Traditional Risk Factors for Incident Cardiovascular Events Have Limited Importance in Later Life Compared With the Health in Men Study Cardiovascular Risk Score

Christopher Beer, MB, BS; Helman Alfonso, PhD; Leon Flicker, PhD; Paul E. Norman, DS; Graeme J. Hankey, MD; Osvaldo P. Almeida, PhD

Background and Purpose—This study aimed to determine, among older men, the risk and independent significant baseline prognostic factors for first-ever stroke and MI.

Methods—We performed a prospective cohort study of 4382 community-dwelling older men (mean age, 75.4 ± 4.2 years) with no history of stroke or MI. Baseline data comprised questionnaire responses, clinical measurements, and comorbidity.

Results—After a median of 6 years (interquartile range, 5.2–7.2) of follow-up, the overall rate of stroke/MI was 2.61 (95% CI, 2.42–2.81) per 100 person-years. Among major traditional risk prediction variables, only age and smoking were significantly associated with stroke/MI. In our final multivariate model, the independent significant predictors of stroke/MI were age (HR for age older than 85, 3.18; 95% CI, 2.05–4.93), diastolic blood pressure <70 mm Hg (Hazard ratio [HR], 1.45; 95% CI, 1.18–1.78), high-sensitivity C-reactive protein >3 mg/L (HR, 1.29; 95% CI, 1.05–1.59), homocysteine >15 umol/L (HR, 1.35; 95% CI, 1.09–1.67), waist-to-hip ratio >1 (HR, 1.47; 95% CI, 1.20–1.18), and fair or poor self-reported health (HR, 1.52; 95% CI, 1.19–1.94). A new risk model incorporating these variables performed well compared with the Framingham risk equation (Harrell C of 0.660 versus C of 0.620; integrated discrimination improvement of 1.85%; z = 4.95; P < 0.001; net reclassification index of 0.08; z = 2.0; P = 0.023). The model was used to develop an 8-point clinical risk score comprising the independent predictors of stroke/MI among this population.

Conclusions—Traditional vascular risk factors did not optimally predict stroke/MI among this cohort of community-dwelling older men. We have constructed a new risk score that requires validation in other data sets. (Stroke. 2011; 42:00-00.)

Key Words: aging • myocardial infarction • risk factors • stroke

Age and the traditional vascular risk factors are major contributors to lifetime risk of vascular events and mortality.1 The effectiveness of lifestyle changes (such as smoking cessation), antiplatelet therapy, and the control of hypertension, dyslipidemia, and diabetes in the prevention of vascular events is established.2 These interventions are now the cornerstone of medical prevention of vascular diseases and have led to a decline in the incidence of stroke/MI in high-income countries.3 Despite these improvements, population aging will be associated with increased prevalence of vascular disease, presenting a need to further understand and ameliorate risk factors for cardiovascular events among older people. Commonly used cardiovascular risk charts are based on the Framingham risk equation, which was derived from individuals aged 30 to 74 years.4 Few older people have been included in observational studies and randomized trials of the effect of interventions to reduce vascular events.5 In addition, the association between individual traditional risk factors and cardiovascular risk appears to diminish among older people.6,7 and current risk prediction tools may not be applicable to this population.8 Assessment of nontraditional risk factors is not currently recommended for screening for coronary heart disease risk, although the need for further research is recognized.9

We undertook a prognostic study of community-based older men who were free of stroke and MI at baseline to: (1i) examine the performance of current risk prediction tools; (2)

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From the Western Australian Centre for Health and Ageing (C.B., H.A., L.F., O.P.A.), Centre for Medical Research, Western Australian Institute for Medical Research, Perth, Australia; School of Medicine and Pharmacology (C.B., L.F., G.J.H.), University of Western Australia, Perth, Australia; Department of Geriatric Medicine (C.B., L.F.), Royal Perth Hospital, Perth, Australia; School of Psychiatry and Clinical Neurosciences (O.P.A.), University of Western Australia, Perth, Australia; Department of Psychiatry (O.P.A.), Royal Perth Hospital, Australia, Perth, Australia; School of Surgery (P.E.N.), University of Western Australia, Perth, Australia; Stroke Unit (G.J.H.), Royal Perth Hospital, Perth, Australia.
The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
Correspondence to Christopher Beer, Level 6 Ainslie Hse, GPO Box X2213, Perth WA 6847, Australia. E-mail cbeer@graduate.uwa.edu.au

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determine the lifestyle and clinical factors that may influence risk of incident stroke and MI among community-dwelling older men; and (3) determine participants’ future risks of fatal and nonfatal stroke and MI.

Methodology

Study Design

The Health in Men Study (HIMS) is a prospective cohort study.

Setting

HIMS recruited community-dwelling older men in Perth, Western Australia. Of 19,552 men randomly selected from the electoral roll and invited to participate, 12,203 (63%) men aged between 65 and 83 years attended for screening in the Western Australian randomized controlled trial of screening for abdominal aortic aneurysms between April 1996 and January 1999. Between 2001 and 2004, 10,940 surviving members of this cohort were invited to complete a risk factor survey and a face-to-face clinical review.

