CHAPTER 4

# T3B PROTOCOL

## THE COMPREHENSIVE MANAGEMENT OF UNSTABLE ANGINA AND NON-Q-WAVE MI: THE ROLES OF T-PA AND REVASCULARIZATION

### 4.1 INTRODUCTION

The specific aim of this protocol is to study the comprehensive management of unstable angina and non-Q-wave MI. Patients will be randomly assigned to t-PA or placebo therapy (in addition to conventional therapy) and to two approaches to follow-up therapy: routine early angiography with revascularization if indicated (Invasive Strategy) versus angiography with revascularization only after failure of initial therapy (Conservative Strategy).

The study will be double-blinded for t-PA therapy. Analysis of objective end points will also be blinded.

During an initial 90-minute phase, patients will receive an infusion of t-PA or placebo, depending on the assigned therapy.

Patients within each of the two treatment groups will also be randomized to undergo routine early angiography (within 18 to 48 hours of treatment) with PTCA and/or CABG if indicated or to undergo angiography only upon failure of initial therapy.

Outcomes in the therapy groups will be analyzed by means of methods traditionally utilized for a factorial design. Attention will be paid to possible antagonistic and/or synergistic interactions.

The primary end point for the comparison of t-PA with placebo, to be assessed six weeks after randomization, will be the number of patients experiencing death, post-randomization infarction, or failure of initial therapy (see Section 4.7.1).

The primary end point for the comparison of the Invasive Strategy with the Conservative Strategy, to be assessed at six weeks after randomization, will be the number of patients experiencing death, post-randomization infarction, or an unsatisfactory ETT result at six weeks (see Section 4.7.1.2).

### 4.2 PATIENT POPULATION

A log will be maintained of all patients with a diagnosis of unstable angina or rule out myocardial infarction admitted to the Coronary Care Unit(s), telemetry units, or other specialized care units of the participating institution. The inclusion and exclusion criteria will be noted.

## 4.3 ELIGIBILITY CRITERIA

Since prospective classification of patients with non-Q-wave MI as distinct from those with unstable angina is often impossible, the eligibility criteria (inclusion criteria plus exclusion criteria) will be the same for the two conditions.

### 4.3.1 Inclusion Criteria

All patients who have experienced an episode of rest pain, presumed to be ischemic in origin and lasting five or more minutes (but no longer than six hours) which was present within the 24* hours prior to the time of enrollment, will be evaluated for enrollment in the study. Patients may be eligible if pain is present within the 24 hours prior to enrollment. Pain need not start within the 24-hour period.

In addition, the patient must have evidence of coronary artery disease. Such evidence may consist of one of the following:

1. New or presumably new ECG evidence of myocardial ischemia in a standard 12-lead ECG obtained during any attack of pain within 24 hours before enrollment or new enzyme evidence of non-Q-wave MI (see below). This may consist of transient or persistent ST-segment depression of at least 0.10 mV (0.80 seconds after the J-point) in two or more contiguous leads, OR transient or persistent T-wave inversion in two or more contiguous leads, OR transient (< 30 minutes in duration) ST-segment elevation of at least 0.10 mV in two or more contiguous leads. "New" ST-segment or T-wave changes are defined as those not present on an ECG recorded during the year prior to the qualifying episode of pain. (If a previous ECG is not available, ST-segment or T-wave changes noted on recordings obtained prior to randomization that can be ascribed to no other cause [e.g., digitalis, electrolyte disturbance] will be considered "presumably new.") ECG changes persisting after the termination of ischemic pain may be used as "new" changes.

   Patients may qualify for T3B with a known non-Q-wave MI evidenced by elevated enzymes within the 24-hour period prior to enrollment, providing the qualifying episode of rest pain occurred during the same 24-hour period.

2. New or presumably new ECG evidence of myocardial ischemia obtained during the presenting illness, but more than 24 hours before enrollment in T3. The ECG evidence should be obtained no more than seven days prior to enrollment. ECGs obtained during an episode of pain associated with ST-T-wave deviation (as described above), occurring at a referring hospital or physician's office within the seven days prior to enrollment may be used as evidence of coronary artery disease provided a legible copy of the ECG is available.

