

Asymptomatic Carotid Artery Stenosis: Past, Present and Future

How to Improve Patient Selection?

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Key Words

Asymptomatic carotid artery stenosis · Natural history · Risk of stroke · Carotid endarterectomy · Cerebral hemodynamics · Cerebral metabolism · Plaque morphology

Abstract

Background: The role of carotid endarterectomy (CEA) for asymptomatic carotid artery stenosis (aCAS) remains a matter of debate. It seems that not only the degree of stenosis, but also other factors have to be taken in account to improve patient selection and increase the benefit of CEA for aCAS. **Methods and Results:** The literature pertaining aCAS was reviewed in order to describe the natural history, risk of stroke and benefit of CEA for patients with aCAS in regard to several factors. **Conclusion:** The benefit of CEA for aCAS is low. Current factors influencing the indication for CEA are severity of stenosis, age, contralateral disease, stenosis progression to >80%, gender, concomitant operations and life expectancy. To improve patient selection investigations will concentrate on plaque characteristics and instability and cerebral hemodynamics and metabolism.

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Introduction

Since the publication of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) results in 1991, the benefits and indications of CEA in symptomatic patients are clearly defined [1, 2]. The results of these studies have led to an increasing number of CEAs.

Because of the impressive results of CEA for symptomatic disease, studies on the effect of CEA for asymptomatic CAS as primary prevention were conducted.

The most two striking studies were the Asymptomatic Carotid Atherosclerosis Stenosis Study (ACAS) with 1,662 patients, which was published in 1995 and the Asymptomatic Carotid Surgery Trial (ACST) with 3,120 patients, which was published in 2004 [3, 4]. These studies showed that CEA was beneficial for asymptomatic patients if a CAS >60% was present. In addition, it was shown that the perioperative neurological complication rate was less than 3%. As a result, the number of CEAs for asymptomatic CAS was rising in several countries, although the benefits were not as convincing as those shown in the NASCET and ECST. Although a relative risk reduction of more than 50% in stroke for patients who underwent CEA seems substantial, a meta-analysis of CEA for asymptomatic CAS, performed in 1998 before

the results of ACST, only showed a 2% absolute risk reduction in stroke [5]. It was concluded that the benefit of CEA was small, because the annual stroke rate in medically treated patients with an asymptomatic CAS >60% is 2–6%. In addition, especially in the ACAS trial, both surgeons and patients had to fulfill certain selection criteria to be included. In the ACAS, surgeons had to have proven competence and expertise performing more than 12 CEAs annually and having a complication rate of less than 3%, in the ACST trial less than 6% [4, 6]. Some exclusion criteria in ACAS for patients were diabetes and age older than 79 years. It was calculated that number needed to treat (NNT) was 17 patients for ACAS and 19 patients for ACST. Compared to symptomatic carotid stenosis the NNT is between 2 and 12 patients [7].

Finally, there is evidence that 20–45% of strokes in patients with CAS are not attributed to the stenosis, but have small vessel disease or cardioembolic causes [8].

The finding of an asymptomatic CAS constitutes a dilemma for the surgeon. At present, the natural history of an asymptomatic CAS in the individual patient is unknown. Most likely a subgroup exists that will benefit from an operation, whilst other asymptomatic patients are better treated with medication. Clearly, the risk of perioperative neurological morbidity and mortality must be weighed against the risk of an ischemic event after medical treatment. In addition, the effectiveness of carotid surgery can also be improved by focusing on a reduction in complication rate, taking into account both surgical technique and type of anesthesia.

The purpose of the present review was to provide an overview of the various aspects of asymptomatic CAS that are important for appropriate patient selection. In addition, the potential role of some risk factors in identifying patients with increased risk of stroke who would benefit for surgery is discussed and potential developments in patients selection are described.

Prevalence of Asymptomatic CAS

A stenosis of the carotid artery greater than 50% is considered to be significant carotid artery disease. As asymptomatic CAS patients have no complaints, they can only be detected through screening or by chance. Screening tests are performed for several reasons, although the clinical consequences of these tests can be discussed. Screening tests are for example performed in case of preoperative evaluation of coronary artery bypass grafting (CABG), cervical bruits by physical examination or eval-

uation of ipsilateral symptomatic carotid artery disease with by chance detection of asymptomatic contralateral CAS. The prevalence rate of asymptomatic CAS >50% is estimated to lie between 2 and 8% and that of asymptomatic CAS >80% between 1 and 2% [9]. There is a strong dependency on age. Obviously, prevalence rates of asymptomatic CAS are higher in selected patients (table 1) [10–28]. An association between several (vascular) risk factors and asymptomatic CAS has been demonstrated. Prevalence rates for asymptomatic CAS >50% as high as 10–30% have been found in patients with cervical bruits, coronary artery disease, hypercholesterolemia, diabetes, peripheral atherosclerotic occlusive disease (PAOD) and in smokers (table 1). Stratification, however, is only useful if it affects patients' management. Prevalence of asymptomatic CAS therefore is closely related to risk of stroke and benefit of CEA.

Severity of Stenosis and Risk of Stroke

Knowledge about the natural history of asymptomatic CAS has not only been derived from screening and follow-up studies, but also from trials in which the effect of CEA was compared with medical treatment and from studies in patients with CEA for ipsilateral symptomatic stenosis and asymptomatic contralateral disease.

Risk of any ipsilateral neurological deficit increases with the severity of the asymptomatic CAS. Published annual risk of ipsilateral neurological deficits for asymptomatic CAS <50%, between 50 and 80% and >80% are 0–3.8%, 2–5% and 1.7–18%, respectively (table 2) [3, 12, 18, 29–44]. The majority of these neurological deficits seems transient neurological attacks (TIAs) or amaurosis fugax, but risk of ipsilateral stroke or permanent neurological deficit must not be underestimated and can affect up to half of these patients. Asymptomatic CAS <50%, between 50 and 80% and >80%, carry a risk of stroke of less than 1%, 0.8–2.4% and 1–5% per year, respectively (table 2).

