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Lidocaine Prophylaxis in Acute Myocardial Infarction

James E. Tisdale, PharmD*

The prophylactic administration of lidocaine for the prevention of primary ventricular fibrillation (VF) following suspected acute myocardial infarction (MI) is controversial. The incidence of primary VF following acute MI ranges from 1.8% to 10.5%. "Warning arrhythmias" have not been shown to be reliable predictors of VF. In-hospital prophylactic administration of lidocaine has been shown to decrease the incidence of primary VF, whereas prehospital administration has not. However, prophylactic administration of lidocaine has not been shown to have a beneficial effect on mortality and may in fact increase mortality. The incidence of lidocaine-induced adverse effects during prophylaxis ranges from 4% to 85%, with an average of approximately 35%. In view of the low incidence of primary VF following acute MI, the high incidence of lidocaine-induced adverse effects, and the lack of evidence of beneficial effect on mortality, prophylactic lidocaine administration to all patients with suspected MI is not recommended. The American Heart Association and American College of Cardiology recommend prophylactic lidocaine administration in patients with acute myocardial ischemia or MI who have ventricular premature beats that occur frequently (> 6 per minute), are closely coupled (R on T), multiform in configuration, or occur in short bursts of three or more in succession. (Henry Ford Hosp Med J 1991;39:217-25)

The prophylactic administration of lidocaine to patients with suspected acute myocardial infarction (MI) for the prevention of primary ventricular fibrillation (VF) has been a controversial issue for more than 20 years. In the late 1960s it was suggested that suppression of so-called "warning arrhythmias" such as ventricular premature beats (VPBs), couplets, multiform complexes, and nonsustained ventricular tachycardia may result in complete prevention of primary VF in patients in coronary care units (1). It soon became evident, however, that these "warning arrhythmias" were not reliable predictors of VF (2-4), and the routine administration of lidocaine to all patients with suspected acute MI was advocated (5,6). Since then, prophylactic administration of lidocaine has become standard therapy for patients with suspected MI in many centers in the United States (7,8). However, many clinicians and investigators have discouraged routine lidocaine prophylaxis based on the low frequency of primary VF following acute MI, the occurrence of lidocaine toxicity during routine lidocaine prophylaxis, and the lack of evidence of beneficial effect on mortality (9,10). This article reviews the incidence of primary VF following acute MI, the reliability of "warning arrhythmias" as predictors of VF, published studies evaluating the efficacy of lidocaine prophylaxis in patients with suspected MI, and the incidence of lidocaine toxicity during primary VF prophylaxis. The guidelines for lidocaine prophylaxis published by the American College of Cardiology and the American Heart Association also are reviewed.

Primary VF Complicating Acute MI

The incidence of primary VF, defined as one or more episodes of VF that occur in the absence of congestive heart failure or shock (11), in patients with confirmed acute MI ranges from 1.8% to 10.5% (Table 1) (3,4,9,12-28). The incidence of primary VF following MI is inversely proportional to the duration of time from the onset of symptoms to hospital admission (3,13,23). In one study of patients with acute MI who experienced primary VF, 71% did so within 4 hours, 83% within 8 hours, and 96% within 24 hours of the onset of symptoms (13). In a study reporting the incidence of primary VF in untreated patients with acute MI and in those treated prophylactically with lidocaine, 28% of VF episodes occurred within 2 hours, 61% within 4 hours, and 78% within 6 hours of the onset of symptoms (3). All patients who experienced primary VF did so within 24 hours of the onset of symptoms (3). In another trial, 41% of MI patients who developed VF did so within 4 hours, 65% within 8 hours, and 94% within 24 hours of the onset of symptoms (23).

A number of factors have been associated with an increased risk of VF following MI. In an analysis of factors that predicted cardiac arrest in 905 patients admitted with the diagnosis of acute MI, history of congestive heart failure and previous MI were identified as significant predictors (24). The incidence of primary VF following MI may be higher in patients with diabetes mellitus (29). Primary VF post-MI appears to occur less commonly in patients who are greater than 65 or 70 years of age than in younger individuals (2,3,13,22,23,27). The influence of

