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MUHC -Technology Assessment Unit

An evaluation of glycoprotein IIb/IIIa inhibitors during percutaneous coronary interventions at the MUHC: Is there a difference between the drugs?

By

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This analysis was prepared for the Technology Assessment Unit (TAU)

of the McGill University Health Centre (MUHC)

by

Jay Brophy MD PhD, Director of the TAU

and approved and adopted by the committee of the TAU:

Dr. J. Barkun, Mr. W. Brodie, Mr. J. Johnston, Ms M. Kaplow,

Ms J. MacPhail, Dr. G. Pekeles, Dr. R. Rajan, Dr J. Ritchie,

Dr. F. Salevsky, Dr. S. Suissa, Dr. J. Brophy, Dr. M.McGregor.

With the additional ad hoc membership of

two MUHC interventional cardiologists

Dr. Pierre Beaudry, Dr. Yves Beaudry

REVIEWERS

The following individuals provided review comments on this report. MUHC-TAU takes sole responsibility for final form and content.

External Reviewers

Dr Pierre Beaudry, interventional cardiologist MUHC (RVH)

Dr Yves Beaudry, interventional cardiologist MUHC (MGH)

Madame Christiane Berubé, administrative manager cardiac catheterisation lab

Invitation. *This document was designed to assist decision-making in the McGill University Health Centre. Others are welcome to make use of it, preferably with acknowledgment. More important, to assist us in making our own evaluation, it would be deeply appreciated if potential users could inform us whether it has influenced policy decisions in any way, and even if it has not, whether it has been helpful in informing decision makers.*

e-mail maurice.mcgregor@mcgill.ca

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Foreword

On May 16, 2002, the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC) received a request from the Associate Director of Professional Services, Dr. Michel Marcil, to provide some guidance on the use of Glycoprotein IIbIIIa (GP2b3a) inhibitors to treat acute coronary syndromes at the McGill University Health Centre (MUHC). GP2b3a inhibitors are intravenous drugs administered for 24 to 96 hours to hospitalized patients. As a consequence, the costs incurred are to be assumed by the hospital. The TAU agreed to proceed to a formal evaluation at the June 18, 2002 Committee Meeting.

The report was first presented to the full TAU committee on October 8, 2002 and accepted at the TAU meeting of November 21, 2002.

EXECUTIVE SUMMARY

This report is an evaluation of the role and choice of glycoprotein IIb/IIIa inhibitors during percutaneous coronary interventions at the MUHC. Ischemic heart disease remains a leading cause of patient morbidity and mortality. Percutaneous coronary interventions (PCI) are an accepted treatment, in certain situations, for both its stable and unstable variants. The major benefit of PCI is in improving patient quality of life. However, this technique is not devoid of complications, particularly in certain high-risk patient groups. The most frequent complication is a peri-procedural myocardial infarction.

Glycoprotein IIbIIIa (GP2b3a) inhibitors are powerful anti-platelet medications which have been studied in over 18,000 patients undergoing PCI. At present, 3 GP2b3a inhibitors (abciximab, eptifibatide, tirofiban) have been extensively studied against placebo and all are approved for use in Canada and are on the MUHC formulary. Abciximab was the first studied and the majority of the published reports have concerned this drug. Not surprisingly, this has become the standard GP3b2a drug used at the MUHC.

There has been only one comparative study between these drugs, abciximab versus tirofiban. The short term (30 day) results of this study demonstrated the superiority of abciximab in reducing non-fatal myocardial infarctions (no difference in mortality or the need for urgent revascularizations). However, by 6 months there were no differences in clinical outcomes. Moreover, a recent placebo controlled trial with eptifibatide showed similar reductions in adverse outcomes as seen with abciximab. Finally acute coronary syndrome patients admitted, and not proceeding directly to PCI, have demonstrated similar benefits with tirofiban and eptifibatide but surprisingly not with abciximab.

While there appears to be little difference in efficacy, there are major differences in acquisition costs between the drugs, with abciximab being approximately $1,350 more expensive per dose than the others. Even allowing for some continued use of abciximab (10-20%) for special clinical situations, the switch to eptifibatide or tirofiban could amount to yearly savings of approximately $400,000.

Based on the synthesis of all available information, this evaluation concludes that there is probable therapeutic equivalence between the GP 2b3a inhibitor drugs. Given the incremental cost associated with abciximab, the TAU Committee recommends;

"Routine use of GP 2b3a inhibitors during PCI is not recommended in the MUHC catheterization laboratories. Rather, treatment should be reserved for high-risk patients as defined by clinical and angiographic assessments. Since there are no clinically meaningful differences in outcomes between the different agents, in most cases the lower priced agents, tirofiban or eptifibatide, should be favored. It is nevertheless recognized that the more expensive agent, abciximab, may be the preferred drug for certain specific clinical indications."

INTRODUCTION

Ischemic heart disease remains the leading cause of patient mortality and morbidity. Percutaneous coronary interventions (PCI) have become an accepted means of treating the symptoms of ischemic heart disease. According to the American Heart association over 600,000 angioplasties were performed in the United States in 2001 and approximately 1,000 are performed annually at the MUHC. PCI is generally a safe technique with low rates of mortality and morbidity.

However, PCI with uncontrolled plaque rupture may expose underlying plaque debris, such as von Willebrand factor and vitronectin, which then interact with the glycoprotein IIb/IIIa receptor on the platelet membrane leading to platelet aggregation. This cross-linking of activated platelets with fibrinogin is known as the final common pathway of platelet aggregation and may mediate many of the complications associated with interventional procedures, including death, myocardial infarction, or recurrent ischemia requiring repeat intervention.

In the mid 1980's a mouse monoclonal antibody was produced against this platelet receptor that was known initially as 7E3and later as abciximab. Logically the first clinical trials to investigate the therapeutic benefits of this new class of drugs were performed in high risk patients undergoing coronary angioplasty. Subsequently these agents have been studied as routine therapy in patients admitted with acute coronary syndromes who may not proceed to the catheterization laboratory.

Given the potential volume, relative high cost and abundance of clinical information regarding efficacy, it was felt that the role and choice of GP 2b3a inhibitors would be a useful topic for a health technology assessment. This first report addresses the utilization of GP 2b3a

inhibitors in the cardiac catheterization laboratory and a later report will examine their role in the coronary care unit.

