A Critique of Selected Aspects of the Thrombolysis in Myocardial Infarction IIB (TIMI IIB) and the Thrombolysis in Myocardial Infarction IIIB (TIMI IIIB) Trials

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ABSTRACT: The Thrombolysis in Myocardial Infarction IIB trial (TIMI IIB) compared a particular invasive treatment strategy to a particular conservative strategy.[1] A single 80mg dose of aspirin was routinely used in the invasive strategy patients prior to undergoing angioplasty. This low dose of aspirin, which results in suboptimal inhibition of platelet aggregation, may have adversely affected the outcome of the patients undergoing angioplasty.

Both the TIMI IIB trial and the Should We Intervene Following Thrombolysis trial (SWIFT) showed a trend for a higher early adverse cardiac event rate for the invasive strategy group, subsequently followed by a trend for a lower adverse outcome rate.[2,3] A short duration of follow up potentially biases the outcome data against the invasive strategy group. Additional follow–up data beyond one year is needed to definitively determine the relative outcome of the invasive and conservative groups.

The ongoing Thrombolysis in Myocardial Infarction IIIB trial (TIMI IIIB) compares an invasive treatment strategy to a conservative treatment strategy for patients with unstable angina and non–Q–wave myocardial infarction.[4,5] The TIMI IIIB trial, similar to the TIMI IIB trial, uses a suboptimal dosage of aspirin prior to angioplasty and has a relatively short duration of follow–up.

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The TIMI (Thrombolysis in Myocardial Infarction) trials have substantially influenced the treatment of patients presenting with an acute myocardial infarction. The TIMI IIB trial compared a conservative treatment strategy to a delayed invasive treatment strategy in the setting of an acute Q–wave myocardial infarction following thrombolytic therapy[1] (Table 1).

The ongoing TIMI IIIB trial compares a conservative treatment strategy to an invasive treatment strategy for patients presenting with unstable angi-

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na or a non–Q–wave myocardial infarction[4,5] (Table 2). Given the major impact that large clinical studies have on the standards of optimal clinical practice and the development of future practice guidelines, careful evaluation of these trials is important.

TIMI IIB

Was the Aspirin Dose Used in the TIMI IIB Trial Insufficient for Achieving Optimal Angioplasty Results?

The TIMI IIB trial used a low dose of aspirin which would not achieve optimal antiplatelet effects in patients prior to angioplasty being performed. This would potentially adversely affect the outcome of the patients assigned to the invasive strategy undergoing angioplasty.

In the TIMI IIB trial, a particular delayed invasive strategy was compared to a defined conservative strategy for the treatment of the postmyocardial infarction patient following tissue plasminogen activator (tPA).[1] The invasive strategy consisted of pretreatment of patients with systemic heparinization and low dose aspirin prior to cardiac catheterization which was performed 18 to 48 hours after thrombolytic therapy (Table 1).[1] Percutaneous transluminal angioplasty (PTCA) was performed at the same time as the initial catheterization if suitable coronary anatomy was present. In the TIMI IIB trial, aspirin was started as an 80 mg dose on day one in the first 328 patients. In the subsequent 2,934 patients after a protocol modification was made because of an initial high cerebrovascular event rate, the tPA dose was decreased and aspirin was started on day two rather than day one as an 80 mg dose. The dosage of aspirin increased to 325 mg on the 6th day following randomization for all patients. *Since angioplasty was most frequently performed 18 to 48 hours after the initiation of tPA therapy, most patients undergoing angioplasty in the invasive strategy group would have received only a single 80 mg dose of aspirin prior to PTCA.*

Table 1. TIMI IIB Trial

Patients entered: 3262 patients with an acute myocardial infarction with ST elevation.

Treatment strategy arms:

A. *Invasive Strategy* — Received tPA, aspirin 80 mg, and underwent cardiac catheterization with PTCA if suitable coronary anatomy present at same setting as catheterization 18-48 hours after the thrombolytic therapy initiated.

