Progress in Stroke Prevention and Treatment

By JAMES D. MARSH, MD

Stroke is a major cause of death and disability for Americans and, among older citizens, it is often an event more greatly feared than myocardial infarction (MI) or cancer. This is because a state of dependency is often a permanent consequence of a major stroke. In 2002, there were 700,000 patients in the United States (US) who suffered a new or recurrent stroke; of these, 162,000 died. The economic impact of stroke is estimated to be $57 billion per year.[1] Stroke disproportionately occurs among African American and Native American populations, but can have a devastating personal and economic impact, regardless of ethnic origin or socio-economic status. These contemporary facts are all the more regrettable since many strokes, particularly those of ischemic, hypertensive, or embolic origin, are often preventable with prudent medical care. For the American population, the majority of strokes are due either to hypertensive cerebrovascular disease (often producing lacunar strokes), atherosclerosis of the carotid or basilar arteries, or emboli from the cardiac chambers. Indeed, one-third of all ischemic strokes are due to emboli from atrial fibrillation (AF). In addition to these mechanisms that produce cerebral ischemia, less commonly, an intracranial hemorrhage can produce a stroke, often with devastating consequences. Finally, there are rare causes of stroke, such as vasculitis. This issue of *Cardiology Rounds* discusses the causes, diagnosis, and treatment of stroke.

It has long been established that medical control of hypertension is the cornerstone of stroke prevention. There are well-considered, data-derived guidelines for diagnosis and treatment of hypertension (eg, the Joint National Committee [JNC]-7) that provide excellent guidance to the clinician.[2] Therefore, control of hypertension will not be reviewed further at this point, except to stress that tight control of hypertension is of great importance, particularly in high-risk patients, including those with diabetes and renal impairment. There is a recent analysis[3] suggesting that beta-blockers may have less efficacy in stroke reduction than other classes of drugs for the same degree of blood pressure control.

Cardiac causes of cerebral ischemia

The heart chambers and inadequate cardiac output account for a substantial proportion of ischemic strokes, although the exact proportion remains a subject of debate. Table 1 enumerates the important mechanisms and these can be broadly divided into cardiac sources of emboli and inadequate cerebral perfusion. In the US, AF is by far the most common cause of cardiac emboli to the cerebral circulation. This is an extremely common arrhythmia and its prevalence is age-dependent. For people >60-years-old, the prevalence is at least 4% and, for those aged >80 years, the prevalence approaches 10%.[1] With the demographic shift in age distribution of the US population to older ages, the absolute number of people at risk for AF will increase dramatically over the next 20 years. Because of the loss of organized contraction in the atrium, AF produces stasis in the left atrium, most notably in the left atrial appendage[4] and, subsequently, thrombus formation. Growing evidence suggests that AF is also an inflammatory process and that the atrial endothelium is more prone to thrombus formation because of ongoing inflammation. Left-sided valvular endocarditis, with consequent sterile or septic emboli, is a common cause of embolic stroke, particularly in younger age groups and in patients with a history of intravenous drug abuse. Acute and chronic disruption of the endothelial lining of the left ventricle (LV) due to MI, with or without aneurysm formation, leads to a thrombogenic site and the opportunity for subsequent embolization.

Cardiologists are able to manage a number of conditions that can lead to cerebral infarction due to poor blood perfusion in the territory of the end-arteries. Thus, low cardiac output states, as noted in Table 1, can produce cerebral infarction. Moreover, overzealous correction of blood pressure in hypertensive

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Table 1: Cardiac causes of cerebral ischemia

Cardiac sources of emboli
- Atrial fibrillation- left atrial appendage and left atrium
- Endocarditis
- Left ventricular aneurysm
- Acute myocardial infarction
- Prosthetic valve
- Patent foramen ovale with systemic embolism of venous thrombus
- Other

Inadequate cerebral perfusion
- Low cardiac output state (cardiogenic shock)
- Bradyarrhythmias and tachyarrhythmias
- Too rapid correction of hypertensive emergency or urgency

Table 2: Antithrombotic therapy in acute ischemic stroke

Do use:
- First 180 minutes – Consider intravenous tPA, if head CT excludes intracranial hemorrhage and all inclusion/exclusion criteria are met
- First 48 hours – Aspirin 160-325 mg daily
- Day 3-4 – Start warfarin (without intravenous heparin); target INR 2.0-3.0

Do not use:
- Intravenous tPA if it cannot be administered safely in first 180 minutes
- In first 48 hours – IV or sc unfractionated heparin, low-molecular-weight heparin, heparinoids, abciximab

sc = subcutaneous

emergencies can cause a stroke because of the failure of normal autoregulation of cerebral circulation in the setting of marked hypertension.

