Perinatal Risk Factors for Ischemic Heart Disease
Disentangling the Roles of Birth Weight and Preterm Birth

Magnus Kaijser, MD, PhD; Anna-Karin Edstedt Bonamy, MD; Olof Akre, MD, PhD; Sven Cnattingius, MD, PhD; Fredrik Granath, PhD; Mikael Norman, MD, PhD; Anders Ekbom, MD, PhD

Background—Several studies have reported an association between low birth weight and ischemic heart disease, but it remains unclear whether the association is mediated through poor fetal growth or short gestational duration.

Methods and Results—In a cohort study, we have identified all subjects born preterm or with a low birth weight at 4 major delivery units in Sweden from 1925 through 1949. For comparison, an equal number of subjects with none of these criteria were identified within the same source population. The study population consists of 6425 subjects, of whom 2931 were born before 37 weeks of gestation and 2176 had a birth weight < 2500 g. Fetal growth was estimated through birth weight for gestational age. The cohort was followed up for occurrence of ischemic heart disease through the nationwide Hospital Discharge and Cause of Death Registries during the period of 1987 through 2002. In the cohort, 617 cases of ischemic heart disease occurred. Compared with subjects with a normal fetal growth, those born small for gestational age (birth weight < −2 SD below the mean) were at increased risk of ischemic heart disease (adjusted hazard ratio, 1.64; 95% confidence interval, 1.23 to 2.18). The negative association between fetal growth and risk of ischemic heart disease was independent of gestational duration.

Conclusions—The association between low birth weight and adult risk of ischemic heart disease appears to be mediated entirely by poor fetal growth. (Circulation. 2008;117:405-410.)

Key Words: cardiovascular diseases • fetus development • infant, low birth weight • infarction • premature birth

An increased risk of ischemic heart disease in people born small has been shown in a vast number of studies.1–14 Because low birth weight could reflect fetal growth restriction, adverse influences in the intrauterine environment such as malnutrition have been proposed to be an explanation for this association.1,15 However, given the strong correlation between duration of gestation and birth weight, it is possible that the association between low birth weight and ischemic heart disease may be linked in part to preterm birth. This hypothesis is supported by the fact that associations between preterm birth and common risk factors for ischemic heart disease have been reported in children and young adults.16–18

Editorial p 341
Clinical Perspective p 410

Most studies on perinatal risk factors for ischemic heart disease in adult life either lack information on gestational duration or rely on information on gestational duration collected from study subjects themselves several decades after birth.2–4 Studies with prospectively recorded data on gestational duration contain only a limited number of subjects in the lower ranges of birth weight and gestational duration.10–13,19

We have established a cohort comprising all children born before 35 weeks of gestation and/or with a birth weight < 2000 g (girls) or 2100 g (boys) by manually examining ≈250 000 birth records at 4 major delivery units in Sweden during the period of 1925 through 1949. This cohort was then followed up in population-based Swedish registers to disentangle whether the association between low birth weight and ischemic heart disease was due to fetal growth restriction and/or short gestational duration.

Methods

Setting
Since the late 17th century, all Swedish parishes have been obliged by law to keep ledgers with information on all births, marriages, and deaths. In 1947, all living Swedish residents were assigned a unique national registration number in their respective parish ledgers. This number has been used ever since and is referred to in all official documents, registries, and medical files.
The Swedish National Board of Health and Welfare has been responsible for a complete Cause of Death Register since 1952. The board also is responsible for the Hospital Discharge Register. This register collects information on all public inpatient care in Sweden and became nationwide in 1987. Completeness varies with county and diagnosis, but for the diagnosis of acute myocardial infarction, the proportion of false positives and false negatives has been reported to be 5% and 3%, respectively. Since 1960, Statistics Sweden provides annually revised information on name, community, and county of domicile for all residents in Sweden through the Register of Population and Population Changes.

