Prediction of Cardiovascular and All-Cause Mortality at 10 Years in the Hypertensive Aged Population

Quan L. Huynh,1 Christopher M. Reid,2 Enayet K. Chowdhury,2 Molla M. Huq,2 Baki Billah,2 Lindon M.H. Wing,3 Andrew M. Tonkin,2 Leon A. Simons,4 and Mark R. Nelson;1 on behalf of the Second Australian National Blood Pressure Management Committee*

BACKGROUND
We have previously developed a score for predicting cardiovascular events in the intermediate term in an elderly hypertensive population. In this study, we aimed to extend this work to predict 10-year cardiovascular and all-cause mortality in the hypertensive aged population.

METHODS
Ten-year follow-up data of 5,378 hypertensive participants in the Second Australian National Blood Pressure study who were aged 65–84 years at baseline (1995–2001) and without prior cardiovascular events were analyzed. By using bootstrap resampling variable selection methods and comparing the Akaike and Bayesian information criterion and C-indices of the potential models, optimal and parsimonious multivariable Cox proportional hazards models were developed to predict 10-year cardiovascular and all-cause mortality. The models were validated using bootstrap validation method internally and using the Dubbo Study dataset externally.

RESULTS
The final model for cardiovascular mortality included detrimental (age, smoking, diabetes, waist–hip ratio, and disadvantaged socioeconomic status) and protective factors (female sex, alcohol consumption, and physical activity). The final model for all-cause mortality also included detrimental (age, smoking, random blood glucose, and disadvantaged socioeconomic status) and protective factors (female sex, alcohol consumption, body mass index, and statin use). Blood pressure did not appear in either model in this patient group. The C-statistics for internal validation were 0.707 (cardiovascular mortality) and 0.678 (all-cause mortality), and for external validation were 0.729 (cardiovascular mortality) and 0.772 (all-cause mortality).

CONCLUSIONS
These algorithms allow reliable estimation of 10-year risk of cardiovascular and all-cause mortality for hypertensive aged individuals.

Keywords: algorithms; blood pressure; cardiovascular disease, death, hypertension, risk assessment.

doi:10.1093/ajh/hpu213

Atherosclerotic cardiovascular disease (CVD) is the leading cause of death and disability worldwide.1 In 2008, 17.3 million people died from CVD, contributing to 48% of deaths from noncommunicable disease and 30% of all deaths.2 Aging is a major and nonmodifiable CVD risk factor.3–5 Older people also have higher risk of developing other CVD risk factors including elevated blood pressure.6 Indeed, normotensive individuals at the age of 55 years have 90% lifetime risk of developing hypertension7 that is associated with greater risk of major CVD events—such as stroke, myocardial infarction, and heart failure8—and hypertension is the leading modifiable cause of CVD worldwide.9 Although aging is nonmodifiable, therapies that prevent or delay the adverse effects of aging on cardiovascular health may reduce the associated disease burden. Reliable estimates of risk are therefore needed to target these therapies to people who are most likely to benefit from them. One of the most common equations used to estimate individual absolute cardiovascular risk has been developed from the Framingham Heart Study10 and has proven to be clinically useful. However, underestimations or overestimations may occur when the scores derived from these equations are applied to the aged population who have higher risks and were underrepresented in such studies.11 It may be so because although similar risk factors may be at play, their relative importance changes with age.12 Given the increasing number of elderly people, many of whom have hypertension, a risk score relevant to them is needed.