Like prevalence rates, these data depend on the study population examined. There is agreement that screening of asymptomatic CAS in the general population using duplex ultrasound is not justified, because of the low prevalence rates and the very low annual stroke rates. Based on the results of the ACAS, it was estimated that 1,700 persons must need to be screened to prevent 1 ipsilateral stroke from an asymptomatic CAS \geq 80% [9]. In patients with vascular risk factors like cervical bruits, PAOD or advanced age, the prevalence of asymptomatic CAS

Table 1. Reported prevalence rates of aCAS in several different study population

Reference	Year	Screening population	Patients	Mean age years	Male/female	Examination	Prevalence aCAS %	Risk factors aCAS
Hennerici et al. [10]	1981	cardiovascular disease	2,009	58	1,647 M 362 F	doppler	≥ 50 9.1	vascular disease
Ramsey et al. [11]	1987	general, age >50	102	62	45 M 57 F	doppler	≥ 40 5.9	heart disease
Hennerici et al. [12]	1987	vascular risk factors	3,225	62	n.a.	doppler	50–80 80–99 occlusion 6.2 1.3 1.7	
Josse et al. [13]	1987	general	526	45–84	222 M 304 F	duplex	≥ 50 2.1	age >75 years
Colgan et al. [14]	1988	general	348	61	139 M 209 F	duplex	50–79 ≥ 80 3 1	age ≥70 years, hypertension
Faggioli et al. [15]	1990	CABG	539	63	376 M 163 F	duplex	≥ 75 8.7	age >60 years
Ahn et al. [16]	1991	PAOD	78	70	54 M 24 F	duplex	50–75 ≥ 75 9 4	age ≥68 years, hypertension
Klop et al. [17]	1991	PAOD	416	67	282 M 134 F	duplex	50–75 75–99 occlusion 10.1 7.7 7.2	
Ellis et al. [18]	1992	vascular disease	1,196	68	826 M 370 F	doppler duplex	50–79 ≥ 80 11 2.8	
O'Leary et al. [19]	1992	age >65	5,116	n.a.	2,210 M 2,906 F	duplex	50–75 75–99 occlusion M 5.3/F 4.0 M 2.3/F 1.1 M 1.0/F 0.6	men, hypertension, smoking, coronary artery disease, wall thickness
Fine-Edelstein et al. [20]	1994	general population	1,116	66–93	441 M 675 F	duplex	≥ 50 M 9/F 7	age, smoking, hypertension, cholesterol
Gentile et al. [21]	1995	infrainguinal bypass surgery	252	67	117 M 108 F	duplex	60–99 occlusion 12 3	
Marek et al. [22]	1996	claudication	188	64	142 M 46 F	duplex	50–80 80–99 occlusion 20 1.6 2.7	age >65 years, cervical bruit, ABI <0.7
House et al. [23]	1999	PAOD	486	71	302 M 184 F	duplex	50–70 70–99 occlusion 17 13 5	aneurysm, smoking and creatinine (males)
Ascher et al. [24]	1999	referred to vascular surgeon	307	>65	157 M 150 F	duplex	≥ 70 21	
Simons et al. [25]	1999	PAOD	162	61	104 M 58 F	duplex	≥ 50 14	age ≥67 years, weight ≤68 kg, DBP ≤75 mm Hg
Cheng et al. [26]	1999	PAOD	186	71	121 M 65 F	duplex	≥ 70 25	age, smoking, cervical bruit
Qureshi et al. [27]	2001	general	1,331	66	439 M 892 F	duplex	≥ 60 18	age >65 years, smoking, coronary artery disease, hypercholesterolemia
Cina et al. [28]	2002	PAOD	620	72	376 M 244 F	duplex	50–80 ≥ 80 30 2.5	age >70 years, diabetes, ABI <0.8

n.a. = Not available or not mentioned; PAOD = peripheral arterial occlusive disease; ABI = ankle brachial index; DBP = diastolic blood pressure.

Table 2. Risk of annual (ipsilateral) neurological deficits, stroke and risk factors in selected patients with asymptomatic CAS according to severity of stenosis

