Effects of Prophylactic Lidocaine in Suspected Acute Myocardial Infarction

An Overview of Results From the Randomized, Controlled Trials

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The effects of prophylactic lidocaine hydrochloride on early ventricular fibrillation and death in patients with suspected acute myocardial infarction were investigated in an overview of 14 randomized trials. During follow-up intervals of one to four hours in the trials of intramuscular lidocaine infusion (6961 patients) and 24 to 48 hours in the trials of intravenous lidocaine injection (2194 patients), a total of 103 cases of ventricular fibrillation and 137 deaths were recorded. Overall, allocation to lidocaine was associated with a reduction in the odds of ventricular fibrillation of about one third, with a 95% confidence interval that ranged from a 3% to a 56% reduction. There was no evidence of any beneficial effect on early mortality; indeed, the odds of early death were about one third greater among patients allocated lidocaine, though this difference was not statistically significant (95% confidence interval, 2% reduction to 95% increase). Because of the small numbers of reported events, the short follow-up periods, and the unavailability of data for some specific causes of death, even an overview of all the trial results does not provide good evidence as to whether prophylactic lidocaine is likely to be helpful or harmful. To answer this question reliably, future trials will need to involve large numbers of patients and prolonged follow-up.

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PATIENTS with acute myocardial infarction (AMI) are at particular risk of ventricular fibrillation (VF) during the first day or two after infarction, and a proportion of the episodes of VF will be fatal even if defibrillation facilities are available. Therefore, in some countries, including the United States[1,2] but not Britain (British Heart Foundation, unpublished data, 1987), prophylactic lidocaine hydrochloride is frequently given to patients presenting with suspected AMI in an effort to prevent VF. However, while lidocaine may be an effective treatment for certain ventricular arrhythmias,[3,4] there is considerable uncertainty about its prophylactic effects on VF[5,6] and death.[7] Although several randomized trials of prophylactic lidocaine have been conducted in patients with suspected AMI,[8-21] only one has reported a statistically significant reduction in the risk of VF,[15] and none has demonstrated a significant mortality benefit. This may be because lidocaine does not have any worthwhile effect on VF or mortality, or because any real effects of treatment are only moderate in size (eg, a reduction of 20% or 30%). Although moderate risk reductions might be worthwhile, the trials conducted to date have all been too small individually to detect them reliably. It may be better, therefore, to base inference about the effects of this treatment on a systematic overview of the results of all relevant randomized trials.[22,23] Not only will this minimize random errors resulting from the inadequate sample size of individual trials, but it will also help to avoid any systematic errors (biases) that might result from undue emphasis on the results of unrepresentative subsets of all the relevant trials.[24,25] The main aim of this article, therefore, is to provide an overview, both for VF and for mortality, of all randomized tri-

Prophylactic Lidocaine—MacMahon et al

als of prophylactic lidocaine in patients with suspected AMI.

METHODS
Identification of Trials and Acquisition of Data

To identify all randomized trials of prophylactic lidocaine in patients with suspected AMI, we have scanned the English- and non–English-language literature by formal computer-aided searches and by scrutiny of the reference lists of relevant articles. We have also made informal inquiry of other investigators about the existence of other published or unpublished trials. Only trials in which patients were *randomly* allocated to receive lidocaine or control were included in the overview. In one multicenter trial[26] in which treatment allocation was intended to be random, the principal investigators stated that nonrandom allocation may have occurred. That trial has, therefore, been excluded from the main analysis. (Its inclusion would not, however, materially affect the overall results; see footnotes to Tables 2 and 3.) Other controlled trials in which the investigators could determine the treatment allocation before deciding whether to enter a patient (for example, trials with allocation that was alternate[27] or based on date of birth[28,29]) were not included, since such methods may introduce bias into the allocation of treatment and thereby obscure or exaggerate any treatment effects.

For each trial, fatal and nonfatal events were defined using the criteria adopted by the investigators in that particular study. While this may result in some differences between trials in the exact definition of events, it will not bias the comparison of event rates between treatment and control patients within each particular trial, which is what is chiefly required for the unbiased assessment of treatment effects in an overview of trials (see "Statistical Methods" section). When the published results did not include data about VF, asystole, or other cause-specific mortality for some or all patients, we sought extra details by correspondence with the investigators.