Antithrombotic approaches for atrial fibrillation

Over the past 15 years, numerous clinical trials have clearly demonstrated that AF – whether paroxysmal, persistent, or permanent – carries a significant risk of stroke due to embolization from a thrombus in the left atrium.[5-7] In most cases, the left atrial appendage is the actual locus of the thrombus. For patients in the placebo arm of the initial Stroke Prevention in Atrial Fibrillation Trial (SPAF I),[6] the stroke rate was 8% per year, with a linear increase in risk through at least 3 years, and a cumulative 3-year risk of 24%. This trial was stopped prior to the point specified by the original study design because it was very clear that the risk of stroke in AF patients not taking antithrombotic therapy was high and that either aspirin (325 mg/day) or warfarin decreased stroke risk dramatically.[5]

Subsequently, SPAF II and other studies established that for low-risk patients, aspirin at a dose of 325 mg/day, provided good stroke protection. For higher-risk patients, warfarin, with a target international normalized ratio (INR) of 2.0-3.0 provided good protection from stroke, albeit not perfect.[6] Low-dose aspirin (81 mg/day) does not provide any measurable benefit for stroke prevention in AF and this dose should not be used.[8,9]

Antithrombotic and thrombolytic therapy in the treatment of acute ischemic stroke

This area of therapy has been the subject of much debate for many years, but it is also an area with a paucity of large, well-designed, definitive clinical trials. Currently, tissue plasminogen activator (tPA) is the only thrombolytic drug approved by the Food and Drug Administration (FDA) for intravenous administration to treat ischemic stroke. The tPA Stroke Trial, sponsored by the National Institutes of Health (NIH), established that patients with ischemic stroke, who receive the drug infusion within the first 180 minutes after the onset of symptoms and who meet rigorous inclusion and exclusion criteria, have a clinically and statistically significant improvement in functional outcome compared to patients who receive routine care (Table 2).[10]

To be eligible for tPA treatment, a computed tomography (CT) head scan must be performed first to exclude intracranial hemorrhage. Furthermore, if hypertension is present, it must be

adequately controlled. Currently in the US, <5% of patients with stroke receive this therapy. The main reason for its under-utilization is that most patients present for medical care more than 180 minutes after the onset of symptoms, or a head CT scan and expert consultation cannot be obtained in a sufficiently expeditious manner to permit treatment within this time frame.

Numerous large medical centers are developing an acute stroke team whose role is to expedite the care of acute stroke patients.[11] Currently, a few highly specialized centers with an active interventional neuro-radiology program are undertaking intra-arterial lysis of thrombi in major cerebral vessels within the time-window of approximately 3-8 hours after symptoms develop. Rapid brain-imaging studies, followed by arteriography, permit selection of suitable candidates. A small catheter is advanced to the arterial site just proximal to the thrombus and a lytic drug is infused using urokinase, tPA, or reteplase. As an alternative approach, a few centers are performing acute cerebral thrombus extraction in the setting of acute stroke. A specially developed, corkscrew-shaped guidewire is inserted through a mini-catheter and used to retrieve the thrombus into a guide catheter. In carefully selected patients, the initial results appear promising.[12]

For patients presenting with symptoms and signs of an ischemic stroke outside the time-window for thrombolytic therapy, there has been much debate over the role of anticoagulation with intravenous heparin. The goal of this therapy is to prevent the propagation of thrombi *in situ*, or further embolization from AF or other sources of thromboemboli. Evidence to support this common practice is scant and the American Academy of Neurology, as well as the Stroke Council of the American Heart Association, now recommend that intravenous unfractionated heparin (UFH) not be given during the acute stage (within the first 48 hours) of an ischemic (or hemorrhagic) stroke.[13] For patients with AF not on warfarin who have an embolic stroke, the risk of an additional embolic stroke within the first 14 days is 1%-2%, whereas the risk of hemorrhagic conversion of an ischemic stroke in patients receiving intravenous UFH within the first 48 hours may be as high as 7%-14%. Hemorrhagic conversion of an ischemic stroke is very often associated with marked clinical worsening and is sometimes fatal. Furthermore, abciximab, low-molecular-weight heparins, and heparinoids have not been shown to reduce mortality or stroke-related morbidity when used within 48 hours of symptom onset in patients with acute ischemic stroke.[14,15]