Reference	Year	Screening population	Patients	Age (mean) years	Male/female	Examination	Prevalence aCAS %	Median follow-up, m	Risk annual ipsilateral neurological event	Risk annual ipsilateral stroke	Risk factors any neurological event	
Chambers et al. [29]	1986	cervical bruits	500	63	212 M 288 F	doppler angiography	<75 ≥75	77.4 22.6	23	3.6% 1st year 18%	1.5% 5%	aCAS >75%, progression, heart disease, men
Autret [30]	1987	cardiovascular disease	242	67	149 M 93 F	duplex	<50 50–75 ≥75	53 31 16	29	0.23% 2.48% 1.71%	0% 0.8% 1.7%	aCAS >50%, age, cholesterol, systolic blood pressure
Hennerici et al. [12]	1987	cardiovascular disease	284	62	201 M 138 F	duplex	50–80 ≥80	70.1 29.9	29	3.5%*	0.97%*	occlusion, progression
O'Holleran et al. [31]	1987	cardiovascular disease	293	n.a.	n.a.	duplex	<75 ≥75	59 41	46	2.5% 12.5%	0.6% 3.2%	aCAS >75%, soft plaques
Norris et al. [32]	1991	cervical bruits	696	64	327 M 369 F	doppler	<75 ≥75	74.6 25.4	41	2.0% i+c 10.5% i+c	1.3% i+c 2.5% i, 3.3% i+c	heart disease, aCAS >75%
Ellis et al. [18]	1992	vascular disease	1,196	68	826 M 370 F	doppler duplex	<50 50–79 ≥80	86.2 11 2.8	20	2.5% 4.2% 7.5%	1.2% 2.2% 0%	aCAS >80%
Mess et al. [33]	1992	n.a.	446	n.a.	n.a.	n.a.	≥80		61	n.a.	1.7%	
Shanik et al. [34]	1992	vascular disease	188	69	114 M 74 F	duplex	<50 50–79 ≥80	51 18 31	48	0.5% 15% 3.6%	0.5% 1% 1.8%	progression, aCAS >80%
Bock et al. [35]	1993	cervical bruits vascular disease	242	68	191 M 51 F	duplex	<50 50–79 80–99	73 19 3	27	3.8% 3.1% 5.1%	n.a. n.a. n.a.	progression, echolucent plaques
Hobson et al. [36]	1993	aCAS ≥ 50%	233	65	233 M	duplex angiography	≥ 50		48	5.1%	2.4%	
ACAS3	1995	aCAS ≥ 60%	834	67	550 M 284 F	angiography doppler	≥ 60		31	3.8%	2.2%	
ECST37	1995	contralateral sCAS	2,295	62	1,629 M 666 F	angiography	<70 ≥70 occlusion	92.1 5.5 2.4	44	n.a.	0.65% 1.9% 1.2%	
Naylor et al. [38]	1995	contralateral CEA	219	n.a.	n.a.	angiography duplex	<70 ≥70 occlusion	85 4 11	48	2%*	1%*	
Tong et al. [39]	1996	cervical bruits	336	65	149 M 187 F	duplex angiography	<60 ≥60 occlusion	81.7 15.3 3.0	58	0.6% 3.9% 4.2%	0.1% 0.85% 1%	aCAS >80%
Mackey et al. [40]	1997	cervical bruits	715	65	283 M 432 F	duplex	<50 ≥50 80–99	50 50 15.8	42	2.7 i+c 6.8% i+c, 4.2% i (7.5% i)	1.3 i+c 2.2 i+c, 1.4% i (2.8% i)	aCAS >80%
Irvine et al. [41]	1998	aCAS ≥ 40%	487	69	292 M 195 F	duplex	≥ 40		41	n.a.	1% (2.74% i+c)	bilateral disease
Longstreth et al. [42]	1998	age >65 years	5,441	73	2,231 M 3,210 F	duplex	≥ 70	0.5	60	1.8%	1%	
Nadareishvili et al. [43]	2002	cervical bruits	106	64	62 M 44 F	duplex	<50 50–99	48 pat. 58 pat.	120	n.a. n.a.	5.7% (10 years) 9.3% (10 years)	
ACST4	2004	aCAS ≥ 60%	1,560	68	1,023 M 537 F	duplex	≥ 60		40	n.a.	1.4%	Age <75 years
Nicolaides et al. [44]	2005	aCAS ≥ 50%	1,115	n.a.	n.a.	duplex	≥ 50		37	1.4%	0.6%	aCAS ≥ 90%, creatinine ↑, contralateral TIA

n.a. = Not available or not mentioned. * Risk of event in all patients not specified to the degree of carotid artery stenosis; i = ipsilateral; c = contralateral. A difference between ipsilateral and contralateral has not been made in all studies.

Table 3. Percent sensitivity and specificity of duplex, MRA and CTA for carotid artery stenosis according to the literature

	Stenosis $\geq 50\%$		Stenosis $\geq 70\%$		Occlusion	
	sensitivity	specificity	sensitivity	specificity	sensitivity	specificity
Duplex	87–95	83–96	65–97	75–97	80–100	90–100
MRA	92	74	94–100	85–100	100	100
CTA	85–90	82–91	67–100	84–100	69–100	87–100

$\geq 50\%$ and/or $>80\%$ raises to between 10 and 59%, but the annual risk of ipsilateral stroke in this groups remains low (1–4%) and therefore the benefit of screening to prevent stroke is questionable.

To improve the efficacy of screening tests, decision trees were developed, including different strategies and variables, such as prevalence and natural history of asymptomatic CAS, annual risk of stroke and death, accuracy of diagnostic tests, risk of surgery and angiography. It was estimated that the prevalence rate of asymptomatic CAS $>50\%$ in the population to be screened should be between 20 and 50% to be effective [45, 46]. At present, this prevalence rate is not even achieved in selected populations and therefore screening for asymptomatic CAS seems not effective.

Not only does the severity of the stenosis affect the decision to operate for asymptomatic CAS, but also the risk of stroke in case of an occlusion. For asymptomatic patients, it was estimated that about 20% of all occurring carotid occlusions were associated with ischemic events and that the annual stroke rate after an occlusion was 2–6% [47–50]. To prevent these occlusions and because of the elevated risk of stroke for asymptomatic CAS $>80\%$, the (worldwide) tendency is to operate on asymptomatic CAS $>80\%$ [51].

Diagnostic Imaging of CAS

The degree of carotid stenosis in ACAS, ECST and NASCET was determined with angiography. The main disadvantages of angiography, however, are its invasiveness and the reported 0.16–3% morbidity and mortality rate. The most widely used method for determining the degree of stenosis with angiography is according to the NASCET method, which relates the point of greatest stenosis to the normal distal ICA. In the ECST study, the greatest stenosis was related to the estimated diameter of the normal carotid bulb, which provides a more severe stenosis compared with the NASCET method.

Nowadays, several noninvasive diagnostic imaging techniques are available to evaluate the degree of a CAS (table 3).

Sensitivity and specificity are between 62 and 100%, but are depending on technique and diagnostic criteria [52].

Duplex ultrasound provides an excellent noninvasive, inexpensive instrument to assess the degree of a stenosis and was used in the ACST. With duplex both the peak systolic velocity (PSV) and end-diastolic velocity (EDV) are determined in the common and internal carotid arteries. In case of bilateral carotid artery disease the measurement of absolute velocities can overestimate the degree of the stenosis and ratios of velocities are recommended. The main difficulties with duplex ultrasound are the interlaboratory variations in stenosis evaluation and interpretation criteria. Therefore, recommending CEA only based on duplex ultrasound remains a matter of debate. MRA and CTA are promising noninvasive techniques, although not available everywhere. A proposed strategy is to combine imaging techniques. Duplex ultrasound is used as the primary screening tool for CAS and if CEA is considered, MRA or CTA is performed. In case of discrepancies angiography is recommended [52, 53].