Participants

Five thousand five hundred eighty-three men completed the risk factor survey. We excluded participants (n = 1,211) with a history of stroke (n = 330), MI (n = 746), or both (n = 125) before baseline using a search of all available inpatient and outpatient diagnosis fields recorded in the Western Australian Data Linkage System dating back to 1988. The Western Australian Data Linkage System is a comprehensive population-based linkage system that connects together up to 40 years of data for >30 collections for residents of Western Australia. All diagnostic fields were included to ascertain a history of stroke/MI among participants not admitted for the actual event. Participants were thus 4,382 older men who enrolled in HIMS and were free from a history of stroke/MI at baseline, of whom 3,382 consented to donate a blood sample.

Baseline Measures: Clinical Features

Participants were invited to undergo physical examination, provide an early morning blood sample, and complete a brief cognitive assessment. Girth at hips and waist (in centimeters) and blood pressure were measured using standard procedures. Blood samples were collected between 0800 and 1030 hours, and assays were performed on the day of collection. Assays were performed in the Biochemistry Department, PathWest, Royal Perth Hospital, Western Australia, to determine glucose, homocysteine, lipids, creatinine, and high-density lipoprotein cholesterol, and triglycerides were assayed using a Roche Immunoassay (Immulite 2000; Diagnostic Products). The coefficient of variation for creatinine were 6.6% at 70.5 μmol/L and 2.4% at 484 μmol/L; for glucose, coefficients of variation were 2.9% at 4.8 mmol/L and 2.2% at 15.2 mmol/L; for cholesterol, coefficients of variation were 2.3% at 3.2 mmol/L and 2.1% at 6.7 mmol/L; for high-density lipoprotein, coefficients of variation were 2.4% at 0.8 mmol/L and 2.5% at 1.7 mmol/L; and for triglycerides, coefficients of variation were 4.8% at 0.9 mmol/L and 2.4% at 2.0 mmol/L. CRP was measured using particle-enhanced immunonephelometry using a Dade Behring BNII analyzer (Dade Behring Marburg GmbH). Between-day imprecision was 8.0% at 0.36 mg/L, 4.5% at 4.13 mg/L, 5.2% at 13.5 mg/L, and 3.2% at 51.3 mg/L. Homocysteine concentrations were determined using competitive immunoassay (Immulite 2000; Diagnostic Products). The coefficient of variation was 7.3% at 12.4 μmol/L and 7.0% at 34.6 μmol/L. Creatinine and age were used to calculate an estimate of glomerular filtration rate using the Modification of Diet in Renal Disease study formula.13 Cognitive function was assessed with the standardized Mini-Mental State Examination, a structured version of the original Folstein Mini-Mental State Examination.14 Smoking history, included in the questionnaire, was categorized into smoker (current or past) and nonsmoker. Western Australian Data Linkage System inpatient data were used to assign a baseline comorbidity profile to each participant. This was based on the Charlson Index,15 which was applied to the 10-year period before baseline. The Charlson Index identifies 17 common medical conditions: myocardial infarction, congestive heart failure, peripheral arterial disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes (including diabetes with end-organ damage), hemiplegia, renal disease, leukemia, lymphoma, other tumors, metastatic tumors, and AIDS.

Follow-Up and Outcome Events

Patients were followed-up by means of the Western Australian Data Linkage System between the date of HIMS recruitment (2001–2004) and October 15, 2009 (or death if sooner). The primary outcome of the study was incident stroke/MI, defined as a stroke (fatal and nonfatal) or MI (fatal and nonfatal), and was collected using the Western Australian Data Linkage System. Incident stroke/MI during follow-up was identified by searching all available diagnosis fields (to ascertain a history of stroke/MI among participants not admitted for the actual stroke/MI event). The International Classification of Disease codes for stroke and TIA were 362.3, 430, 433.x1, 434.x1, 435, 436, G45, H34.1, I60, I61, and I67-6 and for MI were 410, 411, and I21.x.

Statistical Analysis

Data were analyzed using the statistical software package Stata (version 11, StataCorp). We used Cox proportional hazards regression modeling to examine the association of vascular risk factors with incident stroke/MI. This commenced with a series of univariate models to identify all candidate predictor variables. Continuous variables were evaluated as such and, when possible, as categories to increase the potential clinical utility of any final risk model. CRP concentration was >3.0 mg/L and was considered elevated.16 Hyperhomocysteinemia was defined as a homocysteine concentration of ≥15 μmol/L.17 Diastolic blood pressure was categorized at 70 mm Hg based on the point of inflection of a plot of risk of stroke/MI. Charlson Index scores were categorized (0, 1 or 2, 3, and ≥4). The waist-to-hip ratio was dichotomized (≥1 or <1). Age was categorized in 5-year increments. Body mass index was categorized as normal (25 <30), overweight (≥25 <30), or obesity (≥30). Mini-Mental State Examination scores were handled as a binary variable with cut-point of 24 to indicate cognitive impairment. Other continuous variables (such as estimates of glomerular filtration rate, creatinine, systolic blood pressure) were categorized by quartiles. Self-reported health was dichotomized as poor/fair compared with good/excellent. Variables with P <0.1 were then included in a multivariate Cox regression model and removed using a backward stepwise process if their significance was not retained. No violations of the Cox proportionality assumption (assessed by scale Schoenfeld residuals during follow-up) were detected. Goodness of fit of the model was evaluated by plotting the observed number of failures in the data and the number predicted in the model by using Martingale residuals.18 We determined the association between incident stroke/MI and risk factors identified in current risk prediction tools using Cox regression.

