The Incidence of Stroke after Myocardial Infarction: A Meta-Analysis

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ABSTRACT

PURPOSE: While the risk of stroke after myocardial infarction (MI) is increased compared with the risk among those without MI, the magnitude of this risk remains unclear. Although numerous clinical trials have reported the incidence of stroke following MI, these are among selected populations. We reviewed cohort studies reporting the incidence of stroke after MI to better define the risk of ischemic stroke in an unselected population.

METHODS: A computerized literature search (MEDLINE and PubMed) and manual review of reference lists of identified articles were conducted. Population-based studies published from 1978-2004 with at least 100 subjects that reported number or percent of ischemic strokes experienced by MI survivors were identified. Data were extracted using standardized forms, and study quality was assessed by 2 independent reviewers. Ischemic stroke rates were reported as number of events per 1000 MI with 95% confidence intervals (CI) calculated by Poisson distribution. A combined stroke rate was calculated for in-hospital, 30 days, and 1-year post-MI using weights of 1/variance. A random-effects model also was created to estimate in-hospital stroke rate. Variability in study designs and outcome definitions limit synthesis of available data.

RESULTS: During hospitalization for the index MI, 11.1 ischemic strokes occurred per 1000 MI compared with 12.2 at 30 days and 21.4 at 1 year. Using a random-effects model, 14.5 strokes occurred per 1000 MI. Positive predictors of stroke after MI included: advanced age, diabetes, hypertension, history of prior stroke, anterior location of index MI, prior MI, atrial fibrillation, heart failure, and nonwhite race.

CONCLUSIONS: The public health implications of stroke among MI survivors, as well as the large number of MI survivors, underscore the need to be aware of this devastating complication. Further research is needed to determine the optimal stroke prevention strategies for MI survivors. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Myocardial infarction; Stroke; Meta-analysis

Myocardial infarction (MI) remains the number one cause of death among men and women in the United States, while stroke is the third leading cause of death and number one cause of disability.1 As the population ages, MI and stroke will become even greater public health issues, given that the risk of both diseases increases with age.2,3 Thus, a better estimate of the incidence of stroke after MI is needed to better care for patients and potentially prevent stroke as a complication of MI.

Coronary heart disease and some subtypes of ischemic stroke share similar pathophysiology, including inflammation and the development of atherosclerosis.3,4 Additionally, MI can itself be a risk factor for stroke through mechanisms such as emboli, either during revascularization5,6 or from atrial fibrillation in association with acute MI,7,10 or from blood stasis in a poorly functioning left ventricle.3 Further-
more, stroke and MI share a number of risk factors including hypertension, hypercholesterolemia, smoking, diabetes, and age. Modification of such risk factors, as well as treatment with antiplatelet medications, can attenuate the risk of both disease processes. Despite the evidence that treatment with antiplatelet medications can attenuate the combined endpoint, or defined stroke only by diagnostic imaging or autopsy without clinical corroboration of the event. Studies reporting on stroke and transient ischemic attacks (TIA) were included only if the rate of stroke was reported separately from TIA.

The primary investigator collected data using a data extraction form created prior to data collection. Data collected included: the full reference for the article, study dates, study size, age and sex distribution of the study population, risk factors for stroke examined in the study, details of the study design, method of MI and stroke ascertainment, duration of follow-up, and number (or percent) of persons with MI experiencing stroke. No a priori decisions were made about the number or type of variables to be collected; rather, all available information was collected from each study. Decisions regarding the grouping of studies for analysis were made after all data were collected and were based on the number of studies reporting stroke rates at various time points in follow-up.

**CLINICAL SIGNIFICANCE**

- Although many studies have examined stroke risk in selected populations, little is known about the risk of stroke among the general population of MI survivors.
- Our study shows that 11.1 ischemic strokes occurred per 1000 MI during hospitalization for the index MI compared to 12.2 at 30 days and 21.4 at 1 year.
- These findings emphasize the need for stroke awareness among clinicians treating patients with myocardial infarction.