Statistical Methods

The statistical methods used in this overview have been described previously.[30,31] The underlying principle is that patients allocated to active treatment in one trial are compared only with those allocated to control in the same trial. For each trial, therefore, the number of disease events *observed* in the treatment group (O) is contrasted with

the number that would have been *expected* if treatment had no effect (E). If, in one particular trial, treatment was without effect on outcome, the difference between the observed and expected number of events (O − E) would differ only randomly from zero (with variance given by standard formulas for 2 × 2 tables[30]). If treatment was beneficial, O − E would tend to be negative (and approximately equal in magnitude to half the number of events prevented by treatment). Although in a single trial this tendency might be obscured by the play of chance, it is likely to stand out more clearly in the grand total of the individual O − E values, one from each trial. If, however, treatment were wholly without effect in any trial, this grand total would itself differ only randomly from zero (with variance equal to the sum of the individual variances of the separate O − E values and with an SD equal to the square root of this total variance). Formal statistical tests of whether treatment is without effect involve calculation of z, the number of SDs by which the grand total of O − E values differs from zero (so, z = grand total/SD), and comparison of z with tables of the standard normal distribution (where, for example, $z = -1.96$ would suggest a two-sided P value of about .05).

Assessment of treatment effects from the combined data assumes that unbiased information from all, or from an unbiased sample of all, randomized trials is included (without important bias due to the unavailability of data from unpromising trials or from patients withdrawn after randomization). It does not, however, assume that the real effects of treatment are the *same size* in different trials, but merely that any real effects of treatment will tend to be in the *same direction* in most or all trials. An estimate of the "typical" ratio of the odds of a disease event among patients allocated lidocaine compared with that among controls is given by the exponential function $exp(z/SD)$, with approximate 95% confidence limits given by $exp(z/SD \pm 1.96/SD)$. Odds ratios less than 1.0 indicate protection, and an odds ratio of 0.80 could be described as a reduction of 20% (with the SD of a reduction of R% estimated as $-R/z$). Approximate tests for heterogeneity between the treatment effects observed in different trials (or groups of trials) can be calculated by subtracting the χ^2 statistic for the overall result from the sum of the χ^2 statistic for each separate result.[30] In general, however, such tests of heterogeneity are of limited value because they are rather insensitive to any

real differences that may exist; moreover, some real heterogeneity is almost certain to exist no matter what a formal test of heterogeneity may indicate.

RESULTS
Features of Trials Identified and Data Available

This overview includes results from 14 randomized, controlled trials of lidocaine[8-21] in patients with suspected AMI (Table 1). Of these, ten were double-blind, one was single-blind, and three were open trials (ie, both the physician and the patient knew the treatment allocation). Patients were ineligible for randomization because of previous VF or ventricular tachycardia in 13 trials,[8,9,11-21] congestive heart failure in 11 trials,[8,9,11,13,15-21] cardiogenic shock or hypotension in ten trials,[8,9,11-13,15-18,20] and bradycardia in eight trials.[9,10,13,15,16,19-21] In four trials,[15,16,19,20] patients were randomized only if they presented within six hours of the onset of symptoms. Two thirds of the patients studied were male and the average age ranged from 56 to 66 years in the different trials.

With regard to treatment regimens and follow-up periods, the trials fall into two main groups: *(1) Trials of intravenous (IV) lidocaine infusion.* There were nine small trials[8-16] (total patients, 2194) in which the study treatment involved an IV infusion of lidocaine hydrochloride (0.5 to 3.0 mg/min for 24 to 48 hours; average infusion dose for all IV trials, 2.0 mg/min), usually preceded by an IV bolus of lidocaine hydrochloride (50 to 100 mg). Data on VF and death during the 24 to 48 hour treatment periods were available from all IV trials, with subsequent deaths in the hospital available from six.[9-13,16] *(2) Trials of intramuscular (IM) lidocaine injection.* In five trials[17-21] (total patients, 6961), the study treatment involved an IM lidocaine hydrochloride injection (200 to 400 mg) without an IV infusion (except one trial in which an IV bolus was also given). The scheduled follow-up period continued only during the first few hours after randomization in three trials[19-21] and for three to four hours in the other two,[17,18] with subsequent deaths occurring in the hospital available from two IM trials.[19,20] In the largest of all these trials,[21] follow-up for death continued for up to 30 months after randomization, and the total number of deaths at the end of follow-up (for 98% of all patients randomized), together with Kaplan-Meier product-limit estimates of survival, were available for each of the two randomized groups (R.W.K., unpublished data, 1985).

