Efficacy of Intravenous Magnesium in Acute Myocardial Infarction in Reducing Arrhythmias and Mortality

Meta-Analysis of Magnesium in Acute Myocardial Infarction

S.M. Horner, MA, MBBS, MRCP

Background. To ascertain the effect of the intravenous administration of magnesium in acute myocardial infarction on the frequency of arrhythmias and mortality, a meta-analysis of randomized controlled trials was performed.

Methods and Results. The study included 930 patients with acute myocardial infarction admitted to primary referral hospitals. Administration of magnesium in acute myocardial infarction was associated with a 49% reduction in ventricular tachycardia and fibrillation. The incidence of cardiac arrest was reduced by 58%. The frequency of supraventricular tachycardias was also lower. Overall, there was a 54% reduction in mortality.

Conclusions. Intravenous magnesium is a safe and effective method of reducing the frequency of arrhythmias and mortality in acute myocardial infarction. (Circulation 1992;86:774–779)

Key Words • myocardial infarction • coronary artery disease • tachycardia, ventricular • fibrillation, ventricular

Magnesium is known to lower systemic vascular resistance, dilate coronary arteries,1 decrease platelet aggregation,2 improve myocardial metabolism,3 protect against catecholamine-induced myocardial necrosis,4 and stabilize cell membranes.5 It is also cheap and easy to handle. Thus, it would appear to be an excellent contender for a place in the routine treatment of myocardial infarction, but it has not achieved this status. Several small trials have assessed its role in this context, but either these have not shown statistical differences, or if they have, their own authors have questioned to what extent such an important conclusion can be drawn from such a small trial.6 Therefore, the use of magnesium in myocardial infarction is a worthy topic for the meta-analysis presented here.

Methods

Data Acquisition

To find all randomized controlled trials of magnesium in acute myocardial infarction that concern a reduction in mortality or arrhythmias, a MEDLINE search was conducted. The search was conducted by intersecting “magnesium” with “myocardial infarction,” “ischemia,” “mortality,” “death,” or “arrhythmia.” The articles so found were themselves carefully read for references to other studies not found by MEDLINE to cross-check whether this computer search strategy was sound. None were found; thus, it was felt that for this topic, this was a sound search strategy. Only randomized controlled trials were included. The authors of each trial were sent a questionnaire, and replies were obtained for every trial. The trials were analyzed for sources of possible bias, side effects of treatment, and effect of treatment in terms of arrhythmia suppression or reduction in mortality.

The analysis was based on those patients with a proven myocardial infarction and not all patients for the following reasons. These trials come from several different parts of the world where triage of patients with chest pain is very different, leading to large numbers with “thoracic chest pain of other origin”7 in some trials and very few in others. Obviously, magnesium would not be expected to reduce the mortality in those with thoracic chest pain of other origin; thus, the apparent effect would be diluted. These two factors would potentially lead to a differential diluting effect between the trials, depending on the triage. This would alter the odds ratio and confidence interval of the final result and, in addition, make the results difficult for the reader to interpret in the light of practice in his or her area. However, the other form of analysis is also included for completeness.

The definition of ventricular tachycardia was consistent across the trials: at least three consecutive ventricular premature beats with a rate >100 beats per minute.

Statistics

Data concerning death and arrhythmias were collected. Pooled mortality rates were calculated. Rates of death and arrhythmias in the control and treatment

From the Department of Cardiology, The Middlesex Hospital, London.
Supported by a grant from the National Heart and Circulation Trust.
Address for correspondence: Dr. S.M. Horner, Department of Cardiology, The Middlesex Hospital, London W1N 8AA, UK.
Received August 15, 1991; revision accepted May 28, 1992.
groups were compared by calculating odds ratios by use of the method described by Yusuf et al. and by Coplen et al. For each trial, the difference between observed and expected deaths was calculated. Different groups in different trials were not compared, and no assumptions regarding the magnitudes of the differences in mortality between the different trials were necessary. If there was no effect from the intervention, then the differences between observed and expected values should vary from zero only at random. Observed (O) minus expected (E) values and the variance of each study were then pooled. The statistical significance could then be found by calculating $z$, where SD is the standard deviation and is equal to the square root of the total variance, which is equal to the sum of the individual variances.

$$z = \frac{O - E}{\text{pooled SD}}$$

By comparing this $z$ value to tables of the normal distribution, the statistical significance ($p$) of this result could be found.