The role of aspirin as an antithrombotic early in the course of an ischemic stroke has been investigated. Aspirin (160 mg or

Table 3: Percentage of patients reaching the primary endpoint (combination of stroke, MI, vascular death, peripheral embolism) in the ACTIVE-W trial

Treatment	Primary endpoint	
Warfarin	3.9%/year	P = 0.0006
Clopidogrel plus aspirin	5.6%/year	

Figure 1: Evidence for a nonsignificant reduction in stroke and systemic embolic events with ximelagatran

325 mg daily) results in a small, but statistically significant reduction in death and disability when given within 48 hours after ischemic stroke, as indicated by a combined analysis of available studies.[13] At this time, warfarin is the mainstay of antithrombotic therapy after an ischemic stroke. If there are no contraindications, warfarin should be started 3 to 4 days after an ischemic stroke, without prior or concomitant intravenous heparin.[13]

Combined antiplatelet agents for stroke prevention in AF

Numerous clinical trials have provided compelling evidence that stroke risk in AF is highly variable, that several risk factors can identify patients at high risk for embolic stroke, and that aspirin therapy is adequate in low-risk and in some intermediate-risk patients. However, intermediate-risk and all high-risk patients have less risk of embolic stroke if they receive dose-adjusted warfarin.[8,16]

Alternative strategies to dose-adjusted warfarin (target INR 2.0-3.0) in intermediate- and high-risk patients, or to aspirin (325 mg/day) in low-risk patients, have been investigated. The SPAF III trial compared standard, dose-adjusted warfarin therapy with fixed, low-dose warfarin therapy plus aspirin for stroke prevention in high-risk AF patients. Standard, full-dose warfarin proved to be significantly superior to the alternative strategy.

Clopidogrel plus aspirin is a potentially attractive alternative strategy compared to dose-adjusted warfarin for high-risk patients with AF. A recent clinical trial (ACTIVE-W) was designed to test the hypothesis that clopidogrel (75 mg daily) plus aspirin (81-100 mg daily) provided at least 50% of the conservatively estimated proven benefit of warfarin for stroke prevention in AF.[17] In this large trial (6,700 patients in 31 countries), the INR was relatively well-controlled in patients randomized to warfarin, with 64% of INR determinations being in the target range of 2.0-3.0. The trial was halted early because of the clear superiority of warfarin compared to clopidogrel plus aspirin. The primary endpoint was a combination of stroke, MI, vascular death, and peripheral embolus (Table 3).[17]

Of note, the rate of major bleeding was not different in the 2 regimens (2.2%/year). Initial analysis suggests that for patients who have difficult-to-control INRs for medical or social reasons, clopidogrel plus aspirin is as effective as warfarin in protection against vascular endpoints.