Outcome data on VF and mortality during the early scheduled follow-up pe-

Table 1.—Design Characteristics of All Randomized Trials of Prophylactic Lidocaine Hydrochloride in Suspected Acute Myocardial Infarction*

Study	No. Patients Reported	Randomized Patients Excluded Because AMI Not Confirmed?	Treatment Allocation	Study Treatment Regimen		Follow-up Duration for VF, h†
				Loading Dose, mg	Infusion Dose, mg/min	
Trials of IV lidocaine infusion						
Kostuk and Beanlands[8]	65	Yes	Double-blind	. . .	1.0	48
Bennett et al[9]	374	Yes	Open	IV 60	0.5-1.0	48
Baker et al[10]	44	Yes	Double-blind	. . .	1.5	48
Chopra et al[11]	82	No	Double-blind	IV 50	1.0-2.0	48
Pitt et al[12]	222	Yes	Open	IV 75-100‡	2.5	48
Darby et al[13]	203	Yes	Open	IM 200	2.0	48
O'Brien et al[14]	659	No	Double-blind	IV 75	2.5	48
Lie et al[15]	212	Yes	Double-blind	IV 100	3.0	48
Wyse et al[16]	333	No	Double-blind	IV 100 + IV 100§	3.0	24
Trials of IM injection (without IV infusion)						
Sandler et al[17]	181	Yes	Double-blind	IM 200 or IM 300	. . .	4
Singh and Kocot[18]	54	No	Double-blind	IM 4.5 mg/kg	. . .	3
Lie et al[19]	300	Yes	Double-blind	IM 300	. . .	1
Dunn et al[20]	402	No	Double-blind	IM 300 + IV 100	. . .	1
Koster and Dunning[21]	6024	No	Single-blind	IM 400	. . .	1

*AMI indicates acute myocardial infarction; VF, ventricular fibrillation; IV, intravenous; and IM, intramuscular.
†For the IV trials, the duration of the infusion equals this follow-up duration.
‡A loading dose of 75 to 100 mg was administered to only about half of all patients allocated lidocaine.
§The first bolus was administered immediately; the second was administered 30 minutes later.

riods (IV trials, 24 to 48 hours; IM trials, one to four hours) were available for all randomized patients (with no postrandomization exclusions) in six trials involving a total of 7554 individuals. One[21] of these six trials was conducted prior to hospital admission in patients with suspected AMI, and two thirds of those randomized did not have the initial diagnosis of AMI confirmed. The other five trials[11,14,16,18,20] were conducted in the hospital, and about one third of the randomized patients did not have the diagnosis of AMI confirmed. In the eight remaining trials, all of which were conducted in the hospital, outcome data were available for only those randomized patients in whom the initial diagnosis of AMI was confirmed (total, 1601). The exact number of patients excluded after randomization because the diagnosis of AMI was not confirmed is not known, but the proportions of such patients in the other trials suggest that data may be missing from about 800 patients (ie, about 8% of all patients randomized in all trials). However, few, if any, of these would have suffered VF or early death.

Effects of Treatment on Ventricular Fibrillation and on Early Mortality

Ventricular Fibrillation.—In the 14 trials, a total of 89 nonfatal and 14 fatal cases of VF were reported during the scheduled follow-up periods of one to 48 hours (Table 2 and Fig 1); only one case of VF was reported among the approximately 4500 patients without confirmed AMI. In six trials, the frequency of total

VF (nonfatal plus fatal) in patients allocated lidocaine was lower than that in controls, but in only one trial[16] was this difference statistically significant. Overall, when the data from all trials were considered together, the difference in the incidence of VF was of only borderline statistical significance ($P = .04$). Typically in these trials, the odds of VF were reduced by about one third among patients allocated lidocaine, but the 95% confidence interval (CI) for this difference ranged from about zero to about one half (typical odds ratio for total VF, 0.65; 95% CI, 0.44 to 0.97). The apparent effect of treatment was similar when the analyses were restricted either to trials in which data were available for all randomized patients (typical odds ratio, 0.59; 95% CI, 0.33 to 1.04) or to patients in whom the diagnosis of AMI was confirmed (typical odds ratio, 0.64; 95% CI, 0.43 to 0.95).

