High Density Lipoprotein Cholesterol and the Risk of Stroke in Elderly Men

The Honolulu Heart Program

J. David Curb1,2, Robert D. Abbott1,3,4, Beatriz L. Rodriguez1,2,3, Kamal H. Masaki1,2,3, Randi Chen1, Jordan S. Popper3, Helen Petrovitch1,2,3, G. Webster Ross1,2,3, Irwin J. Schatz2, Gina C. Belleau1, and Katsuhiko Yano1

1 Pacific Health Research Institute, Honolulu, HI.
2 Departments of Geriatric Medicine and Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI.
3 Honolulu Heart Program, Kuakini Medical Center, Honolulu, HI.
4 Division of Biostatistics and Epidemiology, University of Virginia School of Medicine, Charlottesville, VA.

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High density lipoprotein (HDL) cholesterol has been inversely associated with coronary heart disease. Associations with stroke are less clear, particularly among the elderly. In this study, the authors examined the relation between HDL cholesterol levels and the risk of stroke in elderly men. Levels of HDL cholesterol were measured in 2,444 Honolulu Heart Program men aged 71–93 years at the 1991–1993 examinations. The participants, who were free of prevalent stroke, coronary heart disease, and cancer at baseline, were followed to the end of 1998 for thromboembolic and hemorrhagic stroke. While HDL cholesterol was unrelated to hemorrhagic events, incidence of thromboembolic stroke declined consistently with increasing HDL cholesterol level (p = 0.003). There was a nearly threefold excess of thromboembolic stroke in men with low HDL cholesterol levels (<1.0 mmol/liter (<40 mg/dl)) compared with men with high levels (≥1.6 mmol/liter (≥60 mg/dl)) (10.6/1,000 person-years vs. 3.6/1,000 person-years; p = 0.001). Adjustment for other risk factors had little effect on these findings, although associations appeared strongest in elderly men with “desirable” total cholesterol levels, hypertension, or diabetes mellitus. These findings suggest that HDL cholesterol level is inversely related to the risk of thromboembolic stroke in elderly men. Whether HDL cholesterol alters the effect of other factors on stroke risk in elderly men warrants further study.

High density lipoprotein (HDL) cholesterol has been inversely associated with the incidence of coronary heart disease in population-based studies (1–9). Associations with stroke, however, have not been clearly identified, particularly in the elderly (10–13). To our knowledge, no studies have prospectively examined the relation between HDL cholesterol and risk of stroke in older persons without prevalent disease, while also having the capacity to examine effects within risk factor strata. Such studies in the elderly are especially important in light of increasing evidence that relations between traditional risk factors and cardiovascular disease appear to change with advancing age. In the study described here, we examined the association between HDL cholesterol and risk of thromboembolic and hemorrhagic stroke in elderly men without clinical cardiovascular disease or cancer.

MATERIALS AND METHODS

Background and study sample

From 1965 to 1968, the Honolulu Heart Program began following 8,006 men of Japanese ancestry living on the island of Oahu, Hawaii, for the development of coronary heart disease; cerebrovascular accident; lipoproteins, HDL cholesterol; men

Abbreviation: HDL, high density lipoprotein.
HDL Cholesterol and Stroke

Participants received complete physical examinations at the time of study enrollment, when they were aged 45–68 years. Since that time, subjects have undergone repeat examinations, with comprehensive follow-up regarding all hospital discharges, death certificates, and autopsy records for morbidity and mortality due to coronary heart disease, cancer, and stroke. Procedures used have been in accordance with institutional guidelines and approved by an institutional review committee. Informed consent has been obtained from the study participants.

For this report, follow-up for stroke began at the examination given to 3,741 participants in the Honolulu Heart Program between 1991 and 1993 (approximately 80 percent of the surviving cohort members). Follow-up for morbidity and mortality due to stroke was complete through the end of 1998. After the exclusion of 1,192 men with prevalent stroke, coronary heart disease (including angina pectoris and coronary insufficiency), or cancer at the time of the baseline examination (1991–1993) and 105 men with missing data on HDL cholesterol, 2,444 men remained available for follow-up to the end of 1998. The average age at which follow-up began was 78 years (range, 71–93 years).

