± 9.4	159 (72.6)	91 (41.6)	–	51 (23.3)	77 (35.2)	NR
		8–14 d	136 (17.9)	71.0 ± 9.2	102 (75.0)	54 (39.7)	–	33 (24.3)	49 (36.0)	NR
		15–180 d	200 (26.3)	68.5 ± 9.5	146 (73.0)	45 (22.5)	–	41 (20.5)	114 (57.0)	NR

Continued

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Table 2-*continued*

Article (Year)	CEA / CAS	Time periods	Symptomatic CEA / CAS	Age	Male sex	Type of event				New events before intervention
						TIA	Crescendo TIA / stroke in evolution	Afx	Minor / major stroke	
Tsivgoulis[49] (2014)	CEA	All (0–14 d)	165 (100)	69 ± 10	114 (69)	50 (30)	–	–	115 (70)	NR
		0–2 d	20 (12)	70±12	11 (55)	7 (35)	–	–	13 (65)	NR
		3–14 d	145 (88)	68 ± 10	154 (71)	44 (30)	–	–	101 (70)	NR
Shahidi[53] (2013)	CEA	All	115 (100)	NR	NR	39 (34)	–	11 (9)	65 (56.5)	NR
Sharpe[15] (2013)	CEA	All	475 (100)	NR	NR	72 (57)	–	94 (20)	109 (23)	
Faggioli[54] (2013)	CEA	All (0–180 d)	162 (100)	NR	NR	81 (50)	–	9 (5.6)	72 (44.4)	NR
		0–14	60 (37)	NR	NR	36 (60)	–	2 (3.3)	22	NR
		15–30	18 (11.1)	NR	NR	12 (66.7)	–	2 (11.1)	4	NR
		31–180	84 (51.9)	NR	NR	33 (39.3)	–	5 (5.9)	46	NR
Annambhotla[59] (2012)	CEA	All (0–180 d)	312 (100)	NR	200 (64.1)	106 (34.0)	–	–	205 (65.6)	
		0–7 d	27 (8.7)	68.6 ± 9.8	16 (59.3)	7 (25.9)	–	–	20 (74.1)	
		8–14 d	17 (5.4)	68.8 ± 14.7	9 (52.9)	3 (17.6)	–	–	14 (82.4)	
		15–21 d	12 (3.8)	67.5 ± 14.3	8 (66.7)	3 (25)	–	–	9 (75)	
		22–30 d	12 (3.8)	70.7 ± 9.3	8 (66.7)	1 (8.3)	–	–	11 (91.7)	
		31–180 d	243 (77.9)	70.4 ± 9.7	159 (65)	92 (38)	–	–	151 (62)	
Lin[61] (2009)	CAS	All (0–180 d)	224 (100)							
		0–30 d[†]	122 (54.5)	72 ± 10.2	80 (65.6)	77 (62.6)	–	–	46 (37.4)	
		31–180 d	102 (45.5)	69 ± 9.9	63 (61.8)	72 (71.3)	–	–	29 (28.7)	
				$p = .002$	$p = .39$					
Ballotta[68] (2008)	CEA	0–14 d	102 (100)	NR	65 (65.7)	0 (0)	0 (0)	0 (0)	102 (100)[‡]	NR
Setacci[69] (2008)	CAS	All (0–30 d)	57 (100)	76.7 ± 8.0	37 (64.9)	–	–	–	–	NR
		0–2 d	24 (42)	–	–	24 (100)	–	–	0 (0)	NR
		14–30 d	33 (58)	–	–	0 (0)	–	–	33 (100)	NR
Suzue[74] (2007)	CEA	All (0–180 d)	72 (100)							NR
		0–30 d	15 (20.8)	65.4 ± 7.0	14 (93.3)	7 (46.7)	–	–	8 (14.0)	NR
		31–180 d	57 (79.2)	69.2 ± 7.4	47 (76.9)	27 (47.4)	–	–	30 (52.6)	NR
Dellagrammaticas[71] (2007) GALA Trial	CEA		867 (100)	71.5 ± 3.5	687 (69)	303 (35)	–	146 (17)	231 (27)	NR
Flanigan[72] (2007)	CEA		170 (38.5)	NR	NR	NR	NR	NR	NR	NR
Sbarigia[76] (2006)	CEA		96 (100)	69.4 ± 9.8	81 (84.3)	NR	NR	NR	NR	NR
Imai[77] (2005)	CAS		17 (100)	69.9	13 (76.4)	NR	NR	NR	NR	NR
Rantner[78] (2005)	CEA	All (0–180 d)	104 (100)	69.4 ± 9.8	80 (87.1)	NR	NR	NR	NR	NR
		0–6 hours	7 (6.7)							
		0–27 d	29 (27.9)							
		28–180 d	62 (59.6)							
Welsh[81] (2003)	CEA	All (0–180 d)	40 (100)							
		0–1 d	19 (47.5)	65.8 ± 8.9	11 (57.9)	NR	NR	NR	NR	NR
		60–180 d	21 (52.5)	68.3 ± 9.5	12 (57.1)	NR	NR	NR	NR	NR
ECST[84] (1988)	CEA *vs.* BMT		1 807 (100)	NR	NR	NR	NR	NR	NR	NR
National audits										
Kuhrij[21] (2019) Dutch Audit for Carotid Intervention	CEA	All	8 620 (100)	72 ± 9.0	6010 (70)	NR	NR	NR	NR	NR
		0–14 d	6 645 (78)	NR	NR	NR	NR	NR	NR	NR
Faateh[39] (2018) National Quality Improvement	CEA	All	9 271 (100)	NR	NR	NR	NR	NR	NR	NR
	eCEA		546 (5.9)	70.5 ± 11.2	348 (63.7)	206 (37.7)	–	61 (11.2)	279 (51.1)	NR
	Non-eCEA		8 725 (94.1)	70.8 ± 9.9	5 390 (61.8)	3 282 (37.6)	–	1 507 (17.3)	3 935 (45.1)	NR
Tsantilas[40] (2018) German Statutory Quality Assurance	CAS	All (0–180 d)	4 717 (100)	69.8 ± 9.8	3 201 (67.8)	1 351 (28.6)	–	797 (16.9)	2 126 (45.1)	NR
		0–2 d	550 (11.6)	69.1 ± 10.1	386 (70.2)	155 (28.2)	–	65 (11.8)	268 (48.7)	NR
		3–7 d	1 579 (33.4)	69.6 ± 9.9	1070 (67.8)	472 (29.9)	–	212 (13.4)	796 (50.4)	
		8–14 d	1 244 (26.3)	70.1 ± 9.9	835 (67.1)	306 (24.6)	–	234 (18.8)	622 (50.0)	NR
		15–180 d	1 344 (28.4)	69.9 ± 9.5	910 (67.7)	418 (31.1)	–	286 (21.3)	440 (32.7)	NR
Blay[41] (2018)	CEA	All (0–180 d)	3 427 (100)	NR	2181 (63.6)	NR	NR	NR	NR	NR
ACS-NSQIP		0–7d	3 247 (94.7)	NR	NR	NR	NR	NR	NR	NR
		8–180 d	180 (5.3)	NR	NR	NR	NR	NR	NR	NR
Rocco[20] (2018)	CEA / CAS		110 (100)	NR	78 (70.9)	10 (9.1)	–	–	100 (90.9)	NR

