T3 MANUAL OF OPERATIONS

TABLE OF CONTENTS

CHAPTER 2

OBJECTIVES AND DESIGN OF THE TRIAL

2.1 Introduction

The Thrombolysis in Myocardial Ischemia (T3) Study consists of two multicenter, randomized controlled clinical trials in patients with unstable angina or non-Q-wave myocardial infarction. T3A will compare recombinant tissue plasminogen activator (t-PA) to placebo (administered double-blind) for improvement of coronary artery stenosis and perfusion. T3B will compare in a 2x2 factorial design, double-blind treatment with t-PA or placebo and management with or without cardiac catheterization (and percutaneous transluminal coronary angioplasty or coronary artery bypass surgery, if appropriate) at 18 to 48 hours after presentation.

These two studies will be conducted independently; results of one trial will not be used to decide if the other trial should be continued.

2.1.1 Patient Population

Patients eligible for T3 will be those who have experienced an episode of rest pain, presumed to be ischemic in origin, for five minutes or longer within the 24-hour period preceding study entry. The pain should be suggestive of pain that is cardiac in origin. In addition, the patients will have documented evidence of coronary artery disease. Chapter 7 of this Manual contains the specific inclusion criteria for entry into the T3 studies.

At the time of presentation patients with unstable angina and patients with evolving non-Q-wave myocardial infarction may be indistinguishable. Furthermore, both unstable angina and non-Q-wave myocardial infarction patients have residua of uninfarcted myocardium. Thus, both unstable angina and non-Q-wave myocardial infarction patients are appropriate for the treatments in T3. Creatine kinase myocardial band (CK-MB) enzyme activity assayed on specimens drawn at the time of patient enrollment and four hours after study entry will be used to distinguish patients experiencing non-Q-wave infarction from patients

experiencing unstable angina. This distinction between unstable angina and non-Q-wave myocardial infarction is important because the two conditions may differ in the likelihood of treatment benefit from t-PA, or cardiac catheterization, and may have different six-week event rates for the primary end points in T3B. However, at present, results of CK-MB enzyme activity can not be immediately obtained. The treating physician making use of T3 results will probably have to make the decision to use t-PA (should it prove to be efficacious) in the absence of knowledge about whether the event is a non-Q wave myocardial infarction or unstable angina. Thus, primary analyses of efficacy will focus on all enrolled patients rather than these two subgroups.

2.1.2 Primary Objective for the Thrombolysis in Myocardial Ischemia Trial A (T3A)

T3A will be conducted as a randomized, double-blind, controlled clinical trial assessing whether the administration of recombinant tissue plasminogen activator (t-PA) in conjunction with intravenous heparin and aspirin can improve the perfusion characteristics of an ischemia-related coronary artery more than heparin and aspirin therapy alone in patients with unstable angina or non-Q-wave infarction.

2.1.3 Primary Objectives for the Thrombolysis in Myocardial Ischemia Trial B (T3B)

The proposed T3B clinical trial will be conducted as a 2x2 factorial with random assignment of patients to t-PA or matching placebo infusion and to one of two approaches to follow-up therapy: angiography performed in the interval 18 to 48 hours with revascularization if indicated (Invasive Strategy) versus angiography with revascularization only if the patient has spontaneous or provokable ischemia (Conservative Strategy). The administration of t-PA will be double-blind whereas both the patient and physician will know which cardiac catheterization strategy is assigned.

Eligible patients, who give consent, will have an equal chance of receiving one of two initial treatments: t-PA or matching placebo

infusion. Each patient will also be randomly assigned to one of two follow-up strategies: Invasive Strategy or Conservative Strategy. Assignment to Invasive or Conservative Strategy will occur at the same time as the randomization to t-PA or placebo.

The objectives of the T3B investigation are to determine if t-PA reduces the incidence of death, myocardial infarction, or short-term severe recurrent ischemia, and if the Invasive Strategy reduces the incidence of death, myocardial infarction, or poor performance on an exercise treadmill test performed at six weeks.

2.2 Primary End Points

In T3A, the primary end point is a two-grade improvement in perfusion or at least a 10% improvement in stenosis as determined by quantitative angiography. The estimates of improvement will be made by comparing the status of the presumed culprit lesion on the angiogram taken before initiation of t-PA or placebo treatment and status on a follow-up angiogram taken 18 to 48 hours later.