BACKGROUND FOR GP2b3a INHIBITOR USE

General

Abciximab was the first FDA approved GP 2b3a inhibitor and has been the most intensively studied. It is a chimeric human murine monoclonal antibody. Abciximab is different from most other GP IIb/IIIa receptor inhibitors in that it is not as specific in its binding. It has been shown that abciximab binds equally well to both the vitronectin surface receptor found on the surface of activated endothelial cells and smooth muscle cells as well as to specific leukocyte receptors. Abciximab has the longest half-life of these drugs. Tirofiban is a nonpeptide, tyrosine-derivative fibrinogen receptor antagonist. Eptifibatide is a low molecular weight synthetic cyclic heptapeptide GP 2b3a inhibitor with a short half-life (90 minutes) and rapid onset of action.

At therapeutic levels all these agents have generally been showed to suppress platelet aggregation by at least 80%. These drugs are administered intravenously over 1 to 4 day period in the acute episode. Typically, the drugs are started before PCI and continued for 12 to 18 hours. The standard doses and acquisition costs of these drugs are shown in Tables 1 and 2. The approved indications for these drugs are given in Appendix 1.

Guidelines as to the use of GP2b3a inhibitors

Essentially there are two different clinical scenarios that may lead to the introduction of these medications. The drugs were initially studied as adjunctive therapy in the cardiac catheterization laboratory with patients undergoing percutaneous coronary interventions

(angioplasty) and this is the indication evaluated in this report. Subsequently, studies have been undertaken where the drug therapy was initiated in patients admitted to the coronary care unit with acute coronary syndromes (unstable angina or myocardial infarction) where PCI was not acutely planned. This second scenario will be discussed in a separate report.

The most recent clinical guidelines on the treatment of the acute coronary syndromes come from the American College of Cardiology and the American Heart Association (ACC/AHA) and include indications for the use of GP2b3a inhibitors(1). The classification scheme used in the recommendations and in summarizing the evidence, as well as the actual recommendations, are given in Appendix 2. Basically, the guidelines endorse the use of GP2b3a inhibitors in all cardiac patients undergoing PCI. These practice guidelines are based exclusively on efficacy and safety issues, with no consideration of total cost or cost-effectiveness.

Only one health technology assessment was found. The National Institute for Clinical Excellence of the United Kingdom, a health technology assessment agency concerned with cost as well as safety and efficacy has been equally enthusiastic and concludes(2);

> *For patients undergoing acute or elective percutaneous coronary intervention (PCI), the intravenous use of GP IIb/IIIa inhibitors (consistent with current UK licensing) is recommended.*

Given the high financial stakes (see Table 3), it was decided to thoroughly review the evidence for support of GP2b3a inhibitors in PCI, rather than simply accepting existing interpretations of the literature with the recommendations mentioned above. In this report, we examine not only the clinical benefits but also the choice of which GP2b3a inhibitor to use during PCI.

THE EVIDENCE FOR GP2B3A INHIBITORS USED WITH PERCUTANEOUS CORONARY INTERVENTIONS (PCI)

The first randomized study comparing a GP2b3a inhibitor to placebo was published in 1994 and addressed a population of high risk angioplasty patients(3). Subsequently, 10 other trials have been published comparing GP2b3a drugs to placebo both in stable and unstable patients undergoing PCI (4-13). The results from these trials are presented in Table 4 and show a total of 18,545 patients randomized. The three different drugs used are abciximab, eptifibatide and tirofiban. The study quality has been high with proper randomization, excellent treatment concealment and no loss to follow-up. Consequently there are no selection, performance or attribution biases and, we have no reservations about the internal validity of these studies.

Mortality: Despite the high risk populations studied, death rates have been remarkably low both for those receiving GP2b3a drugs (90 deaths in 10,421 patients, 0.9%) and placebo (105 deaths in 8,124 patients, 1.3%), especially considering that some of these trials evaluated patients with evolving acute myocardial infarction (9;10;12;13). We have performed a meta-analysis of all the trials and the results are presented in Figure 1. This shows that these agents are associated with a 28% reduction in mortality at 30 days (OR 0.72, 95% CI 0.54-0.96). While this result is statistically significance, the absolute mortality reduction is exceedingly small (the number needed to treat (NNT) = 277).

Myocardial Infarctions: The benefit in the reduction of myocardial infarctions for patients receiving GP2b3a inhibitors during PCI is more impressive in both relative (OR 0.61 95% CI 0.50-0.73) and absolute terms (NNT = 38, 95% CI 31, 48) (see Figure 2). However, it should be noted

that most of these myocardial infarctions represent only small enzyme rises (micro-infarcts) and their long-term prognostic impact is unresolved.

Composite Endpoints: The commonly reported composite endpoint of death, myocardial infarction or the need for urgent revascularization shows similar relative (OR 0.63 95% CI 0.53 - 0.74) and absolute (NNT = 28, 95% CI 22, 37) benefit (see Figure 3). In terms of composite endpoints, the trials clearly demonstrate, well beyond the possible play of chance, the benefit of treating PCI patients with these agents, regardless of whether they are admitted with AMI or not (see Figure 4). Nevertheless, it should be recalled that 27 of every 28 treated patients derive no benefit from the treatment. In practice, clinicians attempt to circumvent this problem by identifying clinical (example, diabetics) and angiographic (example, presence of thrombus) high-risk profiles that may be expected to gain maximally from this therapy. Thus at present only approximately 1/3 of patients undergoing PCI at the RVH receive these drugs.

A major issue, due to the large cost differentials, is whether there are clinically significant differences between these drugs. This important question is addressed in the next section.

IS THERE A CLINICAL DIFFERENCE BETWEEN THE DIFFERENT GP2B3A AGENTS WHEN USED IN PCI?

This question is most pertinent since there are major cost differences between the three drugs as marketed in Quebec (Table 2). A meta-analysis of all the randomized trials of GP2b3a drugs in PCI stratified according to agent is presented in Figure 5. Although, the majority of the studies have been performed with abciximab, it can be appreciated that there exists favorable data on event reduction compared to placebo for the other agents and that the wealth of evidence is considerable, involving over 18,000 randomized patients.

