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Cognitive Impairment and Risk of Stroke

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Summary

Predictive value of the conventional risk factors for stroke attenuates with age. Cognitive impairment has been implicated as a potential predictor for stroke in older subjects. Our aim was to compare the Framingham stroke risk score with cognitive functioning for predicting first-time stroke in a cohort of the oldest-old individuals. We included 480 subjects aged 85 years old from the Leiden 85-plus Study. At baseline, data on the Framingham stroke risk score and the Mini-Mental State Examination (MMSE) score were obtained. Risk of first-time stroke was estimated in tertiles of Framingham and MMSE scores. Receiver operating characteristic curves with corresponding areas under the curves (AUC) and 95% confidence intervals (CI) were constructed for both Framingham and MMSE scores. Subjects with high Framingham risk score compared to those with low Framingham risk score did not have a higher risk of stroke (Hazard Ratio (HR): 0.77, 95% CI: 0.39-1.54). Conversely, subjects with high level of cognitive impairment compared to those with low level of cognitive impairment had a higher risk of stroke (HR: 2.85, 95% CI: 1.48-5.51). In contrast to the Framingham risk score (AUC: 0.48, 95% CI: 0.40-0.56), MMSE score had discriminative power to predict stroke (AUC: 0.65, 95% CI: 0.57-0.72). There was a significant difference between AUC for Framingham risk score and MMSE score (p=0.006). In the oldest-old, the Framingham stroke risk score is not predictive for first-time stroke. In contrast, cognitive impairment, as assessed by MMSE score, identifies subjects at a higher risk of stroke.
Introduction

Oldest old subjects form a growing part of the stroke population in developed countries\(^1\). Since stroke in very old age puts a great burden on patients and health care systems, novel strategies for early identification of very old subjects at high risk of stroke is crucial\(^2\).

With advancing age, conventional vascular risk factors such as hypertension and hypercholesterolemia lose their predictive value for stroke\(^3,4\). This phenomenon has raised doubt whether well-established predictive models such as Framingham stroke risk score, which were constructed based on such factors in middle age and younger elderly, can accurately identify very old subjects at high risk of stroke\(^5\). Cognitive impairment is common in old age and is strongly associated with brain vascular pathologies and disturbances in cerebrovascular hemodynamics\(^6\). Some studies have shown that impaired cognitive function is a potential predictor for first-time stroke in middle aged and younger elderly people\(^7,8\). Whether these findings can be extrapolated to very old subjects is unclear.

The Framingham stroke risk score has been validated in subjects younger than 85 years old\(^9\) and there is a lack of evidence on the predictive value of cognitive impairment for first-time stroke in the oldest old. The aim of our study was to investigate the performance of Framingham stroke risk score and cognitive impairment in predicting five-year risk of first-time stroke in a population-based sample of very old subjects. We hypothesized that level of cognitive impairment better predicts risk of stroke in the oldest old.

Material and methods

Study design and participants

The Leiden 85-plus Study is an observational, prospective population-based cohort study of inhabitants of Leiden, the Netherlands. Between September 1997 and September 1999, all inhabitants of 1912-1914 birth cohort (n = 705) were contacted in the month of their 85th birthday. There were no selection criteria on demographic features or health status. Fourteen people died before enrollment; a total of 599 (397 women and 202 men) subjects agreed to participate (85%). As described previously, there was no significant difference between the demographic features and health status of those who participated and those who did not\(^10\). In this analysis we excluded 61 subjects who had a previous stroke. In
addition, 58 subjects were excluded because of missing data for the components of Framingham risk score or cognitive function, leading to a final sample size of 480 subjects. All participants were visited at their homes, where they underwent face to face interview, physical examination, blood sampling, electrocardiography and cognitive assessment. The Medical Ethical Committee of the Leiden University Medical Centre approved the study, and informed consent was obtained from all subjects.

Vascular risk factors included in the Framingham stroke risk score

Blood Pressure

Blood pressure was measured at baseline in the seating position, using a mercury sphygmomanometer. During the home visits, two blood pressure measurements were done two weeks apart and average of these two measurements were used in the analyses. Blood pressure measurements were recorded after at least 5 min of rest and no vigorous exercise in the preceding 30 min. The systolic blood pressure (SBP) was measured at Korotkoff sound 1, and the diastolic blood pressure (DBP) was measured at Korotkoff sound 5. Use of antihypertensive medication was extracted from pharmacy records.

Diabetes mellitus

Diabetes mellitus was considered present when present in the records of the primary care physician, when non-fasting glucose concentrations were greater than 11.0 mmol/l, or when a participant was taking antidiabetic medication according to their pharmacy records.

Smoking

All participants were interviewed about present and past smoking habits. Current and past smokers of cigarettes, cigars, and pipes were judged to have a history of smoking.

