Results of a Markov Model Analysis to Assess the Cost-Effectiveness of a Single Tablet of Fixed-Dose Amlodipine and Atorvastatin for the Primary Prevention of Cardiovascular Disease in Korea

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ABSTRACT

Background: In Korea, the treatment of hypertension and dyslipidemia constitutes an important strategy for the prevention of cardiovascular disease (CVD).

Objective: This study sought to investigate the cost-effectiveness (from the Korean health care system perspective) of prescribing a proprietary formulation single-tablet fixed-dose combination of amlodipine and atorvastatin (at weighted mean doses of 5 mg and 10.25 mg, respectively) to all eligible patients aged ≥45 years for the primary prevention of CVD (ie, coronary heart disease and ischemic stroke) in Korea, compared with currently observed patterns of blood-pressure and lipid-lowering medication prescription and use.

Methods: A Markov model was developed with 4 health states: alive without CVD, alive with CVD, dead from CVD, and dead from non-CVD causes. The model population comprised 244 Koreans aged ≥45 years from the 2005 Korean National Health and Nutrition Examination Survey (KNHNES) without a history of myocardial infarction (MI) or stroke who met current criteria for both blood-pressure and lipid-lowering treatment. From a 2008 baseline, follow-up was simulated for 40 years. Cardiovascular risk was estimated for each subject individually using a multivariate, Asian population-specific equation, and updated with ongoing cycles. Decision analysis compared the effects of prescribing the fixed-dose combination to all subjects versus currently observed patterns of treatment. Data regarding the blood-pressure and lipid-lowering efficacies of combination therapy were drawn from the Respond trial. Costs of the fixed-dose combination tablet and CVD were sourced from pharmaceutical pricing lists and Korean Health Insurance Review and Assessment Services estimates, respectively. Utility values for CVD were obtained from a large Korean utility study.

Results: In the model, of the 244 treatment-eligible subjects, 126 (51.6%) and 13 (5.3%) were taking blood-pressure and lipid-lowering therapy, respectively. Use of single-tablet fixed-dose combination amlodipine and atorvastatin by all subjects was associated with estimated incremental cost-effectiveness ratios of 7,773,063 Korean won (KRW) per quality-adjusted life-year gained and 10,378,230 KRW per overall life-year gained (1300 KRW = US $1). Sensitivity and uncertainty analyses indicated these results to be robust.

Conclusions: In this model, based on data from the 2005 KNHNES, hypertension and dyslipidemia were undertreated among Koreans aged ≥45 years without a history of MI or stroke. The administration of single-tablet fixed-dose combination amlodipine and atorvastatin to all such individuals was likely to represent a cost-effective means of preventing first-onset CVD (ie, coronary heart disease and ischemic stroke) in this subgroup, compared with current patterns of treatment. (Clin Ther. 2009;31:2189–2203) © 2009 Excerpta Medica Inc.

Key words: atorvastatin, amlodipine, single-pill combination, cardiovascular disease, cost-effectiveness.

INTRODUCTION

In Korea, as in most developed countries, cardiovascular disease (CVD) is a leading cause of death and
disability, and associated health care costs are high. In 2005, coronary heart disease and stroke accounted for 329 billion Korean won (KRW) (2.0%) and 449 billion KRW (2.7%) of all insurance-covered health care costs, respectively. For both diseases, the bulk of the expenditure was devoted to inpatient services: 273 billion KRW (4.2%) for coronary heart disease and 388 billion KRW (6.0%) for stroke.

There has been increasing focus in Korea on the prevention of CVD via the treatment of cardiovascular risk factors. Of these, hypertension and dyslipidemia are highly prevalent and often concurrent among Korean adults. Furthermore, they act synergistically to increase the risk of CVD. Although the importance of treating hypertension and dyslipidemia is well established in treatment guidelines, the current control of these risk factors remains poor.

