How Does Number of Risk Factors Affect Prognosis in Young Patients With Ischemic Stroke?

Jukka Putaala, MD, PhD*; Elena Haapaniemi, MD, PhD*; Markku Kaste, MD, PhD; Turgut Tatlisumak, MD, PhD

Background and Purpose—We aimed to explore clinical features of young patients with ischemic stroke with no traditional vascular risk factors and to assess the impact of risk factor counts on outcomes.

Methods—We included 990 patients aged 15 to 49 years with first-ever ischemic stroke followed for a mean of 9.0 ± 3.8 years (survivors). Risk factors were categorized as well-documented and less well-documented. Outcome measures were unfavorable functional outcome (3-month modified Rankin Scale 2–6); recurrent ischemic stroke; myocardial infarction or other arterial noncerebrovascular event; and death from any cause.

Results—Compared with those with at least 1 well-documented risk factor, the 127 (12.8%) patients without risk factors were younger (median age, 37 versus 44 years; P < 0.001), likely to be females (54.3% versus 34.9%; P < 0.001), and they had more frequently a low-risk source of cardioembolism (21.3% versus 8.1%; P < 0.001), internal carotid artery dissection (12.6% versus 6.4%; P = 0.011), or vertebral artery dissection (17.3% versus 7.2%; P < 0.001). The groups had similar 3-month functional outcomes. Patients without well-documented risk factors had less frequently recurrent ischemic strokes (4.7% versus 13.6%; log rank P = 0.014), noncerebrovascular arterial events (0% versus 6.1%; P = 0.008), and lower long-term mortality (3.4% versus 14.3%; P = 0.003) than those with at least 1 risk factor. Adjusted for demographics and stroke etiology, the number of well-documented risk factors was associated with higher risk for noncerebrovascular events. Increasing count of less well-documented risk factors was, in turn, independently associated with higher long-term mortality.

Conclusions—In young adults with first-ever ischemic stroke, risk factor counts added independent prognostic information regarding noncerebrovascular events and mortality. (Stroke. 2012;43:356-361.)

Key Words: ischemic stroke • myocardial infarction • prognosis • recurrence • risk factors • stroke in the young

Young patients with ischemic stroke without any vascular risk factors are not rare in clinical practice. On the other hand, we often encounter young patients having a cluster of traditional vascular risk factors. Data based on our and others’ cohorts of young patients with first-ever ischemic stroke suggest risk factor accumulation along aging and in males.

In our patient cohort, compared with the group with none or only 1 risk factor, a cluster of ≥4 vascular risk factors was independently associated with a higher risk for composite of arterial events. However, it remains poorly studied how patients stratified by burden of risk factors differ from each other and whether number of risk factors could serve as an independent indicator of better or worse prognosis when accounting for demographic factors and stroke subtype.

We studied how the young patient with ischemic stroke free of well-documented risk factors differs—in terms of demographics, clinical stroke features, underlying etiology, and long-term outcome—from those having at least 1 risk factor. We investigated further what number of these vascular risk factors and additive information from less well-documented risk factors would add on prognostic models regarding functional outcome, recurrent ischemic stroke, new cardiovascular events, or death from any cause.

Methods

This study, conducted at the Helsinki University Central Hospital and approved by the relevant local authorities and the institutional ethics committee, was based on a data set of all consecutive patients aged 15 to 49 years with first-ever ischemic stroke occurring between January 1994 and May 2007. Definitions of risk factors appear in a prior publication. To construct a vascular risk factor score, the following well-documented risk factors were counted and added up in each patient: family history of any stroke, dyslipidemia, current smoking, hypertension, obesity, coronary heart disease, heart failure, prior myocardial infarction, peripheral arterial disease, prior transient ischemic attack,

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Type 1 or type 2 diabetes mellitus, atrial fibrillation, and hormone replacement therapy. We also counted less well-documented risk factors, which included heavy drinking, recent heavy drinking, preceding infection, history of migraine, oral contraceptive use, gravidity or postpartum period, obstructive sleep apnea, active malignancy, impaired kidney function, illicit recent drug use, inherited thrombophilia (factor V Leiden or prothrombin gene mutations or deficiencies of natural anticoagulants), and antiphospholipid antibodies (lupus anticoagulant or anticardiolipin antibodies).

