Results of a Markov Model Analysis to Assess the Cost-Effectiveness of Statin Therapy for the Primary Prevention of Cardiovascular Disease in Korea: The Korean Individual-Microsimulation Model for Cardiovascular Health Interventions

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ABSTRACT

Background: Although hyperlipidemia is well recognized as a risk factor for cardiovascular disease (CVD), there has been no appraisal of the economic impact of statin therapy in Korea.

Objective: The aim of this model analysis was to determine the cost-effectiveness of statin therapy versus no treatment for the primary prevention of CVD over a lifetime in Korea, from a health care system perspective.

Methods: We developed the Korean Individual-Microsimulation Model for Cardiovascular Health Interventions (KIMCHI), an epidemiologic and economic Markov model of first-onset CVD in Korea in which all individuals began the simulation in the health state alive without CVD, and moved among the 4 health states (alive without CVD, alive with CVD, dead from CVD, and dead from non-CVD causes) in yearly cycles for any specified time horizon, up to 40 years. KIMCHI was populated with 372 subjects from the 2005 Korean National Health and Nutrition Examination Survey (KNHNES) who were aged ≥45 years, did not have a history of myocardial infarction or ischemic stroke, and met current Korean reimbursement criteria for treatment with lipid-lowering medications. The probability of first-onset CVD was estimated for each study participant individually, based on an Asian population-specific risk equation that relied on an individual’s sex, age, serum total cholesterol, systolic blood pressure, current smoking status, diabetes mellitus status, and body mass index. Statin treatment was represented by a hybrid of atorvastatin and simvastatin (the most popular statins in Korea), the lipid-modifying effects of which were derived from a published meta-analysis. Data regarding utilities and costs of CVD (both those covered and not covered by insurance) were derived from published local sources.

Results: In the base case, the estimated incremental cost-utility ratio was 15,134,284 Korean won (KRW) per quality-adjusted life-year (QALY) gained, and the estimated incremental cost-effectiveness ratio was 20,657,829 KRW per life-year gained (LYG) (1200 KRW ≈ US $1). Based on a willingness-to-pay (WTP) threshold of 30 million KRW per QALY saved, there was a 93.7% probability that statin therapy would be cost-effective. Given a WTP threshold of 20 million KRW per QALY, there was a 53.8% probability of being cost-effective. The probabilities at WTP thresholds of 30 and 20 million KRW per LYG were 62.4% and 25.8%, respectively.

Conclusions: Based on this analysis using data from the 2005 KNHNES and the KIMCHI model, statin therapy is likely to be cost-effective for the primary prevention of CVD among Koreans aged ≥45 years. The probability of being cost-effective was greater at a threshold of 30 million KRW per QALY (93.7%) than at 20 million KRW per QALY (53.8%). (Clin Ther. 2009;31:2919–2930) © 2009 Excerpta Medica Inc.

Key words: cardiovascular disease, cost-effectiveness, hyperlipidemia, statins, stroke.
INTRODUCTION
Recently, there has been increasing focus on cardiovascular disease (CVD) in Korea because of rising prevalence, mortality, and associated costs. The prevalence of cerebral infarction among Korean men increased from 1.2% in 1998 to 2.2% in 2005, and from 1.3% in 1998 to 2.0% in 2005 among women. During the same period, the prevalence of ischemic heart disease increased from 0.7% to 1.7% among men and from 0.8% to 2.2% among women. Since 2000, CVD has been the second leading cause of death in Korea. In 2006, total insurance-covered health care costs devoted to the management of CVD in Korea amounted to US $850 million, representing 4% of Korean National Health Insurance expenditures.

As in other developed countries, hyperlipidemia is well recognized in Korea as a risk factor for CVD, and lipid-lowering therapy is commonplace. Among the various treatment options used to control serum lipid level and prevent CVD, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (ie, statins) are the most commonly used. Indeed, statins are among the most widely prescribed pharmaceuticals in Korea. Driven by unequivocal and robust efficacy data, there is ample evidence of the cost-effectiveness of statins for the prevention of CVD across the world.