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Table 2-*continued*

Article (Year)	CEA / CAS	Time periods	Symptomatic CEA / CAS	Age	Male sex	Type of event				New events before intervention
						TIA	Crescendo TIA / stroke in evolution	Afx	Minor / major stroke	
Avgerinos[43] (2017) VSGNE Database	CEA	All (0–180 d)	989 (100)	69.6 ± 10.7	653 (66)	NR	NR	NR	NR	NR
		0 d	477 (48.2)	69.4 ± 10.5	307 (64.4)	NR	NR	NR	NR	NR
		1–2 d	96 (9.8)	70.1 ± 10.9	66 (68.8)	NR	NR	NR	NR	NR
		3–5 d	322 (32.6)	69.9 ± 10.8	210 (65.2)	NR	NR	NR	NR	NR
		6–180 d	94 (9.1)	69.3 ± 11.4	70 (74.5)	NR	NR	NR	NR	NR
Kjorstad[18] (2017) National Norwegian Carotid Study	CEA		368 (100)	NR	NR	135 (36.7)	–	64 (17.4)	167 (45.4)	12 (3.3%)
Hobeanu[42] (2017)	CEA/CAS		187 (100)	71 ± 10	142 (75.9)	NR	NR	NR	NR	NR
Loftus[24] (2016) UK National Vascular Registry	CEA		23 235 (70.0)	72.8 ± 3.7	15 510 (66.8)	11 029 (47.5)	–	3 553 (15.3)	8 229 (35.4)	NR
Villwock[12] (2014) NIS Registry	CEA *vs.* CAS	All (0–14 d)	72 797 (100)	NR				NR		
		0–2 d	41 008 (56.3)	NR	22 601 (55.1)	38 001 (52.2)	3 007 (4.1)	NR		NR
	CEA		31 899 (43.8)	NR	17 105	29 936 (41.1)	1 963 (2.7)	NR		NR
	CAS		9 109 (12.5)	NR	5 496	8065 (11.1)	1 044 (1.4)	NR		NR
		3–14 d	31 789 (43.7)	NR	25 146 (79.1)	22 207 (30.5)	12 582 (17.3)	NR		NR
	CEA		30 428 (41.8)	NR	22 436	19 729 (27.1)	10 699 (14.7)	NR		NR
	CAS		4 361 (6.0)	NR	2 710	2 478 (3.4)	1 883 (2.6)	NR		NR
Stromberg[27] (2012) Swedvasc Registry	CEA	All (0–180 d)	2 596 (100)	71.9 ± 8.2	1 731 (66.7)	1 041 (40.1)	54 (2.1)	508 (19.6)	993 (38.3)	NR
		0–2 d	148 (100)	69.8 ± 8.6	104 (70.3)	70 (47.3)	17 (11.5)	23 (15.5)	38 (25.7)	NR
		3–7 d	804 (100)	72.6 ± 8.2	526 (65.4)	363 (45.1)	19 (2.4)	122 (15.2)	300 (37.3)	NR
		8–14 d	677 (100)	72.7 ± 8.2	438 (64.7)	279 (41.2)	14 (2.1)	107 (15.8)	259 (38.3)	NR
		15–180 d	967 (100)	71.0 ± 8.1	663 (68.6)	329 (34.0)	4 (0.4)	256 (26.5)	411 (42.5)	NR
Garg[60] (2011) National Surgery Quality Improvement	CEA		8 103 (46.6)	NR	NR	NR	NR	NR	NR	NR
Palombo[62] (2009) Italian Vascular Registry	CEA		1 894 (32.6)	NR	NR	NR	NR	NR	NR	NR
Halliday[86] (2009) UK Surgeons undertaking CEA	CEA	All (0–180 d)	4 576 (100)	NR	NR	1 914 (41.8)	–	916 (20.0)	1 634 (35.7)	NR
		0–2 d	944 (20.6)	NR	NR	NR	NR	NR	NR	NR
		3–4 d	654 (14.3)	NR	NR	NR	NR	NR	NR	NR
		5–12 d	1 621 (35.4)	NR	NR	NR	NR	NR	NR	NR
		13–180 d	1 372 (30.0)	NR	NR	NR	NR	NR	NR	NR
Vogel[65] (2009) Nationwide Inpatient Sample (2005)	CEA/CAS		2 237 (100)	NR	NR	NR	NR	NR	NR	NR
Gladstone[63] (2009) Canadian Stroke Network	CEA		105 (100)	NR	NR	NR	NR	NR	NR	NR
Goodney[66] (2008) VSGNE (2003–2007)	CEA	All	1 360 (100)	NR	NR	680 (50)	–	572 (42.1)	340 (25)	NR
		Emergency / Urgent	309 (22.7)	NR	NR	NR	–	NR	NR	NR
Pell[79] (2004) National Prospective Survey Scotland	CEA	All (0–60 d)	855 (100)	NR	510 (58.2)	NR	NR	NR	NR	NR
		0–30 d	103 (27)	NR	NR	NR	NR	NR	NR	NR
		31–60 d	222 (58)	NR	NR	NR	NR	NR	NR	NR
Tu[82] (2003) Ontario Carotid Endarterectomy Registry	CEA		4 192 (69.4)	NR	NR	NR	NR	NR	NR	NR

Data are presented as *n* (%) or mean ± standard deviation, unless stated otherwise. NA = not applicable; NR = not reported. *p* value is considered significant if ≤ .050.

* Of the most recent neurological event before intervention.

† Early category was subclassified into ultra-early (0–14 d) with not significant difference compared with other categories.

‡ Only minor strokes were included.

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Table 3. Analysis of post-procedural outcomes after carotid endarterectomy (CEA) or carotid artery stenting (CAS), stratified by delay after index event