Progression of the Severity of the Stenosis

The risk of progression of an asymptomatic CAS increases with time and varies from 4 to 29% per year, depending on the definitions of stenosis progression and studied population (table 4) [28, 35, 40, 51, 54–60]. Several studies have tried to describe the natural history of asymptomatic CAS, to define risk factors or predictors for stenosis progression by multiple linear regression analysis, and to find a relation between stenosis progression and neurological symptoms.

The sometimes conflicting results of all these studies are difficult to compare, because the target population,

Table 4. Reported incidence of progression rate of asymptomatic CAS and risk of neurological events

	Year	Pa-tients	Age (mean) years	Sex	Initial stenosis		Mean follow-up months	Progression rate		Progression vs. no-progression group		Risk factors progression
					%	%				ipsilateral neurological event rate	ipsilateral stroke rate	
Roederer et al. [60]	1984	162	64	110 M 52 F	<50 50-79 80-99 occlusion	64 29 3 4	15	overall aCAS ≥ 50%	20%/year 8%/year	to ≥ 80 vs. <80%; 33% vs. 0.4%	to ≥ 80 vs. <80%; 12.5% vs. 0%	smoking, diabetes, age <65
Hatsumaki et al. [55]	1990	200	65	138 M 62 F	<50 50-79 80-99	63 33 4	54	aCAS ≥ 50% aCAS ≥ 80%	3.9% 1.2%	no difference	no differences	
Bock et al. [35]	1993	242	68	191 M 51 F	<50 50-79 80-99	61 25 5	27	overall in follow-up	14.8%	11% vs. 1.7%	n.a.	
Johnson et al. [55]	1995	232	63	136 M 96 F	<50 50-79	59.5 43.5	84	to 80-99% aCAS <50% aCAS 50-79%	4% in 7 years 26% in 7 years	n.a.	14.8% vs. 2.3% after 7 years	
Mackey et al. [40]	1997	715	65	283 M 432 F	<50 50-79 80-99 occlusion	50 29 15.8 5.2	42	8.3% 16.4% 12.2%		to ≥ 80% vs. <80%; 19.2% vs. 2.9% to ≥ 50% vs. <50%; 13% vs. 2.9%		
Rockman et al. [51]	1997	425	75	219 M 206 F	50-79		38	4.9% 16.7% 26.5%	1 year 3 year 5 year	37.5% vs. 7.3% in follow-up	10.4% vs. 2.1% in follow-up	
Olin et al. [59]	1998	465	69	255 M 210 F	60-79		24	5% 11% 20%	1 year 2 year 3 year		5.6% vs. 0.76% in follow-up	
Mansour et al. [57]	1999	344	71	344 M	50-79		25	overall	15.5% in follow-up	26% vs 12% in follow-up	10.2% vs. 2.5% in follow-up	heart disease, black race
Muluk et al. [58]	1999	1,004	66	984 M 20 F	<50 50-79 ≥ 80	75 14 11	28	overall	9.3%/year	21.1%-11.9% in follow-up		ipsilateral aCAS ≥ 50% ipsilateral ECAS ≥ 50% contralateral ICAS ≥ 50% systolic BP >160 mm Hg
Liapsis et al. [56]	2000	442	69	320 M 122 F	<50 ≥ 50	69 31	44	overall	15%/year	20.7% vs. 6.1% in follow-up (TIAs)	11.2% vs. 1.9% in follow-up	coronary artery disease, echolucent plaques
Cina et al. [28]	2002	417	73	259 M 158 F	<50 50-99	72.4 23.3	6 to 9	overall	16% in follow-up		no difference (short follow-up)	

n.a. = Not available or not mentioned.

initial stenosis and follow-up period differ in most studies and not always a difference was made between transient versus permanent neurological deficit.

Most studies show an increasing rate of ipsilateral neurological events with stenosis progression especially for stenosis progression greater than 80%, although the an-

nual incidence rate of stroke in the progression patients remains low (<5%). Prophylactic CEA is only suggested after progression occurs to a more than 80% stenosis, as rapidly progressive carotid stenosis seems to increase the risk of stroke. The problem is that in probably half of the patients' progression will be detected after the onset of

neurological symptoms and it is therefore not always a useful predictor of future neurological events. The ideal time interval between repeated duplex measurements to detect stenosis progression is unknown and has yet to be determined.

Carotid Plaque Morphology

Histological studies have shown that in symptomatic plaques, the amount of lipids is greater, rupture or ulceration, inflammation and thin fibrous capping more common. Plaque rupture can cause intraplaque hemorrhage and lumen thrombosis and eventually embolization [61].

By ultrasonographic evaluation, the degree of echogenicity of a carotid plaque can be assessed and expressed on a grey scale. A low grey scale suggests a lipid-rich plaque. Characterization of the carotid plaque is according to Gray-Weale (type 1–4) or to Geroulakos (type I to V) classification (type 1/I: uniformly echolucent plaques with or without a thin echogenic cap; type 2/II: predominantly echolucent plaques with less than 50% echogenic areas; type 3/III predominantly echogenic plaques with less than 50% echolucent areas; type 4/IV: uniformly echogenic plaques; type V: plaques that cannot be classified due to heavy calcification producing acoustic shadows) [62, 63].

Echolucent or hypoechoic plaques are characterized by low values of the grey scale median (GSM) and are associated with symptomatic lesions, suggesting plaque instability. Echorich or hyperechoic plaques have high values of GSM and are related to asymptomatic stenosis [64–66]. In addition, a positive relation has been described between echolucent plaques and nonlacunar silent brain infarcts [67].

