However, the importance of these pathways is undefined, particularly in men, who have an overwhelming excess of circulating androgens anyway. There is some evidence for the therapeutic use of DHEA in patients with primary or secondary adrenal insufficiency,[3] though most studies of this group have focused on improvements in the quality of life.

Further research focusing on the action of DHEA and its role in patients with DHEA deficiency is certainly indicated. Establishing the hormone's safety or lack thereof might lead to the reclassification of DHEA as a drug, since supplements are defined as causing no harm. To date, the DHEA trials involving elderly patients have shown neither meaningful benefits nor adverse events. Concern has been expressed about the downstream metabolism of DHEA to more potent androgenic metabolites within prostate or mammary glands, but no deleterious changes in prostate-specific antigen or prostate volume have been observed.[4,5] However, the report on the Women's Health Initiative study of estrogen replacement in postmenopausal women is a telling reminder that reversing an age-related endocrine deficit may actually cause more harm than good,[12] and ongoing vigilance is needed in cohorts of patients with adrenal insufficiency who are prescribed DHEA.

The search for eternal youth will continue, but the reversal of age-related decreases in the secretion of DHEA and testosterone through "physiologic" replacement regimens offers no answer and should not be attempted. In light of an evidence base for the efficacy of DHEA in patients with adrenal insufficiency, DHEA should no longer be accepted as a food supplement and should instead be treated as a regulated drug. Appropriate regulation would dispel much of the quackery associated with this elusive hormone.

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Carotid-Artery Stenting — Case Open or Closed?

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As compared with carotid endarterectomy, carotid-artery stenting has uncertain efficacy and safety in patients at risk for stroke from atherosclerotic stenosis of the internal carotid artery. The benefits of carotid endarterectomy for both symptomatic and asymptomatic patients have been established in several randomized trials comparing surgery with medical therapy. The benefits of surgery in reducing the long-term risk of stroke need to be weighed against the immediate risk of death or stroke as a complication of the surgery. For symptomatic patients with stenosis of the internal

carotid artery of 70% or more, carotid endarterectomy is superior to medical therapy alone, assuming a risk of perioperative stroke or death of less than 6%.[1,2] For asymptomatic patients with stenosis exceeding 60%, carotid endarterectomy is also superior to medical therapy alone, assuming a risk of perioperative stroke or death of less than 3%.[3,4] All these clinical trials of carotid endarterectomy involved patients who had an average risk of perioperative stroke or death after surgery; patients who had a high surgical risk owing to severe coronary artery disease were excluded.

Currently, the only use of carotid stenting that has been approved by the Food and Drug Administration (FDA) is in symptomatic patients with stenosis of the internal carotid artery exceeding 70% who are at high risk for complications after surgery. The limited FDA approval of stenting is largely based on the results of the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE)[5] trial, involving patients who had symptomatic stenosis of the internal carotid artery exceeding 50% or asymptomatic stenosis exceeding 80% and who were at high surgical risk mainly owing to severe coronary artery disease. The SAPPHIRE trial showed that carotid stenting was safer than carotid endarterectomy in patients at high surgical risk, because of a lower risk of myocardial infarction within 30 days after carotid stenting as compared with surgery. There was no significant difference in the rates of stroke or death between carotid stenting and endarterectomy at either 30 days (3.6% vs. 3.1%) or at 1 year. Although the SAPPHIRE trial included more asymptomatic patients than symptomatic patients, the FDA approved carotid stenting only for symptomatic patients at high surgical risk. In asymptomatic patients, carotid stenting was safer than carotid endarterectomy, but the perioperative risk for stenting in the SAPPHIRE trial was still 6.7%, which may outweigh any long-term reduction in the incidence of stroke among asymptomatic patients. Furthermore, the SAPPHIRE trial did not include a control group that received medical therapy only, which could have further addressed this concern.

In this issue of the *Journal,* Mas et al., writing for the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) investigators,[6] report that the trial was stopped early because of an excess 30-day incidence of stroke or death among patients who underwent stenting (9.6%), as compared with those who underwent surgery (3.9%). There were no significant differences between the two groups in the 30-day incidence of myocardial infarction.

How can we explain the opposite results of the SAPPHIRE and EVA-3S trials, and how safe is carotid-artery stenting? In contrast to patients in the SAPPHIRE trial, patients in the EVA-3S study were not at high surgical risk because of severe coronary artery disease. Furthermore, all patients in the EVA-3S study had symptomatic atherosclerotic stenosis of the internal carotid artery, whereas the majority of patients in the SAPPHIRE trial were asymptomatic. However, these differences in trial design do not fully explain the conflicting results; the 30-day incidence of death, stroke, and myocardial infarction after stenting among symptomatic patients in the SAPPHIRE trial was only 2.1%, as compared with a 30-day incidence of any stroke or death of 9.6% in the EVA-3S trial.