Study, year	CEA/CAS	0–2 d	3–7 d	8–14 d	15–30 d	31–180 d
30 day stroke – % (n)						
Jankowittz, 2020[13]	CEA	5.1 (3)	–	–		–
	CAS	3.3 (2)	–	–		–
Huang, 2018[14]	CEA	27 (3)	0 (0)	4.3 (1)		0.6 (1)
Tsantilas, 2018[40] German Statutory Quality	CAS	3.8 (21)	3.5 (56)	1.8 (22)		2.2 (30)
Sharpe, 2013[15]	CEA	2.4 (1)	1.8 (3)	0.8 (1)		0.8 (1)
Stromberg, 2012 Swedvasc[27]	CEA	10.8 (16)	2.5 (20)	3.4 (23)		4.0 (39)
Nordanstig, 2017[8]	CEA	8.0 (6)	3.0 (9)			–
Avgerinos, 2017 VSGNE[43]	CEA	3.5 (20)		2.4 (10)		
Tsantilas, 2016[23]	CEA	0 (0)	1.8 (2)	1.5 (1)		1.8 (3)
Loftus, 2016 UK National Vascular Registry[24]	CEA	3.1 (24)	2.0 (103)	1.7 (107)		1.8 (199)
Jonsson, 2015[16]	CAS	0 (0)	3.5 (3)	6.3 (5)		3.5 (5)
Rantner, 2014[48]	CEA	8 (3.9)	4 (1.8)	6 (4.4)		5 (2.5)
Villwock, 2014	CEA	1.1 (341)	1.6 (496)			–
NIS *,[12]	CAS	1.7 (154)	1.8 (77)			–
Roussopoulou, 2019[9]	CEA	7.9 (5)	4.4 (11)		–	–
Seguchi, 2017[10]	CAS	2.5 (1)	–		6.2 (4)	
Setacci, 2007[69]	CEA	0 (0)	0 (0)		–	–
Blay, 2018 ACS-NSQIP[41]	CEA	2.7 (86)			2.8 (5)	
Rantner, 2017[44]	CEA	1.3 (3)			3.4 (63)	
	CAS	8.0 (23)			6.8 (122)	
Annambhotla, 2012[59]	CEA	0 (0)		0 (0)		1.6 (4)
Chisci, 2016[19]	CEA	3.0 (3)			0.4 (1)	–
Kretz, 2015[26]	CEA	1.3 (2)				1.5 (4)
Charmoille, 2014[47]	CEA	0 (0)				3.5 (3)
Faggioli, 2013[54]	CEA	6.6 (4)				2.9 (3)
Ballotta, 2008[68]	CEA	0 (0)			–	–
Suzue, 2007[74]	CEA	0 (0)				0 (0)
30 day myocardial infarction – % (n)						
Jankowittz, 2020[13]	CEA	3.4 (2)	–	–		–
	CAS	4.9 (3)	–	–		–
Huang, 2018[14]	CEA	0 (0)	0 (0)	0 (0)		3.3 (6)
Tsantilas, 2018 German Statutory Quality[40]	CAS	0.3 (1)	0.1 (1)	0 (0)		0.1 (1)
Jonsson, 2015[16]	CAS	0 (0)	3.5 (3.0)	2.5 (2)		1.4 (2)
Avgerinos, 2017 VSGNE[43]	CEA	1.4 (8)		1.2 (5)		
Tsantilas, 2016[23]	CEA	2.0 (1)	1.0 (1)	0 (0)		1.0 (1)
Roussopoulo, 2019[9]	CEA	0 (0)	0.8 (2)		–	–
Seguchi, 2017[10]	CAS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Setacci, 2007[69]	CEA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Annambhotla, 2012[59]	CEA	0 (0)	0 (0)	0 (0)	0 (0)	0.8 (2)
Chisci, 2016[19]	CEA	0 (0)	0 (0)	0 (0)	1.8 (4)	–
Charmoille, 2014[47]	CEA	0 (0)	0 (0)	0 (0)		3.5 (3)
Faggioli, 2013[54]	CEA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ballotta, 2008[68]	CEA	0 (0)	0 (0)	0 (0)	–	–
Blay, 2018 ACS-NSQIP[41]	CEA	0.99 (32)			0.56 (1)	
Kretz, 2015[26]	CEA	0.6 (1)				1.2 (3)
30 day mortality – % (n)						
Jankowittz, 2020[13]	CEA	0 (0)	–	–		–
	CAS	1.6 (1)	–	–		–
Huang, 2018[14]	CEA	0 (0)	0 (0)	0 (0)		0.6 (1)
Tsantilas, 2018 German Statutory Quality[40]	CAS	2.2 (12)	0.9 (14)	0.6 (8)		0.7 (10)
Jonsson, 2015[16]	CAS	0 (0)	0 (0)	3.8 (3)		0.7 (1)
Sharpe, 2013[15]	CEA	0 (0)	0 (0)	0.8 (1)		0 (0)
Stromberg, 2012 Swedvasc[27]	CEA	2.0 (3)	1.2 (10)	1.5 (10)		1.7 (16)
Avgerinos, 2017 VSGNE[43]	CEA	1.2 (7)		1.4 (6)		
Tsantilas, 2016[23]	CEA	3.0 (2)	1.0 (1)	0 (0)		1.0 (1)
Loftus, 2016[24] UK National Vascular Registry	CEA	1.0 (8)	0.9 (46)	0.7 (44)		0.8 (88)
Rantner, 2014[48]	CEA	0.5 (1)	0 (0)	0.7 (1)		0.5 (1)
Villwock, 2014	CEA	0.4 (129)	0.8 (258)		–	–
NIS *,[12]	CAS	2.1 (191)	1.6 (69)		–	–
Roussopoulo, 2019[9]	CEA	0 (0)	0.4 (1)		–	–
Nordanstig, 2017[8]	CEA	0 (0)	0.3 (1)		0 (0)	0 (0)
Seguchi, 2017[10]	CAS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Annambhotla, 2012[59]	CEA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Chisci, 2016[19]	CEA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Please cite this article as: Coelho A et al., Timing of Carotid Intervention in Symptomatic Carotid Artery Stenosis: A Systematic Review and Meta-Analysis, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.08.021

Table 3-*continued*

Study, year	CEA/CAS	0–2 d	3–7 d	8–14 d	15–30 d	31–180 d
Blay, 2018 ACS-NSQIP[41]	CEA	1.2 (38)			2.8 (5)	
Kretz, 2015[26]	CEA		1.9 (3)			1.5 (4)
Charmoille, 2014[47]	CEA		1.7 (1)			1.2 (1)
Faggioli, 2013[54]	CEA		1.6 (1)		0 (0)	3.6 (3)
Ballotta, 2008[68]	CEA		0 (0)		–	–
30 day death / stroke – % (n)						
Jankowittz, 2020[13]	CEA	5.1 (3)	–	–		–
	CAS	4.9 (3)	–	–		–
Roussopoulou, 2019[9]	CEA	7.9 (5)	4.8 (12)	–		–
Huang, 2018[14]	CEA	27 (3)	0 (0)	4.3 (1)		1.1 (2)
Nordanstig, 2017[8]	CEA	8.0 (6)	3.0 (9)			–
Tsantilas, 2016[23]	CEA	3.0 (2)	3.0 (3)	2.0 (1)		2.0 (3)
Loftus, 2016 UK National Vascular Registry[24]	CEA	29 (3.7)	128 (2.5)	132 (2.1)		254 (2.3)
Jonsson, 2015[16]	CAS	0 (0)	4.7 (4)	6.3 (6)		4.1 (6)
Rantner, 2014[48]	CEA	4.4 (9)	1.8 (4)	5.1 (7)		2.5 (5)
Sharpe, 2013[15]	CEA	2.4 (1)	1.8 (3)	0.8 (1)		0.8 (1)
Stromberg, 2012	CEA	11.5 (17)	3.6 (29)	4.0 (27)		5.4 (52)
Swedvasc[27]						
Nordanstig, 2017[8]	CEA	6 (8)	10 (3)			–
Seguchi, 2017[10]	CAS	2.5 (1)		6.2 (4)		
Rantner, 2017[44]	CEA	1.3 (3)			3.6 (65)	
	CAS	8.4 (24)			7.1 (129)	
Chisci, 2016[19]	CEA		3.0 (3)		0.4 (1)	–
Mean 30 day death / stroke ± standard deviation						
Jankowittz, 2020[13]	CEA	5.6±3.2	–	–		–
	CAS	5.3±4.1	–	–		–
		p=.66	–	–		–
Huang, 2018[14]	CEA	4.7±7.2	3.3±1.7	2.0±1.5		1.8±1.5
Tsantilas, 2018 German Statutory Quality[40]	CAS	3.5±1.2	3.3±0.9	2.5±0.6	–	–
Villwock, 2014[12] NIS*	CEA for Stroke	3.5±1.2	7.3±1.5		–	–
	CAS for Stroke	4.3±1.5	7.3±1.5		–	–
	CEA for TIA/AFX	1.8±0.1	6.5±1.2		–	–
	CAS for TIA/AFX	1.3±0.4	6.0±1.2		–	–
Roussopoulo, 2019[9]	CEA	6.5±1.7	10.3±2.0		–	–
Seguchi, 2017[10]	CAS	22.5±6.3		21.5±4.6		
Chisci, 2016[19]	CEA		3.7±2.2		2.5±1.5	–

TIA = transient ischaemic attack; AFX = amaurosis fugax
* In hospital data

Quality assessment

The methodology of the studies and risk of bias were systematically assessed by two independent reviewers (AC and JP) using the Methodological Index for Non-Randomized Studies (MINORS) score,[7] with a maximum score of 16 for non-comparative and 24 for comparative studies. A score $\leq$ 8 was considered poor quality, 9 – 14 moderate quality, and 15 – 16 good quality for non-comparative studies. Cut off points were $\leq$ 14, 15 – 22, and 23 – 24, respectively, for comparative studies.

Authorship of the studies was unblinded during review. Discrepancies between the reviewers during the search, selection, and quality assessment were resolved by discussion. In case of persisting disagreement, a third reviewer was consulted.

Statistical analysis

The software Review Manager 5.4 (REVMAN) was used to analyse data. Odds ratios (OR) and 95% confidence intervals (CI) were used for dichotomous variables, and mean differences (MDs) with 95% CI for continuous data.

Statistical heterogeneity, defined as a measure of the variability of outcomes between studies, was assessed by the Cochran's Q test: the H^2 test (Higgins and Thompson) was used to quantify the magnitude of heterogeneity. The parameter I^2 retrieved from the H^2 test was used with a cut off of 25% for low, 25% – 50% for intermediate, and above 50% for high heterogeneity. A fixed effects model was used when heterogeneity (I^2) was less than 50% and a random effects model was used when heterogeneity (I^2) was high.

