

CHAPTER 13
STUDY END POINTS

13.1 INTRODUCTION

The Thrombolysis in Myocardial Ischemia Trial (T3) is designed a) to evaluate the effect of t-PA on coronary angiographic findings (i.e., degree of stenosis and coronary blood flow) in patients with unstable angina and non-Q-wave MI and b) to study the comprehensive management of unstable angina and non-Q-wave MI.

13.2 T3A

T3A will determine whether t-PA produces improvement in angiographically determined coronary artery blood flow or stenosis.

13.2.1 Primary End Points

The primary end point will be the number of patients with a successful result of therapy, defined as either an improvement in TIMI perfusion by two grades (from 0 to 2 or 3, or from 1 to 3) or a 10% absolute reduction in the severity of stenosis (e.g. a reduction from 70 to 60% stenosis) without the need for emergency revascularization in the period between the initial and follow-up angiograms. The improvement in perfusion and reduction in stenosis will be based on a comparison between the initial angiogram and the followup angiogram obtained 18 to 48 hours later with regard to the severity of the presumed culprit lesion. Lesions will be measured by quantitative arteriography performed by the Quantitative Angiography Core Laboratory. Patients in whom culprit lesions cannot be identified on the basis of the initial ECG and angiographic findings will be analyzed separately for changes in any vessel from the first to the second angiogram.

13.2.2 Secondary End Points

These will include

1. Disappearance of intracoronary filling defects considered to represent thrombi. An estimate will be made of the percent change in obstruction due to thrombus as opposed to the percent change in obstruction caused by thrombus and plaque combined.
2. Death, recurrent ischemia and MI occurring between the time of randomization and hospital discharge, six weeks and one year.

Study criteria for documentation of post randomization nonfatal myocardial infarction are presented in Exhibit 13-1.

3. The incidence of hemorrhagic complications.

13.3 T3B

T3B will determine the optimal initial and follow-up management strategy: Initially, is the addition of t-PA superior to conventional therapy (including heparin)? In follow-up, is there a need for routine angiography followed, if the anatomy is suitable, by revascularization?

13.3.1 Primary End Points

The primary end point of the t-PA versus placebo comparison, to be evaluated at six weeks after randomization, will be the number of patients experiencing an unfavorable outcome--death, post-randomization MI (recurrent MI in the initial non-Q-wave infarction group), or failure of initial therapy, the latter defined below. (Disabling stroke will be recorded as a side effect of therapy.)

The primary end point of the invasive versus conservative strategy, to be evaluated at six weeks after randomization, will be the number of patients experiencing death, post-randomization MI, or an unsatisfactory outcome prior to completion of Stage II on the six-week symptom-limited standard Bruce protocol ETT defined as follows:

1. Ischemic pain before completion of Stage II.
2. ≥ 2 mm of ischemic ST-segment deviation from baseline with or without symptoms before completion of Stage II.
3. A hypotensive response (reduction in systolic pressure of more than 10 mm Hg from baseline or a prior recording during the ETT) before completion of Stage II.

13.3.1.1 Failure of Initial Therapy

Initial therapy may fail to control spontaneous ischemia or may leave the patient with significant evidence of provokable ischemia. Spontaneous ischemia may occur at any time from enrollment to the six-week follow-up visit. Provokable ischemia will be assessed at the time of the predischarge ETT with thallium and after discharge according to the response to medical therapy. (Patients in the no early routine angiography group who fail medical therapy should undergo angiography when initial therapy fails.)

1. Failure to control spontaneous ischemia is defined as one of the following:
 - a. Occurrence of a single episode of rest ischemic pain accompanied by at least one of the following:
 - (1) Ischemic pain lasting at least five minutes, with marked changes on ECG (at least 2-mm ST-segment elevation or depression in two or more contiguous leads documented on a standard 12-lead electrocardiogram).
 - (2) Single episode of ischemic pain lasting at least 20 minutes, with:
 - a) ST-elevation/depression ≥ 1 mm in ≥ 2 contiguous leads; or
 - b) T-wave inversion in ≥ 2 contiguous leads.
 - b. Occurrence of two or more episodes of ischemic pain occurring at rest and lasting at least five minutes with:
 - a) ≥ 1 mm ST-elevation/depression in ≥ 2 contiguous leads; or T-wave inversion in ≥ 2 contiguous leads.
 - c. More than 20 minutes of ischemic ST-segment depression on the day 3 to 5 Holter monitor recording.
2. Failure to minimize provokable ischemia is defined as follows:
 - a. An unsatisfactory result on the obligatory predischARGE stress thallium ETT (persantine thallium if patient cannot exercise), defined as the occurrence of any one of the following:
 - (1) Ischemic pain occurring before completion of Stage II of the modified Bruce ETT.
 - (2) ≥ 2 mm of ischemic ST-segment deviation from baseline with or without symptoms before completion of Stage II of the modified Bruce ETT.
 - (3) A hypotensive response (reduction in systolic pressure of more than 20 mm Hg from control) before completion of Stage II of the modified Bruce ETT.
 - (4) Significant thallium abnormalities.
 - (i) Increased lung uptake (indicative of decreased left ventricular function) with one region of reversible hypoperfusion.
 - (ii) Two or more regions with reversible hypoperfusion.