However, no published appraisal of the cost-effectiveness of statin therapy in Korea was identified in a literature search. A search of the MEDLINE database using the terms atorvastatin and cost-effectiveness, with no time limits, did not identify any cost-effectiveness studies that assessed the use of atorvastatin in Korea. Data from overseas are compelling, but they are not entirely applicable to the Korean health care setting. It is common for a drug to be cost-effective in some countries but not others, given high variability in input parameters, including drug costs, disease costs, and epidemiologic characteristics. The aim of this model analysis was to determine the cost-effectiveness of statin therapy versus no treatment for the primary prevention of CVD over a lifetime in Korea, from a health care system perspective.

METHODS
Cost utility was primarily measured as incremental cost per quality-adjusted life-year (QALY) gained. Modeled outcomes were also quantified in terms of cost per life-year gained. The reference condition in the modeled evaluation was untreated CVD, comprising nonfatal or fatal myocardial infarction (MI) and/or ischemic stroke.

Decision Model
We developed the Korean Individual-Microsimulation Model for Cardiovascular Health Interventions (KIMCHI), an epidemiologic and economic model of first-onset CVD in Korea that can be applied to cost-effectiveness analyses of cardiovascular interventions. KIMCHI is a Markov model with yearly cycles and the following health states: alive without CVD, alive with CVD, dead from CVD, and dead from non-CVD causes. Figure 1 provides a conceptual representation of KIMCHI, which was developed and analyzed with Microsoft Excel (Microsoft Corporation, Redmond, Washington).

In each health intervention strategy (ie, no statin or statin therapy), all individuals began the simulation in the health state alive without CVD, and moved among the 4 health states in yearly cycles for any specified time horizon, up to 40 years. Subjects entered the state alive with CVD if they developed nonfatal incident CVD (ie, developed CVD and survived until the end of the cycle). They entered the state dead from CVD if they developed a fatal cardiovascular event, either when CVD was previously nonexistent (ie, transition from the health state alive without CVD) or when CVD was already existent (ie, transition from the health state alive with CVD). Finally, the state dead from non-CVD causes represented those who died from non-CVD causes, either with or without preexisting CVD (ie, transitions from the health states alive without CVD or alive with CVD, respectively).

KIMCHI was populated at baseline by individual subjects representative of the Korean population for whom data were available regarding cardiovascular risk profile. Annual probabilities of CVD incidence were estimated for each individual using the Asian-specific cardiovascular risk equation by Wu et al, which was based on follow-up of >11,000 Chinese participants in the United States and People’s Republic of China Collaborative Study of Cardiovascular and Cardiopulmonary Epidemiology. The equation estimated the probability of the composite outcome of coronary heart disease and/or ischemic stroke, based on an individual’s demographic and risk factor status (ie, sex, age, serum total cholesterol [TC], systolic blood pressure [SBP], smoking, diabetes mellitus [DM] status, and body mass index [BMI]).
Study Subjects and Data Collection

The population used in the modeled economic evaluation was a subset of the population enrolled in the 2005 Korean National Health and Nutrition Examination Survey (KNHNES).2 The 2005 KNHNES was the latest of a series of cross-sectional national surveys conducted every 3 years by the Korean Ministry for Health, Welfare, and Family Affairs. It obtained informed consent from participants and only released unidentified (ie, not reidentifiable) data to researchers. In 2005, KNHNES collected comprehensive information regarding the health and well-being of Koreans based on self-reports of disease, health behavior, and nutritional habits, physical examination, and blood sampling. Overall, 34,145 subjects representative of the national demographic profile were included in the survey; of these, 10,816 subjects underwent physical examination and blood sampling.

The cohort used in KIMCHI comprised 372 men and women aged ≥45 years with complete data for their cardiovascular risk profile who did not have a history of CVD and who met current Korean reimbursement criteria for treatment with lipid-lowering medications: serum TC ≥250 mg/dL, or ≥220 mg/dL with ≥1 other CVD risk factor (hypertension, DM, or both).17

Variables in the Model

Key data inputs used in the analysis are summarized in Table I.