RESULTS

A total of 1 495 potentially relevant articles were identified initially. After reviewing title or abstract, 112 articles were retrieved and 71 judged eligible for inclusion (Fig. 1). Agreement between reviewers was reached for all articles and arbitration by the third reviewer was unnecessary.

Overall, there were 24 retrospective analyses of prospective national databases, 10 retrospective analyses of prospective databases, nine prospective studies, three RCTs, and three case control studies. The remaining 22 studies

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were retrospective, single centre, or multicentre, analysis of patient data. The total number of symptomatic patients in the constituent studies was 232 952 (Table 1). Methodological quality is reported in Supplementary Table S1. A total of 18 non-comparative studies of moderate quality and 53 comparative studies (50 moderate, two poor quality, and one good quality) were included (Supplementary Table S1).

Definitions

The definitions of "delay" and "index event" were heterogeneous (Table 1). Most studies defined "early intervention" when CEA or CAS were performed within 14 days of the index event, although some studies applied stricter or looser definitions (Table 1). Stratification of the timing of events within the first 14 days was described in some studies, for example as "acute/urgent/emergency/ultra-early interventions" (Table 1). One study was identified that defined the timing of intervention as the time from the qualifying event (defined as the most recent neurological event before intervention, rather than the index event).[8]

Symptomatic status and timing of intervention

Considering all symptomatic patients (232 952), the time to intervention was reported for 148 653 patients (63.8%), of whom 44 410 (29.9%) underwent either CEA or CAS within the first 48 hours and 108 139 (72.7%) within the first 14 days after the index event.

Thirty-five studies reported outcomes after CEA alone (73 242), while five studies reported outcomes after CAS alone (5 443). Five studies reported mixed outcomes, three of which compared CEA (64 430) with CAS (15 624) (Table 2).

Stratification of demographic data, type of neurological index event, and occurrence of new neurological symptoms, stratified by intervention delay are detailed in Table 2.

Where reported, patients presenting with crescendo TIAs were more likely to undergo an early intervention.[9,10] The remaining presenting events (TIA, amaurosis fugax and stroke) were evenly distributed by intervention delay, with few exceptions (Table 2).

Primary and secondary outcomes

Peri-operative (30 day) outcomes along with data on hospitalisation duration (in days), stratified by intervention delay and by type of revascularisation (CEA *vs.* CAS) are detailed in Table 3. Almost all of the CAS procedures in the varying meta-analyses were performed via the transfemoral route. No published studies have evaluated outcomes for transcarotid artery revascularisation (TCAR) *vs.* CEA, with stratification for delays to treatment.[11]

Carotid endarterectomy *vs.* carotid artery stenting

Overall data. Outcome data from eight CEA studies (88 129) and two CAS studies (3 551) are detailed in Table 4. In CEA patients, 30 day stroke was 1.4% (95% CI 0.9 — 1.8) when performed within 0 — 2 days, *vs.* 1.8% (95% CI. 1.5 — 2.0) when performed between three and 14 days. In CAS patients, 30 day stroke was 1.8% (95% CI 1.3 — 2.3) when performed within two days, *vs.* 2.2% (95% CI 0.3 — 4.2) between three and 14 days (Table 4). Across all intervention timings, there were higher rates of stroke after CAS (*vs.* CEA), while there were higher rates for MI after CEA (*vs.* CAS). Individual study data used to calculate the pooled rates are available in Supplementary Table S2 (Supplementary material).

Carotid endarterectomy vs. carotid artery stenting when performed ≤ 2 days after the index event. Two moderate quality studies reported outcomes after CEA *vs.* CAS (75 917) when performed within two days of the index event, including one retrospective analysis of prospective single centre data (120) and one retrospective analysis of Nationwide Inpatient Sample (NIS) database (72 797).[12,13] Compared with CEA, meta-analysed data revealed significantly higher risks for 30 day stroke when CAS was performed within ≤ 2 days (OR 0.70; 95% CI 0.58 — 0.85) as well as significantly higher rates of 30 day death (OR 0.41; 95% CI 0.31 — 0.53) (Fig. 2). One of the above mentioned registries (72 797) analysed patients with and without cerebral infarction separately and concluded that expedited revascularisation in patients with cerebral infarction on admission increased the risk of iatrogenic stroke and death; the increase in mortality was more dramatically seen in patients treated by CAS. No differences were found in stroke/death rates between CEA and CAS if patients presented without infarction.[12]

Carotid endarterectomy vs. carotid artery stenting when performed 3 — 14 days after index event. The same large national registry (72 797) cited in the previous section also reported comparative outcomes between CEA *vs.* CAS when performed 3 — 14 days after the index event (with or without cerebral infarction). There was no statistically significant difference in 30 day stroke after CAS (1.8%) *vs.* after CEA (1.6%; OR 1.1; 95% CI 0.9 — 1.4). However, 30 day mortality was statistically significantly higher after CAS (1.6%) *vs.* after CEA (0.8%; OR 1.9; 95% CI 1.4 — 2.5). Again, no differences were found in stroke/death rates between CEA and CAS if patients presented without infarction.[12]

Outcomes after carotid endarterectomy

≤ 2 days vs. 3 — 14 days after index event. A total of nine moderate quality manuscripts were included in this analysis, three of which were retrospective analyses of national registries, two prospective multicentre studies, and four retrospective studies. CEA performed 3 — 14 days after the index event was associated with a statistically significantly lower 30 day death/stroke risk (OR 2.05; 95% CI 1.56 — 2.68) compared with performing CEA within ≤ 2 days of index event. No statistically significant difference was attained regarding 30 day stroke, MI, and mortality (OR 1.87; 95% CI 0.99 — 3.51, OR 1.50; 95% CI 0.21 — 10.45, and OR 1.11; 95% CI 0.58 — 2.14, respectively) (Fig. 3).

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Meta-analysis of 30 day stroke, mortality, and MI included the same core studies, while in the analysis of 30 day death/stroke, three studies were excluded as they did not report the composite outcome,[9,12,14] while one study was included that only reported combined stroke/death data, with worse outcomes reported in the expedited cohort (Fig. 3).[15]

≤ 7 days vs. 8 − 14 days after index event. A total of five moderate quality manuscripts were included in this analysis, two of which were retrospective analyses of national registries and three retrospective studies. Meta-analyses (Fig. 4) revealed that CEA performed within 7 days of the index event was associated with a significantly lower risk of 30 day stroke compared with 8 − 14 days (OR 0.67; 95% CI 0.54 − 0.84). There was no difference regarding CEA performed within 7 days of the index event (*vs.* 8 − 14) in the outcomes 30 day mortality (OR 1.86; 95% CI 0.19 − 18.21), 30 day death/stroke (OR 0.79; 95% CI 0.47 − 1.34), or 30 day MI (OR 1.94; 95% CI 0.09 − 41.03) (Fig. 4).

Outcomes after carotid artery stenting

≤ 2 days vs. 3 − 14 days after index event. This systematic review identified 17 578 patients who underwent CAS ≤ 14 days of symptom onset, including 9 833 (55.9%) who underwent CAS within ≤ 2 days of the index symptom. Two moderate quality national registries compared outcomes when CAS was performed within ≤ 2 days vs. 3 − 14 days of the index symptom.[14,16] Compared with CAS interventions within 3 − 14 days, performing CAS ≤ 2 days was not associated with significant differences in 30 day stroke (OR 1.36; 95% CI 0.84 − 2.21) or 30 day MI (OR 2.23; 95% CI 0.34 − 14.41) However, performing CAS within ≤ 2 days of the index symptom was associated with significantly higher risks of 30 day death (OR 2.76; 95% CI 1.39 − 5.50) compared with CAS interventions within 3 − 14 days of the index event (Fig. 5). A single study ($n = 323$) reported the results of a comparative analysis of 30 day death/stroke and showed no significant difference when CAS was performed in either time period (OR 0.61; 95% CI 0.03 − 11.06).[16]

≤ 7 days vs. 8 − 14 days after index event. The same national registries that compared outcomes when CAS was performed ≤ 2 days *vs.* 3 − 14 days, also analysed outcomes ≤ 7 days *vs.* 8 − 14 days.[14,16] Forest Plot analyses (Fig. 6) revealed that there was no significant difference in 30 day stroke, MI, or mortality when CAS was performed ≤ 7 days *vs.* 8 − 14 days after the index event (OR 1.18; 95% CI 0.29 − 4.83, OR 1.62; 95% CI 0.35 − 7.43, and OR 0.67; 95% CI 0.04 − 10.12, respectively).