B. *Conservative strategy* — Received the same medication, including tPA and underwent catheterization with consideration of mechanical revascularization only if recurrent ischemia or a positive exercise treadmill occurred.

A Single Acute Dose of 80 mg of Aspirin is Not Adequate to Achieve the Full Antiplatelet Effects of Aspirin.

A single acute dose of 80 mg of aspirin is not adequate to achieve the full antiplatelet effects of aspirin.[6] Given the intense thrombotic stimuli in

Table 2. TIMI IIIB Trial — Multicenter cooperative ongoing trial

Patient Population:
Patients presenting with unstable angina or an acute non–Q–wave myocardial infarction.

Goal of Study:
1) Comparison of an invasive to a conservative management strategy.
2) Comparison of tPA vs. no tPA.

Treatment Strategy Arms
Invasive – routine catheterization and PTCA when appropriate coronary anatomy present.
Conservative – catheterization only if recurrent ischemia or failed treadmill test.

Medication Regimen (antithrombotic)
1) Enteric–coated aspirin (Ecotrin) 325 mg po qd beginning on day 2.
2) Aspirin 80 mg po qd beginning on day 2 was the aspirin dosage used for the initial patients entered into the trial. Subsequently changed to 325 mg of enteric–coated aspirin.
3) Heparin intravenously.
4) 50% with tPA vs. 50% receive placebo.

the coronary artery during an acute myocardial infarction,[7] a very potent stimuli to platelet aggregation like a collagen stimulus is appropriate to consider. The crucial biologic parameter in regards to the effect of aspirin on angioplasty outcome is the inhibition of platelet aggregation. Low dose aspirin, when used as a single dose, may markedly inhibit platelet thromboxane production, but not result in the full inhibitory effects of aspirin on platelet aggregation.[6]

When a single acute dose of 100 mg of aspirin was studied in regards to the inhibition of platelet aggregation in response to a collagen stimulus, it was found that only a small portion of the potential inhibitory effect of aspirin was achieved by that dose even at 24 hours.[6] The effects of low dose aspirin on platelets develop in a cumulative fashion over a number of days.[6,8] Hence, the majority of patients in the invasive strategy of the TIMI IIB trial who were pretreated with a single 80 mg aspirin dose underwent angioplasty without the benefit of the full antiplatelet effects of aspirin.

Pretreatment with Aspirin is Important in Reducing Periprocedural Complications Occurring with PTCA.

The pretreatment of patients with effective doses of aspirin has been shown to significantly influence the outcome of PTCA.[9,10] A prospective randomized trial of patients undergoing angioplasty comparing placebo vs. aspirin plus dipyridamole, showed a 6.9% incidence of myocardial infarction following PTCA in the placebo group, compared to a 1.6% incidence in those patients receiving aspirin.[10] Hence, the early myocardial infarction and reocclusion rate was decreased more than fourfold in those patients receiving aspirin. (The patients received three separate doses of 330 mg of aspirin prior to angioplasty and in no case was an enteric–coated formulation of aspirin used.)[10] A subsequent study indicated that dipyridamole did not have an additive effect beyond that of aspirin, suggesting that the benefit previously documented was solely the result of aspirin.[11]

The use of thrombolytic therapy prior to angioplasty does not appear to eliminate the need for aspirin therapy. Platelet activation occurs in vivo with tPA therapy in the setting of an acute myocardial infarction.[12] Pretreatment with aspirin prior to thrombolytic therapy appears to markedly limit the platelet activation which is seen following tPA therapy in patients experiencing a myocardial infarction.[12]

There is also suggestive evidence from the European Cooperative Study Group Trial that the dose of aspirin is an important variable affecting the acute reocclusion rate in the setting of thrombolytic therapy in patients with an acute myocardial infarction.[13] In the invasive treatment strategy group of that study, PTCA was performed very early in the course of an acute myocardial infarction during thrombolytic therapy.