There are two primary end points for T3B. The principal end point for the t-PA versus placebo comparison is the composite of: 1) death, 2) subsequent myocardial infarction or 3) treatment failure defined as failure to control spontaneous ischemia or existence of provokable ischemia within the first six weeks following study drug infusion. This end point will be referred to as the initial treatment primary end point. The principal end point for the invasive versus conservative strategy comparison is the composite: 1) death or 2) subsequent myocardial infarction within the first six weeks, or 3) unsatisfactory outcome of a standard or modified Bruce exercise treadmill test (ETT) performed at six weeks. This end point will be referred to as the follow-up management primary end point. Definitions of these clinical events are presented in Chapter 13. The six-week time period was selected because the preponderance of the above events occur in the first six weeks after the initial diagnosis, and because close scrutiny

for the first six weeks following diagnosis is routine clinical practice for these patients.

There are three reasons why different primary end points have been chosen for the two T3B comparisons. The first reason for the different end points is that patients assigned to the Invasive Strategy of cardiac catheterization may have protocol tests (Holter, Thallium, etc.) performed later, on average, than patients assigned to the Conservative Strategy. If the probability of detecting ischemia on a test varies over time, the performance of tests later for patients assigned to the Invasive Strategy could produce a systematic bias in the assessment of this end point. Second, the comparison of Invasive Strategy versus Conservative Strategy is unblinded. There could be a difference in way recurrent ischemia is assessed in hospital between patients assigned to the two different strategies. Finally, since two strategies of catheterization are being tested, severe recurrent ischemia is interpreted as an indication for catheterization and subsequent revascularization if necessary, and not as a failure of the Conservative Strategy.

2.3 Power Considerations for T3

2.3.1 Power Considerations for T3A

The proposed number of patients to be enrolled in T3A is 300 equally allocated into two groups, one group is to receive t-PA and one group is to receive placebo for t-PA. All patients will receive heparin and aspirin. The proportion of placebo-treated patients expected to show a two-grade improvement in perfusion or a 10% improvement in percent stenosis has been estimated to be 0.25. Table 1 of Appendix 1 shows the power to detect specified alternative probabilities of improvement in coronary artery stenosis and perfusion for the t-PA-treated group compared to different probabilities for the placebo-treated group. T3A has adequate power to detect differences between the placebo group and the t-PA group if the probability that patients in the placebo group show improved stenosis diameter ($\geq$ 10%) or improved

perfusion characteristics (two-grade improvement) is 0.25 and the probability for the same event in the t-PA group is 0.40 (76% power) or 0.45 (94% power). These power calculations are based on a test for two proportions conducted at the two-sided 5% level (1).

2.3.2 Power Considerations for T3B

The proposed number of patients to be enrolled in T3B is 2,000 equally allocated among four treatment groups in a 2x2 factorial design. In this randomized trial, treatment with t-PA will be compared to treatment with placebo, and routine early angiography with revascularization if appropriate, i.e., the Invasive Strategy Group, will be compared to cardiac catheterization with revascularization only if the patient has spontaneous or provokable ischemia, i.e., the Conservative Strategy Group.

The advantage of the factorial design is that under a model of no interaction, the effective sample size for any two contrasting treatments is the number of patients assigned to each of the contrasting treatments regardless of other assigned treatments. There is no interaction with study-drug treatment for comparing Invasive versus Conservative Strategy if and only if the percent change in risk of occurrence of the primary end point for the Invasive Strategy versus the Conservative Strategy is the same for patients receiving t-PA and placebo. Likewise there is no interaction with strategy for comparing t-PA versus placebo treatment if and only if the percent change in risk of occurrence of the initial therapy end point is the same for patients assigned to the Invasive Strategy or for patients assigned to Conservative Strategy. For instance, if t-PA therapy produces a 30% reduction in the initial therapy primary end point and the Invasive Strategy treatment produces a 40% reduction in the occurrence of the initial therapy end point then the combination of these therapies would produce a 58% = 100 x (1-(1-0.3)(1-0.4)) reduction in the occurrence of this primary end point.

In comparing t-PA therapy versus placebo under a model of no interaction, the results of the two combinations of patients managed according to the two follow-up catheterization strategies are pooled. Thus, there are 2 x 500 or 1000 patients in the t-PA treatment group and 1000 in the placebo treatment group. The variance estimator for this analysis will be different than the variance estimates for a standard two-group comparison of proportions, but under the balanced design, power is roughly comparable to that for the conventional test of two proportions.

