Background—Information has been sparse on the comparison of 4 blood pressure (BP) indexes (systolic BP [SBP], diastolic BP, pulse pressure, and mean BP [MBP]) in relation to long-term incidence of stroke and myocardial infarction, particularly in middle-aged and older Asians.

Methods and Results—The Japan Arteriosclerosis Longitudinal Study Group conducted a meta-analysis of 16 cohort studies in Japan. A total of 48,224 men and women 40 to 89 years of age participated at baseline, and 1,231 stroke events and 220 myocardial infarction events occurred during an average 8.4-year follow-up. Multivariate-adjusted hazard ratios with a 1-SD higher value for each BP index were determined by Poisson regression. Analyses were also done in 4 age-sex groups. All 4 BP indexes were significantly related to all stroke risk. Stroke risk was most strongly related to MBP and SBP in both sexes and most weakly related to pulse pressure. Both stroke subtypes, ischemic and hemorrhagic, were most strongly related to MBP and SBP in both sexes. In addition, in men and women 70 to 89 years of age, MBP or SBP showed the strongest relation to all stroke risk. Myocardial infarction risk was most strongly related to SBP or MBP in both sexes. For any end points in any age-sex groups, pulse pressure was not the strongest predictor.

Conclusions—The long-term incident risk of stroke and myocardial infarction associated with high BP in East Asian populations should be assessed mainly on the basis of SBP. MBP also may be an important predictor, but pulse pressure is a less important predictor for cardiovascular disease risk. (Circulation. 2009;119:1892-1898.)

Key Words: blood pressure • cohort studies • myocardial infarction • meta-analysis • stroke

Blood pressure (BP) is an established major risk factor for cardiovascular diseases.1–4 Risk relationships for both systolic BP (SBP) and diastolic BP (DBP) are generally regarded to be continuous, graded, strong, independent of other risk factors, and etiologically significant. Some data suggest that SBP is a stronger predictor of cardiovascular diseases than DBP,5–8 and several epidemiological studies have reported that pulse pressure (PP), the difference between SBP and DBP, is a useful predictor for coronary heart disease, especially in older people.9–11 However, cohort studies including older people have revealed that the relationship between PP and mortality from all cardiovascular diseases and coronary heart disease is not as strong as those for other BP indexes.12–15 Regarding stroke, 2 large-scale cohort study collaborations, as well as other cohort studies, have shown that PP is less useful in predicting long-term stroke risk than SBP.14–18 However, the majority of the study participants in these studies were white (even in 1 study from the Asia Pacific region), and there are few investigations including only Asian people, in whom stroke occurrence is relatively high compared with that in Western countries. Two relatively small-scale studies have been reported recently from Japan, although investigations by sex, age groups, and stroke subtype (ischemic and hemorrhagic) have not been fully performed.19,20 Therefore, it is still uncertain which BP index is the best for predicting future incidence of cardiovascular diseases in various age-sex groups of pure East Asian populations or whether the importance of BP indexes differs for predicting ischemic stroke and hemorrhagic stroke risks.
Clinical Perspective p 1898

The Japan Arteriosclerosis Longitudinal Study—Existing Cohorts Combine (JALS-ECC) is a pooling project based on individual participant data from existing high-quality prospective cohort studies in Japan. This meta-analysis of 16 cohort studies allowed detailed investigations with >1000 stroke events and 200 myocardial infarction (MI) events from >400 000 person-years of follow-up in middle-aged and older Japanese men and women. The specific goals of this research are to assess in these East Asian population samples which of these 4 BP indexes is the best predictor of incident stroke and MI risk among the 4 indexes, whether the best predictor differs by sex, whether the best predictor differs between middle-aged people and older people, and whether the best predictor differs by stroke subtype (ischemic and hemorrhagic).

