

Headquartered in Indianapolis, Indiana, with manufacturing and/or research facilities in the states of Minnesota, California, and Washington, as well as in Puerto Rico and Ireland, Guidant Corporation is a leader in the research, development, and manufacturing of medical technologies used primarily in treatment of cardiovascular and vascular illnesses. Guidant develops technologies that offer physicians and patients options to improve their health status and quality of life. Guidant is a strong supporter of evidence-based medicine and has played a major role in sponsoring research on the clinical outcomes of carotid stenting. We were the initial sponsor of the ongoing randomized controlled CREST trial in collaboration with the National Institutes of Health to study carotid stenting in moderate and low risk patients. Additionally, we sponsored the ARChER clinical trials to evaluate carotid artery stenting in treatment of high-risk patients with significant carotid artery disease.

Based on current clinical evidence and the need to assure a range of treatment options for patients at high risk of stroke, we believe that CMS should modify the proposed coverage decision as follows:

- I. Coverage should be provided for asymptomatic high-risk patients with stenosis  $\geq 80\%$
- II. Coverage should be expanded for symptomatic high-risk patients with stenosis between 50% and 70%
- III. The determination as to whether a patient is at high risk for surgery should be made by physician(s) with knowledge of interventional treatment options in addition to medical therapy. This may be a multidisciplinary team, a surgeon, neurologist, and/or interventionalist depending on the specific hospital. The expertise may not always reside with the surgeon alone.

Our detailed comments follow.

## **I. Coverage for Asymptomatic Patients**

The CMS proposed coverage decision states that “patients with asymptomatic carotid artery stenosis have a different risk profile than patients with symptoms. Asymptomatic patients with hemodynamically significant carotid artery stenosis have an annual stroke event rate of **2-5%** (about 2% stroke occurrence per year among controls in ACST). In contrast, about 10.5% of patients with symptoms, such as a TIA, will have a stroke in the short term. While CEA has been well accepted for patients with symptomatic carotid artery stenosis  $> 70\%$ , **there remains controversy for asymptomatic patients, due, in part, to the lower event rates and the development of medications, such as antiplatelet and lipid lowering drugs, for stroke prevention.**”

Guidant Corporation believes that this statement cannot be generalized to the asymptomatic patients with significant carotid stenosis evaluated in the ARChER and similar high-risk trials. Furthermore, it is our position that recent studies have clearly established that carotid intervention, when combined with medical management of modifiable risk factors, is superior to medical management alone in the treatment of asymptomatic patients with high grade stenoses. Within the subset of severe asymptomatic carotid patients there is a group who due to their surgical risk profile or anatomic conditions are poorly served by CEA. Due to the limitations of CEA, physicians require an alternative treatment modality for carotid artery disease. This is of particular importance for the patient with severe carotid artery disease who has multiple risk factors for stroke and surgery, as this patient requires the protective effects that both medical management and carotid intervention can offer. The ARChER trials, as well as other well

executed trials (e.g. SAPHIRE), have established carotid artery stenting as a safe and effective alternative to CEA in these patients and therefore the option of carotid artery stenting should be extended to patients requiring this intervention.

We offer the following to support this position.

### **The Effectiveness of Contemporary Medical Therapy In Patients with High Grade Asymptomatic Carotid Disease is Inconclusive**

While Guidant acknowledges that there have been significant advances in pharmacological therapy, including improved antiplatelet, antihypertensive and lipid-lowering agents which have reduced the risk of all vascular events, the specific stroke reduction benefit of these therapies has not been established specifically for patients with asymptomatic carotid artery disease. In pharmacologic studies performed to date evaluating the latter two agents in particular, specific attention was focused on a broad group of patients at risk for vascular events (mostly coronary disease - see Table 1), and few studies have examined stroke reduction specifically in patients with *carotid disease*, especially those at particularly high risk for stroke (e.g., high grade stenosis). For example, within the PROGRESS trial, designed to evaluate the effectiveness of ACE inhibitors for stroke prevention in patients with coronary heart disease and other risk factors for cerebrovascular events, only 7% of patients in the treatment and control arms were noted to have carotid artery disease. [1] In other published studies, the prevalence of carotid artery disease among the patient populations is not known or provided. It is unclear, then, how generalizable the results of pharmacologic trials are to patients in the ARCHeR and SAPHIRE trials who have risk factors which were similar or more severe and also have been identified with carotid artery disease.