In previously published work,13 we developed a score for predicting CVD events in the hypertensive aged population during a median follow-up of 4.1 years. In this study, we aimed to extend this work by developing a risk score to predict 10-year cardiovascular and all-cause mortality in the hypertensive aged population.
METHODS

Study population

This study used data from the Second Australian National Blood Pressure (ANBP2) study that commenced in 1995 and finished in 2001 and data from the ANBP2 cohort follow-up study (post-trial completion data). The ANBP2 study was a prospective randomized trial conducted among 1,594 Australian general practices that compared initial angiotensin-converting enzyme inhibitor (recommended enalapril) and thiazide diuretic-based (recommended hydrochlorothiazide) therapy in people with mild-to-moderate hypertension. Inclusion and exclusion criteria were previously reported elsewhere. Briefly, all participants had hypertension at entry. Hypertension was defined using the contemporary definition at the time of study commencement (systolic pressure ≥ 160 mm Hg and/or diastolic pressure ≥ 90 mm Hg). Blood pressure was measured at 2 study entry visits that were at least 1 week apart and had 3 measurements at each visit. For those who were receiving antihypertensive medications, medication was discontinued under medical supervision at least 1 week before the study entry visits. The study included 6,083 hypertensive participants with a mean age of 71.8 years (range: 65–84 years) at study entry during 1995–1997. Their characteristics at baseline are described elsewhere. The majority of these participants were previously otherwise healthy (8% had a previous coronary heart disease event, 5% a cerebrovascular event, and 7% had diabetes) although approximately two thirds of them had previously taken antihypertensive medication(s). After excluding 705 participants who had a prior CVD event(s), we included 5,378 participants (47.5% men) who had no prior CVD events in the present study. These participants were followed up for a median of 10.8 years (interquartile range: 9.6–11.4 years).

This study has been approved by the Royal Australian College of General Practitioners, the Tasmanian Health and Medical Human Research Ethics Committee, and the Monash University Standing Committee on Ethics in Research Involving Humans.

Measurements of CVD risk factors

At study entry, blood pressure was taken at 2 office visits (with 3 readings on each occasion) at least 1 week apart by a study nurse using a standard mercury sphygmomanometer. All blood biochemical markers were derived from the existing medical record or, where this was unavailable for the preceding 12 months, a measure was taken during the screening phase of the study. Disease status, personal history of CVD, and antihypertensive or other medication use were reported by the usual treating physician. Information on smoking (never/current smoker/ex-smoker), alcohol consumption (never/current drinker/ex-drinker and drinking frequency), and family history of CVD were self-reported using a questionnaire. Socioeconomic status based on residential postcodes was derived using the Australian Bureau of Statistics Index of Relative Socioeconomic Disadvantage.

Using Cox’s simple regression analysis, over 40 baseline factors were identified a priori as possible CVD risk factors. These possible predictors have been described in detail elsewhere. Causes of death were determined using data from the Australian National Death Index.

Development of predictive model

This study was restricted to participants who had no previous history of a coronary or cerebrovascular event. For modeling purpose, potential variables were identified using clinical assessments and Cox’s univariable regression model. A variable with a P value <0.25 in Cox’s univariable regression analysis was listed as a potential risk factor.

Bootstrap (resampling) methods were used to develop a parsimonious model using Cox’s multivariable regression. The method was based on 1,000 repeated random samples from the original data. For each sample, a Cox’s multivariable regression model with all potential variables was run, and the proportion of times each variable was identified as significant (P value ≤ 0.05) in 1,000 repeated samples was recorded. Five models were developed from the variables that were significant in at least 90%, 80%, 70%, 60%, and 50% of the bootstrap samples. The final model was selected as the one that provides the lowest Akaike information criterion and Bayesian information criterion and the highest C-statistic. For the final model, Cox’s proportionality condition, multicollinearity, and first-order interaction effects were investigated.

Validation

The model’s performance was evaluated using both internal and external validation. The final model was internally validated using bootstrapped resampling methods. External validation was undertaken using data from a similar incident cohort of 2,100 subjects aged 60–79 years at baseline from the Dubbo Study. This was an observational cohort of residents in Dubbo (New South Wales, Australia) who were broadly representative of the Australian population born before 1930. For cardiovascular mortality, the discriminatory power of our predictive model was also compared to that of the Framingham predictive model using our sample and the Dubbo Study sample.