Recently, a proprietary single-tablet fixed-dose combination of amlodipine (a dihydropripridine calcium channel antagonist) and atorvastatin (a 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor, or statin) was developed.* It is the first combination of its kind designed to target 2 major cardiovascular risk factors simultaneously. The efficacy of single-tablet fixed-dose combination amlodipine and atorvastatin was recently assessed in the Respond study, a randomized, placebo-controlled 3 × 5 factorial trial that assigned 1660 hypertensive patients with dyslipidemia to 15 possible combinations of placebo, amlodipine (5 or 10 mg), and atorvastatin (10, 20, 40, or 80 mg). At 8 weeks, patients who received the single-tablet fixed-dose combination therapy experienced dose-related and statistically significant reductions in systolic blood pressure and low-density lipoprotein cholesterol compared with those who received placebo alone (P < 0.001 for all comparisons). Overall, the single-tablet fixed-dose combination therapy was well tolerated and no adverse pharmacodynamic interactions were reported in the Respond trial.

In November 2004, the Korean Food and Drug Administration approved the proprietary single-tablet combination of amlodipine and atorvastatin for use in patients for whom treatment with both drugs was appropriate; the following fixed-dose combinations were approved: amlodipine/atorvastatin 5 mg/10 mg, 5 mg/20 mg, and 5 mg/40 mg. The proprietary formulation was introduced to the Korean market in March 2006.

A number of economic evaluations of amlodipine have been undertaken previously and have generally recommended using amlodipine to prevent CVD. Equivalent data supporting the cost-effectiveness of atorvastatin are also in abundance. However, published data regarding the cost-effectiveness of these agents specific to the Korean health care setting are sparse, and are limited to amlodipine alone. A search of the MEDLINE database on July 25, 2009, using the terms amlodipine, atorvastatin, and cost-effectiveness, with no time limits, did not identify any cost-effectiveness studies that assessed the use of a single-tablet fixed-dose combination of amlodipine and atorvastatin in Korea.

We sought to investigate the cost-effectiveness (from the Korean health care system perspective) of prescribing a proprietary formulation of single-tablet fixed-dose combination amlodipine and atorvastatin (at weighted mean doses of 5 mg and 10.25 mg, respectively) to all eligible patients aged ≥45 years for the primary prevention of CVD (ie, coronary heart disease and ischemic stroke) in Korea, compared with currently observed patterns of blood-pressure and lipid-lowering medication prescription and use. An age threshold of 45 years was applied because use of blood-pressure and/or lipid-lowering medications among Koreans aged <45 years is rare.

**PATIENTS AND METHODS**

**Approach and Model Structure**

A cost-utility analysis was performed, the main aim of which was to assess the effects of prescribing the proprietary formulation of single-tablet fixed-dose combination amlodipine and atorvastatin to all eligible Koreans aged ≥45 years without CVD compared with the effects of currently observed patterns of treatment. The key outcome of interest was incremental KRW per quality-adjusted life-year (QALY) gained. Modeled outcomes were also quantified in terms of KRW per overall life-year gained (LYG).

QALYs acknowledge the fact that a year lived with disease is not equivalent to a year lived in good health. Mathematically, 1 QALY = 1 life-year × utility ascribed to existing disease. For example, if the utility ascribed to a disease is 0.8, then 1 life-year with that disease is equivalent to 0.8 QALY.

The reference condition in the modeled evaluation was CVD, comprising nonfatal or fatal myocardial

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1 Exchange rate: 1300 KRW = US $1.45
infarction (MI) and/or ischemic stroke. A state-transition Markov model with yearly cycles was constructed with the following health states: alive without CVD, alive with CVD, dead from CVD, and dead from non-CVD causes. Decision analysis was applied to the comparison of single-tablet fixed-dose combination treatment versus currently observed treatment patterns. The model is conceptualized in Figure 1.

All individuals began the model analysis in the first health state, alive without CVD; follow-up of each individual was simulated from his or her age at baseline participation through death, until age 99 years, or over a period of 40 years, whichever came first.

The baseline year of the model was 2008, beyond which future costs, LYGs, and QALYs gained were discounted at an annual rate of 5%, as recommended by the Korean Health Insurance Review and Assessment Services (HIRA), the national drug reimbursement authority. The perspective adopted was that of the Korean health care system.

The decision analytic model was developed and analyzed with Excel (Microsoft Corporation, Redmond, Washington).