The power to detect a specified reduction in the initial therapy end point with t-PA is a function of the event rate (p_o) for patients assigned to placebo and assigned to the Conservative Strategy for the above end point, and the percent reduction in the risk of this end point associated with the Invasive Strategy. Similarly, the power to detect a specified reduction in incidence of the follow-up management end point associated with the Invasive Strategy is a function of the event rate (p_o) for this end point for patients assigned to placebo and assigned to Conservative Strategy and the percent reduction in risk of this end point associated with t-PA treatment. Table 2 in Appendix 1 presents the power to detect specified percent reductions (and increases in risk) associated with t-PA and Invasive Strategy for two different levels of p_o that should encompass the incidence of both primary end points. The proposed study size has ample power (80-90%) to detect a 20-30% reduction in either primary end point for the specified treatment comparisons. For instance, if the event rate (p_o) for the initial therapy end point is 0.3 and the reduction in the initial therapy end point incidence due to the invasive strategy (for this end point) is 20%, the proposed design has 99% power to detect a 30% reduction in incidence due to treatment with t-PA when testing at the 5% two-sided level.

Considering the Invasive versus Conservative Strategy, a similar calculation for the follow-up management end point with p_o equal 0.3, and

the percent reduction due to t-PA treatment (for this end point) equal to 40%, the proposed design has 74% power to detect a 20% reduction in incidence due to the Invasive Strategy when testing at the 5% two-sided level. Power considerations for each treatment are calculated under the assumption that no interaction between the two therapies is present.

The power of the T3B design to detect an interaction between t-PA and cardiac catheterization strategy is also a concern. Table 3 in Appendix 1 presents the power to detect specified interactions over a range of t-PA effects and follow-up management strategy effects when the event rate (p) is 0.4. There is ample power (75-95%) to detect moderate levels of interaction. Figure 1 of Appendix 1 shows the effects that small levels of interaction will have on the planned main effect comparisons. Synergistic interactions will enhance the power of the proposed main effect comparisons, and antagonistic interactions will diminish the power of main effect comparisons. In the extreme, when antagonistic interactions are present, it is possible that a minimum 30% reduction associated with treatment or strategy will be necessary to detect treatment effects with adequate power.

There is no a priori reason to believe that the combination of t-PA and the Invasive Strategy should interact, either synergistically or antagonistically for either end point. However, if there is an interaction, it may not be possible to combine results across treatment or follow-up strategy groups. Then, the comparisons of initial therapy (t-PA versus placebo) and follow-up management (Invasive versus Conservative Strategy) will be made within strata without subsequent combination of these results. For instance the effective sample size for the two resulting t-PA versus placebo comparisons (one for patients assigned to the Invasive Strategy and one for patients assigned to the Conservative Strategy) would be 500 patients in each group. Table 4 in Appendix 1 presents the power associated with the same percent reductions as in Table 2 for this sample size when testing at the two-sided alpha level of 2.5% (rather than 5% to adjust for two comparisons).

Comparison of Table 4 with Table 2 indicates that larger treatment differences will be necessary to have adequate power if there is an interaction of t-PA and cardiac catheterization strategy. For instance, considering the p_o to be 0.3, the power to detect a 30% reduction due to treatment is 0.83 compared to 0.99 under the model of no interaction. However, initial versus subsequent therapy interactions can be detected only with a factorial design and if found, would be very interesting.

2.4 Power Considerations for Secondary End Points

2.4.1 Power Considerations for Secondary End Points in T3A

All group comparisons of secondary end points will be tested using an alpha level of 0.01 rather than 0.05. Many of the secondary end points used in the T3A studies are continuous in nature. A list of these end points can be found in Chapter 13. Treatment comparisons for these end points will be performed using t-tests. The proposed sample size of 300 patients in T3A is sufficient to detect a 0.39 standard deviation (S.D.) difference in the group means with a power of 0.8 when testing at the 0.01 alpha level. This difference in means is small enough that most true differences of clinical relevance should be detected with the proposed sample size. For instance, if the absolute diameter of stenosis for the placebo group was 92 $\pm$ 12 (S.D.), a mean percent stenosis diameter for patients treated with t-PA of 87.3 $\pm$ 12 could be detected with 80% power.

2.4.2 Power Considerations for Secondary End Points in T3B

A variety of secondary end points are to be analyzed in T3B. These end points are listed in Chapter 13 and can broadly be classified according to the type of end point. The classifications for these end points are: 1) time to event end points; 2) binary end points and 3) continuous end points. The methods for dealing with each of these types of end points are different, thus different power considerations will be given for each.

All of these analyses are considered secondary to the analyses of the two primary end points. As such, statistical power will be considered at an alpha (α) level of 0.01 rather than the 0.05 level that is used for the primary end points.

