Editorial Comment

Prevention and treatment of ischemic stroke and myocardial infarction: not birds of a feather?

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Both acute myocardial infarction (MI) and acute ischemic stroke are leading causes of death and disability in our world—the former in most American and European countries and the latter in many of Asian countries. Although these common acute vascular disorders share some similarities, there are important differences regarding pathophysiology, diagnostic evaluation, and management. The differences between acute MI and acute ischemic stroke are manifold, and imply different prevention and treatment strategies. Given that the paradoxical differences in incidence density of coronary heart disease (CHD) and stroke between different populations has long been known, and the great burden placed by these disorders on human being, one may wonder at the paucity of literature to compare them. In this issue of the *Journal of Geriatric Cardiology*, we publish two articles addressing the similarity and differences of CHD and stroke to highlight this important question in medicine. Wei et al. performed cerebral angiography and coronary angiography in 34 patients who had both coronary and cerebral ischemia related symptoms and found significant correlation between the severity of these two vascular beds; Yu and Wu analyzed data of patients admitted to their hospitals because of either acute stroke or acute MI, and they found that acute stroke patients were significantly older than acute MI patients while hypertension was more common in acute stroke patients than in acute MI patients.

Paradoxical differences of CHD and stroke

As early as in the beginning of 1970s, Kuller and Reisler proposed the hypothesis that risk factors for atherosclerosis differ in different arterial beds, based on the long-observed paradox of high risk of stroke in populations with low risk of CHD. Their hypothesis was supported by the subsequent Honolulu Heart Study, which followed two cohorts of Japanese men for 20 years, one being residents of Hawaii and the other of Japan. The study results showed that three variables had opposing patterns of association for stroke and CHD. Serum cholesterol level was positively associated with the risk of CHD but not with thromboembolic stroke and even negatively with the risk of hemorrhagic stroke. Alcohol intake was negatively associated with the risk of CHD but not with thromboembolic stroke; it, too, was positively associated with the risk of hemorrhagic stroke. The western diet characterized by total fat and animal protein intake, was positively associated with CHD but negatively associated with thromboembolic stroke. This study, consistent with numerous other studies, confirmed that systolic blood pressure and cigarette smoking were positively associated with the risk of CHD, thromboembolic stroke, and hemorrhagic stroke.

Lawlor, et al. estimated the secular trends in cerebral infarct and hemorrhage throughout the 20th Century, for England and Wales, with data from autopsy studies and found that there was a steady fall in mortality from cerebral hemorrhage throughout the 20th Century, whereas mortality from cerebral infarct increased to a peak in the 1970s and then fell. They concluded that the closely related trends in cerebral infarct and CHD suggest common causes. A more recent study by Wilhelmsen and associates, which compared the incidence and mortality of all coronary (n=559,341) and stroke (n=530,689) events in Sweden from 1987 to 2001, again, confirmed that serum cholesterol is a strong risk factor for coronary events, but not for stroke, not even when only pure thrombotic strokes are analyzed, a finding that is contrary to what was proposed by Lawlor et al. They also found that high blood pressure and high BMI were more important risk factors for stroke than for coronary events. However, in their study, 50% of men with both stroke and coronary disease died from coronary disease, suggesting similar background pathology for the two diseases. The Asia Pacific Cohort Studies Collaboration (APCSC) also found that whereas there is clear evidence of potential benefit for CHD of increases in HDL cholesterol and decreases in TC relative to HDL cholesterol, there is no evidence of an association between either HDL cholesterol or TC/HDL cholesterol and ischemic stroke, and increasing HDL cholesterol relative to TC may even increase the risk of hemorrhagic stroke.

Pathophysiology of acute MI and acute ischemic stroke

All types of ischemic heart disease share the concept...
of a mismatch between myocardial oxygen supply and demand. In individuals with coronary artery disease, the oxygen supply is limited by obstructive plaque and when plaque is unstable, the degree of obstruction becomes dynamic, creating the syndrome of unstable angina. Plaque becomes unstable when its fibrous cap is broken by a fissure or ulcer, exposing the lipid-rich core to blood. The interaction between blood and ulcerated plaque results in platelet activation and adherence, thrombus formation, and vasospasm. Through this mechanism, previously stable, nonobstructive plaque may become occlusive, resulting in ischemia and infarction. The type of infarction-ST-segment elevation or non-ST-segment elevation depends on whether the occlusion is complete or partial. When unstable plaque is less than totally occlusive, subendocardial ischemia and infarction may result, usually accompanied by ST-segment depression or T-wave abnormalities on electrocardiogram (i.e. non-ST-segment elevation MI). When unstable plaque causes total occlusion of a coronary artery, transmural ischemia and infarction result, accompanied by ST-segment elevation (i.e. ST-segment elevation MI).10

In contrast with acute ischemic stroke, acute MI is almost always the result of unstable plaque in the arteries of the affected organ and not embolization from a remote source. Although embolic coronary artery occlusion may occur, it is uncommon. In addition, the interplay between oxygen supply and demand is variable in the heart but remains relatively constant in the brain.