A prospective study confirmed the association between future risk of stroke and echolucency of carotid atherosclerotic plaques, but only in previously symptomatic patients and not in asymptomatic patients [68].

Variations in plaque echoicity distinguish homogeneous from heterogeneous plaques, but conflicting data exist between variation in plaque echoicity and risk of stroke [64, 69, 70]. The disadvantage of ultrasonographic plaque morphology evaluation is its observer variability and visual analysis. Computer-aided methods are needed and already used for objective evaluation of plaque echoicity, but larger studies are necessary to investigate the risk of stroke and plaque echoicity [71].

TCD was in addition used to study plaque instability and embolization. A relation between the number of si-

lent embolic signals and the risk of ipsilateral neurological symptoms has been described in both symptomatic and asymptomatic carotid stenosis [72–76]. Spiral CT of plaque calcification and histological analysis have demonstrated that symptomatic plaques are less calcified and more inflamed than asymptomatic plaques [77]. Also with specific MRI techniques, morphology of carotid plaques can be obtained. MRI characterization and identification of unstable vulnerable plaques (ruptured fibrous cap) correlates well with histological sections and is associated with recent ischemic events [78–80].

Although the prognostic implications are not completely clear, plaque characteristics might contribute to proper patient selection for CEA. This selection should not only be confined to symptomatic patients with stenosis <70%, but also to asymptomatic patients with all degrees of stenosis.

Silent Cerebral Infarcts on the Asymptomatic Site

It is conceivable that asymptomatic CAS patients with cerebral infarction on CT or MRI are prone to a stroke and that the stenosis has already resulted embolisms, with silent cerebral infarctions and/or nondetectable neurological symptoms.

A relation between number of cerebral infarctions and the severity of the symptoms was described in ACST. Although the ACST randomized asymptomatic patients for CEA or best medical treatment and investigated the stroke free survival, an analysis was performed for patients with contralateral symptoms. In this group of patients, the number of infarctions on CT decreased from 62, 30, 17 to 10% for, respectively, contralateral stroke, TIAs, amaurosis fugax and asymptomatic patients, respectively. With MRI, the incidence of hemispheric infarctions decreased from 53%, 27 to 14% for patients with prior contralateral stroke, TIAs or amaurosis fugax and no prior symptoms, respectively [81].

Hougaku et al. [82] demonstrated silent cerebral infarctions on MRI in 42% of 117 subjects with asymptomatic carotid lesions. Multivariate analysis revealed a significant correlation of silent infarcts with age, hypertension, plaque score, high-grade stenosis and/or ulcerated lesions. In contrast, Cao et al. [83] found no relation between degree of stenosis and silent cerebral infarctions on CT in asymptomatic patients with CAS <60% and >60%. In fact, as patients with silent cerebral infarctions had a shorter 10-year survival and a poorer neurologic outcome, they proposed a less aggressive approach towards

CEA in asymptomatic patients with silent cerebral infarctions. Brott et al. [84] also found no association between silent infarcts and the degree of stenosis in the ACAS study.

Although a relation between symptoms and number of cerebral infarctions seems clear, the benefit of CEA in asymptomatic patients for silent cerebral infarctions alone is not proven.

Influence of Contralateral Carotid Artery Disease

Studies on the natural history and/or surgical risks of an asymptomatic CAS in the presence of contralateral carotid artery disease are difficult to compare. A difference between symptomatic and asymptomatic ipsilateral CAS is not always made, and the number of patients is usually limited and several subgroups with contralateral disease can be distinguished, such as patients with a contralateral occlusion (symptomatic or asymptomatic), patients with a contralateral stenosis (symptomatic or asymptomatic), patients with different degrees of stenosis, and patients with no stenosis.

The stroke risk in unilateral asymptomatic CAS seems to be lower than in bilateral asymptomatic CAS. In a follow-up study (mean 41 months) of 487 asymptomatic patients, the risk of ipsi- and contralateral stroke was significantly increased in bilateral disease (relative risk 2.35). A stroke rate of 9.6% in patients with bilateral disease and a >90% contralateral stenosis was seen after 1 year of follow-up [41].

An interesting observation was made in a post hoc analysis of the ACAS trial, where patients with asymptomatic CAS >60% and contralateral occlusion were stratified to surgery or medical management. The 5-year ipsilateral stroke rate in the medically treated patients with a contralateral occlusion had a remarkably better outcome, not only compared with surgery (3.5% vs. 5.5%), but also with the medically treated patients without contralateral occlusion (11.7%). It was hypothesized that the contralateral occlusion stimulates the development of collateral circulation. No difference was found in 5-year ipsilateral stroke in operated patients with and without a contralateral occlusion (5.5 vs. 5.0%), suggesting that there was no increased surgical risk in asymptomatic patients with a contralateral occlusion [85]. In contrast, in ACST the status of the contralateral carotid artery showed no influence in 5-year outcome, but the number of patients with contralateral occlusion in both studies was small. AbuRahma et al. [86] reported a 5-year ipsilateral stroke rate of 27% in

conservative management of patients with asymptomatic CAS >60% and a contralateral occlusion.

Goldstein et al. [87] studied risk factors in CEA for asymptomatic CAS in 463 patients and found an increased, but not significant, complication rate in patients with a higher degree of contralateral stenosis and/or occlusions compared with patients with no contralateral CAS (3.6–4.0% vs. 1.4–1.6%). Nicolaidis et al. [44] found in the Asymptomatic Carotid Stenosis and Risk of Stroke Study Group (ACSRS) that severity of aCAS, history of contralateral TIA and elevated creatinine were independent risk factors. If all three were present, the annual stroke risk in patients with 90–99% aCAS increased from 1 to 6.3%. In CAS, with contralateral ICA occlusion there is a trend that the risk of CEA is slightly elevated, especially in the presence of a contralateral symptomatic ICA occlusion [88–90]. Other studies (including both asymptomatic and symptomatic patients) found similar results of perioperative, all stroke and survival rates in patients with and without contralateral ICA occlusion [91–94].

