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STROKE PREVENTION: FOCUS ON CAROTIDS

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EXECUTIVE SUMMARY

Surgical carotid endarterectomy (CEA) is known to be superior to medical therapy in normal-risk symptomatic and asymptomatic patients when performed by a skilled surgeon, but the safety and efficacy of surgery in patients with significant surgical or anesthetic risk is unclear. As an alternative approach in these high-risk patients, carotid artery stenting (CAS) has been tested in a number of randomized and registry trials and has demonstrated at least equivalency to CEA. The Cordis Precise® stent and Angioguard™ guidewire was shown to be non-inferior to CEA in the randomized SAPPHIRE trial, and the Guidant ACCUNET™ stent and ACCULINK™ filter demonstrated safety and efficacy in high-risk patients when compared to historical surgical controls in the pivotal registry trial, ARCHeR. In regards to normal surgical risk patients and carotid stenting, two large randomized trials are currently enrolling patients, CREST and ACT1. Future directions for carotid artery interventions include clarification of outcomes in octogenarians as well as investigation of physiologic characteristics that place subjects at increased risk.

Introduction

Prevention of embolic stroke related to carotid atherosclerotic disease includes medical therapy with antiplatelet agents, correction of medical risk factors, and mechanical improvement of the carotid lumen. Surgical carotid endarterectomy (CEA) has been performed since 1954, and has been proven to be significantly more beneficial than medical therapy alone in both symptomatic and asymptomatic normal-risk patients when performed by a skilled surgeon. In symptomatic patients, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) trial enrolled 659 patients with a 70-99% stenosis in the symptomatic carotid artery and randomized them to CEA versus medical therapy alone (1). At two years, the risk of stroke was 9% in the surgical patients versus 26% in the medical patients ($p < 0.001$) (Figure 1). In asymptomatic patients, both the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST) demonstrated a late benefit of CEA (Figure 1) (2,3). In all of these trials, high surgical risk patients were excluded (Table 1). Although the American Heart Association recommended that CEA be performed by surgeons with a stroke and death rate of < 3% in asymptomatic patients and < 6% in symptomatic patients in order to maintain benefits over medical therapy (4), the excellent surgical outcomes in the landmark ACAS and NASCET trials were not replicated in the real world experience (Figure 2). Because of the apparent need for alternative treatment strategies, particularly in higher-risk patients, percutaneous techniques have been developed.

Percutaneous Approach to Carotid Disease

High-Risk Patients

A number of carotid stent trials have demonstrated at least equivalency of carotid artery stenting (CAS) to CEA in high-risk patients. Carotid stenting began in the 1990s prior to the advent of dedicated devices, including embolic protection devices (EPD), and was limited, in part, by embolization of plaque debris to the brain. In the EPD era, there are multiple randomized controlled trials, both completed and ongoing, using different stent and protection devices, as well as a number of carotid stent registries (Table 2). In general, the carotid stent trials have been conducted in symptomatic patients with a stenosis > 50% and in asymptomatic patients with a stenosis > 80%. When high-risk subjects are enrolled, inclusion criteria are generally similar to those used in Table 3.

The first randomized trial comparing carotid stenting with an EPD to CEA in high-risk patients was the SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) trial (5). In this trial, the Angioguard™ Emboli Capture Guidewire was used with the Precise® nitinol Self-Expanding Stent (Cordis, Miami Lakes, Florida) (Figure 3). The trial was designed to show non-inferiority of CAS to CEA for the primary endpoint of cumulative incidence of death, stroke, or myocardial infarction (MI) within 30 days after the procedure or death or ipsilateral stroke between 31 days and 1 year. A total of 334 symptomatic and asymptomatic high-risk patients were randomized and the primary endpoint was reached in 12.2% of those receiving stenting versus 20.1% of those receiving surgery. This difference was non-inferior ($p = 0.004$) and approached significance for superiority ($p = 0.053$) in favor of CAS. This randomized trial led to a Food and Drug Administration (FDA) advisory panel

recommendation for approval of the Cordis endovascular carotid stent system, although these devices are not yet FDA approved for clinical use.