Stroke subtype was assigned to each patient using the Trial of Org 10172 in Acute Stroke Treatment criteria.2 The classification was done independently by pairs of investigators reaching consensus when necessary. Sources of cardioembolism (Trial of Org 10172 in Acute Stroke Treatment 2) were divided into low-risk and high-risk sources. Other determined etiology (Trial of Org 10172 in Acute Stroke Treatment 4) fell into groups of internal carotid artery dissection, vertebral artery dissection, or other nondissection etiology. Initial stroke severity was assessed with the National Institutes of Health Stroke Scale.

Infarct size was assessed based on documented templates6 and fell into small, lesion in the anterior or posterior circulation <1.5 cm; medium, lesion in a cortical superficial branch of the anterior cerebral artery, middle cerebral artery, posterior cerebral artery, or in a deep branch of the middle cerebral artery or posterior cerebral artery, or lesion in internal border-zone territories; large posterior, lesion involving brain stem or cerebellum >1.5 cm or involving complete territory of the posterior cerebral artery together with border-zone territories; and large anterior, lesion involving complete territory of anterior cerebral artery or middle cerebral artery or lesion involving >1 artery territory. Lesions not visible in any of the brain imaging studies were considered small. Furthermore, we registered the presence of silent brain infarcts (ischemic lesion in CT or MRI without a history of a corresponding history of neurological symptoms or signs) and leukoaraisis (periventricular or subcortical white-matter hypodensity in CT or hyperintense lesions in periventricular or subcortical regions or in the pons on fluid-attenuated inversion recovery or T2-weighted MRI sequences).

Three-month functional outcome was assessed with modified Rankin Scale based on routine evaluation by a neurologist at the outpatient clinic or at a rehabilitation site by the treating neurologist. In some patients, outcome was assessed with a telephone interview of the patient, relative, or a caregiver. Unfavorable 3-month outcome was defined as a score of 2 to 6 on modified Rankin Scale.9

Long-term follow-up of our patients is described in detail elsewhere.4 Briefly, patients were contacted over telephone or with a letter during November 2009 to January 2010. All outcome events reported by patients or caregivers were verified from the hospital or primary care patient records. Mortality data were obtained from Statistics Finland. The outcome measures in the present analysis were (1) nonfatal or fatal ischemic stroke; (2) composite of noncerebrovascular arterial events (myocardial infarction, revascularization, or other arterial occlusive event); and (3) death from any cause.

Chi-square, Fisher exact, Mann-Whitney U, and Kruskal-Wallis tests allowed univariable comparisons between patients without and at least 1 well-documented risk factor. Kaplan-Meier curves depicted the long-term risk for outcome events stratified by well-documented risk factor count (none, 1, 2, 3, or ≥4 risk factors). To meet the assumptions of multivariable analyses, the following groups were constructed: 0 to 2, 1 to 3, or ≥4 well-documented risk factors. To depict the risk of events according to number of less well-documented risk factors, patients were divided into groups having none, 1, or ≥2 of these risk factors. Event rates were also compared between patients having none and ≥1 well-documented or less well-documented risk factor. Logistic regression was used to investigate factors associated with favorable 3-month functional outcome. Cox proportional hazards analysis served to explore the association between risk factor scores and outcomes, the groups with 0 to 1 well-documented risk factor and no less well-documented risk factor serving as references, respectively. Patients dying within 30 days after the index event were excluded from the long-term mortality analysis because their death was likely attributable to index event.

Log-minus-log survival plots were used to assess that the proportionality assumption was met for all tested covariates; no violations occurred. Multivariable models exploring the association between well-documented risk factors and outcome events were adjusted first for demographics and subsequently for stroke subtype. The impact of less well-documented risk factors was analyzed similarly and the final model, adjusted for age, gender, and stroke subtype, included both risk factor counts. Statistical analyses used SPSS 19.0 for Macintosh. For 2-sided values, significance was set at P<0.05.