One study[15] contributed substantially to the apparent reduction in VF observed in the overview. The effect observed in that trial was significantly different from the overall result in the remaining studies and, as a consequence, the test for heterogeneity of effects between the various trial results was also significant ($P<.05$). If this trial were to be deleted from the analyses, an overview of the remaining trial results would not indicate any statistically significant effect of treatment on VF, and the apparent risk reduction would be only about one sixth. Nonsignificant

trends in favor of active treatment were observed both in the overview of trials of IV infusion and in the overview of trials of IM injection, with no evidence of significant heterogeneity of effect between the two groups of trials ($P>.6$). All of the apparent difference in outcome between patients allocated lidocaine and those allocated control was in nonfatal VF (typical odds ratio, 0.58; 95% CI, 0.38 to 0.89), but there were too few deaths ascribed to VF for reliable assessment of the effects of treatment on fatal VF alone (95% CI, 0.49 to 4.23).

Early Mortality.—In the 14 trials, a total of 137 deaths were reported during the early scheduled follow-up periods (one to 48 hours) (Table 3 and Fig 2); only seven of these deaths were recorded among patients without confirmed AMI. Neither in the trials individually nor in an overview of all the trial results was there any significant difference in early mortality rates between patients allocated lidocaine and those allocated control. Indeed, early mortality was about one third greater among patients allocated lidocaine than among controls, but the 95% CI for this difference was wide and included the possibility of no effect of treatment as well as the possibility of harm (typical odds ratio, 1.38; 95% CI, 0.98 to 1.95). The estimated treatment effects for early mortality were similar when analyses were restricted either to trials in which data were available for all randomized patients (typical odds ratio, 1.39; 95% CI, 0.89 to 2.19) or to patients in whom the

Prophylactic Lidocaine—MacMahon et al

diagnosis of AMI was confirmed (typical odds radio, 1.34; 95% CI, 0.94 to 1.90). The test for heterogeneity between the effects of treatment on early mortality in all trials was nonsignificant ($P>.5$), as was the test for heterogeneity between trials of IV infusion and trials of IM injection ($P>.2$).

In the eight trials from which data on in-hospital mortality rates were available,[9-13,16,19,20] a further 79 deaths were recorded after the one to 48 hours of scheduled follow-up and before discharge from the hospital. Mortality rates over this interval were not significantly different in patients allocated lidocaine and in those allocated control (38 vs 41; $P>.3$). Data on deaths occurring in the hospital were not separately available from the largest trial,[21] although Kaplan-Meier survival curves from that study suggested similar mortality rates during the first three weeks of follow-up among patients allocated lidocaine and those allocated control. Later follow-up in the same study (maximum duration, 30 months; median time to death, about three months) indicated a slightly higher mortality rate among patients allocated lidocaine than among those allocated control (total deaths during follow-up, 598 vs 559), but the difference was not statistically significant ($P>.1$).

Table 2.—Ventricular Fibrillation (Nonfatal and Fatal) by Allocated Treatment During Scheduled Follow-up Periods of One to 48 Hours in All Randomized Trials of Prophylactic Lidocaine Hydrochloride in Suspected Acute Myocardial Infarction

| | Basic Data (Lidocaine/Control) | | Statistical Calculations for Lidocaine Group | | | |
| | | | Total VF† | | Fatal VF‖ | |
Study	No. of Patients	Nonfatal Plus Fatal VF*	O−E‡	Variance of O−E§	O−E	Variance of O−E
IV infusion (mainly 48 h of follow-up)						
Kostuk and Beanlands[8]	34/31	0+0/0+0	...	...	...	...
Bennett et al[9]	249/125	12+4/6+1	+0.7	4.8	+0.7	1.1
Baker et al[10]	21/23	0+0/2+0	−1.0	0.5	...	...
Chopra et al[11]	39/43	1+0/0+0	+0.5	0.2	...	...
Pitt et al[12]	108/114	0+1/0+0	+0.5	0.2	+0.5	0.2
Darby et al[13]	103/100	4+0/1+2	+0.4	1.7	−1.0	0.5
O'Brien et al[14]	328/331	5+4/10+0	−0.5	4.6	+2.0	1.0
Lie et al[15]	107/105	0+0/10+1	−5.6	2.6	−0.5	0.2
Wyse et al[16]	168/165	0+0/1+0	−0.5	0.3	...	...
Subtotal (IV)	**1157/1037**	**22+9/30+4**	**−5.5**	**14.9**	**+1.7**	**3.0**
IM injection (mainly 1 h of follow-up)						
Sandler et al[17]	91/90	0+0/0+0	...	...	...	...
Singh and Kocot[18]	27/27	0+0/0+0	...	...	...	...
Lie et al[19]	147/153	6+0/4+0	+1.1	2.4	...	...
Dunn et al[20]	207/195	0+0/3+0	−1.5	0.7	...	...
Koster and Dunning[21]	2987/3037	8+0/16+1	−4.4	6.2	−0.5	0.3
Subtotal (IM)	**3459/3502**	**14+0/23+1**	**−4.8**	**9.3**	**−0.5**	**0.3**
Total (All Trials)¶	**4616/4539**	**36+9/53+5**	**−10.3**	**24.2**	**+1.2**	**3.3**