**Modeled Population**

The population used in the modeled economic evaluation comprised a subset of the population enrolled in the 2005 Korean National Health and Nutrition Examination Survey (KNHNES). 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 collected

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**Figure 1.** Conceptual representation of a Markov model analysis of the cost-effectiveness of single-tablet fixed-dose combination amlodipine and atorvastatin at weighted mean doses of 5 mg and 10.25 mg, respectively (Caduet®, Pfizer Inc., New York, New York), versus current treatment patterns in 244 Koreans aged ≥45 years without a history of myocardial infarction or ischemic stroke who met the criteria for both blood-pressure and lipid-lowering treatment, based on data from the 2005 Korean National Health and Nutrition Examination Survey. Follow-up was simulated for 40 years. CVD = cardiovascular disease; M = Markov node.
comprehensive information on the health and well-being of Koreans based on self-reports of disease, health behavior, and nutritional habits; physical examination; and blood sampling. In the 2005 KNHONES, 34,145 subjects representative of the national demographic profile were included in the survey. Of these, 10,816 underwent physical examination and blood sampling.

The initial cohort used in the model comprised 244 males and females aged ≥45 years without a history of MI or stroke who met current Korean criteria for treatment with single-tablet fixed-dose combination amlodipine and atorvastatin. Treatment of cardiovascular risk factors in Korea is largely dictated by the Korean National Health Insurance (NHI), which sets reimbursement criteria for various drug therapies. Under the current NHI scheme, lipid-lowering therapy for the primary prevention of CVD is reimbursable for Koreans with total cholesterol levels of ≥220 mg/dL (5.7 mmol/L) who have ≥1 other risk factor (eg, hypertension, smoking, diabetes mellitus, or obesity) or ≥250 mg/dL (6.5 mmol/L) without an additional risk factor. The NHI does not impose specific restrictions to the use of antihypertensive therapy, but treatment recommendations issued by the Korean Society of Hypertension are based on the US National Heart, Lung, and Blood Institute’s seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

Therefore, subjects were assumed to be eligible for single-tablet fixed-dose combination amlodipine and atorvastatin therapy if they met NHI criteria for lipid-lowering therapy and if their blood pressure was >140/90 mm Hg at the time of participation in KNHINES, and/or if there was a self-reported history of hypertension.

**Transition Probabilities**

Information regarding the values and data sources for the transition probabilities and other key inputs are summarized in Table I.

In the model, cardiovascular risk was estimated for each subject individually. The cardiovascular risk equation used was that published 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 (nonfatal or fatal) based on an individual’s sex, age, serum total cholesterol (in units of mmol/L), systolic blood pressure (SBP, in units of mm Hg), current smoking status (yes/no), diabetes mellitus status (yes/no), and body mass index (in units of kg/m²).

The Wu et al equation relies on age- and sex-specific cardiovascular risks drawn from the population to which the equation is applied, and is therefore self-calibrating. For our analysis, age- and sex-specific cardiovascular risks were derived from epidemiologic data on CVD in Korea in 2004, as provided by HIRA. The Wu et al equation also estimates the probability of total CVD (ie, a composite of nonfatal and fatal CVD). We were able to stratify this into separate probabilities for fatal and nonfatal CVD by applying sex- and age-specific proportions of first-onset CVD that was fatal within 365 days; these data were also available for 2004 from HIRA.

In the first cycle of the model, the cardiovascular-related transition probabilities were calculated for each subject using the values of the risk factor variables reported directly in 2005 KNHONES. With subsequent cycles, cardiovascular risk profiles were updated by changing the age, SBP, and possible diabetes mellitus status of each subject. Other risk factors were assumed to remain unaltered with age. SBP and diabetes mellitus status were increased according to predicted age-related trends. Trends were determined (separately for sex) by first calculating the mean SBP levels and prevalence of diabetes mellitus for each age based on available cross-sectional data from 2005 KNHONES, then by fitting polynomial mathematical functions to quantify the relationships between age, mean SBP, and diabetes mellitus prevalence.

For subjects in the health state alive with CVD, the probabilities of recurrent cardiovascular events and death were derived from the HIRA data for the year 2004. These probabilities were expectedly much higher than those for subjects without CVD, but were not determined individually because there were no applicable risk equations for this setting. Instead, the same probabilities are assumed for all subjects within the same age-and-sex stratum.