To compare this HIMS cardiovascular risk model (HIMS-CVR) with the traditional Framingham model,19 we initially compared their Harrell C statistics, which measure discrimination ability by indicating the correct ranking of each individual’s risk. Harrell C statistic of 0.5 indicates random assignment. We also assessed discrimination of the new model compared to the Framingham risk equation by calculating the integrated discrimination improvement.20 We then compared calibration of these models by examining how close the predicted risks were to the observed risk for each decile of risk. Finally, we constructed a reclassification table and graph for people with and without stroke/MI and determined the net reclassification improvement.20 The reclassification table compared participants according to quartiles of risk calculated with the HIMS-CVR and Framingham risk equation.
We then converted the HIMS-CVR to a clinical risk scoring system (HIMS-CVR score [HIMS-CVRS]) by inspecting the B-coefficients associated with each independent predictor of stroke/MI and assigning points values to categories accordingly. We calculated the risk of stroke/MI over the course of 6 years for each increment of the HIMS-CVRS. To do this, we determined the distance of each category from the base category in regression units and set the fixed multiplier to the risk associated with a 6-year
increase in age.\textsuperscript{22} We then compared the risk predicted using the model coefficients against the risk predicted using the points from the score system. Finally, we used Poisson regression modeling to build a matrix of rates of stroke/MI comprising the independent model coefficients against the risk predicted using the points from the score system. Finally, we used Poisson regression modeling to build a matrix of rates of stroke/MI comprising the independent predictors of stroke/MI among this population.

Ethics Approval
The Health Department of Western Australia and the Human Research Ethics Committee of the University of Western Australia approved the study. All participants provided written informed consent.

Results
Participants and Rate of Stroke/MI
The cohort comprised 4382 men with a mean age of 75.4 years (SD, 4.2). Baseline clinical characteristics of the cohort are described in Table 1. Median follow-up was 6 years (interquartile range, 5.2–7.2). During this period, we identified 686 men with incident stroke/MI (overall rate, 2.61; 95% CI, 2.42–2.81 per 100 person-years).

Risk Profile for Incident Stroke/MI in This Cohort
In univariate analyses (Table 1), age, smoking, comorbidity (both Charlson score and self-reported history of hypertension, diabetes, arthritis, respiratory disease, and depression), central obesity, visual or cognitive impairment, poor self-reported health, estimate of glomerular filtration rate, diastolic hypotension, hyperhomocysteinemia, and elevated CRP were associated with incident stroke/MI. However, in the final parsimonious multivariate model (Table 2), only age (HR for age 85 or older, 3.18; 95% CI, 2.05–4.93), diastolic blood pressure $\leq 70$ mm Hg (HR, 1.45; 95% CI, 1.18–1.78), high-sensitivity CRP $\geq 3$ mg/L$^{-1}$ (HR, 1.29; 95% CI, 1.05–1.59), homocysteine $\geq 15$ umol/L$^{-1}$ (HR, 1.35; 95% CI, 1.09–1.67), waist-to-hip ratio $> 1$ (HR, 1.47; 95% CI, 1.20–1.18), and fair or poor self-reported health (HR, 1.52; 95% CI, 1.19–1.94) remained independently associated with incident stroke/MI.

Utility of Framingham Risk Equation-Based Prediction Tools
The risk of stroke/MI among this population, described according to the risk factors identified in current risk assessment tools, is summarized in Table 3. Traditional vascular risk factors (diabetes, cholesterol, and blood pressure) were not independently associated with incident stroke/MI in this cohort, with the exception of age (relative risk for age 85 or older, 4.87; 95% CI, 3.00–7.89) and smoking (relative risk, 1.67; 95% CI, 1.12–2.50).

Assessment of the HIMS-CVR
The HIMS-CVR, comprising age group, diastolic blood pressure $\leq 70$ mm Hg, high-sensitivity CRP $\geq 3$ mg/L$^{-1}$, homocysteine $\geq 15$ umol/L$^{-1}$, waist-to-hip ratio $> 1$, and fair or poor self-reported health, performed well compared to the Framingham risk equation in prediction of stroke/MI among the cohort. Harrell C statistic for the HIMS-CVR was 0.66 compared with 0.62 for the Framingham risk equation. The integrated discrimination improvement associated with the HIMS-CVR compared to the Framingham risk equation was 1.85% ($\Delta C=0.005$). Calibration figures comparing observed and expected events for each decile of risk calculated using the HIMS-CVR and the Framingham risk equation models are presented in Figures 1 and 2.

Table 2. Multivariate Parsimonious Cox Proportional Hazards Model of Vascular Predictors of Stroke/MI Among Community-Dwelling Older Men

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Age 75–79 yr</td>
<td>1.62 (1.29-2.03)</td>
</tr>
<tr>
<td>Age 80–84 yr</td>
<td>2.10 (1.61-2.74)</td>
</tr>
<tr>
<td>Age 85 yr or older</td>
<td>3.69 (2.42-5.63)</td>
</tr>
<tr>
<td>Diastolic blood pressure $\leq 70$ mm Hg</td>
<td>1.46 (1.20-1.77)</td>
</tr>
<tr>
<td>Homocysteine $\geq 15$ umol/L$^{-1}$</td>
<td>1.35 (1.11-1.64)</td>
</tr>
<tr>
<td>Waist-to-hip ratio $&gt; 1$</td>
<td>1.41 (1.15-1.72)</td>
</tr>
<tr>
<td>Fair/poor self-reported health</td>
<td>1.51 (1.19-1.91)</td>
</tr>
</tbody>
</table>

Table 3. Multivariate Cox Regression Analysis of Association Between Traditional Risk Factors and Stroke/MI Among Community-Dwelling Older Men