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<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Time From Onset of Symptoms to Admission</th>
<th>Number of Patients with VF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goble et al, 1966 (12)</td>
<td>67</td>
<td>&lt; 24 hrs</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td>Lawrie et al, 1968 (13)</td>
<td>198</td>
<td>0-4 hrs (58%)</td>
<td>20 (10.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 4 hrs (42%)</td>
<td></td>
</tr>
<tr>
<td>Church &amp; Bierrn, 1969 (14)</td>
<td>183</td>
<td>0-4 hrs (48%)</td>
<td>19 (10.4)</td>
</tr>
<tr>
<td>Bennett et al, 1970 (15)</td>
<td>125</td>
<td>&lt; 12 hrs (73%)</td>
<td>7 (5.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-3 hrs (34%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-12 hrs (38%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>13-48 hrs (28%)</td>
<td></td>
</tr>
<tr>
<td>Mogenson, 1970 (16)</td>
<td>242</td>
<td>0-3 hrs (40%)</td>
<td>8 (3.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-6 hrs (22%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 6 hrs (38%)</td>
<td></td>
</tr>
<tr>
<td>Baker et al, 1971 (17)</td>
<td>23</td>
<td>&lt; 4 hrs (35%)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 12 hrs (65%)</td>
<td></td>
</tr>
<tr>
<td>Church &amp; Bierrn, 1972 (18)</td>
<td>44</td>
<td>0-4 hrs (68%)</td>
<td>3 (6.8)</td>
</tr>
<tr>
<td>Darby et al, 1972 (19)</td>
<td>100</td>
<td>0-3 hrs (46%)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-12 hrs (35%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>13-48 hrs (19%)</td>
<td></td>
</tr>
<tr>
<td>Bleifeld et al, 1973 (20)</td>
<td>48</td>
<td>1-5 hrs (25%)</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-24 hrs (35%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25-48 hrs (21%)</td>
<td></td>
</tr>
<tr>
<td>O'Brien et al, 1973 (21)</td>
<td>146</td>
<td>Not reported</td>
<td>5 (3.4)</td>
</tr>
<tr>
<td>Lie et al, 1974 (3)</td>
<td>255</td>
<td>&lt; 24 hrs (mean = 4 hours)</td>
<td>11 (4.3)</td>
</tr>
<tr>
<td>Lie et al, 1974 (22)</td>
<td>105</td>
<td>&lt; 2 hrs (49%)</td>
<td>11 (10.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-4 hrs (34%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-6 hrs (17%)</td>
<td></td>
</tr>
<tr>
<td>Lie et al, 1975 (4)</td>
<td>262</td>
<td>&lt; 6 hrs (mean = 4.5 hrs)</td>
<td>20 (7.6)</td>
</tr>
<tr>
<td>El-Sherif et al, 1976 (23)</td>
<td>450</td>
<td>&lt; 24 hrs (mean = 4 hrs)</td>
<td>20 (4.4)</td>
</tr>
<tr>
<td>Conley et al, 1977 (24)</td>
<td>527</td>
<td>Not reported</td>
<td>45 (8.5)</td>
</tr>
<tr>
<td>Lie et al, 1977 (25)</td>
<td>76</td>
<td>&lt; 6 hrs</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Koster &amp; Dunning, 1985 (26)</td>
<td>929</td>
<td>2-3 hrs (median)</td>
<td>17 (1.8)</td>
</tr>
<tr>
<td>Dubois et al, 1986 (28)</td>
<td>1,265</td>
<td>8.4 hrs (mean)</td>
<td>96 (7.6)</td>
</tr>
<tr>
<td>Volpi et al, 1987 (27)</td>
<td>11,712</td>
<td>&lt; 12 hrs</td>
<td>332 (2.8)</td>
</tr>
</tbody>
</table>

VF = ventricular fibrillation.

The incidence of recurrence of VF in patients who experience primary VF following acute MI ranges from 8% to 67% (3, 13, 23). Recurrences of primary VF typically occur within 8 hours of the initial episode (3).

Primary VF following acute MI appears to be associated with increased in-hospital mortality. In-hospital mortality for such patients ranges from 0% to 50% (2,3,12,13,16,22,23,28,32-34). Pooled results from 13 studies indicate that the mean incidence of mortality associated with postinfarction VF is 19% (35). In comparison, in-hospital mortality for patients with uncomplicated MI who do not experience primary VF ranges from 3% to 13% (mean 8%) (12,16,28,32-35). This difference was not evaluated statistically (35). However, most studies indicate that the long-term prognosis of patients who survive primary VF postinfarction is not significantly different from that of MI patients who do not have an episode of primary VF (24,35-38).