Diagnosis of stroke

A diagnosis of stroke was made when a neurologic deficit was accompanied by blood in the cerebrospinal fluid or by evidence of an infarct or hemorrhage based on confirmation from neuroimaging (conducted in more than 90 percent of stroke victims). Probable strokes included neurologic deficits that persisted for at least 2 weeks or until death but were not accompanied by blood in the cerebrospinal fluid or by findings based on available neuroimaging data. All diagnoses were reviewed and confirmed by a study neurologist and the Honolulu Heart Program Morbidity and Mortality Review Committee. Possible strokes (neurologic deficits lasting for at least 24 hours but less than 2 weeks or of unknown duration) were not included among the stroke events because of a lack of diagnostic certainty. A stroke was considered thromboembolic if the focal neurologic deficit usually occurred without prolonged unconsciousness, nuchal rigidity, fever, pronounced leukocytosis, or blood in the spinal fluid. Identification of hemorrhagic stroke was based on a focal neurologic deficit accompanied by a loss of consciousness, headache, and the presence of blood in the spinal fluid (determined by atraumatic lumbar puncture, computerized tomography, or surgical findings). Subjects who experienced focal neurologic episodes attributed to other conditions such as blood dyscrasia, neoplastic disease, head injury, surgical accident, meningoencephalitis, fat embolism, epilepsy, or cardiac arrest were not included among the stroke victims. Further details on the diagnosis of stroke are provided elsewhere (15).

HDL cholesterol levels and risk factors

Procedures for preparing collected blood specimen for laboratory analysis adhered to the guidelines of the Lipid Standardization Laboratory of the Centers for Disease Control and Prevention. Blood specimens were collected after an overnight fast of at least 12 hours. Plasma was later separated in a refrigerated centrifuge at 4°C and frozen at −70°C for up to 2 months. Samples were then shipped on dry ice to the University of Vermont for determination of total cholesterol and HDL cholesterol levels. HDL cholesterol was separated by precipitation with dextran sulfate and magnesium chloride (16).

Other risk factors assessed or measured at the time blood was drawn included age; hypertension; diabetes mellitus; ankle-brachial index, a marker of peripheral vascular disease; electrocardiographic evidence of atrial fibrillation; body mass index (weight (kg)/height (m)²); alcohol intake (ounces/day); and an index of physical activity. A diagnosis of hypertension was made when either systolic blood pressure was ≥160 mmHg or diastolic blood pressure was ≥95 mmHg or the subject was taking medication for high blood pressure. Diabetes was defined on the basis of medical history or the use of insulin or oral hypoglycemic agents. Diabetes was also considered present when fasting glucose concentrations exceeded 6.9 mmol/liter (125 mg/dl) or when glucose levels were at least 11.1 mmol/liter (200 mg/dl) 2 hours after ingestion of a 75-g glucose load. Peripheral vascular disease was defined as an ankle-brachial index (the ratio of a systolic blood pressure measurement in the ankle to a systolic measurement in the arm) less than 0.9 (17). Assessment of physical activity was based on the physical activity index, a common measure that is used to quantify overall metabolic output in a typical 24-hour period and is known to be inversely associated with the risk of cardiovascular disease (18). Cigarette smoking was not included among the risk factors, since only 170 of the 2,444 men continued to smoke cigarettes in this age group. Control of past and current smoking also had no effect on the reported findings.

Statistical methods

For this report, HDL cholesterol categories were created on the basis of the current recommendations of the National Cholesterol Education Program (19). The categories included levels that were low (<1.0 mmol/liter (<40 mg/dl)) and high (>1.6 mmol/liter (>200 mg/dl)). Intermediate levels were defined as those that ranged from 1.0 mmol/liter to 1.5 mmol/liter (40–59 mg/dl). Strata for total cholesterol also adhered to National Cholesterol Education Program guidelines. The categories included levels that were “desirable” (<5.2 mmol/liter (<200 mg/dl)), “borderline-high” (5.2–6.1 mmol/liter (200–239 mg/dl)), and “high” (>6.2 mmol/liter (>240 mg/dl)).