At first, a lower dose of oral aspirin (75 to 125 mg) was used in the European Cooperative Trial as the initial dose of aspirin. However, with this dosage of aspirin, PTCA was associated with transient acute reocclusion in four out of every seven patients undergoing PTCA, and one out of every seven patients developed persistent reocclusion with PTCA. A protocol change was therefore made during the trial and the dose of aspirin for the remaining patients was increased to 250 mg intravenously. This was followed by an apparent reduction in the acute occlusion rate at the time of angioplasty in subsequent patients. Hence, the European Cooperative trial provides further support that full dose aspirin given as pretreatment in the early post thrombolytic state for patients with an acute myocardial infarction is important in obtaining and maintaining optimal angioplasty results.

Can Pretreatment with Medication Significantly Influence the Acute and Early Complication Rate of Angioplasty?

The acute and early complication rate occurring with PTCA is in part determined by the interaction of the balloon dilation with a specific set of medications given to pretreat the artery prior to balloon inflation. Aspirin in effective doses, as noted earlier, markedly decreases the acute and early reocclusion rates associated with PTCA.[9,10] Adequate heparinization is also necessary to avoid acute reocclusion. A relatively prolonged course of heparin appears to reduce the acute complication rate associated with angioplasty in the setting of unstable angina.[14]

An area that needs further study is whether the particular thrombolytic pretreatment regimen influences the outcome of subsequent PTCA in the setting of an acute ischemic syndrome. In the TAMI V trial, none of the small number of patients given combination thrombolytic therapy with urokinase and tPA who underwent successful rescue angioplasty experienced reocclusion during the hospital course.[15] This parallels the overall lower reocclusion rate found in that study for all patients, including those not undergoing PTCA, treated with combination thrombolytic therapy (2%) compared to patients receiving urokinase (7%) or tPA monotherapy

(12%). Interestingly, the overall reocclusion rate in the TAMI studies taken in aggregate also suggests a higher reocclusion rate for tPA.[15] The numbers though, are not adequate to draw any conclusions in regard to a difference in angioplasty outcome as a result of a particular thrombolytic agent or combination of agents. However, this remains an interesting area for further research. Of note, the ongoing TIMI IIIB trial has the potential to provide information concerning whether tPA monotherapy compared to placebo positively or negatively impacts the angioplasty periprocedural complication rate.

The Early Reocclusion Rate of Angioplasty Plays a Pivotal Role in Affecting Comparative Outcomes of an Invasive vs. a Conservative Strategy.

The early reocclusion rate following angioplasty, which is affected by aspirin, is an important determinate influencing the relative outcome of an invasive treatment strategy approach when compared to a conservative treatment strategy approach. The European Cooperative Study Group published an analysis of why their study showed a lack of benefit for immediate PTCA performed following thrombolytic therapy.[16] They suggested "that reocclusion and reinfarction might be responsible for the lack of benefit of the invasive strategy. This implies that immediate coronary angioplasty may be beneficial in selected patients, provided these complications can be prevented."[16]

The TIMI IIB trial outcome data demonstrated a worse outcome for the invasive strategy group at one week after randomization in regards to reinfarction and survival.[3] If the initial high early complication rate of PTCA was selectively reduced, it is possible that the invasive strategy group might have had a better outcome that what otherwise resulted.

The Duration of Follow–up of the TIMI IIB Trial and the SWIFT Trial have been of Insufficient Duration at One Year to Reliably Assess Outcome.