Transition Probabilities

In the model, cardiovascular risk (ie, probability of transitioning from alive without CVD to alive with CVD or dead from CVD) was estimated for each of the 372 subjects individually, based on the risk equation from Wu et al.16 For each subject, the equation estimated the probability of the primary incidence of CVD (ie, MI and/or ischemic stroke [nonfatal or fatal]), based on an individual’s sex, age, serum TC, SBP (in units of mm Hg), current smoking status (yes/no), DM status (yes/no), and BMI (in units of kg/m²). As
probabilities for fatal and nonfatal CVD by applying sex- and age-specific proportions of first-onset CVD that were fatal within 365 days, based on data for the year 2004 from HIRA. In the first cycle of the model, the CVD-related transition probabilities were calculated for each subject using the values of the risk factor variables reported directly in the 2005 KNHNES. With subsequent cycles, cardiovascular risk profiles were updated by changing age, SBP, and possible DM status of each subject. Other risk factors were assumed to remain unaltered with age. SBP and DM status were increased according to predicted age-related trends. Trends were determined (separately for each sex) by first calculating the mean SBP levels and prevalence of DM for each age based on available cross-sectional data from the 2005 KNHNES, then

Table I. Key input data used in the Korean Individual-Microsimulation Model for Cardiovascular Health Interventions, a 40-year epidemiologic and economic model of first-onset cardiovascular disease in Korea, populated with 372 subjects from the 2005 Korean National Health and Nutrition Examination Survey who were aged ≥45 years, did not have a history of myocardial infarction (MI) or ischemic stroke, and met current Korean reimbursement criteria for treatment with lipid-lowering medications.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base-Case Value</th>
<th>Uncertainty Range</th>
<th>Data Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy of statin treatment: reduction in TC*</td>
<td>27.3%</td>
<td>95% CI, 25.8%-28.8%</td>
<td>Rogers et al²²</td>
</tr>
<tr>
<td>Annual statin acquisition cost*</td>
<td>335,273 KRW</td>
<td>N/A</td>
<td>HIRA²⁴ and IMS Health²¹</td>
</tr>
<tr>
<td>Cost of MI per person (per person)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>7,814,848 KRW</td>
<td>±25% (uniform)</td>
<td>HIRA²⁴</td>
</tr>
<tr>
<td>Year 2+</td>
<td>1,285,656 KRW</td>
<td>±25% (uniform)</td>
<td></td>
</tr>
<tr>
<td>Fatal event</td>
<td>1,661,503 KRW</td>
<td>±25% (uniform)</td>
<td></td>
</tr>
<tr>
<td>Cost of ischemic stroke (per person)</td>
<td></td>
<td></td>
<td>HIRA²⁴</td>
</tr>
<tr>
<td>Year 1</td>
<td>8,074,965 KRW</td>
<td>±25% (uniform)</td>
<td></td>
</tr>
<tr>
<td>Year 2+</td>
<td>1,046,679 KRW</td>
<td>±25% (uniform)</td>
<td></td>
</tr>
<tr>
<td>Fatal event</td>
<td>2,293,845 KRW</td>
<td>±25% (uniform)</td>
<td></td>
</tr>
<tr>
<td>Persistence with statin treatment</td>
<td></td>
<td></td>
<td>Perreault et al²⁶</td>
</tr>
<tr>
<td>Utilities</td>
<td></td>
<td></td>
<td>Kang et al²³</td>
</tr>
<tr>
<td>MI</td>
<td>0.80</td>
<td>±25% (uniform)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.58</td>
<td>±25% (uniform)</td>
<td></td>
</tr>
</tbody>
</table>

*TC = total cholesterol; KRW = Korean won (1200 KRW ≈ US $1)²⁵; N/A = not applicable; HIRA = Health Insurance Review and Assessment Services.

The Wu et al¹⁶ equation estimates the probability of total CVD; that is, a composite of nonfatal and fatal CVD. We were able to stratify this into separate
fitting polynomial mathematical functions to quantify the relationships between age and mean SBP/DM prevalence.

For subjects in the health state alive with CVD, the probabilities of recurrent cardiovascular events were not determined individually because there were no applicable risk equations for this setting. Instead, the same probabilities were assumed for all subjects within the same sex-and-age stratum. Relevant probabilities were derived from HIRA data.18

Age- and sex-specific risks of noncardiovascular deaths were based on year-2005 Korean population and mortality statistics from the Korean Statistical Information Services.3 The risk of noncardiovascular mortality was calculated as the difference between the risk of all-cause mortality and the risk of cardiovascular mortality. Specific Korean data regarding noncardiovascular mortality were not available for this study. Instead, the risks of noncardiovascular mortality were assumed to differ between those with existing CVD and those without existing CVD; we used differential probabilities based on data from the Danish Monitoring Trends and Determinants in Cardiovascular Disease study,19,20 a long-term follow-up of Danish subjects after first-ever MI and ischemic stroke.

