Published in final edited form as:

J Interv Cardiol. 2013 April ; 26(2): 123–130. doi:10.1111/j.1540-8183.2013.12020.x.

Would Tirofiban Have Been Shown Non-Inferior to Abciximab Had the TENACITY Trial Not Been Terminated for Financial Reasons?

Peter B. Berger, MD¹, Judson B. Williams, MD², Vic Hasselblad, PhD², Karen Chiswell, PhD², Karen S. Pieper, PhD², and Robert M. Califf, MD²

¹Geisinger Clinic, Danville, PA

²Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC

Abstract

Objectives—To investigate whether tirofiban would have been non-inferior to abciximab had the trial completed enrollment, and we place the termination of this trial in a broader research ethics context.

Background—TENACITY was terminated by the sponsor for financial reasons. At the time, event rates for the 2 treatment arms were unknown.

Methods—TENACITY was designed to compare tirofiban with abciximab in approximately 8000 patients; however, enrollment was terminated after 383 (4.8%) patients. The primary endpoint was a composite of 30-day death, myocardial infarction, and urgent target vessel revascularization. Non-inferiority was defined as the likelihood that tirofiban would preserve at least 50% of the ability of abciximab to reduce the primary endpoint at 30 days, based on abciximab's demonstrated ability to reduce such events by 43% (relative risk, 0.573; 95% confidence interval [CI], 0.507–0.648; $P < 0.001$). To determine the probability of non-inferiority given the patients already enrolled, a Bayesian approach was used.

Results—The primary composite endpoint occurred in 8.8% of patients randomized to abciximab vs. 6.9% receiving high-bolus-dose tirofiban (odds ratio, 0.77; 95% CI, 0.37–1.64). The estimated conditional power for the test that tirofiban would be non-inferior to abciximab if all patients been enrolled is 93.7%. Using the estimated predictive power method, the likelihood was 84.8%.

Conclusions—TENACITY was well-powered to identify non-inferiority with tirofiban vs. abciximab, and the patients enrolled strengthened the probability that this would have been the outcome had the trial been completed. When a clinical trial is terminated solely for financial reasons, it is incumbent upon the sponsor to provide proper patient follow-up and publication of the findings.

Keywords

glycoprotein IIb/IIIa inhibitors; clinical trial; tirofiban; abciximab

Introduction

Three glycoprotein (GP) IIb/IIIa inhibitors are commercially available in the United States and in most other parts of the world: abciximab, eptifibatide, and tirofiban. Tirofiban is a highly selective non-peptide antagonist of the GP IIb/IIIa receptor whose structure mimics the RGD peptide sequence in fibrinogen.¹ Tirofiban is similar to eptifibatide in that it is small (495 Daltons vs. 832 Daltons for eptifibatide) and has a short half-life (2 hours vs. 2.5 hours for eptifibatide), and neither are immunogenic; in contrast, abciximab is large (46,700 Daltons), has a long half-life (10–30 minutes), and is immunogenic.^{2–4} Tirofiban, unlike eptifibatide, shares the property of high affinity IIb/IIIa receptor binding with abciximab.²

Multiple clinical trials using tirofiban at the presently approved label dose (10 µg/kg over 3 minutes followed by a 0.15 µg/kg/min maintenance infusion) have demonstrated the efficacy and safety of this compound in reducing acute ischemic events in a broad range of patients with an acute coronary syndrome (ACS), moderate to high-risk coronary lesion anatomy, or both.^{5–10} However, the Do Tirofiban And ReoPro Give Similar Efficacy Outcomes (TARGET) trial, designed to determine whether tirofiban was non-inferior to abciximab among percutaneous coronary intervention (PCI) patients receiving a coronary stent, found that it was associated with significantly more adverse events.¹¹ Subsequent studies revealed that the bolus dose of tirofiban achieved insufficient inhibition of aggregation at just the time that balloon and stent inflations were performed in the trial, and that a bolus dose 2.5 times higher achieved inhibition of aggregation similar to abciximab.^{12–14} This led to the performance of 5 undersized randomized trials comparing this new “high bolus dose” of tirofiban with abciximab, each of which suggested that high-bolus-dose tirofiban was associated with efficacy and safety similar to abciximab.^{15–19}

These studies led to the launch of the Tirofiban Evaluation of Novel Dosing versus Abciximab with Clopidogrel and Inhibition of Thrombin (TENACITY) study.^{20,21} TENACITY was a randomized, controlled study assessing high-bolus-dose tirofiban vs. abciximab in patients undergoing coronary stent placement. TENACITY was designed to recruit approximately 8000 patients; however, based solely on financial considerations related to lack of funds to complete the study and a decision by the board to sell the company, the sponsor (Guilford Pharmaceuticals, Inc.) terminated enrollment before 5% of patients had been enrolled and before the results of enrolled patients were known. With follow-up of randomized patients now complete, the question arises of how likely it is that the results of TENACITY would have found tirofiban to be non-inferior to abciximab had the sponsor permitted completion of the trial. To answer this question, we performed a statistical analysis of the TENACITY trial.