In contrast, results of a major contemporary trial have clearly established the superiority of best medical therapy AND carotid intervention (e.g. CEA) over best medical therapy alone for preventing stroke in asymptomatic patients with carotid artery disease. [2] The ACST trial published in 2004 provides additional strong evidence that carotid intervention is superior to contemporary medical therapy alone in asymptomatic patients with carotid stenosis. In ACST, 3120 asymptomatic patients (with 60% or greater stenosis by ultrasound) all managed with contemporary medical therapy were randomized to immediate CEA or usual treatment consisting of indefinite deferral of CEA. Exclusion criteria included previous ipsilateral CEA, an expectation of poor surgical risk (e.g., recent acute myocardial infarction) or a major life-threatening condition. The ACST protocol included specific guidelines for appropriate medical therapy consisting of optimal and rigorous control of hypertension, diabetes, and advice regarding cessation of smoking and either antiplatelet or anticoagulation treatment. Cholesterol lowering was advised if total cholesterol was greater than five mmol/l at baseline [3]. The use of anti-platelet therapy, anti-hypertensive and lipid-lowering treatment was similar in both treatment groups not only at randomization but also during follow-up. Despite patients receiving best medical therapy, a positive benefit of immediate CEA compared with usual treatment was demonstrated, as immediate CEA nearly halved the net 5-year stroke risk from 11.8% to 6.4%; a difference of 5.35% (95% CI 2.96-7.96). Half of this 5-year benefit involved disabling or fatal strokes. In addition, formal subset analysis showed the large benefit of carotid intervention was not abrogated by either lesser

degree of carotid stenosis or better levels of lipid or blood pressure control. In summary, the protective benefit of immediate CEA was realized even in subset analyses of patients with or without hypercholesterolemia or hypertension.

When evaluating the ACST results, it is important to note that a significant number of patients (n=229) allocated to deferred CEA underwent endarterectomy relatively early during the follow-up period (median 2 years from randomization). Only fifty percent of these patients were noted to be symptomatic prior to CEA [4]. It would appear then that results attributed to ‘usual care’ include a subset of patients (approx. 7%) having undergone CEA for asymptomatic carotid artery disease. Further, approximately 112 patients allocated to immediate CEA did not undergo the procedure. In the authors’ own admission, full compliance with the treatment allocation would have produced an even larger difference in the net 5-year benefits of immediate CEA.

It is agreed that anti-hypertensive and lipid-lowering agents do appear to reduce the risk of stroke in patients with multiple risk factors including advanced age and other vascular stroke risk factors. However, the magnitude of the protective effect is relatively low (**Table 1**) and for all studies listed the magnitude of the effect was substantially lower than that associated with immediate endarterectomy in ACST. For example, within the HOPE trial evaluating the ACE-inhibitor rimipril vs. placebo the absolute reduction in stroke over 5 years was only 1.5%. [5] In the HPS trial, the stroke reduction using simvastatin, considered to be a potent statin, was established to be 1.8% over 5 years. [6] Although it is expected that wider use of statins may reduce the overall risk of carotid stroke, this has yet to be established. A key question the HPS trial attempted to answer was whether statin therapy reduced stroke in a *cerebrovascular disease* population. In fact, the study demonstrated a surprising finding that stroke was statistically significantly reduced *in all patients groups except* those with prior cerebrovascular disease. The subpopulation of patients with cerebrovascular disease had over a 2 fold increase in their stroke risk at five years compared to all patients, underscoring the finding that those patients at highest risk for stroke benefited the least from this medical therapy. Of note, since HPS excluded patients with recent stroke (<6 months), many in this cerebrovascular disease subgroup would be considered asymptomatic in recent carotid artery stenting trials and for the purpose of the CMS coverage decision.

While medical therapy has advanced, the protective benefits of both modern medical management and carotid revascularization are needed in patients with high grade asymptomatic carotid artery disease. In asymptomatic carotid disease patients, the early procedural risks of intervention are clearly outweighed by reduction of later risk of stroke and the magnitude of this benefit relative to medical therapy alone progressively increases over time. Thus, in asymptomatic patients with significant life expectancies, carotid intervention in addition to medical therapy is an essential treatment option. The ARCHeR trials and other trials of similar high-risk patient populations have shown that carotid stenting is now an option that should be available for both asymptomatic and symptomatic high surgical risk patients with significant carotid stenosis.