Cardiovascular diseases

Data on history of cardiovascular diseases including coronary artery disease,
heart failure, or peripheral vascular disease were obtained through interviewing individual’s general practitioners or nursing home physicians.

*Electrocardiogram based left ventricular hypertrophy and atrial fibrillation*

Electrocardiograms were recorded on a Siemens Sicard 440 (Erlangen, Germany) and transmitted to the electrocardiograms core laboratory in the Glasgow Royal Infirmary for automated Minnesota coding. All electrocardiograms were reviewed to exclude coding errors due to technical causes. Left ventricular hypertrophy was defined by Minnesota codes 3-1-0, 3-3-0, or 3-4-0. Atrial fibrillation was defined as the presence of Minnesota Code 8-3-1.

*Cognitive assessment*

At baseline, global cognitive function was assessed in all participants using the Mini-Mental State Examination (MMSE). The MMSE assesses five areas of cognitive function: orientation, registration, attention and calculation, recall and language. The MMSE has a maximum score of 30 in which higher scores indicate better cognitive function. We categorized participants based on the tertiles of MMSE score to low (MMSE >27), intermediate (MMSE =25-27) and high (MMSE <25) levels of cognitive impairment.

*Stroke*

In the Netherlands detailed information on health status, emergency events and patients’ hospitalizations are all recorded with general practitioners. Occurrence of clinically recognized stroke during five years of follow up was assessed by annually interviewing general practitioners (for subjects living independently) or nursing home physicians (for subjects living in a nursing home). We used the World Health Organization definition of stroke of “rapidly developing clinical signs of focal (at times global) disturbance of cerebral functioning lasting > 24 hours” to identify subjects with stroke events. To obtain exact date of fatal stroke events, we retrieved specific data on causes of death from Statistics Netherlands, which assigns codes for all national death certificates according to the International Classification of Diseases and Related Disorders, 10th revision (ICD-10). Death due to stroke was classified as ICD-10 codes I60-I69.13

*Statistical analysis*
Characteristics of the study participants are reported as mean (standard deviation) for continuous variables and number (percentage) for categorical variables. Differences in values of continue parameters between participants who developed stroke and participants who did not were tested by independent samples t-tests. Differences in frequency of categorical parameters between the two groups were evaluated using Chi-Square tests. To assess the performance of Framingham risk score and MMSE score in prediction of stroke we used following analyses. First, incidence rate of stroke with corresponding 95% confidence intervals, in each tertile of Framingham and MMSE score was estimated by dividing the number of events by the person-year at risk. In addition, we compared cumulative incidence of stroke in tertiles of both Framingham and MMSE scores. Kaplan-Meier method was used and strata were compared with log-rank test. In the next step, hazard ratios with corresponding 95% confidence intervals for stroke outcomes (second and third tertile of Framingham and MMSE score versus first tertile as reference) were calculated using Cox regression models. Finally, receiver operating characteristic (ROC) curves with corresponding areas under the curves (AUC, neutral value 0.50= risk prediction by pure chance) and 95% confidence intervals were constructed for the Framingham risk score and MMSE score. Significant difference between area under the curve for the Framingham and MMSE scores was tested using Chi-Square test. All analyses were carried out using SPSS software (version 20.0.0, SPSS Inc., Chicago, IL) except for the comparing of the AUC of ROC curves which was performed by STATA version 10.0 (Stata Corp., College Station, TX).

**Results**

Table 1 summarizes baseline characteristics of the participants. During five years of follow up 56 subjects developed a stroke (incidence rate: 30.3 per 1000 person-year). At age 85 years, prevalence of cardiovascular diseases, diabetes mellitus, smoking, atrial fibrillation, left ventricular hypertrophy and use of antihypertensive medication was not statistically different in participants with and without stroke events in subsequent years (all \(P>0.05\)). Moreover, systolic and diastolic blood pressure at age 85 years was also similar in participants with and without stroke events in subsequent years (both \(P>0.05\)). In contrast, subjects who developed stroke had significantly lower MMSE score at age 85 years (\(P<0.001\)).