<table>
<thead>
<tr>
<th>Risk Factor*</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.20 (0.92-1.56)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.70 (1.19-2.42)</td>
</tr>
<tr>
<td>Age 75–79 yr</td>
<td>1.80 (1.45-2.23)</td>
</tr>
<tr>
<td>Age 80–84 yr</td>
<td>2.39 (1.86-3.07)</td>
</tr>
<tr>
<td>Age 85 yr or older</td>
<td>4.43 (2.95-6.64)</td>
</tr>
<tr>
<td>Total cholesterol:HDL 5</td>
<td>1.10 (0.88-1.37)</td>
</tr>
<tr>
<td>Total cholesterol:HDL 6</td>
<td>1.07 (0.85-1.34)</td>
</tr>
<tr>
<td>Total cholesterol:HDL 7-9</td>
<td>0.91 (0.74-1.12)</td>
</tr>
<tr>
<td>BP $\geq 140/85 (&lt;160/95)$</td>
<td>0.81 (0.62-1.05)</td>
</tr>
<tr>
<td>BP $\geq 160/95 (&lt;180/105)$</td>
<td>0.78 (0.51-1.19)</td>
</tr>
<tr>
<td>BP $\geq 180/105$</td>
<td>1.20 (0.92-1.56)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; HDL, high-density lipoprotein.
*Baseline groups were age 69–74 years for age, 1–4 for total cholesterol:HDL, and $<140/85$ mm Hg for BP.

Figure 1. Calibration of Health in Men Study cardiovascular risk model: observed and expected events by deciles of risk.
Participants who did not experience a stroke/MI, classification improved for 601 using the HIMS-CVR and deteriorated for 557 (net gain in reclassification proportion 0.017; \( z = 1.29; P = 0.098 \)). The overall net reclassification index for the HIMS-CVR was 0.076 (\( z = 2.0; P = 0.023 \)). A scatter plot of risk predicted by the HIMS-CVR compared to the Framingham risk equation is presented at Figure 3.

Development and Assessment of the HIMS-CVRS and Risk Matrix
The HIMS-CVR risk assessment matrix, comprising the significant independent risk factors for stroke/MI, among this cohort of community-dwelling older men is presented in Figure 4.

We translated the HIMS-CVR to an 8-point clinical risk score (HIMS-CVRS) by assigning 1 point to the adverse category of each of the binomial variables (ie, diastolic blood pressure >70 mm Hg, 0 points; diastolic blood pressure \( \leq 70 \) mm Hg, 1 point; CRP <3, 0 points; CRP \( \geq 3 \), 1 point; homocysteine <15, 0 points; homocysteine \( \geq 15 \), 1 point; waist:hip ratio <1, 0 points; waist:hip ratio \( \geq 1 \), 1 point; good self-reported health, 0 points; poor self-reported health, 1 point) and assigning 0 to 3 points according to the categories of age (ie, age 69–74, 0 points; 75–79 years, 1 point; 80–84 years, 2 points; 85 years or older, 3 points). Estimation of risk using the resulting HIMS-CVRS performed similarly to the full HIMS-CVR model (Table 4) with no substantial difference in risk estimates for people in each of the 8 categories of the HIMS-CVRS.

Discussion
Our results show that traditional vascular risk factors are less useful in predicting future stroke/MI among community-dwelling older men than in young men. Instead, the independent predictors of stroke/MI in this population were age, diastolic hypotension, elevated CRP or homocysteine, central obesity, and poor self-perceived health. The risk score we have developed presents a simple and potentially useful approach to improve the assessment of cardiovascular risk among community-dwelling older men.

Diastolic blood pressure was independently associated with stroke/MI in this cohort of older men. Other cohort studies also have observed an association between lower blood pressure and poorer health outcomes. For example, in a sample of older hypertensive men and women older than age 80, of whom 84.5% were receiving antihypertensive medication, systolic blood pressure levels <140 mm Hg were associated with shorter survival (independent of known predictors of death). Nonetheless, we cannot dismiss entirely the possibility that the association between low diastolic blood pressure and stroke/MI has been confounded by other unmeasured factors, such as previous cardiovascular diseases other than MI. Furthermore, these data should be considered in light of evidence that antihypertensive therapy is beneficial among older people who are hypertensive.

Systemic low-grade inflammation, measured using CRP, remained independently associated with incident stroke/MI among this cohort, suggesting an association between clinical or subclinical inflammatory processes and stroke/MI. However, other data are conflicting. For example, genetic deter-
minants of CRP levels are not strongly related to risk of coronary heart disease, indicating that the association between CRP and heart disease may not be causal. Notwithstanding these cautions, our findings are consistent with recent intervention trials establishing that rosuvastatin therapy reduced stroke/MI among participants free from known cardiovascular disease and with CRP levels. The present data suggest that these results (among relatively young participants; mean age, 66 years) also may be relevant to older men. Our data support the rationale of evaluating the anti-inflammatory hypothesis in patients with cardiovascular disease and suggest that the appropriate management of inflammation may be a valuable strategy to minimize the risk of cardiovascular events among older community-dwelling men.