Subsequently, CASES-PMS (Carotid Artery Stenting With Emboli Protection Surveillance-Post-Marketing Study), a large prospective, single arm, open-label, peri-approval study of 1493 high-risk patients was conducted. The purpose of this study was to determine if patients had similar outcomes of carotid stenting with the Cordis system in a non-trial setting as patients treated during the SAPPHIRE trial. Results presented at the 2006 annual meeting of the Americal College of Cardiologists (ACC) showed that for the first 1,279 patients 30 day major adverse events were 4.8%, which was comparable to the 30-day CAS outcomes of SAPPHIRE (4.8%) (6).

The ACCULINK™ nitinol Carotid Stent System and ACCUNET™ Embolic Protection System (Guidant, Santa Clara,CA) (Figure 3) have also undergone a pivotal trial for use in high-risk patients. The ARCHeR (ACCULINK for Revascularization of Carotids in High-Risk Patients) trial was a series of three separate single-arm, prospective, multi-center trials (ARCHeR 1, 2, and 3) utilizing the Guidant endovascular carotid stent system in a total of 581 patients and comparing their outcomes to a surgical historical control group. The 1-year composite primary endpoint of all-cause death, stroke, and MI in the first 30 days, plus any ipsilateral stroke between 31 days and one year was 8.3 % in ARCHeR 1 and 10.2 % in ARCHeR 2. These rates compared favorably to the surgical historical control rate of 14.5%. At 30 days, the rates of major stroke and death for ARCHeR 2 and 3 were 2.5 and 2.8%, respectively. This data was presented at ACC 2004 and are currently in press (7).

The results of ARCHeR led to FDA approval of the ACCULINK/ACCUNET devices with mandated post-market surveillance, which was performed through the CAPTURE (Carotid Acculink/Accunet Post Approval Trial to Uncover Rare Events) registry (8). In CAPTURE, over 2500 high-risk patients have been enrolled at 137 different centers. The patients were older and included more women than in the ARCHeR trial, but fewer were symptomatic (9% vs. 24%). The majority (91%) of the physicians performing the procedure had low to medium prior operator experience. The 30-day event rate, a combined end point of death, stroke, or MI, was 5.7%, significantly lower than the 8.3% observed in the ARCHeR trial. This difference was mostly driven by a reduction in MI. In addition, major stroke and death rates were significantly lower in the asymptomatic patients compared to the symptomatic patients (2.2% vs. 6%; $p < 0.05$). Predictors of adverse outcomes included symptoms, age > 80 years, history of congestive heart failure, multiple carotid stents, and predilation prior to EPD placement. Finally, it was concluded that a training program successfully led to equivalent outcomes to ARCHeR in the hands of less experienced operators. Currently, CAPTURE-2 is continuing to enroll these patients in a much larger registry effort.

Normal-Risk Patients

In regards to normal-risk patients and carotid stenting, two large randomized trials are currently enrolling patients. CREST (Carotid Revascularization Endarterectomy versus Stenting Trial) is a phase III National Institutes of Health (NIH) sponsored trial comparing CAS with the Guidant ACCULINK/ACCUNET device to CEA in both symptomatic and asymptomatic

normal-risk patients (9). The randomization is 1:1, and the expected enrollment is 2500 patients. The endpoints are 30-day death, stroke, or MI, and multiyear ipsilateral stroke.

ACT 1 (Asymptomatic Carotid Stenosis, Stenting Versus Endarterectomy Trial) is a prospective randomized trial of CEA versus CAS utilizing the Xact® Carotid Stent System with the Emboshield® Embolic Protection System (Figure 3) (Abbott Vascular, Redwood City, CA). This is a pivotal trial with a lead-in enrollment of 200 patients and a maximum of 1540 pivotal patients at 50 sites (10). The trial is intended to study asymptomatic normal-risk patients randomized in a 3:1 fashion leading to performance of three CAS for every CEA. Primary endpoints are 30-day major adverse events and 31-365 day ipsilateral stroke. It is anticipated that these trials will answer questions regarding CAS in normal-risk populations.