Methods

TENACITY was a double-blind, randomized controlled study comparing a high-dose bolus regimen of tirofiban with abciximab in intermediate- to high-risk patients with an ACS. A second randomization was performed in which patients were assigned to receive either unfractionated heparin or bivalirudin; this comparison will not be discussed in the present manuscript.²¹ All patients received clopidogrel and aspirin before randomization. Enrollment began in January 2005 but was halted in June 2005, after enrollment of 383 out of a planned 8000 patients (4.8%). The study's primary endpoint was a composite of all-cause death, myocardial infarction (MI), and urgent target vessel revascularization.

TENACITY utilized a non-inferiority design. Sample size was based on abciximab's demonstrated benefit relative to placebo in a pooled estimate from randomized trials in terms of a composite endpoint of death, MI, and urgent target vessel revascularization (relative risk, 0.573; 95% confidence interval [CI], 0.507–0.648). The non-inferiority boundary for tirofiban was calculated using a 50% preservation of abciximab's benefit over placebo and an assumed event rate of 7.0% with abciximab. With a total sample size of 8000 patients, the study would have 90% power (1-sided alpha = 0.025) for the non-inferiority analysis. All patients gave informed consent, and the authors conformed to institutional guidelines and to those of the American Physiological Society. A clinical events committee (CEC) was originally planned to adjudicate events in patients; however, given the premature termination due to financial considerations, a CEC did not review events reported in this study.

Statistical analysis

Two methods are commonly used to determine the probability of success of a trial at an interim point: 1) the calculation of conditional power and 2) the calculation of predictive power. Conditional power is a calculation made conditional on the observations available at the interim timepoint, based on the assumption that the expected values of the endpoints of the 2 arms in the future are known.²² For this analysis, it was assumed that had all 8000 patients been enrolled, and the expected event rates in both arms would have been 0.07. Accordingly, we used exact probability calculations (see Appendix) to estimate the conditional probability that the completed TENACITY trial would have an observed result that preserved 50% of the effect seen in the abciximab vs. placebo trials, a standard definition used in many recent trials of cardiovascular drugs accepted by the U.S. Food and Drug Administration (FDA) and the margin of inferiority on which the TENACITY trial was based. Although for a superiority trial it would be appropriate to calculate conditional power assuming different scenarios of potential future values, such as a range of relative treatment differences,²³ conditional power for a non-inferiority trial such as TENACITY is calculated assuming no expected difference between groups in the future, as there is no basis for having assumed other scenarios *a priori*.

The second method for predicting the result of a trial based on an interim analysis, calculation of predictive power, is a Bayesian calculation.²⁴ This method is based on the assumption that the only information available about the expected results from future observations is described by 2 functions: 1) the previous distribution of endpoints, which is

typically non-informative, and 2) the likelihood of the data observed to date. In this study, we used the formulas of Spiegelhalter²⁴ to calculate the posterior probability of any particular result (see Appendix). These results were summed over those results where 50% of the abciximab effect was preserved in order to obtain the predictive probability of success. Computations for both methods were made using Compaq Visual Fortran.²⁵

Results

Baseline patient characteristics and procedural details have been reported elsewhere (Table 1).²¹ Endpoint data were available in 383 randomized patients. The composite endpoint of death, MI, and target vessel revascularization occurred in 17 of 194 (8.8%) abciximab patients vs. 13 of 189 (6.9%) tirofiban patients (odds ratio, 0.77; 95% CI, 0.37–1.64). These observed values are applied in recalculating the estimates of power. The observed difference was driven primarily by an almost 2% absolute difference in rates of non-fatal MI between high-bolus-dose tirofiban and abciximab (5.9% vs. 7.7%). There were no differences in Thrombolysis In Myocardial Infarction (TIMI) major bleeding (0.5% vs. 0.5%) or TIMI minor bleeding (1.1% vs. 1.5%). The estimated conditional probability that tirofiban would be non-inferior to abciximab if all 8000 patients been enrolled is 0.937, a 93.7% likelihood that the study would have found tirofiban non-inferior if future events occurred at a rate of 7% in both arms. This represents an increase in power from the initial design of the trial (0.90), as a result of the early results from the 383 patients enrolled with endpoint data. The estimated predictive power that tirofiban would be non-inferior to abciximab was 84.8%.