2.4.2.1 Secondary Analyses Involving Survival Analysis

Table 5 in Appendix 1 can be used to evaluate the statistical power for all secondary analyses involving outcome measures defined as the time to a specific event. Power in survival analysis is more appropriately based on the number of events rather than the number of patients. Thus, Table 5 presents the power to detect specified reductions in relative risk as a function of the number of events observed in the study. For a secondary analysis to have reasonable statistical power (0.8 to 0.9) to achieve a significant result, 100 events will be necessary to detect 50% reductions in relative risks, 200 events will be necessary to detect 40% reductions, and 400 or more events are necessary to detect 30% reductions.

2.4.2.2 Secondary Analyses Involving Tests of Proportions

The proposed analysis for binary end points will, at a minimum, use the same model as for the primary end points. As mentioned, the only difference will be that tests of significance will be made at the 0.01 level rather than at the 0.05 level. Each test (t-PA versus Placebo or Invasive versus Conservative Strategy) is a function of the event rate for patients randomly assigned to placebo and to the Conservative Strategy (p_o). The value for p_o (for any secondary end point) can be no lower than 0.20 and still maintain adequate power (80-90%) to detect a 35% reduction in incidence associated with a treatment intervention. Table 6 in Appendix 1 shows the statistical power to detect specified percent reductions associated with t-PA usage assuming p_o to be 0.20. Due to the symmetric nature of the 2x2 factorial design, this table can also be used to evaluate power for the two follow-up strategies by interchanging row and column headings.

Analyses of secondary end points with event rates lower than 0.2 will likely not detect significant treatment effects unless these treatment effects are large (e.g., > 50% reductions in risk associated with an intervention).

2.4.2.3 Secondary Analyses Involving Tests of Means

The simplest model to test for differences in means among study drug groups will be an Analysis of Variance (ANOVA) for 2x2 factorial designs with only one dependent variable (i.e., variables that are only collected once over the course of T3 or a single time point analysis of a repeated measures variable). Under the assumptions that the observations are independent, and errors about the population means are constant, the standard contrasts used for a 2x2 factorial analysis yield tests of hypotheses that are analogous to the two sample t-test. Under the above assumptions, a sample size of 2000 will have an effective per group sample size of 1000 for the tests of the t-PA, follow-up catheterization strategy, and interaction effects of t-PA and follow-up catheterization strategy. Thus, statistical power will be evaluated for a simple two sample t-test. The proposed sample size of 2000 is sufficient to detect mean differences of 0.17 standard deviations with adequate statistical power (0.9) when testing at the alpha level of 0.01. This difference is small enough that most differences of clinical relevance in the treatment effects for outcome measures that are continuous in nature will be detectable using the proposed study design.

2.4.2.4 Summary of Statistical Power Considerations

Statistical power evaluations have been made for each of the different types of analyses that are anticipated for the T3B study. There appears to be adequate statistical power with the present study design of 2000 patients to detect 20% to 30% reductions in occurrence of the designated primary end point for each of the tests of main treatment effects, i.e., t-PA versus placebo and Invasive Strategy versus Conservative Strategy.

2.5 Reference

1. Casagrande JT, Pike MC and Smith PG. An improved approximate formula for calculating sample sizes for comparing two binomial distributions. Biometrics 1978;34:483.

APPENDIX 1

STATISTICAL ANALYSIS AND POWER CONSIDERATIONS

T3A

The primary analysis planned for T3A is a test of two proportions: (1) the proportion of patients assigned to receive t-PA with concomitant heparin and aspirin who experience an improvement in stenosis or perfusion characteristics in their ischemia-related artery, within 24 to 48 hours of study entry and (2) the proportion of patients assigned to receive only heparin and aspirin who experience an improvement in stenosis or perfusion characteristics in their ischemia-related artery within 24 to 48 hours of study entry. The power associated with this test of two proportions can be conservatively estimated as:

$$\text{power} \doteq \varphi\left(\frac{(*p_1 \& p_2 *\& 1/N) \;\&\; 1.96\sqrt{4pg/N}}{\sqrt{4\,(p_1q_1 \% p_2q_2)/N}}\right) \quad ,$$

where p_1 = the expected proportion of patients having improved stenosis or perfusion characteristics in the t-PA group,

p_2 = the expected proportion of patients having improved stenosis or perfusion characteristics in the placebo group,

$\bar{p}$ = $(p_1 + p_2)/2$, and

N = the total number of patients participating in T3A, i.e., N = 300.

This power calculation (1) was used to construct Table 1 which shows the power of T3A to detect alternate differences in proportions associated with t-PA and heparin treatment versus heparin only.

