Potential New Risk Factors for Ischemic Stroke
What Is Their Potential?
Graeme J. Hankey, MD, FRCP, FRACP

Background and Purpose—About 60% to 80% of all ischemic strokes can be attributed to increasing blood pressure, blood cholesterol, cigarette smoking, carotid stenosis, and diabetes mellitus (atherosclerotic ischemic stroke), and atrial fibrillation and valvular heart disease (cardiogenic ischemic stroke). The aim of this review was to examine the potential role of other risk factors in the etiology of ischemic stroke.

Summary of Review—About 10% to 20% of atherosclerotic ischemic strokes can probably be attributed to recently established, causal risk factors for ischemic heart disease: raised apoB/apoA 1 ratio, obesity, physical inactivity, psychosocial stress and low fruit and vegetable intake. However, their causal role remains to be proven. The direct genetic contribution of any single gene towards ischemic stroke is likely to be modest and apply in selected patients only and in combination with environmental factors or via other epistatic (gene-gene or gene-environmental) effects.

Conclusions—Research resources should not be allocated disproportionately to emerging novel risk factors that may account for up to only 20% of all strokes at the expense of researching the determinants of the relatively few established causal factors that account for up to 80% of all strokes. (Stroke. 2006;37:2181-2188.)

Key Words: cerebral infarct ■ risk factors

A risk factor for ischemic stroke is a characteristic in an individual that indicates that the individual has an increased risk of ischemic stroke compared with an individual without that characteristic. It does not necessarily imply that the risk factor causes ischemic stroke; it may simply be a marker of a causal risk factor (eg, having a cigarette lighter is a risk factor for stroke but only as a marker of current smoking). The causal significance of any risk factor depends on the factors listed in the Table 1.

Causal Risk Factors for Ischemic Stroke
Increasing blood pressure, increasing blood cholesterol, carotid stenosis, and atrial fibrillation are definite causal risk factors for ischemic stroke because randomized controlled trials (RCTs) have shown that treating them reduces the incidence of ischemic stroke.1-5

Cigarette smoking, diabetes mellitus, ischemic heart disease, and valvular heart disease are probably also causal risk factors for ischemic stroke because epidemiological case-control and cohort studies have shown that these characteristics are significantly associated with an increased risk of stroke; moreover, the association is strong, consistent among studies, biologically plausible, and independent of other factors that were measured and analyzed (Table 1).6-11 However, it is possible that these associations are confounded by other factors that have not been measured and analyzed in epidemiological studies—uncontrolled confounding—as highlighted by recent unequivocal evidence from RCTs that hormone replacement therapy and antioxidant vitamins do not reduce the risk of stroke,12,13 despite strong previous evidence from epidemiological studies suggesting the contrary.14-16

Population-Attributable Risk of Causal Risk Factors
Population-based studies in Rochester, Minn, in which the prevalence of risk factors for stroke in the population and the relative risk of stroke for each risk factor were analyzed by means of multiple logistic-regression techniques, estimate that the population-attributable risk (PAR) of ischemic stroke due to all 7 of the major risk factors combined is ≈57% (95% CI, 48% to 67%; Table 2).17 The PAR is the risk of ischemic stroke in a total population that can be attributed to exposure to a specific risk factor or constellation of risk factors: the difference between the risk in the total population and the risk in the unexposed group. This means that 57% of all cases of ischemic stroke in the population of Rochester, Minn (at the time of the study) could be attributable to the 7 causal risk factors listed in Table 2. If serum cholesterol and carotid stenosis3-4 had also been included in this analysis, it is likely that up to 80% of all ischemic strokes could be attributed to these risk factors. If this is correct, potential new risk factors for ischemic stroke are unlikely to account for more than ≈20% of all ischemic strokes.
Is there evidence that leads to a reduction in the risk of stroke?

Is the association

Interactions in the Multiple-Regression Model

Rochester, Minn, Adjusted for All Modifying Variables and Their

TABLE 2. PAR of Ischemic Stroke for Risk Factors in

attributed to 7 major risk factors, 3 of which are established
government reports and international databases), which have
be internally valid because the bootstrap method, which is
model, the coefficient estimates, and their standard errors.

The estimates derived from the Rochester data are likely to
be internally valid because the bootstrap method, which is
a multiple resampling procedure, was used to validate the
model, the coefficient estimates, and their standard errors.