Age- and sex-specific risks of noncardiovascular deaths were based on Korean population and mortality statistics for 2005, as supplied by the Korea National Statistical Office. Risks of noncardiovascular mortality were simply the differences between risks of all-
Table I. Key data inputs used in a Markov model analysis of the cost-effectiveness of single-tablet fixed-dose combination amlodipine and atorvastatin* versus current treatment patterns in 244 Koreans aged ≥45 years without a history of myocardial infarction (MI) or stroke who met the criteria for both blood-pressure and lipid-lowering treatment, based on data from the 2005 Korean National Health and Nutrition Examination Survey.1 Follow-up was simulated for 40 years.

<table>
<thead>
<tr>
<th>Data Input</th>
<th>Base-Case Value</th>
<th>Uncertainty Range</th>
<th>Data Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying risk of CVD</td>
<td>Individually estimated for the modeled population</td>
<td>±25% (uniform) ±25% (uniform)</td>
<td>Wu et al50 cardiovascular risk equation and Korean cardiovascular epidemiologic data51</td>
</tr>
<tr>
<td>Efficacy of single-tablet fixed-dose combination amlodipine and atorvastatin treatment</td>
<td></td>
<td></td>
<td>Preston et al8 (Respond study) and IMS Korea52 Preston et al8 (Respond study) and IMS Korea52</td>
</tr>
<tr>
<td>Change in systolic blood pressure</td>
<td>−9.2 mm Hg</td>
<td>95% CI: −12.3 to −6.3 mm Hg</td>
<td>Preston et al8 (Respond study) and IMS Korea52 Preston et al8 (Respond study) and IMS Korea52</td>
</tr>
<tr>
<td>Change in total cholesterol</td>
<td>−39%</td>
<td>95% CI: −43.0% to −35.0%</td>
<td>Preston et al8 (Respond study) and IMS Korea52 Preston et al8 (Respond study) and IMS Korea52</td>
</tr>
<tr>
<td>Annual single-tablet fixed-dose combination amlodipine and atorvastatin acquisition cost</td>
<td></td>
<td></td>
<td>HIRA53 and IMS Korea52 HIRA47</td>
</tr>
<tr>
<td>Cost of MI (per person)</td>
<td>402,397 KRW</td>
<td></td>
<td>HIRA53 and IMS Korea52 HIRA47</td>
</tr>
<tr>
<td>Year 1</td>
<td>7,814,848 KRW</td>
<td>±25% (uniform)</td>
<td>HIRA53 and IMS Korea52 HIRA47</td>
</tr>
<tr>
<td>Year 2+</td>
<td>1,285,656 KRW</td>
<td>±25% (uniform)</td>
<td>HIRA53 and IMS Korea52 HIRA47</td>
</tr>
<tr>
<td>Fatal event</td>
<td>1,661,503 KRW</td>
<td>±25% (uniform)</td>
<td>HIRA53 and IMS Korea52 HIRA47</td>
</tr>
<tr>
<td>Cost of ischemic stroke per person</td>
<td>8,074,965 KRW</td>
<td>±25% (uniform)</td>
<td>HIRA53 and IMS Korea52 HIRA47</td>
</tr>
<tr>
<td>Year 1</td>
<td>1,046,679 KRW</td>
<td>±25% (uniform)</td>
<td>HIRA53 and IMS Korea52 HIRA47</td>
</tr>
<tr>
<td>Year 2+</td>
<td>2,293,845 KRW</td>
<td>±25% (uniform)</td>
<td>HIRA53 and IMS Korea52 HIRA47</td>
</tr>
<tr>
<td>Annual rate of increase in costs of MI and ischemic stroke</td>
<td>0%</td>
<td>0% to 9% (uniform)</td>
<td>Kang54</td>
</tr>
<tr>
<td>Annual discount rate</td>
<td>5%</td>
<td>0% to 7.5% (uniform)</td>
<td>Kang54</td>
</tr>
<tr>
<td>Utilities</td>
<td></td>
<td></td>
<td>Kang54</td>
</tr>
<tr>
<td>MI</td>
<td>0.69</td>
<td>±25% (uniform)</td>
<td>Kang54</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.50</td>
<td>±25% (uniform)</td>
<td>Kang54</td>
</tr>
<tr>
<td>Persistence with single-tablet fixed-dose combination amlodipine and atorvastatin at 1 year</td>
<td>63.9%</td>
<td>33.1% to 63.9% (uniform)</td>
<td>Patel et al55</td>
</tr>
</tbody>
</table>

