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CME Information

CME Released: 06/24/2010; Valid for credit through 06/24/2011

Target Audience

This article is intended for clinicians who want to maintain a current understanding of recent research and evidence in risk factors for ischemic and intracerebral hemorrhagic stroke.

Goal

The goal of this activity is to provide medical news to primary care clinicians and other healthcare professionals in order to enhance patient care.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Inform clinicians of the latest medical information on the risk factors for ischemic and intracerebral hemorrhagic stroke, as presented at the World Congress of Cardiology (WCC) 2010.
2. Describe the relevance of the findings on risk factors for ischemic and intracerebral hemorrhagic stroke to clinicians in the care of their patients.

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From Heartwire CME INTERSTROKE: Ten Modifiable Risk Factors Explain 90% of Stroke Risk CME



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June 24, 2010 — A large case-control study evaluating risk factors for stroke has shown that 10 risk factors are associated with 90% of the risk of stroke and that of these modifiable risk factors, hypertension is the most important for all stroke subtypes and is a particularly dangerous risk factor for intracerebral hemorrhage [1].



Dr Martin O'Donnell

"A lot of the evidence for stroke comes from inference from heart disease, and certainly the risk factors are the same, but the relative importance of the risk factors is different," lead investigator **Dr Martin O'Donnell** (McMaster University, Hamilton, ON) told *heartwire*. "We've gone through phases where we've thought the risk factors for heart disease and stroke were different, or where we thought they were the same. The important message is that these identified risk factors are important for reducing the risk of stroke, and some appear to be more important than anticipated."

The results of the study, known as **INTERSTROKE**, were presented this week here at the **World Congress of Cardiology** (WCC) and are published online June 18, 2010 in the *Lancet*. Not unlike the previously published **INTERHEART** study of coronary heart disease, a trial led by **Dr Salim Yusuf** (McMaster University, Hamilton, ON) that identified nine modifiable risk factors accounting for 90% of disease, this study showed that many strokes can be predicted and that relatively simple measures, such as blood-pressure control, could reduce the burden of disease.

"If you take myocardial infarction, where, say, 50% of the risk is just the lipids, in low-income settings you have to take and analyze the blood, which might not always be available," said O'Donnell. "Blood pressure is different. You can tell the patient they have a risk factor, which can be measured in any setting, and it doesn't require a lot of medical expertise. It can be modified with generic medications, and it can also be modified at the population level by implementing such policies as those aimed at reducing salt intake."

The INTERSTROKE Study

At the WCC meeting, organizers and presenters have highlighted the global burden of stroke, noting that countries of low and middle income are disproportionately affected by the disease. These low- and middle-income countries, for example, account for more than 85% of stroke mortality worldwide. The contribution of various risk factors to stroke burden is not entirely known, however, particularly in lower-income countries, because most of the data from clinical trials are derived from developed or Westernized countries.

INTERSTROKE is a standardized, case-control study looking at the importance of established and emerging risk factors for the common stroke subtypes in different regions. In total, 3000 first acute-stroke cases and 3000 controls from 22 countries were included in the analysis. Of the stroke patients, just 14% were from a high-income country, while 81% were from Southeast Asia, India, or Africa.

Overall, self-reported hypertension was the strongest risk factor for stroke and was stronger for intracerebral hemorrhage than for ischemic stroke. A history of hypertension was associated with a more than 2.5-fold increased risk of stroke. When a stricter definition of hypertension was used--blood pressure >160/90 mm Hg--the strength of the association increased.

Along with hypertension, current smoking, abdominal obesity, diet, and physical activity accounted for 80% of the global risk of stroke, explaining 80% of the risk of ischemic stroke and 90% of the risk of hemorrhagic strokes. When additional risk factors were included in the model, including diabetes mellitus, alcohol intake, psychosocial factors, the ratio of apolipoprotein B to A1, and cardiac causes (atrial fibrillation or flutter, previous MI, and valve disease), these 10 risk factors accounted for 90% of the risk of stroke. Hypertension, smoking, abdominal obesity, diet, and alcohol intake were the most important risk factors for intracerebral hemorrhagic stroke.