Octogenarians

Outcomes in octogenarians need further clarification. In the carotid surgery trials, a significant number of patients over the age of 75 years were excluded in order to limit confounding variables. In NASCET, CEA conferred less benefit in symptomatic patients over the age of 75 years than in younger patients when compared to medical therapy (1). A similar lack of benefit in asymptomatic patients was seen in the ACST trial (3). Likewise, in carotid stenting trials, CREST lead-in data suggests a higher 30 day risk of stroke and death in subjects over age 80 years (11). The CAPTURE 2500 registry showed that the combined outcome of death, stroke, and MI (DSMI) was significantly worse in subjects over age 80 years than those under age 80 years, particularly in asymptomatic patients (Figure 4) (8). The mechanism of the increased risk in octogenarians has not been defined.

FDA Approval and Reimbursement

Based on the above data, the FDA has approved two carotid device systems in high-risk patients with mandated post market surveillance. On August 30, 2004, the Guidant ACCULINK and ACCUNET carotid stent system was FDA approved for high-risk patients with > 50% stenosis if symptomatic and > 80% stenosis if asymptomatic (12). On September 6, 2005, the Abbott Xact Carotid Stent System with the Emboshield Embolic Protection System received similar FDA approval for high-risk patients (13). The Centers for Medicare and Medicaid Services (CMS) will reimburse for carotid stenting only in select patients, however. For high-risk, symptomatic patients with a > 70% stenosis, CMS coverage is limited to FDA approved devices only. High-risk symptomatic patients with a 50-70% stenosis and high-risk asymptomatic patients with a stenosis > 80% are covered if enrolled in a post-approval or investigational device exemption (IDE) study (14).

Credentialing

In order to ensure acceptable patient outcomes, proper training and credentialing for carotid stenting is necessary. In January 2005, a writing committee consisting of representatives from the Society for Cardiac Angiography and Interventions (SCAI), the Society for Vascular Medicine and Biology (SMB), and the Society for Vascular Surgery (SVS) composed a clinical competence statement on carotid stenting (15). In regards to physician training, the committee outlined the cognitive requirements which include knowledge of stroke and carotid

pathophysiology, competent clinical evaluation of neurovascular patients, knowledge of diagnostic imaging for stroke and carotid disease, knowledge of the major stroke and revascularization trials, and appropriate case selection with post-procedure evaluation. In addition to cognitive knowledge, the committee recognized the importance of technical requirements in angiographic and interventional skills. The minimum number of procedures to achieve competence includes 30 diagnostic cervico-cerebral angiograms and 25 carotid stent procedures. The committee also outlines training pathways through accredited fellowship training programs, and a practice pathway for those who want to be trained in a clinical practice environment. The committee recognizes that industry-sponsored device certification programs can assist in the completion of the above requirements, however, completion of such a certification program is not solely adequate for performance as a primary operator.

Conclusions

To date, carotid stent trials have been completed in high-risk patients, and many are ongoing in normal-risk patients. Benefit has been demonstrated in high-risk patients, and other subgroups that might benefit from carotid stenting are still being defined. In addition, areas of ongoing research, such as characterization of plaque morphology and vascular reserve, may aid in the risk stratification of patients pre-procedure. With continued refinement of percutaneous devices and optimal cognitive and technical training of operators, carotid stenting will become a mainstream procedure for preventing stroke in patients with significant carotid disease.

Table 1. High Risk Surgical Criteria (NASCET and ACAS Exclusions)

• Age>79 • Prior ipsilateral CEA • Unstable coronary syndrome • Myocardial infarct in previous 6 months • Cardiac valvular or rhythm abnormality likely to cause embolic cerebrovascular symptoms • Contralateral occlusion • A more severe lesion cranial to the surgical lesion	• Contralateral CEA within previous 4 months • Uncontrolled hypertension or diabetes • Organ failure likely to cause death within 5 years • Total occlusion • Major surgical procedure in previous 30 days • Prior severe CVA • Progressing neurologic syndrome

Table 2. US Carotid Stent Trial Data

	Trial	Year	n
Pre-EPD			
Normal-risk/randomized	WallStent	1999	223
Post-EPD			
Normal-risk/randomized	CREST (lead-in)	2003	484
	ACT-1 (lead-in)	2005	200
Normal-risk/non-randomized	CARESS	2003	143
High-risk/randomized	SAPPHIRE	2002	334
High-risk/registry	SAPPHIRE	2002	406
	ARCHeR	2003	581
	SECuRITY	2003	305
	BEACH	2004	408
	CABERNET	2004	454
	CAPTURE	2006	2500
	CASES-PMS	2006	1500