Results

Of the 1008 patients in our registry, we excluded 4 patients who turned out to be stroke mimics in later follow-up, 5 who refused the follow-up study, and a further 9 who were lost to follow-up. Patients were followed for a mean of 9.0±3.8 years (survivors). Follow-up time did not differ between the groups defined by risk factor counts. No information on 3-month outcome was available in 5 patients.

In 127 (12.8%) patients, no well-documented vascular risk factors were identified, whereas 251 (25.4%) had single, 277 (28.0%) had 2, 187 (18.9%) had 3, and 148 (14.9%) had ≥4 risk factors. Compared with patients having well-documented risk factors, those with no risk factor were younger, more likely females, less frequently heavy drinkers, or harbored antiphospholipid antibodies, but they had more often history of migraine (Table 1). There were 50 (5.1%) patients without any of the well-documented or less well-documented risk factor, whereas 460 (46.6%) had none of the less well-documented risk factors, 328 (33.2%) had single, and 199 (20.2%) had ≥2.

No difference in initial stroke severity or infarct size emerged between patients with or without well-documented risk factors. Those without well-documented factors less often demonstrated silent brain infarcts or leukoaraisis. Furthermore, they were more likely to have a low-risk source of cardioembolism, internal carotid artery dissection, or vertebral artery dissection as their underlying cause of stroke. None of those without well-documented risk factors had small-vessel occlusion and they were less often assigned any secondary preventive medication (Table 1).

Neither difference appeared in the proportions of unfavorable 3-month outcome (modified Rankin Scale 2–6) between patients without (48.8%) or with well-documented risk factors (50.3%, P=0.747) nor between those without (47.0%) or with less well-documented risk factors (52.8%, P=0.070). Correspondingly, in logistic regression analysis, no association was found between number of well-documented or less well-documented risk factors and functional outcome (data not shown).

Patients without well-documented risk factors had less frequently recurrent ischemic strokes (n=6 [4.7%] versus n=117 [13.6%]; log rank P=0.014), noncerebrovascular arterial events (n=0 versus n=53 [6.1%; P=0.008), and lower long-term mortality (n=4 [3.4%] versus n=121 [14.3%; P=0.003] than did those with ≥1 well-documented risk factor. The corresponding event rates for patients without and with less well-documented risk factors were 14.1% (n=65) versus 10.9% (n=58) for recurrent ischemic stroke (P=0.210), 5.2% (n=24) versus 5.5% (n=29) for noncerebrovascular arterial events (P=0.627), and 8.7% (n=40)
Table 1. Baseline Differences Between Patients Having No Well-Documented Vascular Risk Factors and Those Having at Least 1 Such Risk Factor