Reliability of “Warning Arrhythmias” for the Prediction of Primary VF Following MI

In the 1960s, several investigators promoted the use of specific “premonitory” or “warning arrhythmias” for the prediction of the occurrence of primary VF postinfarction (1,30,39). Lown et al (1) observed no episodes of primary VF in 130 consecutive patients admitted with acute MI and attributed this to the routine
administration of lidocaine to all patients exhibiting the R-on-T phenomenon, two or more consecutive VPBs, multiform VPBs, or greater than five VPBs per minute. Another group of investigators reported that six of 32 MI patients in whom VPBs occurred frequently (one VPB to every 2 to 10 beats) developed VF, compared to one of 35 MI patients who had less frequent VPBs (31). Meltzer and Kitchell (39) suggested that the occurrence of greater than six VPBs per minute, ventricular tachycardia, third-degree heart block, or a previous episode of VF should be considered predictors of primary VF. As a result of these findings and recommendations, based on data obtained in uncontrolled studies, routine administration of lidocaine to MI patients with “warning arrhythmias,” or specific ventricular ectopic activity (VEA), became common.

Since the publication of those early papers, however, the utility of specific VEA for the prediction of primary VF has been challenged. While some investigators have found specific VEA to occur in 71% to 81% of MI patients who experience primary VF (2,40,41), the majority of studies indicate that the incidence of specific VEA in patients with primary VF postinfarction is substantially lower. Lawrie and associates (13) detected specific VEA in only two (17%) of 12 MI patients who experienced primary VF. Church and Biem (14) observed specific VEA in six (46%) of 13 post-MI patients experiencing primary VF. Other studies have reported the occurrence of specific VEA in only 43% to 60% of MI patients prior to the onset of primary VF (3,4,9,22,23,42). Furthermore, specific VEA has been detected in 29% to 59% of MI patients who do not develop primary VF (4,22,23,30). Because VEA occurs with similar frequency in MI patients who develop primary VF and in those who do not, the occurrence of VEA cannot be considered a reliable predictor of primary VF following MI (35,43).

**Efficacy of In-hospital Administration of Lidocaine for the Prevention of Primary VF Following Acute MI**

Randomized studies investigating the efficacy of in-hospital administration of lidocaine for the prophylaxis of primary VF following MI are presented in Table 2. The majority of studies found no significant difference in the incidence of primary VF in patients randomized to receive lidocaine compared to those randomized to receive placebo (15,18,21,23,44-49) or no treatment (19,20). However, interpretation of the results of some of these trials is impaired by deficiencies in study design. Small sample sizes were evaluated in a number of these studies (16-18,20,44,46). Some of these trials were not blinded (15,16,19,20,45) or placebo-controlled (15,19,20). Many of these studies included patients who had chest pain up to 48 (15,16,19,20) to 72 hours (46) prior to hospital admission. In one study, the mean duration of chest pain prior to admission was 8 to 9 hours (45). Other studies neglected to report or reported incompletely the duration of chest pain in patients included in the study (17,18,21,44,47). Since the majority of MI patients who experience primary VF do so within 6 hours of the onset of chest pain (3,13,23), many of these trials included patients who were well beyond the period of risk for primary VF. Moreover, in many of these studies relatively low lidocaine bolus and/or maintenance doses were administered (15,16,18-20,44,46), and some trials evaluated single intramuscular doses of lidocaine (25,47,48). Additionally, the majority of investigators did not determine plasma lidocaine concentrations in study patients (15,17,20,25,44-46,49), and plasma lidocaine concentrations were subtherapeutic or barely therapeutic (therapeutic range: 2 to 6 µg/mL [50]) in some studies in which they were determined (47,48). Therefore, the lack of efficacy of prophylactic lidocaine administration in many studies may have been due to the administration of inadequate doses of the drug. Deficiencies of study design, therefore, leave the results of many of these studies open to some question.

Perhaps the most well-designed study for the evaluation of the efficacy of prophylactic lidocaine administration in acute MI was performed by Lie and associates (22) (Table 2). In this double-blind trial, 212 patients with confirmed MI who were admitted within 6 hours of the onset of chest pain were randomized to receive intravenous lidocaine (100 mg load followed by a continuous infusion of 3 mg/minute for 48 hours) or placebo. Plasma lidocaine concentrations in patients randomized to the treatment group were within the therapeutic range (mean 3.5 ± 0.9 µg/mL, range 1.5 to 6.4 µg/mL). The incidence of primary VF was significantly lower in the lidocaine group than in the placebo group. Based on the results of this trial, it has been concluded that prophylactic lidocaine administration decreases the incidence of primary VF following acute MI (43).