The potential causes of acute ischemic stroke, however, are substantially more heterogeneous than for acute MI. The three main underlying mechanisms for acute ischemic stroke are large-artery atherosclerosis, small-vessel disease, and cardioembolism. Approximately 25% of the total etiologic burden of acute ischemic stroke is ascribed to each of these potential etiologies. Approximately 5% of cases are caused by a variety of much less common mechanisms, such as arterial dissection, vasculitis, and hypercoagulability. The etiology remains uncertain in approximately 20% of cases despite comprehensive evaluation with advanced diagnostic techniques.11 For the three major etiologic categories, substantial differences are apparent in disease mechanism and extent, prognosis, results of diagnostic evaluation, potential acute therapies, and secondary prevention. Furthermore, the prognosis associated with acute ischemic stroke varies depending on etiology. Patients with large-vessel and cardioembolic strokes have a much greater mortality rate and residual neurologic deficits than patients with small-vessel lacunar stroke.12 This poorer prognosis reflects the much larger volume of ischemic injury associated with cardioembolic and large vessel-related stroke. The risk of recurrent stroke also varies in relationship to stroke subtype. Lacunar stroke appears to have the lowest risk of recurrence over subsequent years, whereas cardioembolic stroke has the highest risk of recurrence without appropriate treatment to reduce risk. Large vessel-related stroke is associated with intermediate risk. The number of underlying stroke risk factors, such as age, sex, hypertension, diabetes mellitus, and atrial fibrillation, is also directly related to risk of recurrence.13

Prevention of acute MI and acute ischemic stroke

Both primary and secondary prevention of acute MI requires management of the known modifiable risk factors for coronary artery disease, especially cigarette smoking, diabetes mellitus, hypertension, dyslipidemia, obesity, and physical inactivity. Because a common pathway to both acute MI and acute ischemic stroke is atherosclerosis, the need for managing these risk factors is shared by both conditions. In particular, treatment with HMG-CoA reductase inhibitors (statins) is beneficial in prevention of both acute MI and acute ischemic stroke.14 In the recently reported Stroke Prevention by Aggressive Reduction in Cholesterol Levels study, stroke and transient ischemic attack patients randomized to 80 mg atorvastatin daily had 16% relative risk reduction of subsequent stroke and a 20% relative risk reduction for the combined endpoint of stroke and coronary events.15 These results, along with the previously reported results in the British Heart Protection Study with simvastatin, suggest that statin therapy should also be routinely used after ischemic stroke.16

Antiplatelet drugs are recommended for secondary prevention of both acute MI and acute ischemic stroke. The prostaglandin pathway of platelet activation is inhibited by aspirin, which has been proven effective in reducing recurrence of both MI and stroke. The adenosine diphosphate pathway of platelet activation is inhibited by both ticlopidine and clopidogrel. Inhibition of both pathways is beneficial for acute MI and acute ischemic stroke. Dipyridamole has effects on inhibiting platelet aggregation by increasing adenosine levels and by inhibiting cyclic guanosine monophosphate formation.17

Beta-blockers and angiotensin-converting enzyme inhibitors are both recommended for secondary prevention of acute MI.18 Beta-blockers in particular act by reducing the risk of arrhythmic death, but both are thought to act through membrane stabilization from neurohumoral effects (obviously, arrhythmia is not an issue for acute ischemic stroke patients). Neither beta-blockers nor angiotensin-converting enzyme inhibitors have been demonstrated to have consistent effects on secondary prevention of stroke; however, to the extent that both control hypertension, an indirect benefit is plausible.