The external validity (ie, generalizability to other populations
and to the year 2006) of the estimates are supported by a
comprehensive review of published work and other sources (eg,
government reports and international databases), which have
reported that 70% to 76% of the disease burden associated with
stroke and 65% to 73% of mortality due to stroke could be
attributed to 7 major risk factors, 3 of which are established
causal risk factors for stroke (high blood pressure, tobacco use,
high cholesterol) and 4 of which are “newer” risk factors (low
fruit and vegetable intake, physical inactivity, obesity as measured
by a high body mass index [BMI], and alcohol use) for
stroke and myocardial infarction (see following section and
Table 3).

Another way of assessing whether the estimates are exter-
nally valid is to explore whether the established causal risk
factors for ischemic stroke also account for a similar propor-
tion of ischemic heart disease (IHD) events. One caveat of
this approach is that the etiology of ischemic stroke is more
heterogeneous than that for IHD (~50% of ischemic stroke is
caused by large-artery atherosclerosis; 25%, small-vessel
disease; 20%, cardiac embolism; and 5%, a miscellany of
causes such as arterial dissection). Moreover, risk factors
may be different for different etiological subtypes of ischemic
stroke (eg, atrial fibrillation and mitral valve disease are risk
factors for cardioembolic ischemic stroke only but not for
atherosclerotic ischemic stroke or IHD). Hence, the PAR of
all causal risk factors for atherosclerotic ischemic stroke can
be only ~50% to 75% for all ischemic stroke (as high as 75% if
large-artery atherosclerosis and intracranial small-vessel
disease share the same causal risk factors and as low as 50% if
they do not).

Nevertheless, 3 studies of patients with IHD suggest that the
aforementioned causal risk factors for atherosclerotic ischemic
stroke (Table 2) are also causal risk factors for atherosclerotic
IHD. The Framingham Study and the Third National Health and
Nutrition Examination Survey reported that raised levels of at
least 1 of 5 causal risk factors (blood pressure, low-density
lipoprotein [LDL] and high-density lipoprotein [HDL] choles-
terol levels, glucose intolerance, and smoking) accounted for
90% of the PAR of IHD events. The INTERHEART study of
15 152 cases of acute myocardial infarction (MI) and of 14 820
controls found that 9 risk factors (Table 4) accounted for 90% of
the PAR of acute MI. Although a substantial proportion of
cases of MI could be attributed to known causal risk factors for
stroke (smoking, hypertension, diabetes), a substantial propor-
tion could be attributable to other, newer risk factors for MI,
such as a raised apolipoprotein (apo) B–apo A1 ratio, abdominal
obesity, psychosocial stress, lack of daily fruit and vegetable
intake, lack of exercise for 4 hours or more per week, and lack
of regular alcohol consumption 3 or more times per week
(Table 4).

Are the Newer Risk Factors for MI Also New
Risk Factors for Atherosclerotic
Ischemic Stroke?

Raised Apo B–Apo A1 Ratio

Apo B plasma levels reflect the concentration of the proathero-
genic lipoproteins very low-density lipoprotein (VLDL) and
LDL because each VLDL and LDL particle has 1 molecule of
apo B. The plasma concentration of apo B has recently been
reported to be the best lipid predictor of coronary heart dis-
ease. Among 286 patients with transient ischemic attack who
were assessed at baseline and followed up for 10 years, a raised
apo B–apo A1 ratio was also a stronger risk factor to subsequent
stroke, after adjusting for other vascular risk factors (hazard ratio

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prevalence Before Stroke</th>
<th>OR (95% CI)</th>
<th>PAR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>74%</td>
<td>2.0 (1.6–2.5)</td>
<td>26%</td>
<td>12–41%</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>17%</td>
<td>5.6 (3.7–8.5)</td>
<td>14%</td>
<td>11–17%</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>47%</td>
<td>2.0 (1.5–2.7)</td>
<td>12%</td>
<td>8–16%</td>
</tr>
<tr>
<td>IHD</td>
<td>25%</td>
<td>1.8 (1.3–2.5)</td>
<td>12%</td>
<td>7–17%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>18%</td>
<td>2.0 (1.5–2.8)</td>
<td>8%</td>
<td>4–12%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13%</td>
<td>2.0 (1.5–2.8)</td>
<td>5%</td>
<td>2–9%</td>
</tr>
<tr>
<td>Mitral valve disease</td>
<td>6%</td>
<td>2.4 (1.5–4.1)</td>
<td>3%</td>
<td>0.6–5%</td>
</tr>
<tr>
<td>All above risk factors</td>
<td></td>
<td></td>
<td>57%</td>
<td>48%–67%</td>
</tr>
</tbody>
</table>
than other lipid measurements (apo B [HR, 2.3; 95% CI, 1.1 to 4.5], total cholesterol [HR, 1.8; 95% CI, 0.9 to 3.3], LDL cholesterol [HR, 1.5; 95% CI, 0.8 to 2.8]; LDL/HDL [HR, 1.3; 95% CI, 0.7 to 2.4], apo A1 [HR, 1.2; 95% CI, 0.6 to 2.2], and HDL [HR, 1.0; 95% CI, 0.5 to 1.9]).28 These results await confirmation in other studies.