Methods

Study Population

The rationale, study design, and methods of the JALS-ECC have been described elsewhere. In brief, cohort studies were potentially eligible for inclusion in this project if they satisfied the following criteria: (1) Japanese population; (2) prospective cohort study; (3) at least 3000 persons-years of follow-up; (4) date of birth (or age), gender, height, weight, BP, and total cholesterol recorded at baseline; and (5) date of death or age at death (for death from stroke or coronary heart disease at least) recorded during follow-up. Quality control of collected cohort data was performed at the JALS Coordinating Center. Consequently, individual records for each of the 16 cohorts analyzed were included in this project, with 82.7% of the participants from community-based cohorts and 17.3% from workplace-based cohorts. Permission to submit cohort data to the JALS central office was obtained from each institutional review board for ethical issues.

Baseline Data

The JALS Study Group requested data for individual participants from the collaborating investigators. The data requested for each participant included date of baseline survey, date of birth or age at baseline, gender, height, weight, history of cardiovascular diseases, BP (SBP and DBP), total cholesterol, high-density lipoprotein cholesterol, triglycerides, smoking habits, and alcohol consumption. Among the 16 cohorts analyzed, BP was measured by standard sphygmomanometer in 13 cohorts, by random-zero sphygmomanometer in 1 cohort, and by automatic cuff–oscillometric device in 2 cohorts. BP was measured once in 11 cohorts, twice in 4 cohorts, and 3 times in 1 cohort. Mean values were used in cohorts with ≥2 BP values.

End Points

In each cohort, vital status and the incidence of stroke and/or MI were ascertained during the follow-up period through the use of population-based stroke and/or MI registration systems, death certificates, medical records in hospitals, and/or questionnaires. The diagnosis of stroke was based on typical clinical features and characteristic changes on computed tomographic and/or magnetic resonance imaging brain scans and typically was based on criteria from the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study or from the World Health Organization. The diagnosis of MI was based on chest pain, cardiac enzyme levels, and ECGs and typically was based on criteria from the MONICA study. Disease classifications were made with the International Classification of Disease, 9th revision (ICD-9), as follows: stroke (ICD-9: 430, 431, 433, 434, 436), cerebral infarction (ICD-9: 433 to 434), cerebral hemorrhage (ICD-9: 431), subarachnoid hemorrhage (ICD-9: 430), and MI (ICD-9: 410). Cerebral hemorrhage and subarachnoid hemorrhage were classified as hemorrhagic stroke.

Exclusions

From 21 cohorts of the JALC-ECC, 3 cohorts were excluded because of a lack of assessment of stroke and/or MI incidence as a study end point, and 2 cohorts were excluded because of a lack of baseline assessment of body mass index, serum total cholesterol, and/or cigarette smoking. From the remaining 60 616 participants in 16 cohorts, participants <40 or ≥90 years of age (n=7484) and those lacking baseline examination data (n=4223) were excluded. Among the remaining 48 909 participants, 685 participants (1.4%) withdrew during the follow-up period. Thus, the report was based on a total of 48 224 participants (21 061 men, 27 163 women) with the following age-sex breakdown: 18 596 men 40 to 69 years of age, 2465 men 70 to 89 years of age, 23 557 women 40 to 69 years of age, and 3606 women 70 to 89 years of age. Among the 16 cohorts, analyses for stroke were performed in 15 cohorts (40 982 participants) in which stroke events were surveyed, and analyses for MI were performed in 13 cohorts (36 015 participants) in which MI events were surveyed.