### Treatment Effects of Statin Therapy

Statin treatment was represented by a hybrid of atorvastatin and simvastatin, currently the most widely used statins in Korea (together accounting for 56.8% of the statin market).21 The combined weighted mean efficacy of atorvastatin and simvastatin for reducing TC was calculated from statin- and dose-specific efficacy measures drawn from a meta-analysis of the lipid-modifying effects of statins.22 That meta-analysis included a total of 8420 subjects in 18 randomized head-to-head trials evaluating atorvastatin at doses of 10, 20, 40, and/or 80 mg and simvastatin at doses of 10, 20, 40, and/or 80 mg. Using the relative market share between atorvastatin and simvastatin in 2008 in Korea (Table II), the combined weighted mean efficacy of atorvastatin and simvastatin in reducing TC was estimated to be 27.30% (95%CI, 25.80%–28.80%).

In the current model, for subjects in the statin group who were already taking lipid-lowering therapy, TC levels were not altered. For subjects in the nonstatin group who were already taking lipid-lowering therapy, TC levels were increased by 27.3% to reflect the effects of ceasing therapy. Therefore, the underlying assumption for subjects already taking lipid-lowering therapy was that they were taking the

### Table II. Treatment effects, costs, and year-2008 market share of atorvastatin and simvastatin at available doses in Korea, as used in the Korean Individual-Microsimulation Model for Cardiovascular Health Interventions, a 40-year epidemiologic and economic model of first-onset cardiovascular disease in Korea, populated with 372 subjects from the 2005 Korean National Health and Nutrition Examination Survey who were aged ≥45 years, did not have a history of myocardial infarction or ischemic stroke, and met current Korean reimbursement criteria for treatment with lipid-lowering medications.2,21,22

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose, mg</th>
<th>Reduction in TC, % (95% CI)</th>
<th>Annual Acquisition Cost, KRW</th>
<th>Year-2008 Share of Atorvastatin and Simvastatin Market, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>27.47 (26.22%–28.72%)</td>
<td>361,963</td>
<td>34.9</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>33.28 (30.34%–36.22%)</td>
<td>362,328</td>
<td>7.2</td>
</tr>
<tr>
<td>40</td>
<td></td>
<td>37.66 (33.94%–41.38%)</td>
<td>548,971</td>
<td>1.2</td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>25.96 (24.62%–27.30%)</td>
<td>306,080</td>
<td>52.0</td>
</tr>
<tr>
<td>40</td>
<td></td>
<td>28.88 (26.65%–31.10%)</td>
<td>363,424</td>
<td>4.8</td>
</tr>
<tr>
<td>Weighted mean</td>
<td></td>
<td>27.30 (25.80%–28.80%)</td>
<td>335,273</td>
<td>–</td>
</tr>
</tbody>
</table>

TC = total cholesterol; KRW = Korean won (1200 KRW ≈ US $1).25

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equivalent to the hybrid atorvastatin–simvastatin treatment being modeled. TC levels were unaltered for subjects in the nonstatin group who were not taking lipid-lowering therapy at baseline.

**Utilities**

Utility values for MI and stroke (0.80 and 0.58, respectively) were derived from the additional analysis of the 2005 KNHONES by Kang et al.²³ To derive a composite utility weight for prevalent CVD (0.631), the individual utility weights for MI and stroke were applied to the proportional distribution of MI alone (23.08%), stroke alone (75.52%), and concurrent MI and stroke (1.40%), as observed in the 2005 KNHONES.² For concurrent MI and stroke, the lesser of the 2 utilities (ie, 0.58) was applied. The utility weight for subjects without CVD was assumed to be 1.0. Because the utility values derived by Kang et al pertained to the prevalent (ie, chronic) state, they were applied only to the annual cycles that followed the one in which CVD first occurred. No utility penalty was applied to the cycle in which CVD first occurred. Although this approach was conservative and may have underestimated the cost-effectiveness of statin therapy, the impact would have been small in the context of a 40-year model time horizon.