Abdominal Obesity
General obesity, as measured by a raised BMI, and abdominal obesity, as measured by a raised waist-to-hip ratio, have been reported as independent risk factors for stroke.29–33 A prospective, observational, cohort study of 21,414 US male physicians followed up for 12.5 years (mean) for the occurrence of 631 ischemic strokes found that a BMI ≥30 kg/m² was associated with an adjusted relative risk (RR) of ischemic stroke of 2.0 (95% CI, 1.5 to 2.7) compared with men with a BMI <30 kg/m².30 Furthermore, each unit increase in BMI was associated with a 6% (95% CI, 3% to 8%) increase in the RR of ischemic stroke.30 Almost identical results were reported subsequently in an observational study of 7402 healthy Swedish men aged 47 to 55 years who were followed up for 28 years for the occurrence of 495 ischemic strokes.32 Although hypertension, diabetes, and cholesterol levels are mediators in the link between obesity and stroke (as evidenced by attenuation of the magnitude of the RR of stroke after adjusting for these factors), the significant association between obesity and stroke risk persists, independent of these factors.

Lack of Exercise for 4 Hours or More per Week
A meta-analysis of 23 studies from 1966 to 2002 reported that compared with low physical activity, individuals with high physical activity have a significantly lower risk of stroke (RR, 0.79; 95% CI, 0.69 to 0.91).34 A more recent observational study of 47,721 Finnish people aged 25 to 64 years followed up for 19 years (mean) for the occurrence of 2264 ischemic strokes found that, compared with low leisure time physical activity (sedentary), self-reported moderate leisure time physical activity (≥4 hours per week of walking, cycling, or light gardening) was associated with an adjusted RR of ischemic stroke of 0.87 (95% CI, 0.79 to 0.95).35 High leisure time

### TABLE 3. Independent and Joint Contributions of 7 Major Risk Factors to the Global Burden of Stroke, Expressed in Disability-Adjusted Life-Years (DALY) and Global Mortality

<table>
<thead>
<tr>
<th>% GBD (Total 1.46 billion DALY)</th>
<th>% Global Mortality (Total 55.9 million deaths)</th>
<th>Contributing Risk Factors</th>
<th>Joint PAF (Disease Burden)</th>
<th>Joint PAF (Mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1%</td>
<td>9.6%</td>
<td>High blood pressure (62%)</td>
<td>70–76%</td>
<td>65–73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High cholesterol (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High BMI (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tobacco (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low fruit and vegetable intake (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physical inactivity (7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alcohol (4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GBD indicates global burden of disease; PAF, population-attributable fraction.

### TABLE 4. PAR of Acute MI for Risk Factors in the INTERHEART Study, Adjusted for All Modifying Variables and Their Interactions in the Multiple-Regression Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prevalence</th>
<th>OR (95% CI), Adjusted for All Risk Factors</th>
<th>PAR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>22%</td>
<td>1.9 (1.7–2.1)</td>
<td>18%</td>
<td>16–20%</td>
</tr>
<tr>
<td>Cigarette smoking*</td>
<td>48%</td>
<td>2.0 (1.9–2.2)</td>
<td>36%</td>
<td>32–39%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8%</td>
<td>2.4 (2.1–2.7)</td>
<td>10%</td>
<td>8–11%</td>
</tr>
<tr>
<td>Apo B/Apo A1 † † †</td>
<td>20%</td>
<td>3.2 (2.8–3.8)</td>
<td>49%</td>
<td>44–54%</td>
</tr>
<tr>
<td>Abdominal obesity‡</td>
<td>33%</td>
<td>1.6 (1.4–1.8)</td>
<td>20%</td>
<td>15–26%</td>
</tr>
<tr>
<td>All psychosocial§</td>
<td>...</td>
<td>2.7 (2.2–3.2)</td>
<td>32%</td>
<td>25–41%</td>
</tr>
<tr>
<td>No vegetables and fruit daily</td>
<td>42%</td>
<td>0.7 (0.6–0.8)</td>
<td>14%</td>
<td>10–19%</td>
</tr>
<tr>
<td>No exercise¶</td>
<td>19%</td>
<td>0.9 (0.8–0.97)</td>
<td>12%</td>
<td>5–25%</td>
</tr>
<tr>
<td>No alcohol intake#</td>
<td>24.4%</td>
<td>0.9 (0.8–1.02)</td>
<td>7%</td>
<td>2–20%</td>
</tr>
<tr>
<td>All risk factors combined</td>
<td>...</td>
<td>129 (90–185)</td>
<td>90%</td>
<td>88–92%</td>
</tr>
</tbody>
</table>

