Lifestyle Modifications Versus Antihypertensive Medications in Reducing Cardiovascular Events in an Aging Society: A Success Rate-oriented Simulation

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Abstract

Objective   It is difficult to compare directly the practical effects of lifestyle modifications and antihypertensive medications on reducing cardiovascular disease (CVD). The purpose of this study was to compare the hypothetical potential of lifestyle modifications with that of antihypertensive medications in reducing CVD in an aging society using a success rate-oriented simulation.

Methods   We constructed a simulation model for virtual Japanese subpopulations according to sex and age at 10-year intervals from 40 years of age as an example of an aging society. The fractional incidence rate of CVD was calculated as the product of the incidence rate at each systolic blood pressure (SBP) level and the proportion of the SBP frequency distribution in the fractional subpopulations of each SBP. The total incidence rate was calculated by the definite integral of the fractional incidence rate at each SBP level in the sex- and age-specific subpopulations.

Results   If we consider the effects of lifestyle modifications on metabolic factors and transfer them onto SBP, the reductions in the total incidence rate of CVD were competitive between lifestyle modifications and antihypertensive medications in realistic scenarios. In middle-aged women, the preventive effects of both approaches were limited due to a low incidence rate. In middle-aged men and extremely elderly subjects whose adherence to antihypertensive medications is predicted to be low, lifestyle modifications could be an alternative choice.

Conclusion   The success rate-oriented simulation suggests that the effectiveness of lifestyle modifications or antihypertensive medications in preventing cardiovascular events largely depends on the baseline incidence rate and sex- and age-specific behavioral factors.

Key words: adherence, aging, antihypertensive medication, lifestyle modification, simulation


Introduction

Hypertension frequently develops as an accumulation of multiple cardiovascular risk factors. Metabolic syndrome is a significant factor for the development of cardiovascular disease (CVD) in sedentary lifestyles (1, 2). Although traditional antihypertensive medications with usual lifestyle modifications by primary physicians (AM) is effective in reducing CVD (3-6), many researchers have recently focused on intensive lifestyle modifications by health nurses (LM) as a first-line treatment option for hypertension, especially with metabolic syndrome (7-9). Direct evidence is still lacking because epidemiological studies take several years and incur huge costs to draw conclusions about whether LM could substitute for traditional AM in reducing the total incidence rate of CVD (IR_{CVD}, events/person x year) in age- and sex-specific subpopulations at the stage of primary care. Further-
more, randomized controlled trials with LM have an inevitable problem since blinding is theoretically impossible and the full effect of LM on preventing CVD takes more than several years. Simulation studies may provide useful information to help patients and their primary physicians to select a possible course of action (10-12). We have recently reported that AM has greater potential on preventing CVD compared with LM in a success rate-oriented simulation of 60-year-old Japanese men when we assumed that LM prevents CVD mainly through lowering blood pressures (13). In the National Nutrition Survey in Japan, SBP was measured for approximately 10,000 individuals from randomly selected families in Japan (20). The average and standard deviation of the SBP values were obtained from the above website in reference 20.

As the SBP levels were hypothesized to be normally distributed (13), the sex- and age-specific probability density function of SBP equals

\[
f(x) = \frac{1}{\sqrt{2\pi}\sigma} \exp \left( -\frac{(x-\mu)^2}{2\sigma^2} \right)
\]

where \( x \) (mmHg), \( \mu \) (mmHg) and \( \sigma \) (mmHg) represent SBP, the mean and standard deviation of SBP, respectively.

The fractional IRCVD at the specific SBP level was assumed by the following formula:

\[
IRCVD(x) = P(x) \left( 1 - \frac{1}{l} \exp \left( \frac{x-m}{k} \right) \right)
\]

where \( x \) (mmHg) represents SBP and \( k \) (mmHg), \( l \) (no unit) and \( m \) (mmHg) are virtual constants related to the slope of the exponential curves, the absolute value of IRCVD and the rising point from \( e^0 \) at \( \mu \).

CVD was estimated to be smaller in Asia than in Western countries because the incidence of coronary heart disease in Asia is approximately 1/3 of that in Western countries (15, 17). The sex- and age-specific probability density function of SBP is as high as 60% in Asian countries (17). Therefore, we assumed that SBP could be a representative risk factor for CVD (13). In the National Nutrition Survey in Japan, SBP was measured for approximately 10,000 individuals from randomly selected families in Japan (20). The average and standard deviation of the SBP values were obtained from the above website in reference 20.