**Cost of CVD**

The estimated cost of treating CVD was derived from HIRA,⁷ which provided mean medical costs, with and without insurance coverage, for fatal and nonfatal MI, and for fatal and nonfatal stroke, based on the national population. Using the proportional distributions of incident stroke and MI among the Chinese population in the US–Chinese study,¹⁶ weighted mean costs for fatal and nonfatal CVD were estimated (Table I). Year-2 costs were applied in cycle 2 and beyond, with an assumption that annual costs remained the same in all subsequent years until recurrence. In the base-case analysis, the cost of CVD was assumed to increase by 9% annually, as recommended by HIRA.⁷

**Cost of Statin Therapy**

Dose-specific costs of atorvastatin and simvastatin were based on current pharmaceutical price lists in Korea,²⁴ and the weighted mean cost of the hybrid statin was estimated to be 335,273 Korean won (KRW) per year (1200 KRW = US $1).²⁵ The ancillary costs of statins, arising from physician visits to obtain prescriptions and monitoring for lipid levels and potential adverse events, were estimated by HIRA to be 118,597 KRW per year.²⁷ With a baseline year of 2008, all future costs were discounted at a 5% annual rate, as were years of life and QALYs lived overall, as well as QALYs gained and life-years gained (LYGs).

**Sensitivity and Uncertainty Analyses**

A series of 1-way sensitivity analyses were undertaken, based on the 95% CI of the expected change to TC (ie, triangular uncertainty distribution) and ±25% uniform variations to the Wu et al¹⁶ cardiovascular risk predictions, CVD costs, and utility weights (Table I). That is, the values of these key inputs were varied one at a time while maintaining the other inputs at base-case values. The annual discount rate applied to future costs, years of life lived, and QALYs lived was varied uniformly between 0% and 10%, and the annual rate of increase in CVD costs was varied uniformly from 0% to 9%. Finally, incomplete persistence with (ie, discontinuation from) statin treatment was also considered. Because no published data regarding long-term persistence with statins in Korea, or in Asia overall, were identified before the inception of the present study, values were extracted from a large Canadian data set.²⁶ Other than its size, the main advantages of these data were that they were specific to a middle-aged population (aged 50–64 years) and stratified by use for primary and secondary CVD prevention. There were 13,642 subjects in the primary prevention cohort, among whom persistence with statins was 65% at 6 months and 35% at 3 years. Therefore, in sensitivity analyses, 65% persistence was assumed in cycle 1 of the model (ie, the first year of treatment), with a subsequent linear decrease to 35% in cycle 3. From cycle 4 onward, 35% persistence was assumed. The effects of incomplete persistence were mediated by proportional reductions in the TC-reducing efficacy and costs of statin treatment from cycle 2 onward. Costs in cycle 1 were not reduced to account for discontinuation because statins would still have been purchased at the time of treatment initiation, even if they were not ultimately taken.

The effects of variations to these key inputs (except incomplete persistence) were then assessed simultaneously in multivariate uncertainty analyses (probabilistic sensitivity analyses) via Monte Carlo simulation, with 2000 iterations.²⁷ Monte Carlo simulation was enabled by adding the software @Risk for Excel (Palisade Corporation, New York, New York).
RESULTS

Baseline Characteristics of the Modeled Subjects

The baseline characteristics of the 372 modeled subjects are summarized in Table III. The mean (SD) age was 59.3 (9.5) years and the majority of modeled subjects (64%) were female. Mean TC and LDL-C were 249.1 (27.6) and 244.2 (64.1) mg/dL, respectively. Twenty-one percent of the population had DM and 26.1% were smokers. Of note, despite the fact that all of the modeled subjects met current Korean reimbursement criteria for treatment with lipid-lowering medication, only 3.5% were taking these medications.