While all three drugs have demonstrated efficacy against placebo, there is only one comparative trial between the different drugs. This published randomized trial(14) was designed and statistically powered to demonstrate the non-inferiority of tirofiban as compared with abciximab in the setting of percutaneous coronary revascularization. This trial was double-blinded with the intent that PCI would include coronary stenting, as this is now the accepted standard practice. The primary end point (composite of death, nonfatal myocardial infarction, or urgent target-vessel revascularization at 30 days) occurred more frequently among the 2,398 patients in the tirofiban group than among the 2,411 patients in the abciximab group (7.6 percent vs. 6.0 percent; hazard ratio, 1.26; one-sided 95 % CI 1.51). This arbitrary, but nonetheless pre-specified protocol definition of equivalence, required an upper bound of the 95% CI of the hazard ratio for the comparison of tirofiban with abciximab < 1.47, consistent with the preservation of a difference of at least 50% in the effect of abciximab as compared with that of placebo observed in the EPISTENT trial. The data therefore failed to show the non-inferiority of tirofiban and are compatible with a lack of equivalence. Subsequently the protocol design permitted re-testing the data and the superiority of abciximab over tirofiban was demonstrated (two-sided 95 % CI 1.01 - 1.57, P=0.038).

There were few deaths (0.5% vs. 0.4%, P = 0.66) and urgent revascularizations (0.8% vs. 0.7%, P = 0.49) and the composite endpoint was driven by an increase in non-fatal myocardial infarction in the tirofiban group (6.9% vs. 5.4%, P = 0.04). A new myocardial infarction was defined as creatine kinase MB isoform levels at least three times the upper limit of the normal range in two separate blood samples or by the finding of abnormal Q waves on the electrocardiogram. The proportion of small micro-infarcts consisting only of minor increases of

myocardial enzymes was not stated and, as mentioned earlier, the significance of such "infarcts" is unclear.

Abciximab was the first commercial GP2b3a inhibitor introduced and consequently there is increased experience and familiarity with its use. This, reinforced by the TARGET results, has resulted in abciximab remaining the GP2b3a inhibitor therapy of choice when initiation occurs in the catheterization laboratory. Since, it appears unlikely that other comparative trials will be forthcoming to further address this issue, it is important to assess the strength of the evidence from the TARGET trial.

First, one should not overstate the strength of the evidence for the superiority of abciximab from the TARGET trial. It is not always appreciated that a P value of 0.038 is not very strong evidence against the null hypothesis, in this case the non-inferiority of tirofiban. For example, if the probability of the null hypothesis before the trial was 50%, a P value of 0.04 means that there remains an approximate 10% probability that the null hypothesis is still true(15;16).

Second, innovative means of using other data to complement and enhance the results of randomized trials are being increasingly examined(17). In spite of the lack of direct comparative studies, some indirect evidence about their comparative efficacy may be gleaned from trials in patients admitted for acute coronary syndromes. Contemporary statistical theory suggests a more informed decision might be reached by attempting to incorporate other knowledge (prior information) that we have about the relative efficacy of these drugs(18;19) with the results of the only comparative trial, TARGET. To avoid erroneous conclusions, careful attention to study populations and outcome measures are required. While the population in the TARGET trial is not fully described, it appears that a substantial portion had acute coronary syndromes (40% with myocardial infarction) similar to the populations of the PRISM+(20) (tirofiban) and GUSTO

IV(21) (abciximab) acute coronary syndrome trials. In addition, the mean age and percentage with diabetes are very similar between the trials and all record the same standard outcomes at 30 days. Therefore it is not unreasonable to combine some of the prior data from these placebo-controlled acute coronary syndrome trials with the TARGET results. The amount of prior data employed can be varied (discounted) to allow a sensitivity analysis to be performed.

In PRISM+ and GUSTO IV, treated patients had an exactly equal incidence of death or non-fatal MI at 30 days of 8.6%. Incorporating this prior evidence with the TARGET results may enlighten our decision-making process about the relative efficacy of these 2 drugs. In TARGET, the absolute difference of the combined endpoint death/MI was 1.5% (7.2% vs. 5.7%) in favor of abciximab. This is plotted in Figure 6 where the probability curve considering TARGET data alone is centered at this difference. The area under the curve to the left represents the probability that abciximab is superior to tirofiban. For example based on TARGET alone, there is a 98% probability that abciximab is superior to tirofiban. However, the inclusion of the data from PRISM+ and GUSTO IV shifts this curve to the right and the probability of abciximab's superiority falls to only 39%. Even incorporation of only 10% of this prior knowledge results in a reduction of the probability of additional benefit with abciximab to 93%.

Moreover, this approach allows us to consider not merely the probability of superiority but rather that the difference is clinically meaningful by a chosen amount. Previous research in cardiovascular medicine has suggested that a benchmark 1% mortality difference is of clinical significance(22). In the present case, mortality differences are much smaller and for the sake of argument we will propose that a 1% difference of the composite endpoint (death/MI) is clinically important. Since the prognostic significance of a peri-procedural micro-infarct is not completely resolved, others may well argue that an even larger difference is required for clinical significance.

We can evaluate the probability that abciximab is associated with at least a 1% further reduction in the combined outcome of death or myocardial infarction compared to tirofiban by examining the area under the curve to the left of a perpendicular line drawn at –0.01. This gives the probability of a clinically meaningful additional benefit with abciximab to be 75%, 51% or 2% depending on whether one considers only TARGET, TARGET and 10% of the prior data, or TARGET and all prior data, respectively.

This analysis demonstrates the fragility of the evidence from this one study and that consideration of the totality of evidence suggests that there is no clinical difference between the two drugs. This opinion is consistent with longer-term follow-up data from the TARGET trial, which reports that at 6 months, tirofiban provided a similar level of overall protection to abciximab against the composite of death, myocardial infarction, and any target vessel revascularization (356 events among 2,398 (14.8%) tirofiban patients versus 345 in the 2,411 (14.3%) abciximab patients, hazard ratio 1·04, 95% CI 0·90–1·21; P=0·591)(23).

An additional observation supports the conclusion of equivalence. Subgroup analyses of clinical trials have consistently shown that abciximab versus placebo is particularly beneficial among diabetic patients undergoing coronary stenting (24;25) resulting in the largest relative risk reduction in 1-year mortality(26). However, the diabetic sub-population from TARGET had comparable event rates, including similar rates of 6-month target vessel revascularization and 1-year mortality(27). The authors of this study conclude that the unique properties of abciximab do not translate into a discernible long-term clinical benefit compared to tirofiban among diabetic patients.