**METHODS**

The primary investigator (BJW) searched two medical literature databases (MEDLINE and PubMed) using the medical subject headings “myocardial infarction” and “cerebrovascular accident,” and all subheadings. Search terms were entered individually into the OVID search engine (OVID Technologies, Inc., New York, NY) and exploded, then combined using the “and” operator. Non-English language studies were included and evaluated with language assistance when needed from the Mayo Clinic Translation Services, as well as colleagues fluent in non-English languages. The reference lists of all studies found through computerized search of the medical literature that met inclusion criteria for this meta-analysis were searched manually for additional articles. Studies were included if they were published between 1978 and May 2004, were observational in design, and included a minimum of 100 subjects. Additional inclusion criteria were assessment of stroke and MI individually, rather than as part of a combined endpoint. Finally, included studies must have reported stroke as the percentage of MI experiencing ischemic stroke, or reported the raw number of ischemic strokes experienced by the study subjects. Studies were excluded from this meta-analysis if they were clinical trials, only reported stroke as part of a combined endpoint, or defined stroke only by diagnostic

**Quality Assessment**

Although reporting measures of study quality in meta-analyses is controversial, we reasoned that a structured assessment of the potential for bias in the stroke rates reported by the studies included in this meta-analysis would be useful to the reader. The literature contains a number of scales developed to assess both internal and external validity of studies, as well as checklists, including the widely used versions by Chalmers et al. and Jadad et al. However, these scales are not specific to the cohort studies included in this meta-analysis, and none addressed all of the specific aspects that may affect the reported stroke rate. Therefore, we developed a study-specific 7-item quality rating scale. Each item was scored on a numeric scale, with a 0 indicating poorest quality and higher numbers indicating better quality. A score of 0 was given in all cases in which the article did not state the information. The highest possible total score, indicating highest quality, was 23. Factors considered in the quality rating included patient selection with studies that excluded subgroups, such as those with prior stroke, receiving lower score than studies without such exclusions. Likewise, studies that excluded subjects based on age were given a lower score than those that included all ages. Studies that excluded based on sex were given a lower score than those that included both sexes. Prospective ascertainment of MI and stroke received higher scores than retrospective ascertainment. Studies that identified MI or stroke by diagnostic code only received lower scores than those using methods to validate events. Finally, studies with
larger sample sizes received higher scores than those with small sample sizes. The “Methods” section of each article was reviewed by two reviewers masked to the reported stroke rates using a standardized form to score each study on the preceding items. The score for each item was then added to give a composite score for the study. Composite scores from each reviewer were averaged to give an overall composite score.

**Statistical Analysis**

Ischemic stroke rates for each study are reported as the number of events per 1000 MI with 95% confidence intervals (CI) calculated according to the Poisson distribution. Pooled stroke incidence was calculated at several time points including in-hospital (11 studies), 30 days (3 studies), and 1 year (2 studies), using a fixed-effects model accounting for sample size and weighting each study by the reciprocal of its variance. The remaining 6 studies reported stroke rates at time points other than in-hospital, 30 days, or 1 year and were not included in the pooled rates.

A beta-binomial hierarchical model, the random effects model, was constructed using SAS (Version 6.12; SAS Institute Inc., Cary, NC) to estimate the average number of events per 1000 MI. The model assumes that study $i$ has a true event rate, $p(i)$, which is sampled from a beta distribution with parameters $r$ (the number of MI patients with stroke events), $s$ (the number of MI patients without a stroke event), and mean $r/(r+s)$. The mean of the estimated beta distribution is set equal to the observed average stroke rate. Newton-Raphson iterations were used to calculate the maximum likelihood estimates of $r$, $s$. The observed information matrix was then used to calculate the 95% CI. In the model, each study was treated as a separate variable. The random effects model was used only to estimate the in-hospital (post-MI) stroke rate because there were too few studies (three or less) reporting stroke rates at other time points post-MI. A sensitivity analysis was performed by removing one study and re-running the model to determine the effect on overall estimate. This was done for each study. Due to variation in method of estimation, quantitative summarization of risk factors was not possible; therefore, a qualitative summary was done.

**RESULTS**

The search of PubMed resulted in 1508 articles, and a search in MEDLINE resulted in 903 articles. As shown in Figure 1, evaluation of these articles for relevance and by the inclusion and exclusion criteria yielded 9 articles from MEDLINE and 9 articles from PubMed for inclusion in the study. Manual search of the reference lists of these 18 articles yielded another 4 articles, resulting in a total of 22 articles included in this review, presented in Table 1.