Recurrent events while awaiting a carotid intervention

Recurrent neurological events occurring after a decision to perform CEA but before it was performed were reported rarely. In one single centre study, 42% of patients who waited 0 − 180 days to undergo CEA suffered a recurrent TIA or stroke prior to CEA.[17] The National Norwegian Carotid Study reported that 3.3% suffered recurrent symptoms prior to undergoing CEA within 14 days of the index event (Table 2).[18]

Neurological outcome

Surprisingly, few studies used the National Institutes of Health Stroke Scale (NIHSS) to quantify improvements in neurological disability after carotid interventions, stratified for the timing of carotid interventions (Table 3). A single centre study reported improved neurological outcomes for interventions performed within 14 days *vs.* 15 − 30 days of the index event (NIHSS range 0.9 ± 0.4 *vs.* 0.5 ± 0.2; $p = .011$).[19] Other studies report NIHSS range but with no discriminative data concerning carotid intervention delay from index event.[13,18,20]

Hospital stay

Hospital stay analysis presented a trend towards prolonged stay in patients undergoing CEA between 3 − 14 days after the index event *vs.* ≤ 2 days, with a mean difference (MD) of −1.28 (95% CI −6.96 − 4.40) (Fig. 7).

Only one study[10] reported length of hospital stay after CAS, with non-significant difference between intervention ≤ 2 *vs.* 3 − 14 days (MD −1.0; 95% CI −3.1 − 1.1).

DISCUSSION

The ESVS guidelines advise that CEA (CAS) should be performed within 14 days of symptom onset.[1] Evidence suggests that there has been a major drive towards performing interventions < 14 days (especially in Europe), where the median delay to CEA is now 11 days in the Netherlands,[21] 7 days in Sweden,[22] 9 days in Germany,[23] and 11 days in the UK.[24] A temporal trend towards a progressive decrease in delays from index event to undergoing CEA (or CAS) has been reported by several national registries.[24−26] The proportion of Danish Stroke Registry patients[17] undergoing carotid interventions within two weeks of the index event increased from 13% in 2007 to 47% by 2010 (OR 5.8; 95% CI 4.3 − 10.1).[25] Similar findings were reported by the UK National Vascular Registry.[24] However, uncertainty persists regarding the ideal timing for either CEA or CAS within the 14 day time frame to balance the dichotomy between recurrent stroke prevention and minimising peri-operative risks.[25]

The Swedish Vascular Registry (Swedvasc) were the first to highlight concerns about intervening within ≤ 48 hours of the index event, as they observed an 11.5% rate of 30 day death/stroke, compared with 3.6% (3 − 7 days), 4% (8 − 14 days), and 5.4% (> 14 days) for CEA. However, only a small proportion of Swedvasc patients were treated ≤ 48 hours (5.7%), which may have limited the generalisability of the Swedish registry data.[27] Other (much larger) national

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Table 4. Pooled estimated prevalence in different sized samples on main outcomes, stratified by intervention timing and type of procedure

	CEA		CAS	
	0–2 days – % (95% CI)	3–14 days – % (95% CI)	0–2 days – % (95% CI)	3–14 days – % (95% CI)
30 d stroke	1.4 (0.9–1.8); SE 0.2*,‡	1.8 (1.5–2.0); SE 0.1†,‡	1.8 (1.3–2.3); SE 0.2*,‡	2.2 (0.3–4.2); SE 0.5†,‡
30 d MI	1.5 (0.7–2.2); SE 0.2	0.9 (0.0–1.7); SE 0.2	0.6 (0.0–2.5); SE 0.6	0.2 (0.0–1.3); SE 0.3
30 d mortality	0.5 (0.4–0.6); SE 0.0	0.8 (0.8–0.9); SE 0.0	2.2 (1.8–2.6); SE 1.4	1.3 (0.3–2.2); SE 0.3
30 d death/stroke	4.9 (2.0–7.9); SE 1.2	2.5 (1.8–3.2); SE 0.2	3.5 (0.0–8.4)	2.4 (0.7–6.1)

CAS = carotid artery stenting; CEA = carotid endarterectomy; CI = confidence interval; MI = myocardial infarction; SE = standard error.
* Lower risk of stroke with CEA *vs.* CAS within two days of index event.
† Lower risk of stroke with CEA *vs.* CAS within 3–14 days of index event.
‡ In either category (CEA or CAS) stroke risk is lower within two days *vs.* 3–14 days of index event.

registries have not corroborated the Swedvasc findings. In the German CEA registry (56 000 CEAs), there was no difference in 30 day death/stroke between patients treated ≤ 48 hours by CEA (3%) *vs.* later time periods (2.5% between 3 – 7 days; 2.6% between 8 – 14 days; 2.3% for CEA thereafter).[23] In the UK national registry involving 20 000 patients, conclusions were that the pathway from most recent symptom to surgery for patients with symptomatic carotid stenosis, could be shortened to maximise the benefit of intervention, without increased peri-operative risk in the period. However, they admitted a slight increase in peri-operative risk of stroke and death in the first 48 hours.[24]

In this systematic review, 44 410 (29.9%) carotid interventions were undertaken within ≤ 2 days of the index event with no significant difference in 30 day stroke, mortality, and MI, while CEA performed 3 – 14 days after the index event was associated with a significantly lower risk of the composite outcome 30 day death/stroke. On the other hand, CEA within 7 days was associated with a significantly lower risk of stroke (*vs.* 8 – 14 days).

These contradictory results may be explained by the differences in included studies in each analysis, as already shown. Compared with the analysis of the outcomes stroke and mortality, analysis of the composite outcome stroke/death did not include data from two national registries and one prospective multicentre study,[9,12,14] while it included data from one retrospective single centre study that only reported combined stroke/death data.[15] Therefore, studies included in the analysis of 30 day stroke, death, and MI are of better study design compared with the studies in the 30 day death/stroke analysis, even though quality assessment is similar.

There were inconsistent findings regarding timing and outcomes in CAS patients. In patients undergoing CAS ≤ 2 days of the index event (*vs.* 3 – 14), there was no apparent difference in 30 day stroke or MI but there was a statistically significantly higher risk of death. Conversely, there were no differences in 30 day outcomes between CAS performed ≤ 7 days (*vs.* 8 – 14). The pathophysiology of procedural stroke may differ with expedited (*vs.* delayed) interventions in line with acute changes in atherosclerotic plaque vulnerability, which have been associated with an increased risk of embolism and neurological events after CAS.[28]

The systematic review also addressed the question of whether CEA or CAS was safer (or equivalent) when performed in the first 14 days after symptom onset. Compared

