Prediction of Cardiovascular Events in Subjects in the Second Australian National Blood Pressure Study

Mark R. Nelson, Philip Ryan, Andrew M. Tonkin, Emmae Ramsay, Kristyn Willson, Lindon W.H. Wing, Christopher M. Reid, on behalf of the Second Australian National Blood Pressure Study Management Committee

Abstract—Estimating absolute risk rather than measurement of blood pressure alone is considered the best way to identify those who would most likely benefit from medical intervention. Risk calculators used to estimate risk in those without previous cardiovascular disease (CVD) events are based on the Framingham Heart Study, which had no person >74 years of age at baseline. This needs to be addressed, because age is the most important determinant of risk. We estimated the predictive value of 3 risk equations for CVD end points in the Second Australian National Blood Pressure study cohort (mean age: 71.9 years at baseline). Observed and predicted 5-year incidence rates, $\chi^2$ goodness-of-fit tests, and Harrell C statistic and area under the receiver operator characteristic curve were used to assess the ability of the equations to predict CVD outcomes over 5 years. A recalibration analysis was undertaken. Significant ($P<0.05$) $\chi^2$ goodness-of-fit statistics were observed using each of the risk equations for myocardial infarction, coronary heart disease, stroke, or CVD morbidity or mortality across age groups and both sex. All of the overall C statistics or the area under the receiver operator characteristic curve indicated modest discrimination of the algorithms for prediction of the outcomes for coronary heart disease and CVD morbidity and mortality, myocardial infarction, or stroke (Framingham); cardiac death (Pocock); and CVD events (Dubbo). Recalibration analyses showed that it would be inappropriate to apply the risk equations to the Second Australian National Blood Pressure study population. New risk equations for CVD events in the hypertensive aged are needed. (Hypertension. 2010;56:44-48.)

Key Words: hypertension ■ algorithms ■ cardiovascular diseases ■ risk assessment ■ aged

One in 4 adults worldwide is estimated to have hypertension. Prevalence rises with age. For example, in the United States, 71% of those aged ≥65 years have hypertension. Hypertension is associated with an increased risk of a number of major cardiovascular disease (CVD) events, including stroke, acute myocardial infarction, and heart failure. The relationship between blood pressure and such events is exponential and is steeper with increasing age. Other factors, such as cigarette smoking, increased serum cholesterol concentration, and diabetes mellitus, are independent risk factors for CVD events and enhance the risk of such events in hypertensive individuals. The inclusion of all known risk factors in an individual’s profile determines his or her “absolute risk” of experiencing a subsequent cardiovascular event within a defined period of time (usually 5 or 10 years). Traditional thinking in hypertensive patients has been that it is the level of blood pressure that is particularly important in determining whether an intervention (eg, lifestyle modification or drug therapy) is indicated. However estimating an individual’s absolute risk of CVD events has proven to be a superior method for guiding treatment compared with use of one risk factor, such as blood pressure. The concept of using “absolute cardiovascular risk” to guide therapy has now been incorporated into major guidelines relating to the treatment of known CVD risk factors.

An individual’s absolute cardiovascular risk is usually determined by applying regression equations derived from prospective population studies, the best known of which is the Framingham Heart Study initiated in Framingham, Massachusetts, in the late 1940s. Such equations acknowledge the multifactorial causation of CVD, sex differences in disease incidence, and the steep increase in risk with aging. The risk scores obtained from these regression equations have proven to be very useful but have potential problems when applied to special high-risk groups not represented in the Framingham population. For example, no persons aged >74 years were enrolled at baseline in that study, and more than half of the initial cohort were aged <50 years.

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Other risk equations have also been developed. The Pocock equation was developed specifically for use in patients with hypertension. It used data from 8 large randomized, controlled trials of antihypertensive treatment including from 840 to 17,354 individuals recruited from European and North American populations. This should potentially have the best predictive value in other cohorts of individuals with hypertension, but 2 of the 3 largest trials, which accounted for more than half the participants included in the analysis, excluded participants aged ≥65 years at study entry, and all of the studies were conducted in the 1970s and 1980s. The equation derived from the Dubbo Study relates to a prospective cohort study of Australians aged ≥60 years, which commenced in 1988. Only half of this cohort had hypertension at baseline.

In the current study we aimed to compare outcome predictions using the Framingham, Pocock, and Dubbo risk equations in an elderly population of individuals with hypertension who participated in the Second Australian National Blood Pressure study (ANBP2) with their observed outcomes. The primary hypothesis tested was that absolute risk assessment for the hypertensive aged should be based on algorithms derived from age-specific local and contemporary populations rather than from the Framingham Heart Study, as is usual practice at this time.