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All (n=990)</th>
<th>No Well-Documented Risk Factor (n=127)</th>
<th>At Least 1 Well-Documented Risk Factor (n=863)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>44 (37–47)</td>
<td>37 (29–44)</td>
<td>44 (39–47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age &gt;40 y</td>
<td>657 (66.4)</td>
<td>50 (39.4)</td>
<td>607 (70.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>370 (37.4)</td>
<td>69 (54.3)</td>
<td>301 (34.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Well-documented risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of any stroke</td>
<td>125 (12.6)</td>
<td>0</td>
<td>125 (14.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>592 (59.8)</td>
<td>0</td>
<td>592 (68.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>442 (44.6)</td>
<td>0</td>
<td>442 (51.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Hypertension</td>
<td>389 (39.3)</td>
<td>0</td>
<td>389 (45.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Obesity</td>
<td>105 (10.6)</td>
<td>0</td>
<td>105 (12.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>48 (4.8)</td>
<td>0</td>
<td>48 (5.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Heart failure</td>
<td>48 (4.8)</td>
<td>0</td>
<td>48 (5.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>36 (3.6)</td>
<td>0</td>
<td>36 (4.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>18 (1.8)</td>
<td>0</td>
<td>18 (2.1)</td>
<td>NA</td>
</tr>
<tr>
<td>History of transient ischemic attack</td>
<td>89 (9.0)</td>
<td>0</td>
<td>89 (10.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes mellitus, Type 1</td>
<td>44 (4.4)</td>
<td>0</td>
<td>44 (5.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes mellitus, Type 2</td>
<td>59 (6.0)</td>
<td>0</td>
<td>59 (6.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>41 (4.1)</td>
<td>0</td>
<td>41 (4.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Hormone replacement therapy*</td>
<td>17 (4.6)</td>
<td>0</td>
<td>17 (5.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Less well-documented risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy drinking</td>
<td>141 (14.2)</td>
<td>9 (7.1)</td>
<td>132 (15.3)</td>
<td>0.013</td>
</tr>
<tr>
<td>Recent heavy drinking</td>
<td>88 (8.9)</td>
<td>8 (6.3)</td>
<td>80 (9.3)</td>
<td>0.272</td>
</tr>
<tr>
<td>Preceding infection</td>
<td>131 (13.2)</td>
<td>13 (10.2)</td>
<td>118 (13.7)</td>
<td>0.286</td>
</tr>
<tr>
<td>History of migraine</td>
<td>168 (17.0)</td>
<td>30 (23.6)</td>
<td>138 (16.0)</td>
<td>0.032</td>
</tr>
<tr>
<td>Oral contraceptive use*</td>
<td>66 (17.8)</td>
<td>17 (24.6)</td>
<td>49 (16.3)</td>
<td>0.102</td>
</tr>
<tr>
<td>Gravidity or postpartum period*</td>
<td>10 (2.7)</td>
<td>4 (5.8)</td>
<td>6 (2.0)</td>
<td>0.095</td>
</tr>
<tr>
<td>Obstructive sleep apnea syndrome</td>
<td>38 (3.8)</td>
<td>1 (0.8)</td>
<td>37 (4.3)</td>
<td>0.078</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>15 (1.5)</td>
<td>1 (0.8)</td>
<td>14 (1.6)</td>
<td>0.708</td>
</tr>
<tr>
<td>Impaired kidney function</td>
<td>44 (4.5)</td>
<td>2 (1.6)</td>
<td>42 (4.9)</td>
<td>0.095</td>
</tr>
<tr>
<td>Illicit recent drug use</td>
<td>12 (1.2)</td>
<td>0</td>
<td>12 (1.4)</td>
<td>0.382</td>
</tr>
<tr>
<td>Inherited thrombophilia (n=472)</td>
<td>33 (7.0)</td>
<td>3 (3.8)</td>
<td>30 (7.6)</td>
<td>0.233</td>
</tr>
<tr>
<td>Antiphospholipid antibodies (n=533)</td>
<td>34 (6.4)</td>
<td>1 (1.1)</td>
<td>33 (7.4)</td>
<td>0.029</td>
</tr>
<tr>
<td>Stroke severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS score, median (IQR)</td>
<td>3 (1–7)</td>
<td>3 (1–10)</td>
<td>2 (1–6)</td>
<td>0.655</td>
</tr>
<tr>
<td>Brain imaging</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Size of the largest lesion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>431 (43.5)</td>
<td>48 (37.8)</td>
<td>383 (44.4)</td>
<td>0.162</td>
</tr>
<tr>
<td>Medium</td>
<td>273 (27.6)</td>
<td>40 (31.5)</td>
<td>233 (27.0)</td>
<td>0.290</td>
</tr>
<tr>
<td>Large posterior</td>
<td>123 (12.4)</td>
<td>14 (11.0)</td>
<td>109 (12.6)</td>
<td>0.584</td>
</tr>
<tr>
<td>Large anterior</td>
<td>163 (16.5)</td>
<td>25 (19.7)</td>
<td>138 (16.0)</td>
<td>0.295</td>
</tr>
<tr>
<td>Silent brain infarcts</td>
<td>126 (12.7)</td>
<td>7 (5.5)</td>
<td>119 (13.8)</td>
<td>0.009</td>
</tr>
<tr>
<td>Leukoaralosis</td>
<td>55 (5.6)</td>
<td>1 (0.8)</td>
<td>54 (6.3)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

(Continued)
versus 20.6% (n=109) for death from any cause (P<0.001).

Event rates per each risk factor are shown in Supplemental Table I (http://stroke.ahajournals.org).