By use of the data from all trials, an odds ratio was calculated, i.e., the likelihood of dying if given magnesium compared with the likelihood if not given magnesium. The 95% confidence intervals were also calculated.

The equivalent calculations for the occurrence of an arrhythmia were also performed.

**Odds ratio-exp(z/SD)**

$95\%$ Confidence interval = $\exp\left(\frac{z \pm 1.96}{\text{SD} \pm \text{SD}}\right)$

**Results**

**General**

The MEDLINE computerized literature search revealed 420 papers concerning magnesium and myocardial infarction, of which 14 concerned mortality. Eight of these were randomized controlled trials of magnesium in acute myocardial infarction. These trials involved a total of 930 patients and are summarized in Table 1, showing the same criteria for inclusion but different exclusion criteria.

The differences between the control and treatment groups that could give rise to bias are listed in Table 2, together with the dosages and peak serum levels of magnesium. Randomization procedures were used in all trials; they were based on preceding, usually from computer-generated random numbers.

There were 31 withdrawals from the trials among those suffering a myocardial infarction. No further

**Table 1. Trial Details: Inclusion and Exclusion Criteria**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study number</th>
<th>Year of publication</th>
<th>Number of patients</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>1</td>
<td>1984</td>
<td>76</td>
<td>MI-ECG,C-ENZ</td>
<td>Age &gt;70, onset of MI &gt;8 hours before, Killip class III, IV, 2HB</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>1986</td>
<td>130</td>
<td>MI-ECG,C-ENZ</td>
<td>Creat&gt;300, 2HB, CHB, IDDM</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>1986</td>
<td>200</td>
<td>MI-ECG,C-ENZ</td>
<td>Creat&gt;300, CHB</td>
</tr>
<tr>
<td>13</td>
<td>4</td>
<td>1987</td>
<td>94</td>
<td>MI-ECG,C-ENZ</td>
<td>Systolic BP &lt;90 mm Hg, bifascicular block, 2HB, CHB</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>1989</td>
<td>48</td>
<td>MI-ECG,C-ENZ</td>
<td>Systolic BP &lt;100 mm Hg, AV disturbances, pulmonary edema, other therapy</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>1990</td>
<td>103</td>
<td>MI-ECG,C-ENZ</td>
<td>Circulatory shock, complete bundle branch block, or advanced AV block</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>1990</td>
<td>132</td>
<td>MI-ECG,C-ENZ</td>
<td>Systolic BP &lt;90 mm Hg, bradyarrhythmia requiring frusemide</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>1991</td>
<td>162</td>
<td>MI-ECG,C-ENZ</td>
<td>Systolic BP &lt;80 mm Hg, sinoatrial or AV blocks of second or third degree, Q wave infarction of more than 8 hours duration, insulin-dependent diabetes mellitus, Creat&gt;300</td>
</tr>
</tbody>
</table>

MI-ECG,C-ENZ, diagnosis of myocardial infarction based on ECG changes and a rise in cardiac enzymes; 2HB, second-degree heart block; Creat>300, plasma creatinine greater than 300 μmol/l; CHB, complete heart block, IDDM, insulin-dependent diabetes mellitus; BP, blood pressure; AV atrioventricular.