In conclusion, although the first and the majority of trials examining the use of GP2b3a medications in PCI have studied abciximab, there is good evidence that both eptifibatide and

tirofiban are also effective treatments in this situation and protection during PCI is an accepted indications for all these drugs (see Appendix 1). Although the one comparative head to head trial reported that tirofiban was less effective than abciximab at one month, longer term follow-up from this comparative trial shows the dissipation of any early differences, and showed also that high-risk diabetic patients are equally served by both agents. Furthermore an integrated Bayesian approach using all the existing data suggests that the conclusions of even the one month analysis are unlikely to be true.

ECONOMIC STUDIES

Cost-effectiveness. Given the large investments by pharmaceutical companies to bring these molecules into the clinical arena and given that some local authorities are now requiring economic analyses before accepting to reimburse new drug costs, it is not surprising that numerous cost-effective analyses of these agents have been performed. A PUB MED search using the keywords "economics" and "platelet glycoprotein" produced 61 references. A typical example is the prospective economic assessment performed in the 2792 patients enrolled in EPILOG study, an evaluation of abciximab during angioplasty. The average drug cost was $1450 US but this was partly offset by reduced ischemic events and associated costs leading to a net incremental cost of $914 (28). Many studies, usually sponsored by the pharmaceutical companies, arrive at the same conclusion, namely that the costs of these drugs during PCI are partially offset by decreased clinical events and that they are economically attractive interventions by conventional economic analyses(29-31). However, these studies all suffer from the same limitations of selectively choosing favorable efficacy estimates and modeling assumptions that may not reflect our local experience(32).

One comparative economic study between abciximab and eptifibatide has been performed(33). This randomized, double- blind study assessed the 30-day economic and clinical outcomes of 320 consecutive patients undergoing elective coronary balloon angioplasty or stent implantation. The primary study end point was total in-hospital costs based on an intention-to-treat analysis. The median and interquartile ranges of total in- hospital costs were $8268 ($6505, $9958) and $7207 ($5659, $9307), respectively, between the abciximab- and eptifibatide-treated patients (P =.009) with no difference in the composite secondary clinical end points of death/nonfatal myocardial infarction/urgent revascularization (4.9% versus 5.1%, P =.84). This cost differential is very similar to the difference in drug acquisition costs at the MUHC (see Table 1).

Economic Impact. Based on our assessment of equivalence and given the substantially higher cost of abciximab it seems obvious that significant saving, without any appreciable deterioration in patients outcomes, can be realized by substituting other GP2b3a inhibitors for abciximab in the catheterization laboratory. Last year, $546,693 was spent on abciximab for this indication within the MUHC. As demonstrated above, equal patient outcomes can be expected by substituting tirofiban or eptifibatide. These drugs cost only 13-19% of the amount presently spent on abciximab. This change in policy could be expected to save between $440,000 and $475,000 based on last year's utilization rate. Obviously if utilization rates of GP2b3a inhibitors continue to increase as in past years, our potential savings in switching away from abciximab will also increase.

Based on the above should abciximab use in the catheterization laboratory be completely abolished? The answer appears no. Special clinical cases may exist where the unique characteristics of abciximab may still favor its utilization. For example, if a high-risk patient

following a PCI is to return immediately after his procedure to his referring hospital, abciximab may be the preferred agent. In this scenario, the drug may be stopped during the transport without risk, due to its long half-life, and re-started on arrival. This may provide maximum patient safety while maintaining cardiovascular protection. The alternative of keeping the same patient an additional 24 hours in our institution would obviously reduce the imperative to switch to a lower cost agent. Therefore, while the replacement of abciximab in the vast majority of PCI seems appropriate, there may exist special situations, estimated initially to be ≈ 10-20%, (Dr P. Beaudry personal communication) where abciximab remains useful. It should therefore remain on the hospital formulary. It is possible that with increased familiarity of the lower price agents the use of abciximab will fall even lower.

CONCLUSIONS

The use of GP2b3a inhibitors during PCI has been extensively studied in 11 randomized trials involving over 18,500 patients. Individual trials have confirmed the efficacy and safety of 3 GP2b3a drugs, abciximab, tirofiban and eptifibatide. Death rates have been remarkably low in these studies, and although the mortality reduction at 30 days is statistically significant the absolute mortality reduction is be exceedingly small. GP2b3a inhibitors during PCI have been shown to reduce the combined outcome of death, myocardial infarction or urgent revascularization both in terms of relative (OR 0.63 95%CI 0.53-0.74) and absolute (NNT = 28, 95%CI 22 , 37) risk. Nevertheless since 27 of every 28 treated patients derive no additional benefit, it is appropriate to continue to allow clinical judgment to identify the high-risk patients most likely to derive benefit.

Critical analysis of all the available data indicates that there is no reason to conclude that abciximab is superior to other GP2b3a inhibitors when used in this setting. Substantial economic saving could be attained (approximately $400,000 / year), without any discernible impact on patients' outcomes, by largely replacing abciximab in the catheterization laboratory by eptifibatide or tirofiban.

RECOMMENDATION

Based on this evaluation of therapeutic equivalence between the GP 2b3a inhibitors and the incremental cost associated with abciximab, the TAU Committee recommends that;

"Routine use of GP 2b3a inhibitors during PCI at the MUHC catheterization laboratories is not recommended, rather treatment should be reserved for high-risk patients as defined by clinical and angiographic assessments. Since there are no clinically meaningful differences in outcomes between the different agents, in most cases the lower priced agents, tirofiban or eptifibatide, should be favored. It is nevertheless recognized that the more expensive agent, abciximab, may be the preferred drug for certain specific clinical indications."