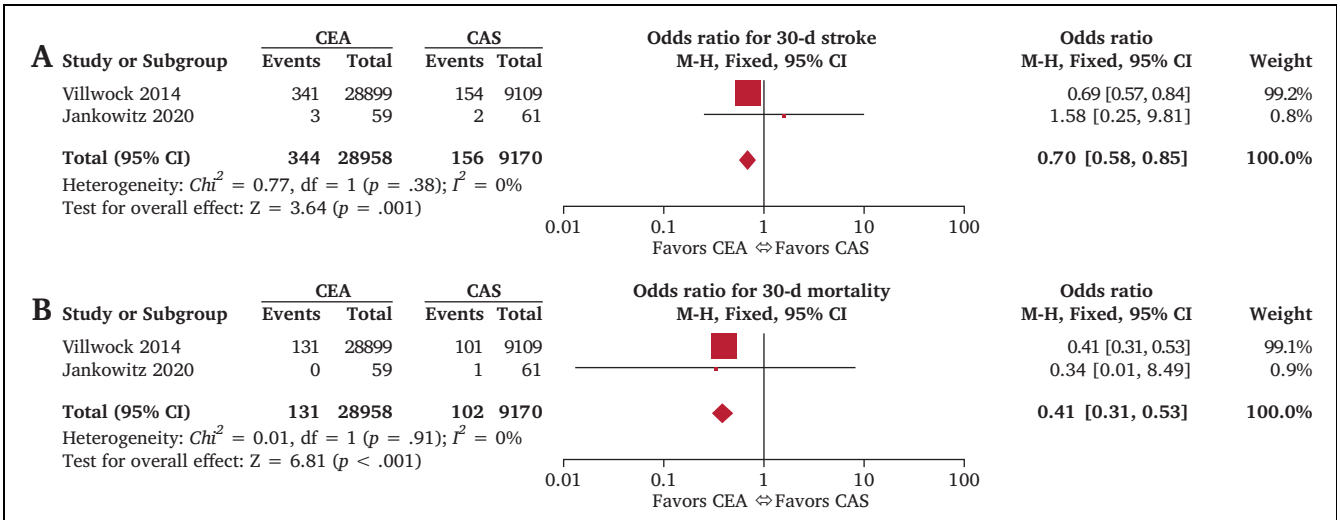

Figure 2. Forest plot showing the odds ratio (OR) for (A) 30 day stroke and (B) 30 day mortality after carotid endarterectomy (CEA) *vs.* carotid artery stenting (CAS) within two days of index event. A Mantel-Haenszel (M-H) fixed effect model was used for meta-analysis. OR are shown with 95% confidence intervals (CI).

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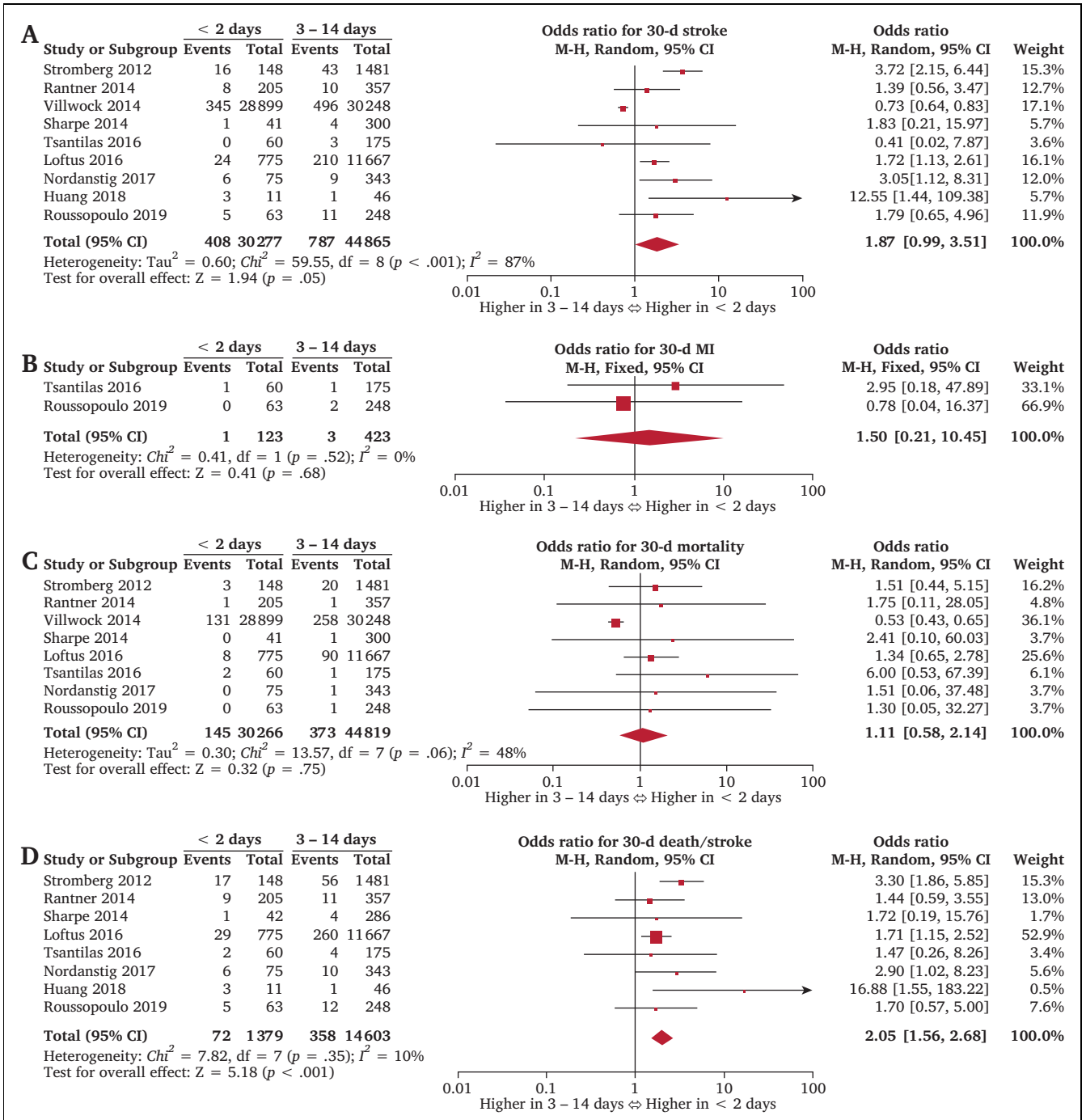

Figure 3. Forest plot showing the odds ratio (OR) for (A) 30 day stroke, (B) 30 day myocardial infarction (MI), (C) 30 day mortality, and (D) stroke/mortality after carotid endarterectomy (CEA) within $\leq$ 2 *vs.* 3 − 14 days of the index event. A Mantel-Haenszel (M-H) fixed effect model was used for meta-analysis. OR are shown with 95% confidence intervals (CI).

with CEA, CAS was associated with significantly higher 30 day stroke and death rates when performed within $\leq$ 2 days of symptom onset. In an individual patient meta-analysis of data from the four largest RCTs comparing CEA with CAS (4 138 patients), CAS was associated with significantly higher risks of 30 day stroke, mortality, and death/stroke when performed within $\leq$ 7 days of the index event.[12]

These data suggest that, at the current time, CEA is probably safer than CAS both when performed $\leq$ 2 days and $\leq$ 7 days after symptom onset. However, virtually all of the CAS procedures in the current meta-analyses were performed via the transfemoral route. Registry data suggest that TCAR can be performed with 30 day outcomes similar to CEA in symptomatic patients.[29] Unfortunately, no studies