**Study Cohort**

The source population for this cohort study was all births from 1925 through 1949 at 4 major delivery units in Sweden (Allmänna BB and Södra BB in Stockholm, Uppsala University Hospital, and Sundsvalls County Hospital). Information in birth records was recorded by the attending midwife at time of admission for delivery (maternal age, maternal/paternal occupation, date of last menstrual period, proteinuria or preeclampsia during pregnancy, and proteinuria at time of admission), immediately after delivery (birth weight, birth length, sex, and twin status), or when the mother was discharged from hospital (proteinuria postpartum and breast-feeding at time of discharge). By manually examining the ~250,000 births records during this period, we identified a cohort of infants born preterm, small for gestational age, or both by selecting all newborn infants with a gestational duration of <35 weeks or a birth weight of <2000 g for girls and <2100 g for boys. We chose different cutoff points for girls (ie, boys) because the average weight is more than girls and we wanted to obtain groups of equal size. Subjects for whom no information was available on gestational duration or for whom only the month for the mother’s last menstrual period was given were not included in the cohort. Subjects who emigrated or died before 1987 were excluded.

As a reference cohort, we selected subjects with no history of preterm birth or low birth weight (ie, infants born after 35 weeks of gestation with a birth weight >2000 g [girls] or 2100 g [boys]). For convenience, we selected the first child of same sex and hospital of birth born after each study subject.

In addition to birth weight and gestational age, we used birth records to collect information on maternal age; maternal/paternal occupation; proteinuria during pregnancy, at admission for delivery, and postpartum; and information on hypertension, twin status, and breast-feeding at time of hospital discharge.

**Perinatal Definitions and Categorization**

We used last menstrual period to estimate gestational duration, which was categorized into 4 groups: ≤32 completed weeks (very preterm), 33 to 36 weeks (preterm), 37 to 42 weeks (term), and ≥43 weeks (postterm). For mothers who did not recall an exact date of last menstrual period but who could indicate if the last menstrual period was in the beginning, middle, or end of a given month, we approximated last menstrual period to the 5th, 15th, and 25th of the same month, respectively. If only the month of the last menstrual period was remembered or if it was not recalled at all, the subjects were not included in the cohort. Birth weight was categorized in 7 groups of 500-g intervals from <1500 to ≥4000 g. To reduce misclassification of pregnancy duration and/or birth weight, we excluded subjects whose birth weight was >4 SD above or below the mean birth weight for gestational age.

As a measure of fetal growth, we used birth weight for gestational age. We also considered using the ponderal index, which is based on the relation between weight and length. The maximum increase in fetal length occurs in the second trimester, whereas the increase in fetal weight mainly occurs in the third trimester. We had a large proportion of preterm infants in our study, and we considered that using the ponderal index may result in misclassification of growth-restricted preterm infants. In estimating birth weight for gestational age, we could use either the Swedish reference curve for estimated intrauterine fetal growth based on ultrasound estimations of fetal weights in normal pregnancies ending at term or a conventional reference curve based on information on birth weights at different gestational ages. We decided to estimate birth weight for gestational age using fetal growth curves because fetal growth curves will, compared with conventional birth weight standards, probably correctly classify a larger proportion of preterm births as being small for gestational age. Birth weight for gestational age was categorized into 5 groups according to their distance from average in numbers of standard deviations (≤−2, >−2 to −1, >−1 to 0, >0 to 1, and ≥1 SD).

Study subjects were considered exposed to pregnancy-related hypertensive disorders when their mothers met one of the following criteria: proteinuria during pregnancy, several measurements of proteinuria postpartum, or a clinical diagnosis of preeclampsia noted in the birth record. Maternal age was categorized as ≤19, 20 to 36, and ≥37 years.

The socioeconomic status of the family was assessed by the father’s or single mother’s occupation using 3 categories: high (college education), medium (white-collar workers and farm owners with no college education), and low (blue collar workers and farm hands).