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TABLE 1

STANDARD DRUG DOSAGES AND PROTOCOLS FROM THE EPISTENT, PURSUIT, AND PRISMPLUS TRIALS, RESPECTIVELY

Drug	Bolus	Infusion	Duration (hours)	Cumulative dose (70 kg patient)	Cost*
Abciximab	0.25 mg/kg 10 minutes before PCI	0.125 µg/kg/min (10 µ g/min maximum)	12	24.7 mg	$1671
Eptifibatide	180 µ g/kg 10 minutes before PCI	2 µg/kg/min	18	151 mg	$224
Tirofiban	0.4 µg/kg/min for 30 minutes, starting 10 minutes before PCI	0.10 µg/kg/min	18	8.4 mg	$322

* Based on the unit prices given in Table 2 below

TABLE 2 GP2B3A DRUG COSTS PER UNIT

Name of Drug	**Unit Cost of Each Treatment**	**Dosage**
Tirofiban (AGGRASTAT)	$322.88	0.25 mg/ml – 50 ml vial
Abciximab (RHEOPRO)	$557.85	2.00 mg/ml – 5 ml vial
Eptifibatide (INTEGRELIN)	$112.72	0.75 mg/ml – 100 ml vial

TABLE 3 GP2B3A DRUG UTILIZATION AND COSTS AT THE MUHC

PURCHASED UNITS (BY YEAR)

Name of Drug	1997-98	1998-99	1999-2000	2000-01	2001-02
Tirofiban (AGGRASTAT)	0	0	20	110	82
Abciximab (RHEOPRO)	10	268	706	1058	980
Eptifibatide (INTEGRELIN)	0	0	0	0	8

TOTAL COST OF UNITS (BY YEAR)

Name of Drug	1997-98	1998-99	1999-2000	2000-01	2001-02
Tirofiban (AGGRASTAT)	$ 0	$ 0	$ 6,300	$ 35,359	$ 26, 476
Abciximab (RHEOPRO)	$ 5,904	$ 146,515	$ 385,123	$ 590,205	$ 546,693
Eptifibatide (INTEGRELIN)	$ 0	$ 0	$ 0	$ 0	$ 902

Note that approximately 3 units of abciximab are required to treat 1 patient for 12 hours.

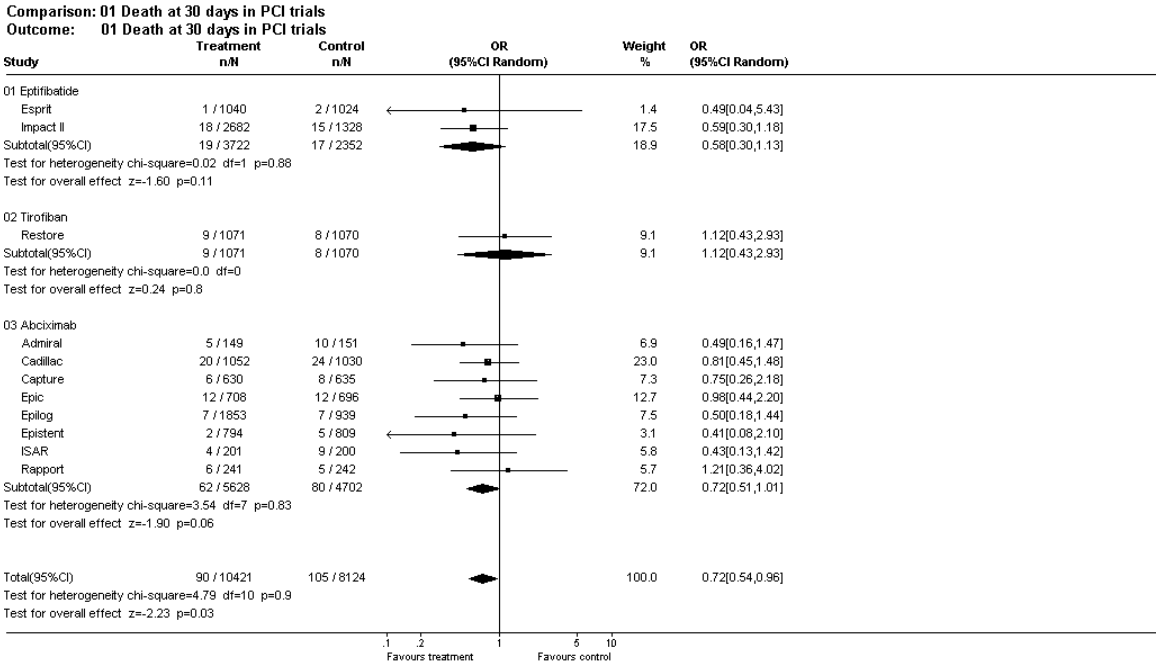
TABLE 4 RANDOMIZED PLACEBO CONTROLLED TRIALS OF GP2B3A INHIBITORS IN PERCUTANEOUS CORONARY INTERVENTIONS

Trial	Drug	Stents	AMI <24 h	Number randomized		Deaths				Myocardial Infarction				Composite death/mi/revasc			
				GP2b3a	Placebo	GP2b3a		Placebo		GP2b3a		Placebo		GP2b3a		Placebo	
Epistent	abciximab	100%	NA	794	809	0.6%	5	0.3%	2	4.5%	36	9.6%	78	5.3%	42	10.8%	87
Epic	abciximab	0%	3%	708	696	1.7%	12	1.7%	12	5.2%	37	8.6%	60	8.3%	59	12.8%	89
Capture	abciximab	0%	0%	630	635	1.0%	6	1.3%	8	4.1%	26	8.2%	52	11.3%	71	15.9%	101
Epilog	abciximab	13%	0%	1853	939	0.4%	7	0.8%	7	3.7%	69	8.7%	81	5.2%	97	11.7%	109
Rapport	abciximab	16%	100%	241	242	2.5%	6	2.1%	5	3.3%	8	4.1%	10	13.3%	32	16.1%	39
Impact ll	eptifibatide	4%	3%	2682	1328	0.7%	18	1.1%	15	6.4%	172	7.3%	97	9.5%	256	11.4%	151
ISAR 2	abciximab	100%	78%	201	200	2.0%	4	4.5%	9	0.5%	1	1.5%	3	5.0%	10	10.5%	21
Restore	tirofiban	0%	7%	1071	1070	0.8%	9	0.7%	8	4.2%	45	5.7%	61	10.3%	110	12.2%	130
Esprit	eptifibatide	100%	0	1040	1024	0.1%	1	0.2%	2	5.4%	56	9.0%	92	6.6%	69	9.3%	97
Cadillac	abciximab	56%	100	1052	1030	1.9%	20	2.4%	24	0.8%	8	0.9%	9	4.6%	48	3.3%	72
Admiral	abciximab	100%	100	149	151	3.4%	5	6.6%	10	1.3%	2	2.6%	4	6.0%	9	14.6%	22