**Odds ratio-exp(z/SD)**

$95\%$ Confidence interval = $\exp\left(\frac{z \pm 1.96}{\text{SD} \pm \text{SD}}\right)$

**Results**

**General**

The MEDLINE computerized literature search revealed 420 papers concerning magnesium and myocardial infarction, of which 14 concerned mortality. Eight of these were randomized controlled trials of magnesium in acute myocardial infarction. These trials involved a total of 930 patients and are summarized in Table 1, showing the same criteria for inclusion but different exclusion criteria.

The differences between the control and treatment groups that could give rise to bias are listed in Table 2, together with the dosages and peak serum levels of magnesium. Randomization procedures were used in all trials; they were based on preceding, usually from computer-generated random numbers.

There were 31 withdrawals from the trials among those suffering a myocardial infarction. No further

**Table 2. Details of Patients and Administration of Magnesium**

<table>
<thead>
<tr>
<th>Study number</th>
<th>Mean age (Mg/cont)</th>
<th>Sex (% male) (Mg/cont)</th>
<th>Previous MI (%) (Mg/cont)</th>
<th>Anterior MI (%) (Mg/cont)</th>
<th>Dosage</th>
<th>Peak magnesium concentration in treatment group (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54/57</td>
<td>80/89</td>
<td>28/25</td>
<td>30/47</td>
<td>26 mmol/l/12 hr for 36 hours</td>
<td>1.45</td>
</tr>
<tr>
<td>2</td>
<td>65/68</td>
<td>70/58</td>
<td>50/43</td>
<td>NS</td>
<td>62 mmol in 48 hours</td>
<td>1.23</td>
</tr>
<tr>
<td>3</td>
<td>60/58</td>
<td>85/75</td>
<td>0/0</td>
<td>40/48</td>
<td>65 mmol in 24 hours</td>
<td>1.51</td>
</tr>
<tr>
<td>4</td>
<td>64/61</td>
<td>60/74</td>
<td>NA</td>
<td>42/48</td>
<td>10 mmol in 20 minutes</td>
<td>1.07</td>
</tr>
<tr>
<td>5</td>
<td>59/62</td>
<td>80/70</td>
<td>20/9</td>
<td>56/22</td>
<td>33.3 mmol in 24 hours</td>
<td>0.99</td>
</tr>
<tr>
<td>6</td>
<td>62/62</td>
<td>58/74</td>
<td>12/21</td>
<td>50/28</td>
<td>91 mmol in 48 hours</td>
<td>1.38</td>
</tr>
<tr>
<td>7</td>
<td>50/50</td>
<td>85/87</td>
<td>20/21</td>
<td>33/31</td>
<td>2.1 mmol/12 hr for 72 hours</td>
<td>0.96</td>
</tr>
<tr>
<td>8</td>
<td>NA</td>
<td>86/80</td>
<td>NA</td>
<td>NA</td>
<td>80 mmol in 24 hours</td>
<td>1.54</td>
</tr>
</tbody>
</table>

Mg/cont, patients treated with magnesium/control patients; MI, myocardial infarction; NS, not significantly different but figures not given; NA, not available.

Downloaded from http://circ.ahajournals.org/ by guest on November 19, 2017
information was supplied about these, which necessitated their omission from this analysis. These were as follows: in study 3, 15 patients were withdrawn, nine because of administrative problems, usually their discharge to the ward before completion of the monitoring period. In the placebo group of that study, three were withdrawn because of “atrioventricular dissociation” and one with a raised level of creatinine; in the magnesium-treated group, one with atrioventricular dissociation and one with a ventricular septal defect requiring surgery were withdrawn. In study 7, nine patients in the magnesium-treated group and three in the placebo group were withdrawn because of “acute coronary insufficiency.” In study 4, one patient in the magnesium-treated group and two in the placebo group were withdrawn because of hypotension. Finally, in study 1, one patient was withdrawn at the patient’s own request. Thus, only 31 of 961 patients were withdrawn (3.2%) with no further information being supplied about their outcome, so there is little chance that ascertainment bias affected the results.

