Current Concepts of Cerebrovascular Disease and Stroke

Asymptomatic Coronary Artery Disease in Patients With Stroke
Prevalence, Prognosis, Diagnosis, and Treatment

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The results of recent multicenter studies of stroke prevention are encouraging. Carotid endarterectomy is highly beneficial for patients with recent transient ischemic attacks (TIA) or nondisabling stroke and ipsilateral high-grade stenosis (70–99%); ticlopidine significantly lowers the risk of stroke in patients with TIA or minor stroke compared with aspirin or placebo, and coumadin and aspirin are effective for preventing stroke in patients with nonrheumatic atrial fibrillation. However, if long-term benefits of medical or surgical therapy for cerebrovascular disease are to be achieved, coronary artery disease (CAD), the major cause of death in stroke patients, must be identified and treated effectively.

Although strategies for evaluating and treating symptomatic CAD in patients with stroke are well established, this is not true of asymptomatic CAD. Therefore, a detailed cardiovascular evaluation is rarely incorporated into the management of patients with cerebrovascular disease and without symptoms of CAD. Accumulating evidence suggests that asymptomatic CAD is common in patients with cerebrovascular disease and that the prognosis of a subset of patients with asymptomatic CAD is poor. Furthermore, preliminary data from nonrandomized studies suggest that the prognosis of patients with asymptomatic 3-vessel or left main CAD is improved after coronary artery bypass surgery. In this article we review available data on the prevalence and prognosis of asymptomatic CAD in patients with cerebrovascular disease and suggest possible diagnostic and therapeutic strategies for management of asymptomatic CAD in these patients.

Prevalence

Using noninvasive studies, a few investigators have prospectively evaluated the frequency of asymptomatic CAD in patients presenting with asymptomatic bruits, TIA, or stroke. Rokey et al performed exercise thallium-201 scintigraphy and exercise radionuclide ventriculography on 34 patients presenting with TIA or stroke and without symptoms of CAD. Fourteen of 34 patients (41%) had abnormal nuclear scans. Coronary angiography was performed in nine patients and showed 70% or greater stenosis of at least one coronary artery in eight patients. The specific arteries involved were not described.

Di Pasquale et al performed electrocardiographic exercise tests on 83 consecutive patients with TIA or minor stroke and without symptoms of CAD. Patients with positive exercise electrocardiography subsequently underwent exercise thallium-201 myocardial scintigraphy. The studies were abnormal in 28% of patients. Coronary angiography was performed in only two patients: one patient had 3-vessel CAD, and the other had 2-vessel CAD.

In another study Di Pasquale et al performed dipyridamole thallium cardiac imaging in 23 patients without angina or previous myocardial infarction who presented with cerebral ischemia. Sixteen patients (70%) had perfusion defects (reversible in 15 patients, fixed in one patient). Although coronary angiography was not performed, it is likely that several of these patients had multivessel CAD since the average number of myocardial segments with defects was 2.4/patient (thallium activity was measured in 8 myocardial segments). Love et al performed thallium 201 myocardial scintigraphy in 27 patients presenting with asymptomatic carotid disease, TIA, or small stroke and without symptoms of CAD. Nine patients (33%) had perfusion defects (reversible in seven patients, fixed in one patient, and both in another).

Although these studies confirm that abnormal thallium myocardial imaging is common in patients without cardiac symptoms who present with cerebrovascular disease, they provide limited data on the severity and anatomic substrate of asymptomatic CAD and on the frequency of left ventricular dysfunction in these patients. These data are important because the prognosis of CAD is a function of the number of coronary vessels involved, the location of CAD (worse prognosis with left main or left anterior descending CAD), the severity of stenosis, and the presence of left ventricular dysfunction.

Only one study systematically utilized coronary angiography to define the frequency of asymptomatic CAD in a population with cerebrovascular disease. Hertzler et al performed coronary angiography on 200 patients without symptoms of CAD who presented with carotid bruit, TIA, or stroke. Eighty patients (40%) had severe CAD defined by greater than 70% stenosis of at least one coronary artery, 93 patients (46%) had mild or moderate CAD, and only 27 patients (14%) had normal coronary arteries. Although the number of patients with single vessel, multivessel, and left main CAD were not
described, 22% were considered to have severe but compensated CAD, 16% had severe, surgically correctable CAD, and 2% had inoperable CAD.