Within the ranges of HDL cholesterol values, crude and age-adjusted incidences of stroke per 1,000 person-years were estimated on the basis of follow-up from the baseline examination (1991–1993) to the end of 1998 (20). Age-adjusted levels of risk factors across the HDL cholesterol ranges were also derived. To test for an independent effect of HDL cholesterol on the risk of stroke, we used proportional hazards regression (21). Adjustments were made for age and the other risk factors. While HDL cholesterol was modeled as a continuous variable, relative risks of stroke (and 95 percent confidence intervals) were also estimated.
TABLE 1. Percentage distributions of high density lipoprotein cholesterol level and incidence of thromboembolic stroke according to age at the beginning of study follow-up (1991–1993), Honolulu Heart Program, 1991–1998

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sample size</th>
<th>Low: &lt;1.0 mmol/liter (&lt;40 mg/dl)</th>
<th>Intermediate: 1.0–1.5 mmol/liter (40–59 mg/dl)</th>
<th>High: ≥1.6 mmol/liter (≥60 mg/dl)</th>
<th>Incidence of stroke†</th>
</tr>
</thead>
<tbody>
<tr>
<td>71–74</td>
<td>758</td>
<td>18.1 (137)‡</td>
<td>60.4 (458)</td>
<td>21.5 (163)</td>
<td>2.9/1,000 person-years</td>
</tr>
<tr>
<td>75–79</td>
<td>1,003</td>
<td>18.3 (184)</td>
<td>58.1 (583)</td>
<td>23.5 (236)</td>
<td>5.9/1,000 person-years</td>
</tr>
<tr>
<td>80–84</td>
<td>425</td>
<td>16.2 (69)</td>
<td>55.5 (236)</td>
<td>28.2 (120)</td>
<td>7.7/1,000 person-years</td>
</tr>
<tr>
<td>85–93</td>
<td>258</td>
<td>17.4 (45)</td>
<td>58.9 (152)</td>
<td>23.6 (61)</td>
<td>13.1/1,000 person-years</td>
</tr>
<tr>
<td>Total</td>
<td>2,444</td>
<td>17.8 (435)</td>
<td>58.5 (1,429)</td>
<td>23.7 (580)</td>
<td>5.8/1,000 person-years</td>
</tr>
</tbody>
</table>

* The percentage of men within each category of high density lipoprotein cholesterol did not change significantly with age.
† The incidence of thromboembolic stroke increased significantly with age (p < 0.001).
‡ Numbers in parentheses, number of men.

RESULTS

Among the 2,444 men who were followed for incident stroke, the average HDL cholesterol concentration was 1.3 mmol/liter (51 mg/dl) (range, 0.5–3.3 mmol/liter (20–129 mg/dl)). Table 1 shows the percentages of men with low (<1.0 mmol/liter (<40 mg/dl)), intermediate (1.0–1.5 mmol/liter (40–59 mg/dl)), and high (≥1.6 mmol/liter (≥60 mg/dl)) concentrations of HDL cholesterol according to age at which the HDL cholesterol determinations were made (1991–1993). Overall, the percentages of men with low, intermediate, and high HDL cholesterol levels were 17.8, 58.5, and 23.7, respectively. Between age groups, the distribution of men across HDL cholesterol strata was similar. Age had no association with HDL cholesterol concentrations in this elderly sample.

In the course of follow-up to the end of 1998, 137 strokes could be attributed to either a thromboembolic cause or a hemorrhagic cause. Among the strokes, 89 were identified as thromboembolic events, while 48 were identified having a hemorrhagic origin. The incidence of thromboembolic stroke (table 1) increased consistently from 2.9/1,000 person-years in men aged 71–74 years to 13.1/1,000 person-years in men aged 85 years or older (p < 0.001). Data for hemorrhagic events are not provided, since associations with age were absent. Here, incidence varied from 3.1/1,000 person-years to 3.2/1,000 person-years across age groups.