Prevention of recurrent stroke and MI

The recommended management of risk factors, such as hypertension, diabetes mellitus, and hyperlipidemia, for secondary stroke prevention is similar to the recommendations in MI patients.19 However, recommendations for the
use of antithrombotic medications to reduce secondary stroke risk do differ substantially when compared with recommendations for MI patients.20 The benefits of oral anti-coagulation to reduce secondary stroke risk are clear for patients with atrial fibrillation and should be used unless a major contraindication is present.21 In several other cardiac conditions associated with high risk for brain emboli, the use of oral anticoagulants is also recommended.17 For acute ischemic stroke patients with large-vessel disease who are not candidates for carotid endarterectomy or arterial stenting, platelet antiaggregant therapy for secondary prevention is recommended. Platelet antiaggregants are also recommended for patients with small-vessel disease and stroke of uncertain etiology. Three platelet antiaggregants are currently recommended and widely used. Aspirin is the oldest, cheapest, and most widely used platelet antiaggregant, and meta-analyses of the myriad aspirin secondary stroke prevention trials suggest a modest benefit with no obvious dose-response effect.21 Because higher aspirin doses are associated with increasing side effects (predominantly gastrointestinal bleeding), a dose of 50 to 325 mg is most often given.

Clopidogrel is another platelet antiaggregant that is commonly used for secondary stroke prevention that was approved by regulatory agencies on the basis of the results of the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events trial.22 This megatrial enrolled more than 19 000 patients with cerebral vascular disease, coronary artery disease, or peripheral artery disease. Patients were randomized to clopidogrel 75 mg daily or aspirin 325 mg daily. A small but statistically significant reduction in the primary endpoint of stroke, MI, or vascular death was observed in the clopidogrel arm. However, in the more than 6 400 stroke patients included in the trial, there was no significant difference in the primary combined outcome measure or stroke in the two study arms. For the MI subgroup, which also contained more than 6 400 patients, there was also no significant difference in the occurrence of the primary outcome. The combination of aspirin plus clopidogrel was shown to be more effective than aspirin alone in patients with acute coronary syndromes.23

In the recently reported Clopidogrel for High Risk and Ischemic Stabilization, Management, and Avoidance study, clopidogrel (75 mg daily) plus aspirin (75-162 mg daily) was compared with aspirin alone in patients with documented coronary disease, cerebrovascular disease, or peripheral artery disease.24 Patients with multiple atherosclerotic risk factors without documented arterial disease were also included. The primary composite endpoint of MI, stroke, or cardiovascular death was not significantly different between treatment arms. Prespecified subgroup analyses demonstrated a 1% absolute decrease in occurrence of the primary endpoint in patients with documented vascular disease ($P=0.046$) and an increase of 1.1% in the asymptomatic patients with multiple vascular risk factors ($P=0.20$) among those patients randomized to combination therapy. Severe bleeding, defined as fatal bleeding, intracranial hemorrhage, or bleeding causing hemodynamic compromise, occurred in 1.7% of patients in the combination therapy arm and 1.3% in the aspirin arm (PS 0.09). Moderate bleeding, defined as that requiring transfusion but not meeting criteria for severe bleeding, occurred in 2.1% of patients in the combination therapy arm and 1.3% in the aspirin arm ($P < 0.001$). The investigators concluded that clopidogrel plus aspirin was not significantly better than aspirin alone in reducing occurrence of the primary combined endpoint.

In patients with cerebrovascular disease, this combination was marginally but not significantly better than clopidogrel alone in reducing the occurrence of the combined endpoint of acute ischemic stroke, MI, vascular death, or rehospitalization for an ischemic event when studied in the Management of Atherothrombosis With Clopidogrel in High-Risk Patients trial.23 The risk of serious, life-threatening bleeding was almost doubled with combination therapy. This has led to the recommendation that the combination of aspirin plus clopidogrel should not be used after acute ischemic stroke outside of clinical trials, unless the patient has recently undergone coronary artery stenting.25

The third platelet antiaggregant available currently is the combination of aspirin plus extended-release dipyridamole. This combination was studied in a large secondary stroke prevention trial that led to regulatory approval. In this trial, the European Stroke Prevention Study, a placebo group was included. Monotherapy with aspirin 25 mg twice daily and extended-release dipyridamole 200 mg twice daily were both observed to be significantly better than placebo for preventing the primary endpoint of stroke or vascular death.26 Combination therapy was twice as effective as aspirin monotherapy in reducing the risk of the primary endpoint. The risk of bleeding side effects was increased significantly in both aspirin-containing arms of the study compared with the placebo arm but did not differ significantly in the aspirin monotherapy arm versus the combination therapy arm. Patients in both dipyridamole-containing arms had a significant increase in the rate of headache. In the European/Australian Stroke Prevention in Reversible Ischemia Trial, the combination of aspirin and dipyridamole (primarily extended-release dipyridamole) was confirmed in the intention-to-treat analysis to be superior to aspirin alone for reducing the occurrence of the primary combined endpoint of vascular death, nonfatal stroke, nonfatal MI, and major bleeding complications.27 A meta-analysis of the trials comparing aspirin alone with aspirin plus dipyridamole demonstrates an overall risk ratio of 0.82 for the composite endpoint.23 The Prevention Regimen for Effectively Avoiding Second Strokes study is an ongoing study to directly compare clopidogrel and extended-release dipyridamole plus aspirin in stroke patients.
Treatment of acute MI and acute ischemic stroke