All trials had 30 day follow-up except Esprit which reported 48 hour follow-up. However, 88% of the 30 day events occurred in the first 48 hours and there was no difference in the hazard ratios beyond this point

FIGURE 1

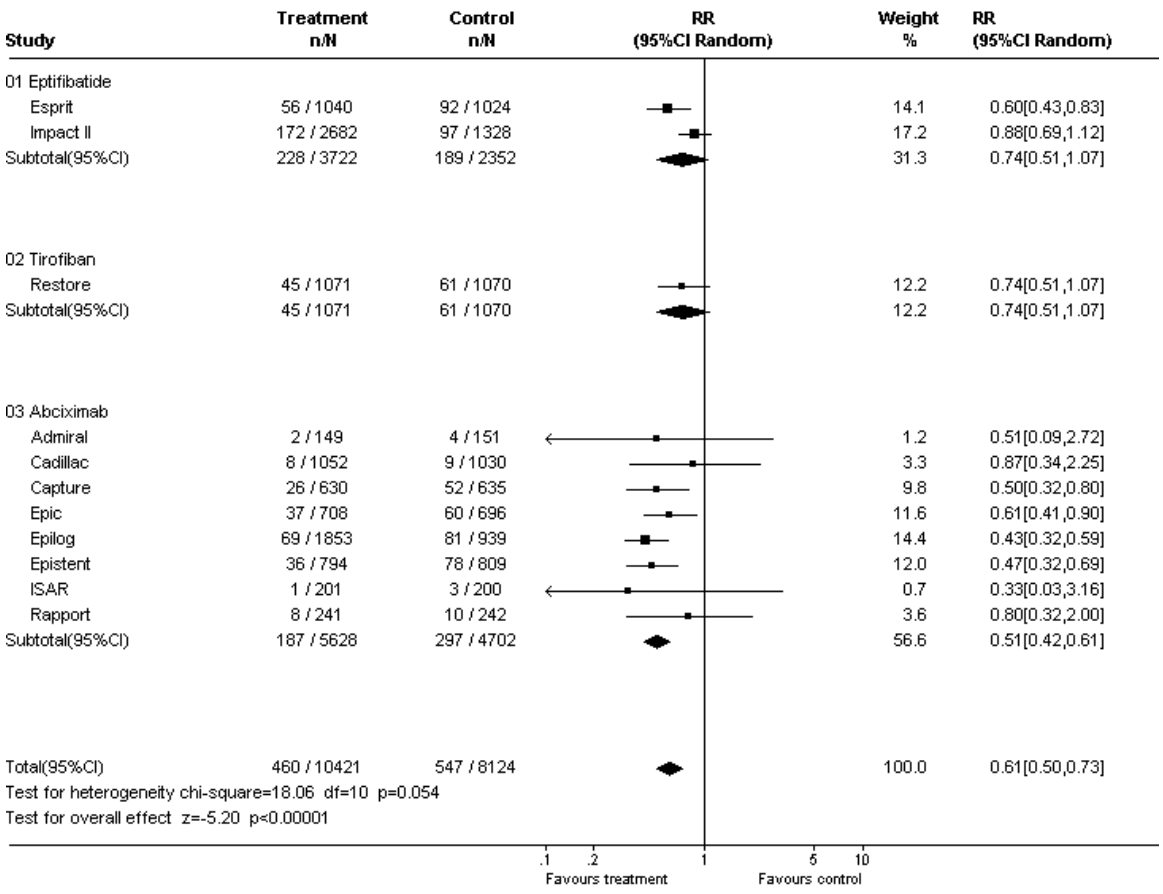
META-ANALYSIS OF DEATH AT 30 DAYS IN PCI TRIALS



uses a random effects model

FIGURE 2

META-ANALYSIS OF AMI AT 30 DAYS IN PCI TRIALS



uses a random effects model

FIGURE 3

META-ANALYSIS OF COMPOSITE ENDPOINT (DEATH, MI OR URGENT REVASCULARIZATION) AT 30 DAYS IN PCI TRIALS

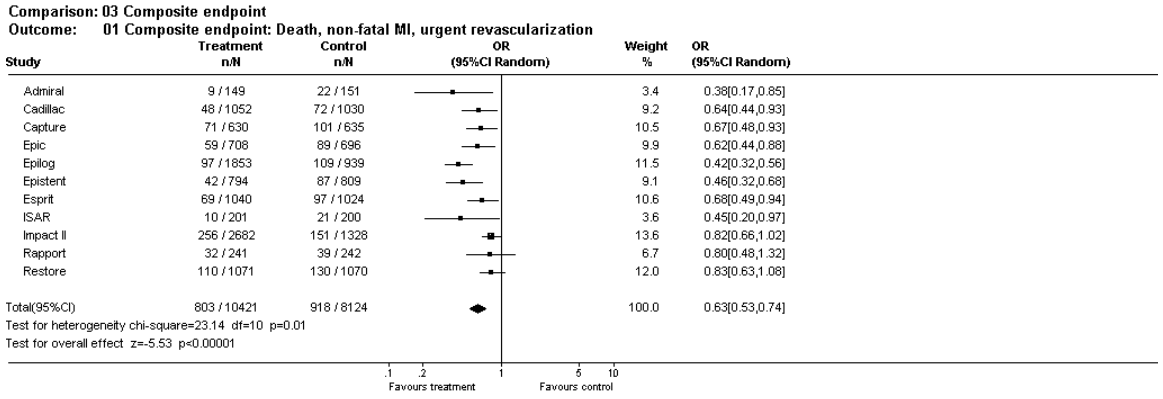


FIGURE 4

META-ANALYSIS OF COMPOSITE ENDPOINT (DEATH, MI OR URGENT REVASCULARIZATION) IN PCI TRIALS ACCORDING TO BASELINE ADMISSION DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