The TIMI IIB and the SWIFT trials are two large studies which have compared a delayed invasive strategy to a conservative strategy following thrombolysis in patients with recent myocardial infarction where mortality and reinfarction were primary endpoints (Table 3).[1,2] *One year of follow–up in regards to mortality and reinfarction rates for the TIMI IIB and SWIFT trials has not been of sufficient duration to reliably assess differences between treatment groups. The outcome data from both trials suggests that the invasive strategy group may have a worse outcome early in the trials, but then tended to have a lower rate of adverse events as the trials continued to proceed*[2,3] *(Figures 1, 2).* Neither study established that this lower adverse cardiac event rate was statistically significant with the current one year duration of published follow–up. The TIMI IIB trial did show a statistically significant worse initial outcome for the invasive strategy group at one week. Since that

Table 3. Large Trials Comparing and Invasive Strategy to a Conservative Approach in the Setting of an Acute Myocardial Infarction Following Thrombolytic Therapy

TRIAL	Number of Patients	Aspirin dose prior to angioplasty	Thrombolytic Agent	Published duration of follow–up
TIMI IIB (Thrombolysis in Myocardial Infarction)	3262	80 mg	tPA	1 year
SWIFT Trial (Should We Intervene Following Thrombolysis)	800	Variable, aspirin use not defined by protocol	Anistreplase	1 year
TIMI IIIB (includes non–Q–wave MI patients and unstable angina patients)	ongoing	80 mg for initial patients, 325 mg enteric–coated aspirin for subsequent patients	tPA	Planned duration of followup is six weeks and one year

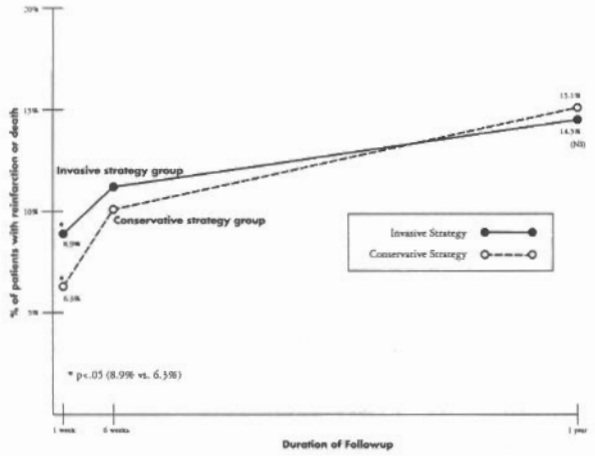

Figure 1. *TIMI IIB Invasive Strategy Group vs. Conservative Strategy Group; Comparison of Combined Endpoint of Reinfarction or Death. Invasive Strategy Group had more frequent adverse outcome (8.9% vs. 6.3%, invasive vs. conservative, p ≤ .05) at one week, but not at one year (14.5% vs. 15.1%, invasive vs. conservative, NS).*

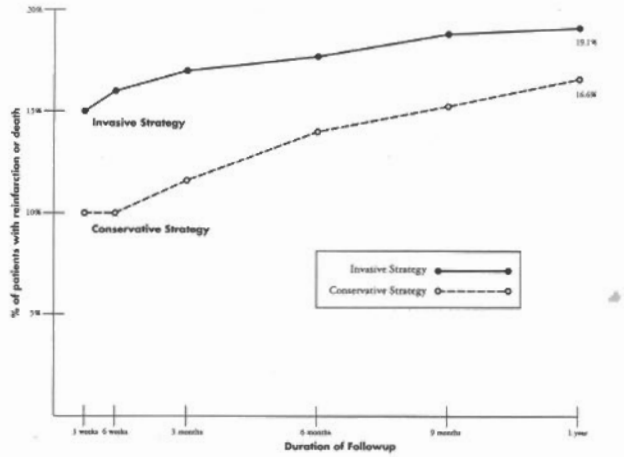

Figure 2. *SWIFT Trial; Conservative Strategy Group vs. Invasive Strategy Group; Comparison of Combined Endpoint of Reinfarction or Death.*

time there has been a crossing over the curves comparing the two treatment groups in regards to reinfarction and mortality at one year (Figure 1). Whether this trend will continue after one year resulting in a significant difference in outcome developing between the invasive and conservative treatment groups after two or three years of follow up, is not yet known.

Should the Duration of Follow–up for a Trial Comparing an Invasive Strategy vs. a Conservative Treatment Strategy be Similar in Duration to Prior Trials of Medical Therapy vs. Coronary Artery Bypass Grafting Surgery?