- b. Unstable angina with rest pain sufficient to justify rehospitalization or moderate to severe angina (Canadian Class III or IV) after hospital discharge despite maximal medical therapy.

13.3.2 Secondary End Points

These will include:

1. The components of the primary end point evaluated independently at hospital discharge and at one year.
2. The presence of coronary artery thrombi and degree of obstruction, in those undergoing routine (and urgent) angiography.
3. The sum of mortality, confirmed MI, disabling stroke, and the need for revascularization (or additional revascularization) at one year (determined by telephone contact).
4. Development, prior to hospital discharge, of ischemic chest pain (with documented ECG changes confirmed by ECG core lab) not severe enough to qualify as failure of initial therapy.
5. Symptomatic, electrocardiographic, or thallium evidence of ischemia induced during exercise testing carried out at the time of hospital discharge but not severe enough to qualify as failure of initial therapy.
6. Holter evidence of ischemia not sufficient to qualify as failure of initial therapy. The number of episodes of ST-segment depression or elevation ≥ 1 mm that lasts more than one minute and are separated from prior episodes by more than one minute will be compared.
7. Hemorrhagic complications.

EXHIBIT 13-1

THROMBOLYSIS IN MYOCARDIAL ISCHEMIA (T3)

Mortality and Morbidity Classification Committee
Criteria for Nonfatal Myocardial Infarction (NFMI)

Thrombolysis in Myocardial Ischemia (T3) patients are distinguished as unstable angina (UNA) patients and non-Q myocardial infarction in progress (MIP) patients according to their presentation and first enzyme measurements. Unstable angina patients will not have enzymes meeting study criteria for myocardial infarction at baseline (0 hours) or at any time less than 12 hours after study entry. Patient without pain between study entry and the collection of creatine kinase (CK) specimens at 12-hours, but enzymes meeting criteria for non-Q myocardial infarction only on the 12-hour serum specimen, will be assigned MIP status. Other MIP patients will have enzymes meeting study criteria for non-Q myocardial infarction at baseline (0 hours) or on the 4-hour specimen. Depending upon subsequent events - new or more intense chest pain of sufficient duration, new ECG findings and abrupt increases in CK and CK MB - MIP patients may also be classified as having outcome myocardial infarctions on the basis of findings at 12-hours.

<u>UNA/MIP Status</u>	<u>Enzyme Measurements</u>		
	BL	4-Hour	12-Hour
UNA	-	-	-
MIP*	-	-	+
MIP	-	+	-
MIP*	-	+	+
MIP	+	-	-
MIP	+	+	-
MIP*	+	-	+
MIP*	+	+	+

*Also possible outcome MI depending upon degree of elevation of enzymes and ECG findings after 12 hours.

The criteria for establishing the occurrence of a myocardial infarction after study entry are defined below.

A. Enzyme Changes

Creatine kinase (CK) is collected routinely over the first three days (at 0, 4, 12, 24, 48 and 72 hours) of enrollment, and on indication (usually pain) thereafter.

- 1) If CK MB or CK are greater than two times the upper limit of normal, and 25% increase over the previous value. Qualitative CK MB must be positive when available, and CK MB takes precedence over CK.
- 2) If CK MB or CK are less than two times the upper limit of normal, and 50% increase over the previous value, and must exceed the upper limit of normal by at least 50%. Qualitative CK MB must be positive when available, and CK MB takes precedence over CK.
- 3) If coronary artery bypass graft surgery is performed, for a twenty-four-hour period starting at the time of surgery, the CK MB or CK must exceed the upper limit of normal by at least five fold.

or

B. ECG

- 1) Major, new Q-waves in at least two or more leads.

or

C. Committee Vote

- 1) Failing independent classification by two MMCC members according to Enzyme or ECG Criteria, a simple majority vote of MMCC members (chairman casts tie breaking votes) at a meeting of the MMCC as a whole.

All classified cases will have a written note declaring the reasons for classification or rejection of classifications as NFMI. Patients for whom a laboratory error is suspected by an MMCC member will be reviewed in committee.

THROMBOLYSIS IN MYOCARDIAL ISCHEMIA

MANUAL OF OPERATIONS

TABLE OF CONTENTS

CHAPTER		PAGE
13	STUDY END POINTS	
13.1	Introduction	13-1
13.2	T3A	1 3 - 1
	13.2.1 Primary End Points	13-1
	13.2.2 Secondary End Points	1 3 - 2
13.3	T3B	13-2
	13.3.1 Primary End Points	13-2
	13.3.1.1. Failure of Initial Therapy	13-3
	13.3.2 Secondary End points	13-5
EXHIBIT 13-1	Criteria for Nonfatal Myocardial Infarction (NFMI)	13-6