*χ^2 for heterogeneity between all trials = 20.3, df = 10, $P<.05$; χ^2 for heterogeneity between intramuscular (IM) and intravenous (IV) trials = 0.1, df = 1, not significant. Typical odds ratio (95% confidence interval), 0.65 (0.44, 0.97).
†VF indicates ventricular fibrillation.
‡O − E indicates observed minus expected events. O − E is approximately equal in magnitude to half the absolute difference in events between treatment and control groups of equal size.
§The size of the variance of O − E is an approximate index of the amount of information contributed by each trial to the subtotal and total results.
‖Typical odds ratio (95% confidence interval), 1.44 (0.49, 4.23).
¶The corresponding numbers from one trial of IM lidocaine (300 mg)[23] excluded because of possible nonrandom allocation were 207/157 and 1 + 2/2 + 5. Inclusion of these data would alter the overall results only slightly, to a typical odds ratio for total VF of 0.61.

Fig 1.—Odds ratios (treatment:control) for ventricular fibrillation (fatal plus nonfatal) over follow-up intervals of one to 48 hours. Size of square indicates amount of information available from each trial or from overview of trials; line, 95% confidence interval for individual trials; and diamond, 95% confidence interval for overview of trials.
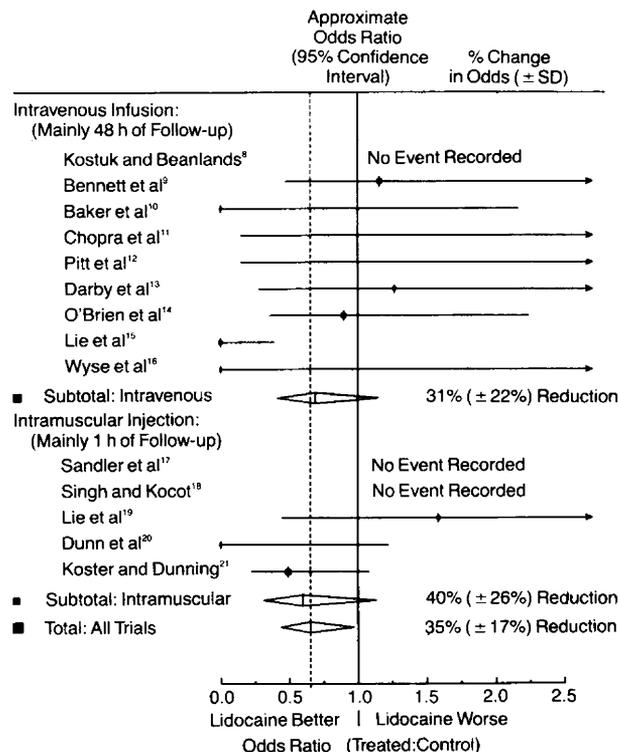
Table 3.—Death by Allocated Treatment During Scheduled Follow-up Periods of One to 48 Hours in all Randomized Trials of Prophylactic Lidocaine Hydrochloride in Suspected Acute Myocardial Infarction