*Current and former smokers.
†Top 4 quintiles vs lowest quintile.
‡Top 2 tertiles of BMI vs lowest tertile.
§A model-dependent index combining positive exposure to depression, perceived stress at home or work (general stress), low locus of control, and major life events, all referenced against nonexposure to all factors.
¶Regular involvement in moderate (walking, cycling, or gardening) or strenuous (jogging, football, or vigorous swimming) exercise for 4 hours or more per week.
#Consumption of alcohol 3 or more times per week.
physical activity (≥3 hours per week of jogging, swimming, heavy gardening, or regular sports several times per week) was associated with an adjusted RR of ischemic stroke of 0.80 (95% CI, 0.63 to 0.93; P for trend = 0.001). Active commuting (walking/cycling) to work for 30 or more minutes daily was also associated with a significant reduction in risk of ischemic stroke (RR, 0.86; 95% CI, 0.76 to 0.96).

Lack of Daily Fruit and Vegetable Intake
A meta-analysis of 7 cohort studies involving a total of 242,049 men and women followed up for 3 to 20 years for the occurrence of 2955 strokes reported that the risk of stroke decreased by 11% (RR, 0.89; 95% CI, 0.85 to 0.93) for each additional portion per day of fruit, by 5% (RR, 0.95; 95% CI, 0.92 to 0.97) for fruit and vegetables, and by 3% (RR, 0.97; 95% CI, 0.92 to 1.02) for vegetables, after adjusting for factors known to be more common among fruit consumers such as (less) smoking, (more) exercise, and (higher) education.

Lack of Regular Alcohol Consumption 3 or More Times per Week
A meta-analysis of 35 studies from 1966 to 2002 reported that, compared with abstainers of alcohol, individuals who consumed <12 g daily (1 standard drink) of alcohol had a significantly lower adjusted RR of ischemic stroke (RR, 0.80; 95% CI, 0.67 to 0.96), as did individuals who consumed 12 to 24 g daily (1 to 2 standard drinks) of alcohol (RR, 0.72; 95% CI, 0.57 to 0.91). However, individuals who consumed >60 g daily of alcohol had a significantly higher adjusted RR of ischemic stroke (RR, 1.69; 95% CI, 1.3 to 2.1). A recent observational study of 38,156 US male health professionals followed up for 14 years (mean) for the occurrence of 412 ischemic strokes found that, compared with abstainers of alcohol, the adjusted RR of ischemic stroke was 0.99 (95% CI, 0.97 to 1.01) for light drinkers who consumed 0.1 to 9.9 g daily (≤1 standard drink), 1.26 (95% CI, 0.90 to 1.76) for moderate drinkers of 10 to 29.9 g daily (1 to 2 standard drinks), and 1.42 (95% CI, 0.97 to 2.09) for heavy drinkers of ≥30 g daily (≥3 standard drinks). Moderate consumption of alcohol (10.0 to 29.9 g per day on 3 or 4 days per week) was associated with the lowest RR of ischemic stroke (RR, 0.68; 95% CI, 0.44 to 1.05). These results are consistent with those for MI in the INTERHEART study, but they could also reflect uncontrolled confounding (eg, people who drink alcohol in moderation may also be likely to do other unmeasured but stroke-protective behaviors in moderation, in contrast to people who do not drink at all who may be more likely to not do other unmeasured but stroke-protective behaviors at all).