Reperfusion therapy is the treatment of choice for ST-segment elevation MI, provided the patient presents early enough in the course of infarction. Pharmacologic reperfusion was first developed in the 1980s using intracoronary, then intravenous, streptokinase. Next, clot-specific agents (t-PA) were developed and proved more effective than streptokinase in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial. Second-generation agents, such as tenecteplase, are most often used in Western countries today. The benefit of pharmacologic reperfusion is greatest in the first 6 hours after onset of symptoms and even greater in the first 2 hours. Aspirin has been shown to be beneficial both alone and in combination with thrombolytic therapy. Heparin decreases reocclusion during the first 2 days after thrombolytic therapy. Early use of beta-blockers further reduces mortality. Primary percutaneous coronary intervention (PCI) is effective in establishing reperfusion in more than 95% of patients after ST-segment elevation MI. It has been proven superior to thrombolytic therapy when performed at experienced facilities where both treatments are available. Results of subsequent studies showed that PCI is superior to thrombolytic therapy even when transfer to a catheterization center is required, provided the total time for transfer to the catheterization laboratory is less than 2 hours. Therefore, PCI is now considered the reperfusion method of choice for patients who can be on a catheterization table within 90 minutes of arrival to the emergency department.29,30

Treatment of non-ST-segment elevation MI differs from ST-segment elevation MI in several ways. First, thrombolytic therapy has no benefit over placebo for patients with non-ST-segment elevation MI. Presumably, this is because total occlusion of the infarct-related coronary artery is usually not present. Often, non-ST-segment elevation MI is not diagnosed until the results of one or two sets of cardiac enzymes have been obtained. The traditional approach in these patients has been to “cool them down” with use of anticoagulants, antiplatelet agents, beta-blockers, and nitrates. Medical therapy also includes early use of glycoprotein IIb/IIIa inhibitors, clopidogrel, or both, which have been shown to have benefit in patients after non-ST-segment elevation MI. Traditionally, catheterization and revascularization have been performed after a delay of 1 or 2 days, unless the patient fails to stabilize with medical therapy. Recent trials now support a more aggressive approach, with early catheterization and revascularization.31,32

Treatment of acute ischemic stroke differs from that of acute MI in several aspects. In contrast to the treatment of acute MI, the only therapy approved by the U.S. Food and Drug Administration for acute ischemic stroke is intravenous t-PA within 3 hours of stroke onset. This treatment is used in only 3% to 4% of patients in U.S.33 The major barrier for using intravenous t-PA in the 3 hour window is the late arrival of patients at emergency medical facilities. Even when patients present for emergency medical evaluation very early after stroke onset, only a minority are treated with intravenous t-PA. This occurs for a variety of reasons, including rapidly resolving deficits, concomitant use of oral anticoagulants, elevated blood pressure, relative CT contraindications, and refusal to accept the risk of therapy.34 The time window for benefit from reperfusion therapy is more generous in acute MI. Demonstration of myocardial viability is usually not necessary, provided there is evidence of continued ischemia. Late reperfusion of the heart confers less benefit and often is associated with reduced blood flow in the region of the infarct. However, unlike acute ischemic stroke, there is little concern about creation of a hemorrhagic infarct.

In conclusion, despite the similarities between acute MI and acute ischemic stroke, important differences in epidemiology imply different pathophysiology, which necessitate different treatment and prevention strategies. Further research is needed to expand the available treatment options and therapeutic window for the treatment of acute ischemic stroke to extend treatment benefits to a larger patient population. In addition to modification of known coronary disease risk factors, several pharmacologic options have been proven beneficial for the secondary prevention of both acute MI and stroke, and research is ongoing to determine the efficacy of new prevention strategies.

References