In a retrospective data review, Wyman and Hammersmith (5) attributed a substantial reduction in the incidence of primary VF following acute MI to the prophylactic administration of lidocaine. In this study, 1,165 patients admitted with confirmed MI (58% were admitted within 4 hours of the onset of chest pain) over a seven-year period were administered drug therapy for the prophylaxis of primary VF according to different criteria. Of 139 patients for whom prophylaxis was limited to orally administered procainamide or quinidine upon detection of VEA, nine (6.5%) experienced primary VF. Of 1,026 patients who received prophylactic lidocaine, three (0.3%) had an episode of primary VF. Although this was a retrospective, uncontrolled study, these data also lend support to evidence that prophylactic lidocaine administration reduces the incidence of primary VF following acute MI.

Two meta-analyses have been performed to determine the efficacy of lidocaine prophylaxis for the prevention of primary VF in patients following acute MI. DeSilva and colleagues (51) pooled the results of six randomized studies (15,16,18,20-22) according to the following criteria: presence of acute MI, lidocaine loading dose of at least 50 mg intravenously, and lidocaine maintenance infusion of not less than 1 mg/minute for at least 24 hours. The results of the pooled data demonstrated that primary VF occurred in 16 (3.1%) of 517 patients who received prophylactic lidocaine, compared with 29 (5.7%) of 505 patients who received placebo or no treatment (relative risk = 0.53, 95% confidence interval 0.28 to 0.98). These results indicate that prophylactic lidocaine administration significantly reduces the incidence of primary VF following MI. A more recent meta-analysis (52) pooled the results of 14 randomized, controlled studies...
confirmed myocardial infarction. Lie et al
Wyse et al
Sandler et al
Lie et al
O'Brien et al
Bleifeld et al
Darby et al
Church & Biem
Chopra et al
Pitt et al
Kostuk et al
Reference
Baker et al
Bennett et al
Mogensen
Mogensen
Baker et al
Pitt et al
Chopra et al
Church & Biem
Chopra et al
Chopra et al
O'Brien et al
Lie et al
Lie et al
Lie et al
Wyse et al

In summary, interpretation of results of many trials in which the efficacy of prophylactic lidocaine for the prevention of primary VF following MI has been investigated is hampered by inadequacies of study design. However, based on the results of Lie et al’s (22) well-designed study and the results of the two meta-analyses of pooled data (51,52), it can be concluded that in-hospital prophylactic lidocaine administration reduces the incidence of primary VF following acute MI.

Efficacy of Prehospital Administration of Lidocaine for the Prevention of Primary VF Following Acute MI

Randomized studies investigating the efficacy of prehospital administration of lidocaine for the prevention of primary VF following acute MI are outlined in Table 3.

In each of these trials, no significant difference in the incidence of primary VF was demonstrated in patients receiving

### Table 2

**Randomized Studies of In-Hospital Administration of Lidocaine for the Prevention of Primary Ventricular Fibrillation Following Acute Myocardial Infarction**

