CHAPTER 1

BACKGROUND AND STUDY CHRONOLOGY

1.1 INTRODUCTION

The study investigators plan to examine major issues regarding the management of patients with unstable angina and non-Q-wave myocardial infarction (MI). Since 1984, the TIMI Research Group has actively investigated thrombolytic therapy in patients with Q-wave MI. The initial decision to evaluate thrombolytic therapy in patients with Q-wave MI resulted from (a) evidence that occlusive coronary thrombosis is the cause of this condition[1], (b) the availability of effective thrombolytic agents[2-4] and (c) the concept that infarct size can be limited[5, 6].

Although prior TIMI studies--and almost all other studies of thrombolytic therapy for MI--have been conducted in patients with ST-segment elevation, it is possible that the factors which accounted for the successful outcome in this group may also apply to patients who present with ST-segment depression, many of whom develop a non-Q-wave MI. Thrombosis is frequently the cause of the latter condition[7], and the long-term outcome after a non-Q-wave MI is as serious as that after a Q-wave MI[8]. Since coronary thrombosis is now recognized to be present and of etiologic importance in many cases of unstable angina as well[9-11], a test of the hypothesis that thrombolysis will also be of value in this group is timely and appropriate. Nevertheless, the prospects of a beneficial effect in these two groups of patients must be balanced against the possible harmful effects and not inconsiderable expense of thrombolytic therapy.

Equal in importance to defining the role of thrombolytic therapy is the choice between <u>routine</u> early angiography, followed by revascularization with either percutaneous transluminal coronary angioplasty (PTCA)[12, 13] or coronary artery bypass grafting (CABG)[14, 15], and angiography performed only when ischemia is persistent or readily provokable. In most institutions with facilities for catheterization, it is current practice to perform angiography early and routinely in most patients with unstable angina; in hospitals without catheterization facilities (in which the majority of patients are treated), physicians must decide whether to transfer such patients to another facility for angiography and possible revascularization or to initiate management without angiographic data. In the recently completed Veterans Administration study of unstable angina[16], catheterization followed by CABG was found to be of value in

patients with impaired left ventricular function; however, in most cases, only limited data are available on which to base this difficult decision.

1.2 BACKGROUND

The myocardial ischemic syndromes, which account for a large portion of the annual mortality and morbidity from all causes in industrialized countries, encompass a wide clinical-pathologic spectrum. At one end of this spectrum are patients with chronic stable angina. When studied by coronary arteriography, such patients usually have obstructive atherosclerotic disease with no evidence of fresh thrombosis[17]. At the other end of the spectrum are patients with acute MI who present with a discrete episode of prolonged chest pain accompanied by persistent ST- segment elevation. Such patients have a high incidence of thrombotic coronary artery occlusion[1], and the early intravenous administration of thrombolytic agents has been shown to reestablish perfusion, limit the extent of left ventricular dysfunction[18-20], and reduce both early (in-hospital)[21] and late (1-year) mortality[22, 23] in this group.

1.2.1 Non-Q-Wave MI and Unstable Angina

Patients with non-Q-wave MI and unstable angina fall between these two extremes. In the days and weeks following the onset of their disorder, their prognosis for survival is better than that of patients with Q-wave MI but worse than that of patients with stable angina[8, 24, 25]. Some patients with unstable angina progress to acute MI, and some of those with non-Q-wave infarction experience an unstable course with reinfarction[8, 26]. Although others recover from the acute episode without subsequent infarction or reinfarction, they frequently have severe obstructive coronary artery disease and may be left with severe chronic stable angina[27].

Once the results of creatine kinase (MB fraction) measurements and serial ECGs are available, the identification of patients experiencing non-Q-wave MI is relatively simple. Identification of patients experiencing unstable angina is more difficult, since numerous definitions of the condition have been offered. There is agreement, however, on two important features of unstable angina. First, ischemia usually develops at rest or is precipitated by minimal exertion; this differs from chronic stable angina, in which most ischemic episodes are precipitated by physical exertion or strong emotion and the resultant increase in myocardial oxygen demand[17]. Second, ischemia is often associated with transient ST-segment depression or elevation, in contrast to the

persistent ST-segment elevation characteristic of patients who develop Q-wave infarction.

1.2.2 Coronary Artery Thrombosis in Non-Q-Wave MI and Unstable Angina

It has been observed (albeit in small numbers of patients) that unlike patients with chronic stable ischemia, patients with unstable angina or non-Q-wave MI frequently have a thrombus in a major coronary artery[9, 10]. The incidence of thrombosis detected by angiogram has been reported to be as high as 71% in patients with unstable angina[28, 29] and as high as 88% in patients with non-Q-wave MI[7]. In both groups, coronary arteriographic findings[30] and angioscopic observations at operation[9] indicate that the occlusion may be subtotal, that early partial spontaneous lysis may occur, and/or that the area distal to the total occlusion may have sufficient collateral blood flow to prevent or limit the development of necrosis[31]. Samples of peripheral blood obtained from patients with unstable angina have shown increased levels of thromboxane B_2 and fibrinopeptide A, suggesting the presence of intravascular thrombosis[32]. Thus, although angiographic evidence of thrombosis is not as frequently observed in these patients as in those with Q-wave MI, there is abundant evidence that thrombus plays a major role in the pathogenesis of unstable angina in many patients.