Results of the Base-Case Analysis

Table IV presents the results of the base-case modeled economic evaluation, based on simulated 40-year follow-up of 372 Korean adults aged ≥45 years without prior CVD who met criteria for statin treatment. Each subject receiving statins to treat hyperlipidemia for the primary prevention of CVD gained 0.18 life-years (discounted) and 0.25 QALYs (discounted) as a result. The net incremental cost (discounted) was 3,772,282 KRW per subject. The estimated incremental cost-utility ratio was 15,134,284 KRW per QALY gained and the estimated incremental cost-effectiveness ratio (ICER) was 20,657,829 KRW per LYG.

Results of Sensitivity and Uncertainty Analyses

The results of 1-way sensitivity analyses showed that outcomes of the base-case scenario were robust to plausible changes in key input parameters; none of the resultant incremental cost-utility ratios exceeded 30 million KRW per QALY gained (Table V). Cost-effectiveness acceptability curves are presented in Figure 2. The 1900 (95%) middle ranked of the 2000 Monte Carlo results for incremental cost-utility ratios (ICURs) were between 9.4 and 33.0 million KRW per QALY gained and 12.2 and 46.4 million KRW per LYG. Based on a willingness-to-pay (WTP) threshold of 20 million KRW per QALY saved, there was a 53.8% probability that statin therapy would be cost-effective. At a WTP threshold of 30 million, the probability was 93.7%. The probabilities at WTP thresholds of 30 and 20 million KRW per LYG were 62.4% and 25.8%, respectively.

DISCUSSION

A search of the literature did not identify other published economic evaluations of statin therapy versus no statin therapy for the primary prevention of CVD in Korea. The current evaluation was based on a microsimulation model, which applied data inputs (ie, regarding transition probabilities, costs, and utilities), as well as updated them with time, for each subject individually. The resulting ICUR was 15,134,284 KRW per QALY saved, which is cost-effective according to a World Health Organization guideline that a treatment is cost-effective if the treatment cost is lower than the gross domestic product per capita.28 The per-capita gross domestic product in Korea in 2007 was 18,630,000 KRW. Therefore, the ICER in terms of KRW per LYG (20,657,829) approached, but did not reach, the established World Health Organization threshold. Sensitivity and uncertainty analyses indicated that results of the base-case analysis were robust to plausible changes in key input parameters.
Table IV. Results of the base-case analysis in the Korean Individual-Microsimulation Model for Cardiovascular Health Interventions, a 40-year epidemiologic and economic model of first-onset cardiovascular disease (CVD) in Korea, populated with 372 subjects from the 2005 Korean National Health and Nutrition Examination Survey who were aged ≥45 years, did not have a history of myocardial infarction or ischemic stroke, and met current Korean reimbursement criteria for treatment with lipid-lowering medications.2*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Years of Life Lived</th>
<th>QALYs Lived</th>
<th>CVD Costs, KRW</th>
<th>Treatment Costs, KRW</th>
<th>Net Costs, KRW</th>
<th>ICER, KRW/LYG</th>
<th>ICUR, KRW/QALY Gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Statin</td>
<td>4665</td>
<td>4521</td>
<td>4,381,752,790</td>
<td>0</td>
<td>4,381,752,790</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Statin</td>
<td>4733</td>
<td>4614</td>
<td>3,636,679,364</td>
<td>2,148,362,265</td>
<td>5,785,041,630</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Difference</td>
<td>Overall</td>
<td>67.93</td>
<td>–745,073,425</td>
<td>2,148,362,265</td>
<td>1,403,288,840</td>
<td>20,657,829</td>
<td>15,134,284</td>
</tr>
<tr>
<td></td>
<td>Per subject</td>
<td>0.18</td>
<td>–2,002,886</td>
<td>5,775,167</td>
<td>3,772,282</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

QALYs = quality-adjusted life years; KRW = Korean won (1200 KRW ≈ US $1)25; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; ICUR = incremental cost-utility ratio.