RESULTS

At the initial phase of the trial, 83% of the patients received assigned treatment for blood pressure. At the end of the trial (year 5), 58% of those in the angiotensin-converting enzyme inhibitor group and 62% of those in the diuretic group were still receiving the assigned treatment, and the patients had reduced their blood pressure by an average of 26/12 mm Hg.

Table 1 shows the baseline characteristics for participants without prior CVD events in the ANBP2 Study and for participants in the Dubbo Study. Compared with the participants in the Dubbo Study, those in the ANBP2 Study were slightly older, had lower proportion of current smokers, and had higher mean values of blood pressure (P < 0.05). Of the
Table 1. Cohort characteristics for the ANBP2 Study sample without prior cardiovascular events and the Dubbo Study sample

<table>
<thead>
<tr>
<th></th>
<th>ANBP2 Study sample</th>
<th>Dubbo Study sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of observations</td>
<td>5,378 (100%)</td>
<td>2,100 (100%)</td>
</tr>
<tr>
<td>Age (year)a</td>
<td>71.8 (4.9)</td>
<td>68.5 (6.9)</td>
</tr>
<tr>
<td>Female gender</td>
<td>2,825 (52.5%)</td>
<td>1,221 (58.1%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)a</td>
<td>27 (4)</td>
<td>26 (4)</td>
</tr>
<tr>
<td>Waist circumference (cm)a</td>
<td>94.6 (12.1)</td>
<td>N/A</td>
</tr>
<tr>
<td>Waist–hip ratioa</td>
<td>0.90 (0.08)</td>
<td>N/A</td>
</tr>
<tr>
<td>Current smoker</td>
<td>381 (7%)</td>
<td>325 (16%)</td>
</tr>
<tr>
<td>Current alcohol consumption</td>
<td>3,912 (73%)</td>
<td>1,364 (65%)</td>
</tr>
<tr>
<td>Physically active</td>
<td>4,185 (78%)</td>
<td>1,771 (84%)</td>
</tr>
<tr>
<td>Disadvantaged socioeconomic status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st quartile (most disadvantaged)</td>
<td>1,415 (26%)</td>
<td>N/A</td>
</tr>
<tr>
<td>2nd quartile</td>
<td>1,446 (27%)</td>
<td></td>
</tr>
<tr>
<td>3rd quartile</td>
<td>1,717 (32%)</td>
<td></td>
</tr>
<tr>
<td>4th quartile (least disadvantaged)</td>
<td>789 (15%)</td>
<td></td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>2,540 (47%)</td>
<td>690 (33%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>649 (12%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>374 (7%)</td>
<td>142 (7%)</td>
</tr>
<tr>
<td>Mean SBP at registration (mm Hg)a</td>
<td>158 (18)</td>
<td>147 (24)</td>
</tr>
<tr>
<td>Mean DBP at registration (mm Hg)</td>
<td>86 (10)</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean PP at registration (mm Hg)</td>
<td>72 (17)</td>
<td>N/A</td>
</tr>
<tr>
<td>Random blood glucose (mmol/l)a</td>
<td>5.6 (1.9)</td>
<td>5.2 (1.4)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)a</td>
<td>5.7 (1.0)</td>
<td>6.5 (1.2)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)a</td>
<td>1.4 (0.5)</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>Medication history at entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulant/antiplatelet/aspirin</td>
<td>546 (10%)</td>
<td>128 (6%)</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>3,250 (60%)</td>
<td>820 (39%)</td>
</tr>
<tr>
<td>Diabetic medication</td>
<td>172 (3%)</td>
<td>47 (2%)</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>648 (12%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

aData are presented as mean (SD).
Abbreviations: CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; N/A, not available; PP, pulse pressure; SBP, systolic blood pressure.

5,378 ANBP2 participants who were free of prior CVD and were included in this study, 1,547 (28.8%) died during the 10.8 years median follow-up. Of these, 644 deaths (41.6%) were related to CVD.