3. Coronary artery disease confirmed by a documented prior myocardial infarction, or at least 70% luminal diameter narrowing of a major coronary artery on a prior coronary

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*Prior to the November 11, 1990 protocol modification, the qualifying episode of pain had to be present within the 12 hours prior to enrollment. Qualifying ECGs also had to be from this same 12-hour period.

angiogram, or a positive exercise thallium test, defined as the presence of both of the following criteria:

1) ≥ 1 mm ST segment depression during exercise or recovery compared to baseline, and
2) the presence of at least one definite reversible thallium or Sesta-MIBI perfusion defect.

4.3.2 Exclusion Criteria

Patients who fulfill the above inclusion criteria but who manifest any of the following exclusion criteria at the time of randomization will not be eligible for the study.

1. Pain radiating to the back or having other characteristics suggestive of aortic dissection.

2. Constant ischemic pain of more than six hours duration.

3. Age ≥ 76* years or < 21 years.

4. Left bundle branch block.

5. New or presumably new ST-segment elevation of at least 0.10 mV in two or more contiguous leads not reverting to < 0.10 mV within 30 minutes of administration of therapy (e.g., nitroglycerin).

6. A treatable cause for angina pectoris--e.g., arrhythmia, severe anemia, hypotension, or hyperthyroidism.

7. Acute pulmonary edema (rales heard over more than two-thirds of the lung fields that do not clear with cough).

8. Other major illness--e.g., a major infection; active cancer within the past five years; active severe hepatic disease; hemodynamically significant valvular, myocardial, or congenital heart disease; or renal failure with serum creatinine > 3 mg/ml.

9. A documented MI (CK-MB greater than normal, if available, or total CK greater than two times the upper limit of normal; MB takes precedence over total CK) within the past 21 days (excluding suspected infarction within 24 hours of enrollment).

10. Systolic arterial blood pressure less than 90 mm Hg on at least two recordings obtained 15 minutes apart.

11. Inability to cooperate with the protocol.

12. A female of childbearing potential.

13. PTCA within the previous six months.

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*Prior to the November 11, 1990 protocol modification, the upper limit of the exclusion criteria for age was ≥ 76 years. On November 11, 1990 the upper limit of the exclusion criteria was changed to ≥ 80 years. On November 11, 1991 the upper limit was changed back to ≥ 76 years.

14. Prior coronary artery bypass surgery.

15. Oral anticoagulation therapy at the time of initial enrollment.

16. Coronary arteriography within the prior 30 days.

17. Heparin allergy or intolerance.

18. Thrombolytic therapy within prior 72 hours.

19. Contraindications to thrombolytic therapy:

    a. Past or present bleeding disorder or active bleeding.

    b. Any confirmed recording of systolic blood pressure exceeding 180 mm Hg, diastolic blood pressure exceeding 110 mm Hg on two measurements during the presenting illness prior to randomization and prior to the administration of a blood pressure lowering drug (e.g., NTG, calcium antagonist, or vasodilator), or uncontrolled hypertension at any time prior to entry (diastolic blood pressure > 110 mm Hg on several measurements).

    c. Any history of cerebrovascular disease, including any form of stroke and/or transient ischemic attack.

    d. Prolonged cardiopulmonary resuscitation with one minute or more of external cardiac massage within the last two weeks.

    e. Severe trauma within the prior six months.

    f. History of parenteral or other drug abuse.

    g. Significant surgical procedure within the last two months.

    h. Active peptic ulcer disease within the past six months.

    i. Invasive procedure (or lithotripsy) within the preceding 14 days that would significantly increase the risk of hemorrhage, such as biopsy, cardiac catheterization, or unsuccessful central venous puncture.

    j. Probable pericarditis.

4.3.3 Consent

Prior to enrollment, informed consent will be sought from the patient and the attending physician. A draft copy of a standardized consent form will be provided to all Clinical Centers. This form, or a modification based on the local Institutional Review Board recommendations, will be completed for all enrolled patients.

4.3.4 Conventional Therapy

4.3.4.1 General Measures

All patients enrolled in the study will receive standard CCU care, including bed rest and oxygen.