T3B

To accomplish the analyses planned in T3B, a multiplicative model with treatment interactions will be assumed. To discuss this model, the concept of a relative risk, as opposed to the percent reduction will be used. The relative risk associated with a treatment is defined as:

$$r = \left(\frac{100 - \%\ \text{reduction}}{100} \right) \quad ,$$

with the relative risk for the comparison group being set to one. If a treatment produces a 30% reduction in risk relative to the comparison group, the relative risk associated with the treatment is 0.7. In the multiplicative model under consideration, it is the relative risks that are multiplied; if the placebo event rate is p_o and t-PA yields a 30% reduction in risk, the event rate for subjects given t-PA would be $(0.7)\ p_o$. Similarly, if there is a 20% reduction in risk in the Invasive Strategy Group, the event rate for the Invasive Strategy would be $(0.8)\ p_o$. If the two treatments are given in combination, the event rate assuming no interactions between the two treatments would be:

$$(0.7)\ \ (0.8)\ p_o = 0.56\ p_o \quad ,$$

or a 44% reduction in risk as compared to the placebo with Conservative Strategy. To allow for a possible interaction effect, an additional parameter r_i is introduced in the combined group. Thus, the combined event rate in the example is:

P (response * t-PA and Invasive Strategy) = $(0.7)\ (0.8)\ r_i\ p_o$.

For an adverse event, (such as death) if r_i is less than one, the drug-management combination is said to have a synergistic effect, and if r_i is greater than one, the drug-management combination is said to have an antagonistic effect.

Letting r_t, and r_C be the relative risks for t-PA, and Invasive Strategy respectively, the event rates for the different groups in the 2x2 factorial design under consideration will be modeled as:

Effect	Group
p_o	placebo, Conservative Strategy
$r_c\ p_o$	placebo, Invasive Strategy
$r_t\ p_o$	t-PA, Conservative Strategy
$r_t\ r_c\ r_i\ p_o$	t-PA, Invasive Strategy

The analysis proposed for evaluating the effects of initial (t-PA versus placebo) and follow-up (Invasive versus Conservative Strategy) therapy result in three hypotheses of interest. These hypotheses are:

1) Does adopting the Invasive Strategy lead to a reduction in the incidence of the follow-up management primary end point?
2) Does administration of t-PA reduce the incidence of the initial therapy primary end point?
3) Do t-PA treatment and the strategy of Invasive Strategy when they are given in combination interact in changing the incidence of either of the primary end points?

Because the third hypothesis can bear directly on the inferences in testing the first and second hypotheses, the third hypothesis will be addressed first for each of the primary end points being studied. The parameter indicating the presence or absence of an interaction between t-PA treatment and follow-up catheterization strategy is r_i . If r_i equals one, no interaction is present; if r_i is greater than one, the two interventions interact in an antagonistic fashion; and if r_i is less than one, the two interventions interact synergistically. Letting p_{tc}, p_t, p_c and p_o, represent the expected event rates for the t-PA with Invasive Strategy, t-PA with Conservative Strategy, placebo with Invasive

Strategy only and placebo with Conservative Strategy treatment groups, the parameter r_i can be isolated in the following way:

$$r_i = \frac{p_{tc}\, p_o}{p_t\, p_c}$$

Taking the natural log of each side, one obtains:

$$\ln(r_i) = \ln(p_{tc}) + \ln(p_o) - \ln(p_t) - (p_c) \quad .$$

Replacing the parameters with appropriate estimates and employing the delta method as a means of estimating the variance of $\ln(\hat{r}_i)$, the test of no interaction can be accomplished by evaluating:

$$Z = \frac{\left(\ln(\hat{p}_{tc}) + \ln(\hat{p}_o) - \ln(\hat{p}_t) - \ln(\hat{p}_c)\right)}{\sqrt{\frac{1}{500}\left(\frac{(1-\hat{p}_{tc})}{\hat{p}_{tc}} + \frac{(1-\hat{p}_o)}{\hat{p}_o} + \frac{(1-\hat{p}_t)}{\hat{p}_t} + \frac{(1-\hat{p}_c)}{\hat{p}_c}\right)}}$$

as an asymptotically normal random variable with mean zero and variance one. Subtracting $\ln(\hat{r}_i)$ in the numerator of (Z) would allow one to evaluate the alternative distribution of $\ln(\hat{r}_i)$ as a normal (0,1) random variable. This allows one to make very simple power calculations for specified alternatives using the following equation:

$$\text{power} = 1-\varphi\left(Z_{1-\alpha/2} - \frac{*\ln(\hat{r}_i)*}{\sqrt{\frac{1}{500}\left(\frac{(1-\hat{p}_{tc})}{\hat{p}_{tc}} + \frac{(1-\hat{p}_o)}{\hat{p}_o} + \frac{(1-\hat{p}_t)}{\hat{p}_t} + \frac{(1-\hat{p}_c)}{\hat{p}_c}\right)}}\right)$$

This power evaluation is a function of p_o, r_t, r_c, and $\hat{r}_i$ Table 3 shows the power of T3B to detect specified interactions using the above formula. This table has been arranged using the percent change from proportionality (PC) or:

$$PC = 100\ (1 - \hat{r}_i).$$

As can be seen, T3B has approximately 90% power to detect a ±50% change from proportionality when p_o equals 0.4.