Table 3. Typical High Risk Inclusion Criteria

- Either CHF (class III/IV) or severe LV dysfunction (EF < 30%).
- Recent (< 6 weeks) or concurrent need for open heart surgery
- Recent MI (< 4 weeks)
- Active unstable angina
- Coexistent severe 2 vessel CAD
- Severe obstructive lung disease (FEV < 1.0, < 30% predicted)
- Contralateral carotid occlusion
- Contralateral laryngeal nerve palsy
- Prior neck radiation or radical neck surgery
- Restenosis of prior CEA
- High cervical ICA or infra-clavicular CCA lesions
- Serial stenoses
- Uncontrolled diabetes mellitus
- Need for major organ transplantation
- End-stage renal disease on hemodialysis
- Age > 80 years

Figure 1. ACAS, ACST and NASCET: Comparative Results

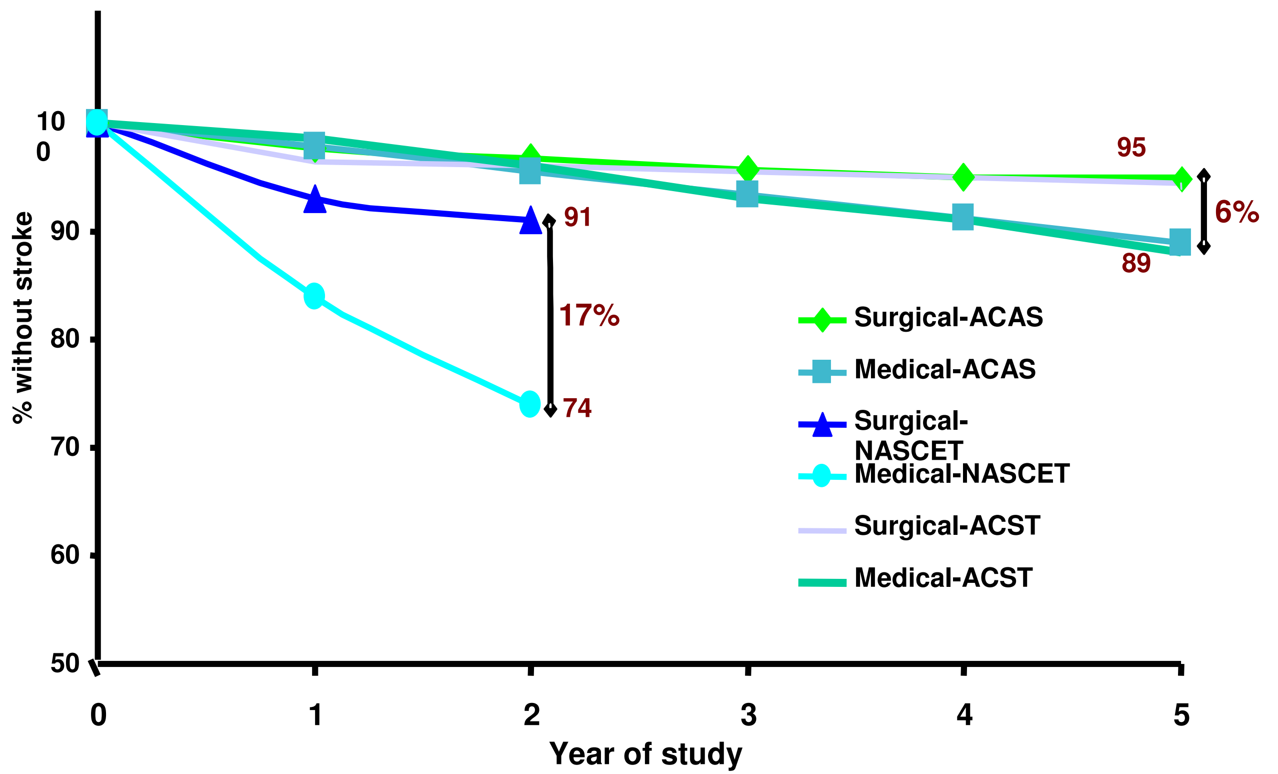


Figure 2. "Real World" Endarterectomy Outcomes (>100,000 Medicare patients, 30-day mortality)