Except for atrial fibrillation and peripheral vascular disease, all of the other risk factors measured at the time of study enrollment (table 2) were associated with differences in concentrations of HDL cholesterol. As might be expected, increases in HDL cholesterol were associated with increases in total cholesterol (p < 0.001). Increases in HDL cholesterol were also associated with less frequent hypertension and diabetes. Body mass index declined with increasing HDL cholesterol levels as well (p < 0.001). In contrast, alcohol intake and physical activity were positively associated with HDL cholesterol concentrations (p < 0.001).

Table 3 provides the crude and age-adjusted incidences of thromboembolic stroke for men with low, intermediate, and high concentrations of HDL cholesterol. For hemorrhagic events, the incidence rates were 2.1/1,000 person-years, 3.5/1,000 person-years, and 2.8/1,000 person-years across the increasing ranges of HDL cholesterol, respectively. Additional data for hemorrhagic stroke are not provided here, since associations with HDL cholesterol were absent.

After adjustment for age, the incidence of thromboembolic stroke declined consistently as HDL cholesterol concentrations increased (p = 0.003). Across the three strata of HDL cholesterol, stroke incidence was 10.6/1,000 person-years, 5.2/1,000 person-years, and 3.6/1,000 person-years in men with low, intermediate, and high levels of HDL cholesterol, respectively. After further adjustment for other risk factors, the association between HDL cholesterol and risk of thromboembolic stroke persisted. Men with low concentrations experienced a 2.7-fold excess risk of a thromboembolic event in comparison with men with high concentrations (p = 0.013). Although it was not significant, there was a 1.4-fold excess incidence of stroke among men with intermediate concentrations of HDL cholesterol versus men whose HDL cholesterol levels were low. However, when HDL cholesterol was modeled as a continuous variable, findings suggested that the risk of stroke declines with rising levels of HDL cholesterol (p = 0.019).

Associations between HDL cholesterol and the risk of stroke also seemed to strengthen within important risk factor strata. In particular, as figure 1 shows, the risk of throm-
boembolic stroke declined consistently with increasing levels of HDL cholesterol for men with desirable total cholesterol concentrations (<5.2 mmol/liter (<200 mg/dl)) (<p> = 0.001) and men with hypertension (<p> = 0.012) or diabetes (<p> = 0.007). Data for men with borderline-high and high total cholesterol levels were combined, since too few stroke events were observed in the high range of total cholesterol values (six of 89 events). Although the effects of HDL cholesterol on the risk of stroke appeared to differ between the total cholesterol strata, the interaction between HDL cholesterol and total cholesterol was not significant. Presumably, this was due to limited statistical power resulting from

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Low: &lt;1.0 mmol/liter (&lt;40 mg/dl)</th>
<th>Intermediate: 1.0–1.5 mmol/liter (40–59 mg/dl)</th>
<th>High: ≥1.6 mmol/liter (≥60 mg/dl)</th>
<th>Test for trend (p value)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean total cholesterol level</td>
<td>4.7 (0.9)†</td>
<td>5.0 (0.8)</td>
<td>5.1 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mg/dl</td>
<td>180 (33)</td>
<td>192 (32)</td>
<td>196 (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>60.8</td>
<td>54.0</td>
<td>45.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>35.4</td>
<td>28.3</td>
<td>20.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>15.0</td>
<td>10.5</td>
<td>10.0</td>
<td>0.063</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>3.5</td>
<td>2.7</td>
<td>1.9</td>
<td>0.134</td>
</tr>
<tr>
<td>Mean body mass index‡</td>
<td>24.6 (2.7)</td>
<td>23.7 (3.0)</td>
<td>21.8 (3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean alcohol intake (ounces§/day)</td>
<td>0.6 (4.8)</td>
<td>0.5 (1.2)</td>
<td>0.9 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean physical activity index¶</td>
<td>30.4 (4.1)</td>
<td>31.2 (4.7)</td>
<td>31.4 (4.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Test for trend (p value)</th>
</tr>
</thead>
</table>

* Test of the significance of the association between high density lipoprotein cholesterol (when modeled as a continuous variable) and each risk factor after adjustment for age.
† Numbers in parentheses, standard deviation.
‡ Weight (kg)/height (m)².
§ 1 ounce = 28.4 g.
¶ A measure used to quantify overall metabolic output in a typical 24-hour period. For details, see Abbott et al. (18).
the low number of cases ($n = 89$) of thromboembolic stroke. Interactions between HDL cholesterol and hypertension and diabetes were less apparent and also not significant.