Many diverse vascular pathologies may cause TIA or stroke. Common causes include atherosclerosis of large extracranial and intracranial arteries, cardioembolism, and lipohyalinosis of small penetrating arteries to the brain. Studies that have addressed the prevalence of asymptomatic CAD in patients with TIA or stroke have not determined whether patients with different vascular causes of TIA or stroke are at similar risk of underlying CAD. Although it is reasonable to hypothesize that patients with atherosclerotic cerebrovascular disease have a higher prevalence of CAD than patients with other causes of TIA or stroke, this hypothesis remains unproven. Patients with nonrheumatic atrial fibrillation (the most common cause of cardioembolic stroke in the United States) or lipohyalinosis of small penetrating vessels have a high frequency of hypertension and diabetes, which are important risk factors for CAD. Therefore, it is possible that the frequency of asymptomatic CAD in patients with atherosclerotic cerebrovascular disease, cardioembolism, or lipohyalinosis is not significantly different; that is, a patient's vascular risk factor profile may be more predictive of underlying CAD than the vascular mechanism of TIA or stroke.

Prognosis of Asymptomatic CAD

The majority of deaths following TIA, stroke, or carotid endarterectomy are cardiac in origin, but only 25–48% of patients presenting with cerebrovascular disease have a history of CAD.19–21 These data suggest that asymptomatic CAD is common in patients with cerebrovascular disease and is an important cause of mortality in these patients. The latter hypothesis has never been tested by studying the natural history of asymptomatic CAD (diagnosed by angiography or noninvasive studies) in patients with cerebrovascular disease.

Limited data on the natural history of asymptomatic CAD in nonstroke patients do exist, however. Hickman et al22 studied 86 patients with 30% or greater stenosis of at least one coronary artery who did not undergo coronary artery bypass surgery. Patients were followed for a mean period of 57 months. Sixty-four patients (74%) remained asymptomatic, and 22 patients (26%) developed symptoms of CAD (12 angina alone, four angina preceding myocardial infarction, four myocardial infarction without preceding angina, two sudden death). The outcome in patients with 30% or greater stenosis of the left main coronary artery, 90% or greater stenosis of the left anterior descending artery, or severe (75% or greater stenosis) 3-vessel disease was not significantly different from that of patients with mild or moderate asymptomatic CAD. Patients with three or more vascular risk factors had a significantly higher rate of cardiac events than patients with fewer risk factors.

In contrast to the results of the study by Hickman et al,22 other investigators have found that patients with multivessel asymptomatic CAD have a higher rate of subsequent cardiac events compared with patients with single vessel asymptomatic CAD. Cohn et al23 compared the outcome in 44 asymptomatic patients with 73% or greater stenosis of at least one major coronary artery with the outcome in 127 patients with angina who had similar coronary anatomy and ventricular function. Over a seven-year period the annual mortality was 2.7% in all asymptomatic patients and 5% in asymptomatic patients with 3-vessel CAD, whereas the annual mortality was 5.4% in all patients with angina and 8.7% in patients with angina and 3-vessel CAD.

In another study of asymptomatic or mildly symptomatic patients with angiographically defined CAD, the annual mortality was 3%. However, the yearly mortality of patients with asymptomatic 3-vessel CAD was 6%.14 Eriksen and Thaulow15 followed 50 men with asymptomatic CAD for eight years. Four of 15 (27%) patients with 1-vessel disease, 9 of 18 (50%) patients with 2-vessel disease, and 13 of 17 (76%) patients with 3-vessel disease experienced angina, myocardial infarction, or died.

These results suggest that the prognosis of asymptomatic patients with 1- or 2-vessel coronary disease is generally good but that patients with asymptomatic 3-vessel CAD have a high rate of subsequent cardiac events. Furthermore, these events are frequently myocardial infarction or sudden death without preceding angina. On the basis of these data, Kent et al16 have recommended coronary bypass surgery in patients with asymptomatic 3-vessel CAD and poor exercise capacity, even in the absence of supporting data from a randomized study.

Limited data from nonrandomized studies support this recommendation. Weiner et al18 studied 692 patients with silent myocardial ischemia induced by exercise testing who subsequently underwent coronary angiography. All patients had 70% or greater stenosis of at least one major coronary artery. The patients were followed for up to seven years after medical therapy (n=424) or surgery (n=268). There was no significant difference in survival rates between the medical and surgical groups among patients with 1-vessel and 2-vessel disease. In patients with 3-vessel disease, however, 58% of medically treated patients survived seven years compared with 85% of patients treated surgically (p<0.0001). Most of the patients with 3-vessel disease who benefited from surgery had impaired left ventricular function.

The most effective treatment of asymptomatic left main CAD also appears to be surgery. Of 53 patients with asymptomatic left main coronary disease (50% or greater stenosis) in the Coronary Artery Surgery Study (CASS) registry, 57% of patients treated medically survived five years compared with 88% of patients treated surgically (p=0.02).17

Suggested Management of Asymptomatic CAD

Diagnostic efforts should be focused on identifying patients with asymptomatic 3-vessel or left main CAD because of the poor prognosis of these subgroups. Although the prevalence of asymptomatic 3-vessel or left main CAD in patients with cerebrovascular disease is not known, the incidence is likely to be low enough that widespread noninvasive screening for asymptomatic CAD in all patients with cerebrovascular disease is not justified. Further studies are needed to determine clinical variables (e.g., vascular risk factors, etiologic subtypes of stroke) that are predictive of underlying, severe CAD in patients with cerebrovascular disease.
These data will enable a rational approach to the selection of patients for noninvasive cardiac imaging.