Methods

Study Population

ANBP2 was a prospective randomized trial conducted in Australian general practices in 1995–2001 that compared angiotensin-converting enzyme inhibitor– and diuretic-based therapies in people with hypertension. The study included 6083 hypertensive participants aged 65.0 to 84.0 years (mean: 71.9 years) at study entry. The majority were previously healthy (8% had a previous coronary heart disease event, 5% a cerebrovascular event, and 7% had diabetes mellitus). Other baseline characteristics are published elsewhere.

The participants in ANBP2 were followed for a median of 4.1 years, during which time 1431 had a CVD event (coronary events including myocardial infarction, other cardiovascular events including heart failure, and cerebrovascular events including stroke) or died.

Measurement of CVD Risk Factors in ANBP2

Individuals enrolled in ANBP2 needed to have an average untreated blood pressure while sitting of ≥160 mm Hg systolic or ≥90 mm Hg diastolic (if systolic BP was >140 mm Hg). This was determined from measurements taken at 2 office visits (3 readings on each occasion) ≥1 week apart by a study nurse using a mercury sphygmomanometer with a cuff appropriate for arm size. All of the participants had either not previously received antihypertensive treatment or had such treatment ceased ≥2 weeks before these measurements (“randomization” blood pressures). Sitting blood pressure was also measured at the first screening visit before cessation of previous antihypertensive therapy (“baseline” blood pressures).

At study entry, if no relevant measurements had been made in the previous 12 months, nonfasting venous blood was taken to determine total and high-density lipoprotein cholesterol concentrations, blood glucose, and glomerular filtration rate, which was calculated using the Modification of Diet in Renal Disease Study equation. Cigarette smoking status and family history of CVD were ascertained by self-report. Diabetes mellitus, left ventricular hypertrophy, personal history of CVD, and antihypertensive and other medication use were documented by the usual treating physician.

This study had approval from the Tasmania Health and Medical Human Research Ethics Committee (H10067) and the Monash University Standing Committee on Ethics in Research Involving Humans (2006/592). ANBP2 had ethics approval by the Royal Australian College of General Practitioners Research Ethics Committee.

Statistical Analysis

Baseline CVD absolute risk was calculated using the data at study entry for all of the ANBP2 participants and the Anderson 1991 equation from the Framingham study, as well as the Pocock and Dubbo equations. The Anderson equation, rather than more recent algorithms derived from the Framingham data set, was used, because it was contemporary with the conduct of the ANBP2 study recruitment phase (1995–1998). These estimates of risk were then compared with the actual event rates observed in the ANBP2 cohort. This was done with the risk estimate/score treated as continuous and categorical variables. Predicted risk was categorized as mild (<10% 5-year risk of a major adverse cardiovascular event), moderate (10% to <15% risk), high (15% to <20% risk), or very high (≥20%) based on the New Zealand cardio-risk chart by sex and age groups for major fatal and nonfatal CVD events derived from the Framingham Heart Study. Analysis was performed using both randomization and baseline blood pressure measurements.

Three methods were used to assess risk prediction with each algorithm. χ² goodness tests (overall and stratified by sex) were used to compare observed values with those predicted. Discrimination of the Anderson and Pocock algorithms was assessed using Harrell C statistic and the area under the receiver operator characteristic curve (AUC) for the Dubbo algorithm. We calculated the CIs for the C statistics using a jackknife estimator. Finally, the product limit survival estimates for the Anderson and Pocock algorithms were stratified by age, sex, and the various risk categories defined above, and then the observed and predicted 5-year event probabilities and total number participants were obtained for each group. For the Dubbo algorithm, a similar method was undertaken using the predicted values rather than the product limit survival estimates, and the number of events observed and predicted and total participants were calculated for each group.

A recalibration analysis was undertaken. The linear predictors (excluding the intercept) from the published Framingham and Dubbo models were used to re-estimate the coefficients in the regression models to predict event rates in the ANBP2 data. There was an insufficient detail in the study by Pocock et al to construct linear predictors, and, hence, recalibration using this model was not performed.

Results

Observed and predicted event probabilities by sex and age groups using the 3 different prediction methods are shown in Tables 1 to 3. Table 1 shows that the Framingham risk equation only moderately predicted CVD events in the ANBP2 cohort. It also suggests that this equation generally overestimated CVD mortality, except for older men, where it underestimated CVD deaths. Table 2 shows modest agreement between observed and predicted CVD deaths by the Pocock score, although there was underestimation in the very old in both sexes. Table 3 shows that the Dubbo score generally estimated events in both sexes and all of the age groups better than the other 2 equations. The overall (ie, unstratified by covariates) goodness-of-fit tests for the Framingham, Pocock, and Dubbo risk equations were all statistically significant (P<0.001), indicating that the observed values varied from the predicted values more than could be ascribed to chance. When event probabilities were assessed by risk category (data not shown), the risk equations performed better but imperfectly, except for Framingham, which correlated well (predicted mild [<10%]: actual, 7.3%; mod-
erate [10% to <15%]: actual, 13.6%; high [15% to <20%]: actual, 19.4; very high [≥20%]: actual, 23.4%).