Statistical Analyses

MBP was calculated as SBP/3+2DBP/3, and PP was calculated as SBP minus DBP. For each BP index considered separately as a continuous variable, a mixed-effect Poisson regression model with a random intercept for each cohort was used to determine multivariate-adjusted hazard ratios (HRs) for a level greater by 1 SD. Wald χ² analyses also were used to compare the strength of relationships. A model included both SBP and DBP simultaneously to assess their independent relationships with adjustment for each other. Another model included both MBP and PP simultaneously to assess their independent relationships. HRs were adjusted for other major risk factors and for potential confounders, which were age (years, continuous) and body mass index (kg/m², continuous), serum total cholesterol (mg/dL, continuous), and cigarette smoking (current smoker or not), as fixed effects. For each end point of all stroke, ischemic stroke, hemorrhagic stroke, and MI, these analyses were done for men and women separately. For all stroke, analyses also were done for each of 4 age-sex groups. HRs were estimated on the basis of a theory of quasi-likelihood by PROC GLIMMIX in the SAS program for Windows, release 9.1.3 (SAS Institute Inc, Cary, NC).

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Characteristics of the 16 cohorts are shown in Table 1. There were 1 cohort from Hokkaido Island, 12 cohorts from Honshu (Main) Island, 1 cohort from Shikoku Island, and 2 cohorts from Kyushu Island. Three cohorts were from workplaces. A total of 48 224 participants were followed up for an average of 8.4 years; there was a total observation of 407 213 person-years. A total of 1231 stroke events and 220 MI events were recorded during the follow-up period. Baseline characteristics of participants are shown in Table 2. Mean age was 56.7 years, and mean body mass index was 23.2 kg/m². The smoking rate was much higher in men (53.8%) than in women (4.5%).

Table 3 shows the numbers and rates of stroke and MI events in the surveyed cohorts. The crude rate of all stroke incidence was higher in men than in women. Ischemic stroke accounted for 74% of all strokes in men and 58% in women. Crude MI incidence rate also was higher in men than in women. MI incidence was less than one third of stroke incidence in men and less than one sixth in women.
Figure 1 shows multivariate-adjusted HRs of all stroke risk for each BP index greater by 1 SD in all men and in all women. All 4 BP indexes were positively and significantly related to all stroke risk in both sexes. Wald $\chi^2$ indicated that MBP was the strongest predictor among 4 BP indexes and that SBP was a similarly strong predictor in both sexes. The relationships remained positive for both SBP and DBP after adjustment for each other in models including both SBP and DBP simultaneously, but these relationships were stronger for SBP. The relationships for PP were not as strong as those for the other 3 BP indexes, and these relationships were even weaker after adjustment for MBP. These results were similar between men and women.

Figure 2 shows results for ischemic stroke incidence in men and women. Wald $\chi^2$ indicated that SBP and MBP were the strongest predictors of the 4 BP indexes in both sexes. DBP was no longer a significant predictor after adjustment for SBP in both sexes.

Table 2. Baseline Characteristics of Total Participants From the 16 Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, n</td>
<td>48 224</td>
<td>21 061</td>
<td>27 163</td>
</tr>
<tr>
<td>Age, y</td>
<td>56.7 ± 10.6</td>
<td>56.0 ± 10.5</td>
<td>57.3 ± 10.6</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>130.4 ± 19.2</td>
<td>131.6 ± 19.0</td>
<td>129.5 ± 19.3</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>77.3 ± 11.5</td>
<td>79.6 ± 11.7</td>
<td>76.3 ± 11.1</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>52.7 ± 13.9</td>
<td>52.0 ± 13.6</td>
<td>53.2 ± 14.1</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>95.3 ± 13.0</td>
<td>96.9 ± 13.1</td>
<td>94.0 ± 12.7</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.2 ± 3.1</td>
<td>22.9 ± 2.9</td>
<td>23.3 ± 3.2</td>
</tr>
<tr>
<td>Serum total cholesterol, mg/dL</td>
<td>200.0 ± 36.6</td>
<td>194.0 ± 36.1</td>
<td>204.1 ± 36.3</td>
</tr>
<tr>
<td>Current cigarette smokers, %</td>
<td>26.1</td>
<td>53.8</td>
<td>4.5</td>
</tr>
</tbody>
</table>

SP indicates sphygmomanometer; AD, automatic device (cuff-oscillometric); and RZ, random-zero sphygmomanometer.