Discussion

The TENACITY trial results revealed the primary composite endpoint of death, non-fatal MI, or urgent target vessel revascularization occurred in 8.8% of patients randomized to abciximab vs. 6.9% of those randomized to high-bolus-dose tirofiban. Based on those TENACITY patients randomized and followed, if tirofiban and abciximab have equal efficacy, we show that the completed trial would have had high power to detect non-inferiority. Despite robust evidence for efficacy of the currently approved dosing of tirofiban in ACS (0.4µg/kg/min loading infusion over 30 minutes followed by a 0.1µg/kg/min maintenance infusion), the timing of therapeutic platelet inhibition (30 minutes) is not optimal when initiating tirofiban at the time of intervention. To facilitate dosing at the time of intervention, a low-bolus-dose regimen was initially explored (10 µg/kg over 3 minutes followed by a 0.15µg/kg/min maintenance infusion). However, studies have shown that the tirofiban low-bolus-dose is suboptimal for PCI, where the rapid (<30 minute) attainment of a high degree of platelet inhibition is required.^{12–14} The 10 µg/kg bolus dose of tirofiban inhibits 20 µM adenosine diphosphate (ADP)-mediated platelet aggregation by only 60% to 66% 15–60 minutes after administration of the bolus, when PPACK (D-Phenylalanyl-L-prolyl-L-arginine Chioromethyl Ketone) is used as the sample anticoagulant. In contrast, abciximab produces 90% to 95% inhibition of platelet aggregation in this same time period. This difference in inhibition of platelet aggregability is believed to be the reason that procedure-related ischemic events occurred more frequently among patients receiving tirofiban in the TARGET trial.²⁰

However, a high-bolus-dose regimen of tirofiban (25µg/kg over 3 minutes, followed by a 0.15µg/kg/min maintenance infusion) has been found to have levels of platelet aggregation inhibition similar to those achieved by abciximab. Data from 15 clinical studies since 2003 suggest excellent efficacy, equivalent to that achieved by abciximab, and subsequent randomized trials comparing high-bolus-dose tirofiban with abciximab have, both individually and collectively, suggested that tirofiban is at least as effective as abciximab (Table 2).^{15–18,26–28} In placebo-controlled trials, tirofiban has been shown superior to placebo at a degree similar to that which abciximab was shown to outperform placebo in trials leading to its approval by the FDA. Although none of those trials were adequately powered to determine how the 2 drugs compared with respect to clinical outcomes, the data revealed numerically lower thrombotic event rates when tirofiban was compared directly with abciximab. A meta-analysis of 31 studies involving 20,006 patients was published by Valgimigli and colleagues in 2010 indicating that tirofiban is an efficacious treatment option in reducing ischemic events in patients with ACS and/or those undergoing PCI.²⁸ When employed as a high-dose bolus just before PCI, the authors concluded that tirofiban provides similar efficacy but with an improved safety profile compared with abciximab. Because tirofiban is considerably less expensive than the other 2 available GP IIb/IIIa agents, adequately determining whether tirofiban is equally as efficacious and safe as the other agents is important beyond even the treatment of coronary artery disease. In an 80 kg patient with normal renal function, the average wholesale price is \$1,836.90 for a 12-hour infusion of abciximab; \$1,121.81 for an 18-hour infusion of eptifibatide; and only \$711.72 for an 18-hour infusion of tirofiban. The degree to which the cost of a drug should influence prescribing patterns is complex and controversial when the less-expensive drug is inferior to any degree;²⁹ however, when 2 drugs are found to be equally safe and effective, price is a responsible and important, if not the most important, determining factor in choosing an agent. The premature termination of TENACITY due to sponsor financial considerations left uncertainty surrounding tirofiban as a non-inferior alternative to abciximab. Had the trial been completed with the expected non-inferior result, and if even half of the more than 1.3 million patients treated with PCI in the United States had received tirofiban, an estimated \$300–\$500 million in health care savings could have been achieved. TENACITY is one of numerous trials that have been terminated for financial reasons.^{30–32} The question necessarily arises as to what responsibility is assumed by a sponsor launching human experiments.^{33,34} Do the risks to a patient outweigh the benefits in a study discontinued for financial reasons? The risk-benefit ratio for patients, who enroll with the understanding that they will contribute to improved future care, is shifted when a trial is terminated for these reasons. Although many consider early termination of a clinical trial for commercial reasons to be generally unacceptable,³⁵ exceptions certainly exist.