In regard to side effects, in three studies no side effects from magnesium administration were found. Studies 1 and 4 reported one patient with hypotension after magnesium infusion, but study 4 also reported hypotension in two patients in the control group. Study 7 was the only other study reporting hypotension, but there was no significant difference between the control and treatment groups. Bradyarrhythmias were the only other major side effects reported by the trials. In study 3, one patient in the treatment group and three in the control group developed atrioventricular dissociation. In study 8, the trial study was stopped because of an increase in the incidence of atrioventricular block of Mobitz type II or higher. Studies 3 and 8 used the highest dose/rate combination of magnesium of all the trials, and as magnesium is known to depress atrioventricular node function,17 it is possible that the incidence of this complication was simply a function of the dosage used.

Arrhythmias

The incidence of ventricular tachycardia and that of ventricular fibrillation for the control group and the group treated with magnesium are given in Table 3, and the odds ratios are displayed graphically in Figure 1. The odds ratio of 0.51 implies that the incidence of ventricular tachycardia and fibrillation was reduced by 49%.

In addition, five of the trials (489 patients) also noted the incidence of other forms of cardiac arrest and supraventricular tachycardias. The incidence of cardiac arrest was reduced, odds ratio 0.42 (p=0.006; confidence interval, 0.21–0.83). The odds ratios for the development of electromechanical dissociation and asystole in the magnesium-treated group were 0.33 (p=0.03; 95% confidence interval, 0.06–1.11) and 0.5 (p=0.09; 95% confidence interval, 0.16–1.44), respectively. Supraventricular tachycardias were also less frequent in the group treated with magnesium; the odds ratio was 0.54 (p=0.02; 95% confidence interval, 0.3–0.99).

Mortality

The mortality in the control group and the group treated with magnesium is given in Table 4, and the odds ratios are displayed graphically in Figure 2. The mortality in the control group was 11%, which is what would be expected; thus, there is no reason to believe that these patients were atypical. The mortality in the magnesium-treated group was 5%. The time of ascertainment of mortality varied from 1 day to 4 weeks after myocardial infarction. The odds ratio of 0.46 suggests a reduction of 54% in mortality from myocardial infarction by administration of magnesium, with the lower 95% confidence limit being a 27% reduction in mortality.

For completeness, these figures were recalculated including all the patients entered into the trials with chest pain and not just those with myocardial infarction. This did not alter the results significantly; the odds ratio was 0.46.

Discussion

Arrhythmias

Intravenous administration of magnesium was associated with a 49% reduction in the incidence of ventric-
ular tachycardia and fibrillation. This would have been of less use, however, if the incidence of asystole and electromechanical dissociation had increased correspondingly. Trials concerning approximately one half the total number of patients noted the incidence of arrhythmias in more detail. They found the incidence of electromechanical dissociation to be reduced, although the upper 95% confidence interval for asystole just exceeds 1.0. The incidence of asystole was reduced in the magnesium-treated group, although this did not reach significance. Overall, the incidence of all forms of cardiac arrest was reduced. The incidence of supraventricular arrhythmias in these trials was found to be significantly reduced.

The mechanism for this reduction in arrhythmias is not known, although there are several physiological effects that may produce this result. Magnesium is a cofactor for Na,K-ATPase and Ca-ATPase, both of which are important in maintaining membrane stability. Myocardial excitability is reduced and may account for the lower incidence of arrhythmias. When the intracellular magnesium concentration is doubled, the membrane must be depolarized by another 6 mV before it generates an action potential, and when it does, the velocity of conduction is increased. In addition, the high intracellular sodium concentration of magnesium deficiency increases the sodium/calcium countertransport mechanism, which leads to a higher intracellular concentration of calcium and a tendency to transient depolarization and arrhythmias. The reverse would be expected with magnesium infusion. Magnesium infusion also increases the absolute refractory period and de-

![Graph showing odds ratio and 95% confidence intervals for the reduction in ventricular tachycardia and fibrillation associated with the intravenous administration of magnesium in acute myocardial infarction. The results for the summation of all trials and individual trials are displayed separately.]