**Assessment of Study Quality**

Scores ranged from 10 to 20 on a 23-point scale, with a mean ± SD of 13.8 ± 2.5. There was no difference in composite scores among non-U.S. studies (mean 13.8) and U.S. (mean 13.6), Table 1. Community-based studies tended to have lower scores (mean 12.9) compared with registry-based studies (mean 14) and prospective studies (mean 14.2). As shown in Figure 2, there was no trend in correlation between reported stroke rate and study score ($r^2 = 0.09$). Additionally, adjusting the fixed effects estimate by composite quality score did not significantly change the estimated number of strokes per 1000 MI, thus, composite scores were not used as weights when calculating pooled stroke rates.

**Stroke Rate after MI**

Stroke rates (number of events per 1000 MI) with 95% CI are presented in Figure 3. During hospitalization for the index MI (11 studies), stroke rates ranged from 8.0 to 24.3. At 30 days (3 studies), stroke rates were 10.7 to 42.7, while 9.9 to 71.7 had suffered a stroke at 1 year after MI (2 studies). According to a fixed-effects calculation used to pool the results, the stroke rate, number of events per 1000 MI, (95% CI) during hospitalization for the index MI was 11.1 (10.7 to 11.5), compared with 12.2 (10.4 to 14.0) at 30 days after MI, and 21.4 (14.1 to 28.7) at 1 year. Due to marked variability in the reported stroke rates and heterogeneity among studies, a random-effects-based estimate also was calculated. Because of the small number of studies reporting stroke rates at other times (30 days and 1 year), a random-effects model was created only for the in-hospital stroke rate. The estimated random-effects stroke rate (95% CI) during hospitalization was 14.5 (11.7 to 17.9), using data from all studies reporting in-hospital stroke rate.
Sensitivity Analysis

As shown in Table 2, the range resulting from sensitivity analysis for the estimated stroke rate during the MI hospitalization was 13.1 to 15.1. For each of 3 studies, their exclusion resulted in greater than 5% change in the stroke rate estimate. Elimination of the study with the greatest outlying stroke rate resulted in an estimate of 13.6 (events per 1000 MI) during the MI hospitalization, which is similar to the estimate of 14.5 when this study is included in the model. As a result of the consistency of values obtained from the sensitivity analysis, we elected to include all studies reporting stroke rate during MI hospitalization in the final model.

Community-samples = studies using unselected, community-based subjects; Registries = studies that included follow-up of subjects enrolled in a randomized clinical trial; Prospective = studies enrolling consecutive hospital admissions and following prospectively for outcome.

Table 1  Population-based Studies of Patients with Stroke After Myocardial Infarction