4.3.4.2 Heparin

The goal is to administer intravenous heparin therapy to maintain the APTT in the range of 1.5 to 2 times the normal recorded when the patient was not receiving heparin. If the patient is already receiving heparin at the time of enrollment, the prior dosage should be continued, the APTT determined and the dosage adjusted according to the guidelines presented below. If at all possible, heparin therapy should be started before study treatment. If heparin therapy has not been started prior to study treatment, it should be started as soon as possible and within one hour of the start of study treatment, in a bolus of 5,000 IU intravenously followed by an infusion at the rate of 1,000 IU per hour to be adjusted by APTT values (determined eight hours after the initial heparin bolus; determined three hours after a change in heparin dosage; and every 12 hours on maintenance therapy) to a level 1.5 to 2 times the patient's normal. Changes in heparin dosage should be managed as follows:

| APTT | Adjustment |
|---|---|
| > 3x control | Decrease infusion rate by 50% |
| 2-3x control | Decrease by 25% |
| 1.5-2x control | No change |
| < 1.5x control | Increase rate of infusion by 25% to a maximum rate of 2,500 units/hour |

Four hours prior to the angiogram for which an arterial puncture must be performed, the heparin dosage should be reduced to 50% of the maintenance level. After the arterial sheath has been placed, a 5,000 IU dose of heparin should be administered intravenously and the full maintenance dose resumed 1 hour after the bolus. Heparin will be discontinued 72 hours after treatment unless other clinical indications warrant earlier termination or continued administration. Measurements of platelets, hemoglobin and hematocrit should be obtained every 24 hours while patient is on maintenance heparin therapy.

4.3.4.3 Anti-ischemic Therapy

At the time of enrollment, therapy with a beta-adrenergic blocking agent, a calcium channel blocker and a nitrate preparation should be initiated, if not already being given. If the patient was receiving and tolerating an agent from these classes of drugs prior to enrollment, the same agent and dosage should be continued. If the patient was not receiving an agent from each of these classes, and the clinical situation permits, the following agents should be given. (Starting doses are indicated.) Dosage should be adjusted as deemed necessary according to the patient's tolerance.

| | | |
|---|---|---|
| Beta-adrenergic blockade | - | Metoprolol 50 mg po q 12 h |
| Calcium Channel blockade | - | Diltiazem 30 mg po q 6 h. Diltiazem should not be given if evidence of left ventricular dysfunction is present. |

Nitrate therapy - Isosorbide dinitrate 10 mg po q 8 h. Sublingual TNG prn.

(NOTE: Diltiazem has been selected as the calcium antagonist for conventional therapy because it is the only agent in this class reported to reduce the incidence of reinfarction. Metoprolol has been selected based on evidence that it is beneficial for the therapy of acute MI.)

If ischemic symptoms occur after enrollment, the dose of the above agents should be increased as clinically indicated. Intravenous nitroglycerin is not to be used as routine initial therapy for unstable angina or non-Q-wave infarction. It may be continued if required prior to enrollment, and initiated if clinical indications develop after enrollment. Intra-aortic balloon counterpulsation should not be utilized unless patients develop symptoms refractory to the above-mentioned therapy.

The above-mentioned anti-ischemic therapy should be continued until completion of the six-week evaluation. Conventional therapy after revascularization will be at the discretion of the investigator.

#### 4.3.4.4 Aspirin

Aspirin will not be administered during the first 24 hours after treatment and possible t-PA therapy. (All patients will receive heparin during this period.) On day two it will be administered orally in a dose of 325 mg. daily and continued by protocol until the six-week follow-up. The Ecotrin preparation of aspirin will be utilized for the 325 mg dosage. If the patient is unable to take aspirin, the treating physician should direct oral anticoagulant therapy.

## 4.4 EXPERIMENTAL TREATMENT GUIDELINES

### 4.4.1 Initial Therapy

Patients will be randomly assigned to placebo or t-PA as well as Invasive or Conservative Strategy by use of sealed, sequentially numbered envelopes. After enrollment, patients will be treated with t-PA or placebo. Treatment must begin within one hour after enrollment, i.e., within 25 hours of the presence of ischemic pain. The total dose of t-PA will be 0.8 mg/kg (not to exceed 80 mg). One-third of the total dose will be given initially as an intravenous push bolus (not to exceed 20 mg). The remaining two-thirds of the total dose will be given intravenously over 90 minutes.

### 4.4.2 Discontinuation of Experimental Therapy and Unblinding

If at any time during the study the physician responsible for the clinical care of the patient decides that t-PA therapy is contra-indicated, administration of the experimental agent will be stopped. The study will remain blinded, unless continued blinding is also considered to be detrimental to optimal clinical care. For instance, if the patient develops fixed ST-segment elevation, it may be clinically important to know if the patient had received t-PA in the preceding hours. Unblinding will be accomplished by opening the unblinding envelope matching the treatment kit number for the patient. (Documentation of reasons for discontinuing the experimental agent and for unblinding will be required.) The determination that an MI was in

progress at the time of enrollment, which is expected in many of the patients, will not by itself be an indication for alteration of the protocol. Routine determination of fibrinogen and FDP levels in an attempt to determine whether the patient received t-PA should not be performed. It is expected that unblinding will be a rare occurrence. It should be avoided if possible, since it complicates analysis of study results.