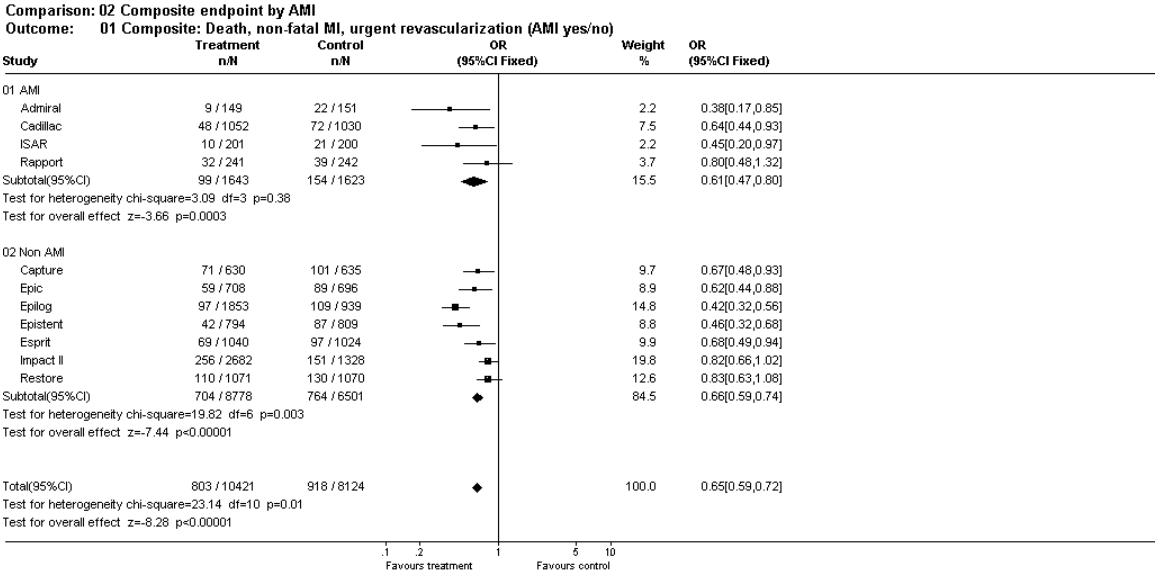


FIGURE 5

META-ANALYSIS OF COMPOSITE ENDPOINT (DEATH, MI OR URGENT REVASCULARIZATION) IN PCI TRIALS ACCORDING TO GP2B3A DRUG

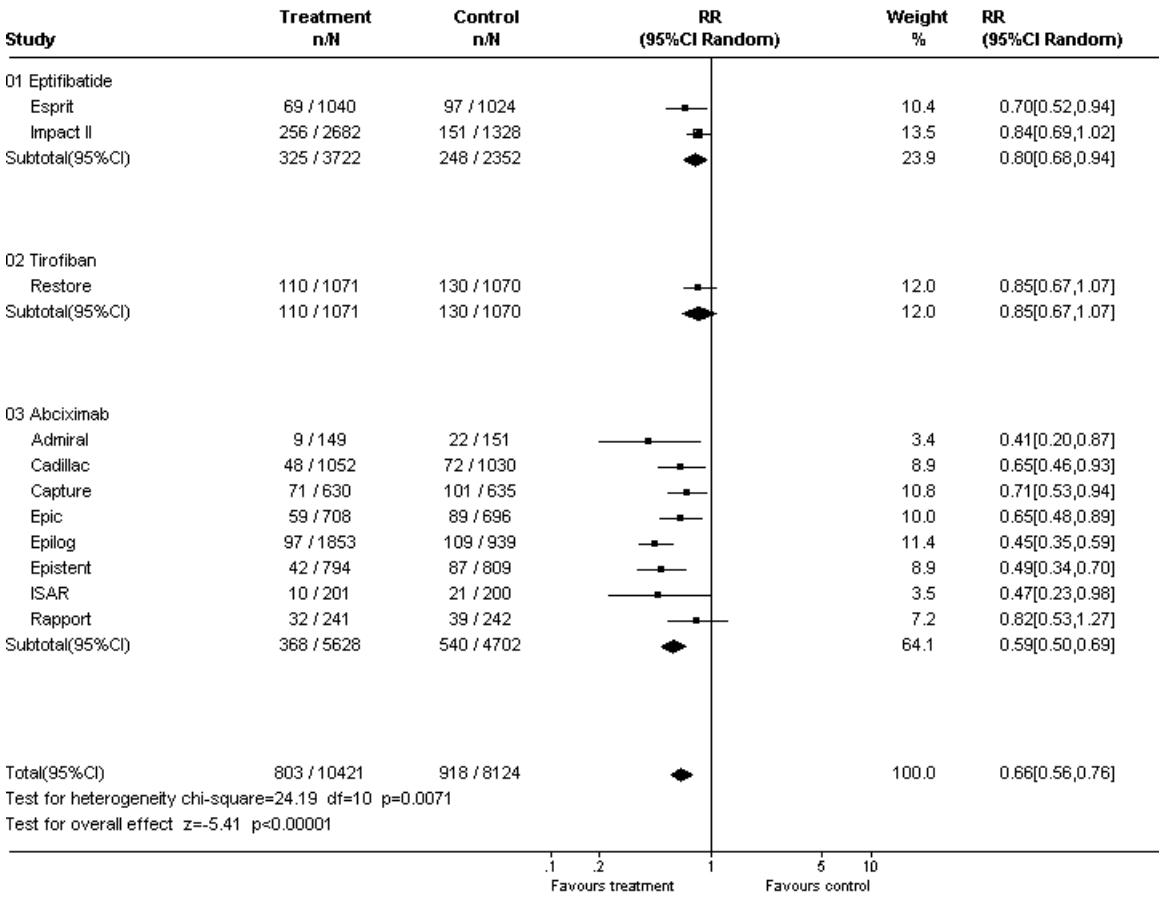
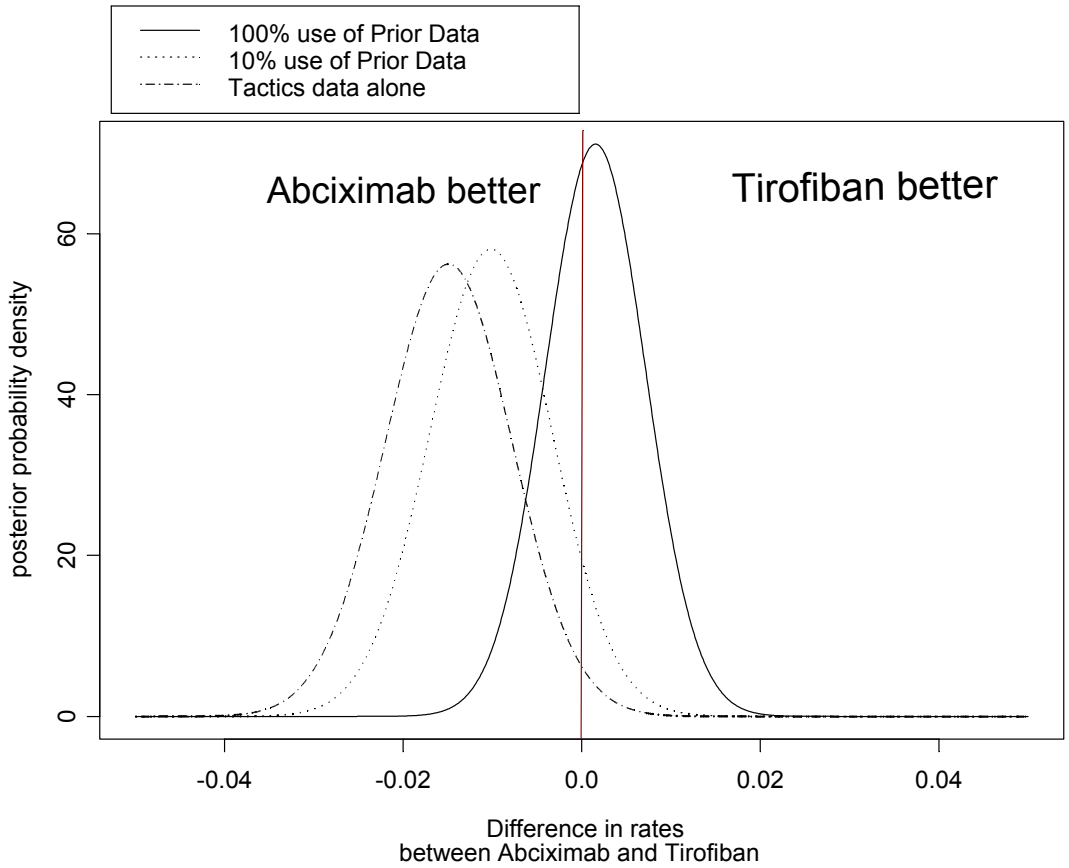