There are now many data suggesting that homocysteine is an independent risk factor for cardiovascular disease. However, to date, homocysteine-lowering interventions have not been effective in the prevention of cardiovascular diseases, although meta-analysis of the available data suggested that homocysteine-lowering treatment with folate may decrease the risk of stroke by 18%. Thus, some uncertainty persists regarding whether hyperhomocysteinemia is causally related to cardiovascular disease. Notwithstanding these controversies, our results indicate that detection of hyperhomocysteinemia may be useful for cardiovascular risk stratification among community-dwelling older men. Similarly, central obesity is a recognized risk factor for stroke/MI. Our results suggest that waist-to-hip ratio measurement should be incorporated into risk assessments for community-dwelling older men. Self-perceived health is also thought to be an independent predictor of mortality, albeit not consistently. The present data suggest that self-perceived health is an independent predictor of future cardiovascular events among community-dwelling older men.

Limitations and Generalizability
Our stroke/MI incidence data rely on administrative coding of stroke/MI, which was not subjected to external validation. Despite periodic auditing of hospital morbidity data, the administrative coding of diagnoses may be somewhat heterogeneous. The degree of error of diagnostic coding for stroke/MI
remains uncertain but is likely to be small.32,33 We have tried to guard against overascertainment and underascertainment of stroke/MI diagnoses by choosing International Classification of Diseases codes that optimize detection of stroke/TIA, although some authors have utilized more34 or less35 restrictive definitions. In addition, our data are observational, and reverse causality and residual confounding cannot be dismissed. Moreover, because we did not have access to data on treatment, we were unable to take the effects of therapy into account in our models. Generalizability of our data is limited by the inclusion of participants of only 1 gender and the potential for healthy volunteer bias. The potential for volunteer bias is limited to some extent by the population-based nature of the original HIMS cohort and the use of follow-up administrative data (which is not subject to volunteer bias).

Conclusions

Among a cohort of community-dwelling older men, those who experienced a stroke or MI during follow-up, compared with those who remained free from these cardiovascular events, were older, had lower diastolic blood pressure, and had greater waist-to-hip ratio than men who remained free from stroke/MI. In addition to the traditional vascular risk factors of age and smoking, diastolic hypotension, elevated high-sensitivity C-reactive protein, hyperhomocysteinemia, central obesity, and self-reported health status should be considered in the evaluation of cardiovascular risk among community-dwelling older men. If our findings are validated externally, then the risk score we have developed may be useful in the assessment of cardiovascular risk among community-dwelling older men.

Acknowledgments

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Table 4. Risk Estimated Using the HIMS-CVRS Compared With Risk Estimated Using the HIMS-CVR Model

<table>
<thead>
<tr>
<th>HIMS-CVRS (Points)</th>
<th>HIMS-CVRS Point Score</th>
<th>HIMS-CVR Regression Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.9</td>
<td>5.9</td>
</tr>
<tr>
<td>1</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>2</td>
<td>6.8</td>
<td>6.6</td>
</tr>
<tr>
<td>3</td>
<td>7.2</td>
<td>6.9</td>
</tr>
<tr>
<td>4</td>
<td>7.6</td>
<td>7.3</td>
</tr>
<tr>
<td>5</td>
<td>8.0</td>
<td>7.7</td>
</tr>
<tr>
<td>6</td>
<td>8.5</td>
<td>8.3</td>
</tr>
<tr>
<td>7</td>
<td>8.9</td>
<td>8.7</td>
</tr>
<tr>
<td>8</td>
<td>9.3</td>
<td>9.2</td>
</tr>
</tbody>
</table>

HIMS-CVR indicates Health in Men Study cardiovascular risk; HIMS-CVRS, Health in Men Study cardiovascular risk score.

Sources of Funding

National Health and Medical Research Council of Australia (project grants 279408, 379600, 403963, and 513823) and MBF Foundation (grant number DS 080608).

Disclosure

None.

References


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Original Contributions

Traditional Risk Factors for Incident Cardiovascular Events Have Limited Importance in Later Life Compared With the Health in Men Study Cardiovascular Risk Score

Christopher Beer, MB, BS; Helman Alfonso, PhD; Leon Flicker, PhD; Paul E. Norman, DS; Graeme J. Hankey, MD; Osvaldo P. Almeida, PhD

Background and Purpose: This study aimed to determine the risk and independent predictors of incident stroke and myocardial infarction in a cohort of community-dwelling older men.

Methods: A prospective cohort study of 4382 men (mean age 75.4 ± 4.2 years) with no history of stroke or myocardial infarction was conducted. Baseline data included questionnaires, clinical parameters, and co-morbid conditions.

Results: After a mean follow-up of 6 years (interquartile range 5.2-7.2), incident stroke/myocardial infarction rate was 2.61 (95% CI, 2.42-2.81)/100 person-years. The traditional risk factors that were significant predictors included age (HR > 85 years: HR = 3.18; 95% CI, 2.05-4.93), systolic blood pressure <70 mmHg (HR, 1.45; 95% CI, 1.18-1.78), C-reactive protein >3 mg/L (HR, 1.47; 95% CI, 1.20-1.18), white blood cell count >15 ×10^9/L (HR, 1.52; 95% CI, 1.19-1.94), and self-rated health (HR, 1.52; 95% CI, 1.19-1.94).

Conclusion: Traditional vascular risk factors do not predict stroke/myocardial infarction in older men as well as cardiovascular risk scores have been developed for this group. The new model has a higher overall discrimination (Harrell C = 0.660 vs 0.620; z = 4.95, P < 0.001; net reclassification index = 0.08; z = 2.00, P = 0.023).