Study	Basic Data (Lidocaine/Control)		Statistical Calculations for Lidocaine Group: Total Mortality*	
	No. of Patients	No. of Deaths	O − E†	Variance of O − E‡
IV infusion (mainly 48 h of follow-up)				
Kostuk and Beanlands[8]	34/31	0/0	...	...
Bennett et al[9]	249/125	15/3	+3.0	3.8
Baker et al[10]	21/23	2/0	+1.0	0.5
Chopra et al[11]	39/43	2/1	+0.6	0.7
Pitt et al[12]	108/114	6/5	+0.6	2.6
Darby et al[13]	103/100	7/5	+0.9	2.8
O'Brien et al[14]	328/331	14/7	+3.5	5.1
Lie et al[15]	107/105	8/10	−1.1	4.1
Wyse et al[16]	168/165	6/2	+2.0	2.0
Subtotal (IV)	**1157/1037**	**60/33**	**+10.5**	**21.6**
IM injection (mainly 1 h of follow-up)				
Sandler et al[17]	91/90	0/0	...	...
Singh and Kocot[18]	27/27	0/0	...	...
Lie et al[19]	147/153	0/0	...	...
Dunn et al[20]	207/195	3/1	+0.9	1.0
Koster and Dunning[21]	2987/3037	19/21	−0.8	9.9
Subtotal (IM)	**3459/3502**	**22/22**	**+0.1**	**10.9**
Total (All Trials)§	**4616/4539**	**82/55**	**+10.6**	**32.5**

*χ^2 for heterogeneity between all trials = 7.4, df = 9, not significant; χ^2 for heterogeneity between intramuscular (IM) and intravenous (IV) trials = 1.6, df = 1, not significant.
†O − E indicates observed minus expected events.
‡Typical odds ratio (95% confidence interval), 1.38 (0.98, 1.95).
§The corresponding numbers from one trial of IM lidocaine (300 mg)[23] excluded because of possible nonrandom allocation were 207/157 and 4/6. Inclusion of these data would alter the overall results only slightly to a typical odds ratio of 1.29.

COMMENT

This overview of all 14 randomized trials of prophylactic lidocaine in patients with suspected AMI indicates that treatment may reduce the incidence of VF, but the results provide no evidence of any mortality benefit. In reviewing these trials, however, four shortcomings of the available data hamper the reliable evaluation of the benefits and risks of this widely used treatment: (1) The numbers of events recorded in these trials and available for inclusion in the overview were too small, even when combined, to allow reliable assessment of the early effects of treatment on either VF or death. (2) While some data were available from all trials for total mortality and for fatal VF, no data were available from several trials for other specific causes of death, such as asystole. (3) The follow-up periods from which precise outcome data were available were, in general, so short that it is not possible to draw definite conclusions about the effects of prophylactic treatment during the first few weeks after AMI. (4) No outcome data at all were available for about 800 patients who were excluded after randomization because the initial diagnosis of

Approximate Odds Ratio (95% Confidence Interval)   % Change in Odds (± SD)

Intravenous Infusion: (Mainly 48 h of Follow-up)
Kostuk and Beanlands[8]   No Event Recorded
Bennett et al[9]
Baker et al[10]
Chopra et al[11]
Pitt et al[12]
Darby et al[13]
O'Brien et al[14]
Lie et al[15]
Wyse et al[16]
■ Subtotal: Intravenous   62% (± 28%) Increase

Intramuscular Injection: (Mainly 1 h of Follow-up)
Sandler et al[17]   No Event Recorded
Singh and Kocot[18]   No Event Recorded
Lie et al[19]   No Event Recorded
Dunn et al[20]
Koster and Dunning[21]
■ Subtotal: Intramuscular   1% (± 30%) Increase

■ Total: All Trials   38% (± 21%) Increase

0.0   0.5   1.0   1.5   2.0   2.5
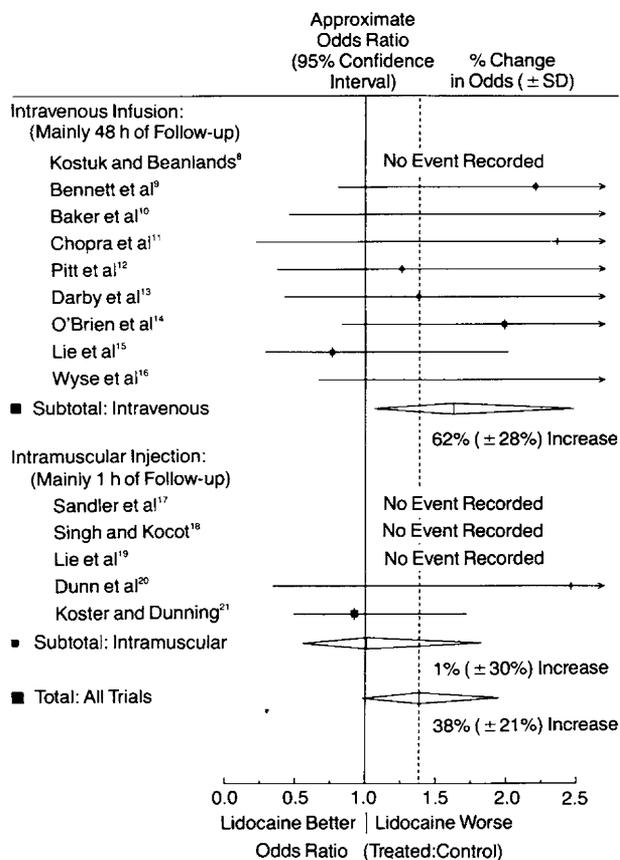Lidocaine Better | Lidocaine Worse
Odds Ratio (Treated:Control)

