Ventricular Arrhythmias in Trials of Thrombolytic Therapy for Acute Myocardial Infarction
A Meta-Analysis

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Background. Although thrombolytic therapy reduces long-term mortality in acute myocardial infarction, many clinicians remain concerned about an increased risk of ventricular arrhythmias associated with the use of these agents.

Methods and Results. To determine whether thrombolytic therapy increases the risk of ventricular tachyarrhythmias and whether an increase in arrhythmias could be responsible for the increased mortality seen in the first 24 hours after lytic therapy, we performed a meta-analysis of 15 randomized trials of thrombolysis in acute myocardial infarction in which the odds of developing in-hospital ventricular fibrillation (VF) and ventricular tachycardia (VT) in patients receiving thrombolysis was compared with that of patients receiving placebo. For trials that reported the incidence of VF during the first 6 hours after thrombolysis, the summary odds ratio for developing VF in the thrombolytic group was 0.98 (95% confidence interval [CI], 0.6 to 1.6; P=.94). For trials that reported the incidence of VF during the first hospital day, the summary odds ratio for developing VF was 1.00 (95% CI, 0.85 to 1.2; P=.95). The summary odds ratio for the development of VT at any time during hospitalization in the thrombolytic group was 0.83 (95% CI, 0.76 to 0.90; P<.0001). In trials that reported the incidence of VT any time during hospitalization, the summary odds ratio for the development of VT in the thrombolytic group was 1.34 (95% CI, 1.15 to 1.55; P<.0001).

Conclusions. The likelihood of developing VF in the early hours after thrombolysis for acute myocardial infarction is similar in patients receiving thrombolytics or placebo. However, throughout the hospital course, the risk of VF is greater in patients receiving placebo, whereas the risk of VT is higher in patients receiving thrombolysis. (Circulation. 1993;88:2575-2581.)

KEY WORDS • fibrinolysis • fibrillation • tachycardia

Since the advent of thrombolytic therapy, concern has been raised regarding the potential danger of ventricular arrhythmias in patients receiving thrombolysis for acute myocardial infarction.1,2 Although the risk of reperfusion ventricular arrhythmias has been proposed as a rationale for the prophylactic use of antiarrhythmic agents in patients receiving thrombolytic therapy in acute myocardial infarction, there has been no definitive evidence of excess ventricular arrhythmias with thrombolysis.3 Indeed, although numerous studies have documented transient ventricular arrhythmias at the time of restoration of antegrade flow and have suggested that these arrhythmias may be markers of reperfusion, the most common arrhythmias in these studies have been premature ventricular contractions, accelerated idioventricular rhythms, and non-sustained ventricular tachycardia (VT).4,5 rather than ventricular fibrillation (VF) or sustained VT.6

Despite the paucity of data, concern that thrombolytic therapy may increase the risk of ventricular arrhythmia has increased with the findings from several large-scale clinical trials of an excess of deaths associated with thrombolysis during the first day of therapy.7-9 Although a variety of explanations have been proposed for this “early hazard,” whether arrhythmia can account for some of these deaths remains unclear.

To estimate the risk of developing ventricular arrhythmias in patients receiving thrombolytic therapy for acute myocardial infarction and to determine whether an increased risk of ventricular tachyarrhythmias could contribute to the excess mortality seen in the first day after thrombolysis, we performed a meta-analysis to evaluate the relation between thrombolysis and the occurrence of VF and VT in randomized controlled trials of thrombolysis in acute myocardial infarction that reported the incidence of these arrhythmias. To address the relation between thrombolytic therapy and timing of VF, studies were subdivided into three categories depending on the timing of arrhythmia relative to the initiation of thrombolytic therapy: first 6 hours, first hospital day, and any time during hospitalization.

Methods

Identification of Trials

Randomized controlled trials of intravenous thrombolytic agents versus placebo or open control that were
Randomized Controlled Trials Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Reference</th>
<th>Study Design</th>
<th>Total No. of Patients</th>
<th>Time Frame of VF Reported</th>
<th>Lytic VF</th>
<th>Placebo VF</th>
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<tr>
<td>Simoons et al</td>
<td>1985</td>
<td>10</td>
<td>SK vs placebo</td>
<td>533</td>
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<td>439/5852</td>
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<td>38</td>
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<td>4/19</td>
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<td>14/206</td>
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<td>IH 3/75</td>
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<td>17 187</td>
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<td>81</td>
<td>&lt;6 h, day 1, IH 0/55</td>
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SK indicates streptokinase; APSAC, anistreplase; TPA, recombinant tissue plasminogen activator; IH, any time in hospital; <6 h, under 6 hours from onset of therapy; and day 1, during day 0 or day 1 of hospitalization (up to 48 h).