INTERSTROKE: Population-Attributable Risk for Common Risk Factors

Risk factor	Population-attributable risk, % (99% CI)
Hypertension	34.6 (30.4–39.1)
Smoking	18.9 (15.3–23.1)
Waist-to-hip ratio (tertile 2 vs tertile 1)	26.5 (18.8–36.0)

Dietary risk score (tertile 2 vs tertile 1)	18.8 (11.2–29.7)
Regular physical activity	28.5 (14.5–48.5)
Diabetes	5.0 (2.6–9.5)
Alcohol intake	3.8 (0.9–14.4)
Cardiac causes	6.7 (4.8–9.1)
Ratio of apolipoprotein B to A1 (tertile 2 vs tertile 1)	24.9 (15.7–37.1)
Psychological factors	
Stress	4.6 (2.1–9.6)
Depression	5.2 (2.7–9.8)

"The issue for us was whether or not the same nine risk factors were as important for stroke," said O'Donnell. "Before INTERHEART was done, there was the belief that 30% to 40% of the risk of myocardial infarction was unexplained. Similarly, some people believe that about 30% of stroke isn't explained and have been pursuing all sorts of other markers, genetics, and so on. Here, we show that these risk factors, known or proposed to be important, have now been quantified and can be extended to other regions of the world."

To **heartwire**, O'Donnell noted that epidemiological studies have failed to show a consistent relationship between total cholesterol and stroke risk, a finding confirmed in the INTERSTROKE study. In this analysis, the researchers found no association with total and non-HDL cholesterol for ischemic stroke risk but did observe a strong association between apolipoprotein and HDL-cholesterol levels and the risk of ischemic stroke. Interestingly, the group observed that the reduction in risk of ischemic stroke associated with elevated apolipoprotein A1 and HDL cholesterol was larger than the increase in risk associated with increased levels of apolipoprotein B or non-HDL cholesterol.

Just Like Your Mom Told You

O'Donnell said the most important message from the study is the importance of blood pressure. In the INTERHEART study, the risk of coronary artery disease attributable to hypertension was 18% but was nearly double that in stroke patients. He advises clinicians to treat blood pressure to target and urges the implementation of policies to lower blood pressure at the population level. In addition to these risk factors, quitting smoking, losing weight, getting active, and eating well—"everything that your mom told you to do"—is highly recommended, he said.

In an editorial accompanying the published study [2], **Dr Jack Tu** (University of Toronto, ON) noted that identifying the cause of stroke across diverse regions is a difficult task, a thought O'Donnell also echoed. The INTERSTROKE researchers weren't sure initially whether the study could be conducted, because the confirmation of stroke and the type of stroke requires access to imaging technology.

Tu noted that INTERSTROKE confirms that hypertension, a well-known risk factor for stroke in developed countries, is also a risk factor in developing nations. "This finding is particularly relevant, because it highlights the need for health authorities in these regions to screen the general population for high blood pressure and, if necessary, offer affordable treatment to reduce the burden of stroke," writes Tu.

References

1. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): A case-control study. *Lancet* 2010; DOI:10.1016/S0140-6736(10)60834-3. Available at: <http://www.thelancet.com>.
2. Tu JV. Reducing the global burden of stroke: INTERSTROKE. *Lancet* 2010; DOI:10.1016/S0140-6736(10)60975-0. Available at: <http://www.thelancet.com>.