Fig 2.—Odds ratios (treatment:control) for total mortality over follow-up intervals of one to 48 hours. Size of square indicates amount of information available from each of the trials or from overview of trials; line, 95% confidence interval for individual trials; and diamond, 95% confidence interval for overview of trials.

AMI was not confirmed. These four limitations each have implications both for the interpretation of the present results and for priorities in future research.

Regarding the first of these limitations, if, as it seems likely, any real effects of prophylactic lidocaine on VF are only moderate in size (eg, a one-third reduction in risk) rather than large (eg, a two-thirds reduction in risk), then each of the 14 trials was too small on its own to detect such effects reliably. Even in the overview of all the trial results, the total number of events available for inclusion was so small that really reliable detection of moderate treatment effects was not possible. So, although the overall observed incidence of VF was about one third less among patients allocated lidocaine, the result was also consistent with there being little real benefit of treatment. Conversely, although there were somewhat more deaths during the early follow-up periods among patients allocated lidocaine, this result was also consistent with there being little or no real adverse effect of treatment. Formally, for early death, as for VF, the overview had only about a 50% probability of detecting differences of one third at conventional levels of significance ($P<.05$).

Given these problems in the comparison of outcome among all patients allocated lidocaine and those allocated control, it is clear that even an overview of the trial results is likely to be wholly inadequate for the indirect comparison of the effects of different lidocaine regimens (eg, IM injection vs IV infusion, or high dose vs low dose), particularly since any real differences between treatment regimens are likely to be less than the overall differences between patients allocated lidocaine and those allocated control. The apparent reduction in VF in one trial[15] was, however, somewhat larger than that observed in the other studies, and this was the principal reason for the significant heterogeneity among the 14 trial results. The exact explanation for this difference is uncertain. It is possible that some of the difference may simply reflect the play of chance, but it is also possible that some of the difference reflects the high infusion dose (3.0 mg/min) used in that trial. While the data from these trials do not permit reliable assessment of dose-response relationships, it is notable that all of the overall reduction in VF observed among patients allocated lidocaine occurred in those trials that involved high IV ($\geq$ 2.5 mg/min) or IM doses of lidocaine.

With regard to the second limitation, if lidocaine has any effect on early mortality, it seems likely that it will do so by increasing or decreasing particular types of death (eg, death due to VF or death due to asystole). Cause-specific mortality analyses may, therefore, provide the most sensitive way to assess the risks and benefits of treatment. However, most episodes of VF were successfully treated or resolved spontaneously, and thus, fatal VF accounted for only about one sixth of all reported cases of VF. Consequently, in estimating the relative effects of treatment on this particular cause of death, it may be better to base inference indirectly on the results for total VF, which suggest a reduction of about one third, rather than directly on the results for fatal VF alone. For other causes of death, cause-specific analyses are limited not only by the small number of events, but also by the unavailability of data from several trials. Deaths from asystole, for example, were reported in only seven trials.[11-14,16,20,21] Koster and Dunning[21] first reported an increase in episodes of asystole of more than 5 s duration (whether or not resuscitation was required) among patients allocated lidocaine compared with those allocated control (nonfatal plus fatal asystole, 25 + 1 vs 12 + 1). Data on total asystole were also available from two other trials (Kevin P. O'Brien, FRACP, written communication, Feb 27, 1987, 6 + 10 vs 0 + 7; Wyse et al,[16] 1 + 1 vs 0 + 0), and data on fatal asystole alone were available from four other studies (total, ten vs five). An overview of the data on deaths ascribed to asystole does not clearly demonstrate an excess associated with lidocaine (22 vs 13; $P>.1$), but as the number of such deaths is small, it may be better, as for VF, to base inference about the relative effects of treatment on an overview of total asystole (54 vs 25; $P<.01$) or of fatal asystole plus nonfatal asystole requiring resuscitation (34 vs 13; $P<.01$). However, because of the incompleteness of these data on asystole, some bias in the assessment of treatment cannot be ruled out, and so the true effects of prophylactic lidocaine on asystole remain substantially uncertain. But if prophylactic treatment were to double the number of early deaths from asystole (given the asystole mortality rate of three per 1000 observed here among patients allocated control), then this might well outweigh the benefits of a one-third reduction in VF, particularly, as in these trials, when so few cases of VF are fatal (one per 1000 among patients allocated control).