**Table 1**  
**Large Scale Trials Evaluating Anti-Hypertensives and/or Statins in High Risk Patients**

Trial	Patients	Follow-up	Intervention	Endpoint	Results	Comment
<i>Anti-Hypertensive</i>						
SHEP N=4736 [7]	Multiethnic cohort >60 yrs + HTN mean age: 70 yrs, DM 10%, MI 4.9%, previous stroke 1.4%	4.5 yr	Chlorthalidone + either oratenolol or low dose reserpine vs. placebo	Stroke, % All  Stroke, % Ischemic	4.4 vs 6.7% RR 0.63 (0.49- 0.81)  3.6% vs. 5.6% RR (0.48-0.82)	Benefit demonstrated
HOPE N=9297 [5]	CHD, stroke, PVD or DM + 1 additional vascular risk factor (HTN, eTC, LHDL, smoking or microalbuminuria): mean age: 66, male 72%, Prior CVA 11%; PVD 45%, Hypertension 46%, Hypercholesterolemia: 66%, LVH 8.7%	5 yr	ACE inhibitor (ramipril) v. placebo	Total stroke, %	3.4  4.9  RR 0.68 (0.56-0.84) p<0.001	Benefit demonstrated
PROGRESS N=6105 [1]	Prior HX of CVD (recent and > 6 months); mean age: 64; 70% prior ischemic stroke, CHD 16%, Carotid Disease (>50% or prior Tx) 7%, AFib 8%	3.9 yr	ACE inhibitor (perindopril + indapamide) vs. placebo	Total stroke, % in pts with CVA ≥ 6 months	9.6%  14%  RR 0.33 (0.18 -0.45)	Benefit demonstrated
PEACE N=8290 [8]	Stable CAD, LVF>40% (normal or slightly reduced) HTN in 50% of patients, prior CVA in 7%, 15% with EF >40% to < 50%	4.8 yr	ACE inhibitor (trandolapril) v. placebo	Total stroke, %	1.7%  2.2% (p=0.09)	No Benefit demonstrated for composite endpoints, or stroke
CAMELOT N=1997 [9]	CHD, patients with LAD obstruction >50% or EF < 40% or moderate to severe CHF excluded, age 58, men 73%, DM 20%, Smoking 27%	2 yr	Amlodipine (n=663) enalapril (n=673) or placebo (n=655)	Stroke or TIA, %	0.9%  1.2%  1.8%	No Statistical Benefit demonstrated for either agent, study may be underpowered

Trial	Patients	Follow-up	Intervention	Endpoint	Results	Comment/
<i>Statins</i>						
ASCOT-LLA N=10305 [10]	HTN + ≥ 3 other vascular risk factors (LV hypertrophy, DM, PAD, previous CVA, male and others), TC ≤ 6.5 mmol/L Approx. 10% of patients had prior history of CVA, 24% Diabetic, 14% LVH	3.3 yr	Atorvastatin vs. placebo (+ hypertension control in both groups)	Total stroke, %	1.7% 2.4% p=0.02	Benefit demonstrated, across pre-specified groups (DM, LVH, Aged >60yrs and >70yrs, PVD, renal dysfunction); however, <b>no protective benefit for women due to insufficient power.</b>
HPS N=20536 [6]	History of vascular disease (CVD, CAD, PVD, HTN) or DM For no CVD: age 64; 69% CHD, 39% HTN, 14% smokers, subset analyses provided for patients with and without history of cerebrovascular disease	5 yr	Simvastatin v. placebo	Total stroke rate, % in pts with no history of prior CV disease  Total rate, % in pts with history of CV disease	3.2% 4.8%  10.3% 10.4%	No benefit demonstrated for patients with history of cerebrovascular disease.
ALLHAT-LLT* N=10355 [11]	Moderately Hypertensive (Stage 1 or 2) + 1 additional CHD risk factor and Hypercholesterolemic Patients Age 66; Male 51%; DM 35%; Hx of CHD 14%; Smokers 23%	4.8	Pravastatin vs usual care (UC)	6 year total-stroke rate per 100 Participants,	5.3% 5.8% p=0.31	Benefit not demonstrated, 10% of UC patients on statin or other Lipid lowering drug by year 2 to 28.5% at year 6 and due to modest cholesterol differential between treatment and control groups
GREASE N=1600 [12]	CHD, age < 75	3 yrs	Atorvastatin vs. usual care (UC)	Total stroke rate %	2.1% 1.1% p=0.034	Benefit demonstrated across all subgroups (women, DM, hypertension, CHF, unstable angina or prior revasc.)