Psychosocial Stress
Major life events and depression have been associated with an increased risk of stroke, but the data are limited. A prospective, observational, cohort study of 2805 Australians ≥60 years of age followed up for 5 years (median) for the occurrence of 306 incident ischemic strokes found that, compared with the lowest tertile of depression, the adjusted RR of ischemic stroke was 1.2 (95% CI, 0.8 to 1.6) for the second tertile and 1.4 (95% CI, 1.0 to 2.0) for the third tertile.

**TABLE 5. Potential New Risk Factors for Ischemic Stroke**

<table>
<thead>
<tr>
<th>Genetic factors/genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme genotype</td>
</tr>
<tr>
<td>Factor V Leiden</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
</tr>
<tr>
<td>MTHFR</td>
</tr>
<tr>
<td>Human platelet antigen type 1</td>
</tr>
<tr>
<td>Factor XIII</td>
</tr>
<tr>
<td>Apo E</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1 4G/5G genotypes</td>
</tr>
<tr>
<td>Phosphodiesterase 4D</td>
</tr>
<tr>
<td>5-Lipoxygenase–activating protein</td>
</tr>
</tbody>
</table>

**Inflammatory markers**
- Leucocyte count
- Monocyte count
- High-sensitivity C-reactive protein
- Soluble CD40 ligand
- Serum amyloid A
- Interleukins (IL-6, IL-18)
- Vascular and cellular adhesion molecules
- Myeloperoxidase
- Matrix metalloproteinase-9

**Infectious agents**
- Cytomegalovirus
- Herpes simplex virus
- Chlamydia pneumonia
- Helicobacter pylori
- Legionella sp
- Periodontal disease

**Lipid-related factors**
- Small, dense LDL
- Lipoprotein (a)
- Remnant lipoproteins
- HDL subtypes
- Lipoprotein-associated phospholipase A2
- Adiponectin

**Oxidative stress**
- Oxidized LDL

**Biomarkers of hemostasis/thrombosis/impaired fibrinolysis**
- Fibrinogen
- Protein Z
- Von Willebrand factor antigen
- Plasminogen activator inhibitor-1
- Tissue-type plasminogen activator
- Factors V, VII, and VIII
- D-dimer
- Fibrinopeptide A
- Prothrombin fragment 1 and 2
- Antiphospholipid antibodies

**Platelet-related factors**
- Platelet aggregation
- Platelet activity
- Platelet size and volume

(Continued)
Functional markers
Endothelial dysfunction
Arterial compliance, elasticity, stiffness (eg, pulse pressure)
Ankle-brachial systolic pressure index
B-type natriuretic peptide
Microalbuminuria
Cystatin C

Interpretation
The aforementioned studies indicate that the newer risk factors for MI reported in the INTERHEART study are also newer risk factors for atherosclerotic ischemic stroke. However, proof of a causal relationship remains elusive in the absence of evidence from RCTs. And if a causal relationship is proven, the incremental PAR of any of these risk factors, over and above that contributed by established causal risk factors, remains to be quantified.

Potential New Risk Factors for Ischemic Stroke
Numerous potential novel risk factors for ischemic stroke have been proposed (Table 5), but the quality and volume of the published data are inconclusive, and there is no evidence (yet) that reducing exposure to any of them reduces the risk of stroke. The evidence for (arguably) the most promising of these factors is discussed next.

Inherited Susceptibility
A family history of stroke is a risk factor for ischemic stroke, but the mechanisms remain uncertain. Inherited susceptibility to ischemic stroke may result from the direct effect of a single gene on the risk of stroke at a young age (before environmental and behavioral factors have had time to modify the phenotype), interactions of a gene with environmental or behavioral factors, an additive effect of several genes (a gene-dose effect), or synergistic effects of several genes. A classical mendelian pattern of inheritance of single-gene disorders is rare, accounting for <1% of cases of ischemic stroke. At least part of any heritability of ischemic stroke is a genetic susceptibility to hypertension (as manifested by a strong association between family history of stroke and hypertension). Another part of any heritability of ischemic stroke may be contributed by common variants in several genes, each exerting a modest effect. A meta-analysis of 120 case-control studies of 32 genes involving 18,000 cases of stroke and 58,000 controls identified statistically significant associations with ischemic stroke for the 4 most heavily investigated candidate genes: angiotensin-converting enzyme insertion/deletion (odds ratio [OR], 1.21; 95% CI, 1.08 to 1.35), factor V Leiden Arg 506 Gln (OR, 1.33; 95% CI, 1.12 to 1.58), prothrombin G20210A (OR, 1.44; 95% CI, 1.11 to 1.86), and methylene-tetrahydrofolate reductase (MTHFR) C677T (OR, 1.24; 95% CI, 1.08 to 1.42). No statistically significant association with ischemic stroke was detected for the 3 next most investigated genes: human platelet antigen type 1 (OR, 1.11; 95% CI, 0.95 to 1.28), factor XIII (OR, 0.97; 95% CI, 0.75 to 1.25), and apo E (OR, 0.96; 95% CI, 0.84 to 1.11). The PARs for the 4 significant polymorphisms ranged from 1.3% for prothrombin G20210A to 4.5% for angiotensin-converting enzyme insertion/deletion, values that are far lower than those reported for established causal risk factors for ischemic stroke (Tables 2 and 3).