**Figure 1.** Line graph showing odds ratio and 95% confidence intervals for the reduction in ventricular tachycardia and fibrillation associated with the intravenous administration of magnesium in acute myocardial infarction. The results for the summation of all trials and individual trials are displayed separately.

Table 4. Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Magnesium Patients (n)</th>
<th>Deaths (n)</th>
<th>Control Patients (n)</th>
<th>Deaths (n)</th>
<th>O−E</th>
<th>Var (O−E)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>1</td>
<td>36</td>
<td>2</td>
<td>−0.58</td>
<td>0.73</td>
<td>0.45</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>4</td>
<td>74</td>
<td>14</td>
<td>−3.75</td>
<td>3.83</td>
<td>0.38</td>
</tr>
<tr>
<td>3</td>
<td>92</td>
<td>2</td>
<td>93</td>
<td>7</td>
<td>−2.48</td>
<td>2.15</td>
<td>0.31</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>2</td>
<td>46</td>
<td>2</td>
<td>−0.04</td>
<td>0.97</td>
<td>0.96</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>1</td>
<td>23</td>
<td>3</td>
<td>−1.08</td>
<td>0.93</td>
<td>0.31</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>1</td>
<td>53</td>
<td>9</td>
<td>−3.85</td>
<td>2.28</td>
<td>0.18</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>3</td>
<td>66</td>
<td>6</td>
<td>−1.5</td>
<td>2.11</td>
<td>0.50</td>
</tr>
<tr>
<td>8</td>
<td>83</td>
<td>10</td>
<td>79</td>
<td>8</td>
<td>0.78</td>
<td>4.02</td>
<td>1.21</td>
</tr>
<tr>
<td>Total</td>
<td>460</td>
<td>24</td>
<td>470</td>
<td>51</td>
<td>−13.50</td>
<td>17.02</td>
<td>0.45</td>
</tr>
</tbody>
</table>

95% CI 0.28–0.73

z −3.27

p 0.0006

O, observed deaths; E, expected deaths; Var, variant; CI, confidence interval.
increases the relative refractory period, thus decreasing the vulnerable period.\textsuperscript{5,21} Serum potassium levels are increased by the raised levels of magnesium, which reduces renal potassium excretion\textsuperscript{22} and thus the possibility of an arrhythmia precipitated by hypokalemia. Conversely, magnesium has been found to antagonize the effects of a high extracellular potassium concentration; this may be important in the genesis of arrhythmias related to ischemia.\textsuperscript{23} Thus, ectopic impulse formation is suppressed, the vulnerable period reduced, and synchronous conduction improved, theoretically reducing the likelihood of a reentrant arrhythmia arising. In practice, it has been shown that the threshold for ventricular fibrillation is increased.\textsuperscript{24} Although there is a significant reduction in arrhythmias, however, it seems unlikely that this is sufficient to account for the whole effect on mortality.

**Mortality**

There is a significant reduction in mortality in the group given magnesium. Comparison with the effect of thrombolysis in acute myocardial infarction is obviously important but is fraught with difficulty,\textsuperscript{25} as there is no direct comparison in the trials with a group given thrombolysis, and the patient characteristics in trials of thrombolysis may have been different. The data presented here, however, suggest that the reduction in mortality by magnesium administration is of clinical relevance. The possibility exists that the effect has been magnified by publication bias, in that trials not showing a significant difference may not have been published. However, this seems unlikely to account for the whole effect seen. If magnesium truly has no effect, an equal number of studies showing a significant disadvantage would have been expected to be published; this was not seen. In addition, other studies support the importance of magnesium in mortality from myocardial infarction; for instance, it has been shown that there are low concentrations of magnesium in the noninfarcted myocardium of individuals who died of acute myocardial infarction.\textsuperscript{26}