**Follow-Up and Analysis**

Follow-up started in January 1, 1987, and continued to December 31, 2002. At the start of follow up, 6801 subjects were in the cohort, 376 of whom were excluded because of a birth weight for gestational age above or below 4 SD from the mean birth weight for gestational duration. We used the Register of Population and Population Changes to ascertain emigration or death during follow-up. Ischemic heart disease was defined from the Cause of Death and the Hospital Discharge Registers using the diagnostic codes 410 to 414 and I20 to I25 according to the 9th and 10th revisions of the International Classification of Disease, respectively.

Because causes of death were available before the start of the Hospital Discharge Registry, we also assessed mortality of ischemic heart disease from 1958 through 1986. We chose 1958 as the starting year of this follow-up because a subset of the cohort was initially created to assess cancer incidence, and 1958 was the starting year for the Swedish Cancer Registry.

Data were modeled through Cox proportional-hazards regression using the TPHREG procedure in SAS Statistical Software, version 9.1 (SAS Institute Inc, Cary, NC). Ischemic heart disease was the failure event, and subjects with no ischemic heart disease were censored at death, emigration, or December 31, 2002, whichever occurred first. Time was modeled from January 1, 1987, to date of event or to date of censoring. We controlled for age at entry in 5-year categories and sex in all analyses by adding these variables in the strata statement. When controlling for birth weight, gestational duration, or fetal growth, we used the same method. Testing for trend was done by scoring categories with equidistant points and using these scores as a continuous variable.

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

**Results**

Of the 6425 included individuals, 2931 were born preterm (<37 weeks). Among those born preterm, one third had a gestational duration of ≤32 weeks. In total, 2176 subjects were in the cohort with low birth weight (<2500 g); of these, 151 had a birth weight of <1500 g. The distribution of birth weight, gestational duration, and fetal growth is presented in further detail in Table 1.

During follow-up, 617 subjects either were treated for or died of ischemic heart disease (Table 2). When analyzing birth weight and gestational duration separately, we found no significant associations between birth weight or gestational duration and ischemic heart disease (P for trend=0.14 and 0.35, respectively) (Table 2). When birth weight was adjusted...
for gestational duration, a strong negative association with ischemic heart disease emerged ($P$ for trend/$H_1$/$H_0.002$). Specifically, compared with subjects with a birth weight from 3000 to 3499 g, those with a birth weight of $<1500$ g faced, after controlling for gestational age, a 139% increase in risk for ischemic heart disease, whereas the corresponding risk increases among those with a birth weight between 1500 and 2999 g ranged from 29% to 38% (Table 2). In contrast, when gestational duration was adjusted for birth weight, we found a significant positive association. Compared with subjects with gestational age between 37 and 42 weeks, those with shorter gestation had, after adjustment for birth weight, a reduced risk of ischemic heart disease (Table 2).

Fetal growth, expressed as 1 SD from the mean weight for gestational age according to fetal growth curves, was strongly associated with risk of ischemic heart disease (Table 3). A birth weight of at least 2 SD below the mean weight for gestational duration was associated with an overall hazard ratio of 1.64 (95% confidence interval, 1.23 to 2.18). We found no evidence that risks were influenced by calendar period of birth. To further assess whether our results were influenced by selective survival, we analyzed the data with the lowest birth weight category ($<1500$ g) excluded. Restricting the analysis to subjects with a birth weight of $\geq 1500$ g had no impact on the results (data not shown). We found no association between ischemic heart disease and maternal age, hypertensive diseases during pregnancy, twin status, or breast-feeding at the time of hospital discharge when these variables were stratified on fetal growth (data not shown).

Adjusting the analyses for socioeconomic status had no impact on the results, and results were similar regardless of fetal sex (data not shown).

Because birth weight (adjusted for gestational age) and preterm birth (adjusted for birth weight) appeared to have opposite effects on risk of ischemic heart disease, we also investigated whether the effect of fetal growth (in SD) was modified by gestational age. However, we found no evidence that the association between fetal growth and ischemic heart disease was modified by gestational age (Table 4).