A subsequent meta-analysis of 7 case-control studies involving 3243 stroke cases and 3804 controls reported a significant association between stroke and the gene encoding phosphodiesterase 4D, single-nucleotide polymorphism (SNP) 87 (pooled P=0.001), SNP 83 (0.003), SNP 56 (0.03), and SNP 41 (0.02). However, there was statistical heterogeneity (P<0.1) among the studies in the direction of association for each of the individual SNPs tested. Preliminary reports suggest that the 5-lipoxygenase–activating protein gene may also be associated with an increased risk of ischemic stroke, but the results are inconsistent, reflecting underpowered case-control studies.

Inflammatory Markers
Leukocyte and Monocyte Counts
A meta-analysis of 19 prospective studies involving 7229 patients followed up for 8 years (mean) revealed that, compared with individuals with a leukocyte count in the lowest tertile, the highest tertile yielded an increased risk of IHD (RR, 1.5; 95% CI, 1.4 to 1.6). In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, patients with a history of stroke, MI, or peripheral arterial disease who had a baseline leukocyte count in the highest quartile had a higher adjusted risk of recurrent ischemic events compared with those in the lowest quartile (RR, 1.42; 95% CI, 1.25 to 1.63 overall; RR, 1.30; 95% CI, 1.56, and 1.51 for stroke, MI, and vascular death). Monocyte count has been reported to be an independent predictor of future carotid artery atherosclerotic plaque formation in subjects without preexisting carotid atherosclerosis.

High-Sensitivity C-Reactive Protein
More than 20 prospective epidemiological studies demonstrate that high-sensitivity C-reactive protein is an independent predictor of stroke, MI, and vascular death in apparently healthy individuals. Among 1462 individuals registered in the Framingham study, each quartile increase in plasma concentration of C-reactive protein at baseline was associated with an increased adjusted RR of ischemic stroke and transient ischemic attack by 1.25 (95% CI, 1.0 to 1.54) in men and by 1.29 (95% CI, 1.07 to 1.55) in women after 12 to 14 years of follow-up.

Infection
Observational studies suggest that infection may be a risk factor for stroke and coronary events. Furthermore, Chlamydia pneumoniae DNA and/or antigen have been detected in at least 40% of atherosclerotic plaques of patients in various parts of the world, and rabbits inoculated with C pneumoniae have developed inflammatory lesions in arteries. However, a meta-analysis of RCTs and 2 subsequent RCTs suggest that antibiotic therapy fails to prevent the occurrence of...
serious cardiovascular events, at least in patients with established coronary artery disease. Prospective epidemiological studies based on serology may help to better distinguish cause from consequence.67

Hemostatic Factors: Fibrinogen
A meta-analysis of 3 prospective studies of 5113 patients with transient ischemic attack and minor ischemic stroke who were followed up for 5 years revealed that fibrinogen concentrations above the median were associated with an increased risk of ischemic stroke, compared with those below the median (HR, 1.34; 95% CI, 1.13 to 1.60).68 The association was stronger in patients with nonlacunar (HR, 1.42; 95% CI, 1.13 to 1.78) than lacunar (HR, 1.09; 95% CI, 0.80 to 1.49) syndromes but not significantly so (P=0.018).68 The relation between increasing fibrinogen levels and risk of ischemic stroke (and also acute coronary events) was linear.68