It appears that there is conflicting information about the role of the contralateral carotid artery in case of an ipsilateral asymptomatic CAS caused by the heterogeneity of the population. Management needs to be based on weighing several risk factors in the individual patient. It seems that the surgical risk in the presence of contralateral carotid disease is about twofold higher than in asymptomatic CAS without contralateral carotid disease and comparable to the surgical results obtained in symptomatic carotid artery disease.

Gender

In conservative treatment of asymptomatic CAS, gender seems to be no risk factor for stroke, but there are several reports indicating that women have a significantly higher risk of perioperative stroke in asymptomatic as well as symptomatic disease than men. ACAS found a complication rate of 3.6% for women, compared to 1.7% for men [3]. These results were confirmed by Goldstein et al. [87] who reported a complication rate of 5.3% for women versus 1.6% for men ($p = 0.02$) in CEA for asymptomatic disease. For symptomatic carotid artery disease similar findings were reported in the ECST [88, 95]. Other studies, including asymptomatic and symptomatic patients, reported no differences in perioperative neurologic events in men and women [96, 97].

In contrast there are no reports of increased risk in men. Although the risk of perioperative stroke in women

Table 5. Reported number of deaths, strokes, cardiac- and stroke-related mortality at follow-up

Reference	Year	Patients	Follow-up months	Deaths	Ipsi-lateral strokes	Stroke-related mortality and % in follow-up	Cardiovascular-related mortality and % in follow-up
Chambers et al. [29]	1986	500	23	45	12	3 13%	27 60%
Hennerici et al. [12]	1987	339	33	82	17	10 12%	35 43%
Autret [30]	1987	242	29	56	10	2 3.6%	na
Hatsukami et al. [55]	1990	200	54	39	6	2 5%	17 44%
Norris et al. [32]	1991	696	41	95	29	5 5.2%	59 62%
Ellis et al. [18]	1992	1,198	60	155	27	11 7.1%	na
Hobson et al. [36]	1993	233	48	77	29	4 5.2%	47 61%
ACAS3	1995	834	31	89	52	9 10.1%	48 54%
Naylor et al. [38]	1995	219	48	44	10	2 4.5%	22 50%
Tong et al. [39]	1996	336	58	41	9	2 4.9%	23 56%
Irvine et al. [41]	1998	487	41	156	45	23 14.8%	79 51%
Mansour et al. [57]	1999	344	25	75	14	11 14.7%	36 48%
Liapsis et al. [56]	2000	442	44	33	16	2 6.1%	25 76%
Nadareishvili et al. [43]	2002	106	120	17	11	2 11.8%	10 59%
ACST [4]	2004	1,560	40	248	62	44 2.8%	127 51%
Nicolaides et al. [44]	2005	1,115	37	163	46	8 17.5%	105 64%

is low, there seem to be a tendency of a similar to twofold higher risk in women. This effect of gender on outcome in CEA especially in asymptomatic disease raised the question whether CEA is beneficial for women with asymptomatic CAS, but so far no consensus has been reached.

Age

The prevalence of CAS is dependent on age. Below the age of 60 years the prevalence of a more than 50% stenosis is estimated to be 0.5%, but it increases to 10% above the age of 80 years. Studies concerning the early operative results and late outcome of patients >75 years show different results, but a distinction between symptomatic and asymptomatic disease is not always made. In most prospective clinical trials like NASCET and ACAS, age >80 years was an exclusion criteria. In ACST benefit for patients >75 years was small, with an absolute 5-year risk reduction of 3.3% (NNT = 30) [4]. In a review on risk factors for asymptomatic disease, an increased postoperative stroke or death rate in those aged 75 years or older (7.8 vs. 1.8% in those younger than 75 years; $p = 0.01$) was described in a study of 463 CEAs [87]. Perler et al. [98] described a perioperative stroke and death rate of 2.6% in 1,036 patients >80 years, but no difference between asymptomatic and symptomatic patients was made. Ker-

diles et al. [99] found that 90.9% of 252 patients >75 years were free from neurological deficiency after CEA for symptomatic and asymptomatic disease after 5 years compared with 92.4% of 660 patients <75 years. The actual 5-year survival was 73% in the older and 85% in the younger patients.

In 182 CEAs (55% for asymptomatic disease and mean age 83 years), O'Hara et al. [100] reported a postoperative neurological event rate of 2.7% in octogenarians and an estimated 5-year stroke-free rate of 85%, although the 5-year survival rate was just 45%.

It appears that age in itself is not an absolute contraindication for carotid artery surgery [90]. The elderly patients should be selected according to the same criteria, but it is important to take into account life expectancy and other risk factors.

Life Expectancy

Clinical studies have shown that asymptomatic CAS is an associated risk factor for cardiovascular disease and death and that it seems to be a stronger predictor of death than self-reported cardiovascular disease or diabetes [101]. In all studies shown in table 2, the annual risk of death seems higher than the risk of a neurological event in patients with all degrees of asymptomatic CAS, especially with regard to the risk of stroke. Follow-up studies have

shown that the number of cardiac-related deaths exceeds the number of strokes and the stroke-related death is low compared to the cardiac-related death (table 5), the latter being accountable for about 30–50% of all mortalities [11, 17, 28, 29, 31, 36–38, 40, 42, 58–60]. To improve life expectancy, it is therefore emphasized that prevention of stroke in asymptomatic CAS should also be accompanied by prevention and analysis of coronary artery disease.