\*It has been argued that the potential benefits of pravastatin in ALLHAT were compromised by substantial use of statins in the usual-care group, leading to minimal differences in total cholesterol and LDL between the treatment and control groups with differences.

## The risk of stroke quoted in the CMS coverage decision underestimates the risk of stroke for the asymptomatic high surgical risk patient population

The cited annual stroke event rate of 2-5% among asymptomatic patients has been established in studies that: 1) included patients with lower grade stenoses ( $\geq 60\%$ ) compared with the ARChER and similar high-risk trials (e.g. SAPHIRE trial) which specifically evaluated patients with high grade stenoses  $>80\%$ ; and 2) by design excluded patients with significant comorbidities that are known risk factors for stroke and/or death. Indeed many of the inclusion criteria identified in the ARChER and SAPHIRE trials were in fact the exclusion criteria for those studies upon which the 2-5% risk of stroke has been based. Therefore, this estimate of annualized ipsilateral stroke rate cannot be generalized to the ARChER and other high-risk cohorts.

It is well documented that the degree of stenosis in asymptomatic patients is associated with an increased risk of neurological events [13-17] and large-artery ischemic stroke. [18] Patients with carotid artery stenoses between 75 and 94% have over a 25% increase in the risk of ipsilateral stroke over a 5-year period compared with patients with stenoses between 60-74% [18]. When investigating literature specific to medical management of asymptomatic carotid disease, the 1-year rate of ipsilateral stroke for patients with high grade stenosis ( $\geq 80\%$ ) ranges from approximately 2% to as high as 15%, with the majority of studies documenting a rate closer to 4%<sup>i</sup> (reference Table 2).

**Table 2**

### Risk of Stroke in Asymptomatic High Grade Stenosis ( $\geq 75-80\%$ ) in Medical Management/Natural History Studies

AUTHOR/YEAR	RANGE OF STENOSIS % (N)	REPORTED ENDPOINT			ESTIMATED RATE OF 1YR STROKE	
		IPSILATERAL RATE	ANY STROKE RATE	TIME	IPSILATERAL	ANY STROKE
ACAS 1995 [19]	$>80\%$ (88)	3.7%	--	5yrs	$<1\%$	$<1\%^*$
Autret, 1987 [20]	75-99% (78)	3.9%	--	2.2 yrs	1.8%	1.8%*
Bock, 1993 [21]	80-99% (13)	--	8.8%	1 yr	--	8.8%
Bogousslavsky, 1986 [22]	$>90\%$ (38)	2.0%	3.3%	1 yr	2.0%	3.3%
Caracci, 1989 [23]	$>75\%$ (62)	18%	--	1.8 yrs	10%	10%
Chambers, 1986[14]	75-100% (113)	--	5.5 %	1 yr	2.8%**	5.5%
ECST, 1995 [17]	80-99%(56) asx side	11.0%		3yrs	3.7%	3.7%*
Ellis, 1992 [24]	$>80\%$ (33)	--	0.0%	1.7 yrs	--	0.0%
Erzurum, 2002 [25]	80-99%(57, men)	5.3%		2.8 yrs	1.9%	1.9%*
Hennerici, 1987 [26]	80-99% (36)	--	8.3%	2.4 yrs	--	3.3%
Hertzer, 1986 [27]	$>90\%$ (18)	--	32.8%	4 yrs	--	8.2%
Inzitari, 2000 [18]	75-94% (74)	18.5%	--	5 yrs	3.7%	3.7%*

<sup>i</sup> ACAS reports a rate of  $<1\%$ , however, the measurement technique used in this study differed from the standard NASCET criteria