cause mortality and risks of cardiovascular mortality. We acknowledged that the risks of noncardiovascular mortality would be different for people with and without existing CVD, and therefore applied differential probabilities based on data from the Danish Monitoring Trends and Determinants in Cardiovascular Disease study, which undertook long-term follow-up of Danish subjects after first-ever MI and ischemic stroke.\textsuperscript{56,57} Specific Korean data were not available for the present analysis.

\textbf{Utilities}
Utility weights for MI and stroke (in their chronic states) were derived from an analysis of 2005 KNHNES data by Kang,\textsuperscript{54} using the EuroQol-5 instrument. These were 0.80 and 0.58, respectively. To derive a composite utility weight for prevalent CVD, which was 0.63, the individual utility weights for MI and stroke were applied to the proportional distribution of MI only (23.08\%), stroke only (75.52\%), and concurrent MI and stroke (1.40\%), as observed in 2005 KNHNES.\textsuperscript{1} For concurrent MI and stroke, we applied the lesser of the utility weights (ie, 0.58). Because the utility values derived by Kang pertained to the prevalent (chronic) state, they were applied only to the cycles subsequent to the cycle in which CVD first occurred. No utility penalty was applied in the cycle in which CVD first occurred. Although this approach was conservative (ie, it would have underestimated the cost-effectiveness of single-tablet fixed-dose combination amlopidine and atorvastatin), the impact would have been small in the context of a 40-year model time horizon.

The utility weight for subjects without CVD was assumed to be 1.0.

\textbf{Costs of Cardiovascular Disease}
The estimated costs of incident (1 time only) and prevalent (annual) MI and stroke were derived from HIRA,\textsuperscript{47} and are summarized in Table I. In the base-case analysis, the costs of CVD were assumed to stay constant with time. In sensitivity analyses, a 9\% annual increase in the costs of CVD was evaluated, as suggested by HIRA.\textsuperscript{47}

\textbf{Effects and Costs of Single-Tablet Fixed-Dose Combination Therapy}
Dose-specific effects of single-tablet combination amlopidine and atorvastatin therapy on SBP and serum total cholesterol (TC) were based on data from the Respond trial,\textsuperscript{8} and dose-specific costs of such therapy were based on 2008 pharmaceutical price lists in Korea.\textsuperscript{53}

In the model, all subjects in the single-tablet fixed-dose combination amlopidine and atorvastatin group were assumed to be taking a weighted mean daily dose of amlopidine 5 mg/atorvastatin 10.25 mg, which was calculated from IMS market data for Korea that were most recent at the time of study design (ie, second quarter of 2008).\textsuperscript{52} The SBP- and TC-modifying effects of this weighted mean daily dose of single-tablet fixed-dose combination amlopidine and atorvastatin were estimated to be –9.2 mm Hg (95\%CI, –12.3 to –6.3 mm Hg) and –39.0\% (95\%CI, –43.0\% to –35.0\%), respectively. Its annual cost amounted to 402,397 KRW. The weighted mean values, including the 95\% CI values of the efficacy measures, were simply the sum products of the dose-specific market distributions (based on IMS data)\textsuperscript{52} and dose-specific efficacy (Respond study)\textsuperscript{8} and cost values.

Among subjects in the single-tablet fixed-dose combination amlopidine and atorvastatin group who were already taking blood-pressure–lowering therapy, their SBP levels were not altered. Similarly, TC was not altered among subjects who were already taking lipid-lowering therapy. Therefore, the underlying assumption for subjects already taking blood-pressure and lipid-lowering therapy was that they were taking the equivalent of 5 mg amlopidine and 10.25 mg atorvastatin, respectively.