The third limitation is the shortness of the scheduled follow-up periods from which data for several trials were available. As the risk of VF is greatest in the first few days after AMI, most cases of VF likely to be affected by treatment would have been recorded in the trials of IV lidocaine infusion (scheduled follow-up for VF, 24 to 48 hours), but these involved only 2194 patients. In contrast, many cases of VF in the trials of IM injection are likely to have occurred after the scheduled follow-up period (one to four hours) and have, therefore, not been analyzed. Similarly, many deaths that might have been affected by treatment are also likely to have occurred outside the scheduled follow-up intervals both in the trials of IM injection and in the trials of IV infusion. In the eight small trials that provided data on in-hospital deaths after the scheduled follow-up period, there was no significant difference in mortality rates between patients allocated lidocaine and those allocated control. Similarly, the survival curves for the largest trial[21] indicated no difference in mortality rates during the first three weeks of follow-up. Overall, therefore, the data available from these trials do not provide any clear evidence that prophylactic lidocaine improves survival during the first few weeks after admission for suspected AMI. But since such data were not available for about one fifth of all randomized patients, there is some potential for selection bias as well as random error in the assessment of treatment effects over this period. For these reasons, potentially important beneficial or adverse effects of prophylactic lidocaine on in-hospital survival cannot be excluded. With regard to survival after discharge from the hospital, nonfatal VF following AMI appears to be associated with a worse prognosis.[32] It is uncertain, however, whether this poor prognosis is the consequence of VF itself or of other factors, which may independently determine the risks of both early VF and later death. Nevertheless, this association does raise the possibility that a reduction in VF following prophylactic lidocaine might result in a beneficial effect on later survival. Data on late mortality were available only from the one large trial,[21] and these did not indicate any survival advantage among patients allocated prophylactic lidocaine. The reliability of this result is, however, limited by the incompleteness of the data on long-term survival in the other trials.

Finally, the fourth limitation of these data involves the exclusion, after randomization, of about 8% of patients because the initial diagnosis of AMI was not confirmed. Any benefit of lidocaine in patients who do not have AMI is likely to be slight, given their very low risk of VF. However, treatment may have some adverse effects in these patients

(for example, one trial reported an increase in asystole among patients without confirmed AMI who were allocated lidocaine[21]). Additionally, lidocaine might alter the likelihood of confirming the diagnosis of AMI, thereby causing certain types of patients to be included in one treatment group but not in the other. For both these reasons, the exclusion of some patients in whom the diagnosis of AMI was not confirmed is undesirable, since it might have introduced some bias into the assessment of treatment. But, while the net effects of these potential biases remain uncertain, restriction of the analyses to those trials in which data were provided for all randomized patients made little difference to the apparent effects of treatment on VF or on early death.

This overview does not concern the therapeutic use of lidocaine in patients who have already suffered VF or in those who are otherwise at particularly high risk of VF (eg, patients with ventricular tachycardia), nor does it concern the prophylactic use of lidocaine outside the hospital or the ambulance, where facilities for defibrillation may not be available. Rather, the present results relate to the routine use of prophylactic lidocaine in patients with suspected AMI, when administered in situations where there are facilities for resuscitation. Important questions remain about both the efficacy and safety of prophylaxis in this setting. There is uncertainty as to whether prophylactic lidocaine produces a worthwhile reduction in VF, and, even if it does, there remains uncertainty both as to the effects on other causes of death, such as asystole, and as to the net effects on overall survival in the days and weeks after AMI. These issues are unlikely to be satisfactorily resolved until further data become available from new trials large enough (and with long enough follow-up) to assess reliably the relative effects on VF and on cause-specific mortality of a policy of early prophylactic administration of lidocaine vs one of the administration of lidocaine only when some clear indication for its use develops.

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