### 4.4.3 Follow-up Experimental Therapy

In addition to being randomized to initial therapy, patients will also be randomly assigned to undergo routine early angiography or no routine early angiography. This assignment will be made at the time of enrollment.

#### 4.4.3.1 Routine Early Angiography and PTCA/CABG

Routine early angiography will be carried out 18 to 48 hours after patients are randomly assigned to this procedure and treated. Emergency angiography may be carried out in this group between the end of the initial 90-minute infusion and before 18 hours, if initial therapy fails (see Section 4.7.1, Failure of Therapy). Following angiography, patients will be treated with a revascularization procedure for significant coronary obstruction considered to be responsible for the presenting symptoms. Selection of the revascularization technique will be based on the standardized guidelines given below. PTCA will be performed at the time of angiography, or as soon as possible after initial angiography and before six weeks. CABG will be performed as soon as feasible and before six weeks.

Patients randomized to angiography will undergo diagnostic cardiac catheterization. This will include left heart catheterization, left ventricular cineangiography, and selective coronary cineangiography. Angiographic technique and projections will be standardized (see Chapter 18, Qualitative Angiographic Core Laboratory Procedures, of Volume I of the T3 Manual of Operations. When catheterization is performed, provision should be made for surgical standby for situations in which angioplasty may be performed.

Once catheterization is completed, angiograms will be reviewed immediately to determine the presence of significant coronary artery stenosis (> 60% reduction in luminal diameter). If significant stenoses are present, the investigator will attempt to determine which coronary arterial system is most likely to be responsible for the acute ischemic syndrome. This judgment will be based upon both angiographic and clinical findings in an attempt to identify the acute ischemia-related artery (the culprit lesion). Based on this identification, the extent of coronary disease, the degree of left ventricular dysfunction and the guidelines presented below, a decision will be made about whether to proceed with PTCA, coronary artery bypass grafting (CABG), or to continue medical therapy. The lesions to be revascularized and the choice of PTCA versus CABG are at the discretion of the T3 Principal Investigator (or his designate), but the lesion(s) suspected of being responsible for the patient's current symptoms must be included among the lesions to be revascularized. The T3 Principal Investigator will be guided in his decision by the descriptions of "Specific Situations," "Exclusion Criteria for PTCA," and "Conditions for Which CABG is Recommended" given below.

For patients undergoing PTCA, a view in which the lesion is optimally seen and a complementary view (not necessarily orthogonal) should be obtained. The proximal and distal segments of the arteries being dilated should be visible so that perfusion grade can be adequately evaluated.

A. Specific Situations

Several specific situations described below will be encountered. For situations not described below, the T3 Principal Investigator will make decisions based on the review of all pertinent information.

1. Single-vessel disease

If single-vessel disease is present, and the diseased vessel is the culprit lesion, PTCA will be performed if the stenosis is suitable for the technique (refer to Table 1 on page 4-9 for exclusion criteria for PTCA). If the stenosis is probably not the culprit lesion, or if the stenosis is not amenable to PTCA, medical therapy will be continued. CABG will be performed only if: 1) the single diseased vessel is the left main coronary artery; 2) unstable angina recurs despite PTCA; or 3) significant symptoms occur despite optimal medical therapy and the stenosis is not amenable to PTCA (refer to Table 2 on page 4-9).

2. Multivessel Disease

If multivessel disease is present, and one or more lesions can clearly be identified as the culprit lesion(s), PTCA of the lesion(s) will be done, if the anatomy is suitable. If a culprit lesion is not suitable for PTCA, CABG will be done. PTCA of other significantly stenosed major arteries will be performed at the discretion of the certified T3 investigator in an attempt to maximize the relief of ischemia while minimizing the risk of procedure-related untoward effects.