The prior major cooperative studies comparing medical therapy versus coronary artery bypass grafting surgery have compared mortality outcome endpoints for at least five years of follow–up.[17,18] Differences in outcome not present at one year may develop later in subsequent follow–up. *In the Coronary Artery Surgery Study (CASS), the patients who had decreased left ventricular function and triple vessel disease had less mortality when treated surgically, though this significant difference in outcome was not present at one year, but developed in later years of subsequent follow–up.*[17] *Analysis at six weeks or even one year of a trial comparing medical versus surgical therapy, may miss important differences in outcome.* Both coronary artery bypass grafting surgery and angioplasty may have many of their untoward clinical events early in the course of treatment as perioperative myocardial infarctions and fatalities. The differences in outcome between medical treatment and surgical treatment can take several years to develop. The appropriate duration of follow–up for angioplasty versus a conservative treatment strategy for the endpoints of mortality or reinfarction should be similar to what has been established for bypass surgery versus medical therapy trials.

The line of reasoning that the TIMI IIB trial requires a shorter follow–up because it is a comparison of two treatment strategies, "conservative" versus "invasive," does not hold up under closer examination. The prior coronary surgery versus medical therapy trials such as CASS, can also be viewed as trials of a conservative strategy versus a routine mechanical revascularization approach. In those trials, the particular conservative strategy consisted of treatment with medication, unless the patient developed uncontrolled ischemia, at which time the patient underwent coronary artery bypass grafting surgery. The conservative strategy in the TIMI IIB trial has different criteria for proceeding (recurrent ischemia or a positive exercise treadmill test), but is fundamentally similar in that the patient is treated conservatively unless prestated criteria develop, which can then lead to proceeding with mechanical revascularization.

The TIMI IIB trial is different in that not all patients assigned to the invasive strategy undergo mechanical revascularization. However, this difference does not inherently decrease the duration of time which is appropriate for comparing a strategy

which uses predominantly mechanical revascularization versus a conservative strategy when the endpoints involved are reinfarction and mortality. Hence, trials comparing an invasive strategy employing angioplasty when the coronary anatomy is appropriate to a conservative treatment strategy should have a similar duration of follow–up as trials evaluating coronary bypass surgery compared to medical therapy. The duration of follow–up appropriate may vary depending on the endpoints being evaluated, with mortality endpoints requiring a long interval of follow–up.

Outcome of Trials Using Higher Doses of Aspirin with Angioplasty Following Thrombolytic Therapy.

Several studies have used larger doses of aspirin prior to performing PTCA.[19-21] A study by Barbash et al., which consisted of 201 patients randomized to an invasive vs. a conservative strategy using 250 mg of aspirin following thrombolytic therapy, did not show a significant difference in mortality when the two groups were analyzed at one year on the basis of intention to treat.[19] There were eight deaths in the invasive group, and four deaths in the conservative group. A small trial by Topol et al. of 50 patients using 325 mg of aspirin following thrombolytic therapy had a lower incidence of reinfarction and angina for the angioplasty treated group compared to the conservative group,[21] but the numbers were too small to be truly meaningful in regards to that issue. Trials that are small in size may not be of sufficient magnitude to reliably evaluate for differences in mortality and reinfarction endpoints.

In the large TIMI IIB trial, the immediate angioplasty outcome for patients in the delayed invasive arm showed an incidence of lesion improvement of 90.4% and a relatively low incidence of emergency bypass surgery at 2.4%.[22] In the Thrombolysis and Angioplasty Myocardial Infarction (TAMI) trial, the delayed angioplasty group, which received pretreatment of 325 mg of aspirin, had a 92% success rate of angioplasty.[20] In the study by Barbash et al. the angioplasty success rate was 91%.[19] The angioplasty success rates are essentially the same for the higher dose aspirin trials, in comparison to the TIMI IIB trial which used a lower dose of aspirin. However, cross comparisons between trials for respective mortality, reinfarction, and angioplasty success rates are confounded by multiple factors and are less reliable than comparisons within a trial between randomized groups of sufficient size.

