

SPECIAL NOTE

Mistaken Guidelines for Thrombolytic Therapy of Acute Myocardial Infarction in the Elderly

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In the recent "ACC/AHA Task Force Report on Guidelines for the Early Management of Patients with Acute Myocardial Infarction" (1), the section on "Thrombolytic Therapy in Older Age Patients" misinterprets the data from the Second International Study of Infarct Survival (ISIS-2) (2) and Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) (3), the only large, placebo-controlled trials of streptokinase with no age exclusion. The Guidelines state:

ISIS-2 reported a 16% reduction in the 5 week vascular mortality rate (18.2% versus 21.6%) in the streptokinase group >70 years of age at entry, a 26% reduction (10.6% versus 14.4%) in the streptokinase group in those 60 to 69 years and a 28% reduction (4.2% versus 5.8%) in the streptokinase group in <60 years. The GISSI trial noted a 13% reduction in mortality at 3 weeks in those >75 years, and 8% reduction in those 65 to 75 years, and a 26% reduction in those ≤65 years.

On this basis, the "Guidelines" conclude that there is an "attenuation of streptokinase effect with increasing age" and that "the administration of thrombolytic therapy to older patients should be judicious."

While the use of thrombolytic therapy in older, as well as younger, patients always should be judicious, the judgment of the Guidelines is flawed in two respects. First, the conclusions are based only on the percent reduction in mortality rate, rather than on the more meaningful analysis of lives saved per 1,000 patients treated. Second, the data that were cited were obtained using streptokinase without aspirin. The results obtained by using a combination of streptokinase with aspirin are significantly better and the standard of care dictates that this or other active adjunct agents be combined with streptokinase or other fibrinolytic agents.

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Table 1 tabulates the data from the trials reported in the "Guidelines" (percent mortality reduction) but, in addition, includes a calculation of the lives saved per 1,000 patients treated. In addition, it indicates the results in ISIS-2 using the combination of streptokinase with aspirin.

In fact, the data indicate results opposite from those cited in the "Guidelines." In ISIS-2 the number of lives saved per 1,000 patients treated with streptokinase alone was 16 for patients <60 years of age, 38 for those 60 to 69 years and 34 for those >70 years. In GISSI, the values are 20 for patients <65 years of age, 15 for the 65 to 75 year age group and 42 for those >75 years. Both studies show a superior effect in the >70 or >75 year groups than in the <60 or <65 year groups.

Even more important and impressive are the results using streptokinase plus aspirin, which show 25 lives saved per 1,000 patients <60 years old, 70 lives for the 60 to 69 year old group and 80 lives for the >70 year old group. These data clearly indicate an even more striking disparity, with the elderly (>70 years old) benefiting to a much greater degree with added aspirin than the patients <60 years old.

Thus, the data from the GISSI and ISIS-2 trials do not support the contention made in the Guidelines of an attenuation of effect by streptokinase in the elderly: rather, the reverse is true. Of course, one should always be judicious about bleeding risks in patient selection, young or old, but the overall benefit in lives saved is the more important consideration and this is achieved in the elderly.

Considering the progressive increase in life span, the number of people in the >70 year age group will grow. Since acute myocardial infarction represents a major problem for these individuals, the "Guidelines" as currently stated misrepresent the facts to their detriment. We recommend that an addendum to the "Guidelines" be published so as to correct this serious mistake.

References

1. Guidelines for the early management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee to Develop Guidelines for the Early Management of Patients with Acute Myocardial Infarction). *J Am Coll Cardiol* 1990;16:249-92.

Table 1. Mortality in Relation to Age in the ISIS-2 (2) and GISSI (3) Trials (Streptokinase or Streptokinase + Aspirin Versus Placebo)

	Pt. Age (yr)	Mortality Rate (%)		Mortality Reduction With SK	
		SK	Placebo	%	Lives Saved/1,000
ISIS-2 (SK alone)	<60	4.2	5.8	28	16
	60-69	10.6	14.4	26	38
	>70	18.2	21.6	16	34
GISSI (SK alone)	<65	5.7	7.7	26	20
	65-75	16.6	18.1	8	15
	>75	28.9	33.1	13	42
ISIS-2 (SK plus aspirin)	<60	3.7	6.2	40	25
	60-69	9.1	16.1	43	70
	>70	15.8	23.8	34	80

Pt. = patient; SK = streptokinase.

- ISIS (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:525-30.
- Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;1:397-402.

RESPONSE

ROLF M. GUNNAR, MD, FACC, Chairman,
*ACC/AHA Subcommittee to Develop
Guidelines for the Early Management of
Patients with Acute Myocardial Infarction (For
the Subcommittee)*

We agree that the use of thrombolytic therapy in all subjects, including those over 75 years, should be judicious. Table VI from the February 1986 GISSI publication reveals differences in subjects over 65 and those over 75 that are *not* statistically significant. The data from ISIS-2 in those over 70 are statistically significant with and without aspirin. Thus, the observed differences in GISSI in those over 65 or 75 could have easily arisen by chance, and the observed differences in ISIS-2 in the over 70 group are unlikely to have arisen by chance. There were 2,886 patients between 65 and 75 randomized in GISSI and 3,411 randomized in ISIS-2 over 70.

The Subcommittee believes that physicians should be judicious in selection of older patients for thrombolytic therapy since the two trials are not congruent in magnitude and statistical significance of observed differences. However, they are congruent in the direction of differences. A recent report (Anderson JL et al., *Circulation* 1990, Suppl III:III-431) reaffirms the caution needed in thrombolysis in patients over 75.

Drs. Sherry and Marder are correct that absolute benefit

appears to increase with increased age, but so also does the burden of chronic illness and probably the risk associated with thrombolytic therapy. Thus, the selection of older patients with myocardial infarction for thrombolytic therapy should be done cautiously. The guidelines do give permissive recommendation for thrombolysis in patients between 70 and 75 years (class IIa) and patients over 75 (class IIb) rather than the firm recommendation of class I. The Subcommittee continues to feel this recommendation appropriate and perhaps Drs. Sherry and Marder have misinterpreted the grading of recommendations used in these guidelines.

REBUTTAL TO SUBCOMMITTEE RESPONSE

Dr. Gunnar on behalf of the Subcommittee implies that we are responsible for misinterpreting their report. However, their response does not adequately address the issue we raised. The Subcommittee report stated that there is an attenuation of the effect of thrombolytic therapy in the older age group based on an analysis of the GISSI 2 and ISIS 3 data. Proper analysis of these data, as we pointed out, shows that there is no attenuation of mortality reduction in the aged based on the GISSI 2 and ISIS 3 data and, if anything, there is a strong trend toward a greater mortality reduction in this group. It is surprising that the Committee continues to beg the question of the use of thrombolytic therapy in the aged rather than simply correcting their error. Regardless of the presence of chronic illness and the usual cautions associated with thrombolytic therapy, patients should not be denied the mortality benefits of thrombolytic therapy because of age.

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