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\]

where \( x \) (mmHg), \( \mu \) (mmHg) and \( \sigma \) (mmHg) represent SBP, the mean and standard deviation of SBP, respectively.

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\]

where \( x \) (mmHg) represents SBP and \( k \) (mmHg), \( l \) (no unit) and \( m \) (mmHg) are virtual constants related to the slope of the exponential curves, the absolute value of IRCVD and the rising point from \( e^0 \) at \( \mu \).

The sex- and age-specific total IRCVD was calculated by the definite integral from the lowest (L) (mmHg) to the highest SBP (H) (mmHg) of the fractional IRCVD at each SBP level.

Sex- and age-specific total IRCVD

\[
= \int_{L}^{H} f(x) \times P(x)\,dx
\]

\[
= \int_{L}^{H} \left( \frac{1}{\sqrt{2\pi}\sigma} \times \exp \left( -\frac{(x-\mu)^2}{2\times\sigma^2} \right) \right) \times \frac{1}{l} \exp \left( \frac{x-m}{k} \right)\,dx
\]

where \( x \), \( f(x) \) and \( P(x) \) represent SBP, the probability density function and IRCVD according to SBP, respectively (Fig. 2, 3) (10, 13).

The sex-specific, age-standardized total IRCVD in this simulation was calculated from the sex- and age-specific total IRCVD using the sample model Japanese population in 1985. The male and female age-standardized total IRCVD were comparable with those of the JMS Cohort study.
Table 2. Annual Incidence Rate of Cardiovascular Events.

<table>
<thead>
<tr>
<th>Population</th>
<th>Hisayama\textsuperscript{a}</th>
<th>Nippon DATA80\textsuperscript{b}</th>
<th>Study JMS</th>
<th>This simulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>(&lt; 0.001)</td>
<td>0.0014</td>
<td>0.0014</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>(0.002)</td>
<td>0.0035</td>
<td>0.0041</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>(0.005)</td>
<td>0.0097</td>
<td>0.0095</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>(0.02)</td>
<td>0.018</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td></td>
<td></td>
<td>0.048</td>
<td></td>
</tr>
<tr>
<td>age-standardized</td>
<td>0.0014 (0.00045)</td>
<td></td>
<td>0.0059</td>
<td>0.0082</td>
</tr>
</tbody>
</table>

Female, age (years) |                               |                               |           |                |
| 40-49       | (< 0.001)                     | 0.0004                        | 0.00041   |                |
| 50-59       | (< 0.001)                     | 0.0021                        | 0.0046    |                |
| 60-69       | (0.005)                       | 0.0047                        | 0.0050    |                |
| 70-79       | (0.02)                        | 0.014                         | 0.021     |                |
| 80+         |                               |                               | 0.049     |                |
| age-standardized | 0.0015 (0.00049) |                               | 0.0035   | 0.0060 |

\textsuperscript{a}Values within parentheses represent mortality rate due to cardiovascular disease.

JMS: the Jichi Medical School (JMS) Cohort study

Risk reduction after interventions

We assumed that the fractional IR\textsubscript{CVD} after the interventions would gradually converge with the fractional IR\textsubscript{CVD} directly calculated from the SBP levels after the interventions (13), and half of the expected decrease in SBP would contribute to the fractional IR\textsubscript{CVD} reduction. Accessibility to primary physicians and adherence to AM is dependent on the subpopulations (7, 24-26). In the elderly subpopulation, accessibility would become lower (27).

**The sex- and age-specific total incidence rate of CVD after lifestyle modifications**

\[
\int_{-\infty}^{\infty} \left\{ f_1(x) \times P_1(x) \right\} dx = \int_{-\infty}^{\infty} \left\{ f_0(x) \times P_0(x) \right\} dx \times \alpha \times \beta
\]