*All future outcomes and costs were discounted at 5% annually.
Statin therapy has generally been evaluated as a cost-effective strategy for the primary prevention of coronary heart disease and stroke in several countries, including the United States, United Kingdom, and Canada.\textsuperscript{29-32} However, cost-effectiveness varied according to the underlying risk of the target population and duration of treatment. For example, Grover et al\textsuperscript{29} found that lifelong statin therapy was cost-effective among Canadians aged 40 to 74 years (ICER, $16,700 per LYG) but not among women aged <50 years. Among US patients with type 2 DM and 1 additional risk factor for CVD, primary prevention with atorvastatin was found to be cost-saving over a 25-year time horizon.\textsuperscript{30} Our findings are consistent with this theme, having found long-term statin therapy to be cost-effective among Koreans at relatively high risk for CVD (as indicated by eligibility for lipid-lowering treatment). In any comparison of ICERs from different studies, however, one must be mindful that the methods used in each are disparate, and that the costs of statins and disease vary from population to population.

The main strength of the present study was its use of a microsimulation model populated with a nationally representative sample of Korean adults. In more traditional cohort-analysis models, there is an unrealistic assumption that all subjects in the modeled cohort, or within the same stratum of the modeled cohort, share the same characteristics and behave in the same manner. Microsimulation models overcome this limitation by using individual-level data and simulating the health experiences of each subject separately, based on his or her unique characteristics.\textsuperscript{33,34} In this way, microsimulation models reduce the need for first-order Monte Carlo simulation,\textsuperscript{27} especially if the modeled subjects are representative of the population to whom results are to be applied. Because our analysis was based on individual data drawn from a subset of nationally representative 2005 KNHINES subjects, our results are likely to be generalizable to Korean patients aged ≥45 years without CVD but who meet current treatment criteria for lipid-lowering therapy.

This analysis required several assumptions that limit its findings. However, it should be noted that all assumptions were made according to the best available evidence and, in the majority of cases, the most consen-

### Table V. Results of 1-way sensitivity analyses in the Korean Individual-Microsimulation Model for Cardiovascular Health Interventions, a 40-year epidemiologic and economic model of first-onset cardiovascular disease (CVD) in Korea, populated with 372 subjects from the 2005 Korean National Health and Nutrition Examination Survey who were aged ≥45 years, did not have a history of myocardial infarction or ischemic stroke, and met current Korean reimbursement criteria for treatment with lipid-lowering medications.\textsuperscript{2}

<table>
<thead>
<tr>
<th>Variation to Key Input Data</th>
<th>KRW/LYG</th>
<th>KRW/QALY Gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>20,657,829</td>
<td>15,134,284</td>
</tr>
<tr>
<td>95% CI for TC-lowering effect of statins</td>
<td>22,595,332–19,025,521</td>
<td>16,548,440–13,927,996</td>
</tr>
<tr>
<td>25% Reduction in estimated Wu et al\textsuperscript{16} cardiovascular risk</td>
<td>26,426,673</td>
<td>19,471,394</td>
</tr>
<tr>
<td>25% Increase in estimated Wu et al\textsuperscript{16} cardiovascular risk</td>
<td>17,393,521</td>
<td>12,650,462</td>
</tr>
<tr>
<td>25% Reduction in estimated CVD costs</td>
<td>23,360,438</td>
<td>17,093,634</td>
</tr>
<tr>
<td>25% Increase in estimated CVD costs</td>
<td>17,898,809</td>
<td>13,099,669</td>
</tr>
<tr>
<td>25% Reduction in utility values</td>
<td>20,657,829</td>
<td>13,691,876</td>
</tr>
<tr>
<td>25% Increase in utility values</td>
<td>20,657,829</td>
<td>17,051,410</td>
</tr>
<tr>
<td>Persistence with statins: 65% in cycle 1 followed by linear decrease to 35% by cycle 3</td>
<td>23,190,894</td>
<td>16,930,664</td>
</tr>
<tr>
<td>0% Annual rate of increase in CVD costs</td>
<td>28,520,967</td>
<td>20,893,802</td>
</tr>
<tr>
<td>0% Discount rate</td>
<td>8,640,373</td>
<td>6,837,710</td>
</tr>
<tr>
<td>10% Discount rate</td>
<td>38,121,694</td>
<td>25,889,057</td>
</tr>
</tbody>
</table>

TC = total cholesterol; KRW = Korean won (1200 KRW = US $1)\textsuperscript{25}; LYG = life-year gained; QALY = quality-adjusted life-year.
Initially without CVD at baseline; that is, the initial model cohort did not include subjects with prior CVD. Because secondary cardiovascular risk is greater than primary risk, and because secondary events are usually associated with greater mortality, the absolute benefit and cost-effectiveness of statin therapy could have been greater in the secondary preventive setting. Therefore, the restriction of our analysis to just the primary preventive setting underestimated the overall cost-effectiveness of statin therapy.