Figure 1 shows cumulative incidence of stroke by tertiles of Framingham and
Table 1. Baseline characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n=480)</th>
<th>Occurrence of stroke during follow up</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=480)</td>
<td>Yes (n=56)</td>
<td>No (n=424)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>163 (33.8)</td>
<td>16 (27.6)</td>
<td>147 (34.7)</td>
</tr>
<tr>
<td>History of CVD, n (%)</td>
<td>283 (58.7)</td>
<td>37 (66.1)</td>
<td>246 (58.0)</td>
</tr>
<tr>
<td>History of DM, n (%)</td>
<td>75 (15.6)</td>
<td>8 (14.3)</td>
<td>67 (15.8)</td>
</tr>
<tr>
<td>Ever smoking, n (%)</td>
<td>233 (48.3)</td>
<td>24 (42.1)</td>
<td>209 (49.3)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>42 (8.7)</td>
<td>6 (10.3)</td>
<td>36 (8.5)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, n (%)</td>
<td>48 (10.0)</td>
<td>8 (13.8)</td>
<td>40 (9.4)</td>
</tr>
<tr>
<td>Use of antihypertensive medication, n (%)</td>
<td>213 (44.3)</td>
<td>22 (38.6)</td>
<td>191 (45)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg mean (SD)</td>
<td>155 (18.3)</td>
<td>153.4 (20.1)</td>
<td>156 (18.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg mean (SD)</td>
<td>77 (9.3)</td>
<td>77.8 (9.8)</td>
<td>76.9 (9.3)</td>
</tr>
</tbody>
</table>

* P-value indicates significant difference between subjects with and without stroke occurrence

Abbreviations: CVD: cardiovascular diseases, DM: diabetes mellitus, BMI: body mass index, HDL: high density lipoprotein, LDL: Low density lipoprotein, SD: standard deviation, MMSE: mini mental state examination, IQR: inter quartile range
Chapter 9 – Cognitive Impairment and Risk of Stroke

Figure 1. Cumulative incidence of fatal and nonfatal stroke during five years of follow-up according to level the Framingham risk score (1-A) and cognitive impairment (1-B)

MMSE scores. There was no significant difference in cumulative incidence of stroke among subjects with low, intermediate and high Framingham risk scores (log-rank p=0.39). In contrast, there was a significant difference in cumulative incidence of stroke among subjects with low, intermediate and high levels of cognitive impairment (log-rank p=0.004).

Number of stroke events and risk of stroke in tertiles of Framingham and MMSE scores are presented in table 2. Incidence rate of stroke was 23.3 (95% CI: 11.1-35.5) per 1000 person-year in subjects with high Framingham risk score, 37.1 (95% CI: 21.9-52.3) per 1000 person-year in subjects with intermediate Framingham risk score and 30.2 (95% CI: 16.6-43.8) per 1000 person-year in subjects with low Framingham risk score. Incidence rate of stroke was 49.5 (95% CI: 31.2-67.8) per 1000 person-year in subjects with high level of cognitive impairment, 27.8 (95% CI: 13.7-41.9) per 1000 person-year in subjects with intermediate level of cognitive impairment and 17.4 (95% CI: 8.1-26.8) per 1000 person-year in subjects with low level of cognitive impairment. Furthermore, subjects with high Framingham risk score did not have a higher risk of stroke compared to those with low Framingham risk score (HR: 0.77, 95% CI: 0.39-1.54) whereas subjects with high level of cognitive impairment had a higher risk of stroke compared to those with low level of cognitive impairment (HR: 2.85, 95% CI: 1.48-5.51). We further explored whether cognitive performance predicts risk of first-time
stroke independent of socio-demographic and cardiovascular factors and found similar associations between cognitive impairment and risk of stroke (table S-1 http://stroke.ahajournals.org/content/44/7/1866/suppl/DC1).

Figure 2 shows the ROC curve for Framingham risk score as well as MMSE score in prediction of stroke events. Framingham risk score did not predict stroke (AUC 0.48, 95%CI: 0.40-0.56). Conversely, MMSE score had discriminative power to predict stroke (AUC 0.65, 95%CI: 0.57-0.72). The AUC for MMSE score was significantly higher than the AUC for Framingham stroke risk score (p=0.006). In addition, to explore whether the association between cognitive impairment and risk of stroke was not only dependent on subjects with very low cognitive function, in a sensitivity analysis, we excluded subjects with MMSE score 16 or less (n= 42) and found similar outcomes (data not shown). In another sensitivity analysis, to test whether our findings are not due to short term stroke events, we excluded subjects who developed stroke in the first year of follow-up (n=14). This sensitivity analysis showed that the predictive value of MMSE score for stroke is not dependent on short term stroke events (table S-2 http://stroke.ahajournals.org/content/44/7/1866/suppl/DC1 ).