**DISCUSSION**

In this population-based sample of elderly men, low concentrations of HDL cholesterol ($<1.0$ mmol/liter ($<40$ mg/dl)) were more likely to be associated with a future risk of thromboembolic stroke than were high concentrations ($\geq 1.6$ mmol/liter ($\geq 60$ mg/dl)). Given the consistent decline in the risk of stroke with increasing levels of HDL cholesterol that was observed in this sample, data further suggest that stroke risk increases with each unit decline in HDL cholesterol level. Even after adjustment for other risk factors, the relation between HDL cholesterol and thromboembolic stroke was significant.
boembolic stroke persists. These findings are especially important because they are the first to have been observed in a sample of elderly men who were without stroke, coronary heart disease, or cancer when HDL cholesterol determinations were made. In addition, follow-up for stroke was prospective and was based on diagnoses that adhered to a rigid protocol of case ascertainment.

Findings further suggest that, in elderly men with a low total cholesterol level, hypertension, or diabetes, the association between HDL cholesterol and stroke may be more important than in other groups. Conversely, in the presence of high levels of HDL cholesterol, the effects of cholesterol, hypertension, and diabetes on the risk of stroke seem modest (see figure 1). Whether raising HDL cholesterol concentrations in the elderly can reduce the cardiovascular consequences associated with traditional risk factors warrants consideration. In the presence of low HDL cholesterol levels, control of hypertension and diabetes may be especially important. The association between HDL cholesterol and stroke risk observed when total cholesterol level is low is also consistent with findings from the Framingham Study, where significant associations occurred between HDL cholesterol and myocardial infarction among men in the bottom quartile of total cholesterol but not among men in quartiles that were higher (2).

While the Honolulu Heart Program has many strengths, study limitations prevent follow-up on several issues for which clarification is needed. For example, observations from the current sample were based on a single measurement of HDL cholesterol, and it is not known whether effects of HDL cholesterol on the risk of stroke are modified by unknown changes in HDL cholesterol levels over time. Levels of HDL cholesterol could also be reduced by both obesity and poor health. While simple adjustment for body mass index may be inadequate, with only 89 thromboembolic events it is difficult to explore the possibility that HDL cholesterol predicts stroke because it is a marker of poor health or subclinical frailty. Although there was a small excess incidence of stroke in men with a body mass index greater than 25, there was no clear excess incidence of stroke in men who were lean (body mass index, \(<22\)), nor was there an excess in men with cachexia (men who lost more than 15 percent of their body weight over a 25-year period). The removal of the leanest men, men with cachexia, and deaths and strokes that occurred within the first year of follow-up also failed to alter the reported findings. The exclusion of 32 percent (\(n = 1,192\)) of the original sample of 3,741 men because of prevalent stroke, coronary heart disease, or cancer may also have resulted in a sample of elderly men in which the confounding effects of frailty and poor health could have been minimized. For persons who are overtly frail, cachexic, or malnourished, the relation between HDL cholesterol and stroke may be more complex and may require further study.

In addition to stroke, low levels of HDL cholesterol have been independently and strongly linked with increased risk of coronary heart disease in a number of studies comprising largely middle-aged persons (1–9). To a far lesser extent, extensions to the elderly have been less clear (10–13). However, HDL cholesterol was inversely associated with the risk of ischemic stroke in an elderly multiethnic community in the Northern Manhattan Stroke Study (13). Although findings were similar to those described for the Honolulu sample, HDL cholesterol concentrations were measured after the stroke event had occurred among the selected cases. While it is uncertain whether stroke can influence HDL cholesterol levels, the current report provides some assurance that the findings from this case-control study are real.