In a systematic review of the literature through 2002,[7] the 30-day rate of death or stroke after carotid stenting was 5.5% among patients treated without protection from embolism (6.4% in symptomatic patients vs. 1.0% in asymptomatic patients), as compared with 1.8% among those treated with protection (separate results for symptomatic and asymptomatic patients were not given). In the SAPPHIRE trial, a single type of protection device (Accunet) was used in all patients. Early in the EVA-3S trial, protection from embolism was not used among patients who underwent stenting, and the incidence of stroke was 25% (5 of 20). In fact, the study was briefly stopped, and routine cerebral protection was then incorporated into the protocol. Even with the use of protection, however, the incidence of stroke after carotid stenting (7.9%) was still worse than that after carotid endarterectomy.

Neither the SAPPHIRE trial nor the EVA-3S trial provides information on the specific causes of periprocedural strokes (e.g., occlusion, embolism, dissection) or other potential factors related to periprocedural strokes in patients treated with stents. In the EVA-3S study, the majority of strokes among patients who underwent stenting (17 of 24) occurred on the day of the procedure, suggesting that they were direct complications of the intervention. Although the angiographic appearance of the lesion was not an eligibility criterion, plaque morphology (length, degree of ulceration,

and presence or absence of thrombus) could be related to complication rates for stenting. Administration of aspirin and clopidogrel or ticlopidine 3 days before carotid-artery stenting was recommended in the EVA-3S trial but was required in the SAPPHIRE trial. Although compliance with antiplatelet therapy in the SAPPHIRE trial is unclear, 42 and 36 patients who underwent stenting in the EVA-3S trial received only single (unspecified) antiplatelet therapy before and after the procedure, respectively. Neither trial provides data on clopidogrel loading or antiplatelet resistance testing.

Perhaps most important, Mas et al. discuss the "learning curve" for carotid stenting. It is well known that the risk associated with carotid endarterectomy varies among surgeons (and was actually lower than expected in the EVA-3S study), and there is no reason to believe differently for interventional physicians performing stenting. Indeed, because of these concerns, several societies have recently published training and credentialing guidelines for carotid stenting.[8,9] In the EVA-3S trial, interventional physicians used five different stents and seven different cerebral protection devices, and experience with only two procedures was required for any new device used. By comparison, the ongoing Carotid Revascularization Endarterectomy versus Stenting Trial (CREST),[10,11] funded by the National Institutes of Health, enrolled 1472 patients for a lead-in phase that required a training program of up to 20 implantations per investigator using a single type of stent (Acculink) and cerebral protection system (Accunet). Of those enrolled for the lead-in phase, 519 were symptomatic patients with stenosis of the internal carotid artery exceeding 70%, almost as many as the 527 patients randomly assigned to treatment in the EVA-3S study. The number of randomly assigned patients in CREST is expected to be 2500; 799 symptomatic patients who have stenosis of the internal carotid artery exceeding 70% are already enrolled. All patients enrolled in CREST have an average surgical risk similar to those in the EVA-3S study.

Recently, the Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial was unable to prove the noninferiority of carotid stenting with regard to endarterectomy.[12] The 30-day rate of ipsilateral stroke or death was 6.84% among patients who underwent carotid stenting, as compared with 6.34% among those who underwent endarterectomy; this difference did not achieve statistical significance for noninferiority. However, since the trial was stopped early, the results remain inconclusive.

For all these reasons, although the EVA-3S trial raises concerns about the safety of carotid stenting and bolsters the call for standardized training and credentialing requirements, it cannot be considered the final word on carotid stenting for patients with an average surgical risk. Given the evidence to date, and assuming a complication rate of less than 6% for stenting, the only widely accepted indication for carotid-artery stenting remains its use in symptomatic patients who have stenosis of the internal carotid artery exceeding 70% and who also have a high surgical risk. All other patients should be treated medically, undergoing carotid endarterectomy if indicated, or should be placed in a clinical trial.

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CORRECTION

Carotid-Artery Stenting — Case Open or Closed?

Carotid-Artery Stenting — Case Open or Closed? . On page 1727, in the 9th line of the second paragraph of the right column, the sentence should have read, ``In the SAPPHIRE trial, a single type of protection device (Angioguard) was used in all patients,'' not ``(Accunet),'' as printed.

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