Concomitant Operations

There is no evidence that patients with asymptomatic CAS >70%, who have to undergo noncarotid surgery benefit from a prophylactic CEA, except probably in case of coronary artery bypass grafting (CABG) [102]. A recent review by Naylor et al. [103] analyzed several factors influencing the risk of stroke after CABG. An increased risk was found in neurologically symptomatic patients compared with asymptomatic patients (8.5 vs. 2.2%) and in patients with severe carotid artery stenosis. It seems, however, that about 60% of perioperative stroke cannot be attributed to carotid artery disease. There is just one study investigating asymptomatic patients only [104]. The risk of an ipsilateral stroke was 3.6% for an 80–99% stenosis compared with 0.4% in a normal or <80% CAS. Because the prevalence of 80–99% stenosis in asymptomatic patients undergoing CABG is only 5%, the benefit of prophylactic CEA in asymptomatic patients before CABG is low. A staged procedure is to be preferred, as there is evidence that the risk of stroke or death is higher in asymptomatic patients who had CEA performed in combination with coronary artery bypass surgery (18.7%) [87].

Cerebral Hemodynamics and Metabolism

The proposed mechanism of cerebral ischemia due to thrombo-embolic events from the atherosclerotic stenosis in the carotid artery is proven, but there is also supportive evidence that hemodynamic factors and the lack of collaterals can contribute to an ischemic event [50]. In addition, the recovery after a stroke depends on the ability of collateral pathways. The hemodynamic consequences of a CAS or occlusion depend on the collateral flow. If collateral flow is not adequate, reduction in cerebral blood flow (CBF) or cerebral hypoperfusion can occur, which can produce low-flow neurological symptoms. The main collateral pathways are the contralateral common carotid artery and the vertebral arteries, but they can only serve as

Table 6. Diagnostics tools for investigating cerebral hemodynamics and metabolism

Transcranial doppler	TCD
Trans color-coded duplex ultrasonography	TCCD
Computer angiography	CTA
Magnetic resonance imaging/angiography	MRI/MRA
Proton magnetic resonance spectroscopy	MRS
Single photon emission computer tomography	SPECT
Positron emission tomography	PET

collaterals if there is a complete circle of Willis. Other collaterals are the ipsilateral ophthalmic artery and the leptomeningeal arteries. The circle of Willis seems to be the most important pathway between the extracranial arteries. Increased flow and vessel diameter of the circle of Willis have been demonstrated by MRA in patients with unilateral carotid occlusion [105]. This circle, however, shows a great variability. Anatomical, MRA and TCCD studies in neurological asymptomatic persons have shown, respectively, just 20–50, 42 and 50% complete circles [106–108]. In people with cerebrovascular disease an incomplete circle of Willis is found in probably more than 50%.

To improve selection of those patients with asymptomatic CAS who have an increased risk for stroke, investigations are focused on cerebral hemodynamics and metabolism.

In normal subjects with an intact cerebral autoregulation, both cerebral perfusion pressure (CPP) and cerebral blood flow (CBF) are maintained despite fluctuations in blood pressure (stage 0).

Reduced collateral flow causes diminished CPP and is accompanied by vasodilatation of cerebral vessels. This, in turn, leads to a decrease in the vascular resistance and an increase in CBF, which is associated with an increase of the cerebral blood volume (CBV). This is called cerebrovascular reactivity (CVR) or hemodynamic reserve capacity (stage 1). If CPP diminishes further, this compensatory vasodilatation mechanism is exhausted and CBF will decline (hypoperfusion). The only remaining mechanism to maintain normal cerebral metabolic rate of oxygen (CMRO₂) is to increase cerebral oxygen extraction fraction (COEF), which is called the oxygen reserve capacity (stage 2). A further drop in CPP will result in a decrease in CMRO₂, which characterizes the stage of reversible or irreversible ischemia (stage 3).

Most other diagnostic modalities (table 6) for patient selection in asymptomatic CAS attempt to assess the

above-mentioned (regional) cerebral hemodynamic and metabolic parameters and to relate these parameters with improvement in cerebral autoregulation after CEA or with risk of future neurological symptoms.

TransCranial Doppler (TCD) and/or TransCranial Color-Coded Duplex (TCCD)

CVR can be assessed using TCD and/or TCCD by measuring blood flow velocity in the middle cerebral artery, which is proportional to CBF. In the healthy brain, an increase in blood velocity will be measured after administration of vasodilatory agents (inhalation of 3–8% CO₂, acetazolamide) or by induction of hypercapnia using the breath-holding test. In the hemodynamically compromised brain with impaired cerebral autoregulation or exhausted CVR no increase of the blood velocity after vasodilatation occurs, because the vessels are already maximally vasodilated. There are data to suggest that reduced CVR ipsilateral to a carotid occlusion constitutes an increased risk of ipsilateral stroke compared with carotid occlusion with normal reactivity [109]. After CEA, diminished collateral flow is founded and CVR improves, not only on the side of surgery, but also on the side of contralateral carotid occlusion, suggesting an improved hemodynamic state [110–113].

Recent prospective data have confirmed that patients with impaired CVR and/or decreased number of collaterals or incomplete circle of Willis have an increased risk of neurological ischemic events. Markus et al. [114] found an odds ratio of 14.4 of ipsilateral stroke and TIA in patients with carotid occlusion and/or stenosis and exhausted reactivity. Vernieri et al. [115] found a significant risk of ipsilateral stroke in patients with impaired CVR on the side of a carotid occlusion and a decreased number of collaterals (32.7 vs. 0%).

With TCCD, a relative new technique, the configuration of the circle of Willis and the flow direction and velocity of the intracranial vessels can be studied. A higher incidence of deficiency of anterior collateral flow and stroke was described [116].

The encouraging results of all these studies justify further investigations to clarify the value of TCD and/or TCCD in selecting patients with asymptomatic CAS who are at high risk for stroke.