where \( x, f_0(x) \) and \( P_0(x) \) represent SBP, the probability density function and the fractional IR\textsubscript{CVD} before intervention, respectively, and \( f_1(x) \) and \( P_1(x) \) represent the probability density function and the fractional IR\textsubscript{CVD} after intervention, respectively. \( \alpha \) (mmHg), \( \alpha' \) (mmHg) and \( \beta \) (no unit) represent the SBP-lowering effect when LM is successful, the SBP-lowering effect when LM is unsuccessful and the success rate of LM, respectively. In this simulation, LM indicates intensive lifestyle modifications supported by health nurses, such as the special health promotion program initiated in 2008 in Japan (28). LM included several components such as salt reduction, weight reduction, healthy dietary patterns, mild exercise, and alcohol moderation. LM did not include the usual guidance along with AM in medical offices. In our previous simulation study, we did not estimate the effect of unsuccessful LM on the fractional IR\textsubscript{CVD} (13). When we estimate the IR\textsubscript{CVD} for longer periods than a few years, we could not neglect the slight, but widespread potential of unsuccessful LM. The PREMIER trial has recently reported that LM for BP resulted in a decrease in SBP by 10 mmHg in middle-aged, healthy, untreated individuals with prehypertension or stage I hypertension (7). A pilot study in Japan...
has recently indicated that a 27-month community-based lifestyle approach resulted in 1 mmHg and 3 mmHg reductions in SBP for men and women, respectively (8). We estimated that the direct effects of LM on SBP were 3 to 10 mmHg in this study.

How can we estimate the effect of LM on IR_{cvo} by im-

Figure 2. Preventing effects of lifestyle modification (LM) and antihypertensive medications (AM) in the fractional incidence rate of cardiovascular events in each systolic blood pressure level according to age in men (a: LM in 40- to 49-year-old men, b: AM in 40- to 49-year-old men, c: LM in 60- to 69-year-old men, d: AM in 60- to 69-year-old men, e: LM in over 80-year-old men and f: AM in over 80-year-old men, respectively). The solid thin, dotted thin, solid thick, broken thick, and broken and dotted thick lines demonstrate the fractional incidence rate of no interventions, pessimistic, realistic, optimistic and ideal scenarios in LM, respectively (a, c, e). The solid thin, dotted thin, grey thick, solid thick, and broken thick lines demonstrate the fractional incidence rate of no interventions, loose, modest, realistic, and strict scenarios in AM, respectively (b, d, f).
proving metabolic factors, rather than through SBP? Okada et al. reported that the effect of LM on low-density lipoprotein-cholesterol (LDL-C) was approximately 13 mg/dL (29). Saito et al. reported that mean reductions in the total cholesterol levels and fasting blood glucose after 12-month LM were 3 mg/dL and 3 mg/dL, respectively (30). Our recent study has demonstrated that the effects of LM on the LDL-C and fasting blood glucose levels were 15 mg/dL and 2 mg/dL, respectively (28). Therefore, we estimated that the effects of LM on the LDL-C and fasting blood glucose
levels were 3 to 15 mg/dL and 2 to 3 mg/dL, respectively, which corresponded to 0.5 to 5 mmHg and 2 to 3 mmHg SBP-lowering effects, respectively, calculated from the regression coefficients in the epidemiological studies (31-33).

The total effects of LM on SBP including metabolic factors, \( \alpha \), are substituted at the following four levels: (1) pessimistic, \( \alpha = 5 \); (2) realistic, \( \alpha = 8 \); (3) optimistic, \( \alpha = 15 \); and (4) ideal, \( \alpha = 20 \) mmHg (Table 3) (13).

We provisionally assumed that even an unsuccessful LM would result in the following four levels of SBP-lowering effect compared with that of a successful LM: (1) pessimistic, \( \alpha' = 0.5 \); (2) realistic, \( \alpha' = 2 \); (3) optimistic, \( \alpha' = 5 \); and (4) ideal, \( \alpha' = 10 \) mmHg.

The Trials of Hypertension Prevention, Phase II, reported that 13% of the lifestyle intervention participants achieved a reduction in body weight and maintained this reduction for 3 years (34). Because the Ministry of Health, Labour and Welfare in Japan aimed at a 10% reduction in subjects with metabolic syndrome by LM, we estimated the success rates at the following four levels as previously described (13): (1) pessimistic, \( \beta = 0.075 \); (2) realistic, \( \beta = 0.1375 \); (3) optimistic, \( \beta = 0.275 \); and (4) ideal, \( \beta = 0.5 \) (13).