Figure 3 shows results for hemorrhagic stroke incidence in men and women. Wald $\chi^2$ indicated that MBP was the strongest predictor of the 4 BP indexes in both sexes but that both SBP and DBP were strong predictors. In men, a model including SBP and DBP simultaneously showed that DBP was strongly related to hemorrhagic stroke risk independently of SBP. PP was the weakest of the 4 BP indexes for predicting risk.

Figure 4 shows multivariate-adjusted HRs for all stroke incidence in each of the 4 age-sex groups. In men 40 to 69 years of age, Wald $\chi^2$ indicated that MBP was the strongest of the 4 predictive indexes. In men 70 to 89 years of age, the strongest relationship also was observed for MBP. PP was the weakest predictor in both younger men and older men. A model including SBP and DBP simultaneously showed that both BP indexes were significantly and independently related to stroke risk in younger men but that only SBP was a significant predictor in older men. In both younger and older women, MBP showed stronger relationships to all stroke risk. The relationship of PP was not as strong as that of other BP indexes in both female age groups. There was no significant relationship between PP and stroke risk after adjustment for MBP in all four age-sex groups.

Figure 5 shows multivariate-adjusted HRs of MI incidence in all men and in all women. All 4 BP indexes were positively related to MI risk in both sexes, but some relationships were not statistically significant. Wald $\chi^2$ indicated that SBP tended to be the strongest predictor among the 4 BP indexes and that MBP was a similarly strong predictor in both sexes. The relationships tended to be stronger for SBP after adjustment for DBP.

Information on antihypertensive medication at baseline was obtained in 7 cohorts (n=18 587). When all the above
analyses were done in 15,878 participants without antihypertensive medication, the results were similar.

**Discussion**

The main findings from this meta-analysis of 16 cohort studies on stroke and MI incidence in middle-aged and older Japanese men and women are as follows. First, for predicting the incidence of all stroke, ischemic stroke, and MI, MBP or SBP was generally the strongest and PP was the weakest in any of the age-sex groups. Second, for hemorrhagic stroke incidence, MBP was the strongest predictor in both sexes, and DBP was more important than SBP in men. Third, PP was not the strongest of the 4 predictive indexes for any subtype of stroke in any of the age-sex groups, including older people.

Although several studies have shown PP to be a strong predictor of coronary heart disease and all cardiovascular diseases, especially in older people, more recent larger cohort studies including older people have indicated that the relationship between PP and mortality from cardiovascular diseases and coronary heart disease was not as strong as other BP indexes.9–11 Regarding stroke, 2 large-scale cohort studies collaborations and other recent cohort studies have reported PP to be less useful in predicting long-term stroke risk than SBP.14–20 In one of those studies, the Asia Pacific Cohort Studies Collaboration, analyses similar to our study were performed for BP and fatal events of stroke and ischemic heart disease, comparing HRs for a 1-SD difference in each of 4 BP indexes.15 The study showed that the strongest relationships to fatal stroke were observed for SBP in men 50 to 69 years of age (HRs ranged between 1.5 and 2.0) and in women.

**Table 3. Total Numbers and Rates of Stroke and MI Incidence in 16 Cohorts***

<table>
<thead>
<tr>
<th>End Point</th>
<th>Men Events, n</th>
<th>Rate per 10 000 Person-Years</th>
<th>Women Events, n</th>
<th>Rate per 10 000 Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke (total participants)</td>
<td>632</td>
<td>43.8</td>
<td>599</td>
<td>29.2</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>466</td>
<td>32.2</td>
<td>349</td>
<td>16.9</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>167</td>
<td>11.4</td>
<td>246</td>
<td>11.9</td>
</tr>
<tr>
<td>All stroke (baseline 40–69 y of age)</td>
<td>452</td>
<td>34.6</td>
<td>412</td>
<td>22.3</td>
</tr>
<tr>
<td>All stroke (baseline 70–89 y of age)</td>
<td>180</td>
<td>131.6</td>
<td>187</td>
<td>92.3</td>
</tr>
<tr>
<td>All stroke (total participants)</td>
<td>148</td>
<td>12.3</td>
<td>72</td>
<td>4.6</td>
</tr>
</tbody>
</table>

*Stroke events were from 15 cohorts; MI events were from 13 cohorts.