<table>
<thead>
<tr>
<th>Study Name (reference)</th>
<th>Study Period</th>
<th>Number</th>
<th>Mean Age (years)</th>
<th>Male Sex (%)</th>
<th>Strokes/1000</th>
<th>Endpoint</th>
<th>Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population-based Community samples</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spencer (66)</td>
<td>1986-99</td>
<td>6325</td>
<td>72.7</td>
<td>59</td>
<td>14.5</td>
<td>In-hosp</td>
<td>13.5</td>
</tr>
<tr>
<td>Lichtman (21)</td>
<td>1994-95</td>
<td>111023</td>
<td>76</td>
<td>51</td>
<td>22.8</td>
<td>6 mos</td>
<td>14</td>
</tr>
<tr>
<td>Ng (29)</td>
<td>1994-95</td>
<td>279</td>
<td>71.9</td>
<td>70</td>
<td>71.7</td>
<td>1 year</td>
<td>11.5</td>
</tr>
<tr>
<td>Klungel (23)</td>
<td>1986-96</td>
<td>1956</td>
<td>65.8</td>
<td>61</td>
<td>37.3</td>
<td>3.3 years</td>
<td>13</td>
</tr>
<tr>
<td>Kaplan (24)</td>
<td>1986-96</td>
<td>2677</td>
<td>63.8</td>
<td>62</td>
<td>46.3</td>
<td>3.4 years</td>
<td>16.5</td>
</tr>
<tr>
<td>Kaarisalo (6)</td>
<td>1983-92</td>
<td>2160</td>
<td>?</td>
<td>84</td>
<td>71.8</td>
<td>5.8 years</td>
<td>11</td>
</tr>
<tr>
<td>Dexter (25)</td>
<td>1960-79</td>
<td>1502</td>
<td>65</td>
<td>?</td>
<td>49.3</td>
<td>10 years</td>
<td>11</td>
</tr>
<tr>
<td>Registries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angeja (67)</td>
<td>1998-00</td>
<td>114724</td>
<td>71</td>
<td>0</td>
<td>12.7</td>
<td>In-hosp</td>
<td>17</td>
</tr>
<tr>
<td>Becker (30)</td>
<td>1994-98</td>
<td>170143</td>
<td>67.4</td>
<td>61</td>
<td>10</td>
<td>In-hosp</td>
<td>15.5</td>
</tr>
<tr>
<td>Behar (68)</td>
<td>1981-83</td>
<td>5839</td>
<td>?</td>
<td>74</td>
<td>8</td>
<td>In-hosp</td>
<td>16</td>
</tr>
<tr>
<td>O'Neill (69)</td>
<td>1985-92</td>
<td>11620</td>
<td>65.9</td>
<td>?</td>
<td>10.7</td>
<td>30 days</td>
<td>13.5</td>
</tr>
<tr>
<td>Mooe (35)</td>
<td>1987-90</td>
<td>2231</td>
<td>63</td>
<td>83</td>
<td>46.2</td>
<td>42 mos</td>
<td>12</td>
</tr>
<tr>
<td>Consecutive hospital admissions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Komrad (18)</td>
<td>1970-81</td>
<td>740</td>
<td>65</td>
<td>67</td>
<td>24.3</td>
<td>In-hosp</td>
<td>15</td>
</tr>
<tr>
<td>Longstreth (19)</td>
<td>1988-91</td>
<td>5635</td>
<td>?</td>
<td>?</td>
<td>20.6</td>
<td>In-hosp</td>
<td>11</td>
</tr>
<tr>
<td>Nakaoka (20)</td>
<td>1984-87</td>
<td>140</td>
<td>?</td>
<td>69</td>
<td>50</td>
<td>In-hosp</td>
<td>15.5</td>
</tr>
<tr>
<td>Puletti (28)</td>
<td>1975-83</td>
<td>1277</td>
<td>68</td>
<td>82</td>
<td>11</td>
<td>In-hosp</td>
<td>13</td>
</tr>
<tr>
<td>Thompson (33)</td>
<td>1973-76</td>
<td>783</td>
<td>?</td>
<td>?</td>
<td>16.6</td>
<td>In-hosp</td>
<td>11</td>
</tr>
<tr>
<td>Wienbergen (34)</td>
<td>1994-98</td>
<td>21330</td>
<td>72</td>
<td>65</td>
<td>12.1</td>
<td>In-hosp</td>
<td>20</td>
</tr>
<tr>
<td>Brodie (36)</td>
<td>1984-00</td>
<td>1841</td>
<td>60.2</td>
<td>69</td>
<td>14.1</td>
<td>30 days</td>
<td>15</td>
</tr>
<tr>
<td>Pullicino (26)</td>
<td>1986-88</td>
<td>445</td>
<td>65.4</td>
<td>85</td>
<td>42.7</td>
<td>30 days</td>
<td>14.5</td>
</tr>
<tr>
<td>Heller (37)</td>
<td>1995-97</td>
<td>1218</td>
<td>70</td>
<td>59</td>
<td>9.9</td>
<td>1 year</td>
<td>13</td>
</tr>
</tbody>
</table>