If an interaction between t-PA and Invasive Strategy is detected, then evaluation of whether t-PA changes the incidence of the initial therapy primary end point can serve only to augment the fundamental finding that there is at least one of the four treatment strategies which has a different incidence of the primary end point than the other three. Should a significant result be found, the analysis will be stratified according to the guidelines at the end of this appendix. Rewriting the model in tabular form (Table 7), two sets of independent analyses arise as a result of this model, when no interaction is present (r_i=1).

The margins in Table 7 are summed over their respective rows or columns. The independence of initial therapy and follow-up management treatment effects implies that the analysis can proceed according to the marginal entries in Table 7. This means that to evaluate the efficacy of t-PA we would compare the results in patients assigned to receive t-PA to the results in patients assigned to receive placebo. The expected event rates for these two groups are:

for t-PA	$[(r_c + 1)/2]$	$r_t\ p_o = r_t p_c$	and
for placebo	$[(r_c + 1)/2]$	$p_o = p_c$	.

The variances for the event rates in these two groups will not be $r_c\ r_t\ (1 - p_c r_t)$ and $p_c\ (1 - p_c)$ respectively, but rather a linear combination of the variances for the two groups that make up the marginal proportion. One can show using Jensen's Inequality (1) that the standard variances for proportions shown above are conservative. In Table 2 we have presented the power of T3B to detect specified alternatives using the actual variance estimates for the linear combination of four proportions making up each of these two comparison groups; there is adequate power to detect 20% reductions in incidence of the initial therapy end point due to t-PA administration. The symmetry involved in the design of t-PA and follow-up catheterization strategy comparisons means that T3B has the same power to detect Invasive versus Conservative Strategy differences in the occurrence of the follow-up management end

point as to detect t-PA versus placebo differences for the initial therapy end point (Table 2).

Should a significant interaction be found, the T3B comparisons will be performed as follows. Two evaluations of the efficacy of Invasive Strategy will be made, one for patients who received t-PA and one for patients who received placebo. These two tests of treatment comparisons will be performed at the 2.5% level to adjust for multiple comparisons. The sample size for each of these two comparisons would be 500 per group (Total N = 1000). Likewise for comparisons of t-PA versus placebo there are two follow-up catheterization strategy strata, therefore each proposed comparison (t-PA versus placebo) will be conducted at the 2.5% level. The effective sample sizes for these comparisons will also be 500 per group (Total N = 1000). With 500 patients in each of two groups compared and a test at the 2.5% level, Table 4 presents the power of T3B to detect specified alternative reductions associated with the strategy of invasive cardiac catheterization and t-PA usage.

References

1. Feller W. An Introduction to Probability Theory and Its Applications. Volume II, Second Edition. New York. J. Wiley and Sons; 1971: 153-54.

TABLE 1

POWER TO DETECT ALTERNATE PROPORTIONS IN T3A
Alpha = 5% N = 300

Proportion Showing Improved Stenosis or Perfusion Characteristics

	Placebo						
	0.200	0.250	0.300	0.350	0.400	0.450	0.500
t-PA							
0.200	-----	-----	-----	-----	-----	-----	-----
0.250	0.14	-----	-----	-----	-----	-----	-----
0.300	0.46	0.13	-----	-----	-----	-----	-----
0.350	0.80	0.42	0.12	-----	-----	-----	-----
0.400	0.96	0.76	0.39	0.12	-----	-----	-----
0.450	1.00	0.94	0.73	0.38	0.11	-----	-----
0.500	1.00	0.99	0.93	0.71	0.37	0.11	-----
0.550	1.00	1.00	0.99	0.92	0.70	0.37	0.11
0.600	1.00	1.00	1.00	0.99	0.92	0.92	0.37
0.650	1.00	1.00	1.00	1.00	0.99	0.99	0.71
0.700	1.00	1.00	1.00	1.00	1.00	1.00	0.93
0.750	1.00	1.00	1.00	1.00	1.00	1.00	0.99
0.800	1.00	1.00	1.00	1.00	1.00	1.00	1.00