Magnetic Resonance Imaging (MRI)

Morphology of the circle of Willis, flow patterns and size of vessels can be assessed by MRA [105]. Patients with an occluded internal carotid artery and an incomplete circle of Willis, as shown by MRA, have a signifi-

cantly increased risk of ipsilateral stroke, compared with similar patients with a complete circle of Willis [117]. In asymptomatic patients, prevalence of anterior collateral flow and vessel diameter of the anterior communicating artery was increased, compared to symptomatic patients [118]. The role of MRA in selecting asymptomatic patients with CAS for CEA has still to be determined, but it was suggested that asymptomatic patient with CAS and adequate collateral compensation will probably not benefit from CEA [119].

Another option of MRI is that with the use of intravenous contrast, CBV and CBF can be measured. Increased CBV is indicative of compensatory vasodilatation according to stage 1 (hemodynamic reserve capacity). In perfusion-weighted MRI semiquantitative values of CBV can be obtained and differences in cerebral hemodynamics in carotid artery stenoses < and >80% have been reported [120, 121]. With dynamic susceptibility-contrast-enhanced MRI and the use of an arterial input function, also absolute values of CBF and CBV can be obtained. Consistent values of CBF and CBV have been described in PET and MRI studies in patients with carotid artery disease [122]. There have been no reports yet investigating whether diminished cerebral hemodynamics calculated with MRI is associated with increased risk of stroke in asymptomatic CAS.

Magnetic Resonance Spectroscopy (MRS)

With MRS the concentrations of N-acetyl-aspartate (NAA), a marker of neuronal integrity, lactate, a marker of anaerobic metabolism, and choline, a molecule involved in cellular membranes and synthesis of acetylcholine in neurons, can be measured. It has been hypothesized that cerebral hypoperfusion or ischemia is accompanied with reduced concentrations of NAA and/or increased concentrations of lactate, while the interpretation of choline is more complicated. In symptomatic and asymptomatic patients changes of metabolite ratios and lactate has been reported before and after CEA [123–125]. Comments on these studies are variation in tissue sampling, large voxel sampling and absolute values of metabolites seems to be preferred above ratios, because ratios depend on two changing metabolites [126, 127]. Lythgoe et al. [127] studied absolute values of NAA and lactate in asymptomatic patients with CAS or carotid occlusion and an abnormal carbon dioxide reactivity. Normal values of NAA and no lactate was demonstrated. It was concluded that MRS, in spite of the reduced CVR as indicator for cerebral hypoperfusion, seems to be unlikely to help in the selection of patients with asymptomatic CAS for CEA.

Single Photon Emission Computer Tomography (SPECT)

In SPECT radiopharmaceutical tracers, such as technetium-hexamethyl propyleneamine oxine (HMPAO), are used to determine regional CBF. In combination with acetazolamide (ACZ) inducing cerebral vasodilatation, CVR can be assessed. Resting (without ACZ) and stress studies (with ACZ), comparable to the persantin-thallium scan in cardiology, are necessary to demonstrate changes in CBF and to detect areas of impaired hemodynamic reserve capacity. Studies in symptomatic as well as asymptomatic CAS have shown improvement of the hemodynamic reserve capacity in 50–80% of patients after CEA [128–131]. For selecting asymptomatic patients for CEA, SPECT seems not specific and sensitive compared to other diagnostic modalities.

Positron Emission Tomography (PET)

The only available diagnostic imaging modality which can quantify not only cerebral perfusion, but also cerebral metabolic rate of oxygen and especially the cerebral oxygen extraction fraction (OEF) in different regions of the brain is PET [132]. In patients with compromised cerebral perfusion increased OEF can be found. In these patients cerebral vascular reactivity is severely disturbed not only leading to maximal vasodilatation of the cerebral vessels but also to increased oxygen extraction from the blood. There is ample evidence to suggest that patients with increased OEF have a significantly increased risk to develop stroke, particularly patients with a carotid occlusion [133–136]. Improvement of cerebral hemodynamics according to PET has been described after extracranial-to-intracranial surgery and after CEA for symptomatic patients [137]. Most benefit will probably be achieved in patients with symptomatic carotid occlusion using extracranial-to-intracranial bypass [138]. If a carotid occlusion exists, restoration of cerebral hemodynamics can also be achieved by CEA of an asymptomatic contralateral CAS or by endarterectomy of an ipsilateral external carotid artery. In the presence of bilateral asymptomatic CAS and disturbed cerebral hemodynamics as determined by PET, prophylactic CEA seems justified, although the prevalence of this constellation is unknown and is likely to be very low.

Although presently the availability of PET is limited, its application in other disciplines of medicine (oncology, cardiology) warrants the expectation that PET will be introduced in general practice in the future and can have its merits in selecting patients with asymptomatic CAS and increased risk of stroke for CEA.

Conclusion

According to the results of ACAS and ACST, there is a small, but significant benefit of operating asymptomatic CAS >60%, but follow-up studies and prospective data have shown that, in general, the natural history of asymptomatic CAS is mild, that surgical results are not always comparable and that more information is needed to identify high risk patients for cerebrovascular events. Nowadays, a more selective approach is noticed, operating only patients aged <75 years with asymptomatic CAS >80% stenosis or patients with carotid pathology on both sides and an abnormal CVR. More convincing evidence is needed to determine whether certain patients with reduced CVR are prone to cerebrovascular events. Studies must be concentrated on plaque characteristics and instability, cerebral hemodynamics and metabolism to improve patient selection. The limitation of TCD, TCCD, MRI and SPECT is that they can only give information on CVR and the hemodynamic reserve capacity (stage 1), while PET also can determine the oxygen reserve capacity (stage 2). In theory, only PET can identify patients with the highest degree of hemodynamic compromise and the highest risk for neurological symptoms caused by chronic cerebral hypoperfusion.

It is hypothesized that in the future three groups of patients with asymptomatic CAS will benefit from CEA or a revascularization procedure. The first group consist of patients with plaque instability identified with MRA and/or duplex, with or without silent embolic signals, the second of patients with insufficient collateral circulation detected by TCD, TCCD and/or MRA, and the third of patients with severe metabolic compromise, characterized by increased OEF as measured with PET.

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