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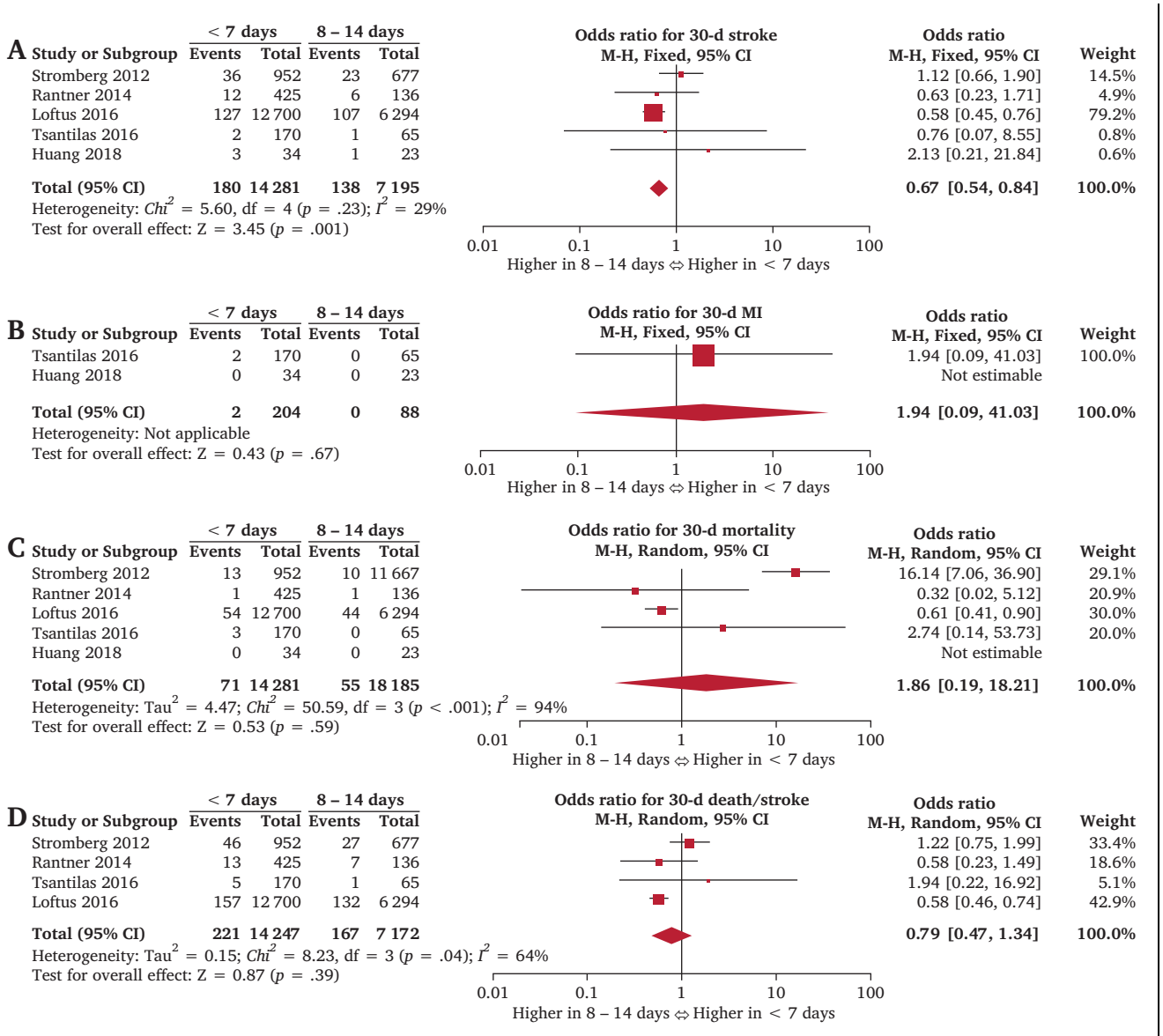

Figure 4. Forest plot showing the odds ratio (OR) for (A) 30 day stroke, (B) 30 day myocardial infarction (MI), (C) 30 day mortality, and (D) stroke/mortality after carotid endarterectomy (CEA) within ≤ 7 *vs.* 8 — 14 days of the index event. A Mantel-Haenszel (M-H) fixed effect model was used for meta-analysis. OR are shown with 95% confidence intervals (CI).

have published outcome data for TCAR when used in the first 14 days after symptom onset,[11] and these data are keenly awaited.

There are relatively few data published on the incidence of recurrent events prior to expedited interventions. A prospective cohort study concluded that the risk was about 12% with modern best medical therapy, but that half of all recurrent events occurred within two days of the index event.[30] On the other hand, a recent meta-analysis revealed a cumulative 120 day risk of recurrent stroke of 1.97% (95% CI 0.75 — 3.17) in recent large RCTs, which was statistically significantly lower than in historical controls.[31]

Historically, vascular surgeons have not really considered the prevention of recurrent stroke in the time period between initiating investigation and initial management and undergoing CEA as being their primary responsibility. However, this attitude is likely to change as more symptomatic patients are started on dual antiplatelet therapy (DAPT) within 24 hours of symptom onset. The 2017 ESVS guidelines recommended that early treatment with DAPT "may be considered" to prevent recurrent events (prior to CEA) in patients with TIA or minor ischaemic stroke and an ipsilateral 50% — 99% stenosis awaiting CEA (Evidence IIb, Level C).[1] At the time, the ESVS Writing Group were unable to recommend routine DAPT in all symptomatic patients because there was no compelling evidence that this strategy conferred additional benefit over antiplatelet monotherapy.

However, based on a meta-analysis of three recent RCTs (CHANCE, POINT, and FASTER) in which 10 447 patients

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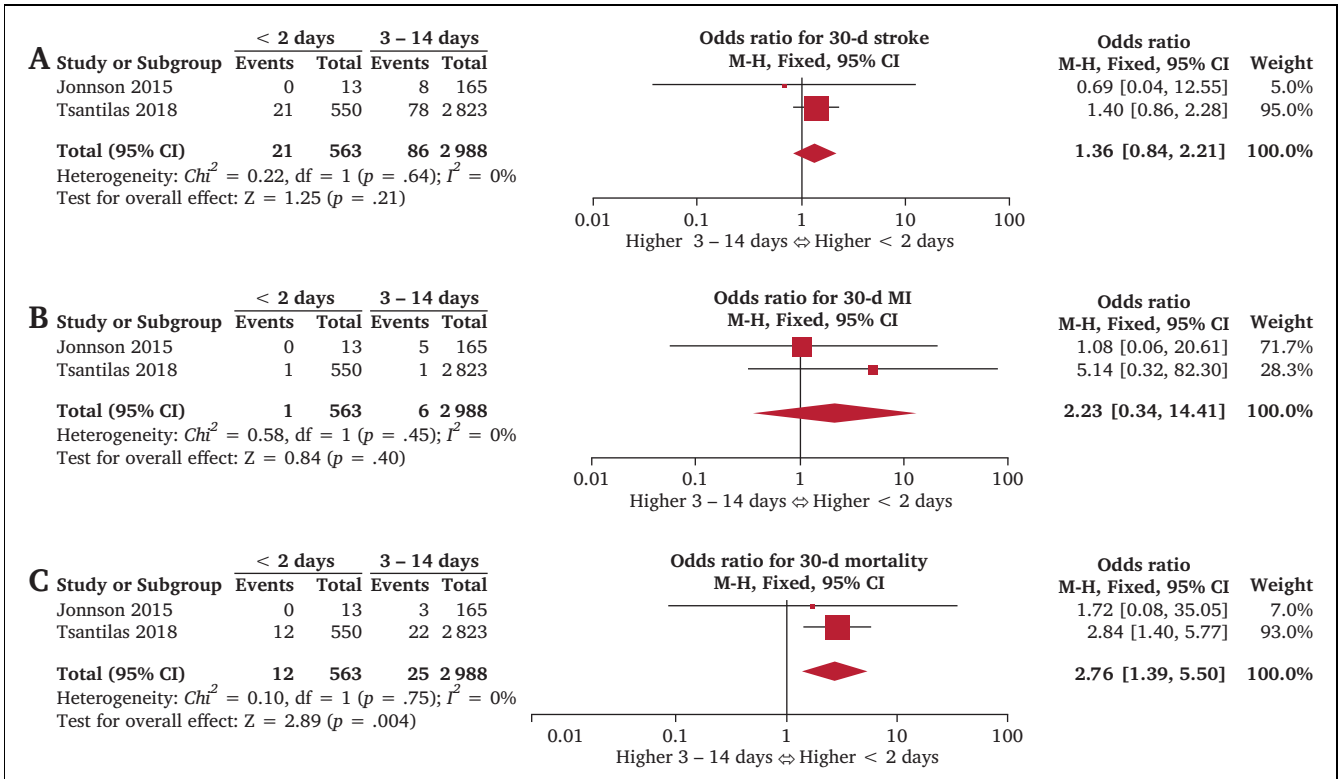

Figure 5. Forest plot showing the odds ratio (OR) for (A) 30 day stroke, (B) 30 day myocardial infarction (MI), and (C) 30 day mortality after carotid artery stenting (CAS) within ≤ 2 *vs.* 3 − 14 days of the index event. A Mantel-Haenszel (M-H) fixed effect model was used for meta-analysis. OR are shown with 95% confidence intervals (CI).