TABLE 2

POWER TO DETECT SPECIFIED EVENT RATE REDUCTIONS

Total N = 2,000 Alpha = 5%

I. rt-PA versus Placebo

A. Placebo Event Rate = 0.3

% Reduction Due to Invasive Cardiac Catheterization Strategy	% Reduction due to t-PA: 10	20	30	40	50
10	0.30	0.83	0.99	1.00	1.00
20	0.28	0.80	0.99	1.00	1.00
30	0.26	0.78	0.99	1.00	1.00
40	0.25	0.74	0.98	1.00	1.00
50	0.23	0.71	0.97	1.00	1.00

B. Placebo Event Rate = 0.4

% Reduction Due to Invasive Cardiac Catheterization Strategy	% Reduction due to t-PA: 10	20	30	40	50
10	0.42	0.95	1.00	1.00	1.00
20	0.40	0.93	1.00	1.00	1.00
30	0.37	0.91	1.00	1.00	1.00
40	0.34	0.89	1.00	1.00	1.00
50	0.31	0.86	1.00	1.00	1.00

TABLE 2 (Continued)

POWER TO DETECT SPECIFIED EVENT RATE REDUCTIONS

Total N = 2,000 Alpha = 5%

II. Invasive versus Conservative Cardiac Catheterization Strategy

		% Reduction due to t-PA				
A. Placebo Event Rate = 0.3		10	20	30	40	50
% Reduction Due to Invasive Cardiac Catheterization Strategy	10	0.30	0.28	0.26	0.25	0.23
	20	0.83	0.80	0.78	0.74	0.71
	30	0.99	0.99	0.99	0.98	0.97
	40	1.00	1.00	1.00	1.00	1.00
	50	1.00	1.00	1.00	1.00	1.00
B. Placebo Event Rate = 0.4		10	20	30	40	50
% Reduction Due to Invasive Cardiac Catheterization Strategy	10	0.42	0.40	0.37	0.34	0.31
	20	0.95	0.93	0.91	0.89	0.86
	30	1.00	1.00	1.00	1.00	1.00
	40	1.00	1.00	1.00	1.00	1.00
	50	1.00	1.00	1.00	1.00	1.00

TABLE 2 (Continued)

POWER TO DETECT SPECIFIED EVENT RATE INCREASES

Total N = 2,000 Alpha = 5%

IV. Invasive versus Conservative Cardiac Catheterization Strategy

		% Reduction due to t-PA				
A. Placebo Event Rate = 0.3		10	20	30	40	50
% Increase in Risk Due to Invasive Cardiac Catheterization Strategy	30	0.98	0.98	0.96	0.95	0.94
	20	0.78	0.75	0.72	0.68	0.65
	10	0.28	0.27	0.25	0.23	0.22
B. Placebo Event Rate = 0.4		10	20	30	40	50
% Increase in Risk Due to Invasive Cardiac Catheterization Strategy	30	1.00	1.00	1.00	1.00	0.99
	20	0.93	0.91	0.88	0.86	0.82
	10	0.41	0.38	0.35	0.32	0.30

TABLE 2 (Continued)

POWER TO DETECT SPECIFIED EVENT RATE REDUCTIONS

Total N = 2,000 Alpha = 5%

III. rt-PA versus Placebo

		% Reduction due to t-PA				
A. Placebo Event Rate = 0.3		10	20	30	40	50
% Increase in Risk Due to Invasive Cardiac Catheterization Strategy	30	0.38	0.92	1.00	1.00	1.00
	20	0.36	0.90	1.00	1.00	1.00
	10	0.34	0.88	1.00	1.00	1.00
B. Placebo Event Rate = 0.4		10	20	30	40	50
% Increase in Risk Due to Invasive Cardiac Catheterization Strategy	30	0.55	0.99	1.00	1.00	1.00
	20	0.51	0.98	1.00	1.00	1.00
	10	0.48	0.97	1.00	1.00	1.00

TABLE 3

POWER TO DETECT SPECIFIED INTERACTIONS AS A FUNCTION OF THE PERCENT REDUCTION FOR t-PA, INVASIVE CARDIAC CATHETERIZATION STRATEGY AND THE PLACEBO EVENT RATE