AUTHOR/YEAR	RANGE OF STENOSIS % (N)	REPORTED ENDPOINT			ESTIMATED RATE OF 1YR STROKE	
		IPSILATERAL RATE	ANY STROKE RATE	TIME	IPSILATERAL	ANY STROKE
NASCET	asx side					
Mackey, 1997 [15]	>=50% (150)	2.8%	4.2% (unheralded)	1 yr	2.8%	4.2%
Moneta, 1987 [28]	80-99% (73) pts refused for surg	15%	--	1 yr	15%	15%*
Norris, 1991 [16]	>75% (177)	2.5%	3.3%	1 yr	2.5%	3.3%
Rockman, 1997 [13]	Progressive >80% (48)	10.4%	--	3.2 yrs	3.3%	3.3%*
Roederer, 1984 [29]	80-90% (24)	16.7%	--	3 yrs	5.6%	5.6%*
<b>Overall (Weighted Average Method)</b>					<b>4.4%</b>	<b>4.5%</b>
<b>Excluding ACAS (Weighted Average Method)</b>					<b>4.8%</b>	<b>4.8%</b>

\* When all stroke was unavailable, ipsilateral stroke rate was utilized to provide a conservative estimate

\*\* taken from Barnett et al [30]

The true incidence of stroke in a high grade stenosis patient population is difficult to establish in more contemporary medicine as these patients are often referred for CEA once disease has progressed to a stenosis rate of 70% [31] or 75% or higher [13,15,32,33,34]. Even within ACST, 92/201 patients allocated to medical therapy with deferred CEA were considered “non-compliant” with respect to treatment allocation because the physician or patient changed their mind or due to disease progression. Therefore, it likely that the rate of stroke for patients with severe stenoses (>80%) in the medical management arm of the trial is underestimated.

A significant limitation of the asymptomatic natural history/medical therapy literature and recent studies (e.g., ACST) is that it does not focus particular attention on the impact that clinical comorbidities have on neurologic risks. The studies shown in Table 2 did include some patients with clinically compromised states at baseline such as coronary disease, CHF, recent MI and diabetes as well as angiographic criteria such as contralateral occlusions. However, unlike the ARChER and other high-risk trials, patients were not specifically selected based on the presence of comorbidities and in fact for many of the studies cited, these high risk factors were specific exclusion criteria. The particular comorbid conditions selected for the ARChER trials (e.g., recent unstable coronary disease, heart failure, hypertension, diabetes, etc.) have been found to be associated with increased rate of stroke in asymptomatic carotid stenosis patients compared with patients without these comorbidities [14,18, 29]. For example, the relative risk of stroke ranges from 1 to 5 in carotid artery patients with coronary artery disease, [15,16,18, ], is 5 for patients following cardiac surgery [34], and 2.6 in patients with contralateral occlusion [35]. Observational data indicates that coexistent risk factors generally exert a multiplicative effect on the risk of experiencing cardiovascular events [10] and therefore, it is reasonable that the rate of ipsilateral stroke in asymptomatic patients with both severe stenosis ( $\geq 80\%$ ) and 2 or more comorbidities as evaluated in ARChER is likely to be much higher than 5% per year.

## **Established Medical Practice Guidelines Recommend Revascularization for Specific Patients with Asymptomatic Carotid Artery Disease**

Several practice guidelines, developed from evidence-based medicine, have been established within the medical community both in the United States and abroad recommending endarterectomy for certain patient populations with asymptomatic carotid artery disease (listed below). Furthermore, many researchers specifically reference institutional policies of offering CEA to asymptomatic patients with >80% stenosis. [13,33,36] This recognized standard of care was also evident in the randomized carotid disease clinical trials. In many cases, patients that were in the medical management arm of a study were referred for surgery when their stenosis progressed to a level of 75% or higher. The fact that similar standards have been developed by medical experts worldwide in consideration of available research data strongly suggests that there is consensus among the medical community that there is evidence sufficient to conclude that revascularization (CEA) in specific patients with asymptomatic carotid artery disease is appropriate and will improve net health outcomes of patients treated.