reported between 1980 and 1991 were identified on the MEDLINE databases of the National Library of Medicine using the following search terms: "myocardial infarction," "thrombolysis," "fibrinolytic agents," "tissue plasminogen activator," "streptokinase," "anistreplase," and "anisoylated streptokinase" crossed with "randomized-controlled trials" or "clinical trials." In addition, known references and references from identified studies were used to supplement the computerized search. Identified articles were included in the analysis if they reported the number of patients in both the thrombolytic and placebo groups who developed VF at any time during hospitalization. Trials of intracoronary thrombolysis for myocardial infarction were excluded from the analysis so as to avoid the potential confounding effect of cardiac catheterization on development of arrhythmia. The definition of VF had to be explicit; sudden death was not accepted as a surrogate marker. The definition of VT varied among trials and ranged from a minimum of three consecutive beats of ventricular origin at a rate of >100 beats per minute to sustained VT. The incidence of VT was reported in a subset of the total number of trials reporting the incidence of VF, and a separate meta-analysis was conducted for this end point. A total of 15 trials were included in the meta-analysis.7,8,10-22

All identified randomized controlled trials reporting the incidence of VF were subdivided into three groups based on the time of in-hospital VF: (1) VF reported during the first 6 hours after thrombolysis, (2) VF reported during the first hospital day after thrombolysis, and (3) VF reported at any time during hospitalization.

Statistical Methods: Meta-Analysis

The event rates for VF and VT in the treatment and control groups for each randomized controlled trial were used to calculate the Mantel-Haenszel odds ratios for the development of these ventricular arrhythmias in each individual trial.23 For trials with 0 events, the Haldane-Anscombe 1/2 correction of variance was applied before odds ratios were calculated.24 The calculated odds ratios for these arrhythmias for each trial were pooled by the methods of Mantel-Haenszel,25 and the summary odds ratio for the development of these arrhythmias for the lytic versus placebo groups was calculated.26 Ninety-five percent confidence intervals (CI) of the odds ratios for individual and pooled studies were calculated by use of the variance formula of Robins et al.27 Heterogeneity between studies was determined by subtracting the \( \chi^2 \) statistic for the overall result from the sum of \( \chi^2 \) statistics for each separate trial. Because the Mantel-Haenszel method assumes homogeneity between treatment groups (fixed-effects model), a random-effects model based on the method of DerSimonian and Laird28 was therefore also used to assess the risk difference between treatment and control groups, which adjusts for between-study differences in calculation of the variance (reported as a corrected risk difference). The random-effects model accounts for heterogeneity between studies by weighting within-study results and incorporating between-study differences in calculation of the variance and characteristically has wider 95% CIs than the Mantel-Haenszel method.29 The excess number of cases of arrhythmia per 1000 patients was calculated by multiplying the event rate difference by 1000.

Results

Fifteen randomized controlled trials reported the incidence of VF any time during hospitalization (Table). The thrombolytic agent was streptokinase in 7 studies, recombinant tissue plasminogen activator in 4 studies, and anistreplase in 4 studies.

Ventricular Fibrillation in the First 6 Hours

The odds ratios of the individual trials and the summary odds ratio for four trials that reported the
incidence of VF during the first 6 hours after thrombolytic therapy or placebo are shown in Fig 1, top. Overall, the VF event rate was 3.15% for 1018 patients in the thrombolytic group and 3.23% for 1024 patients in the placebo group. The summary odds ratio of developing VF in the thrombolytic group during the first 6 hours after thrombolysis was 0.98 (95% CI, 0.6 to 1.6; P=.93). \( \chi^2 \) for heterogeneity for these studies was 1.19 (\( P=.755 \)). The mean corrected risk difference by the method of DerSimonian and Laird was \(-0.2\% (95\% \text{ CI}, -1.7\% to 1.3\%); P=.38\).