Discussion

In a cohort of very old individuals without a previous history of stroke, we observed that Framingham stroke risk score, composed of conventional vascular
Table 2. Risk of stroke in relation to Framingham risk score and level of cognitive impairment

<table>
<thead>
<tr>
<th>Framingham five-year stroke risk</th>
<th>Number of participants</th>
<th>Number of stroke events</th>
<th>Incidence Rate* (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (3.7%-13.2%)</td>
<td>160</td>
<td>19</td>
<td>30.2 (16.6-37.2)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>Intermediate (13.3% -22.2%)</td>
<td>161</td>
<td>23</td>
<td>37.1 (21.9-52.3)</td>
<td>1.22 (0.66-2.42)</td>
<td></td>
</tr>
<tr>
<td>High (22.3%-97.4%)</td>
<td>159</td>
<td>14</td>
<td>23.3 (11.1-35.4)</td>
<td>0.77 (0.39-1.54)</td>
<td>0.501</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cognitive impairment</th>
<th>Number of participants</th>
<th>Number of stroke events</th>
<th>Incidence Rate* (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (MMSE&gt;27)</td>
<td>180</td>
<td>13</td>
<td>17.4 (8.0-26.9)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>Intermediate (MMSE 25-27)</td>
<td>136</td>
<td>15</td>
<td>27.8 (13.7-41.9)</td>
<td>1.59 (0.76-3.35)</td>
<td></td>
</tr>
<tr>
<td>High (MMSE&lt;25)</td>
<td>164</td>
<td>28</td>
<td>49.5 (31.1-67.8)</td>
<td>2.85 (1.48-5.51)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Incidence rates were estimated per 1000 person-year
Abbreviation: MMSE: mini mental state examination; HR: hazard ratio.
risk factors, did not predict risk of stroke. In contrast, impaired cognitive function assessed by low scores on the MMSE, identified subjects at higher risk of stroke.

A growing body of evidence indicates that the predictive value of conventional vascular risk factors for mortality and cardiovascular events attenuates with age.\textsuperscript{3,14-16} Previously, we reported that in very old people from the general population with no history of cardiovascular disease, risk factors such as hypertension, hypercholesterolemia, diabetes mellitus and left ventricular hypertrophy did not predict cardiovascular mortality.\textsuperscript{5} Consistently, results from the current study suggest that conventional vascular risk factors included in the Framingham stroke risk score may not predict higher risk of stroke in the oldest old. Well-established prediction models for stroke are basically designed for middle aged or younger elderly people.\textsuperscript{17} The Framingham stroke risk score is not an exception as it was constructed in a study population with an average age of 65 years and is validated for subjects younger than 85 years old.\textsuperscript{9} This might explain why the Framingham risk score in our study population consisting of very old age subjects did not predict risk of stroke.

Cognitive impairment is common in old age and has a clear association with brain vascular pathologies and disturbances in cerebrovascular hemodynamics.\textsuperscript{18-20} Thus, cognitive assessment has been proposed as a tool to identify younger elderly subjects at risk of stroke.\textsuperscript{8,21} In a population-based study including 9451 subjects aged 65 year and older, cognitive impairment was associated with a twofold increased risk for fatal incident stroke.\textsuperscript{22} Similarly, a recent large study on 30959 individuals older than 55 years at increased cardiovascular risk showed that impaired cognitive function is associated with a graded increase in risk of stroke.\textsuperscript{23} Findings of our study extend this evidence to the oldest old population and show that in very old age when the association between conventional vascular risk factors and cerebrovascular events is weak, cognitive assessment might be considered as a tool for identifying subjects at high risk of stroke. Given that the population of very old subjects is rapidly increasing worldwide and particularly in developed countries\textsuperscript{24}, our findings highlight a need for development of new prediction models for stroke in this age group and suggest that cognitive performance can be considered as a potential component in future prediction models.

We performed our analysis in the Leiden 85-plus study which is a population-based cohort with a relatively large number of participants, low attrition rate and a long follow up period. However, limitations of this study should be kept in mind when evaluating the results. Lack of neuro-imaging data to determine type of stroke can be marked as a limitation of this study although it is previously reported that the majority of strokes in very old age are of the ischemic type\textsuperscript{25}. 

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Moreover, silent strokes are frequently observed in older subjects\textsuperscript{26}. Therefore, there is a possibility that subjects in the group with high cognitive impairment had more clinically unrecognized strokes which predisposed them to the subsequent stroke events. In addition, we assessed level of cognitive impairment only based on MMSE scores. Since there is no single criterion or definition for cognitive impairment, MMSE may not be the optimum tool to evaluate level of cognitive impairment. Despite this limitation, MMSE is commonly used in clinical settings and no expertise is involved in its application which makes it an appropriate candidate for identification of the oldest old subjects at high risk of stroke\textsuperscript{27}. It is possible that cognitive tests such as Montreal Cognitive Assessment (MoCA) which are more sensitive to vascular cognitive impairment might better predict stroke events in old age\textsuperscript{28}.

In conclusion, we showed that the Framingham stroke risk score is not predictive for first-time stroke in a general population of the oldest-old individuals. In contrast, low cognitive function predicts higher risk of stroke in the oldest old. Assessment of cognitive function can be considered as an easily accessible tool to identify very old subjects at risk of stroke. Findings of this study need to be validated in the other cohorts of the oldest old people.


cholesterol and vascular mortality by age, sex, and blood pressure: A meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet. 2007;370:1829-1839