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Duration of Symptoms†</th>
<th>L Bolus (mg)</th>
<th>L Infusion Rate (mg/min)</th>
<th>Duration of Infusion (hrs)</th>
<th>Mean Plasma L Conc.</th>
<th>Incidence of Primary VF (%)</th>
<th>Incidence of Mortality (%)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kostuk et al (44)</td>
<td>65</td>
<td>NR</td>
<td>—</td>
<td>1</td>
<td>48</td>
<td>NR</td>
<td>0/34 (0) L</td>
<td>0/31 (0) P</td>
</tr>
<tr>
<td>Bennett et al (15)§</td>
<td>374</td>
<td>&lt; 48 hrs</td>
<td>60</td>
<td>0.5</td>
<td>1</td>
<td>24</td>
<td>NR</td>
<td>16/249 (6.4) L</td>
</tr>
<tr>
<td>Mogensen (16)¶</td>
<td>79</td>
<td>&lt; 48 hrs</td>
<td>75</td>
<td>2</td>
<td>24</td>
<td>2.6 µg/mL (n = 15)</td>
<td>NR</td>
<td>0/21 (0) L</td>
</tr>
<tr>
<td>Baker et al (17)</td>
<td>44</td>
<td>NR (14 pts &gt; 12 hrs)</td>
<td>50-200</td>
<td>1.5-3.5</td>
<td>48</td>
<td>NR</td>
<td>1/108 (0.9) L</td>
<td>7/39 (17.9) L</td>
</tr>
<tr>
<td>Pitt et al (45)§</td>
<td>222</td>
<td>Mean 7.8 to 8.5 hrs</td>
<td>75-100</td>
<td>2.5</td>
<td>48</td>
<td>NR</td>
<td>0/43 (0) P</td>
<td>4/44 (9.3) P</td>
</tr>
<tr>
<td>Chopra et al (46)</td>
<td>82</td>
<td>&lt; 72 hrs</td>
<td>50-150</td>
<td>1-2</td>
<td>26</td>
<td>NR</td>
<td>4/42 (9.5) L</td>
<td>3/44 (6.8) P</td>
</tr>
<tr>
<td>Church &amp; Biem (18)**</td>
<td>86</td>
<td>NR (57 pts &lt; 4 hrs)</td>
<td>50-75</td>
<td>2</td>
<td>48</td>
<td>NR</td>
<td>5/147 (3.4) P</td>
<td>11/154 (7.1) L</td>
</tr>
<tr>
<td>Darby et al (19)¶¶</td>
<td>203</td>
<td>&lt; 48 hrs</td>
<td>200 (IM)</td>
<td>2</td>
<td>48</td>
<td>NR</td>
<td>4/103 (3.9) L</td>
<td>5/100 (5) No Tx</td>
</tr>
<tr>
<td>Biflerfeldt et al (20)¶¶</td>
<td>89</td>
<td>&lt; 48 hrs</td>
<td>100</td>
<td>1.5-3</td>
<td>5 days</td>
<td>NR</td>
<td>0/41 (0) L</td>
<td>2/41 (4.9) L</td>
</tr>
<tr>
<td>O’Brien et al (21)</td>
<td>300</td>
<td>NR</td>
<td>75</td>
<td>2.5</td>
<td>48</td>
<td>NR</td>
<td>3/145 (2.7) L</td>
<td>1/154 (0.7) L</td>
</tr>
<tr>
<td>Lie et al (22)</td>
<td>212</td>
<td>&lt; 6 hrs</td>
<td>100</td>
<td>3</td>
<td>48</td>
<td>NR</td>
<td>0/107 (0.7) L</td>
<td>10/105 (9.5) P</td>
</tr>
<tr>
<td>Sandler et al (47)</td>
<td>181</td>
<td>NR</td>
<td>200 (IM) (n = 89)</td>
<td>—</td>
<td>4</td>
<td>3.5 µg/mL (6 hrs)</td>
<td>0/107 (0.7) L</td>
<td>8/107 (7.5)</td>
</tr>
<tr>
<td>Lie et al (25)</td>
<td>154</td>
<td>&lt; 6 hrs</td>
<td>300 (IM) (n = 92)</td>
<td>—</td>
<td>4</td>
<td>0.96-1.79 µg/mL (1 hr)</td>
<td>0/91 (0) L</td>
<td>0/90 (0) P</td>
</tr>
<tr>
<td>Lie et al (48)</td>
<td>300</td>
<td>&lt; 6 hrs</td>
<td>300 (IM)</td>
<td>—</td>
<td>1</td>
<td>NR</td>
<td>4/78 (5.1) L</td>
<td>0/78 (0) L</td>
</tr>
<tr>
<td>Wyse et al (49)</td>
<td>190</td>
<td>&lt; 6 hrs</td>
<td>100 (&lt;2)</td>
<td>3</td>
<td>24</td>
<td>NR</td>
<td>6/147 (4.1) L</td>
<td>5/147 (3.4) L</td>
</tr>
<tr>
<td>Kostuk et al (54)</td>
<td>150</td>
<td>&lt; 12 hrs</td>
<td>75-150</td>
<td>2-4</td>
<td>24</td>
<td>NR</td>
<td>10/78 (13) L</td>
<td>6/153 (3.9) P</td>
</tr>
</tbody>
</table>

L = lidocaine, Conc = concentration, VF = ventricular fibrillation, P = placebo, NR = not reported, No Tx = no treatment, IM = intramuscular, pts = patients.

*Studies were double-blind and placebo-controlled except where indicated. Administration of lidocaine was intravenous except where indicated. All patients reported in this table had confirmed myocardial infarction.