Keywords: Age, Myocardial infarction, Risk factors, Stroke

From the Western Australian Centre for Health and Ageing (C.B., H.A., L.F., O.P.A.), Centre for Medical Research, Western Australian Institute for Medical Research, Perth, Australia; School of Medicine and Pharmacology (C.B., L.F., G.J.H.), University of Western Australia, Perth, Australia; Department of Geriatric Medicine (C.B., L.F.), Royal Perth Hospital, Perth, Australia; School of Psychiatry and Clinical Neurosciences (O.P.A.), University of Western Australia, Perth, Australia; Department of Psychiatry (O.P.A.), Royal Perth Hospital, Australia; School of Surgery (P.E.N.), University of Western Australia, Perth, Australia; Stroke Unit (G.J.H.), Royal Perth Hospital, Perth, Australia.

Correspondence to Christopher Beer, Level 6 Ainslie Hse, GPO Box X2213, Perth WA 6847, Australia. E-mail cdbeer@graduate.uwa.edu.au

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Method

Background


参与者

5583 例男性完成危险因素调查。我们通过西澳大利亚数据联合系统对 1988 年以后所有可用的住院和门诊病人的诊断记录进行筛查，排除基线前有卒中史（n=330）、心肌梗死（n=746）或两者兼有（n=125），共 1201 例。西澳大利亚数据联合系统是一个以人口为基础的综合性联合系统，整合了西澳大利亚居民近 40 年来 30 多个数据库的数据 [12]。全部诊断信息包括确定的卒中/心肌梗死病史但未住院的参与者。最后有 4382 例在基线水平没有卒中/心肌梗死病史的老年男性纳入 HIMS，其中 3382 例同意抽血检查。

基线测量值：临床特点

参与者进行了体格检查、清晨抽血并完成简单认知评估。按标准程序测量腰臀围（单位：cm）和血压。血标本在 08:00 至 10:30 抽取并当天化验。标准化验在西澳大利亚皇家柏斯医院生化室进行，包括血糖、同型半胱氨酸、脂类、肌酐、甘油三酯、高密度和低密度脂蛋白及超敏 C 反应蛋白 (CRP) 浓度。肌酐、空腹血糖、总胆固醇、高密度脂蛋白胆固醇和甘油三酯用 Roche Hitachi 917 分析仪 (Roche Diagnostic GmbH) 测定。肌酐浓度在 70.5 μmol/L 时，变异系数分别为 6.6% 和 4.1%；血糖浓度在 4.8 mmol/L 和 15.2 mmol/L 时，变异系数分别为 2.9% 和 2.2%；胆固醇浓度在 3.2 mmol/L 和 6.7 mmol/L 时，变异系数分别为 2.3% 和 2.1%；高密度脂蛋白浓度在 0.8 mmol/L 和 1.7 mmol/L 时，变异系数分别为 2.4% 和 2.5%；甘油三酯浓度在 0.9 mmol/L 和 2.0 mmol/L 时，变异系数分别为 4.8% 和 2.4%。CRP 浓度用 Dade Behring BNII 分析仪 (Dade Behring Marburg GmbH) 经颗粒增强免疫比浊法测定，日间不精密度在 0.36 mg/L、4.13 mg/L、13.5 mg/L 和 51.3 mg/L 时分别为 8.0%、4.5%、5.2% 和 3.2%。同型半胱氨酸浓度通过竞争性免疫测定法 (Immulite 2000；诊断性产品) 测定。其浓度在 12.4 μmol/L 和 34.6 μmol/L 时变异系数分别为 7.3% 和 7.0%。采用肾脏疾病饮食研究改良公式将肌酐和年龄用于估算肾小球滤过率 [13]。Charlson 指数能鉴定 17 种常见疾病：心肌梗死、充血性心衰、外周动脉病、脑血管病、痴呆、慢性肺病、结缔组织病、溃疡病、肝病、糖尿病（包括糖尿病伴终末器官损害）、偏瘫、肾病、白血病、淋巴瘤、其它肿瘤、转移瘤以及艾滋病。

随访和终点事件

通过西澳大利亚数据联合系统在 HIMS 招募期（2001-2004）至 2009 年 10 月 15 日期间（或者短期内死亡）对患者进行随访。主要终点事件是新发卒中/心肌梗死，明确为卒中（致命性和非致命性）或心肌梗死（致命性和非致命性）。资料通过西澳大利亚数据联合系统收集。随访期间新发卒中/心肌梗死由全部可用的诊断信息（确定有卒中/心肌梗死病史但未在卒中/心肌梗死急性期住院的参与者）进行鉴定。卒中和短暂性脑缺血发作 (TIA) 的国际疾病分类编码为 362.3, 430, 431, 433.x1, 434.x1, 435, 436, G45, H34.1, I60, I61 和 I6-7, 心肌梗死的国际疾病分类编码为 410, 411 和 I21.x。