TABLE 1

EXCLUSION CRITERIA FOR PTCA

1. Presence of unprotected left main lesion $\geq$ 50% diameter reduction.
2. Sustained occlusion of artery to be dilated would predictably result in hemodynamic collapse.
3. Three-vessel disease with reduced LV function (EF < 0.40).
4. The lesion considered for dilatation is either known to have caused chronic (> 12 weeks) total occlusion, to be long (> 10 mm in length of at least 60% narrowing), to be located in the distal portion of a vessel, to be sharply angulated, to be associated with large thrombus, to be located in a vessel with excessive proximal tortuosity, to be associated with a significant unprotectable side branch, or the normal vessel diameter adjacent to the site of the stenosis is < 1.5 mm.

TABLE 2

CONDITIONS FOR WHICH CABG IS RECOMMENDED

1. Presence of significant ($\geq$ 50%) left main lesion.

2. Presence of three-vessel disease plus depressed LV function (EF < 0.40).

3. Presence of multivessel disease with at least two significantly diseased vessels (culprit or non-culprit lesions) supplying viable myocardium, with neither being suitable for PTCA.

4. Recurrent severe symptoms despite medical therapy in a patient not a suitable candidate for PTCA.

5. Patients with intractable angina following PTCA.

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Patients randomized to the Invasive Strategy whose angiographic findings alone do not justify revascularization may undergo revascularization if the combination of angiographic findings plus subsequent failure of initial therapy warrants such a course.

#### 4.4.3.2 No Routine Early Angiography (Conservative Strategy)

In patients randomized to no routine early angiography (the Conservative Strategy), angiography will be carried out only upon failure of initial therapy, a component of the primary end point for the t-PA vs placebo comparison of the study (see Section 4.7.1). The definition of "failure of initial therapy" applies only to events occurring after the completion of the 90-minute infusion of t-PA or placebo. If and when failure of initial therapy occurs, a component of the primary end point for comparison of t-PA vs placebo has been reached and angiography is indicated. Failure of initial therapy serves only as an indication for angiography for patients randomized to the Conservative Strategy. It is not an end point for the comparison of Invasive vs Conservative Strategies. After angiography (and revascularization, if indicated), conventional therapy as described above should be continued.

### 4.5 METHODS OF MONITORING DURING HOSPITALIZATION

The response to the assigned regimen will be assessed based on the following observations and tests. All observations and tests will be timed from the start of study drug treatment. This includes measurements for enzymes, special coagulation parameters, platelet function studies, and the cardiac catheterization (if randomized to the invasive strategy). The APTT, however, should be timed from the start of heparin infusion if the patient was not previously on heparin.

#### 4.5.1 Clinical Observations

During hospitalization, all patients will undergo standard monitoring for acute ischemic syndrome. This includes measurement of vital signs every six hours, recording of episodes of ischemic pain, and recording of ECG's for all episodes of presumed ischemic pain. A single ECG obtained when ischemic pain is absent (Baseline ECG) will also be recorded to serve as a non-ischemic baseline tracing. If the patient develops failure of therapy with recurrent ischemic pain, this ECG together with the baseline ECG should be sent to the ECG Core Laboratory. An ECG should be obtained within three days of hospital discharge and forwarded to the ECG Core Laboratory. These observations and measurements will be made by the individuals responsible for the clinical care of the patients.

4.5.2 CK-MB Sampling to Detect Infarction

Infarction prior to initial randomization will be detected by CK-MB levels in serum samples obtained at the time of randomization and four hours later. A post-randomization myocardial infarction (a new infarction in patients with unstable angina or recurrent infarction in the subgroup of patients with ongoing infarction at randomization) will be identified by the levels of CK-MB in samples obtained. Blood samples will be obtained in all patients at treatment initiation, and at 4, 12, 24, 48 and 72 hours following treatment initiation. CK-MB will be measured every eight hours for 24 hours when pain recurs or after coronary artery bypass graft surgery. CK-MB greater than normal, if available, or total CK greater than two times the upper limit of normal will be considered enzymatic evidence of infarction. CK-MB will take precedence over total CK.

4.5.3 24-Hour Holter Monitoring to Detect Ischemia

One continuous period of 24-hour Holter monitoring will be performed. The Holter should be performed (started) three to five days (window 60 -120 hours) after the start of treatment and prior to revascularization, if possible. A continuous recording of at least 18 hours should be obtained to detect the presence of symptomatic and asymptomatic myocardial ischemia.