Predictors of Stroke

The 22 studies in the meta-analysis examined a wide variety of variables for association with stroke after MI.
Age, diabetes, hypertension, prior stroke, anterior location of index MI, prior MI, atrial fibrillation, heart failure, and nonwhite race were all associated with increased risk of stroke, whereas angina at admission had a protective effect. Female sex presented conflicting results with two studies reporting a protective effect (hazard ratio [HR] 0.49, odds ratio [OR] 0.3),6,26 while all others (both significant and nonsignificant) reported an increased risk of stroke among females compared with males. Despite examination by multiple studies, no significant relationship was found between smoking, thrombolytics, percutaneous coronary intervention, coronary artery bypass grafting, hyperlipidemia, blood pressure at admission, or Killip class and the risk of stroke after MI. Coronary artery bypass grafting and higher Killip class showed a nonsignificant increased risk of stroke, while smoking, thrombolysis, percutaneous coronary intervention, hyperlipidemia, and lower blood pressure at admission tended to exhibit a nonsignificant protective effect.

Figure 3  Reported stroke rates by study. The solid circle represents the number of strokes per 1000 MIs. The bars represent 95% confidence intervals, calculated according to the Poisson distribution. Summary estimates were calculated using all studies reporting stroke rates at the given follow-up time.

Table 2  Sensitivity Analysis Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Stroke Rate/1000 MI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies together</td>
<td>14.5</td>
<td>11.7-17.9</td>
</tr>
<tr>
<td>Komrad</td>
<td>13.6</td>
<td>11.1-16.7</td>
</tr>
<tr>
<td>Longstreth</td>
<td>13.1</td>
<td>10.9-15.9</td>
</tr>
<tr>
<td>Nakaoka</td>
<td>13.6</td>
<td>11.2-16.5</td>
</tr>
<tr>
<td>Puletti</td>
<td>14.9</td>
<td>11.8-18.7</td>
</tr>
<tr>
<td>Spencer</td>
<td>14.6</td>
<td>11.5-18.7</td>
</tr>
<tr>
<td>Thompson</td>
<td>14.4</td>
<td>11.4-18.0</td>
</tr>
<tr>
<td>Weinbergen</td>
<td>15.0</td>
<td>11.7-19.1</td>
</tr>
<tr>
<td>Angeja</td>
<td>14.9</td>
<td>11.7-19.1</td>
</tr>
<tr>
<td>Becker</td>
<td>15.1</td>
<td>12.1-19.0</td>
</tr>
<tr>
<td>Behar</td>
<td>15.1</td>
<td>12.3-18.4</td>
</tr>
<tr>
<td>O’Neill</td>
<td>14.6</td>
<td>11.7-18.2</td>
</tr>
</tbody>
</table>

All stroke rates are reported as number of events per 1000 myocardial infarctions (MIs). 95% CIs are calculated according to the Poisson distribution.
DISCUSSION

Stroke Rate and Its Implications

In order to provide an estimate of the stroke rate after MI in the community, we performed a meta-analysis of the observational studies while excluding reports from clinical trials. Additionally, the exclusion of clinical trials avoids the potential bias introduced by incomplete ascertainment of the large number of clinical trials in this field. The pooled stroke rate of 14.5 events per 1000 MI is markedly lower than the rate found among persons in Olmsted County, a much higher rate as compared with the general population. Individuals suffering a stroke after MI are at increased risk of death. Additionally, stroke care costs $55.6 billion annually in the U.S., and this cost increases when stroke occurs in conjunction with ischemic heart disease. Furthermore, stroke is the leading cause of long-term disability in the U.S. and results in confinement to a nursing home in 26% of ischemic stroke survivors over the age of 65. Thus, as the population ages and becomes at increasingly higher risk for MI and stroke, the potential public health implications of this devastating complication of MI become enormous. Not only do clinicians need to recognize the problem, it is also important to better identify those at risk and provide therapy to reduce the risk.

Variability in Reported Stroke Rates

Several studies have markedly different stroke rates. As shown in Figure 3, there is no correlation between quality score and reported stroke rate. However, careful examination of individual study designs provides some insights that may explain the observed heterogeneity in stroke rates. For example, the study by Komrad et al was conducted from 1970 to 1981. Because this time frame is before the era of coronary artery reperfusion, the results may not be comparable with a contemporary MI population, such as those represented by the studies of Longstreth et al, Nakaoka et al, Puletti et al, Thompson and Robinson, and Wienbergen et al. While the study by Puletti et al was conducted in a similar time period, the smaller study population and geographic differences may explain the high stroke rate reported by Komrad in comparison.