The effects of magnesium that may contribute to the reduction in mortality are listed in Table 5. The evidence suggests that the reduction in mortality cannot be totally accounted for by the reduction in arrhythmias and that a significant component results from other factors possibly including myocardial salvage. Morton et al.\textsuperscript{16} found that magnesium reduced infarct size as estimated by serial cardiac enzymes by 20% in patients in Killip class I.\textsuperscript{16} In one study,\textsuperscript{27} the difference in mortality rate was attributed to the different incidence of cardiogenic shock. In that study, there was also evidence that fewer of the group with chest pain treated with magnesium went on to develop an acute myocardial infarction: 65 of 135 (48%) versus 85 of 135 (63%) ($p=0.019$). This was presumably related to the antiplatelet activity of magnesium. There is also epidemiological evidence of an association between acute myocardial infarction and low concentrations of magnesium in drinking water.\textsuperscript{28}

As the benefit of magnesium therapy probably has several facets (Table 5), some of which overlap with

**FIGURE 2.** Line graph showing odds ratio and 95% confidence intervals for the reduction in mortality associated with the intravenous administration of magnesium in acute myocardial infarction. The results for the summation of all trials and individual trials are displayed separately.

---

**TABLE 5. Effects of Magnesium**

<table>
<thead>
<tr>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of arrhythmias</td>
</tr>
<tr>
<td>Systemic vasodilation lowering myocardial oxygen demand</td>
</tr>
<tr>
<td>Coronary vasodilation</td>
</tr>
<tr>
<td>Decreased platelet aggregation</td>
</tr>
<tr>
<td>Improved myocardial metabolism</td>
</tr>
<tr>
<td>Protection against catecholamine-induced myocardial necrosis</td>
</tr>
<tr>
<td>Reduction of myocardial infarct size</td>
</tr>
</tbody>
</table>
thrombolysis, it may be especially important to administer magnesium to those who are not receiving the benefit of thrombolysis.

A meta-analysis of magnesium in acute myocardial infarction has recently been published that arrived at exactly the same conclusions regarding overall mortality.29 There are some differences, however, in that the present analysis furnishes additional information regarding arrhythmias from which it is apparent that the effect on mortality cannot be attributed entirely to the reduction in arrhythmias. In regard to other mechanisms of death, in the analysis by Teo et al.,29 the percentage that died of heart failure was 6.7% in the magnesium group and 9.0% in the control group, but this was not significant. The analysis of this aspect was difficult, as the definition of heart failure was different between the trials, and it was felt that the only conclusion that could be drawn was that magnesium was not associated with any large excesses of deaths from heart failure.

ISIS 4 and LIMIT (Leicester Intravenous Magnesium Trial) will investigate the intravenous administration of magnesium after acute myocardial infarction and subsequent thrombolysis and will report results in 1992 and 1993. However, the studies in this article predate thrombolysis and therefore remain the only evidence concerning the use of magnesium in patients not receiving thrombolysis. Thus, they show the importance of magnesium in isolation and give a quantification of the effect, which may be of great practical use in assessing the effect of the combination with thrombolysis in trials such as ISIS 4 and LIMIT.

Conclusions

The treatment of acute myocardial infarction with intravenous magnesium shows a significant reduction in arrhythmias and mortality. It is cheap, easy to handle, and relatively free from side effects. Its mechanism may lie in the preservation of myocardium in addition to arrhythmia suppression. It is at the very least a reasonable form of therapy in acute myocardial infarction.

Acknowledgments

The author wishes to thank Professor A.S. Abraham, Professor D.B. Barnett, Professor L. Cremenyukzynski, Dr. M. Feldstedt, Dr. B.C. Morton, Dr. D. Pereira, Dr. H.S. Rasmussen, Professor M. Shechter, Professor R.B. Singh, Dr. K. Skagen, and Dr. K.L. Woods for their kind help in supplying further details of their trials.

References


Horner Magnesium in Acute MI 779

S M Horner

*Circulation*. 1992;86:774-779
doi: 10.1161/01.CIR.86.3.774

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 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/86/3/774

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/