Direct thrombin inhibitors for stroke prevention in AF

Direct thrombin inhibitors that are currently under development may be useful in AF. Ximelagatran has been investigated in this setting in 2 large clinical trials, SPORTIF III and SPORTIF V. These Phase III trials compared ximelagatran (36 mg twice daily) with well-controlled warfarin (INR 2.0-3.0) in a combined population of >7,000 moderate- to high-risk AF patients. Data from SPORTIF III demonstrate a nonsignificant trend towards an absolute reduction in stroke and systemic
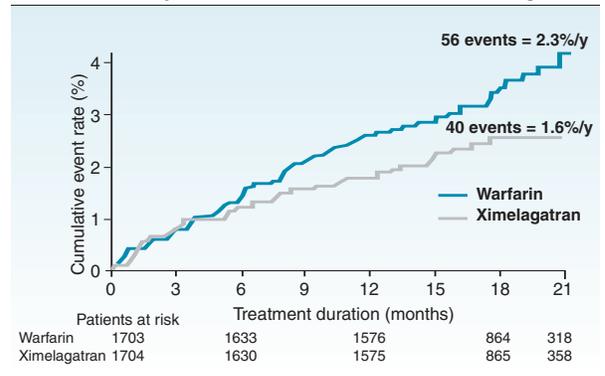
embolic events with ximelagatran compared to warfarin at 21 months (1.6% vs. 2.3% per year, respectively; p = 0.10). Preliminary data from SPORTIF V appear to further support noninferiority between the two agents. On-treatment analysis of the rate of major bleeding events reveals a nonsignificant reduction in the event rate per year with ximelagatran versus warfarin in both studies. The results of SPORTIF III and V demonstrate that a fixed oral dose of ximelagatran, without coagulation monitoring, is comparable to dose-adjusted warfarin in preventing stroke and other thromboembolic complications among moderate- to high-risk AF patients (Figure 1).[18,19] However, an increase in the incidence of elevated liver function tests (6%-7% of patients receiving ximelagatran) was noticed in these trials. The clinical importance and management of this potential complication is under further investigation. The drug has not yet received FDA approval.

Mechanical approaches to eliminating atrial sources of thrombi

There are some AF patients for whom antithrombotic therapy with warfarin or other thrombin inhibitors is very difficult because of recurrent bleeding. For selected patients, an approach that is still investigational may be feasible. The great majority of thromboemboli from the left atrium actually arise in the left atrial appendage (LAA). Occluder devices have been developed that can be placed in the LAA to block the mouth of the appendage and eliminate the possibility that thrombi in the LAA can reach the systemic circulation. The approach to occluder device placement is via a catheter into the right atrium, the device is passed into the left atrium after transseptal catheterization and placed in the LAA mouth under echocardiographic and fluoroscopic guidance. An initial feasibility study appears promising.[20] A more direct way to exclude the LAA is to oversew its mouth, with or without amputation of the LAA, at the time of thoracotomy.

Cryptogenic stroke (stroke with no clear etiology after careful investigation) comprises 26% of total strokes.[21] Evaluation of potential cardiac sources of emboli may include a transesophageal echocardiogram (TEE) and, in a small percentage of patients, a patent foramen ovale (PFO) may be found. A substudy of the Warfarin-Aspirin Recurrent Stroke Study (WARSS) – the Patent foramen ovale In Cryptogenic Stroke Study (PICSS) – demonstrated that for patients with at least a hypothetical chance of venous thromboemboli crossing the

PFO, aspirin (325 mg/day) is as equally effective as anti-coagulation with warfarin (target INR=2.0-3.0) in preventing recurrent stroke.[22] A small fraction of these patients may have a recurrent stroke despite therapeutic anticoagulation, or opt for PFO closure to avoid antithrombotic therapy. Catheter-delivered PFO closure devices show considerable promise in effectively closing the PFO, possibly decreasing the risk of subsequent stroke,[23,24] and avoiding open-heart surgery to close the PFO. However, their role in prevention of recurrent stroke remains an area of uncertainty and active investigation.[25,26]

Medical prevention and management of carotid atherosclerosis

High-risk patients

It is important for the cardiologist, internist, and general medical physician to appreciate that atherosclerosis is a systemic disease, affecting not only the coronary tree, but also the aorta, renal, iliac, and most importantly, carotid circulation. The Heart Protection Study (HPS) and the primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS)[27] have both provided valuable guidance in selecting patients for medical therapy directed toward primary stroke prevention and secondary prevention in high-risk patients.[28,27]

In the HPS, patients were identified who appeared to be at high risk for cardiovascular events (MI, stroke, and cardiovascular death). Inclusion criteria included established vascular disease (eg, coronary artery disease [CAD], previous ischemic stroke, or transient ischemic attack [TIA], or other arterial occlusive disease) and also one of the following: diabetes, hypertension, male sex, and age >65 years. Furthermore, all patients had low-density lipoprotein cholesterol (LDL) levels of 135 mg/dL. Subjects were randomized to 40 mg simvastatin daily or placebo. The follow-up was for a mean of 4.6 years. Over 20,000 patients were enrolled. The primary endpoint was nonfatal MI, coronary death, stroke of any type, or any revascularization procedure. For the primary endpoint, treatment with simvastatin reduced the relative risk; hazard ratio 0.76 (95% CI, 0.72-0.81; p<0.0001). Risk of stroke was decreased (p<0.002). Interestingly, the subgroup analysis, which must be viewed cautiously, demonstrated that the benefit in stroke prevention was for patients with no prior stroke. Indeed, those with a previous stroke did not accrue any benefit. However, it is clear from this very large and well-conducted study that, in a patient group with multiple risk factors for atherosclerotic vascular disease, lipid-lowering with 40 mg simvastatin daily produces a substantial and significant reduction in stroke risk, with no increase in intracranial hemorrhage. Other major vascular events were decreased as well. For these patients at high risk for carotid atherosclerosis, possibly leading to ischemic stroke, lipid-lowering is an important part of preventive management.