FIGURE 6

PROBABILITY DENSITY PLOT FOR THE DIFFERENCE IN COMPOSITE 30 DAY OUTCOMES BETWEEN ABCIXIMAB AND TIROFIBAN IN PCI



APPENDIX 1

APPROVED GP2B3A DRUGS AND THEIR ACCEPTED INDICATIONS AS PUBLISHED IN PRODUCT MONOGRAMS

Abciximab (REOPRO, Lilly) is indicated as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications in patients undergoing percutaneous coronary intervention and in patients with unstable angina not responding to conventional medical therapy when percutaneous coronary intervention is planned within 24 hours. Abciximab use in patients not undergoing percutaneous coronary intervention has not been studied.

Eptifibatide (INTEGRILIN, Key Pharmaceuticals) is indicated for the treatment of patients with acute coronary syndrome (UA/NQMI), including patients who are to be managed medically and those undergoing percutaneous coronary intervention (PCI). In this setting, INTEGRILIN has been shown to decrease the rate of a combined endpoint of death or new myocardial infarction. For the treatment of patients undergoing PCI, including those undergoing intracoronary stenting. In this setting, INTEGRILIN has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction, or need for urgent intervention.

Tirofiban (AGGRASTAT, Merck) in combination with heparin, is indicated for the treatment of acute coronary syndrome, including patients who are to be managed medically and those undergoing PTCA or atherectomy. In this setting, AGGRASTAT has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction or refractory ischemia/repeat cardiac procedure.

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APPENDIX 2

American College of Cardiology and the American Heart Association (ACC/AHA) Guideline Classifications and Recommendation for GP2b3a Inhibitors

Guideline Classifications

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy. Class IIb: Usefulness/efficacy is less well established by evidence/opinion

Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful

The weight of the evidence is ranked highest (A) if the data were derived from multiple randomized clinical trials that involved large numbers of patients and intermediate (B) if the data were derived from a limited number of randomized trials that involved small numbers of patients or from careful analyses of nonrandomized studies or observational registries. A lower rank (C) was given when expert consensus was the primary basis for the recommendation.

Guidelines for the use of GP2b3a Inhibitors

The following recommendations concerning GP2b3a inhibitors were abstracted from their recent guidelines. It should be noted that cost-effectiveness is not a parameter used to develop these guidelines.

Class I

A platelet GP IIb/IIIa antagonist should be administered, in addition to ASA and heparin, to patients in whom catheterization and PCI are planned. The GP IIb/IIIa antagonist may also be administered just prior to PCI. (Level of Evidence: A)

Class IIa

A platelet GP IIb/IIIa antagonist should be administered to patients already receiving heparin, ASA, *and clopidogrel* in whom catheterization and PCI are planned. The GP IIb/IIIa antagonist may also be administered just prior to PCI. (Level of Evidence: B)

Class IIa

1. Eptifibatide or tirofiban should be administered, in addition to ASA and LMWH or UFH, to patients *with* continuing ischemia, an elevated troponin or with other high-risk features in whom an invasive management strategy is *not* planned. (Level of Evidence: A)

Class IIb

Eptifibatide or tirofiban, in addition to ASA and LMWH or UFH, to patients *without* continuing ischemia who have no other high-risk features and in whom PCI is *not* planned. (Level of Evidence: A)

DEFINITIONS

Acute coronary syndromes refer to unstable angina and myocardial infarction.

Unstable angina represents a spectrum of clinical states that fall between stable angina and acute myocardial infarction. It includes angina at rest (typically lasting > 20 minutes), new onset angina (within 2 months of onset), increasing angina (increased frequency, longer duration, and at lower thresholds), variant angina (ST segment elevation), and angina occurring >24 hours post-myocardial infarction.

Myocardial infarction is defined by the WHO as two of the following three conditions 1) prolonged (typically lasting > 30 minutes) chest pain 2) Electrocardiographic (ECG) changes 3) biochemical evidence of myocyte necrosis. However, the majority of the trials reviewed have based their definition of myocardial infarction solely on an at least threefold increase in the biochemical markers. Myocardial infarction can be sub-divided into ST elevation and non-ST elevation according to the ECG modifications.