Significant associations between HDL cholesterol levels and stroke were also found in an elderly Australian sample and in a study of subjects with hypertension who were enrolled in the Systolic Hypertension in the Elderly Program (22, 23). While the latter study comprised selected persons with isolated systolic hypertension, the Australian study was more focused on general risk factors for stroke, and no details were provided on stroke incidence by HDL cholesterol stratum or on possible differences in effects between men and women. In the Australian sample, 22 percent also had prevalent coronary heart disease and 6 percent had prevalent stroke (22). In addition, effects of sex on the association between HDL cholesterol and stroke risk could be important. Although design problems might have contributed to group differences, a report from a nested case-control analysis of four Northern European populations described a modest inverse association between HDL cholesterol and the risk of stroke in men, while in women, associations were positive (11).

Although they are limited to subjects with prevalent disease, clinical studies provide further evidence of an association between HDL cholesterol and stroke risk and support arguments for biologic mechanisms (24, 25). While one review reported that treatment with fibrates and niacin (alone or in combination with other lipid-lowering agents) can raise levels of HDL cholesterol (24), another suggested that therapeutic changes in HDL cholesterol concentrations induced by gemfibrozil can reduce rates of ischemic stroke significantly (25). Although the mechanistic relation between HDL cholesterol and thromboembolic stroke is not clear, it is possible that effects observed in these studies occurred through direct benefits from changes in HDL cholesterol, along with alterations in a number of atherogenic properties and common pathophysiologic antecedents for thrombosis and coronary heart disease (26, 27). Reverse cholesterol transport that is thought to be enhanced by increases in HDL cholesterol and its capacity to initiate the flux of cholesterol from peripheral cells to the liver is likely to be one of the most important factors in this relation. However, other investigators have shown that increases in HDL cholesterol levels resulting from treatment with benzafibrate are not associated with a reduced risk of cerebrovascular events (28).

In general, the relation between lipid levels and cardiovascular disease in the elderly is reported to be weak. In the Framingham Study, carotid stenosis in a sample of men whose average age was 75 years had a markedly reduced association with late-life cholesterol levels as compared with cholesterol levels measured earlier (29). It has also been noted in the Honolulu Heart Program that one-time assessment of total cholesterol level in late life could result in a poor measure of the real risk of disease if past cholesterol levels were high (30).
Associations of HDL cholesterol and other cholesterol measures with the risk of stroke in younger persons are also equivocal. The Atherosclerotic Risk in Communities Study found no relation between HDL cholesterol, low density lipoprotein cholesterol, or triglyceride levels and transient ischemic attack and stroke symptoms based on a standardized questionnaire and algorithm (31). The Framingham Study investigators and other researchers described an inverse relation between HDL cholesterol and ischemic stroke, but associations were weak and not significant (32, 33). In contrast, for men enrolled in the Israeli Ischemic Heart Disease Study, a significant 1.32-fold excess in the incidence of stroke was observed among persons in the lowest tertile of HDL cholesterol versus the highest (12).

The transition from a weak relation between HDL cholesterol and stroke in younger persons to one that is more apparent in the elderly sample in the Honolulu Heart Program could be due to age-related changes in the relation between several risk factors and stroke risk with advancing age (34). The question of whether declines in total cholesterol with advancing age (35, 36) can lead to a suppression of HDL cholesterol concentrations and important reductions in reverse cholesterol transport from peripheral cells to the liver warrants consideration. Other mechanisms that may become increasingly important in the elderly could include inflammatory properties of HDL cholesterol (37, 38) or the possibility that inflammation reduces the concentration of HDL cholesterol or inhibits its protective function (39).

While the current study was also based on a sample of Japanese-American men, results from the Northern Manhattan Stroke Study suggest that findings could extend to Caucasians, Hispanics, and African Americans (13). In general, risk factor associations in the Honolulu sample are similar to those that have been observed in other population-based samples (40, 41). In a recent comparison with the Framingham Study, the effect of risk factors on the incidence of stroke was shown to be quite similar (41).

In summary, these data indicate that HDL cholesterol is an important risk factor for thromboembolic stroke in the elderly. In conjunction with other risk factors, measurement of HDL cholesterol (commonly available from routine lipid screening) could become an increasingly useful tool for identifying elderly persons at high risk of stroke.

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