### Table 3. Representative Patterns of Lifestyle Modifications.

<table>
<thead>
<tr>
<th>Pattern of LM</th>
<th>( \alpha )</th>
<th>( \alpha' )</th>
<th>( \beta )</th>
<th>Proportion of participating LM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pessimistic</td>
<td>2.5</td>
<td>0.5</td>
<td>0.075</td>
<td></td>
</tr>
<tr>
<td>Realistic</td>
<td>5</td>
<td>8</td>
<td>0.1375</td>
<td></td>
</tr>
<tr>
<td>Optimistic</td>
<td>10</td>
<td>15</td>
<td>0.275</td>
<td></td>
</tr>
<tr>
<td>Ideal</td>
<td>20</td>
<td>28</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

LM: lifestyle modifications, \( \alpha \): Systolic blood pressure (SBP)-lowering effect (mmHg) in the previous paper (13), \( \alpha' \): the total effects of successful LM on SBP (mmHg) including metabolic factors, \( \beta \): SBP lowering effect of unsuccessful LM including metabolic factors.

### Table 4. Representative Patterns of Antihypertensive Medications.

<table>
<thead>
<tr>
<th>Pattern of treatment</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strict</td>
<td>130</td>
<td>0.05</td>
<td>130</td>
<td>0.8</td>
<td>140</td>
</tr>
<tr>
<td>Realistic</td>
<td>140</td>
<td>0.03</td>
<td>140</td>
<td>0.7</td>
<td>150</td>
</tr>
<tr>
<td>Modest</td>
<td>150</td>
<td>0.02</td>
<td>140</td>
<td>0.6</td>
<td>160</td>
</tr>
<tr>
<td>Loose</td>
<td>160</td>
<td>0.01</td>
<td>150</td>
<td>0.5</td>
<td>180</td>
</tr>
</tbody>
</table>

a: an alarming systolic blood pressure (SBP), above which patients should be concerned about their SBP, b: an accessibility factor to a primary physician, c: the target SBP level, d: adherence for reaching the target SBP level, e: SBP level of 140, 150, 160 or 180 mm Hg, above which antihypertensive medications were prescribed.

The **sex- and age-specific total incidence rate of CVD after the administration of antihypertensive medications**

\[
\frac{\int_{-\infty}^{e} \left( f(x) \times P_s(x) \right) dx}{\int_{-\infty}^{e} \left( f(x) \times P_s(x) \right) dx + \int_{e}^{\infty} \left( f(x) \times P_u(x - g(x) \times 0.5) \times s(x) \right) dx + \int_{e}^{\infty} \left( f(x) \times P_u(x) \times (1 - s(x)) \right) dx}
\]

where \( f(x) \), \( g(x) \), \( s(x) \) represent SBP, the SBP level at the initial administration of AM, the success rate of AM and the SBP-lowering effect, respectively. The first, second and third terms indicate the subtotal IR_{CVD} in those with SBP below \( e \) and without medications, in those with SBP over \( e \) and after successful AM and in those with SBP over \( e \) and after unsuccessful AM, respectively. The success rate of AM constitutes the following two components: the consultation rate with primary physicians after patients are diagnosed with hypertension at the annual health checkup and the achievement rate in lowering SBP to the target SBP level after taking AM.

First, the consultation rate, \( c(x) = 1 - \exp(-(x-a)\times b) \) (where \( x = \) SBP mmHg; \( a = \) an alarming SBP of 130, 140, 150 and 160 mmHg, above which patients should be concerned about their BP according to strict, realistic, modest and loose applications of AM, respectively; \( b = \) an accessibility factor to a primary physician of 0.05, 0.03, 0.02 and 0.01, respectively). For instance, if the patient’s SBP is 160 mmHg in the realistic application, the consultation rate should be approximately 0.45 (=1-\exp((-160-140)\times0.03)) (Table 4).
Table 5. The Incidence Rate of Cardiovascular Disease by Lifestyle Modifications in Hypothetical Subpopulations.

<table>
<thead>
<tr>
<th>Population</th>
<th>Scenario</th>
<th>No Intervention</th>
<th>Modest</th>
<th>Realistic</th>
<th>Ideal</th>
<th>Romantic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>0.00144</td>
<td>0.00142</td>
<td>0.00137</td>
<td>0.00127</td>
<td>0.00106</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>0.00415</td>
<td>0.00409</td>
<td>0.00396</td>
<td>0.00366</td>
<td>0.00306</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>0.00951</td>
<td>0.00938</td>
<td>0.00908</td>
<td>0.00838</td>
<td>0.00701</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>0.0313</td>
<td>0.0310</td>
<td>0.0301</td>
<td>0.0281</td>
<td>0.024078</td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>0.0616</td>
<td>0.0610</td>
<td>0.0595</td>
<td>0.0560</td>
<td>0.0489</td>
<td></td>
</tr>
</tbody>
</table>