Similarly, Longstreth reported stroke rates that were higher than studies with similar design. While the time period of the study is within the era of reperfusion, the inclusion of a select patient population (the Myocardial Infarction Triage and Intervention Registry in suburban Seattle) may bias the observed stroke rates. Among studies reporting stroke rates at 30 days Pullicino et al report a significantly higher rate than those found by Mooe et al and Brodie et al. Because Pullicino et al conducted their study in Malta (an area with prevalence rates of diabetes of 10%, compared with 6.3% in the U.S.), this population would be expected to exhibit higher stroke rates than the populations studied by Brodie and Mooe.

Finally, among studies reporting stroke rate at 1 year, Ng et al found a much higher rate than Heller et al. This may be explained by the geographic differences in the populations (Ng from China, Heller from the U.S.), as well as study sample size differences (279 for Ng and 1218 for Heller).

Heterogeneity among Studies with Variable Follow-up Times

Marked differences in stroke rates among those with extended follow-up also exist. Because the data utilized by Lichtman et al were from the Medicare database, these patients were notably older than those in similar studies. Although Klungel and Kaplan report stroke rates at similar times in follow-up, it is important to remember that these are mean follow-up times. Thus, although the patient populations are sampled from the same source (a large managed care organization in Washington state), the range of follow-up times may be quite different, leading to differences in the observed stroke rates. Klungel reports a follow-up range of 189 days to 9.9 years, whereas Kaplan does not report a range. The rate reported by Loh et al is nearly identical to that reported by Kaplan. A higher percentage of males, the differences in study period, as well as the fact that the Loh patients are from a clinical trial registry may explain the difference in rate reported by Klungel. Finally, although the follow-up duration by Kaarisalo et al is much shorter than that by Dexter et al, Kaarisalo reports a much higher stroke rate. While the age exclusions by Kaarisalo lead to a younger population with expected lower stroke rate, all patients in this study were revascularized for their index MI, perhaps off-setting the expected decrease in observed stroke rate. Additionally, Dexter does not report the sex distribution of the study population. This, along with geographic differences, may explain the marked differences seen in stroke rates reported by these two studies.

Predictors of Stroke

Given the positive association between advanced age and risk of stroke as well as risk of MI, the finding of increased risk of stroke after MI among older persons is not surprising. This finding does underscore the need for future research to determine additional predictors of stroke among elderly with MI in order to better target screening and treatment. Similarly, diabetes, hypertension, and nonwhite race are well-known predictors of MI and of stroke, and are thus expected to be associated with an increased risk of stroke after MI. Those with stroke are more likely to suffer a second stroke, thus, this finding is also to be expected.

Heart failure and reduced left ventricular ejection fraction (LVEF) have been associated with increased risk of stroke, likely through the increased risk of intra-cardiac thrombus formation and embolic potential of these thrombi. Thus, myocardial infarctions leading to reductions in ventricular function would be expected to be associated with an increased risk of stroke. While some studies have found a positive association between reduced ejection fraction (EF) and stroke risk after MI, others have
Due to variability in inclusion criteria, no clear recommendation exits for the minimum EF at which to start anticoagulant therapy. Additionally, controversy exists regarding the optimal therapeutic regimen. Some studies have found benefit in stroke prevention after MI from a combination of aspirin and warfarin compared with aspirin alone, while others have found no additional benefit of warfarin over aspirin and an increase in the risk of bleeding complications. Clearly, trials are needed to determine the optimal regimen of anticoagulation after MI across all levels of EF. One such study, the WARCEF trial, is ongoing. The association of prior MI with an increased risk of stroke may be similarly explained because prior MI may serve as a surrogate for reduced ejection fraction or a marker of atherosclerotic disease burden in these individuals.

Atrial fibrillation (AF) may also serve as a marker of MI severity and is a known risk for development of intracardiac thrombi. Further, left atrial thrombi have been demonstrated after acute MI even among persons in normal sinus rhythm. Therefore, persons with MI and AF may be at even greater risk for stroke, particularly among the subset with AF, MI, and a reduction in LV systolic function. Additionally, AF can lead to electrical remodeling of the conduction system predisposing to future atrial arrhythmias, which may lead to an additional increase in risk of stroke among persons with MI and AF, irrespective of LV systolic function. However, these theories remain speculative and should be verified in additional studies.