Kaplan-Meier curves showed a gradual increase in long-term risk of nonfatal or fatal ischemic stroke (Figure 1A), a composite of noncerebrovascular arterial events (Figure 1B), and all-cause mortality (Figure 1C) as a function of increasing well-documented risk factor count. Patients without well-documented risk factors had the highest mortality soon after their index stroke (Figure 1C). Death from any cause was the only end point that showed correlation with the count of less well-documented risk factors (Figure 2A–C).

In Cox proportional hazards analysis adjusted for age and gender, presence of ≥4 well-documented risk factors was independently associated with higher risk for recurrent ischemic stroke and death from any cause. After further adjustment for stroke subtype, these associations diminished. Adjustment for demographics and additionally for stroke subtype did not alter the effect of increasing number of well-documented risk factors on higher risk for composite of noncerebrovascular arterial events (Table 2). Count of less well-documented risk factors independently increased risk of death in models adjusted for age, gender, and stroke subtype (data not shown). The final model that included counts of both well-documented and less well-documented risk factors showed count of less well-documented risk factors to be associated with higher mortality risk (Table 2).

**Discussion**

Our study found that many young patients with ischemic stroke harbor no known well-documented vascular risk factors. These patients were likely to be younger females and have stroke caused by cervical artery dissection or cardioembolism of a low-risk source. Risk for future vascular events or
all-cause mortality increased proportionally as this risk factor number increased. Notably, those without vascular risk factors did not experience any noncerebrovascular arterial events during the long-term follow-up. Count of less-well documented risk factors added further information over traditional risk factors and stroke etiology in the prognostic model regarding end point death from any cause.

One study used a score based on 7 vascular risk factors and showed a low risk for recurrent ischemic stroke and nil risk for future myocardial infarction in patients with none or only 1 risk factor, in accordance with our findings. Another study scored up hypertension, migraine with aura, and family history of stroke and found an independent association with that score and recurrent vascular events, mostly ischemic stroke or transient ischemic attack, but without adjustment for stroke etiology. We included 14 well-documented risk factors in our score and all major vascular events as outcome measures and showed gradually increasing risks for all end points. When analyzed by multivariable methods, this risk factor number had, however, no independent predictive value over stroke etiology with regard to recurrent ischemic stroke or death from any cause. As shown previously, large-artery atherosclerosis subtype is a highly relevant prognosticator in young adult patients with regard to end points ischemic stroke or all-cause mortality. This corresponds to the low risk of events in those without vascular risk factors. Well-documented risk-factor count was, however, strongly associated with the risk for noncerebrovascular arterial events even after adjusting for stroke subtype.

Our study further adds to prior literature by showing that counting less well-documented risk factors is prognostically relevant. This count was, independent of age, gender, vascular risk factor count, and stroke etiology, associated with higher mortality. Our finding is likely explained by the presence of large-artery atherosclerosis in young patients. Counting less well-documented risk factors was associated with higher death from any cause.

Table 2. Results of Multivariable Analyses Investigating the Usefulness of Risk Factor Counts in Prediction of the Risk for Vascular or Death End Points During Long-Term Follow-Up*