In the rare case in which a sponsor lacks the fiscal resources to ensure proper patient monitoring and safety, continuing a trial in the face of commercial or financial duress becomes irresponsible. Indeed, the Declaration of Helsinki requires that considerations of the well-being of human subjects take precedence over the interests of society and science.³⁶ Efforts to cut costs could result in increased risk of harm to study participants, or in an extreme case, a sponsor becoming unable to pay for necessary study-related care. Sponsors are within their contractual rights to terminate a trial based on financial considerations.³⁷

Moreover, to take away sponsors' authority regarding decisions related to stopping a trial could result in a reduction of important clinical research, especially studies involving patients in the United States where the cost per enrolled patient may be higher than in other countries. Ultimately, when a trial is terminated by a sponsor based on commercial considerations, we are left with difficult questions. What is incumbent upon any sponsor launching human experiments is provision for proper follow-up for enrolled patients and publication of the findings.

Limitations

Only 4.8% of the total sample size was available in the estimation of conditional power. Thus, the uncertainty of the final results exists for more than 95% of the unobserved patients.

Conclusions

The TENACITY trial was well-powered to identify non-inferiority of tirofiban vs. abciximab. The patients enrolled only strengthened the probability that this would have been the outcome had the trial been completed as planned. In the unfortunate event that a clinical trial is terminated for financial reasons, the sponsor is responsible for ensuring proper patient follow-up and publication of the findings.

Acknowledgments

Funding sources: This research was supported by Medicure (Winnipeg, Manitoba, Canada). Dr. Williams was supported in part by training grant T32-HL069749 from the National Institutes of Health.

References

1. Basani RB, Zhu H, Thornton MA, et al. Species differences in small molecule binding to alpha IIb beta 3 are the result of sequence differences in 2 loops of the alpha IIb beta propeller. *Blood*. 2009; 113:902–910. [PubMed: 18987357]
2. Scarborough RM, Kleiman NS, Phillips DR. Platelet glycoprotein IIb/IIIa antagonists. What are the relevant issues concerning their pharmacology and clinical use? *Circulation*. 1999; 100:437–444. [PubMed: 10421606]
3. Use of a monoclonal-antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. *New Engl J Med*. 1994; 330:956–961. [No authors listed]. [PubMed: 8121459]
4. Kohmura C, Gold HK, Yasuda T, et al. A chimeric murine/human antibody fab fragment directed against the platelet GP IIb/IIIa receptor enhances and sustains arterial thrombolysis with recombinant tissue-type plasminogen-activator in baboons. *Arterioscler Thromb*. 1993; 13:1837–1842. [PubMed: 8241105]
5. Rasoul S, Ottervanger JP, de Boer MJ, et al. A comparison of dual vs. triple antiplatelet therapy in patients with non-ST-segment elevation acute coronary syndrome: results of the ELISA-2 trial. *Eur Heart J*. 2006; 27:1401–1407. [PubMed: 16682384]
6. Juergens CP, White HD, Belardi JA, et al. A multicenter study of the tolerability of tirofiban versus placebo in patients undergoing planned intracoronary stent placement. *Clin Ther*. 2002; 24:1332–1344. [PubMed: 12240783]
7. Tavano D, Visconti G, D'Andrea D, et al. Comparison of bivalirudin monotherapy versus unfractionated heparin plus tirofiban in patients with diabetes mellitus undergoing elective percutaneous coronary intervention. *Am J Cardiol*. 2009; 104:1222–1228. [PubMed: 19840566]

8. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation*. 1997; 96:1445–1453. [No authors listed]. [PubMed: 9315530]
9. Cohen M, Gensini GF, Maritz F, et al. Prospective evaluation of clinical outcomes after acute ST-elevation myocardial infarction in patients who are ineligible for reperfusion therapy: preliminary results from the TETAMI registry and randomized trial. *Circulation*. 2003; 108(16 Suppl 1):14–21. III.
10. Fu XH, Hao QQ, Jia XW, et al. Effect of tirofiban plus clopidogrel and aspirin on primary percutaneous coronary intervention via transradial approach in patients with acute myocardial infarction. *Chin Med J (Engl)*. 2008; 121:522–527. [PubMed: 18364139]
11. Topol EJ, Moliterno DJ, Herrmann HC, et al. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *New Engl J Med*. 2001; 344:1888–1894. [PubMed: 11419425]
12. Schneider DJ, Herrmann HC, Lakkis N, et al. Increased concentrations of tirofiban in blood and their correlation with inhibition of platelet aggregation after greater bolus doses of tirofiban. *Am J Cardiol*. 2003; 91:334–336. [PubMed: 12565092]
13. Schneider DJ, Herrmann HC, Lakkis N, et al. Enhanced early inhibition of platelet aggregation with an increased bolus of tirofiban. *Am J Cardiol*. 2002; 90:1421–1423. [PubMed: 12480064]
14. Lakkis N, Lakiss N, Bobek J, et al. Platelet inhibition with tirofiban early during percutaneous coronary intervention: dosing revisited. *Catheter Cardiovasc Interv*. 2002; 56:474–477. [PubMed: 12124955]
15. Valgimigli M, Campo G, Percoco G, et al. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial. *JAMA*. 2008; 299:1788–1799. [PubMed: 18375998]
16. Marzocchi A, Manari A, Piovaccari G, et al. Randomized comparison between tirofiban and abciximab to promote complete ST-resolution in primary angioplasty: results of the facilitated angioplasty with tirofiban or abciximab (FATA) in ST-elevation myocardial infarction trial. *Eur Heart J*. 2008; 29:2972–2980. [PubMed: 18940887]
17. Valgimigli M, Percoco G, Malagutti P, et al. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. *JAMA*. 2005; 293:2109–2117. [PubMed: 15870414]
18. Danzi GB, Sesana M, Capuano C, et al. Comparison in patients having primary coronary angioplasty of abciximab versus tirofiban on recovery of left ventricular function. *Am J Cardiol*. 2004; 94:35–39. [PubMed: 15219505]
19. Bolognese L, Falsini G, Liistro F, et al. Randomized comparison of upstream tirofiban versus downstream high bolus dose tirofiban or abciximab on tissue-level perfusion and troponin release in high-risk acute coronary syndromes treated with percutaneous coronary interventions: the EVEREST trial. *J Am Coll Cardiol*. 2006; 47:522–528. [PubMed: 16458130]
20. Serebruany V, Malinin A, Pokov A, et al. Effects of escalating doses of tirofiban on platelet aggregation and major receptor expression in diabetic patients: hitting the TARGET in the TENACITY trial? *Thromb Res*. 2007; 119:175–181. [PubMed: 16546241]
21. Moliterno DJ. A randomized two-by-two comparison of high-dose bolus tirofiban versus abciximab and unfractionated heparin versus bivalirudin during percutaneous coronary revascularization and stent placement: the tirofiban evaluation of novel dosing versus abciximab with clopidogrel and inhibition of thrombin (TENACITY) study trial. *Catheter Cardiovasc Interv*. 2011; 77:1001–1009. [PubMed: 21598351]
22. Lan KK, Wittes J. The B-value: a tool for monitoring data. *Biometrics*. 1988; 44:579–585. [PubMed: 3390511]
23. Chan IS. Proving non-inferiority or equivalence of two treatments with dichotomous endpoints using exact methods. *Stat Methods Med Res*. 2003; 12:37–58. [PubMed: 12617507]
24. Spiegelhalter DJ, Freedman LS, Blackburn PR. Monitoring clinical trials: conditional or predictive power? *Control Clin Trials*. 1986; 7:8–17. [PubMed: 3956212]