Table 2 shows the 10-year predictive model for cardiovascular mortality. The final model included age, sex, alcohol consumption, smoking, waist–hip ratio, socioeconomic status, diabetes, and being physically active (C-statistic = 0.712, Akaike information criterion = 10455.74, Bayesian information criterion = 10515.02). While older age, smoking, diabetes, greater waist–hip ratio, and having disadvantaged socioeconomic status were associated with greater risk of death from CVD, being female, alcohol consumption, and being physically active were protective. Systolic (hazard ratio = 1.01, 95% confidence interval (CI): 1.00, 1.01) and diastolic (hazard ratio = 0.99, 95% CI: 0.98, 0.99) blood pressure significantly predicted cardiovascular mortality in univariable analysis, but not in this multivariable predictive model ($P > 0.05$). The C-statistic for internal validation of this model was 0.707.

Table 3 shows the 10-year predictive model for all-cause mortality (C-statistic = 0.680, Akaike information criterion = 23422.65, Bayesian information criterion = 23481.50). The final model included age, sex, alcohol consumption, smoking, socioeconomic status, body mass index, statin use, and random blood glucose. Older age, smoking, higher random blood glucose concentration, and having disadvantaged socioeconomic status were associated with greater risk of all-cause death, whereas being female, alcohol consumption, greater body mass index, and taking cholesterol-lowering.
medications were protective. Similar to cardiovascular mortality, systolic (hazard ratio = 1.01, 95% CI: 1.00, 1.01) and diastolic (hazard ratio = 0.99, 95% CI: 0.98, 0.99) blood pressure significantly predicted all-cause mortality in univariable analysis, but not in this multivariable predictive model (P > 0.05). The C-statistic for internal validation of this model was 0.678.

Figure 1 shows areas under the receiver operating characteristic curve for the external validation of the 2 models using data from a similar incident cohort of 2,100 subjects from the Dubbo Study that show very good discriminatory power (cardiovascular mortality C-statistic = 0.729, 95% CI: 0.700, 0.758; all-cause mortality C-statistic = 0.772, 95% CI: 0.750, 0.794).

In prediction of cardiovascular mortality, the Framingham predictive model had lower discriminatory power than ours when applied to the ANBP2 sample (C-statistic = 0.654, 95% CI: 0.630, 0.678) but had similar discriminatory power when applied to the Dubbo Study sample (C-statistic = 0.739, 95% CI: 0.710, 0.767).

The calibration power of our predictive model for cardiovascular mortality was very good (Figure 2a). For those with low probabilities (0.1–0.4), our model showed perfect estimation of survival probability in relation to ideal survival (Figure 2a, dashed line). For those with intermediate probabilities (0.5–0.8), our model slightly underestimated survival in relation to observed survival (Figure 2a, black line). For those with high probabilities (0.9–1.0), the model predicted perfectly (for both ideal and observed survival). The calibration power of our predictive model for all-cause mortality was also good (Figure 2b). For very low (0.1–0.3) probabilities, this predictive model slightly underestimated survival with respect to observed survival (Figure 2b, black line). For those with intermediate (0.5–0.8) or high (0.9–1.0) probabilities, the model predicted survival perfectly with respect to the observed survival (black line). These calibration results reveal no overestimation and no major underestimation and, therefore, suggest that our predictive models can appropriately predict survival probability across the range.

**DISCUSSION**

We have derived models predicting 10-year risk of cardiovascular and all-cause mortality for a hypertensive population aged over 65 years. The predictive models had very good internal and external validations, and are simple tools.
10-Year Prediction of Mortality in Hypertensive Aged Population

to predict risk of mortality for the hypertensive aged patients in clinical practice, requiring only a medical history and a routine physical examination and blood tests.

Although our model and the Framingham model showed similarly high discriminatory power when applied to the Dubbo Study cohort, the Framingham had substantially lower discriminatory power when applied to the ANBP2 cohort. While all of our study subjects were elderly patients receiving antihypertensive medications, the Dubbo Study subjects were slightly younger with only 39% receiving antihypertensive medications at entry and were thus more representative of the general population. Given that older people are very likely hypertensive and most of them would be prescribed antihypertensive medications, we believe that our population sample is more relevant and resembled to those in the real life practice. The external and internal validation results suggest that our model performs at least as well as the Framingham for the general population, and possibly better than the Framingham for the elderly hypertensive patients receiving blood pressure-lowering medications. The latter requires further validation to be confirmed.