统计分析

数据利用 SPSS 11.0 (StataCorp.) 进行分析。经 Cox 比例风险回归模型验证血管危险因素与卒中/心肌梗死事件的关联性。首先通过一系列单变量模型检验所有备选预测变量，依次评价连续变量，如情况允许，加以分类以增加任何最终风险模型潜在的临床效用。CRP 浓度 >3.0 mg/L 视为升高 [16]。高同型半胱氨酸血症定义为同型半胱氨酸浓度 >15 μmol/L [17]。舒张压值根据卒中/心肌梗死风险图在拐点 70 mmHg 时进行分类。Charlson 指数评分分为 0、1 或 2、3 或 4、及 >5。腰臀比分为 >1 或 ≤1。年龄每 5 岁为一组。
体重指数分为正常 (25-30)、体重过轻 (<25) 或超重 (≥30)。简易精神状态检查评分以 24 分为分界值作为二元变量评定认知损害程度。其它连续性变量 (如肾小球滤过率、肌酐、收缩压的评估) 按四分位数进行分类。自评健康以差/中等、好/优秀进行二分类。P<0.1 的变量被引入多变量 Cox 回归模型, 通过逐步向后法将无显著性差异的因子剔除。没有检测到违背 Cox 比例假定 (由随访过程中 Schoenfeld 残差表评定)。利用数据中失效的观察值和模型中的预测值绘制残差图评估模型拟合优度[18]。通过 Cox 回归确定新发卒中/心肌梗死与经新的风险预测方法验证的危险因素之间的关联性。
表 2 社区老年男性卒中/心肌梗死血管预测因素多变量精简 Cox 比例风险模型
<table>
<thead>
<tr>
<th>危险因素</th>
<th>风险比 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄 75-79 岁</td>
<td>1.62 (1.29-2.03)</td>
</tr>
<tr>
<td>年龄 80-84 岁</td>
<td>2.10 (1.61-2.74)</td>
</tr>
<tr>
<td>年龄 ≥85 岁</td>
<td>3.69 (2.42-5.63)</td>
</tr>
<tr>
<td>舒张压 ≤70 mmHg</td>
<td>1.46 (1.20-1.77)</td>
</tr>
<tr>
<td>C 反应蛋白 ≥3.0 mg/L</td>
<td>1.35 (1.11-1.64)</td>
</tr>
<tr>
<td>同型半胱氨酸 ≥15 μmol/L</td>
<td>1.41 (1.15-1.72)</td>
</tr>
<tr>
<td>腰臀比 &gt;1</td>
<td>1.51 (1.19-1.91)</td>
</tr>
</tbody>
</table>

表 3 社区老年男性传统危险因素与卒中/心肌梗死关联性多变量 Cox 回归分析
<table>
<thead>
<tr>
<th>危险因素*</th>
<th>风险比 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>糖尿病</td>
<td>1.20 (0.92-1.56)</td>
</tr>
<tr>
<td>吸烟</td>
<td>1.70 (1.19-2.42)</td>
</tr>
<tr>
<td>年龄 75-79 岁</td>
<td>1.80 (1.45-2.23)</td>
</tr>
<tr>
<td>年龄 80-84 岁</td>
<td>2.39 (1.86-3.07)</td>
</tr>
<tr>
<td>年龄 ≥85 岁</td>
<td>4.43 (2.95-6.64)</td>
</tr>
<tr>
<td>总胆固醇: HDL 5</td>
<td>1.10 (0.88-1.37)</td>
</tr>
<tr>
<td>总胆固醇: HDL 6</td>
<td>1.07 (0.85-1.34)</td>
</tr>
<tr>
<td>总胆固醇: HDL 7-9</td>
<td>0.91 (0.74-1.12)</td>
</tr>
<tr>
<td>BP ≥140/85 (&lt;160/95) mmHg</td>
<td>0.81 (0.62-1.05)</td>
</tr>
<tr>
<td>BP ≥160/95 (&lt;180/105) mmHg</td>
<td>0.78 (0.51-1.19)</td>
</tr>
<tr>
<td>BP ≥180/105 mmHg</td>
<td>1.20 (0.92-1.56)</td>
</tr>
</tbody>
</table>

将 HIMS 心血管风险模型 (HIMS-CVR) 与传统 Framingham 模型[19] 进行比较，我们最初比较它们的 Harrell C 统计值，后者通过标示每个个体风险的正确等级来衡量分辨力。Harrell C 统计值为 0.5 表明随机分配。通过计算综合判别改善与 Framingham 风险方程式比较以评价新模型的分辨力[20]。然后通过检查预测风险与实测风险每个十分位值的接近度比较这些模型的校准值。最后，我们对伴或不伴卒中/心肌梗死人群建立重新分类图表并确定网络重新分类改善[20]。重新分类表根据 HIMS-CVR 和 Framingham 风险方程式计算得出的风险四分位值对参与者进行比较。接下来我们通过检验与卒中/心肌梗死每个独立预测因素相关的 B 系数及赋予相应分类的位点值将 HIMS-CVR 转换成临床危险评分系统 (HIMS-CVRS)[21,22]。我们利用 HIMS-CVRS 的每一增量计算病程超过 6 年的卒中/心肌梗死风险。这样，我们确定回归单元中每一分类同基础分类的间距并设定与年龄增加 6 年相关风险的固定倍数[23]。接下来比较模型参数预测的风险与评分系统分值预测的风险。最后，利用 Poisson 回归模型建立包含人群独立预测因素的卒中/心肌梗死比率矩阵。

伦理学批准

本研究经西澳大利亚卫生司和西澳大利亚大学人体研究伦理委员会批准，获得所有参与者书面知情同意。

结果

参与者和卒中/心肌梗死比率

该队列包含 4382 例男性，平均年龄 75.4 岁（标准差 4.2）。其基线临床特征见表 1。平均随访 6 年（四分位间距，5.2-7.2），在随访期间，有 686 例新发卒中/心肌梗死（总体率为 2.61；95% CI, 2.42-2.81/100 人年）。
卒中 / 心肌梗死的风险总结见表 3。该队列中传统血管危险因素除年龄 (≥85 岁的相对危险度为 4.87 ; 95% CI, 3.00-7.89) 和吸烟 (相对危险度 1.67 ; 95% CI, 1.12-2.50) 外, 糖尿病、胆固醇及高血压均与新发卒中 / 心肌梗死非独立相关。