Other Factors
Homocysteine
Systematic reviews of observational studies have consistently shown a strong, positive, independent and dose-related association between total plasma homocysteine (tHcy) and the risk of stroke, and laboratory studies have shown that the association is biologically plausible.69 Furthermore, a meta-analysis of genetic association studies shows that natural (men- delian) randomization to the analysis of genetic association studies shows that natural (mendelian) randomization to the MTHFR TT genotype confers a significantly greater mean tHcy (1.93 μmol/L; 95% CI, 1.38 to 2.47) and greater risk of stroke (OR, 1.26; 95% CI, 1.14 to 1.40) than does random assignment of the MTHFR CC genotype.53 However, there is no evidence from RCTs that lowering tHcy reduces the incidence of stroke and other major vascular events.69,70 Ongoing RCTs continue to explore the efficacy of homocysteine-lowering treatment in reducing the risk of ischemic stroke.71

Microalbuminuria
The appearance of trace amounts of albumin (microalbuminuria, 30 to 300 mg/d) and larger amounts (frank proteinuria, >1 g/d) are associated with an increased risk of stroke, MI, vascular death, and renal failure.45,72,73

Cystatin C
Cystatin C is a serum measure of renal function that appears to be independent of age, sex, and lean muscle mass and has been shown to be a stronger predictor of risk of stroke, MI, and death from vascular causes in elderly persons than is creatinine.74

Patent Foramen Ovale
A meta-analysis of case-control studies reported an increased prevalence of patient foramen ovale (PFO) among patients with cryptogenic stroke who were 55 years of age or younger, compared with stroke-free controls (OR, 5.0; 95% CI; 3.2 to 7.7) but not among persons 55 years of age or older (OR, 1.2; 95% CI; 0.6 to 2.6).73 However, many of these studies were prone to biases associated with hospital referral of cases and controls, referral of patients for echocardiography for various indications (with variable thoroughness of assessment of PFO), and nonblinded interpretation of the echocardiograms. A more recent community-based, case–control study found a PFO in 20.8% of 519 randomly selected, asymptomatic, community-based controls and in only 16.5% of 133 patients referred for evaluation of cryptogenic stroke, suggesting that there is no increase in the prevalence of PFO among patients with cryptogenic stroke compared with a random, nonhospitalized, reference population.76 Ongoing trials are evaluating whether closing a PFO reduces the risk of cardioembolic ischemic stroke.77–79

Conclusion
Stroke has many causes.21 Although increasing blood pressure is a causal risk factor for all major pathological subtypes of stroke and etiological subtypes of ischemic stroke, most other causal risk factors for stroke are causal only for specific pathological types of stroke and etiological subtypes of ischemic stroke.22 There is reasonably reliable evidence to suggest that 60% to 80% of all ischemic strokes can be attributed to increasing blood pressure, blood cholesterol, cigarette smoking and carotid stenosis, and diabetes mellitus (atherosclerotic ischemic stroke), and to atrial fibrillation and valvular heart disease (cardiogenic ischemic stroke; Tables 2 and 3).1–11 Another 10% to 20% of atherosclerotic ischemic strokes can probably be attributed to additional, recently established, causal risk factors for MI: raised apo B–apo A1 ratio, obesity, physical inactivity, psychosocial stress, and low fruit and vegetable intake (Tables 3 and 4). However, their causal role remains to be proven, because studies in stroke patients have been limited to small populations with differences in stroke subtype, stroke severity, and lifestyle, and it has not been shown in RCTs that reducing exposure to these risk factors reduces the risk of stroke.19,20,23 It also remains uncertain whether any of the newer emerging risk factors for stroke (Table 5) are causal, and if so, by how much they may also contribute to the burden of stroke. Evidence to date suggests that the direct genetic contribution of any single gene toward ischemic stroke is likely to be modest and to apply in selected patients only, in combination with environmental factors or by other epistatic (gene-gene or gene-environmental) effects. Proteomics, the analysis of the entire protein content of a cell or tissue, promises to identify new biomarkers for stroke.80 Despite the potential for genomics and proteomics to refine stroke risk and personalize stroke medicine,80,81 research resources should not be allocated disproportionately to emerging novel risk factors that may account for up to only 20% of all strokes at the expense of researching the determinants of the few established causal factors that account for up to 80% of all strokes. For example, the yield from future genetic research may be greater from studying the genetics of the established causal risk factors (eg, the genetic determinants of behaviors and other factors that increase blood pressure) than searching for new genes for stroke.82 In addition, strategies to reduce the burden of ischemic stroke should continue to target risk, as defined by established causal risk factors, and aim to reduce risk among individuals and the population by reducing exposure to causal risk factors for stroke.

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