**Figure 1.** Adjusted HRs for 4 BP indexes for all stroke incidence by sex. HRs are calculated for each BP index higher by 1 SD and adjusted for age, body mass index, total cholesterol, and smoking through Poisson regression. *Two BP indexes are included in the same model.

**Figure 2.** Adjusted HRs for 4 BP indexes for ischemic stroke incidence by sex. *Two BP indexes are included in the same model.
of all age groups (HRs ranged between 1.3 and 1.9). MBP and DBP in men <50 years of age (HR, 2.5) and PP and SBP in men ≥70 years of age (HR, 1.4) showed similarly strong relationships. These results are similar to our results. Major differences between this study and ours were that the study end point was mainly fatal events, not incidence, and that, although the study was conducted in the Asia Pacific region, a large number of the study participants were white Australians. Two recent cohort studies on stroke from Japan were small in scale19,20; therefore, the present study is the first large-scale meta-analysis of pure Asian subjects to provide detailed analyses on 4 BP indexes and incident stroke and MI risk by various age-sex groups and by stroke subtypes.

A few studies have investigated the relationship between BP indexes and stroke incidence in older people.16,19 In the Cardiovascular Health Study, 5888 men and women ≥65 years of age (mean age, 73 years) participated from 4 US centers, and the adjusted stroke risk for a 1-SD difference in each BP was higher for SBP (HR, 1.34) than for DBP (HR, 1.29) and PP (HR, 1.21) when analyses were done in men and women combined.16 Another finding from a relatively small Japanese cohort in men and women 65 to 79 years of age (mean age, 70 years) that was PP was less important than SBP in men and than SBP and DBP in women.19 In older participants 70 to 89 years of age in the present study, SBP was more strongly related to stroke incidence than PP in both sexes. SBP appears to be a more effective predictive measure of the future risk of stroke incidence than PP, even in older men and women in both Western and Asian populations.

For MI risk, our findings that SBP and MBP were the best predictors and that PP was less important were similar to previous findings from other large-scale meta-analyses.14,15 However, because of the low MI incidence rate in Japanese and therefore the small number of MI events, analyses by 4 age-sex groups were statistically difficult in this study.
**Myocardial infarction**

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Hazard Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>1.00 (0.81-1.27)</td>
</tr>
<tr>
<td>DBP</td>
<td>1.00 (0.81-1.27)</td>
</tr>
<tr>
<td>PP</td>
<td>1.00 (0.81-1.27)</td>
</tr>
<tr>
<td>MBP</td>
<td>1.00 (0.81-1.27)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Hazard Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>1.00 (0.81-1.27)</td>
</tr>
<tr>
<td>DBP</td>
<td>1.00 (0.81-1.27)</td>
</tr>
<tr>
<td>PP</td>
<td>1.00 (0.81-1.27)</td>
</tr>
<tr>
<td>MBP</td>
<td>1.00 (0.81-1.27)</td>
</tr>
</tbody>
</table>

*Two BP indexes are included in the same model.

Recent discussions on the diagnosis and treatment of high BP have focused on SBP more than DBP, especially in older people.5–8,25 However, in the present study, the relationship between DBP and hemorrhagic stroke incidence was stronger than or as strong as that of SBP in men and women, respectively. Moreover, the relationship between DBP and all stroke incidence was as strong as that for SBP, whereas DBP was positively related to the risk after adjustment of SBP; similar findings were reported in previous reports.15,19 These results indicate a role for DBP in the long-term evaluation of all stroke, especially hemorrhagic stroke, in both sexes. In fact, in middle-aged people, previous epidemiological studies have shown that cardiovascular disease risk generally increased with DBP level in each stratum of SBP level.2,13,26

MBP tended to be the strongest predictor of stroke and MI risk, together with SBP, in both sexes. MBP could be a slightly better predictor of long-term cardiovascular disease risk than SBP and DBP in East Asian populations. However, use of this index may not currently be practical in daily clinical and public health practice because there are no guidelines for hypertension diagnosis and management using MBP.