All overall C statistics and the AUC (Table 4) showed that the 3 risk scores generally poorly discriminated cases from noncases. Results are not presented for the baseline blood pressure analyses because they did not significantly differ from those based on randomization blood pressures.

Recalibration analyses showed, not unexpectedly, that, for some outcomes there were differences in the event rates between the ANBP2 population and the Framingham population (coronary heart disease [CHD] death) or Dubbo population (CVD; see intercepts, Table 5). The relationships of the outcomes, CHD death, and CVD death (Framingham), as well as CVD (Dubbo), with the risk factors were different for the ANBP2 population and the Framingham or Dubbo populations, indicating that it would be inappropriate to apply the risk equations to the ANBP2 population.

As shown in Table 5, there were no differences between ANBP2 intercepts and those published from Framingham for some outcomes there were differences in the event rates from those based on randomization blood pressures.

A study similar to our own looking at prediction within the Framingham population (coronary heart disease [CHD] death) or Dubbo population (CVD; see intercepts, Table 5). The relationships of the outcomes, CHD death, and CVD death (Framingham), as well as CVD (Dubbo), with the risk factors were different for the ANBP2 population and the Framingham or Dubbo populations, indicating that it would be inappropriate to apply the risk equations to the ANBP2 population.

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All of the overall C statistics and the AUC corroborated this poor agreement between observed and predicted CVD deaths. Our findings relating to comparison with the predictions from the Framingham data are consistent with other studies. A study similar to our own looking at prediction within the Framingham population (coronary heart disease [CHD] death) or Dubbo population (CVD; see intercepts, Table 5). The relationships of the outcomes, CHD death, and CVD death (Framingham), as well as CVD (Dubbo), with the risk factors were different for the ANBP2 population and the Framingham or Dubbo populations, indicating that it would be inappropriate to apply the risk equations to the ANBP2 population.

### Discussion

The CVD risk calculators commonly used in clinical practice to estimate future risk of cardiovascular events are most often based on the logistic regression equations generated from observations made since the late 1940s relating to citizens in the town of Framingham. The 1991 Framingham equation is derived from the Framingham cohort study data set and has been widely adopted because it allows estimates of total CVD events rather than individual coronary or stroke events. In its source cohort, the Framingham risk score (FRS) derived from the 1991 Framingham regression equation has good discrimination (AUC: 0.763 [men] and 0.793 [women]). Although it is arguable as to what constitutes a “good score,” it has been suggested that an AUC >0.8 represents good discrimination, 0.6 to 0.8 is moderate, and <0.6 is poor. However when applied to our aged hypertensive cohort, the FRS was less predictive, tending to overestimate risk, except for CVD mortality in older men, where it underestimated risk. This modest predictive performance was moderated by treating risk as a categorical variable. The Pocock score showed poor agreement between observed and predicted CVD deaths. All of the overall C statistics and the AUC corroborated this poor performance.

### Table 3. Observed and Predicted Probabilities by Age Group and Sex of CVD Death in the ANBP2 Cohort Using the Dubbo Equation

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age Group, y</th>
<th>Observed CVD, %*</th>
<th>Predicted CVD Death, %</th>
<th>Total Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>65 to 69</td>
<td>3.8</td>
<td>6.1</td>
<td>990</td>
</tr>
<tr>
<td>Female</td>
<td>70 to 74</td>
<td>5.4</td>
<td>7.8</td>
<td>961</td>
</tr>
<tr>
<td>Female</td>
<td>75 to 79</td>
<td>8.3</td>
<td>10.6</td>
<td>698</td>
</tr>
<tr>
<td>Female</td>
<td>≥80</td>
<td>11.3</td>
<td>12.9</td>
<td>302</td>
</tr>
<tr>
<td>Male</td>
<td>65 to 69</td>
<td>7.8</td>
<td>10.5</td>
<td>1139</td>
</tr>
<tr>
<td>Male</td>
<td>70 to 74</td>
<td>9.7</td>
<td>13.4</td>
<td>896</td>
</tr>
<tr>
<td>Male</td>
<td>75 to 79</td>
<td>13.9</td>
<td>16.5</td>
<td>525</td>
</tr>
<tr>
<td>Male</td>
<td>≥80</td>
<td>23.6</td>
<td>19.8</td>
<td>212</td>
</tr>
</tbody>
</table>