Furthermore, the Wu et al \(^ {16}\) Chinese cardiovascular risk equation was adopted, so that they would have served to increase the estimated ICUR and ICER.

A major assumption was related to the application of the Wu et al \(^ {16}\) Chinese cardiovascular risk equation to Korean subjects. This was undertaken because there were no available cardiovascular risk equations specific to a Korean population. Although this was not ideal, the Wu et al equation was nevertheless contemporary, based on a North Asian population, and the most appropriate equation available.

The risk equation was also limited in that it predicted only primary (first-ever) CVD events. Therefore, the probabilities of recurrent CVD events could not be estimated individually. Rather, they were assumed to be the same for all subjects within the same sex-and-age stratum using HIRA data.\(^ {23}\) The nonavailability of a secondary cardiovascular risk equation also meant that our analysis was restricted to a population initially without CVD at baseline; that is, the initial model cohort did not include subjects with prior CVD. Because secondary cardiovascular risk is greater than primary risk, and because secondary events are usually associated with greater mortality, the absolute benefit and cost-effectiveness of statin therapy could have been greater in the secondary preventive setting. Therefore, the restriction of our analysis to just the primary preventive setting underestimated the overall cost-effectiveness of statin therapy.

Furthermore, the Wu et al \(^ {16}\) risk equation did not incorporate all recognized cardiovascular risk factors. As discussed previously, LDL-C and HDL-C were notable omissions. Other overlooked risk factors included family history and treatment history (eg, whether or not risk factors were being treated). This highlights a limitation inherent in all cardiovascular risk equations—they may not accurately predict absolute cardiovascular risk. We attempted to overcome this

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**Figure 2.** Results of the cost-effectiveness acceptability curves in the Korean Individual-Microsimulation Model for Cardiovascular Health Interventions, a 40-year epidemiologic and economic model of first-onset cardiovascular disease (CVD) in Korea, populated with 372 subjects from the 2005 Korean National Health and Nutrition Examination Survey who were aged ≥45 years, did not have a history of myocardial infarction or ischemic stroke, and met current Korean reimbursement criteria for treatment with lipid-lowering medications.\(^ {2}\) The illustration plots the probability of achieving cost-effectiveness at various incremental cost-effectiveness ratio thresholds (ie, cut-offs). KRW = Korean won (1200 KRW = US $1)\(^ {25}\); QALY = quality-adjusted life-year; LYG = life-year gained.
limitation by allowing for underprediction and overprediction of the Wu et al equation in sensitivity analyses. Another major assumption was that the cost of concurrent MI and stroke was whichever of those individual costs was higher, rather than the sum of both. This conservative assumption was made because treatments for MI and stroke overlap, so it was unlikely that the cost of concurrent MI and stroke would be the sum of the individual costs. This underestimation of the costs of CVD would have led to an underestimation of the costs averted by treatment, and therefore an underestimation of the cost-effectiveness of statin therapy. By the same token, the assumption that concurrent MI and stroke would be associated with a utility value equal to that of only stroke was made to avoid double counting, but was also conservative and would have led to underestimation of the ICUR.

Finally, the discounting of future years of life and QALYs lived (in addition to costs), as was undertaken in our analysis, is a subject of some debate. Some researchers and observers believe that such discounting substantially underestimates the health benefits, and therefore the cost-effectiveness, of interventions. The main argument in favor of discounting is that individuals are not likely to value future good health as much as they would current good health (as with future versus current material wealth). However, the most appropriate discount rate is not known; perhaps it should be different from that used to discount costs. We opted to discount future years of life and QALYs lived at a 5% annual rate (ie, the same rate applied to costs), as recommended by HIRA.

CONCLUSIONS
The results of our modeled analysis suggest that statin therapy is likely to be cost-effective for the primary prevention of CVD among Koreans aged ≥45 years. The probability of being cost-effective was greater at a threshold of 30 million KRW per QALY (93.7%) than at 20 million KRW per QALY (53.8%).

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