Although the initial angioplasty success rate of the TIMI IIB trial was 90.4%, there remains the potential for improvement. The rate of adverse cardiac events (death or reinfarction) for the TIMI IIB invasive strategy group at one week was 8.9%.[3] In the words of the TIMI investigators, "death/nonfatal myocardial infarction occurred early, particularly in invasive patients, possibly implicating procedural related events."[3]

TIMI IIIB

The Ongoing TIMI IIIB Trial Administers Suboptimal Pretreatment with Aspirin Prior to Angioplasty.

The TIMI IIIB trial involves patients with unstable angina or non–Q–wave myocardial infarction.[4,5] The patients are randomized to either an invasive strategy predominantly utilizing coronary angioplasty or a conservative strategy. In both the invasive and conservative treatment groups, half of the patients will receive heparin and aspirin, while the other half of the patients will receive heparin and aspirin following tPA administration (Table 2).

The outcome of the patients assigned to the invasive strategy in the TIMI IIIB trial may be negatively impacted by a suboptimal aspirin dose. Some of the patients in the invasive strategy by protocol design will not have developed the full aspirin antiplatelet effect prior to undergoing angioplasty.

The initial patients entered into the TIMI IIIB trial were treated with an 80 mg dose of aspirin.[4] The initial TIMI IIIB trial protocol called for the patients to receive no aspirin during the first 24 hours after randomization. On day 2 aspirin was to be started at an 80 mg dose. The protocol also called for the patients in the invasive strategy to undergo arteriography and angioplasty if the suitable coronary anatomy is present at 18 to 48 hours after randomization. This resulted in the initial patients in the TIMI IIIB trial usually receiving only an 80 mg dose of aspirin 0 to 24 hours prior to angioplasty. *However, a single acute dose of 80 mg of aspirin is inadequate to achieve the full antiplatelet effects of aspirin.*[6] The pretreatment of patients with aspirin prior to the performance of angioplasty is necessary for obtaining optimal angioplasty results.[9,10] Hence, the initial patients that were entered into the TIMI IIIB trial had suboptimal pretreatment with aspirin prior to undergoing angioplasty. This may tend to increase the early complication rate of angioplasty, and thereby negatively affect the out-

come of the invasive strategy group.

Because of subsequent concern that this dose of aspirin was not optimal, a protocol revision in the TIMI IIIB trial was made which now calls for aspirin to be given in a dose of 325 mg in the form of enteric–coated aspirin (Ecotrin).[5] Hence, some of the patients in the invasive strategy will have been pretreated with 80 mg of aspirin and others will have received a 325 mg dose of enteric–coated aspirin. In addition, it is possible that a small number of patients may have received heparin without aspirin or thrombolytic therapy prior to undergoing angioplasty.

Suboptimal Platelet Inhibitory Effect of a Single 325 mg Acute Dose of Enteric–Coated Aspirin Prior to Angioplasty in the Current Modification of the Ongoing TIMI IIIB Trial.

The revised TIMI IIIB protocol calls for 325 mg of enteric–coated aspirin to be given in the place of the 80 mg dose initially used in the trial.[5] The use of a single acute dose of enteric–coated aspirin prior to angioplasty will potentially result in a variable degree of antiplatelet effect being present depending on the duration of the time elapsing between the dose and the angioplasty, and the individual patient.[23] The patients by protocol design are to receive the first dose of enteric–coated aspirin on day two after randomization. The invasive strategy patients, however, undergo angioplasty 18 to 48 hours after randomization. Hence, the majority of patients in the invasive strategy group will have received only a single acute dose of enteric–coated aspirin 0 to 24 hours prior to angioplasty.