†Prior to hospital admission.
‡During treatment period.
§Not blinded.
¶Not placebo-controlled.
†Treatment assigned by birthdate.
#Nine patients included in mortality analysis were not included in VF analysis.
**Single-blind.
††P < 0.002.
lidocaine compared to those receiving placebo (53,55,56) or no treatment (26,57,58). Deficiencies in the design of these studies warrant consideration. Some of these studies were not blinded or placebo-controlled (26,57,58). In most of these trials, plasma lidocaine concentrations were not determined, and therefore it is unclear whether adequate plasma concentrations were achieved (53,55-58). In a number of these studies, the incidence of primary VF in treatment and control groups was calculated based on all patients with suspected MI, rather than only those with confirmed MI (26,55,57), and therefore many patients included for analysis were likely at very low risk for primary VF. Additional deficiencies include failure to report the duration of chest pain prior to randomization (26,57,58) and short follow-up periods (26,53). Inadequacies in study design may account for the reported lack of efficacy of prehospital lidocaine administration for the prevention of primary VF following acute MI. Nevertheless, currently existing data do not support the prehospital prophylactic administration of intramuscular or intravenous loading doses of lidocaine in patients with suspected acute MI.

**Effect of Prophylactic Lidocaine Administration on Mortality Following Acute MI**

The influence of in-hospital prophylactic administration of lidocaine on mortality following MI in randomized studies is presented in Table 2.

In-hospital prophylactic lidocaine administration did not significantly influence mortality in any study, including Lie et al.'s (22) trial in which lidocaine administration resulted in a significantly lower incidence of primary VF than administration of placebo.

The influence of prehospital prophylactic lidocaine administration on mortality following MI in randomized studies is presented in Table 3.

In the majority of studies, prehospital administration of lidocaine did not significantly influence mortality. Valentine and colleagues (55) reported that the prehospital administration of lidocaine (300 mg intramuscularly) significantly reduced early mortality (2 deaths out of 156 patients in the lidocaine group versus 6 deaths out of 113 patients in the placebo group, P < 0.05). However, the authors indicate that although this was intended to be a randomized trial, nonrandom allocation of treatment may have occurred, raising the possibility of bias. In addition, early mortality was defined as that which occurred within only 2 hours of the injection of drug or placebo. The incidence of late mortality (defined as that which occurred from 2 hours to 30 days following injection) in the two groups was not significantly different.

The influence of prophylactic lidocaine administration on early mortality following MI was evaluated in the meta-analysis performed by MacMahon and associates (52). The pooled incidence of mortality occurring during treatment/follow-up periods of 1 to 48 hours in the 14 studies reviewed was 82 deaths (1.9%) out of 4,616 patients receiving prophylactic lidocaine and 55 deaths (1.2%) out of 4,539 patients receiving placebo or no treatment. These data indicate that the incidence of early mortality was approximately one-third higher in the lidocaine group than in the control group, although this difference did not reach statistical significance (odds ratio = 1.38, 95% confidence interval = 0.98 to 1.95). The influence of prophylactic lidocaine administration on late mortality (death occurring after the treatment/follow-up periods) in eight studies was also examined.

**Table 3**

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Percent Confirmed MI</th>
<th>L Bolus</th>
<th>L Infusion</th>
<th>Mean Plasma L Conc.</th>
<th>Duration of Follow-up</th>
<th>Incidence of VF (%)</th>
<th>Incidence of Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valentine et al (55)**</td>
<td>269</td>
<td>NR</td>
<td>300 mg IM</td>
<td>—</td>
<td>NR</td>
<td>2 hrs</td>
<td>1/156 (0.6) L</td>
<td>2/156 (1.3) L*</td>
</tr>
<tr>
<td>Wennerblom et al (56)</td>
<td>150</td>
<td>36</td>
<td>300 mg IM</td>
<td>—</td>
<td>NR</td>
<td>3 hrs</td>
<td>0/213 (0) P</td>
<td>6/113 (5.3) P</td>
</tr>
<tr>
<td>Dunn et al (53)</td>
<td>402</td>
<td>51</td>
<td>300 mg IM</td>
<td>—</td>
<td>3.57-4.50 µg/mL</td>
<td>1 hr</td>
<td>0/1086 (0) L</td>
<td>5/207 (2.4) L</td>
</tr>
<tr>
<td>Koster &amp; Dunning (26)**</td>
<td>6,024</td>
<td>32</td>
<td>400 mg IM</td>
<td>—</td>
<td>3 µg/mL (n = 369)</td>
<td>1 hr</td>
<td>3/96 (3.1) P</td>
<td>5/195 (2.6) P</td>
</tr>
<tr>
<td>Hargarten et al (57)**</td>
<td>446</td>
<td>29</td>
<td>0.75-1.5 mg/kg IV</td>
<td>1-2</td>
<td>0/261 (0) P</td>
<td>2 hrs</td>
<td>3/222 (1.4) L</td>
<td>15/224 (6.7) L</td>
</tr>
<tr>
<td>Hargarten et al (58)**</td>
<td>1,427</td>
<td>31</td>
<td>0.75-1.5 mg/kg IV</td>
<td>1-2</td>
<td>4/236 (1.7) L</td>
<td>3 hrs</td>
<td>4/200 (2.0) L</td>
<td>2/200 (1.0) L</td>
</tr>
</tbody>
</table>