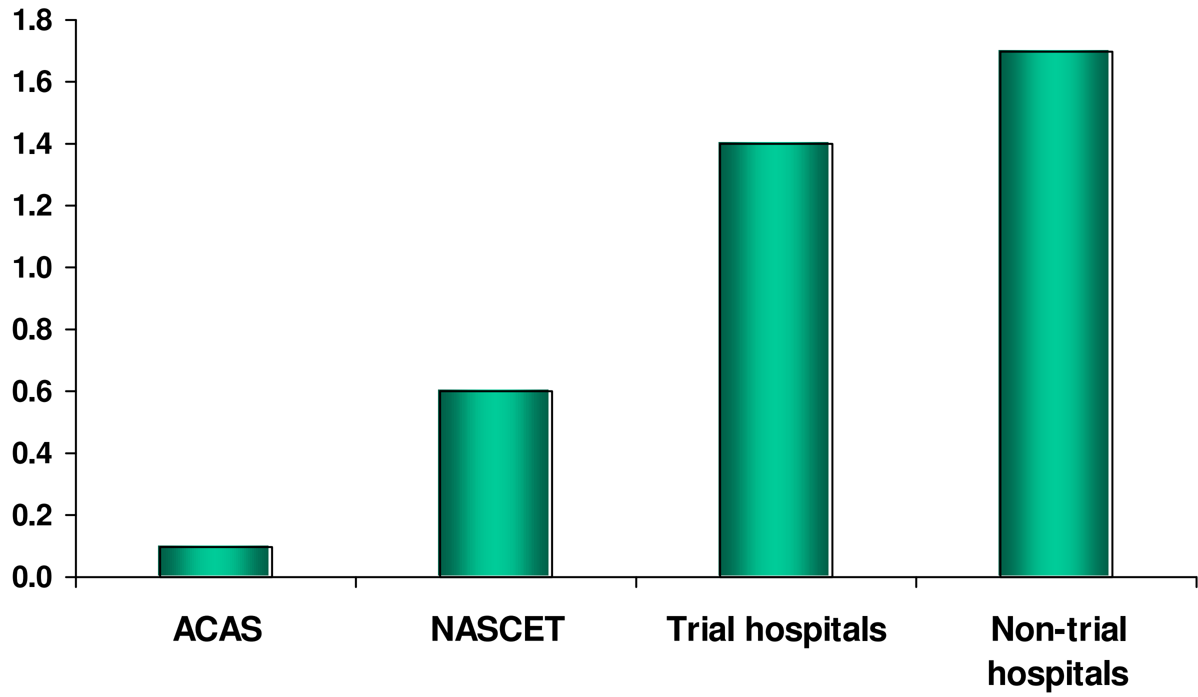
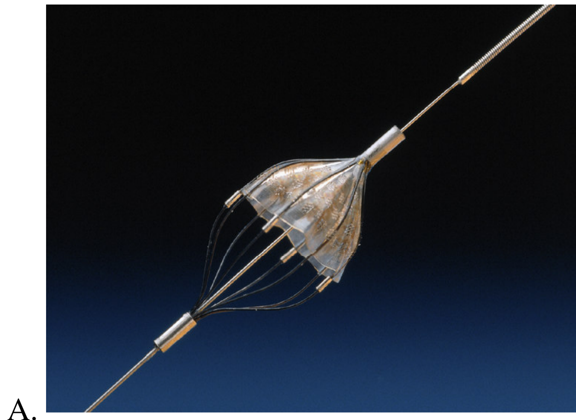
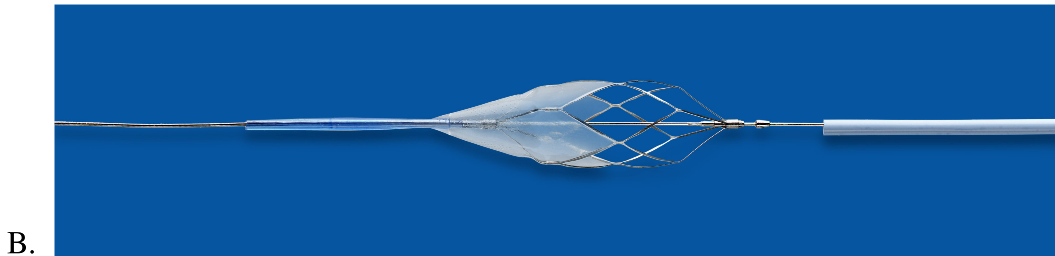


Figure 3. Current Carotid Embolic Protection Devices. A: Cordis Angioguard™; B: Guidant ACCUNET™; C: Abbott Emboshield®

A. 