Results of the Holter ST-segment analysis will be returned to the Clinical Center within 48 hours of receipt at the Holter Core Laboratory and will therefore be available to the Clinical Center to guide management. Patients with 20 minutes of ischemia by Holter should undergo angiography, even if no other signs of failure of therapy occur. For patients in whom the Holter cannot be performed prior to revascularization, it should be performed as soon as feasible after revascularization. For PTCA patients, it should be performed from two to four days after the procedure, and, for CABG patients, within two days after discharge from the surgical intensive care unit.

4.5.4 Predischarge Submaximal Exercise Tolerance Test (ETT) with Thallium

An ETT with thallium will be used to assess the presence of significant provokable ischemia in patients who are able to exercise, including those who have undergone CABG. In patients who cannot exercise, a persantine thallium test will be performed. Substitution of the persantine thallium for the exercise thallium should be avoided, if possible, because the persantine stress is greater than the submaximal ETT. In unusual cases in which a technical problem precludes obtaining the thallium images, the ETT with clinical and ECG end points should still be obtained. A bicycle test is not a suitable alternative to the treadmill test.

Timing - The test should be performed within the three days prior to anticipated hospital discharge. In patients who develop an indication for revascularization, it should be performed after the revascularization procedure. If the patient is discharged prior to the ETT, the test should be performed as an outpatient within five days of hospital discharge.

The modified Bruce protocol has two additional stages, stage 0 and stage 1/2. The patient should be started at stage 1/2 whenever pos-

sible; however, in the rare case where the patient's exercise tolerance is markedly diminished, the patient may be started at stage 0.

Bruce Protocol

| | MPH | Grade |
|---|---|---|
| Stage 0 | 1.7 | 0% |
| 1/2 | 1.7 | 5% |
| 1 | 1.7 | 10% |
| 2 | 2.5 | 12% |
| 3 | 3.5 | 14% |
| 4 | 4.2 | 16% |
| 5 | 5.0 | 18% |
| 6 | 5.5 | 20% |
| 7 | 6.0 | 22% |

Patients will cease exercise when an end point occurs (see Section 4.7) or Stage II of the modified Bruce protocol is completed. Patients with an unsatisfactory clinical or electrocardiographic response to exercise or with significant thallium defects (see Section 4.7) will be considered to have failed initial therapy. Those in whom angiography was not performed prior to failure of initial therapy should then undergo angiography. The clinical decision as to whether the ECG or thallium response was unsatisfactory will be made in the clinical unit in order to guide therapy; the ECG/ETT Core Laboratory and the Thallium Core Laboratory will subsequently confirm that results of the test indicated failure of therapy.

### 4.5.5 Hematologic Monitoring

Blood samples to be analyzed by the Coagulation Core Laboratory will be drawn at the following times: (1) immediately prior to treatment initiation (Time 0), (2) at 50 minutes, (3) 12 hours, (4) 24 hours, (5) 48 hours and (6) 96 hours following treatment initiation. If the patient will be discharged prior to 96 hours, a sample may be obtained at the time of discharge. The Core Laboratory will analyze the samples for fibrinogen, FDP's, d-Dimer, and heparin activity. The total volume of blood drawn will be 150 cc (25 cc per drawing).

## 4.6 FOLLOW-UP AFTER HOSPITAL DISCHARGE

Following discharge from the hospital, patients randomized to the Conservative Strategy will be managed without angiography for at least six weeks unless initial therapy fails, as defined in Section 4.7.1. All patients will continue with conventional medical therapy as described in Section 4.3.4. If ischemic pain occurs, the medical regimen should be intensified as tolerated.

During the period from hospital discharge to six weeks after randomization, patients will be monitored for the occurrence of angina despite optimal medical therapy. Optimal medical therapy will be determined by the treating physician but should include treatment with a nitrate preparation, a beta-blocker and diltiazem, if not contraindicated. Angina of the following severity will be considered a component of failure of initial therapy:

1. Unstable angina with rest pain sufficient to warrant rehospitalization.

2. Exertional angina (Canadian Cardiovascular Society Classification III or IV, refer to Section 4.6.1 for definitions) on optimal medical therapy with documented ischemia during a submaximal ETT. The ETT should not be performed if rest angina had occurred as an outpatient. The ETT should be terminated at the end of Stage II. Ischemic pain, $\geq$ 1 mm ST-deviation or a hypotensive response will be considered signs of ischemia. The results of this ETT should be sent to the ECG Core Laboratory.

Angina of Canadian Cardiovascular Society Classification I or II (refer to Section 4.6.1 for definitions) is not considered failure of initial therapy. Such patients should be continued on medical therapy until the six-week follow-up examination. At that time, the symptom-limited ETT can be performed to determine optimal management.