The development of ischemia at rest or with minimal exertion in patients with unstable angina is consistent with the hypothesis that a sudden reduction in oxygen supply rather than an increase in oxygen demand is the cause. The finding that aspirin improves the long-term prognosis in patients with unstable angina[33, 34] is also consistent with the hypothesis that coronary thrombosis, which causes total or subtotal occlusion, is of etiologic importance in this group.

1.2.3 Magnitude of the Problem

The number of persons with unstable angina or non-Q-wave MI would be difficult to quantitate, but it is enormous. National summaries of hospital records indicate that these two conditions are responsible for the hospitalization of over 1 million individuals per year (750,000 with unstable angina and 250,000 with non-Q-wave MI)[35]. These summary data for non-Q-wave MI are in accord with findings in the Multicenter Investigation of Limitation of Infarct Size (MILIS), in which a careful distinction was made between Q-wave and non-Q-wave MI. Non-Q-wave MI accounted for 30% of all infarcts, a proportion found in other studies as well[36]. Projected rates of complications based on these totals indicate that during the initial hospital stay, unstable angina causes

approximately 70,000 infarctions and 30,000 deaths; non-Q-wave MI causes approximately 12,500 deaths.

1.2.4 Conventional Therapy of Unstable Angina and Non-Q-Wave MI

Initial conventional therapy for unstable angina consists of bed rest, oxygen, nitrates, beta blocking agents, calcium antagonists,[37, 39], and aspirin[33, 34]. The use of heparin has also been recently shown to be effective[40]. In many tertiary care hospitals, angiography followed by PTCA is frequently performed, whereas in community hospitals patients are often managed without angiography.

At present, patients with non-Q-wave MI are usually treated in the same way patients with Q-wave MI were treated prior to the advent of thrombolytic therapy. Thrombolytic therapy is not routinely employed, although knowledge of the role of thrombosis in some patients with this condition[7] has raised the possibility that this approach may be helpful. Although the early prognosis is favorable, awareness that the longer-term prognosis is as serious as that following Q-wave MI[8] has led to increasing use of followup coronary angiography to identify patients for whom PTCA or CABG may be useful[36]. Whether or not revascularization improves prognosis in these patients has not been established.

1.2.5 Thrombolytic Therapy for Unstable Angina and Non-Q-Wave MI

In contrast to the large number of studies evaluating thrombolysis in patients with Q-wave MI, information is limited regarding the effects of thrombolytic therapy in patients with unstable angina or non-Q-wave MI. An early study by Lawrence[41] suggested that streptokinase therapy was beneficial in patients with unstable angina, but only 40 patients were studied. In a subsequent angiographic study, Rentrop et al[42] reported that infusion of streptokinase had no effect on the angiographic appearance of nonobstructive coronary artery lesions. Others have reported minimal[28] or moderate[7] angiographic improvement following intracoronary infusion of streptokinase using qualitative measurements. Ambrose et al found no significant change in the percent diameter stenosis of subtotal coronary artery lesions after infusion of streptokinase[43].

A recent study from Japan[11] indicated some benefit with intracoronary urokinase therapy in patients with unstable angina who underwent catheterization during an episode of pain.

Reports of results with t-PA have been somewhat more favorable than those with streptokinase. In a randomized study of 24 patients, Gold et al observed less angiographic evidence of thrombus and less recurrent angina following a 12-

hour infusion of t-PA; all patients also received full-dose heparin therapy[44]; however, significant bleeding was encountered. Nicklas et al found no difference in clinical outcome among patients randomly assigned to either placebo or t-PA in a study in which all patients received aspirin and heparin. There was a slight improvement in pacing threshold for the t-PA-treated group, which was more marked in patients with angiographically visible thrombi[45].

In summary, previous studies of thrombolytic therapy for unstable angina and non-Q-wave MI are limited in number and size. In aggregate, the results suggest a benefit (which may be less than that for Q-wave MI), but the significance of this benefit and its relation to the risks and costs of therapy remain to be determined.

1.2.6 The Risk of Stroke with t-PA Therapy

The relationship between the potential beneficial effects of t-PA therapy for unstable angina or non-Q-wave MI and the potential for stroke must be evaluated. In the prior TIMI studies of Q-wave MI, a 150-mg dose of t-PA caused an unacceptable 1.6% incidence of stroke[46]; however, a reduction in dose to 100 mg lowered this rate to 0.6%[47], which is balanced by a reported incidence of nonhemorrhagic stroke of approximately 1.0% in patients with MI not receiving thrombolytic therapy[48].