<table>
<thead>
<tr>
<th></th>
<th>Nonfatal or Fatal Ischemic Stroke HR (95% CI)</th>
<th>P</th>
<th>Myocardial Infarction, Revascularization, or Other Noncerebrovascular Arterial Event HR (95% CI)</th>
<th>P</th>
<th>Death From Any Cause HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-documented risk-factor model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1 well-documented risk factor</td>
<td>Reference</td>
<td>NA</td>
<td>Reference</td>
<td>NA</td>
<td>Reference</td>
<td>NA</td>
</tr>
<tr>
<td>2–3 well-documented risk factors</td>
<td>1.52 (0.98–2.38)</td>
<td>0.064</td>
<td>9.13 (2.16–38.58)</td>
<td>0.003</td>
<td>1.28 (0.82–1.98)</td>
<td>0.277</td>
</tr>
<tr>
<td>≥4 well-documented risk factors</td>
<td>2.09 (1.23–3.54)</td>
<td>0.006</td>
<td>29.26 (6.91–123.81)</td>
<td>&lt;0.001</td>
<td>1.83 (1.10–3.04)</td>
<td>0.020</td>
</tr>
<tr>
<td>Etiology model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1 well-documented risk factor</td>
<td>Reference</td>
<td>NA</td>
<td>Reference</td>
<td>NA</td>
<td>Reference</td>
<td>NA</td>
</tr>
<tr>
<td>2–3 well-documented risk factors</td>
<td>1.17 (0.73–1.89)</td>
<td>0.510</td>
<td>6.53 (1.51–28.33)</td>
<td>0.012</td>
<td>0.87 (0.54–1.40)</td>
<td>0.573</td>
</tr>
<tr>
<td>≥4 well-documented risk factors</td>
<td>1.39 (0.77–2.50)</td>
<td>0.277</td>
<td>16.29 (3.59–73.90)</td>
<td>&lt;0.001</td>
<td>1.05 (0.59–1.87)</td>
<td>0.862</td>
</tr>
<tr>
<td>Final model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1 well-documented risk factor</td>
<td>Reference</td>
<td>NA</td>
<td>Reference</td>
<td>NA</td>
<td>Reference</td>
<td>NA</td>
</tr>
<tr>
<td>2–3 well-documented risk factors</td>
<td>1.17 (0.73–1.88)</td>
<td>0.522</td>
<td>6.55 (1.51–27.38)</td>
<td>0.012</td>
<td>0.90 (0.56–1.44)</td>
<td>0.654</td>
</tr>
<tr>
<td>≥4 well-documented risk factors</td>
<td>1.42 (0.79–2.56)</td>
<td>0.244</td>
<td>16.44 (3.62–74.67)</td>
<td>&lt;0.001</td>
<td>1.02 (0.57–1.80)</td>
<td>0.958</td>
</tr>
<tr>
<td>0 less well-documented risk factor</td>
<td>Reference</td>
<td>NA</td>
<td>Reference</td>
<td>NA</td>
<td>Reference</td>
<td>NA</td>
</tr>
<tr>
<td>1 less well-documented risk factor</td>
<td>0.80 (0.53–1.21)</td>
<td>0.294</td>
<td>1.01 (0.53–1.90)</td>
<td>0.389</td>
<td>2.75 (1.74–4.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥2 less well-documented risk factors</td>
<td>0.82 (0.50–1.34)</td>
<td>0.427</td>
<td>1.72 (0.86–3.43)</td>
<td>0.123</td>
<td>3.72 (2.32–5.98)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval; NA, not applicable.

*Risk factor models investigating arterial events were adjusted for age and gender and etiology models were further adjusted for stroke etiology. The final model including both counts of well-documented and less well-documented risk factors was adjusted for age, gender, and etiology. Mortality analysis excluded 24 patients dying within 30 d after index stroke.
previously shown\(^{10,11}\) deleterious effects of heavy drinking, malignancies, and impaired kidney function on long-term risk of death in young adults (Supplemental Table I) and stresses the importance of noting all potentially modifiable risk factors in these individuals.

Although hypertension has been linked to cervical artery dissection—the most frequent ischemic stroke subtype in young adults—patients with dissection generally have lower prevalence of vascular risk factors than do other subtypes,\(^{12}\) obvious in our study as well. Strikingly, 37% of those with no well-documented risk factors and 32% of those with at least 1 such risk factor had undetermined etiology by the Trial of Org 10172 in Acute Stroke Treatment classification, the figure being well comparable to most modern young stroke patient series.\(^{13}\) Given that female subjects were more prone to have no traditional vascular risk factors, future studies should target on finding novel environmental and intrinsic risk factors and their interactions predisposing to stroke\(^{14}\) and affecting its long-term outcome in these patients.

Limitations of our study include lack of information on some well-documented risk factors such as physical inactivity and inability to account for risk factors that might have developed under follow-up. Some of the less well-documented risk factors (eg, thrombophiliaiae and obstructive sleep apnea) were not routinely screened in all patients, which may cause inaccuracy in risk estimates based on the count of these risk factors. Furthermore, true presence of risk factors might be overlooked in some patients with very severe symptoms dying soon after their index stroke, because the group with no vascular risk factors seemed to have higher early mortality than others. However, our study clearly showed that the overall risk factor burden in young patients at the time of their first ischemic stroke correlates with long-term outcomes.

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**Disclosures**

None.