Total N = 2,000 Alpha = 5% Placebo Event Rate = 0.4

		Interaction				
		-50	-20	0	+20	+50
A. % Reduction due to Invasive Cardiac Catheterization Strategy = 50						
	50	0.83	0.19	0.02	0.17	0.64
	40	0.88	0.22	0.02	0.19	0.70
% Reduction due to t-PA						
	30	0.92	0.24	0.02	0.20	0.75
	20	0.94	0.26	0.02	0.22	0.79
B. % Reduction due to Invasive Cardiac Catheterization Strategy = 40						
	50	0.88	0.22	0.02	0.19	0.70
	40	0.93	0.24	0.02	0.21	0.76
% Reduction due to t-PA						
	30	0.95	0.27	0.02	0.23	0.81
	20	0.97	0.30	0.02	0.25	0.85
C. % Reduction due to Invasive Cardiac Catheterization Strategy = 30						
	50	0.92	0.24	0.02	0.20	0.75
	40	0.95	0.27	0.02	0.23	0.81
% Reduction due to t-PA						
	30	0.97	0.30	0.02	0.25	0.85
	20	0.98	0.33	0.02	0.28	0.89
D. % Reduction due to Invasive Cardiac Catheterization Strategy = 20						
	50	0.94	0.26	0.02	0.22	0.79
	40	0.97	0.30	0.02	0.25	0.85
% Reduction due to t-PA						
	30	0.98	0.33	0.02	0.28	0.89
	20	0.99	0.36	0.02	0.30	0.92

TABLE 4

POWER TO DETECT SPECIFIED PERCENT REDUCTIONS AS A FUNCTION OF THE CONTROL EVENT RATE

Total N = 1,000 Alpha = 2.5%

		Control Event Rate		
		0.2	0.3	0.4
Percent Reduction	10	0.06	0.10	0.16
	15	0.14	0.23	0.37
	20	0.25	0.43	0.63
	25	0.40	0.65	0.84
	30	0.58	0.83	0.96
	35	0.74	0.94	0.99
	40	0.87	0.98	1.00
	45	0.95	1.00	1.00
	50	0.98	1.00	1.00

TABLE 5

STATISTICAL POWER TO DETECT CERTAIN RELATIVE RISKS BY TOTAL NUMBER NUMBER OF OBSERVED EVENTS FOR $\alpha = .01$

PERCENT REDUCTION IN RELATIVE RISK	TOTAL NUMBER OF OBSERVED EVENTS				
	100	200	300	400	500
10%	.020	.033	.048	.063	.080
20%	.072	.158	.259	.364	.466
30%	.212	.477	.694	.838	.920
40%	.490	.849	.967	.994	.999
50%	.812	.990	1.0	1.0	1.0

TABLE 6

STATISTICAL POWER TO DETECT VARIOUS PERCENT REDUCTIONS IN OUTCOME EVENT RATES DUE TO t-PA GIVEN VARIOUS PERCENT REDUCTIONS IN OUTCOME EVENT RATES DUE TO THE STRATEGY OF INVASIVE CARDIAC CATHETERIZATION

A. When Study Size is 2000, Expected Event Rate in the Group Receiving Placebo and no early cardiac catheterization is 0.20 and $\alpha = 0.01$

PERCENT REDUCTION IN RATE FOR t-PA	PERCENT REDUCTION IN RATE FOR THE STRATEGY OF INVASIVE CARDIAC CATHETERIZATION							
	50%	45%	40%	35%	30%	25%	20%	15%
50%	1.00	0.98	0.94	0.84	0.67	0.46	0.26	0.13
45%	1.00	0.99	0.95	0.85	0.69	0.48	0.28	0.13
40%	1.00	0.99	0.96	0.87	0.71	0.50	0.29	0.14
35%	1.00	0.99	0.96	0.88	0.73	0.51	0.30	0.15
30%	1.00	0.99	0.97	0.89	0.74	0.53	0.32	0.15
25%	1.00	0.99	0.97	0.91	0.76	0.55	0.33	0.16
20%	1.00	1.00	0.98	0.92	0.78	0.57	0.34	0.17
15%	1.00	1.00	0.98	0.93	0.79	0.59	0.36	0.17

TABLE 7

A TABLE SHOWING THE EXPECTED EVENT RATES FOR T3B
USING THE PROPOSED MULTIPLICATIVE MODEL

Subsequent Management	Initial Therapy: t-PA	Initial Therapy: Placebo	
Invasive Strategy	$r_t r_c \; r_i p_o$ N = 500	$r_c \; p_o$ N = 500	$(r_t r_i + 1) r_c p_o$ N = 1000
Conservative Strategy	$r_t \; p_o$ N = 500	p_o N = 500	$(r_t + 1) p_o$ N = 1000
	$(r_c r_i + 1) r_t p_o$ N = 1000	$(r_c + 1) p_o$ N = 1000	