Female, age (years)

| 40-49 | 0.000411 | 0.000405 | 0.000392 | 0.000362 | 0.000303 |
| 50-59 | 0.002455 | 0.00242 | 0.00234 | 0.00216 | 0.00181 |
| 60-69 | 0.00504 | 0.00497 | 0.00481 | 0.00444 | 0.00371 |
| 70-79 | 0.0211 | 0.0209 | 0.0204 | 0.0192 | 0.0168 |
| 80+ | 0.0493 | 0.0489 | 0.0480 | 0.0457 | 0.0410 |

Values are the incidence rate of cardiovascular events per year in the subpopulations according to the scenarios.

Second, the achievement rate in lowering SBP to the target SBP level constitutes the following two components: the SBP-lowering effect = (x-c)x/d (x = SBP mmHg; c = the target SBP level of 130, 140, 140 and 150 mmHg according to strict, realistic, modest and loose controls, respectively, and d = adherence for reaching the target SBP level of 0.8, 0.7, 0.6 and 0.5, respectively) (5). For instance, if the patient’s SBP is 160 mmHg, the SBP-lowering effect should be 14 (= (160-140)x0.7) mmHg in the realistic scenario (Table 4).

AM is simulated as being initiated from the following SBP levels: e=140, 150, 160 and 180 mmHg according to strict, realistic, modest and loose scenarios, respectively (Table 4). In Japan, many primary physicians answered that they prescribe AM if SBP was over 150 mmHg, although the Japanese Hypertension Guideline recommends 140 mmHg for patients aged 75 years of age or older (35).

Comparison between lifestyle modifications and antihypertensive medications

The comparison between LM and AM is based on the following index: the changes in the incidence rates in cardiovascular disease (ΔIR<sub>CVD</sub>, events/year) in the subpopulations by the two following approaches.

\[ \Delta IR_{CVD} = \int_{x}^{x'} f(x) \times P_{o}(x)dx - \int_{x}^{x'} f(x) \times P_{i}(x)dx, \]

where \( f(x) \) and \( P_{o}(x) \) represent the probability density function and sex- and age-specific fractional IR<sub>CVD</sub> before intervention, respectively, and \( f(x) \) and \( P_{i}(x) \) represent the probability density function and sex- and age-specific fractional IR<sub>CVD</sub> after intervention, respectively.

The numbers of subjects needed to treat and decrease one cardiovascular event per year (N<sub>NT</sub>) were assessed for AM.

\[ N_{NT} = \int_{x}^{x'} f(x) \times c(x)dx \]

where \( c(x) \) represents the consultation rate to primary physicians.

Sensitivity analysis

A one-way deterministic sensitivity analysis was performed for the realistic scenarios of AM and LM. We set the upper and lower 20% intervals from the point estimation of the hypothetical parameters in the mathematical equations excluding c (target SBP level) and e (initiating SBP level), which should be arbitrarily determined mainly by primary physicians.

Results

The total IR<sub>CVD</sub> was extremely different in the subpopulations (Table 5; 6; Fig. 2, 3). In 40- to 49-year-old women, the total IR<sub>CVD</sub> with no intervention was 0.000411 events/year. In over 80-year-old women, the total IR<sub>CVD</sub> with no intervention increased to 0.0493 events/year and 120 times as high as that in 40- to 49-year-old women in an aging society.

\( \Delta IR_{CVD} \) by LM in the realistic scenario was 0.000019 in 40- to 49-year-old women (Table 5). In contrast, in men and women over 60 years of age, \( \Delta IR_{CVD} \) by LM would be estimated to be larger if the success rates had been high. However, \( \Delta IR_{CVD} \) in the realistic scenario was unsatisfactory due to the low success rate of LM.

In 40- to 49-year-old women, \( \Delta IR_{CVD} \) by AM in the realistic scenario was 0.000008 (Table 6). In contrast, in men and women over 60 years of age, \( \Delta IR_{CVD} \) by AM was estimated to be larger when medications were prescribed to patients in the realistic and strict scenarios. However, the N<sub>NT</sub> of individuals who took AM was much larger when the initial SBP level was 140 mmHg (the strict scenario) than when it was 160 mmHg (the modest scenario).
This is a therapeutic dilemma between impact and efficiency for the threshold to initiate AM.