When assessing mortality of ischemic heart disease before 1987, we found 378 deaths in the cohort between 1958 and 1986, and of these, 52 had ischemic heart disease as the underlying cause. Birth weight, gestational duration, and fetal growth were not associated with risk of death from ischemic heart disease before 1987 (data not shown).

### Table 1. Cohort Subjects by Gestational Duration, Birth Weight, and Fetal Growth

<table>
<thead>
<tr>
<th>Gestational Duration, wk</th>
<th>≤32</th>
<th>33–36</th>
<th>37–42</th>
<th>≥43</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1500</td>
<td>132</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>151</td>
</tr>
<tr>
<td>1500–1999</td>
<td>403</td>
<td>392</td>
<td>39</td>
<td>1</td>
<td>835</td>
</tr>
<tr>
<td>2000–2499</td>
<td>307</td>
<td>716</td>
<td>161</td>
<td>6</td>
<td>1190</td>
</tr>
<tr>
<td>2500–2999</td>
<td>144</td>
<td>454</td>
<td>377</td>
<td>25</td>
<td>1000</td>
</tr>
<tr>
<td>3000–3499</td>
<td>0</td>
<td>252</td>
<td>1045</td>
<td>70</td>
<td>1367</td>
</tr>
<tr>
<td>3500–3999</td>
<td>0</td>
<td>110</td>
<td>1105</td>
<td>94</td>
<td>1309</td>
</tr>
<tr>
<td>≥4000</td>
<td>0</td>
<td>2</td>
<td>494</td>
<td>77</td>
<td>573</td>
</tr>
<tr>
<td>Total</td>
<td>986</td>
<td>1945</td>
<td>3221</td>
<td>273</td>
<td>6425</td>
</tr>
</tbody>
</table>

### Table 2. Hazard Ratios for Ischemic Heart Disease by Birth Weight and Gestational Duration

<table>
<thead>
<tr>
<th>Birth weight, g</th>
<th>Crude</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>HR</td>
<td>CI</td>
</tr>
<tr>
<td>Cases, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1500</td>
<td>1.61</td>
<td>(0.98–2.64)</td>
</tr>
<tr>
<td>1500–1999</td>
<td>0.97</td>
<td>(0.72–1.31)</td>
</tr>
<tr>
<td>2000–2499</td>
<td>1.12</td>
<td>(0.88–1.44)</td>
</tr>
<tr>
<td>2500–2999</td>
<td>1.18</td>
<td>(0.91–1.52)</td>
</tr>
<tr>
<td>3000–3499</td>
<td>1.04</td>
<td>(0.81–1.33)</td>
</tr>
<tr>
<td>3500–3999</td>
<td>0.86</td>
<td>(0.61–1.20)</td>
</tr>
<tr>
<td>Total</td>
<td>0.86</td>
<td>(0.61–1.20)</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval.
*Birth weight was adjusted for gestational duration; gestational duration was adjusted for birth weight.
This study is the largest study hitherto conducted on preterm birth, low birth weight, and ischemic heart disease. Moreover, by oversampling subjects who were born preterm and/or were small for gestational age, we were able to evaluate these exposures with considerably greater precision than previous investigations. We found evidence that the association between low birth weight and adult risk of ischemic heart disease was mediated entirely by poor fetal growth.

Our study is population based; information on birth characteristics was based on prospectively collected data; and follow-up was nondifferential through the use of register data. Thus, any differential bias resulting from exposure assessment or case ascertainment is unlikely. One limitation is that the follow-up did not start until 1987. The cohort therefore consists of children born between 1925 and 1949, but the mortality among children with low birth weight.11 However, the period 1915 to 1930 that reported a particularly high mortality cannot be told. In our cohort, ≈65% of subjects born before 33 weeks of gestation had a birth weight for gestational age that was above average. This skewed distribution can be due in part to misclassification of gestational age because the subjects were born up to half a century before ultrasound came into practice. However, another explanation for the skewed distribution in the lowest categories of gestational duration may be selective survival. This is supported by a study on subjects from the same area born during the period 1915 to 1930 that reported a particularly high mortality among children with low birth weight.11 However, excluding subjects with a birth weight <1500 g had no impact on the results.