Among subjects receiving standard current treatment, SBP and TC levels were unaltered.

The price of single-tablet fixed-dose combination amlopidine and atorvastatin therapy was reduced by 10\% after 1 year to simulate the penetration of generic agents into the Korean market.\textsuperscript{53}

\textbf{Persistence With Single-Tablet Fixed-Dose Combination Amlodipine and Atorvastatin Therapy}
It was assumed that there would be 63.9\% persistence with single-tablet fixed-dose combination amlopidine and atorvastatin at 1 year among everyone who received this treatment. This figure was based on a recent cohort study of pharmacy claims data from the United States.\textsuperscript{53} Patients in that study were aged ≥18 years and had been newly prescribed various combinations of a calcium channel blocker and a statin. Of the 4703 study subjects, 795 (16.9\%) had been prescribed single-tablet fixed-dose combination amlo-
dipine and atorvastatin. Given the relative recentness of the entry of this formulation to the Korean market, specific Korean data about persistence with single-tablet fixed-dose combination amlodipine and atorvastatin therapy were not available at the time of our analysis.

Our model assumed a linear decrease in persistence from 100% at baseline to 63.9% at 1 year, with no further decline in persistence thereafter. The assumption about temporal trends in persistence was supported by pharmacoepidemiologic data that suggested that for both statins and antihypertensive medications, discontinuation rates decrease steadily until the end of 1 year and plateau thereafter.\(^{58-60}\) The TC/SBP-modifying effects of single-tablet fixed-dose combination amlodipine and atorvastatin were adjusted downward proportionally to simulate the effect of discontinuing therapy with single-tablet fixed-dose combination amlodipine and atorvastatin; that is, they were also linearly decreased from 100% to 63.9% over the first year, and maintained at 63.9% thereafter. The costs of single-tablet fixed-dose combination amlodipine and atorvastatin were maintained at 100% for the entire first year to simulate complete acquisition of single-tablet fixed-dose combination amlodipine and atorvastatin in the year of its initiation (despite less than complete compliance), and then decreased to 63.9% from the beginning of year 2 onward.

### Sensitivity and Uncertainty Analyses

A series of 1-way sensitivity analyses were undertaken with the limits of the 95% CI surrounding the TC and SBP efficacy measures for single-tablet fixed-dose combination amlodipine and atorvastatin (triangular uncertainty distributions), and ±25% uniform variations to the Wu et al\(^ {30}\) cardiovascular risk predictions, utility weights, and CVD costs. To reflect the possibility that CVD may produce no long-lasting disability, another analysis was conducted that applied the utility penalty for CVD only in the year that a CVD event occurred. The annual discount rate applied to future costs, LYGs, and QALYs gained was also varied uniformly between 0% and 7.5%. The annual rate of increase in CVD costs was varied uniformly from 0% to 9%. Finally, the 1-year persistence with single-tablet fixed-dose combination amlodipine and atorvastatin was assumed to be 33.1%, which was the lowest persistence rate observed among patients in the United States who were prescribed 2-tablet combination therapy with a calcium channel blocker and a statin.\(^ {55}\) In general, uniform variations were applied when the probability distributions of the uncertainty ranges around data inputs were not clearly defined. In 1-way sensitivity analyses, the values of these key inputs were varied 1 at a time while maintaining the other inputs at base-case values.

The effects of variations to the key inputs were then assessed simultaneously in multivariate uncertainty analyses (probabilistic sensitivity analyses) in 2000 repetitions of a Monte Carlo simulation,\(^ {61}\) using Excel (Microsoft Corporation, Redmond, Washington) and the software @Risk for Excel (Palisade Corporation, Ithaca, New York).

### RESULTS

#### Characteristics of the Modeled Population

The characteristics of the modeled population, comprising 244 blood pressure and lipid-lowering treatment-eligible subjects, are summarized in Table II. Because the modeled population comprised subjects who met eligibility criteria for single-tablet fixed-dose combination amlodipine and atorvastatin treatment, the cohort comprised older individuals (mean age, 56.6 years) with elevated lipid levels (mean TC, 245.2 mg/dL) and SBP (mean, 141.7 mm Hg). Of the 244 subjects, 126 (51.6%) were taking blood-pressure medications at baseline and 13 (5.3%) were taking lipid-lowering medications.