Study Highlights

- Subjects were recruited from 84 centers in 22 countries.
- 3000 case patients were hospitalized with first acute stroke within 5 days of onset of symptoms, presented within 72 hours of hospital admission, and had computed tomography or magnetic resonance imaging of the brain planned within 1 week of presentation.
- Acute stroke was defined as rapidly developing symptoms or signs; at times, global loss of cerebral function; symptoms for more than 24 hours or leading to death; and no cause other than vascular.
- 2337 case patients (78%) had ischemic stroke, and 663 (22%) had intracerebral hemorrhagic stroke, based on clinical and neuroimaging assessment.
- 3000 control subjects with no history of stroke were matched with case patients for age within 5 years and sex.
- Mean age was 61.1 years.
- Exclusion criteria were nonvascular cause of stroke, current hospitalization for acute coronary syndrome, or inability to obtain consent from patient or valid proxy.
- Evaluation included questionnaires, physical examinations, blood pressure and heart rate measurements, and blood tests.
- Analysis adjusted for region, sex, age, and potential confounders.
- 260 case patients (9%) died, and 569 (19%) had stroke associated with severe disability or death at 1 month.
- 90% of population-attributable risks were attributable to 10 risk factors.
- Hypertension identified by self-report increased the risk for all stroke (odds ratio [OR], 2.64), ischemic stroke (OR, 2.37), and intracerebral hemorrhagic stroke (OR, 3.80).
- Hypertension based on self-report or blood pressure of more than 160/90 mm Hg increased the risk for all stroke (OR, 3.89), ischemic stroke (OR, 3.14), and intracerebral hemorrhagic stroke (OR, 9.18).
- Current smoker, defined as any tobacco use in the prior 12 months, vs never-smoker or former smoker increased the risk for all stroke (OR, 2.09), ischemic stroke (OR, 2.32), and intracerebral hemorrhagic stroke (OR, 1.45).
- The highest vs the lowest tertile of waist-to-hip ratio had greater risk for all stroke (OR, 1.65), ischemic stroke (OR, 1.69), and intracerebral hemorrhagic stroke (OR, 1.41).
- High diet risk score indicating an unhealthy cardiovascular diet was linked with an increased risk for all stroke (OR, 1.35), ischemic stroke (OR, 1.34), and intracerebral hemorrhagic stroke (OR, 1.41).
- Self-reported diabetes mellitus had an increased risk for all stroke (OR, 1.36) and ischemic stroke (OR, 1.60), but not intracerebral hemorrhagic stroke.
- More than 30 alcoholic drinks per month or binge drinking vs never or former alcohol use was linked with an increased risk for all stroke (OR, 1.51), ischemic stroke (OR, 1.41), and intracerebral hemorrhagic stroke (OR, 2.01).
- Alcohol intake of 1 to 30 drinks per month was linked with a decreased risk for ischemic stroke (OR, 0.79).
- Psychosocial stress was linked with an increased risk for all stroke (OR, 1.30), ischemic stroke (OR, 1.30), and intracerebral hemorrhagic stroke (OR, 1.23).
- Depression was linked with an increased risk for all stroke (OR, 1.35) and ischemic stroke (OR, 1.47), but not intracerebral hemorrhagic stroke.
- Cardiac causes were associated with an increased risk for all stroke (OR, 2.38) and ischemic stroke (OR, 2.74), but not intracerebral hemorrhagic stroke.
- Higher ratio of apolipoprotein B to apolipoprotein A1 was linked with an increased risk for all stroke (OR, 1.89) and ischemic stroke (2.40), but not intracerebral hemorrhagic stroke.
- Regular physical activity was linked with a lower risk for all stroke (OR, 0.69) and ischemic stroke (OR, 2.40), but not intracerebral hemorrhagic stroke.
- Ratio of non-high-density lipoprotein to high-density lipoprotein cholesterol was linked with an increased risk for ischemic stroke and a decreased risk for intracerebral hemorrhagic stroke.
- Body mass index was not linked with stroke risk.

Clinical Implications

- Ten risk factors linked with 90% of the risk for stroke include hypertension, smoking, increased waist-to-hip ratio, high diet risk score, low physical activity level, diabetes mellitus, more than 30 alcoholic drinks per month, stress or depression, cardiac causes, and elevated ratio of apolipoprotein B to apolipoprotein A1.
- The risk for stroke can be decreased by targeted intervention to reduce blood pressure and smoking and to improve physical activity and diet.

CME Test

Which of the following factors is *most* likely to be associated with an increased risk for stroke?

- Low diet risk score
- High physical activity level
- 5 alcoholic drinks per month
- Psychosocial stress
- All of the above

A 60-year-old patient has a blood pressure of 170/95 mm Hg. The patient exercises once a week, eats fast food every day, and has smoked 1 pack of cigarettes a day for the past 40 years. Which of the following measures will decrease his risk for stroke?

- Reduce blood pressure
- Increase physical activity
- Promote healthy eating
- Encourage smoking cessation
- All of the above

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