Validation of the Korean Genome Epidemiology Study Risk Score to Predict Incident Hypertension in a Large Nationwide Korean Cohort

Nam-Kyoo Lim, PhD; Joung-Won Lee, BSc; Hyun-Young Park, MD, PhD

Background: This study aimed to validate the Korean Genome Epidemiology Study (KoGES) risk score to predict the 4-year risk of hypertension (HT) in a large nationwide sample, and compare its discrimination and calibration with the Framingham and blood pressure (BP)-only models.

Methods and Results: This study analyzed 69,918 subjects without HT at baseline from the National Sample Cohort in the National Health Insurance Service database. We compared the Framingham, KoGES, and BP-only models for discrimination using area under the receiver-operating characteristic curves (AROC), calibration using goodness-of-fit tests, and reclassification ability using the continuous net reclassification improvement (NRI) and integrated discrimination improvement. Of 69,918 subjects, 18.6% developed HT during the follow-up. AROC was significantly higher for the KoGES (0.733) than for the Framingham (0.729) or BP-only (0.707) model. Recalibrated Framingham model underestimated HT incidence in all deciles (P<0.001). BP-only model overestimated risk in the lower deciles (P<0.001). KoGES model accurately predicted risk in all except the highest decile (χ²=14.85, P=0.062).

Conclusions: In this validation study, the KoGES model demonstrated better discrimination, calibration, and reclassification ability than either the Framingham or BP-only model. The KoGES model may help identify Korean individuals at high risk for HT. (Circ J 2016; 80: 1578–1582)

Key Words: Framingham risk score; Hypertension; KoGES; Risk score; Validation
Additionally, we also derived a simple model, a BP-only model that included systolic and diastolic BPs, to compare the performance between 3 models. The exact equations used to calculate risk for HT with each of the 3 models are shown in the Appendix.

The parental history of HT was evaluated using 2 categories (1: yes or 0: no) in the validation cohort and 3 categories (neither, one, or both) in the Framingham and KoGES models. To directly apply the regression coefficients of both models to the NSC data, we calculated weighted averages of the distribution of the parental history of HT in the Framingham and KoGES studies. The BP-only model, which used systolic and diastolic BPs, was constructed using multiple logistic regression analysis. We compared discrimination using area under the receiver-operating characteristic curves (AROCs) according to the method of DeLong et al and calibration using the goodness-of-fit test procedure based on Hosmer and Lameshow’s

### Table 1. Baseline Characteristics of the HT Risk Score Validation Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=69,918)</th>
<th>Normotensive (n=56,940)</th>
<th>Hypertensive (n=12,978)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>n, %</td>
<td>100.0</td>
<td>81.4</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td>Sex, women, %</td>
<td>34.640 (49.5)</td>
<td>51.4</td>
<td>41.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>50.3 (7.5)</td>
<td>49.7 (7.3)</td>
<td>52.6 (7.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BP, mean (SD), mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>118.1 (11.3)</td>
<td>116.7 (11.2)</td>
<td>124.3 (9.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73.9 (8.0)</td>
<td>73.0 (7.9)</td>
<td>77.8 (6.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>21.3</td>
<td>20.7</td>
<td>24.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Parental HT, %</td>
<td>8.8</td>
<td>8.4</td>
<td>10.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>23.5 (2.5)</td>
<td>23.3 (2.7)</td>
<td>24.4 (2.9)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

†P-value for χ² or t-test procedure. BMI, body mass index; BP, blood pressure; HT, hypertension; SD, standard deviation.

### Figure 1. Receiver-operating characteristic curves for prediction of hypertension incidence using the Korean Genome Epidemiology Study (KoGES), Framingham, and blood pressure-only models. Respective areas under the receiver-operating characteristic curves are 0.707, 0.729, and 0.733.
Figure 2 shows the agreement between the observed risk and mean predicted risk estimated by the 3 prediction models stratified by deciles. The recalibrated Framingham model consistently underestimated HT incidence, especially in high-risk groups. The BP-only model overestimated risk in the lower deciles. With the exception of the highest decile, risk predicted by the KoGES model was very close to the observed risk compared with the Framingham and BP-only models ($\chi^2=14.85$, $P=0.062$).

The KoGES model improved continuous NRI (0.354, 95% CI: 0.343–0.365; and 0.542, 95% CI: 0.524–0.561, respectively) and IDI (0.023, 95% CI: 0.022–0.024; and 0.041, 95% CI: 0.040–0.043, respectively) over the Framingham and BP-only models.

Discussion

In this validation study of a large, nationwide sample cohort, the HT risk score according to the KoGES model showed good discrimination and calibration for predicting the onset of HT. Additionally, discrimination was significantly better with the KoGES model than with the recalibrated Framingham or BP-only model, and the estimated risk of HT calculated by the

### Table 2. Comparison of Discrimination and Reclassification in KoGES, Recalibrated Framingham, and BP Only Model

<table>
<thead>
<tr>
<th>Measurement</th>
<th>KoGES vs. Framingham recalibrated</th>
<th>P value</th>
<th>KoGES vs. BP only</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$AROC (95% CI)</td>
<td>0.004 (0.003–0.005)</td>
<td>&lt;0.001</td>
<td>0.026 (0.024–0.028)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NRI (95% CI)</td>
<td>0.354 (0.343–0.365)</td>
<td>&lt;0.001</td>
<td>0.400 (0.382–0.418)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IDI (95% CI)</td>
<td>0.023 (0.022–0.024)</td>
<td>&lt;0.001</td>
<td>0.029 (0.027–0.030)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AROC, area under the receiver operating characteristic curve; BP, blood pressure; CI, confidence interval; IDI, integrated discrimination improvement; NRI, continuous net reclassification improvement.
KoGES model was close to the observed incidence. Reclassification analysis showed that the KoGES model led to a statistically significant improvement over the recalibrated Framingham and BP-only models (NRI, 0.354; 95% CI, 0.343–0.365 and 0.542; 95% CI, 0.523–0.561, respectively).