#### Base-Case Analysis

Results of the base-case modeled economic evaluation, based on the simulated 40-year follow-up of 244 Korean adults aged ≥45 years without previous CVD who met criteria for both blood-pressure and lipid-lowering treatment, are summarized in Table III. The results compare predicted outcomes between the single-tablet fixed-dose combination amlodipine and atorvastatin group and the group treated according to current patterns. Compared with the current-treatment group, each subject in the single-tablet fixed-dose combination amlodipine and atorvastatin group gained an additional 0.32 QALY (discounted) and 0.24 LYG. The net incremental cost (discounted) was 2,521,215 KRW per subject. The estimated incremental cost-effective ratio (ICER) was 7,773,063 KRW per QALY gained and 10,378,230 KRW per LYG.

#### Sensitivity and Uncertainty Analyses

As indicated in Table IV, sensitivity analyses indicated the results to be robust against variations to key...
Table II. Baseline characteristics of the modeled population (244 Koreans aged ≥45 years without a history of myocardial infarction or stroke who met criteria for both blood-pressure and lipid-lowering treatment) in a 40-year Markov model of the cost-effectiveness of single-tablet fixed-dose combination amlodipine and atorvastatin* versus current treatment patterns, based on data from the 2005 Korean National Health and Nutrition Examination Survey.¹

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>169 (69.3)</td>
</tr>
<tr>
<td>Male</td>
<td>75 (30.7)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>60.6 (9.3)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>141.7 (18.0)</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mg/dL</td>
<td>245.2 (25.9)</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mean (SD), mg/dL</td>
<td>240.4 (69.6)</td>
</tr>
<tr>
<td>Presence of diabetes mellitus, no. (%)</td>
<td>54 (22.1)</td>
</tr>
<tr>
<td>Smoker, no. (%)</td>
<td>41 (16.8)</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>25.1 (3.0)</td>
</tr>
<tr>
<td>Use of blood-pressure medication, no. (%)</td>
<td>126 (51.6)</td>
</tr>
<tr>
<td>Use of lipid-lowering medication, no. (%)</td>
<td>13 (5.3)</td>
</tr>
</tbody>
</table>

*Trademark: Caduet® (Pfizer Inc., New York, New York), at weighted mean doses of amlodipine 5 mg and atorvastatin 10.25 mg.

Data inputs.

Of the 2000 simulated results from the multivariate sensitivity Monte Carlo analyses, the mean (SD) discounted QALYs gained and LYGs per subject from single-tablet fixed-dose combination amlodipine and atorvastatin treatment were 0.34 (0.15) and 0.27 (0.12), respectively. The mean (SD) discounted net cost per subject was 1,521,538 (719,296) KRW.

The mean (SD), 2.5th percentile, median, and 97.5th percentile values of the uncertainty range derived for the KRW per QALY gained were 5,143,642 (2,566,647), 83,909, 5,235,040, and 9,932,154, respectively. The equivalent values for KRW per LYG were 6,718,588 (3,404,377), 103,009, 6,802,401, and 13,339,537. These ranges of figures fall within generally accepted thresholds for ICERs.²²,²³

Uncertainty in the modeled outputs is graphically illustrated by the cost-effectiveness acceptability curves presented in Figure 2, which emphasizes the high probability that single-tablet fixed-dose combination amlodipine and atorvastatin treatment would be a cost-effective strategy compared with current treatment patterns. Indeed, the analyses suggested ~2% probability that the treatment would be dominant in cost-effectiveness terms.

DISCUSSION

To our knowledge, this is the first economic evaluation of single-tablet fixed-dose combination amlodipine and atorvastatin in the Korean context. The predicted ICERs suggest that compared with current patterns of blood-pressure and lipid-lowering treatment, the prescription of single-tablet fixed-dose combination amlo- dipine and atorvastatin to all treatment-eligible Koreans aged ≥45 years would represent a cost-effective strategy for the primary prevention of CVD.