Judging from the comparison between $\Delta IR_{CV}$ by LM and $\Delta IR_{CV}$ by AM, LM can be an alternative to AM when the SBP level is less than 160 mmHg and physician consultation rates are expected to be low in AM (Fig. 2, 3). For instance, if a 65-year-old man is unwilling to take AM and possibly accept LM, the estimated $IR_{CV}$ of AM in the loose control (0.00942) is higher than that of LM in the realistic scenario (0.00908).

$\Delta IR_{CV}$ by AM was largest in the strict scenario in all subpopulations. The $NNT_{IR}$ in AM was largest in the strict scenario in men and women under 70 years of age. Unexpectedly, in men and women over 70 years of age, the $NNT_{IR}$ in AM was smaller in the strict scenario than in the realistic scenario. This is potential due to the milder slope of the line representing the relationship between SBP and $IR_{CV}$ in those over 70 years of age. To attain the full effects of AM on reducing $IR_{CV}$, it is necessary to lower SBP as in the strict scenario if tolerated.

The results of the one-way deterministic sensitivity analysis are demonstrated in Supplement materials 1 and 2. The variations in the constants, such as $\alpha$, $\alpha'$ and $\beta$ in LM and a, b and d in AM, have smaller effects than those of m and l. Because the constants k, l and m were utilized both in LM and AM, the results of the sensitivity analysis supported the robustness of this simulation, comparing the effects of LM and AM.

<table>
<thead>
<tr>
<th>Population</th>
<th>Scenario</th>
<th>No Intervention</th>
<th>Loose</th>
<th>Modest</th>
<th>Realistic</th>
<th>Strict</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>0.00144</td>
<td>0.00144</td>
<td>0.00144</td>
<td>0.00140</td>
<td>0.00131</td>
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</tr>
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<td></td>
<td>492</td>
<td>857</td>
<td>1270</td>
<td>1330</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>0.00415</td>
<td>0.00414</td>
<td>0.00403</td>
<td>0.00388</td>
<td>0.00346</td>
<td></td>
</tr>
<tr>
<td></td>
<td>210</td>
<td>334</td>
<td>456</td>
<td>461</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>0.00951</td>
<td>0.00942</td>
<td>0.00900</td>
<td>0.00848</td>
<td>0.00730</td>
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</tr>
<tr>
<td></td>
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<td>141</td>
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<td>185</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>0.0313</td>
<td>0.0311</td>
<td>0.0299</td>
<td>0.0284</td>
<td>0.0249</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43.5</td>
<td>59.6</td>
<td>74.2</td>
<td>71.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>0.0616</td>
<td>0.0610</td>
<td>0.0585</td>
<td>0.0556</td>
<td>0.0490</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28.5</td>
<td>36.0</td>
<td>42.9</td>
<td>40.2</td>
<td></td>
<td></td>
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<tr>
<td>Female, age (years)</td>
<td></td>
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<tr>
<td>40-49</td>
<td>0.000411</td>
<td>0.000411</td>
<td>0.000409</td>
<td>0.000403</td>
<td>0.000392</td>
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<td>2470</td>
<td>2240</td>
<td>4200</td>
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<td>50-59</td>
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<td>0.00245</td>
<td>0.00240</td>
<td>0.00232</td>
<td>0.00211</td>
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<td>60-69</td>
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<td>0.00499</td>
<td>0.00478</td>
<td>0.00452</td>
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<tr>
<td>70-79</td>
<td>0.0211</td>
<td>0.0210</td>
<td>0.0203</td>
<td>0.0194</td>
<td>0.0174</td>
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<tr>
<td></td>
<td>78.2</td>
<td>102</td>
<td>125</td>
<td>118</td>
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<tr>
<td>80+</td>
<td>0.0493</td>
<td>0.0490</td>
<td>0.0475</td>
<td>0.0457</td>
<td>0.0415</td>
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<tr>
<td></td>
<td>51.6</td>
<td>61.4</td>
<td>71.6</td>
<td>64.8</td>
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</tbody>
</table>

Values in the upper column are the incidence rates of cardiovascular events per year in the subpopulations according to the scenarios. Values in the lower column are the numbers needed to treat to rescue one cardiovascular event per year in the subpopulations.