A previous study showed that using a risk score to predict the incidence of HT may not be accurate in ethnic groups in which the score has not been validated. Most risk scores used to predict HT have not been validated externally in a different data source. According to a recent review article, only the Framingham and Hopkins scores have been evaluated in populations or ethnic groups that are different from those used for initial development of the model. Data from the Whitehall II Study validated the HT risk score initially developed in the Framingham Offspring Study by showing that the score had good discrimination and calibration, and that the ratio of predicted to observed risk was close to 1.00 among various subgroups. However, these 2 independent cohorts both consisted of white populations. The Multi-Ethnic Study of Atherosclerosis showed that the Framingham model significantly underestimated the risk for HT, and the recalibration is necessary to correct this difference between observed and predicted risk for HT. Similarly, our previous study in a Korean population demonstrated that the Framingham risk score underestimated risk for HT even though the individuals in both studies had similar risk factors at baseline. Although the discrimination was similar to that in the Framingham Offspring Study, concordance between observed and predicted risk was poor even after recalibration of the Framingham model, suggesting that risk models may not be accurate in different ethnic populations even after adjusting the model. Another study in a Chinese cohort showed that the Framingham model had good calibration but lower discrimination than risk models developed from the original cohort.

Differences in ethnicities based on genetic variation, cultural or environmental factors, and socioeconomic status may influence the etiology, prevalence, progression, and outcome of various diseases. Many previous studies show differences in the prevalence of CVD risk factors across ethnicities. Several studies have shown that Asians have a higher risk of HT, CVD, and all-cause death than white Europeans with the same BMI. In clinical practice, differences in health outcomes among ethnicities may be important for implementation of health interventions. Genetic variants between ethnicities may also contribute to differences in CVD-related risk factors and additional validation studies of risk score models using independent data sources will help clarify these discrepancies.

Applying the HT prediction model in the clinical practice may have some positive advantages: (1) improve adherence by high-risk individuals for intensive interventions, (2) motivate high-risk individuals to sustain their efforts in lifestyle modification, and (3) provide personalized medicine and care according to risk category.

The strengths of our study include the use of a large, nationwide sample cohort extracted by stratified random sampling, with proportional allocation among 1,476 categories stratified by sex, age, and income level. These advanced stratification methods suggest the KoGES risk score accurately identifies individuals at high risk for incident HT. This study was also the first to validate a risk score for incident HT that had been previously developed in an Asian population.

However, the study has some limitations. First, this study used a single BP reading to determine hypertensive status, which does not account for variability in BP measurements and potential bias introduced when using single measurements. Second, the KoGES model was validated using independent data from individuals of the same ethnicity and is therefore applicable only in Korean populations. Third, although the model was valid for individuals aged 40–69 years, it may not be accurate in individuals outside this age range.

In summary, this validation study suggested that the KoGES risk score for predicting the incidence of HT had significantly better discrimination, calibration, and reclassification ability than the recalibrated Framingham risk score after a 4-year follow-up period. Furthermore, the KoGES risk score met the requirements for inclusion in the guidelines, as the performance was superior to the BP-only model, and may be useful for guiding lifestyle modifications and early treatment of HT.

Acknowledgments

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**Appendix**

The 4-year risks of the KoGES, recalibrated Framingham, and blood pressure-only models for incident hypertension were calculated as follows.

(1) Estimated risk calculated by the KoGES model.

\[
\hat{P}_{\text{KoGES}} = 1 - \exp \left\{ - \exp \left( \frac{k - \text{age}}{1.0805} \right) \right\}
\]

where, \(k = \ln(4) - 30.3547 \times \text{age} - 0.2838 \times \text{sex} - 0.0642 \times \text{BMI} - 0.3025 \times \text{DBP} - 0.2912 \times \text{smoke} - 0.0875 \times \text{parental history} - 0.0665 \times \text{BMI} - 0.0031 \times \text{age} \times \text{DBP}

(2) Estimated risk calculated by the Framingham recalibrated model.

\[
\hat{P}_{\text{Framingham}} = 1 - \exp \left\{ - \exp \left( \frac{k - \text{age} \times \text{sex} \times \text{BMI} \times \text{DBP}}{1.0805} \right) \right\}
\]

where, \(k = \ln(4) - 22.9495 - 0.1564 \times \text{age} - 0.2084 \times \text{sex} - 0.3059 \times \text{BMI} - 0.2912 \times \text{smoke} - 0.0875 \times \text{parental history} - 0.0339 \times \text{BMI} - 0.0016 \times \text{age} \times \text{DBP}

(3) Estimated risk calculated by the blood pressure-only model.

\[
\hat{P}_{\text{BP only}} = 1 - \exp \left\{ - \exp \left( \frac{k - \text{SBP} \times \text{DBP}}{0.8115} \right) \right\}
\]

where, \(k = \ln(4) - 0.0375 \times \text{SBP} - 0.0291 \times \text{DBP} \times \text{sex}

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