Until such studies are performed, we suggest screening for the presence of asymptomatic CAD in patients less than 65 years of age who present with atherosclerotic carotid disease. We base this recommendation on 1) the high frequency (40%) of asymptomatic, severe stenosis of at least one coronary artery in patients presenting with carotid disease and 2) the high annual cardiac mortality (2–5%) after a TIA or carotid endarterectomy. This rate approaches the cardiac mortality of patients with stable or new onset angina and angiographic evidence of severe 3-vessel disease (2–8.7%), which suggests that 3-vessel or left main CAD is relatively common in patients with carotid disease.

Several diagnostic tests are available for detecting CAD in patients with stroke. The sensitivity, specificity, and predictive value of these tests have recently been reviewed. Our preferred approach is to perform stress thallium-201 myocardial imaging in patients who are able to exercise or adenocardio-dipyridamole thallium-201 imaging in patients unable to exercise.

If a patient has a large defect or multiple reversible defects on thallium myocardial imaging, suggesting multivessel or left main CAD, we recommend coronary angiography, which may be combined with carotid angiography. A recent study showed that the complication rates during combined coronary and carotid angiography in 247 patients were not statistically different from complication rates in 686 patients undergoing coronary angiography alone. If asymptomatic, severe 3-vessel or left main CAD is confirmed at angiography, coronary artery bypass surgery is recommended on the basis of currently available data suggesting a better outcome after surgery in these subgroups. Coronary artery bypass surgery may need to be combined or staged with carotid endarterectomy in patients with symptomatic high-grade carotid stenosis.

In patients with a single, small, reversible defect on thallium-201 myocardial imaging, we institute anti-ischemic therapy (beta blockers or calcium channel blockers) on the basis of studies which show that these agents decrease the number and duration of silent myocardial ischemic episodes in patients with asymptomatic CAD. It is not known, however, whether anti-ischemic agents lower cardiac mortality in patients with asymptomatic CAD associated with silent myocardial ischemia. Recent data also support a role for coronary angioplasty in the treatment of selected patients with asymptomatic CAD.

Regardless of whether patients with cerebrovascular disease and asymptomatic CAD undergo coronary revascularization or are treated with anti-ischemic agents, they should be treated with aspirin because of convincing evidence that aspirin lowers the risk of stroke in patients with TIA or minor stroke and also lowers the risk of myocardial infarction in asymptomatic men.

A particularly important component of the management of patients with coexistent cerebrovascular disease and CAD is modification of vascular risk factors. There is convincing evidence that control of hypertension and cessation of smoking lower the risk of stroke and myocardial infarction. Diabetes should also be rigorously controlled despite lack of convincing evidence that this treatment lowers the risk of stroke or myocardial infarction. Accumulating evidence suggests that aggressive lipid-lowering therapy in patients with elevated low-density lipoprotein or isolated low levels of high-density lipoprotein results in regression of atherosclerosis in both the coronary and carotid arteries. Randomized placebo-controlled studies to determine whether lipid-lowering therapy decreases the risk of cardiac and cerebral events in patients with cerebrovascular disease are needed.

**Summary**

The frequency of angiographically defined asymptomatic CAD in patients with carotid disease is 40%. Although the prognosis of patients with asymptomatic 1-vessel or 2-vessel CAD is good (annual cardiac mortality rate less than 2%), the prognosis of asymptomatic 3-vessel disease or left main CAD is substantially less favorable (annual cardiac mortality 5–8%). Preliminary data from nonrandomized studies suggest that coronary artery bypass surgery significantly lowers cardiac mortality in patients with asymptomatic 3-vessel or left main CAD. Further studies are needed to determine 1) vascular risk factor profiles that are predictive of asymptomatic CAD in patients with cerebrovascular disease and 2) the prevalence of asymptomatic CAD, especially 3-vessel and left main CAD, in patients with a variety of subtypes of cerebrovascular disease (e.g., carotid disease, atherosclerotic vertebrobasilar disease, cardioembolism, penetrating artery disease, stroke of undetermined cause). If the prevalence of asymptomatic 3-vessel or left main CAD is high in a subset of patients with cerebrovascular disease, a randomized study comparing coronary artery bypass surgery with best medical therapy (anti-ischemic agents, lipid-lowering therapy, and aspirin) may be warranted.

**References**

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