HIMS-CVR 评估

HIMS-CVR 包括年龄组、舒张压 ≤70 mmHg、超敏 CRP ≥3 mg/L、同型半胱氨酸 ≥15 μmol/L、腰臀比 >1, 以及差 / 中等自评健康, 与 Framingham 风险方程式相比对该人群较好地预测了卒中 / 心肌梗死发生。Harrell C 分值值在 HIMS-CVR 为 0.66, 而在 Framingham 风险方程式为 0.62。与 Framingham 风险方程式相比, HIMS-CVR 总体分辨力提高 1.85% (z=4.95; P<0.001)。利用 HIMS-CVR 和 Framingham 风险方程式计算得到的实测和预期事件风险的每个十分位值校准图见图 1 和 2。

430 例参与者中有 137 例经历了卒中 / 心肌梗死事件, 相比 Framingham 风险方程式, HIMS-CVR 使其分类得到改善。但有 97 例恶化, 重新分类比例净收益为 0.093(z=2.61; P<0.005)。没有过卒中 / 心肌梗死事件的 2556 例参与者中, HIMS-CVR 使 601 例分类改善而 557 例恶化, 重新分类比例净收益为 0.017(z=1.29; P=0.098)。HIMS-CVR 的总体网络重新分类指数为 0.076 (z=2.0; P=0.023)。HIMS-CVR 和 Framingham 风险方程式风险预测比较的散点图见图 3。

HIMS-CVRS 和风险矩阵的完善和评估

该组社区老年男性中包括卒中 / 心肌梗死的重要独立危险因素的 HIMS-CVR 风险评估矩阵见图 4。

我们根据对每个二项式变量不利的一面赋予 1 分 (舒张压 >70 mmHg, 0 分; 舒张压 ≤70 mmHg, 1 分; CRP <3, 0 分; CRP ≥3, 1 分; 同型半胱氨酸 <15, 0 分; 同型半胱氨酸 ≥15, 1 分; 腰臀比 <1, 0 分; 腰臀比 >1, 1 分; 良好的自评健康, 0 分; 差的自评健康, 1 分) 和按不同年龄范围分为 0-3 分 (年龄 69-74 岁, 0 分; 75-79 岁, 1 分; 80-84 岁, 2 分; ≥85 岁, 3 分) 的方法将 HIMS-CVR 转换为 8 分项临床危险评分 (HIMS-CVRS)。HIMS-CVRS 和完整 HIMS-CVR 模型 (表 4) 对 HIMS-CVRS 8 种类型的每个分类的风险评估作用没有本质区别。

图 2 Framingham 风险方程式校准: 观察事件与预期事件风险十分位数。

图 3 男性健康研究心血管危险模型与 Framingham 风险方程式对比预测新发卒中 / 心肌梗死的 6 年风险值。数据包括有或没有卒中 / 心肌梗死的人数。
讨论

我们的结果显示传统血管危险因素在预测社区老年男性未来卒中/心肌梗死方面比年轻男性的作用更有限。相反，该人群卒中/心肌梗死的独立预测因素有年龄、低舒张压、CRP 或同型半胱氨酸升高、向心性肥胖和差的自评健康。我们建立的危险评分显示是一种改善社区老年男性心血管危险评估简单而可能有效的途径。

该队列老年男性人群中，舒张压与卒中/心肌梗死独立相关。其它队列研究也观察到血压低与预后更差有关。例如在一组年龄超过 80 岁的高血压老年人群中，84.5% 正接受抗生素药物治疗，收缩压水平<140 mmHg 与更短的存活时间相关（独立于已知的死亡预测因素）[23]。但是我们不能完全排除低舒张压与卒中/心肌梗死的关联性被其它未测定因素混杂的可能，例如除心肌梗死以外的既往心血管疾病。此外，这些数据的认证必须遵循证据，老年高血压患者抗高血压药物治疗是获益的[24]。

本队列中通过 CRP 测得的全身低度炎症仍与新发卒中/心肌梗死独立相关，提示临床或亚临床炎症过程与卒中/心肌梗死有关，但也有相反的报告。例如，CRP 水平的遗传决定因素与冠心病风险并不明显相关[25]，提示 CRP 和心脏疾病的关系可能并非因果相关。尽管存在这些疑点，我们的结果与最近的瑞舒伐他汀治疗可降低没有心血管疾病但 CRP 水平>2.0 mmol/L 参与者卒中/心肌梗死风险的结果相一致[26]。现有数据提示这些结果（相对年轻的参与者中；平均年龄 66 岁）亦有可能与老年男性相关。

我们的数据支持对心血管疾病患者评估抗炎假说的理论[27]，并提示合理处理炎症可能是降低老年社区
结论

该社区老年男性队列中，随访期间经历卒中或心肌梗死的患者比没有经历卒中或心肌梗死等心血管事件者年龄更大，舒张压更低，腰臀比更高。此外，年龄、吸烟、低舒张压、超敏 C 反应蛋白升高，高同型半胱氨酸血症，向心性肥胖及自评健康状况等传统血管危险因素须纳入社区老年男性的血管危险评估。如果结果得到外部验证，我们建立的危险评分可能对社区老年男性心血管危险评估有用。

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