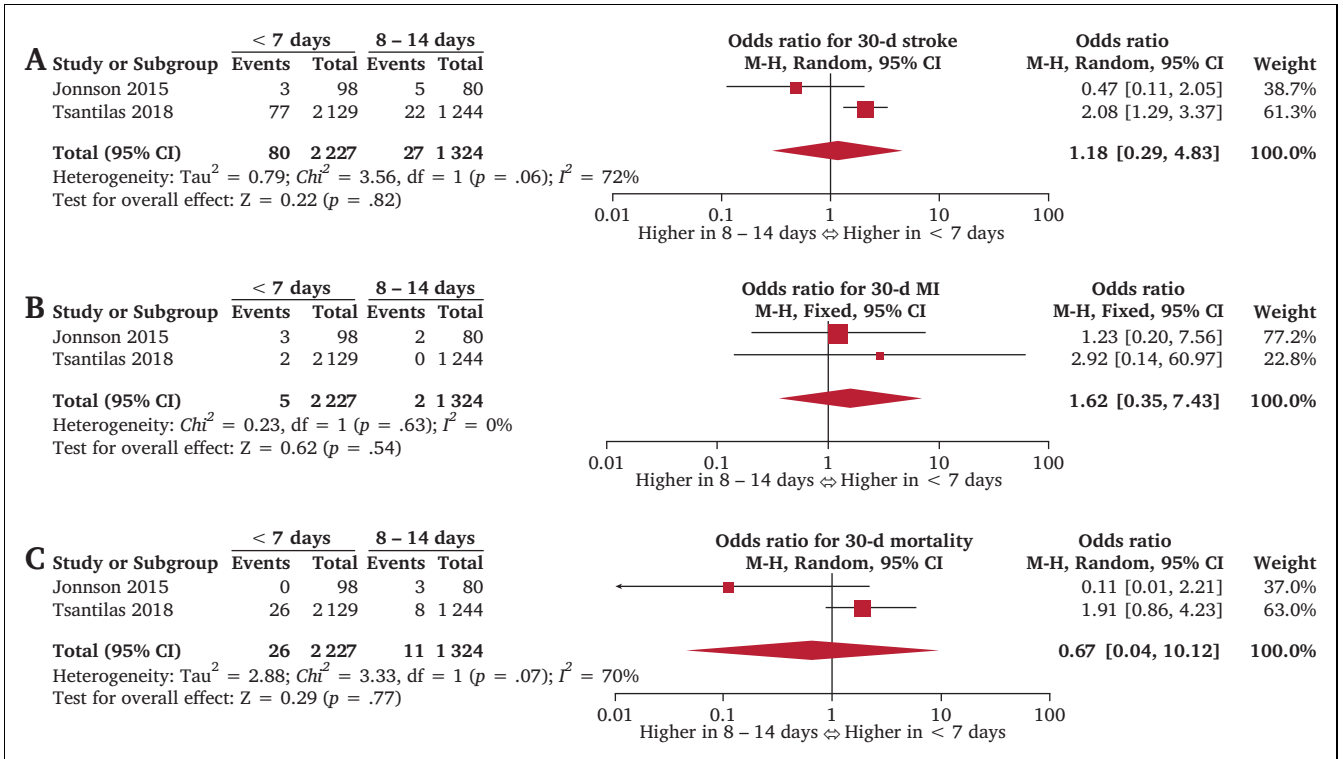

Figure 6. Forest plot showing the odds ratio (OR) for (A) 30 day stroke, (B) 30 day myocardial infarction (MI), and (C) 30 day mortality after carotid artery stenting (CAS) within ≤ 7 *vs.* 8 − 14 days of the index event. A Mantel-Haenszel (M-H) fixed effect model was used for meta-analysis. OR are shown with 95% confidence intervals (CI).

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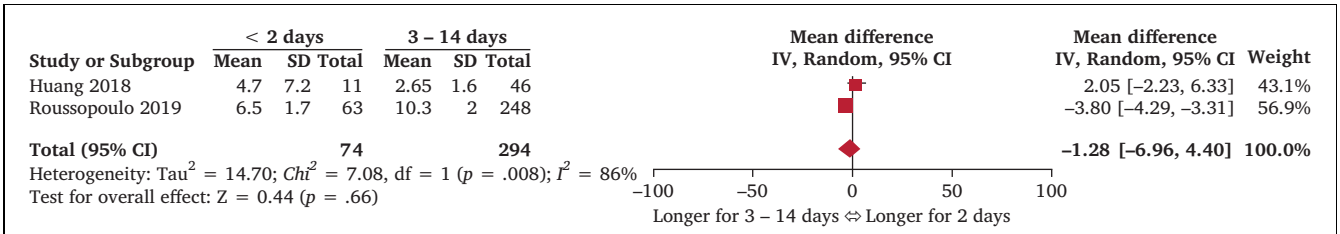

Figure 7. Forest plot showing the mean difference for hospital stay after carotid endarterectomy (CEA) within ≤ 2 vs. 3 − 14 days after the index event. Mean differences are shown with 95% confidence intervals (CI). SD = standard deviation; IV = inverse variance.

were randomised within 24 hours of experiencing a minor ischaemic stroke (NIHSS ≤ 3) or "high risk TIA" (ABCD^2 score ≥ 4) to aspirin monotherapy or short term aspirin and clopidogrel DAPT, there is now compelling evidence to support short term treatment with DAPT in these patient subgroups.[32] A recently published RCT also proved that in the subgroup of stroke patients with carotid artery stenosis, ticagrelor added to aspirin in the first 24 hours after the event, had greater absolute risk reduction of stroke or death at 30 days than stroke patients without carotid artery stenosis with a clinically meaningful benefit with a number needed to treat of 34 (95% CI 19 − 171).[33]

Methodological quality assessment revealed that the included studies are moderate to low quality, with a single high quality study in this analysis. Only a small number of studies was eligible for quantitative analysis, hindering conclusions. Also, heterogeneity of quantitative synthesis is significant, as determined by the I^2 test. Risk of bias is therefore significant. Probably one of the main biases was introduced in the election for CAS/CEA (selection bias), with fit patients treated by CEA while high risk patients were treated by CAS. Also, with the inclusion of mainly prospective cohort studies the risk of confounding is inherent.

In conclusion, the predicted magnitude of procedural risks will ultimately determine whether CEA or CAS is safer in the early time period after onset of symptoms.[34] The evidence from the current systematic review and meta-analysis suggests that (at present) CEA is still safer than transfemoral CAS when performed ≤ 2 days of the index event. Also, considering absolute rates, expedited CEA complies with the accepted thresholds in international guidelines. The ideal timing for performing CAS (when indicated against CEA) is not yet defined and it remains to be seen whether newer CAS technologies (such as TCAR) can provide outcomes similar to CEA when performed in the first 2 − 7 days after symptom onset. Additional granular data and standard reporting of timing of intervention will facilitate future clinical decisions.

CONFLICT OF INTEREST

None.

FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2021.08.021.

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Please cite this article as: Coelho A et al., Timing of Carotid Intervention in Symptomatic Carotid Artery Stenosis: A Systematic Review and Meta-Analysis, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.08.021

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Please cite this article as: Coelho A et al., Timing of Carotid Intervention in Symptomatic Carotid Artery Stenosis: A Systematic Review and Meta-Analysis, European Journal of Vascular and Endovascular Surgery, https://doi.org/10.1016/j.ejvs.2021.08.021