**Ventricular Fibrillation in the First Hospital Day**

The odds ratios of the individual trials and the summary odds ratio for the eight trials that reported the incidence of VF during the first hospital day after thrombolytic therapy are shown in Fig 1, bottom. The VF event rate was 2.99% for 10 040 patients in the thrombolytic group and 2.99% for 10 012 patients in the placebo group. The summary odds ratio for the development of VF in the thrombolytic group was 1.00 (95% CI, 0.85 to 1.2; \( P=.94 \)). \( \chi^2 \) for heterogeneity in these studies was 2.12 (\( P=.95 \)). The mean corrected risk difference was 0.0% (95% CI, \(-0.5\% to 0.5\%; P=.47 \).
Risk of Early Ventricular Fibrillation

Clinical observation and experimental evidence have raised the question of an increased risk of ventricular arrhythmia in patients undergoing thrombolytic therapy for acute myocardial infarction. Initial studies of thrombolytic agents suggested that reperfusion was associated with a variety of ventricular arrhythmias and that these arrhythmias were secondary to restoration of antegrade flow. A variety of possible explanations for reperfusion-induced arrhythmogenesis have been proposed, including increased automaticity secondary to heightened α-adrenergic tone, electrochemical fluxes secondary to washout of metabolites from the formerly ischemic myocardium, and the increased production of free radicals after reperfusion. The experimental evidence for reperfusion-induced arrhythmias is stronger in animals than in humans, with numerous studies in several species documenting high-grade ventricular arrhythmias after reperfusion. Although premature ventricular contractions and accelerated idioventricular rhythms appear to be common during reperfusion in humans, the incidence of VT and VF appears to be lower than in animals.

Primary VF, defined as VF occurring during the first 24 to 48 hours after myocardial infarction that is not associated with shock or severe congestive heart failure, is thought to occur because of electrical instability associated with ischemic or infarcting myocardium, rapid ion fluxes, or increased sympathetic tone. Recent evidence argues that the occurrence of primary VF is related to both infarct size and contractile performance, and patients from the GISSI database who had primary VF showed a significantly higher short-term mortality. In contrast to primary VF, secondary VF is defined as VF occurring in association with heart failure or shock, and late VF is defined as VF occurring after 48 hours that is not associated with heart failure or shock.

Although the data available for this meta-analysis did not allow for the reliable distinction of primary from secondary VF, the results of our study do suggest that there is no increase in VF during or after thrombolysis for myocardial infarction and argue that reperfusion in humans may not be associated with an increased risk of VF. An alternative interpretation of these data, however, is that an increased propensity to arrhythmia secondary to lytic therapy is offset by a decreased likelihood of arrhythmia secondary to other mechanisms, such as reduced ischemia and normalization of transmembrane electrochemical gradients in injured myocardial zones when lytic therapy results in successful reperfusion. The relatively small number of trials included in the subanalyses do not provide the statistical power to exclude the possibility of a very small difference between treatment and control groups. Indeed, the confidence intervals for these analyses suggest that the true odds ratios may be as low as 0.6 or as high as 1.6 in the <6-hour analysis and as low as 0.85 or as high as 1.2 in the first-hospital-day analysis. Nevertheless, the fact that the event rates in both groups were virtually identical for the <6-hour and first-hospital-day analyses, yielding odds ratios of 0.98 and 1.00, respectively, suggests that the likelihood of a larger sample size showing a different overall result is very low.

Despite the marked decrease in overall mortality reported with thrombolytic therapy in the major clinical trials, excess mortality during the first hospital day for
patients given thrombolysis has been noted in several large randomized controlled trials. Given the lack of evidence of an excess risk of early VF, it seems more plausible that these excess deaths are related to causes other than ventricular tachyarrhythmias. It is important to note that all of the studies represented in this meta-analysis report the incidence of VF occurring after hospitalization and after randomization to treatment or placebo. The median time from onset of symptoms for the studies represented ranged from 2.0 to 6.7 hours (mean, 3.6 hours). From our data, there does not appear to be a relation between the time of thrombolysis relative to the onset of symptoms and the propensity to develop VF, although we cannot exclude a difference in VF event rates in patients treated within the first hour of an infarction.

**Risk of Late Ventricular Fibrillation**

Although the risk of early VF was no different in patients receiving lytic therapy and placebo, the overall risk of VF throughout the hospital course in this meta-analysis was reduced in patients undergoing thrombolysis. These results are in accord with the known decreased mortality and improved myocardial salvage associated with lytic therapy. Thus, whereas ascertainment bias would tend to result in an increased event rate in the thrombolytic group because of higher patient survival, leaving more patients alive and at risk for developing VF, the results of this study demonstrate a lower overall risk of VF in the thrombolytic group. Although it is likely that this decrease in total VF represents a decrease in late VF, information on the timing of VF was not provided in several of the trials, making it difficult to definitively distinguish early VF from late VF in those trials.