25. Compaq Fortran Language Reference Manual. Houston, Texas: Compaq Computer Corporation; Digital Equipment Corporation; 1999.
26. van Werkum JW, Gerritsen JC, Kelder CM, et al. Inhibition of platelet function by abciximab or high-dose tirofiban in patients with STEMI undergoing primary PCI: a randomised trial. *Neth Heart J*. 2007; 15:375–382. [PubMed: 18176639]
27. Ernst NM, Suryapranata H, Miedema K, et al. Achieved platelet aggregation inhibition after different antiplatelet regimens during percutaneous coronary intervention for ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2004; 44:1187–1193. [PubMed: 15364318]
28. Valgimigli M, Biondi-Zoccai G, Tebaldi M, et al. Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials. *Eur Heart J*. 2010; 31:35–49. [PubMed: 19755402]
29. Hasman A, McIntosh E, Hope T. What reasons do those with practical experience use in deciding on priorities for healthcare resources? A qualitative study. *J Med Ethics*. 2008; 34:658–663. [PubMed: 18757635]
30. Viberti G, Slama G, Pozza G, et al. Early closure of European Pimagedine trial. Steering Committee. Safety Committee. *Lancet*. 1997; 350:214–215. [PubMed: 9250200]
31. Lievre M, Menard J, Bruckert E, et al. Premature discontinuation of clinical trial for reasons not related to efficacy, safety, or feasibility. *BMJ*. 2001; 322:603–605. [PubMed: 11238162]
32. Black HR, Elliott WJ, Grandits G, et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA*. 2003; 289:2073–2082. [PubMed: 12709465]
33. [Accessed November 04, 2010] Protection of human subjects. Title 45 CFR Part 46. Department of Health and Human Services. 2010. Revised January 15, 2010; <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>
34. Steinbrook R. Improving protection for research subjects. *N Engl J Med*. 2002; 346:1425–1430. [PubMed: 11986426]
35. Iltis AS. Stopping trials early for commercial reasons: the risk-benefit relationship as a moral compass. *J Med Ethics*. 2005; 31:410–414. [PubMed: 15994362]
36. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2000; 284:3043–3045. [No authors listed]. [PubMed: 11122593]
37. Ashcroft R. Responsibilities of sponsors are limited in premature discontinuation of trials. *BMJ*. 2001; 323:53. [PubMed: 11464837]

APPENDIX

Methods for Calculating Conditional and Predictive Power

Conditional and predictive power calculations are made during a trial to answer the question, “What is the chance that the null hypothesis will be rejected at the end of the trial given the observed data to date and given certain very specific assumptions?” Conditional power is a calculation that assumes the expected values of the end-points of the 2 arms are known in the future. The futility index refers to a conditional power calculation wherein the alternative hypothesis, used for the power calculation, is assumed to be true for the observations yet to be sampled. Predictive power is a Bayesian calculation,¹ which assumes that the only information we have about the expected values of the endpoints is described by 2 functions: 1) our prior distribution for the endpoints (usually non-informative) and 2) the likelihood of the data observed to date.

Because some notation is needed to describe the computations for dichotomous (yes/no) endpoints, let:

m_c = number of subjects already observed in the control arm

m_t = number of subjects already observed in the treated arm

e_c = number of events already observed in the control arm

e_t = number of events already observed in the treated arm

n_c = number of future subjects who will be observed in the control arm

n_t = number of future subjects who will be observed in the treated arm

p_c = the postulated event rate for future subjects in the control arm

p_t = the postulated event rate for future subjects in the treated arm

x_c = a possible value for the number of events that might be observed in the future in the control arm

x_t = a possible value for the number of events that might be observed in the future in the treated arm

Conditional power computes the probability of a significant result after observing n_c additional control patients and n_t additional treated patients, given the values of m_c , m_t , e_c , e_t , p_c , and p_t . In order to compute conditional power, some assumptions about the expected event rate of the control and treated arms (p_c and p_t) must be made. The most important variable is that the expected reduction in the event rate from the control arm to the treated arm must be specified. In addition, either the control event rate or the combined event rate must be specified. From this information, the expected event rate in the control and treated arms, p_c and p_t , can be calculated.

The probability of observing x_c control events and x_t treated events can be calculated exactly (assuming p_c and p_t are known):

$$Pr[x_c=i, x_t=j] = \binom{n_c}{i} \binom{n_t}{j} p_c^i (1-p_c)^{n_c-i} p_t^j (1-p_t)^{n_t-j}$$

For each possible value of x_c and x_t , the test of significance can be calculated by letting $A = e_c + x_c$, $B = m_c - e_c + n_c - x_c$, $C = e_t + x_t$, and $D = m_t - e_t + n_t - x_c$. For example, the test could be the standard chisquare test based on A, B, C, and D. By summing those probabilities that yield a statistically significant result, the conditional power, β , can be calculated exactly:²

$$\beta = \sum_{i=0}^{n_c} \sum_{j=0}^{n_t} \delta_{ij} \binom{n_c}{i} \binom{n_t}{j} p_c^i (1-p_c)^{n_c-i} p_t^j (1-p_t)^{n_t-j}$$

where δ_{ij} is one if the test statistic is significant and zero otherwise.