†Late mortality (2-30 hours following injection) not significantly different.

**References**

1. Lie et al.
2. Dunn et al.
3. Valentine et al.
4. Hargarten et al.
5. Koster & Dunning
6. Wennerblom et al.

**Legend:**

- MI = myocardial infarction
- L = lidocaine
- Conc. = concentration
- VF = ventricular fibrillation
- NR = not reported
- IM = intramuscular
- P = placebo
- IV = intravenous
- POH = period of hospitalization

*Studies were double-blind and placebo-controlled except where indicated.
†In-hospital.
§Treatment was intended to be randomized, but authors indicate that nonrandom allocation may have occurred.
¶P < 0.03, early mortality (within 2 hours of injection).
#Late mortality (2-30 hours following injection) not significantly different.
#Not blinded.
**Not placebo-controlled.
The incidence of late mortality in the treatment group and placebo group was not significantly different (P > 0.3).

One published meta-analysis evaluated solely the effect of prophylactic lidocaine administration on mortality following acute MI (59). In this analysis, studies were included for evaluation based on the following criteria: randomized, controlled trials investigating the use of prophylactic lidocaine in patients with proven or suspected MI; patient enrollment within 72 hours of symptoms; and administration of lidocaine bolus ≥ 50 mg followed by continuous infusion of ≥ 1.0 mg/min for at least 24 hours or bolus of at least 300 mg without subsequent infusion. Eight hospital-phase (15,16,19-22,45,46) and six prehospital-phase (26,48,53,55-57) studies were included for evaluation. One of the "prehospital-phase" trials analyzed was actually a hospital-phase study (48). In the hospital-phase trials, the risk of treatment-period mortality was significantly higher in the lidocaine group compared to the placebo group. Meta-analysis of the risk of total in-hospital mortality in the hospital-phase studies revealed no statistically significant treatment effect. Analysis of the "prehospital-phase" studies demonstrated no statistically significant mortality effects related to the prophylactic administration of lidocaine.

In summary, the administration of prophylactic lidocaine following acute MI has not been shown to have a beneficial effect on mortality. In fact, available evidence indicates that the in-hospital administration of prophylactic lidocaine following MI may be associated with an increased risk of mortality during the period of treatment.

**Adverse Effects Associated with Prophylactic Lidocaine Administration**

Lidocaine administration may be associated with adverse effects involving primarily the central nervous system (CNS) and the cardiovascular system. Adverse CNS effects of lidocaine include dizziness, drowsiness, confusion, numbness of the face or extremities or the whole body, respiratory depression, twitching, dysarthria, diplopia, euphoria, tremors, and seizures (60-63). Adverse cardiovascular effects of lidocaine include sinus bradycardia, sinus arrest, atrioventricular conduction disturbances, asystole, hypotension, and respiratory arrest (62-66).

In trials evaluating the use of prophylactic lidocaine for the prevention of primary VF or other arrhythmias in patients with acute MI, the incidence of lidocaine-induced adverse effects has ranged from 4% to 85% (15,16,18-22,45,47-49,53,54,56,58,67,68). In some studies, no adverse effects attributable to lidocaine therapy were reported (17,25,55,57), whereas other investigators failed to indicate whether any side effects occurred (44,46). The report of one large trial simply states that minor side effects were "frequently observed" (26). In the study by Lie and associates (22), in which the incidence of primary VF was significantly reduced by the prophylactic administration of lidocaine, the incidence of adverse effects was 15% and was highest in patients greater than 60 years of age, prompting the authors to suggest that the benefits of prophylactic lidocaine administration may not outweigh the risks in elderly patients. Dunn and colleagues (53) reported that the incidence of adverse effects within one hour following a loading dose of lidocaine (300 mg intramuscularly followed by 100 mg intravenously) was significantly higher than that in patients who received placebo. They recommended against routine lidocaine prophylaxis in patients with suspected acute MI.