**Risk of Ventricular Tachycardia**

In contrast to VF, VT occurred at a higher rate among patients receiving thrombolysis compared with placebo. This finding may result, in part, from ascertainment bias that would tend to overestimate the event rate in the thrombolytic group because of fewer deaths in this group, leaving more patients at risk for developing VT. Additionally, this finding must be viewed in light of the inability to distinguish between different types of arrhythmias that compose the broad spectrum of VT, as reported in the trials herein. A diagnosis of VT was applied to a heterogeneous grouping of rhythm disturbances ranging from asymptomatic three-beat runs on one end of the spectrum to sustained hemodynamically significant VT on the other. The immediate clinical and prognostic implications of VT are markedly different at each end of the broad spectrum of rhythm disturbances, clouding the interpretation of pooled data that places equal weight on all types of VT. Additionally, the timing of VT in relation to thrombolysis was not reported in most of the trials included in the meta-analysis; it was therefore not possible to determine which if any of these arrhythmias were directly related to reperfusion.

The prompt recognition and treatment of arrhythmia in acute MI have contributed to the decreasing mortality of acute myocardial infarction over the past three decades. Originally regarded as predictors of more sinister arrhythmias, warning arrhythmias, including premature ventricular contractions, salvos, and short runs of ventricular tachycardia, have traditionally been treated with antiarrhythmic medication, with the expectation of reducing the risk of more lethal arrhythmias. Numerous studies, however, have argued that this rationale may be flawed and that so-called warning arrhythmias were as common in patients who did not subsequently develop VF as they were in patients who did develop subsequent VF. In addition, there is evidence that the present risk of primary VF in myocardial infarction is decreased compared with the pre-thrombolytic era. The apparent increased risk of VT in the thrombolytic group throughout the hospital course in this analysis occurred concurrently with a decreased risk of both VF and mortality. This raises the possibility that VT, as defined by the original investigators, was not a predictor of either VF or arrhythmia-related excess mortality and suggests that in the setting of thrombolysis, VT should not be considered a “warning arrhythmia” heralding the subsequent development of VF, although this requires more rigorous study.

**Limitations**

Many of the limitations of this study reflect limitations of meta-analyses in general. Because the data available are limited to those provided by the original investigators in the published studies, we were unable to perform certain subgroup analyses that might provide additional insight into the problem of arrhythmia in thrombolysis. Specifically, we were unable to determine the effect of patient age, infarct location, or coadministration of other medication on the incidence of VF.

Coadministration of antiarrhythmic agents such as lidocaine in any of the trials included in the analysis might be expected to modify the risk of VF in the setting of thrombolysis, and it is theoretically possible that these agents have a differential effect on patients treated with lytic therapy compared with placebo. We cannot completely exclude the possibility that lidocaine or other antiarrhythmics might have been prescribed more frequently in the thrombolytic groups and might have contributed, in part, to the decreased overall incidence of VF compared with the placebo group. Additionally, because VF occurs with an exponentially decreasing incidence after the onset of coronary occlusion, it is not clear whether the finding of this meta-analysis, from a population of patients treated in hospital, can be applied to patients seen very early (<1 hour) after the onset of symptoms. The relative risk of VF associated with the administration of thrombolytic therapy in patients treated extremely early in the course of myocardial infarction requires more rigorous assessment.

Although the inclusion of only published studies might result in publication bias that would tend to overestimate the effect size, significant publication bias is unlikely in this meta-analysis because a number of studies included in the analysis are very large (more than 10 000 patients), and the likelihood of a large, unpublished randomized study is very low in this high-profile field. Additionally, publication bias is less likely to occur in randomized studies. Differences among treatments that may occur between studies represent an additional source of potential bias in a meta-analysis. Indeed, since meta-analyses reflect trials that span time,
differences in concurrent treatments that occur over time may affect the overall outcome of the analysis. Although very little information was available from the studies included in this analysis regarding the coadmission of antiarrhythmic medication, a declining incidence of lidocaine use and an increase in β-blocker use for acute infarction during the past decade probably account for some of the heterogeneity between studies in this analysis.

Conclusions and Clinical Implications

In summary, the present meta-analysis of thrombolytic trials for acute myocardial infarction suggests that thrombolytic therapy is not associated with an increased risk of life-threatening VF. Indeed, thrombolyis appears to impart a decreased risk of VF over the entire hospital course. The increased odds of VT anytime during hospitalization are not associated with an increased risk of VF or higher mortality and may reflect ascertainment bias because of increased survival in the thrombolytic group and/or a greater propensity to non-lethal forms of ventricular arrhythmias caused by reperfusion. These data suggest that thrombolysis does not increase the risk of life-threatening arrhythmias and raise the possibility that the concurrent prophylactic administration of antiarrhythmic agents during and immediately after thrombolytic therapy, as is currently practiced in many institutions, may be unnecessary.

References

Ventricular arrhythmias in trials of thrombolytic therapy for acute myocardial infarction. A meta-analysis.
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