**References**


How Does Number of Risk Factors Affect Prognosis in Young Patients With Ischemic Stroke?

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**SUPPLEMENTAL MATERIAL**

**Table S1.** Numbers and percentages of outcome events according to each risk factor.

<table>
<thead>
<tr>
<th>Well-documented risk factors</th>
<th>Nonfatal or fatal ischemic stroke n=123</th>
<th>Myocardial infarction, revascularization or other non-cerebrovascular arterial event n=53</th>
<th>Death from any cause n=149</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of any stroke</td>
<td>17 (13.6)</td>
<td>9 (7.2)</td>
<td>11 (8.8)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>78 (13.2)</td>
<td>39 (6.6)</td>
<td>91 (15.4)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>67 (15.2)</td>
<td>39 (8.8)</td>
<td>80 (18.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>61 (15.7)</td>
<td>36 (9.3)</td>
<td>68 (17.5)</td>
</tr>
<tr>
<td>Obesity</td>
<td>18 (17.1)</td>
<td>10 (9.5)</td>
<td>16 (15.2)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>7 (14.6)</td>
<td>12 (25.0)</td>
<td>17 (35.4)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>9 (18.8)</td>
<td>5 (10.4)</td>
<td>19 (39.6)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>8 (8.3)</td>
<td>7 (19.4)</td>
<td>14 (38.9)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>4 (22.2)</td>
<td>9 (50.0)</td>
<td>10 (55.6)</td>
</tr>
<tr>
<td>History of transient ischemic attack</td>
<td>19 (21.3)</td>
<td>6 (6.7)</td>
<td>20 (22.5)</td>
</tr>
<tr>
<td>Diabetes mellitus, type 1</td>
<td>14 (31.8)</td>
<td>12 (27.3)</td>
<td>14 (31.8)</td>
</tr>
<tr>
<td>Diabetes mellitus, type 2</td>
<td>25 (25.4)</td>
<td>11 (18.6)</td>
<td>15 (25.4)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5 (12.2)</td>
<td>2 (4.9)</td>
<td>8 (19.5)</td>
</tr>
<tr>
<td>Hormone replacement therapy*</td>
<td>0</td>
<td>1 (5.9)</td>
<td>2 (11.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Less well-documented risk factors</th>
<th>Nonfatal or fatal ischemic stroke n=123</th>
<th>Myocardial infarction, revascularization or other non-cerebrovascular arterial event n=53</th>
<th>Death from any cause n=149</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy drinking</td>
<td>20 (14.2)</td>
<td>11 (7.8)</td>
<td>52 (36.9)</td>
</tr>
<tr>
<td>Recent heavy drinking</td>
<td>14 (15.9)</td>
<td>7 (8.0)</td>
<td>24 (27.3)</td>
</tr>
<tr>
<td>Preceding infection</td>
<td>10 (7.6)</td>
<td>5 (3.8)</td>
<td>31 (23.7)</td>
</tr>
<tr>
<td>History of migraine</td>
<td>19 (11.3)</td>
<td>7 (4.2)</td>
<td>14 (8.3)</td>
</tr>
<tr>
<td>Oral contraceptive use*</td>
<td>3 (4.5)</td>
<td>0</td>
<td>3 (4.5)</td>
</tr>
<tr>
<td>Gravidity or postpartum period*</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Obstructive sleep apnea syndrome</td>
<td>5 (13.2)</td>
<td>4 (10.5)</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>2 (13.3)</td>
<td>1 (6.7)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Impaired kidney function</td>
<td>11 (25.0)</td>
<td>8 (18.2)</td>
<td>23 (52.3)</td>
</tr>
<tr>
<td>Illicit recent drug use</td>
<td>3 (25.0)</td>
<td>0</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Inherited thrombophilia (tested in 482)</td>
<td>1 (3.0)</td>
<td>2 (6.1)</td>
<td>5 (15.2)</td>
</tr>
<tr>
<td>Antiphospholipid antibodies (tested in 533)</td>
<td>5 (14.7)</td>
<td>2 (5.9)</td>
<td>4 (11.8)</td>
</tr>
</tbody>
</table>

Data are n (% per risk factor).
*Percentage is for females only.