- American Heart Association guidelines for carotid endarterectomy: This multidisciplinary consensus guideline was developed by recognized experts in neurology, neurosurgery, vascular surgery and healthcare planning [37]. (Notably, this guideline was written prior to insights provided by the ACST trial). This guideline allows for treatment of asymptomatic patients with stenosis  $\geq 60\%$  when the expected surgical risk (stroke/death) is  $< 3\%$  and life expectancy is at least 5 years or  $\geq 75\%$  stenosis with or without ulceration in the presence of contralateral stenosis may be appropriate for surgery when the surgical risk is between 3 and 5%.
- The Canadian practice guidelines allow for treatment of asymptomatic patients with stenoses of greater than 60%. However, physicians are asked to consider factors such as an increasing severity of stenosis, the presence of plaque ulceration, contralateral occlusion and documented progression of carotid stenosis, as well as CT or MRI evidence of asymptomatic cerebral infarction. These guidelines indicate these factors may all contribute to an increased risk of stroke and therefore must be considered during the assessment of individual patients. [38]
- European Stroke Initiative Ischaemic Stroke: Prophylaxis and Treatment Recommendations 2003: These recommendations state that carotid surgery may be indicated for some asymptomatic patients with a 60-99% stenosis of the ICA. The CEA-related risk for stroke or death must be less than 3%, and patients with a life expectancy of at least 5 years (or under the age of 80) may benefit from surgery. [39]
- SIGN (Scottish Intercollegiate Guidelines Network) provides consideration of treatment of both symptomatic and asymptomatic patients with severe ICA stenosis, and states that “carotid endarterectomy can prevent stroke but this benefit has to be balanced against the risk of stroke as a consequence of surgery, the risk of other complications of surgery and the cost of surgery” [40].

In medical practice, CEA is the standard of care for asymptomatic patients who have a high stroke risk, as outlined by medical societies above. However, certain of these patients have both a high stroke risk and thus need for carotid revascularization and also a significant medical comorbid condition that place them in a “high-risk” status for surgery such as severe cardiac, pulmonary or renal dysfunction or by the need for CEA concurrent with CABG [41,



42,43]. It is for these patients and for patients for whom surgery is contraindicated for anatomic reasons that less-invasive alternative procedures such as CAS have been initially considered. This need has been recognized by the American Heart Association (AHA). In affiliation with the AHA, a multidisciplinary panel (including vascular surgeons) has identified current indications in patients considered at high risk for CEA in whom CAS is an appropriate management approach. Indications include recurrent stenosis after CEA, severe medical comorbid conditions, radiation-induced carotid stenosis and high (above C2) lesions [44]. This is the patient population for whom Guidant evaluated the use of CAS in clinical trials designed to establish non-inferiority of CAS with the ACCULINK™ Carotid Stent and ACCUNET™ Embolic Protection Systems to CEA, the standard of care.

### **Results of the ARChER Trials Are Consistent with the American Heart Association Guidelines for Carotid Endarterectomy in Asymptomatic Patients**

A total of 443 asymptomatic patients were treated within the ARChER trials. Only asymptomatic patients with severe stenosis defined as 80% stenosis were eligible for the study. In accordance with the AHA guidelines, ipsilateral carotid endarterectomy is proven for stenotic lesions with  $\geq 60\%$  diameter reduction of distal outflow tract with or without ulceration and with or without antiplatelet therapy, irrespective of contralateral artery status, ranging from no disease to occlusion (Grade A recommendation) when the surgical risk is  $< 3\%$ . Furthermore, endarterectomy is acceptable for lesions ranging from  $>70\%$  or  $>75\%$  in specific patients (e.g., patients requiring concurrent CABG) when the surgical risk is greater than 3% but less than 5%. It should be noted that the guidelines specifically refer to the acceptable risk (stroke/death) of the CEA procedure. In ARChER, it is important to note that approximately 15% of patients required open-heart surgery within 30 days (a study inclusion criteria). Excluding stroke/death associated with open-heart surgery at 30 days, the actual risk associated with the CAS procedure in the asymptomatic subgroup was 4.3%. Similarly, in the Carotid Endarterectomy vs. Stenting Trial (CREST) lead in phase, the periprocedural stroke/death rate in asymptomatic (all risk,  $>70\%$  stenosis) patients following CAS has been reported to be 3.1% (AHA, 2003). Both these results are within the surgical 3-5% risk called out in the AHA guidelines.