B. 

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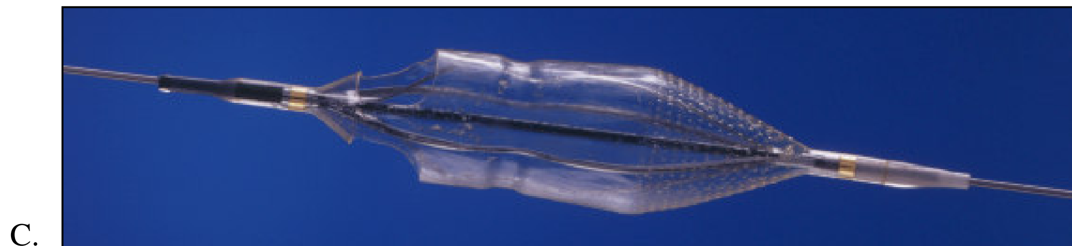
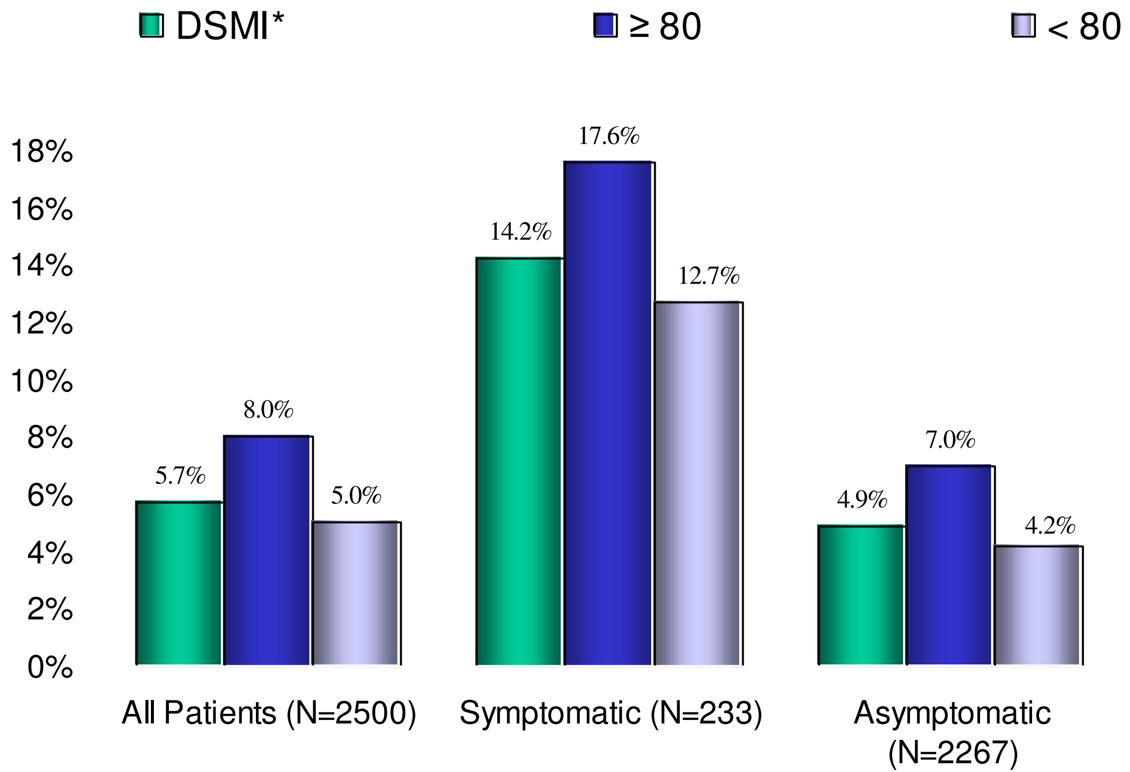
C. 

Figure 4. CAPTURE 2500: DSMI by Combined Octogenarian and Symptomatic Status



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