Another limitation of the study is that the follow-up did not cover the entire lifespan of the subjects. For subjects born in 1925, follow-up started at 61 years of age, whereas for subjects born in 1949, it stopped at the age of 53. Although we were able to address mortality in the cohort between 1958 and 1987, the number of deaths during this period was low, and mortality is a less precise measure of disease than morbidity. Because risk estimates were similar regardless of birth period, however, we find it unlikely that this truncated follow-up had any substantial influence on our results.

In this study, we had no or limited information on exposures during pregnancy, including maternal smoking, diabetes mellitus, or hypertensive diseases. Because these exposures may be associated with both fetal growth and ischemic heart disease, this could be a limitation. During the period when most of our subjects were born, however, female smoking was a rare exposure; it was not until the second half of the 1940s that female smoking in Sweden started to increase.24 This, in combination with our stable risk estimates for successive birth cohorts, makes maternal smoking improbable as an explanation of our findings. Likewise, the lack of an association between pregnancy-related hypertensive disorders and risk of ischemic heart disease argues against any major contribution from maternal preeclampsia to our results. Whether our results would have been modified if we were able to take maternal diabetes mellitus into account cannot be told.

Most2–13 but not all19,25 studies of birth weight and risk of coronary heart disease find an inverse association, but the strength of the association varies between studies. Our data suggest that the previously reported association between low birth weight and risk of ischemic heart disease is a reflection of growth restriction rather than short gestational age. Such an interpretation is supported by the study of Eriksson et al,10 who found no association between birth weight and coronary

### Table 3. Hazard Ratios for Ischemic Heart Disease by Fetal Growth and Calendar Period of Birth

<table>
<thead>
<tr>
<th>Fetal Growth</th>
<th>All*</th>
<th>Birth Year 1925–1939†</th>
<th>Birth Year 1940–1949‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Cases, n</td>
<td>HR</td>
</tr>
<tr>
<td>≥−2 SD</td>
<td>576</td>
<td>73</td>
<td>1.64</td>
</tr>
<tr>
<td>&gt;−2 to −1 SD</td>
<td>942</td>
<td>115</td>
<td>1.54</td>
</tr>
<tr>
<td>&gt;−1 to 0 SD</td>
<td>1836</td>
<td>160</td>
<td>1.08</td>
</tr>
<tr>
<td>&gt;0 to 1 SD</td>
<td>1560</td>
<td>126</td>
<td>1</td>
</tr>
<tr>
<td>&gt;1 SD</td>
<td>1511</td>
<td>143</td>
<td>1.10</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio.

*P for trend=0.003; †P for trend=0.013; ‡P for trend=0.0023.

### Table 4. Evaluation of the Joint Effect of Fetal Growth and Gestational Duration

<table>
<thead>
<tr>
<th>Gestational Duration, wk</th>
<th>≤32</th>
<th>33–36</th>
<th>37–42</th>
<th>≥43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal Growth</td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>≤−2 SD</td>
<td>2.52</td>
<td>1.02–6.20</td>
<td>1.12</td>
<td>0.71–1.77</td>
</tr>
<tr>
<td>&gt;−2 to −1 SD</td>
<td>1.55</td>
<td>0.83–2.89</td>
<td>1.51</td>
<td>1.01–2.28</td>
</tr>
<tr>
<td>&gt;−1 to 0 SD</td>
<td>1.06</td>
<td>0.64–1.76</td>
<td>0.98</td>
<td>0.66–1.44</td>
</tr>
<tr>
<td>&gt;0 to 1 SD</td>
<td>0.73</td>
<td>0.42–1.28</td>
<td>0.71</td>
<td>0.46–1.09</td>
</tr>
<tr>
<td>&gt;1 SD</td>
<td>0.95</td>
<td>0.65–1.40</td>
<td>1.18</td>
<td>0.87–1.59</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval.
heart disease unless birth weight was adjusted for gestational age, and by the study of Leon et al,11 who found an association between birth weight and coronary heart disease that disappeared when it was adjusted for birth weight for gestational age.