Data derived from Reference 15. CVD includes myocardial infarction, coronary death, and stroke.
Table 4. Overall C Statistics and 95% CIs (Anderson and Pocock Algorithm), the AUC, and 95% CI (Dubbo Algorithm) for All-Cause and Cause-Specific Morbidity and Mortality

<table>
<thead>
<tr>
<th>Condition</th>
<th>FRS13+</th>
<th>Pocock14*</th>
<th>Dubbo15†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.57 (0.55 to 0.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD death</td>
<td>0.53 (0.52 to 0.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.58 (0.57 to 0.59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0.51 (0.50 to 0.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>0.58 (0.56 to 0.59)</td>
<td>0.61 (0.58 to 0.63)</td>
<td></td>
</tr>
<tr>
<td>CVD death</td>
<td>0.57 (0.56 to 0.58)</td>
<td>0.58 (0.56 to 0.59)</td>
<td></td>
</tr>
</tbody>
</table>

*Data show the Harrell C statistic and 95% CIs. †Data show the AUC.

Table 5. Results of Recalibration Analyses Using Framingham and Dubbo Risk Equations Applied to ANBP2 Data

<table>
<thead>
<tr>
<th>Model</th>
<th>Published $\beta_0$</th>
<th>Recalibrated $\beta_0$ (95% CI)†</th>
<th>Recalibrated $\beta$ (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>15.53</td>
<td>16.22 (13.19 to 19.26)</td>
<td>1.03 (0.79 to 1.28)</td>
</tr>
<tr>
<td>CHD death</td>
<td>11.29</td>
<td>19.47 (11.73 to 27.20)</td>
<td>2.00 (1.04 to 2.97)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11.47</td>
<td>15.10 (10.09 to 20.24)</td>
<td>1.39 (0.74 to 2.04)</td>
</tr>
<tr>
<td>Stroke</td>
<td>26.51</td>
<td>25.54 (17.84 to 33.24)</td>
<td>0.93 (0.60 to 1.27)</td>
</tr>
<tr>
<td>CVD</td>
<td>18.81</td>
<td>21.15 (17.99 to 24.31)</td>
<td>1.14 (0.94 to 1.33)</td>
</tr>
<tr>
<td>CVD death</td>
<td>-5.04</td>
<td>-11.79 (-16.02 to -7.57)</td>
<td>1.90 (1.36 to 2.44)</td>
</tr>
<tr>
<td>Dubbo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>-8.65</td>
<td>-6.29 (-7.27 to -5.31)</td>
<td>0.60 (0.45 to 0.75)</td>
</tr>
</tbody>
</table>

*Published $\beta_0$ is the intercept of the original Framingham or Dubbo model. 95% CIs were not provided in the original source.
†Recalibrated $\beta_0$ is the intercept of the model relating ANBP2 outcome data to the linear predictor derived from the Framingham or Dubbo model.
‡Recalibrated $\beta$ is the slope of the of the model relating ANBP2 outcome data to the linear predictor derived from the Framingham or Dubbo model. If the 95% CI includes one, there was no statistically significant difference in the relationship of the outcome and the predictors between our (ANBP2) data and the Framingham or Dubbo data.

Because of the deficiencies in the applicability of the FRS to populations not represented in the Framingham data, various groups have looked at new risk scores for prediction in the older population. Generally they show modest-poor predictive value of the FRS and marginally better, although not necessarily statistically significantly so, predictive value of their own.27–30 For example, the British Women’s Heart and Health Study reported a receiver operator characteristic AUC of 0.66 (95% CI: 0.62 to 0.70) for CHD morbidity and mortality, 0.67 (0.64 to 0.71) for CVD morbidity and mortality for their own equation, and 0.65 (95% CI: 0.61 to 0.68) and 0.66 (0.62 to 0.69), respectively, for the FRS.30

The specific age limitations of the FRS have been addressed by other groups who have studied elderly cohorts, such as the Australian community-based Dubbo Study of the elderly (the Dubbo equation) and those using participants included in other hypertension treatment outcome trials15,16 (the Pocock equation). Other proposed solutions to the limitations of the FRS as a predictor of outcome in older people include the addition of new biomarkers, such as C-reactive protein11 and albuminuria,12 to improve predictive power.

In summary, the Framingham and Pocock risk equations and the Dubbo score were, at best, modest predictors of CVD events in the ANBP2 cohort, generally underestimating risk, especially in the very old. New risk equations for prediction of CVD risk in the hypertensive aged are needed. The most appropriate absolute risk assessment for the hypertensive aged should be based on algorithms derived from older local and contemporary populations, such as the ANBP2 cohort.

Perspectives

The Framingham and Pocock risk equations and Dubbo score were, at best, modest predictors of CVD events in the ANBP2 cohort, generally underestimating risk, especially in the very old. New risk equations for the hypertensive aged are needed.

Sources of Funding

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Disclosures

None.

References


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