### 4.6.1 Definitions of Canadian Cardiovascular Society Classification

**Class I** - Ordinary physical activity (such as walking and climbing stairs) does not cause angina. Angina with strenuous or rapid or prolonged exertion at work or recreation.

**Class II** - Slight limitation of ordinary activity, such as walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; or in cold, in wind, or under emotional stress; or only during the few hours after awakening; or walking more than two blocks on the level; or climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

**Class III** - Marked limitation of ordinary physical activity, such as walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace. Comfortable at rest.

**Class IV** - Inability to carry on any physical activity without discomfort. . . .anginal symptoms MAY be present at rest.

Development of unstable angina or moderate to severe angina between hospital and the six-week follow-up evaluation is a component of the primary end point for the t-PA versus placebo comparison. It is an indication for angiography for patients randomized to the conservative strategy but not a component of the primary end point for the comparison of the invasive and conservative management strategies.

### 4.6.2 Six-week Follow-up and Exercise Test

All patients will undergo a symptom-limited ETT six weeks after randomization. This ETT will be an important component of the primary end point for comparison of Invasive and Conservative Strategies. At the six-week follow-up, history, review of events and medications, and major adverse outcomes (recurrent pain, MI, death and the need for angiography) occurring between the time of hospital discharge and the six-week follow-up visit will be recorded. The same outcomes will be evaluated by a telephone interview one year after randomization. The six-week ETT will be performed at the T3 certified Clinical Center, if

possible, or at the referring hospital, if necessary. A complete 12-lead ECG and all exercise ECG tracings and results will be forwarded to the T3 ECG Core Laboratory.

For patients who are physically unable to undergo a symptom limited exercise treadmill test at the six-week follow-up visit, all efforts should be made to have the patient undergo a persantine or adenosine thallium imaging test unless medically contraindicated.

## 4.7 DATA ANALYSIS

The principal 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 myocardial infarction (recurrent MI in the initial non-Q-wave infarction group), or failure of initial therapy. (Disabling stroke will be recorded as a side effect of therapy.)

The principal end point of the Invasive versus Conservative Strategies, 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. $\geq$ 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.

### 4.7.1 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 will undergo angiography when initial therapy fails.

#### 4.7.1.1 Spontaneous Ischemia

Failure to control spontaneous ischemia is defined as one of the following:

1. Occurrence of a single episode of rest ischemic pain accompanied by at least one of the following:

   a. 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);

b. Ischemic pain lasting at least 20 minutes, with documented ECG changes sufficient to satisfy inclusion criteria;*

2. Occurrence of two or more episodes of ischemic pain occurring at rest and lasting at least five minutes, with documented ECG changes sufficient to satisfy inclusion criteria;*

3. More than 20 minutes of ischemic ST-segment deviation on the day three to five Holter monitor recording.

4.7.1.2 Provokable Ischemia

Failure to minimize provokable ischemia is defined as follows:

1. 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:

   a. Ischemic pain occurring before completion of Stage II of the modified Bruce ETT;

   b. $\geq$ 2 mm of ischemic ST-segment deviation from baseline with or without symptoms before completion of Stage II of the modified Bruce ETT;

   c. A hypotensive response (reduction in systolic pressure of more than 10 mm Hg from baseline or a prior recording during the ETT confirmed on a second reading taken 15 seconds later) before completion of Stage II of the modified Bruce ETT;

   d. 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.

2. Unstable angina with rest pain sufficient to justify rehospitalization, or documented (in conjunction with ETT performance) moderate to severe angina (Canadian Cardiovascular Society Classification III or IV) after hospital discharge despite maximal medical therapy.

4.7.2 Determination of Failure of Initial Therapy

The initial determination that therapy has failed will be made by the investigator in each Clinical Center, who will review the evidence documenting failure of therapy obtained by the individuals responsible for the patient's clinical care. An exception to this procedure will be the initial determination of failure of therapy as judged by Holter monitoring. This determination will be made by the Holter Core Laboratory and communicated to the Clinical Center.

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*New ST-segment deviation of 0.1 mV or transient or persistent T-wave inversion in two contiguous leads.