Our data demonstrate associations but cannot establish causality. One explanation for the association between fetal growth restriction and ischemic heart disease could be that fetal malnutrition or undernutrition in the middle to late gestation, as reflected through deviating fetal growth, triggers adaptations in tissues and organs, ultimately resulting in lasting physiological alterations such as insulin resistance, vascular endothelial dysfunction, and deviating neuroendocrine stress responses.26–28 This in turn could lead to increased risks of high blood pressure, stroke, non–insulin-dependent diabetes, and ischemic heart disease in later life, particularly in an affluent postnatal environment.29 This hypothesis has gained support from a large number of experimental and clinical studies on perinatal characteristics and adulthood diseases.30,31 Conflicting data32 exist, however, and it is unlikely that the association between fetal growth and risk of ischemic heart disease can be attributed to the intrauterine environment alone. As indicated by twin studies,33 genetic factors also may be involved. In addition, infant nutrition34,35 and growth36 contribute significantly and independently of fetal growth to later risk of heart disease.

Other studies have shown that risk factors for cardiovascular disease such as hypertension are more prevalent among children and young adults born preterm than among adults born at term.16,18,37 However, these results come from studies conducted on children having received modern neonatal care, and infant survival has improved substantially during recent decades, particularly among those born very preterm (<32 weeks of gestation and with birth weights <1500 g). By contrast, in our cohort of subjects born from 1925 to 1949, we found no association between preterm birth and risk of ischemic heart disease. Whether the discrepant results are due to differences in infant and childhood survival or outcome measurements or gestational age distribution cannot be told, but it emphasizes that caution is called for when the results from our study are generalized to preterm and growth-restricted infants being born today.

Conclusions

In this prospective follow-up study, we have found that fetal growth restriction (ie, birth weight adjusted for gestational age) constitutes a strong perinatal risk factor for ischemic heart disease, whereas neither low birth weight nor short gestational duration per se increases risk. This may explain the inconsistencies in previous studies on the association between low birth weight and risk for cardiovascular disease because many of these studies lack information on gestational duration.

Sources of Funding

This work was supported by a US Army grant (DAMD17–98–1-8117) and the King Gustaf V Jubilee Foundation.

References


Disclosures

None.
Several studies have reported an increased risk for ischemic heart disease in adult life among people with a low birth weight. At present, however, it remains unclear whether the association between low birth weight and ischemic heart disease is mediated through poor fetal growth and/or short gestational duration. To study the associations between poor fetal growth and short gestational duration and risk of ischemic heart disease with greater precision than previous studies, we examined all birth records at 4 major delivery units in Sweden for the period of 1925 through 1949 and assembled a cohort of ~3000 born preterm and/or with a low birth weight. For comparison, an equal number of subjects with no history of low birth weight or short gestational duration were identified within the same source population. We obtained information on ischemic heart disease through the nationwide Hospital Discharge and Cause of Death Registries for the period of 1987 through 2002. The cohort included >600 cases of ischemic heart disease, and we found that compared with subjects with a normal fetal growth, those born small for gestational age (birth weight ≤ −2 SD below the mean) had a statistically significant increase in risk of ischemic heart disease of 64%. The negative association between fetal growth and risk of ischemic heart disease was independent of gestational duration. Our study suggests that the association between low birth weight and adult risk of ischemic heart disease is mediated entirely by poor fetal growth.
Perinatal Risk Factors for Ischemic Heart Disease: Disentangling the Roles of Birth Weight and Preterm Birth
Magnus Kaijser, Anna-Karin Edstedt Bonamy, Olof Akre, Sven Cnattingius, Fredrik Granath, Mikael Norman and Anders Ekbom

Circulation. 2008;117:405-410; originally published online January 2, 2008; doi: 10.1161/CIRCULATIONAHA.107.710715
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 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/117/3/405

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/