Over the last few decades, improved public health promotion, better treatments, extensive primary and secondary prevention efforts, and major technologic advances have resulted in lower premature mortality rates and improved life expectancy in many countries, including Australia. These developments have increased the proportion of people who survive to older age when hypertension and CVD are most prevalent. To determine which patients are at greatest risk and thus likely to benefit most from active risk factor modification, clinicians require evidence-based support for their decision making during clinical work. Therefore, a risk score specifically relevant to the hypertensive aged population is needed.

**Figure 1.** Area under the curve: (a) External validation of the predictive model for cardiovascular mortality using the Dubbo Study dataset. (b) External validation of the predictive model for all-cause mortality using the Dubbo Study dataset.

**Figure 2.** Predictive model calibration: (a) Calibration of the cardiovascular mortality predictive model. (b) Calibration of the all-cause mortality predictive model.
Many other cohort equations have previously been developed to estimate the risk of cardiovascular and all-cause mortality.\textsuperscript{10,24–30} Several of them included the elderly (≥75 years) in their studies.\textsuperscript{24–26,28,30} The Pocock equation\textsuperscript{24} used data from 8 large randomized controlled trials of antihypertensive treatment. However, all of the data were from old studies conducted in 1970s and 1980s, and 2 of the 3 largest samples used in this equation (accounting for >50% of the participants included in the analysis) excluded participants aged ≥65 years at study entry. The SCORE equation\textsuperscript{25} used more contemporary data from 12 European cohort studies but only 2 of the 12 cohort studies had participants aged ≥75 years. Both equations from the Leiden 85+ study\textsuperscript{26} and another Dutch community-based cohort study\textsuperscript{27} included elderly participants but were based on small sample sizes (n = 302 and 403, respectively) and lacked external validation. A new set of risk equations\textsuperscript{28} was derived using data on 3,243 participants aged 40–80 years from the Framingham Heart Study and Framingham Offspring Study but less than half of the participants had hypertension at baseline.\textsuperscript{30}

In our 2 predictive models, age, gender, former and current smoking, and disadvantaged socioeconomic status were consistently associated with both increased cardiovascular and all-cause mortality, whereas alcohol consumption was associated with a decreased risk. It is of note that blood pressure was consistently not included in the final predictive models for both cardiovascular and all-cause mortality in this population (hypertensive elderly). This may be due to the fact that all the participants in this study were hypertensive at baseline, were all treated with blood pressure-lowering medications to a lower blood pressure target than at baseline, and generally had higher adherence to assigned treatment than the general population. Therefore, other predictors play a more important role in predicting mortality risk in this population.

There are some interesting differences between the 2 models. Diabetes was associated with greater cardiovascular mortality. This may be easily explained by the strong association of diabetes with CVD.\textsuperscript{31} Indeed, CVD is responsible for at least 50% of deaths among people with diabetes.\textsuperscript{2,23} The presence of random blood glucose concentration, rather than whether the participants were diabetic, in the final predictive model for all-cause mortality may reflect the importance of the actual concentration of blood glucose to the outcome of other comorbidities. Overweight/obesity (assessed as body mass index) was associated with lower risk of all-cause mortality. This may be explained by the “obesity paradox” that may be due to the deleterious effects of cachexia with end-stage cancer and other diseases associated with aging.\textsuperscript{34} Findings from a large cohort of over 500,000 Americans aged 50–71 years showed that the U-shaped relationship between body mass and mortality risk became flatter with increasing age.\textsuperscript{35} Our findings are also consistent with results from a recent meta-analysis of 12 cohorts of heart failure patients across the world showing that the “obesity paradox” effect on all-cause mortality was confined to older individuals.\textsuperscript{36} These findings, however, do not endorse weight gain to “protect” patients against all-cause mortality risk because visceral adiposity (assessed as waist–hip ratio in our study) was associated with greater risk of cardiovascular mortality. This finding is consistent with those from a meta-analysis that demonstrated superiority of measures of abdominal obesity, over body mass index, for detecting cardiovascular risk in both men and women.\textsuperscript{37} The indicator of whether the participants were physically active in our final predictive model for cardiovascular mortality emphasizes the potential benefits of maintaining physical activity and of having greater cardiorespiratory fitness on cardiovascular health that may be independent of weight loss.\textsuperscript{38}