From a physiological viewpoint, mean arterial pressure is regulated by changes in cardiac output and systemic vascular resistance, and MBP is an approximate measure of mean arterial pressure. PP has been reported to be a good indicator of arterial stiffness, especially in older people.27,28 To look at the independent relationships of these 2 indexes to cardiovascular disease risk, a model including MBP and PP simultaneously was used in this study. Generally, PP was not significantly related to stroke and MI risk after adjustment of MBP. However, because PP is an incomplete metric of arterial stiffness and is affected by other factors, our study results would not definitely deny the physiological importance of arterial stiffness for cardiovascular disease risk.

A limitation of the present study is that, because this is a meta-analysis of 16 cohort studies, the methods of BP measurement were not well standardized. Another limitation is a lack of information at baseline on antihypertensive medication. The inclusion of some participants whose BP was controlled by medication would underestimate the relationship between BP and stroke risk. Similar results were observed in subgroup analyses for participants not receiving antihypertensive medications. Moreover, each BP index was included as a continuous variable in our statistical models under an assumption that there is a linear relationship between BP and stroke risk.

There are a number of possible implications of our results for the primary prevention of cardiovascular diseases in East Asian populations. First, the long-term incident stroke and MI risk of high BP should be assessed mainly by SBP. DBP should be given careful consideration for its independent relationship to stroke risk. Second, emphasis on PP should be avoided, even in older people, for the prediction of future cardiovascular disease risk. Third, the relationships between MBP and the risk of stroke and MI were generally as strong as those for SBP. However, the use of this index may not currently be practical in daily clinical and public health practice.

**Source of Funding**

This study was supported by the Japan Arteriosclerosis Prevention Fund.

**Disclosures**

None.

**References**

Information has been sparse on the comparison of 4 blood pressure (BP) indexes (systolic BP, diastolic BP, pulse pressure, and mean BP) in relation to long-term incidence of stroke and myocardial infarction, particularly in middle-aged and older Asians. The present meta-analysis of 16 cohort studies investigated >1000 stroke events and 200 myocardial infarction events from >400 000 person-years of follow-up in middle-aged and older Japanese men and women. For predicting all stroke, ischemic stroke, and myocardial infarction, mean BP or systolic BP was generally the strongest and pulse pressure was the weakest in any of the age-sex groups. For hemorrhagic stroke, mean BP was the strongest predictor in both sexes, and in men, diastolic BP was more important than systolic BP. Pulse pressure was not the strongest of the 4 BP indexes for any subtype of stroke in any of the age-sex groups, including older people. For the primary prevention of cardiovascular diseases in East Asian populations, the long-term risk of stroke and myocardial infarction should be assessed mainly by systolic BP. Diastolic BP should also be given careful consideration for its independent relationship to stroke risk. Emphasis on pulse pressure should be avoided even in older people for the prediction of future cardiovascular disease risk. Although mean BP was important in addition to systolic BP, use of this index may not be practical in daily clinical and public health practice at present.
Katsuyuki Miura, Hideaki Nakagawa, Yasuo Ohashi, Akiko Harada, Masataka Taguri, Toshio Kushiro, Atsuhiko Takahashi, Masanori Nishinaga, Hirofumi Soejima and Hirotugu Ueshima
for the Japan Arteriosclerosis Longitudinal Study (JALS) Group

_Circulation_. 2009;119:1892-1898; originally published online March 30, 2009;
doi: 10.1161/CIRCULATIONAHA.108.823112
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/119/14/1892

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/