Rademaker and associates (61) performed a systematic evaluation of the incidence and nature of lidocaine-induced adverse effects during the course of a study investigating the efficacy of prophylactic lidocaine administration following suspected or confirmed acute MI (49). A comparison of the incidence of minor, major, and life-threatening adverse effects in the lidocaine and placebo groups is presented in Table 4. The overall incidence of adverse effects was significantly higher in patients who received lidocaine than in those who received placebo (74 [51%] of 145 in the lidocaine group versus 22 [16%] of 140 in the placebo group). The incidences of each of the minor symptoms of dizziness, numbness, and slurred speech and the major symptoms of confusion and slurred speech (listed as both a minor and major symptom) in the lidocaine group were significantly higher compared to the placebo group. The incidences of any minor symptom and any major symptom were also significantly higher in the lidocaine group than in the placebo group. The incidence of life-threatening problems in the two groups was not significantly different, although a trend towards a significantly higher incidence was demonstrated in the lidocaine group. The probability of experiencing minor or major lidocaine-induced adverse effects was greatest within the first 12 hours of drug administration. Of the patients who experienced lidocaine-induced adverse effects, 88% did so within 24 hours of the onset of therapy. The investigators also found that the incidence of minor lidocaine-induced adverse effects was significantly greater in patients in whom acute MI was subsequently ruled out than in those with confirmed MI. Major adverse effects also occurred more frequently in patients without MI than in those with confirmed MI, but the difference did not reach statistical significance. Serum lidocaine concentrations were only weakly related to lidocaine-induced adverse effects, and many patients who experienced side effects had serum lidocaine concentrations within the accepted therapeutic range (50). Based on these data, the authors suggest that the risks of routine lidocaine prophylaxis may outweigh any potential benefits.

In summary, based on the data provided by Rademaker and colleagues (61), adverse effects directly attributable to lidocaine occur in approximately 35% of patients (16% in the placebo group subtracted from 51% in the lidocaine group) with suspected or confirmed MI who receive the drug for the prevention of primary VF. Lidocaine-induced adverse effects occur with equal or greater incidence in patients subsequently found not to have had a MI compared to those with confirmed MI. Adverse effects due to lidocaine are most likely to occur early in therapy and may occur in patients with serum lidocaine concentrations within the accepted therapeutic range.

**Summary and Recommendations**

The administration of lidocaine for the prevention of primary VF in patients with suspected MI has been alternatively advo-
Minor Symptoms:

- Somnolence: 14 (Lidocaine) vs 8 (Placebo) with a P-value of 0.21
- Confusion: 7 (Lidocaine) vs 1 (Placebo) with a P-value of 0.07
- Numbness: 13 (Lidocaine) vs 0 (Placebo)
- Slurred speech: 14 (Lidocaine) vs 5 (Placebo) with a P-value of 0.04
- Any minor symptom: 67 (Lidocaine) vs 20 (Placebo)

Major Adverse Effects:

- Confusion: 9 (Lidocaine) vs 0 (Placebo) with a P-value of 0.004
- Severe nausea and vomiting: 8 (Lidocaine) vs 2 (Placebo) with a P-value of 0.06
- Sinus bradycardia (≤ 45 but > 35 bpm): 1 (Lidocaine) vs 1 (Placebo) with a P-value of 0.99
- Any major adverse effect: 27 (Lidocaine) vs 3 (Placebo)

Life-threatening Problems:

- Sinus arrest/bradycardia (≤ 35 bpm): 2 (Lidocaine) vs 0 (Placebo) with a P-value of 0.50
- Seizure: 2 (Lidocaine) vs 0 (Placebo) with a P-value of 0.50
- Coma/respiratory arrest: 1 (Lidocaine) vs 0 (Placebo) with a P-value of 0.99
- Any life-threatening problem: 5 (Lidocaine) vs 0 (Placebo) with a P-value of 0.06


References