In T3, an even lower dose of t-PA is used (0.8 mg/kg not to exceed 80 mg), so that a lower rate of hemorrhagic stroke would be expected than with the 100-mg dose. Furthermore, unstable angina and non-Q-wave MI are associated with a small risk of stroke in the absence of t-PA therapy because of progression to MI (or reinfarction) and because of the frequent performance of angiography, PTCA, and CABG, each of which increases this risk, albeit slightly. On careful evaluation in the MILIS study, four of 188 patients with ischemic chest pain and ST-segment depression on the initial ECG suffered a stroke (2.1%). These patients were comparable to those who will be enrolled in T3. Thus, the rate of hemorrhagic stroke resulting from the reduced dose of t-PA may be offset by a reduction in the rate of nonhemorrhagic stroke seen without thrombolytic therapy.

1.2.7 Angiography Following Unstable Angina and Non-Q-Wave MI

In both of these conditions, the value of routine, early coronary angiography followed by PTCA and/or CABG is still unclear. The balance between the potentially beneficial effects of revascularization and the risks and costs

of angiography followed by revascularization (if appropriate) is unknown. Because definitive evidence is lacking, clinical approaches to such patients have been inconsistent. In centers with catheterization facilities, early angiography (often followed by PTCA or CABG) is frequently carried out, regardless of the patient's clinical course. In centers that lack these facilities, patients may be transferred for routine angiography only if a specific indication arises, such as persistence of symptoms despite maximal medical therapy or a markedly positive exercise tolerance test (ETT) prior to hospital discharge. The information required to determine the most appropriate course of action for a given patient is not yet available.

1.2.8 Potential Contribution of T3

These crucial questions about the management of unstable angina and non-Q-wave MI--i.e., the value of t-PA, and t-PA plus heparin, as well as the need for early routine angiography followed by revascularization (given the suitable coronary anatomy) are of immense importance in terms of mortality, morbidity, and costs of health care and can be answered only by means of a multicenter study involving a large number of patients. Furthermore, patients must be studied during the acute illness; t-PA therapy, which is associated with some risk, must be administered, and patients and their physicians must agree to the protocol by which patients will be randomly assigned to undergo angiography, followed (if appropriate) by revascularization.

1.3 PRELIMINARY STUDY

1.3.1 Pilot Study of t-PA and Heparin Therapy for Unstable Angina

In preparation for the T3 trial, a pilot study to evaluate the use of t-PA and/or heparin in 400 patients with unstable angina was initiated in July, 1988. The purpose of this study was to determine whether t-PA and/or heparin, when added to conventional therapy for unstable angina, would reduce the incidence of an unfavorable outcome. Unfavorable outcome was defined as follows: death, stroke, MI, failure of medical therapy, or Holter evidence of myocardial ischemia within six weeks. While the study was in progress, data indicating the value of heparin was published[40] so the protocol was altered to include routine heparin therapy. It should be emphasized that the pilot study will not answer the primary management questions which will be addressed by T3. Since angiograms were not required, there will be no information about the effect of t-PA on coronary artery angiographic findings. Most importantly, the pilot

study was not designed to address the issue of routine, early angiography nor did it include patients with non-Q-wave MI.

1.4 T3 CHRONOLOGY (Table 1)

In December 1987, TIMI II investigators agreed to conduct an additional study. Planning meetings were held in 1988 by the TIMI II investigators with the aim of preparing an RO1 application to the National Heart, Lung and Blood Institute. A review meeting regarding the application was held with NHLBI officials in April 1988.

The Principal Investigators of the participating centers (Clinical Centers, Radiographic Core Laboratory, Radionuclide Core Laboratory, ECG Core Laboratory and Coordinating Center), formed the Planning Committee to develop the detailed protocol.

An RO1 application was submitted to the NHLBI on June 1, 1988.

A reverse site visit with NHLBI Clinical Trials Review Committee was held in November 1988.

In April 1989, the T3 grant was awarded.

In June 1989, a separate RO1 grant was awarded to the University of Vermont to establish a Coagulation Core Laboratory for T3.

The commencement date for T3 was September 15, 1989.

1.5 References

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TABLE 1-1

T3 CHRONOLOGY

December 1987 -	Consensus reached by TIMI II investigators to pursue additional study.
April 1988 -	Review meeting with NHLBI officials regarding application
June 1988 -	R01 application submitted to NHLBI
November 1988 -	Reverse site visit with NHLBI Clinical Trials Review Committee
April 1989 -	T3 awarded to Brigham and Women's Hospital and Maryland Medical Research Institute
June 1989 -	R01 grant awarded to University of Vermont for Coagulation Core Laboratory
September 1989 -	Orientation and Training Session for T3
October 1989 -	Initiation of patient recruitment for T3A and T3B
June 1990 -	Selection of additional Clinical Centers for T3B
October 1990 -	Completion of recruitment for T3A

T3 MANUAL OF OPERATIONS

TABLE OF CONTENTS