The degree of LDL-lowering necessary for stroke prevention has yet to be defined. The IDEAL trial enrolled 8,888 patients with a history of acute MI and compared moderate with aggressive lipid-lowering (20 mg/day simvastatin vs. 80 mg/day atorvastatin).

There was no difference in the rates of ischemic stroke.[29] It has been firmly established that statins have pleiotropic effects well beyond lipid-lowering and it is possible that other effects (eg, anti-inflammatory vascular effects and decreasing oxidative stress), may be as important as lipid-lowering.

Low-risk patients

For patients with a lower risk profile for atherosclerosis and no clear or compelling reason to take a statin for lipid-lowering, there is less certainty about the role of statins in stroke prevention. To address this large and important cohort of patients, an additional clinical trial is being conducted, the SPARKL study. To qualify, subjects needed to have had a stroke or TIA in the past, but otherwise, were not at high risk for atherosclerotic disease. In this large trial, 4,700 subjects were randomized to either placebo or atorvastatin 80 mg daily, and followed for a minimum of 5 years. The results of the study are expected in early 2006 and should elucidate our approach to low-risk patients who have had a stroke or TIA.

There is growing evidence that statins may have beneficial effects on the progression of atherosclerosis that are due to more than cholesterol-lowering. For instance, statins may decrease oxidative stress in the arterial wall and help stabilize atherosclerotic plaques.[30] Thus, as further clinical trial evidence accrues, it may become clear that, for patients at risk for stroke, a statin may be of benefit in risk reduction, regardless of their baseline LDL-cholesterol level.
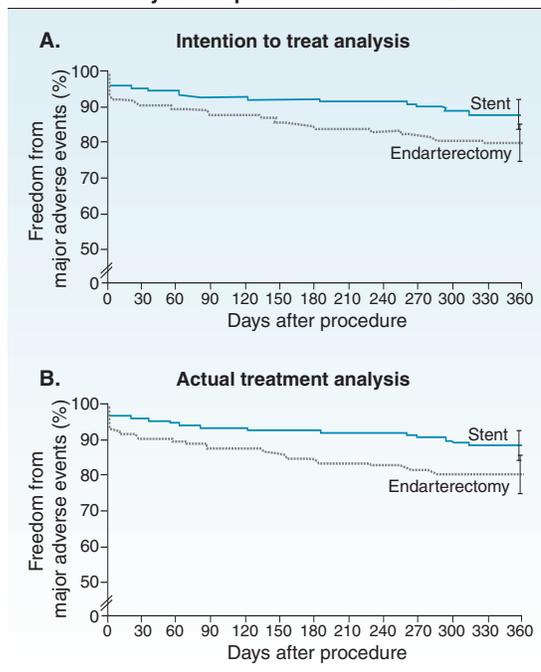
Surgical and catheter-based approach to carotid disease

It is well-established that open surgical carotid endarterectomy (CEA)[31] is effective in preventing stroke when the procedure can be performed with very low morbidity and mortality. The customary acceptable criteria in the US for CEA is angiographic demonstration of a >50% stenosis if a patient has had a prior TIA or stroke, or a >70% stenosis for asymptomatic patients. In recent years, carotid stenting, usually with the use of a distal protection device to capture debris from angioplasty-induced plaque rupture, has been investigated as an alternative to CEA. Numerous small observational studies and a few small randomized trials have been initiated in high-risk subjects and some large, randomized, well-designed clinical trials are also underway in subjects not comparatively viewed as being high-risk.