This study has particular strengths. It was based on follow-up of a large randomized controlled trial conducted in 1594 Australian family practices with a large number of hypertensive aged patients. Standardized measurements of an extensive range of potential risk factors were undertaken and used for model development. Using contemporary data on a hypertensive aged population was an additional strength of this study. As discussed above, other risk scores were developed using data either from old cohorts or including only a small proportion of elderly and hypertensive patients and thus may be not generally applicable for the hypertensive aged population. By using the bootstrapping validation methods, we could avoid losing data (split sample validation) or losing power (normal internal validation). Our predictive models also proved to have very good external validation using data from a similar incident cohort of elderly subjects (the Dubbo Study).

Our study did however have some limitations. Our cohort was mostly Caucasian and so the generalizability of our risk score to other ethnicities is uncertain. Furthermore, because the participants were recruited from family practices, their characteristics might be slightly different from the general population and particularly those mainly cared for in hospital clinics or in other healthcare environments. It has also been conducted in a population in a developed Western country and thus may not be directly applicable to elderly hypertensive populations from developing countries.

In summary, our study addressed the specific age limitations of the other risk scores and provides simple equations to predict cardiovascular and all-cause mortality for hypertensive aged patients. They may guide proper management of risk factors and help clinicians to identify patients who are most likely to benefit from treatment. In countries where life expectancy has been substantially improved due to dramatic decreases in premature mortality from major chronic diseases,\textsuperscript{23,39} these predictive models with very good internal and external validation are a key for early detection of risk and for developing a cost-effective approach to primary disease prevention.

**APPENDIX**

Members of the ANBP2 Management Committee:

- Lawrence J. Beilin,\textsuperscript{a} Garry L. Jennings,\textsuperscript{b} Collin I. Johnston,\textsuperscript{b} Graham J. Macdonald,\textsuperscript{c} John E. Marley,\textsuperscript{d} John J. McNeil,\textsuperscript{c} Trefor O. Morgan,\textsuperscript{c} Christopher M. Reid,\textsuperscript{c} Philip Ryan,\textsuperscript{c} Malcolm J. West,\textsuperscript{b} and Lindon M.H. Wing\textsuperscript{b}

\textsuperscript{a}Department of Medicine, University of Western Australia, Perth, Australia; \textsuperscript{b}Baker IDI Heart and Diabetes Research Institute, Melbourne, Australia; \textsuperscript{c}Merck Sharp and Dohme, Sydney, Australia; \textsuperscript{d}Faculty of Health, University of Newcastle, Newcastle, Australia; \textsuperscript{b}Department of Medicine, University of Western Australia, Perth, Australia.
Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia; Department of Physiology, University of Melbourne, Melbourne, Australia; Discipline of Public Health, University of Adelaide, Adelaide, Australia; Department of Medicine, University of Queensland, Brisbane, Australia; School of Medicine, Flinders University, Adelaide, Australia.

ACKNOWLEDGMENTS

This work was supported by a National Health and Medical Research Council (Australia) General Practice Clinical Research Grant (no. 490042). C.M.R. is supported by a Research Council (Australia) General Practice Clinical Research Grant (no. 490042). C.M.R. is supported by a Research Council (Australia) General Practice Clinical Research Grant (no. 490042). C.M.R. is supported by a Research Council (Australia) General Practice Clinical Research Grant (no. 490042).

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

Huynh et al.