Part of the reason for this finding is the current undertreatment of hypertension and dyslipidemia among Koreans aged ≥45 years. This is especially true of dyslipidemia, with only 1 in 20 eligible patients receiving lipid-lowering treatment.¹ There have been a few studies of the inadequacy of treatment, including poor adherence, among Koreans already using medications for hypertension and dyslipidemia,⁶⁴–⁶⁶ but our literature.
search did not identify any previous studies that addressed the specific issue of treatment-eligible Koreans who received no treatment at all. The possible reasons for the treatment gap we noted in our analysis, which was based on real survey data, warrant further investigation.

The main strengths of our analysis include the use of contemporary, representative data inputs and the adoption of a microsimulation approach to modeling. Compared with the more commonly used traditional cohort analysis model, which is limited by an unrealistic assumption that every subject in the modeled cohort shares the same characteristics, a microsimulation model employs individual-level data and simulates the unique health experiences of every subject. If, as in the case of our analysis, the modeled subjects are representative of the population to whom results are to be applied, uncertainty surrounding the model's results is reduced, and its generalizability is improved.

An added advantage of single-tablet fixed-dose combination amlodipine and atorvastatin treatment is that it has the potential to improve patient adherence compared with the coadministration of separate tablets of amlodipine and atorvastatin.

Several limitations in our study are worth noting. First, because there are no cardiovascular risk equations available that are specific to a Korean population, we applied the Wu et al Chinese cardiovascular risk equation to the model subjects instead. Although this solution was not ideal, it was nevertheless contemporary, based on a North Asian population and self-calibrating (because it was based on age- and sex-specific cardiovascular risks drawn from the Korean population). Therefore, it was the most appropriate equation available. The most commonly applied cardiovascular risk prediction equations are derived from Western populations, such as those from the Framingham Heart Study, and as such are less applicable to Koreans. One compelling, but by no means the sole reason why data from Western populations are not entirely appropriate for Asian populations is that CVD in Asians is dominated by stroke, while among non-Asians, coronary heart disease is more common.

Second, because the Wu et al equation was limited to capturing primary (ie, first-ever) CVD events, we
were only able to analyze the cost-effectiveness of single-tablet fixed-dose combination amlodipine and atorvastatin from a primary prevention perspective. This is not to say that the model ignored the risks and effects of recurrent CVD or death among subjects with existing CVD; it quantified these risks and effects for each age-and-sex stratum, but it did not begin the simulation with subjects with already-existent 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 single-tablet fixed-
dose combination amlodipine and atorvastatin 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 single-tablet fixed-dose combination amlodipine and atorvastatin.

Third, it was assumed that the cost of concurrent MI and stroke was simply the higher of the 2 individual costs, rather than their sum. This assumption was made to avoid double counting; treatments for MI and stroke overlap, and it is unlikely that the cost of concurrent MI and stroke would be the sum of the individual costs. Similarly, the utility weight for concurrent MI and stroke was assumed to be equivalent to that of stroke alone (the lower of the 2 component conditions). These assumptions underestimated the costs of CVD and the disability with which it is associated, and therefore underestimated the ICERs associated with single-tablet fixed-dose combination amlodipine and atorvastatin treatment.

Finally, the discounting of future years of life and QALYs (in addition to costs), as was undertaken in
our analyses, is a subject of some debate. The reason is that many researchers and observers feel that such discounting significantly underestimates the health benefits, and therefore the cost-effectiveness, of interventions.62 The main argument for discounting is that individuals are not likely to value future good health as much as they do current good health, as with future versus current material wealth.62 However, the most appropriate discount rate is not known, and perhaps should be different from that of costs. We opted to discount future years of life and QALYs at a 5% annual rate (the same as for costs), because this is the approach recommended by HIRA.47

CONCLUSIONS

In this model, based on data from the 2005 KNHNES, hypertension and dyslipidemia were undertreated among Koreans aged ≥45 years without a history of MI or stroke. Compared with current patterns of treatment, the administration of single-tablet fixed-dose combination amlodipine and atorvastatin to all such individuals was likely to represent a cost-effective means of preventing first-onset CVD (ie, coronary heart disease and ischemic stroke) in this subgroup.

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