Enteric–coated aspirin in the form of a single 325 mg acute dose does not uniformly give the full antiplatelet effect of aspirin early after a single acute dose.[23] Though any form of aspirin if chewed provides rapid availability of aspirin, enteric–coated aspirin when swallowed whole as a single acute dose results in a variable onset of the timing of platelet inhibition. In normal young, healthy volunteers it was found that some individuals took longer than 10 hours to develop the full antiplatelet effect conveyed by aspirin after a single acute dose.[23] Compared to healthy, young volunteers, the patient population of the TIMI IIIB trial may experience an even greater variability in the delay of the development of platelet inhibitory effects found with a single acute dose of enteric–coated aspirin. This potentially results from the decreased gastrointestinal motility that can occur in an older patient population and from the presence of an acute major illness.

Most of the TIMI IIIB patients assigned to the invasive strategy group, who undergo initial angioplasty, have this performed 0-24 hours after the initial dose of enteric–coated aspirin.[5] *Hence, some patients will undergo angioplasty prior to development of the full antiplatelet effect of aspirin.* Given the individual variability in achieving the full antiplatelet effects of aspirin, some of the patients assigned to the invasive strategy, may have a less favorable outcome with angioplasty than what may occur with the full effects of aspirin being present at the time of balloon angioplasty.

Suboptimal Duration of the Pretreatment with Heparin and Aspirin Prior to Angioplasty in the TIMI IIIB Trial.

The standard of care when angioplasty is performed in the setting of unstable angina, has been the pretreatment of patients with full doses of both aspirin and heparin.[24] It has been suggested that a prolonged duration of heparin prior to the performance of the angioplasty, may improve the outcome of the angioplasty.[14,25-27]

In stable angina, the typical associated coronary artery lesion when viewed by angioscopy is a smooth lipid–lined plaque.[28] Immediate pretreatment with aspirin and heparin prior to angioplasty in this situation may well be adequate. However, in unstable angina there is a ruptured plaque frequently associated with thrombus formation.[28] At the site of the coronary lesion in unstable angina, there are ongoing thrombotic mechanisms as well as fibrinolytic mechanisms. In this situation, the duration of the heparin and aspirin therapy may conceivably influence the state of the plaque at the time of angioplasty. Hence, there are both theoretical rationale and clinical support for prolonged heparin and aspirin therapy prior to dilatation in the setting of unstable angina to optimize results.

However, in the TIMI IIIB trial, the invasive strategy is tied to a relatively short duration of pretreatment with the combination of heparin and aspirin.[4,5] The aspirin is given 0 to 24 hours prior to the performance of angioplasty. Heparin will be given for 18 to 48 hours prior to angioplasty. An even longer duration of heparin therapy may be beneficial in improving angioplasty results for patients with unstable angina,[14,25-27] though the optimal duration of pretreatment with heparin has not been established. In particular, the TIMI IIIB protocol design does not specifically call for an additional time interval of heparin and aspirin to

be administered if a thrombus is seen at the time of catheterization prior to proceeding with angioplasty in a patient that has otherwise become relatively clinically stable.[29,30,31]

Hence, in the TIMI IIIB protocol, before the aspirin dosage was modified, the patients assigned to the invasive treatment strategy were hindered by both a low dose of aspirin and a relatively short duration of heparin and aspirin therapy (Table 4). Even after the aspirin dose had been increased, the duration of full antiplatelet effects resulting from aspirin prior to angioplasty in patients assigned to the invasive strategy will be variable given that aspirin is given as a single, acute, enteric–coated dose. This results in some of the patients randomized to the invasive strategy group receiving heparin alone with suboptimal aspirin effects and no thrombolytic therapy prior to undergoing angioplasty.

The Natural History of Unstable Angina and Non–Q–Wave Myocardial Infarction Makes Comparison of Mortality Endpoints at Six Weeks Premature When Comparing an Invasive vs. a Conservative Strategy.