A predictive power calculation assumes that we have a joint prior distribution on the control and treated event rates. Typically, we choose a uniform non-informative prior. It assumes that the 2 rates are independent of each other and that the only information we have about the rates in each arm are the data we have observed to date. The resulting predictive power

is the probability that we will reject given the observed data and making no assumption about the future reduction in rates.

The standard prior, $f(p)$, for a probability p takes the form:

$$f(p) = \frac{\Gamma(2\alpha)}{\Gamma(\alpha)\Gamma(\alpha)} p^{\alpha-1} (1-p)^{\alpha-1} \text{ for } 0 < p < 1$$

where Γ is the gamma function. The uniform prior corresponds to $\alpha = 1$ and the Jeffries' prior corresponds to $\alpha = 1/2$. Both of these are considered non-informative priors. This allows derivation of the posterior probability function for the event rate p , given that we have so far observed e events in m subjects:

$$f(p|m, e) = \frac{\Gamma(2\alpha+m)}{\Gamma(\alpha+e)\Gamma(\alpha+m-e)} p^{\alpha+e-1} (1-p)^{\alpha+m-e-1} \text{ for } 0 < p < 1.$$

The same formulas apply to the control and treated arms, so the subscripts c and t have been dropped.

Assume that we are about to sample n additional subjects from the same population. Using the posterior distribution for p , we can compute the predictive probability of observing x future events:

$$\begin{aligned} \Pr(X=x|n, m, e) &= \int_0^1 \binom{n}{x} p^x (1-p)^{n-x} \\ &\quad \cdot f(p|m, e) dp \\ &= \frac{\Gamma(n+1)}{\Gamma(n-x+1)\Gamma(x+1)} \\ &\quad \cdot \frac{\Gamma(2\alpha+m)\Gamma(\alpha+e+x)\Gamma(\alpha+m+n-e-x)}{\Gamma(\alpha+e)\Gamma(\alpha+m-e)\Gamma(2\alpha+m+n)} \end{aligned}$$

This is then used to calculate the probability of obtaining a significant result (i.e., the predictive power).

References

1. Spiegelhalter DJ, Freedman LS, Blackburn PR. Monitoring clinical trials: conditional or predictive power? *Control Clin Trials*. 1986; 7:8–17. [PubMed: 3956212]
2. Moussa MA. Exact, conditional, and predictive power in planning clinical trials. *Control Clin Trials*. 1989; 10:378–385. [PubMed: 2691205]

Table 1**Baseline Patient Characteristics and Procedural Details**

	Abciximab (n=194)	Tirofiban (n=189)
Baseline Characteristics		
Age (years)	63 ± 11	63 ± 11
Male	75	71
White	91	93
Weight (kg)	91 ± 21	92 ± 21
Hypertension	79	81
Diabetes	33	28
Dyslipidemia	87	78
History of smoking	58	58
Current smoker	27	27
History of stroke	6	4
History of PVD	17	12
Prior MI	33	29
Prior PCI	42	43
Prior CABG	25	23
Unstable angina	58	61
Non-ST-segment elevation MI	12	11
ST-segment elevation MI	4	3
Procedural Details		
1 treated vessel	77	80
2 treated vessels	23	20
Pre-diameter stenosis	86	85
Pre-TIMI grade 3	86	86
Balloon-only intervention	8	7
Drug-eluting stent	92	88
Bare metal stent	8	11
Post-diameter stenosis	5	4
Post-TIMI grade 3	98	98
Arteriotomy closure device	39	41

Data are reported as means ± standard deviations or as percentages.

Abbreviations: CABG = coronary artery bypass grafting, MI = myocardial infarction, PCI = percutaneous coronary intervention, PVD = peripheral vascular disease, TIMI = Thrombolysis In Myocardial Infarction.

Summary of Randomized Trials Comparing High-Bolus Dose Tirofiban with Abciximab

[illegible]

J Interv Cardiol. Author manuscript; available in PMC 2014 September 06.

Other abbreviations: C/ADP = collagen/adenosine diphosphate, IPA = inhibition of platelet aggregation, MI = myocardial infarction, NS = not significant, PFA = platelet function analyzer, STEMI = ST-segment elevation myocardial infarction.