An interesting association is the protective effect of chest pain or angina at presentation on the risk of subsequent stroke. Murry et al described a phenomenon termed “ischemic preconditioning,” which may in part explain this association. In a canine model, transient ischemia prior to prolonged ischemia (up to 96 hours prior to prolonged ischemia) reduced the severity of myocardial damage observed after an episode of prolonged ischemia. Although controversy exists as to the exact mechanism, it is believed that ischemic preconditioning induces a response pathway via adenosine and other cell mediators such as nitric oxide, resulting in reduced energy demand and slower lactate accumulation during prolonged ischemia and ultimately leading to a reduction in the severity of myocardial damage. A similar phenomenon has been described in the brain with TIA leading to reduced severity of subsequent stroke. Thus, angina at presentation for index MI may indicate a degree of ischemic preconditioning that results in reduced severity of the MI and a subsequent reduction in stroke risk or stroke severity via ischemic preconditioning in the brain through similar molecular pathways.

Female sex in these studies shows no consistent association with risk of stroke after MI. Although male sex is a traditional risk factor for stroke, as well as MI, there is evidence that the risk of MI increases among older females. Thus, the patient population being observed may influence the risk of stroke. Indeed, while the mean age of patients is >70 in most of the studies reporting increased risk of stroke among females, the two studies reporting increased risk among males included younger patients (Pullicino, mean age 65.8 years; Kaarisalo excluded patients aged >74 years). This difference in age distributions may explain the conflicting results found when examining sex as a risk for stroke.

**Study Limitations and Strengths**

The composite score assigned to each study based on prespecified study characteristics did not explain differences in reported stroke rates. Indeed, the use of composite quality measures is controversial in meta-analyses. The seven aspects chosen in this study for indicating study quality were chosen to reflect design characteristics that may bias the reported stroke rate. The lack of correlation between composite score and stroke rate may reflect the instrument’s inability to discern among these qualities, or indicate that the instrument may lack measurement of some other important study characteristics. Through the process of assessing the studies in this manner, we were able to identify those studies that suffered from unclear reporting. Thus, although not helpful in explaining the variability among reported stroke rates, important information regarding study designs was obtained through this process. Further, although differences in study setting, design, and patient population likely contribute to heterogeneity among study results, we are unable to explore other important factors such as temporal trends in treatment for MI and decreasing length of stay. Variation in the methods of stroke ascertainment likely also contributes to heterogeneity in reported stroke rates. However, meticulous review and inclusion of only those studies with comparable definitions minimizes this possibility. Variability in definition and reporting of risk factors for stroke limits our ability to quantitatively examine these associations or draw conclusions regarding them.

Thorough search of the literature, as well as contact with experts in the field were used to ensure complete ascertainment of studies addressing the rate of stroke after MI. Thus, results are unlikely due to incomplete review of the literature. Finally, the methods of studies included in this meta-analysis were reviewed for potential sources of bias. Although a few studies have design characteristics that may skew the reported stroke rate, sufficient high quality studies were analyzed to conclude that the risk of stroke after MI is an important concern.

**CONCLUSION**

Although the absolute number of persons experiencing stroke after MI is relatively small, the public health implications are important. As the population ages and more persons experience MI, the absolute number of persons experiencing stroke after MI also increases. Furthermore, the cost of caring for one stroke is large, thus, prevention of this devastating complication is also paramount from an
economic perspective. The risk appears highest early after MI, a finding corroborated by other studies. 27 Thus, the clinician caring for persons with MI needs to be aware of stroke as a potential complication. Emphasis needs to be placed on primary prevention by ensuring that modifiable risk factors such as blood pressure, diabetes, hyperlipidemia, and smoking are well controlled. Further studies are needed to clarify the role of anticoagulation after MI. Future research should address which antiplatelet agent or anticoagulant is most effective in preventing stroke, the optimal timing of anticoagulation, and duration of anticoagulant therapy after MI in order to prevent stroke.

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