### Discussion

This is the first theoretical report to demonstrate the marked differences in $IR_{CV}$ by implementing LM or AM according to sex and age using a success rate-oriented simulation. For 40- to 49-year-old women in an aging society, the preventive effects of both LM and AM were limited due to the extremely low $IR_{CV}$. In contrast, $\Delta IR_{CV}$ in individuals over 60 years of age was substantially larger for patients with SBP levels over 160 mmHg. If AM were prescribed to patients with SBP levels over 140 mmHg as recommended by the traditional hypertension treatment guidelines (JNC8) has recommended primary physicians to prescribe AM (35, 37). Recently, the Eight Joint National Committee (JNC8) has recommended primary physicians to initiate AM
from a SBP of 150 mmHg and to treat to a goal SBP lower than 150 mmHg in subjects 60 years of age or older (38). The Japanese Society of Hypertension Guideline 2014 has recommended primary physicians to initiate AM from a SBP of 150 mmHg and to treat to a tentative target SBP lower than 150 mmHg in subjects 75 years of age or older. In the realistic scenario of this study, AM was initiated from a SBP of 150 mmHg, treated to reach a SBP level of 143 mmHg. Therefore, we consider that the realistic scenario of AM is compatible with the real practice in Japan and the disciplines of the new guidelines.

Non-adherence of AM was reported to be associated with younger men (39, 40). In an aging society, with people over 80 years of age, it is difficult to achieve a high success rate in taking AM because elderly patients face problems of accessibility to regional primary physicians (27). LM might thus be considered as an alternative approach in situations in which the SBP level is below 160 mmHg (41).

It is unexpected that the NNT in the strict scenario of AM was less than the NNT in the realistic scenario of AM in men and women over 70 years of age. In the elderly subpopulations, the slope of the line representing the relationship between SBP and IRCVD is mild, and it is necessary to keep the target SBP less than 140 to achieve a substantial risk reduction. Therefore, our results did not support the relaxation of the target SBP levels in some hypertension treatment guidelines, which revised the target SBP level from 140 to 150 mmHg in elderly patients. According to the Japanese hypertension guideline, we should gradually and patiently achieve a target SBP level of 140 mmHg if tolerated for patients even 75 years of age or older in an aging society.

A cost-effectiveness analysis is required to make an appropriate decision because an aging society faces the shortage of a medical budget. In 40- to 49-year-old subpopulations, ΔIRIRCVD in the realistic scenario of LM was slightly larger than that of AM. We assumed that the cost of AM to be approximately 70,000 yen/year/capita considering discount rates (42). The consultation rate of the 40- to 49-year-old male subpopulation in the realistic scenario was 5% in this simulation. The costs of LM for the affirmative and motivating supports widely ranged from 20,000 to 30,000 yen (too expensive).

Therefore, the cost-effectiveness is largely dependent on the cost of LM, especially for the motivating supports. The cost-cutting efforts are urgent tasks for LM. The results were similar in 40- to 49- year-old women. In contrast, ΔIRIRCVD in the realistic scenario of AM was slightly larger than that of LM in the subpopulations over 50 years of age. Therefore, in the subpopulations over 50 years of age, AM can be recommended if they ordinarily accept AM.

There are several limitations associated with this study. First, our estimation was limited to the effect of AM and LM within several years. Another simulation is required for a life-long estimation. Second, we estimated IRCVD only when several assumptive constants were concomitantly varied. Third, we did not examine what would happen if LM and AM were performed concurrently since most individuals are willing to accept only one approach at a time (43, 44). Fourth, SBP is not normally distributed in certain populations (45). Fifth, we mainly reported point estimations in reducing IRCVD in the subpopulations. However, we proposed a wide spectrum of possible scenarios related to sex- and age-related behavioral factors both in LM and AM. The constants used in the hypothetical equations require further validation. Patients and their primary physicians can compare the results of the various combinations of the LM and AM scenarios. Sixth, this simulation did not address the effect of smoking and/or non-cardiovascular deaths. Seventh, this simulation is only applied for an aging society that has a low incidence rate of coronary heart disease (46).

In conclusion, the success rate-oriented simulation suggested that the effectiveness of LM or AM in preventing cardiovascular events was largely dependent on the baseline IRCVD and sex- and age-related behavioral factors. Age should primarily be considered to initiate primary prevention of CVD. The impact of LM on preventing CVD is competitive with that of AM in the corresponding scenarios, considering the improvement of metabolic profiles. LM can be an alternative to AM in reducing CVD when the SBP level is less than 160 mmHg and physician consultation rates are expected to be low. Further studies are required to investigate how to improve the success rate of LM according to sex- and age-related behavioral characteristics.

The authors state that they have no Conflict of Interest (COI).

References


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