Discrepancies will occur between investigator and Core Laboratory determination of failure of therapy. For operational purposes, the discrepancy rate for each Clinical Center will be closely monitored by the Data Coordinating Center and corrective measures taken. For purposes of analysis the data will be presented for both the Clinical Center and the Core Laboratory determination of failure of therapy.

4.7.3 Additional End Points

These will include:

1. Each of the components of the primary end point evaluated independently at hospital discharge and 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 post-treatment, 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 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 $\geq$ 1 mm that lasts more than one minute and are separated from prior episodes by more than one minute.

7. Hemorrhagic complications.

4.7.4 Retrospective Differentiation of Patients with Transient Ischemia from Patients with Ongoing MI at Treatment

The study will be conducted in patients who have experienced an episode of pain at rest, presumed to be ischemic in origin, within the 24 hours prior to enrollment. This population will include patients with unstable angina (transient ischemia) and patients with ongoing non-Q-wave infarction. The final decision as to whether myocardial infarction was present prior to treatment initiation will be made by the Data Coordinating Center on the basis of CK-MB isoenzyme activity in serum samples obtained at treatment initiation and at four hours after treatment initiation. These cardiac enzyme results will reflect the presence or absence of ongoing myocardial necrosis at the time of treatment initiation.

4.7.5 Subgroups for Analysis

For analysis, patients will be divided into three groups based on the time of occurrence of their pain and results of CK-MB measurements:

GROUP I: No pain within the 4 hours prior to treatment initiation (i.e, the qualifying pain occurred four to 24 hours prior to treatment initiation)

AND

No CK-MB elevation in blood samples obtained at treatment initiation and 4 hours after treatment initiation;

GROUP II: Pain within the 4 hours prior to treatment initiation

AND

No CK-MB elevation in blood samples obtained at treatment initiation and 4 hours after treatment initiation;

GROUP III: Pain at any time within the 24 hours prior to treatment initiation

AND

CK-MB elevation in at least one of the two samples.

Patients in Groups I and II will presumably be free of ongoing myocardial infarction at the time of treatment initiation. Exclusion of pre-treatment infarction will be most certain in Group I (i.e., no pain in the four hours prior to treatment initiation). In this group, lack of elevated CK-MB at the time of treatment initiation will reliably identify patients without infarction prior to treatment, since over four hours would have elapsed since the last episode of pain, and the biologic time delay for CK-MB to enter the blood stream would have elapsed prior to treatment initiation. In Group II (i.e., pain during the four hours prior to treatment initiation), CK-MB values may be somewhat less reliable as indicators of pre-treatment infarct status because therapy would be initiated after the occurrence of myocardial necrosis but before the appearance of CK-MB in the peripheral circulation. Analysis in this group must take into account the possibility that treatment might affect the CK-MB as a marker of myocardial necrosis. This will be determined by comparison of the CK-MB results among the various treatment groups. Group III patients, all of whom will have documented CK-MB elevation, will have primarily non-Q-wave infarction, since patients with new Q-waves and persistent ST-segment elevation are excluded from the study. The various end points will be analyzed in these three groups of patients.

Other subgroups for analysis will include (1) patients whose acute ischemic syndrome occurred despite prior aspirin therapy versus those whose disorder began without prior aspirin therapy, (2) the older half versus the younger half of the population, (3) those with symptom onset within one week versus those with symptom onset more than one week prior to enrollment, (4) males versus females, (5) those with, versus those without, a history of prior myocardial infarction, (6) those with ST-segment elevation versus those with ST-segment depression, (7) those with only T-wave inversion versus those with only ST-segment changes, (8) those with continued rest pain on maximal medical therapy prior to treatment initiation versus those without rest pain on maximal therapy, (9) those whose last episode of pain was within 4 hours of treatment initiation versus those with pain from 4 to 24 hours prior to treatment

initiation, (10) those with, versus those without, an angiographically visualized thrombus, and (11) patients who failed heparin therapy prior to treatment initiation.

### 4.7.6 Sample Size Considerations

It is expected that 2,000 patients will be randomized into the study, providing adequate power to detect significant clinical differences between 1) the use of t-PA versus placebo and 2) Invasive and Conservative Strategies of catheterization.

## 4.8 TIMETABLE

Randomization of patients began on September 30, 1989 and will continue until 2000 patients are enrolled or the Data and Safety Monitoring Board recommends recruitment be terminated earlier. As soon as possible after the end of recruitment, after collection of six-week data, results will be presented to investigators and prepared for publication.

# T3 MANUAL OF OPERATIONS

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