### **Conclusion Regarding Coverage for Asymptomatic Patients**

In conclusion, the decision to offer CAS to asymptomatic patients with a high grade stenosis is an individualized decision based on careful patient selection guided by comorbid conditions, the patient's life expectancy and other individual risk factors (e.g., familial history for ischemic stroke). Therefore, CAS must be made available to physicians for treatment of asymptomatic patients at high risk of stroke, who in the opinion of the treating physician require revascularization but due to the presence of surgical risk factors and/or anatomic conditions would be an inappropriate candidate for CEA. As with CEA, the decision for intervention should be considered only after evaluation for other treatable causes of stroke and a thorough discussion with the patient concerning the risks and benefits of treatment for asymptomatic carotid artery stenosis has been provided. Additionally, as indicated by CMS, in order to minimize complications, CAS should only be performed by physicians with appropriate qualifications,

high quality training and who are deemed competent to perform these procedures in hospitals with appropriate staff and imaging equipment.

## **II. Coverage for Symptomatic Patients**

In the draft decision CMS proposes that coverage be provided only for symptomatic high-risk patients with stenosis equal to or greater than 70%. In support of this decision, CMS cites a number of trials and analyses that demonstrate the clinical benefit of CEA for symptomatic patients with stenosis equal to or greater than 70% but do not provide clear evidence on the benefit for patients with stenosis of 50-70%.

Guidant believes that there is substantial evidence to demonstrate the clinical benefit of revascularization for symptomatic patients with angiographically documented 50-70% stenosis. The AHA Carotid Stenting and Angioplasty Guideline states that untreated symptomatic patients with 60%-70% stenosis face a high risk of stroke. The NASCET trial demonstrated a meaningful risk reduction in symptomatic patients with 50 to 69% stenosis. Specifically, patients with 50-70% stenosis randomized to CEA had a 5-year rate of any ipsilateral stroke of 15.7% as compared to 22.2% for those treated medically, an absolute risk reduction of 6.5% or 1.3% per annum. The ECST study demonstrated that intervention reduced the risk of major stroke or death in patients with a symptomatic stenosis of  $\geq 60\%$  by NASCET criteria from 26.5% in the control group to 14.9% in the treatment group.[46] As previously mentioned in the discussion of asymptomatic patients, the ARCHeR high surgical risk patients had multiple comorbidities that have been shown in trials to be correlated with an increased risk for stroke. Thus, it is reasonable to assume that these symptomatic patients have an elevated stroke risk as compared to the NASCET or ECST “normal risk” patients and the need for treatment is thus more compelling.

Guidant recommends that CMS modify the draft coverage decision to expand coverage to include symptomatic patients with stenosis of 50-70%.

## **III. Determination of Patient Risk for Surgery**

In the draft coverage decision, CMS states that patients at high risk for CEA are defined as having significant comorbidities and/or anatomic risk factors and who would be poor candidates for CEA *in the opinion of a surgeon*.

Guidant believes that the determination as to whether a patient is a poor candidate for surgery is most appropriately made by the physician(s) with the knowledge of all three treatment options including associated risks and benefits. This may involve interdisciplinary teams working at individual hospitals. Such teams could include a neurologist, neuro/vascular surgeon and interventionalist and thus would be in a unique position to assess all three treatment options for the high-risk patient: CEA, CAS or medical therapy. In addition, an interdisciplinary approach would help to assure that all factors, including patient comorbidities and procedural outcomes of the team involved, are taken into account and appropriately balanced in determining the treatment course.

## Conclusion

We strongly believe that patients and physicians should have the option of selecting CAS to treat asymptomatic high-risk patients with severe (>80%) stenosis. Recent studies have clearly established that carotid intervention, when combined with medical management of modifiable risk factors, is superior to medical management alone in the treatment of asymptomatic patients with high grade stenoses. There also is substantial evidence to demonstrate the clinical benefit of revascularization for symptomatic patients with angiographically documented 50-70% stenosis. In addition, the determination of the patient's high surgical risk status should be made by physician(s) with the knowledge of all three treatment options in order to assure a comprehensive and balanced approach to determining the most appropriate treatment.

We look forward to continuing to work with CMS on a final coverage policy that will meet the needs of patients and providers. Please let us know if you have questions or require additional information.

Sincerely,

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