High-risk subjects: the role of carotid stenting

An important study in high-risk subjects is the SAPPHIRE trial. This was a relatively small study in 315 patients (96 symptomatic and 219 asymptomatic) who were randomly assigned to either CEA or carotid stenting. The primary endpoint was death, stroke, or MI within 30 days of randomization, or ipsilateral stroke or death between 31 days and 1 year. The central hypothesis of the trial was that carotid stenting was not inferior to CEA (Figure 2).[32] The trial had some limitations, including small size, and the fact that enrollment to the prespecified goal was not achieved. Nonetheless, the study demon-

Figure 2: Freedom from major adverse events at one year for patients in SAPPHIRE Trial

A. Intention to treat analysis

Freedom from major adverse events (%) vs Days after procedure. Stent curve higher than Endarterectomy.

B. Actual treatment analysis

Freedom from major adverse events (%) vs Days after procedure. Stent curve higher than Endarterectomy.

Table 4: Preventive measures and therapies for stroke

Preventive measures	Group
Control hypertension	All
Glycemic control	Diabetic patients
Statin therapy	High-risk, and possibly all patients with prior ischemic event
Warfarin	Atrial fibrillation and flutter patients; high- and intermediate-risk patients
Aspirin	Low-risk patients
CEA or stent	High-risk symptomatic patients with >50% carotid stenosis or asymptomatic patients with >70% stenosis
CEA	Not high-risk symptomatic patients with >50% carotid stenosis or asymptomatic patients with >70% stenosis
Stent	Not high-risk patients, symptomatic patients with >50% carotid stenosis or asymptomatic patients with >70% stenosis **(investigational)**

Treatment – ischemic stroke	Group
Intravenous tPA	If treatment possible <3 hours from onset of symptoms
Intra-arterial lytic therapy	Treatment 3-8 hours after onset of symptoms **(investigational)**
Thrombus extraction	**(investigational)**

strated that for these high-risk patients, carotid stenting appears to be noninferior to CEA. These high-risk patients had to have ≥1 of the following characteristics for enrollment: clinically significant cardiac disease, severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal nerve palsy, previous radical neck surgery or radiation therapy, restenosis, or age > 80 years. The SAPPHIRE trial revealed that, regardless of whether the patient underwent CEA or carotid stenting, the 1-year endpoint rate (ipsilateral stroke or death) was high for symptomatic patients, reaching 16% for both groups. It also revealed that, within 12 months, there were many serious outcomes for this particularly ill elderly group.

Lower-risk subjects: the role of carotid stenting

The role of carotid stenting in stroke prevention in symptomatic or asymptomatic lower-risk patients with carotid stenosis remains uncertain at this time. Carotid stenting safety and efficacy relative to CEA in this important group of patients is being studied in the NIH-sponsored CREST study. This large clinical trial is recruiting patients who have symptomatic carotid stenosis of >50%, or asymptomatic stenosis of >70%, determined locally, but confirmed at an angiographic core laboratory. Patients, who are not viewed as high risk are randomized to either CEA or carotid stenting with use of a distal protection device. Both peri-procedural complications, as well as long-term outcomes are being determined, with endpoints assessed by an endpoint committee naïve as to treatment arm. All patients receive state-of-the-art adjunctive medical therapy. It is anticipated that the trial and follow-up will conclude in 2008.[33]

Summary

The primary care physician and cardiologist can make immense contributions to the prevention of stroke and, in collaboration with neurologists and interventionalists,

make critical contributions to the treatment of some stroke patients to reverse or minimize the amount of neurological damage. Preventive measures and therapy are summarized in Table 4. In 2006, the position of physicians relative to stroke prevention and treatment is similar to their position regarding MI prevention and treatment in the early 1970s. At that time, efforts to prevent MI were growing, but slowly. There were therapies to treat the complications of MI (eg, lidocaine for arrhythmias), but the concept of actually treating an MI, salvaging ischemic tissue, and reperfusing an obstructed artery, was considered radical and somewhat dubious. So it is now with ischemic stroke. Strategies for stroke prevention are evolving[17] and acute therapy for stroke, including thrombolytic therapy and mechanical approaches to open occluded arteries, are being slowly introduced. Great opportunities exist to improve stroke prevention and acute treatment.

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Brigham and Women's Hospital,
Cardiovascular Division website:
www.heartdoc.org

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