Unstable angina is associated with a high frequency of adverse cardiac events during the first twelve months after initial presentation.[32,33] The VA Cooperative Study of Unstable Angina documented a high frequency of patients in the medical strategy group requiring surgical therapy during the first 16 months of the trial.[32]

Non–Q–wave myocardial infarctions have a significant adverse cardiac event rate occurring during the first year following the initial infarction.[34,35] Hence, both unstable angina and non–Q–wave myocardial infarction patients continue to have a significant frequency of adverse cardiac events after the initial presentation that persists beyond six weeks, and up to one year.

Analyzing endpoints in regards to mortality and reinfarction when comparing a medical strategy to a predominantly revascularization strategy at six weeks and one year for any type of ischemic heart disease patient has potential problems. Both coronary artery bypass surgery and angioplasty are subject to perioperative myocardial infarctions and fatalities early in the course of treatment. As noted earlier, the TIMI IIB trial and the SWIFT trial exhibited a trend towards a higher, early, adverse cardiac event rate for the invasive strategy group followed by a trend for a lower late cardiac event rate.[2,3] Early evaluation of cardiac endpoints may, therefore, unintentionally bias the outcome against the invasive strategy approach.

Though trials such as the VA Cooperative Study of Unstable Angina in patients with abnormal left ventricular function have shown a difference between surgical and medical treatments developing by one year,[32] this does not provide a guarantee that significant differences that later develop will be manifest within the initial first year. Analysis of mortality data at six weeks, or even at one year, of a trial comparing a conservative treatment strategy to a strategy predominantly involving mechanical revascularization, may miss important differences in outcome that subsequently develop.[17]

Table 4. Factors Predisposing to a Less Favorable Outcome with Angioplasty in the Invasive Strategy Patients with Unstable Angina in the TIMI IIIB Trial.

1. Performing coronary artery angioplasty without the full platelet inhibitory effects of aspirin being uniformly present in patients at the time angioplasty is performed.
2. Allowing the use of enteric–coated aspirin as a single dose prior to angioplasty given the individual variability of the onset of the full antiplatelet effects with this form of aspirin when swallowed whole and used as a single acute dose.
3. Employing a relatively short time period that the unstable coronary artery plaque is pretreated with an effective dose of aspirin and heparin prior to performing balloon dilatation.
4. Not specifying by protocol design an additional *time interval of heparin and aspirin if a throm*bus is seen at the time of catheterization prior to proceeding with angioplasty in a patient who has become otherwise relatively clinically stable.
5. Comparing clinical endpoints early at six weeks and one year since an invasive revascularization strategy has much of its adverse outcome occurring early after the intervention, while the natural history for unstable angina and non–Q–wave myocardial infarctions includes a persistent adverse cardiac event rate which can extend past one year.

CONCLUSIONS

The TIMI IIB and IIIB trials both compare an invasive strategy to a conservative strategy. As inherent in any trial comparing treatment strategies, a particular invasive strategy is compared to a particular conservative strategy. The invasive strategy group in both the TIMI IIB trial and the TIMI IIIB trial receives less than the optimal dose of aspirin needed to uniformly achieve the full antiplatelet effects of aspirin in all patients prior to the performance of angioplasty. This potentially compromises the results of angioplasty and may adversely affect the relative outcome of the invasive strategy group.

The long term comparative outcome of the particular conservative and invasive treatment strategies used in the TIMI trials may not be known at the end of the first year of followup. An invasive strategy with a high rate of mechanical revascularization when compared to a conservative treatment strategy may take longer than one year to manifest differences that involve mortality and reinfarction endpoints. The need for follow–up beyond one year applies as well to the subgroup analysis planned for the TIMI IIIB trial.

Collectively, there are factors in the TIMI IIIB trial protocol design which may negatively affect the relative outcome of the invasive strategy group compared to the conservative strategy group resulting in an unintended bias of trial results. Even if a benefit is documented for the invasive strategy group with this protocol, it may be of a lesser magnitude than would otherwise have been found. In addition, if subgroup analysis of the outcome data is performed as planned in the TIMI IIIB trial, some subgroups which may possible benefit from an invasive approach, might not reveal that benefit given the limitations in the protocol.

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