EDITORIAL COMMENT
The Future of an Illusion*
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Two reports (1,2) in this issue of the Journal describe the results of the PROTECT–TIMI-30 (Randomized Trial to Evaluate the Relative Protection Against Post-Percutaneous Coronary Intervention Microvascular Dysfunction, Ischemia, and Inflammation Among Antiplatelet and Antithrombotic Agents–Thrombolysis In Myocardial Infarction-30) study, a randomized trial whose primary outcome was unexpected. Results in science are hard to accept when they threaten established treatments (3) or violate dogma (4). How can the results of the PROTECT–TIMI-30 trial be put into perspective?

Background. The PROTECT–TIMI-30 trial (1) was sponsored by the manufacturer of Integrilin (eptifibatide) to explicate the results of REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events) (5), a trial sponsored by the manufacturer of Angiomax (bivalirudin). The REPLACE–2 results suggested that bivalirudin monotherapy was not inferior to the combination of heparin and platelet glycoprotein (GP) IIb/IIIa blockade during PCI (5).

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The PROTECT–TIMI-30 investigators (1) randomized patients into three treatment groups: 1) bivalirudin monotherapy; 2) eptifibatide plus unfractionated heparin; and 3) eptifibatide plus enoxaparin. The primary aim was to show that coronary flow reserve after percutaneous coronary intervention (PCI) would be 20% lower after the use of the direct thrombin inhibitor than after GP IIb/IIIa blockade, and the primary safety objective was to show that bleeding differences among the treatment groups could be minimized by using reduced-bolus heparin or enoxaparin. Treatment using bivalirudin produced higher coronary flow reserves (1.43 vs. 1.33, p = 0.036) than the eptifibatide combinations and was associated with lower transfusion rates (0.4% vs. 4.4%, p < 0.001). Were the surprising results of the PROTECT–TIMI-30 trial real observations or merely bad luck?

Primary end point. Coronary flow reserve refers to the maximum capacity of the coronary vascular bed to increase its flow in response to a pharmacologic-induced demand. The measurement is defined by the ratio of maximal coronary flow to basal flow (6). Normal values for coronary flow reserve commonly exceed 3.0. Values of 2.0 or greater are used as the cutoff for selecting or deferring stenoses for PCI (7,8). Lesions of more than 50% to 70% diameter stenosis may reduce maximal coronary flow, but stenoses of more than 85% are required to reduce basal coronary flow (9).

Conventional methods for measuring coronary flow reserve include Doppler-velocity, positron emission, or thermodilution techniques. In the PROTECT–TIMI-30 trial (1), coronary flow reserve was measured with an angiographic method, also called the frame count reserve, that was based on seminal observations by the authors (10) and correlated against Doppler-derived coronary velocity reserve measurements in humans (11,12). The lack of a 1:1 relation in regression analyses (12) might explain that a value of 1.4 measured as frame count reserve is equivalent to a value of 2.2 measured as coronary velocity reserve using Doppler methods (coronary velocity reserve = 0.5 × frame count reserve + 1.5).

Microcirculation. Coronary flow reserve integrates two aspects of perfusion: epicardial flow and distal microvascular resistance. In the absence of a coronary stenosis, coronary flow reserve is a measure of microvascular function (13). Because the technical management of the epicardial stenoses in the PROTECT–TIMI-30 trial (1) was ostensibly equivalent for the treatment groups, it is reasonable to postulate that measurements of coronary flow reserve reflected differences in microvascular flow between the bivalirudin and eptifibatide groups.

Diabetes reduces coronary flow reserve (14). The significantly higher incidence of diabetes in the bivalirudin group than in the eptifibatide groups (44.4% vs. 36.4%) did not interfere with the therapeutic advantage of the direct thrombin inhibitor. The bivalirudin-treated patients were less likely, however, to achieve Thrombolysis In Myocardial Infarction (TIMI) myocardial perfusion grade 3 than the eptifibatide-treated patients (50.9% vs. 57.9%; p = 0.048), but the primary end point of coronary flow reserve still favored bivalirudin treatment.

Observations from previous studies evaluating the effect of GP IIb/IIIa blockade on microcirculatory flow do not clarify the findings of the PROTECT–TIMI-30 trial (1). In one study of 200 patients undergoing PCI (15), those randomized to abciximab had greater coronary flow velocity than patients randomized to placebo. In contrast, patients in CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) (16) trial assigned to abciximab had a similar incidence (17.3% vs. 17.6%) of a normal myocardial blush grade after the procedure as those assigned to the placebo.

In the PROTECT–TIMI-30 trial (1), concomitant treatment with clopidogrel may have reduced the theoretical benefit of GP IIb/IIIa inhibitor therapy (17). The finding that
coronary flow reserve was better in the bivalirudin group may be explained by the effect of the drug on platelets or the weaker-than-expected effect of eptifibatide on the coronary microvascular response. It must be conceded, however, that clinical trials produce only general principles about treatment regimens (18). The human intellect is almost limitless in its ability to generate post-hoc theories about observations, but refined pathophysiologic details of treatment effects are difficult to obtain in multicenter clinical trials.

A profusion of end points. The main objective of any clinical trial is to answer the primary question. In the PROTECT–TIMI-30 trial (1), the measurement of the primary end point supported the alternative hypothesis of bivalirudin superiority and rejected the null hypothesis as well as the primary hypothesis of eptifibatide superiority. Additional insights about treatment differences might be gleaned from the more than 30 secondary end points in the PROTECT–TIMI-30 trial, but certain caveats exist. The number of additional comparisons in the study exceeded the median number of six comparisons per clinical trial previously reported (19). Secondary analyses might be interesting, exploratory or hypothesis-generating, but they should be put into proper perspective (20). When many secondary comparisons are made, the likelihood is high that a p value of 0.05 will reflect a “false-positive” result. Application of Bayes’ theorem shows that if the prior probability of an effect is 10%, a p value of 0.05 from a study with 80% power results in a “false-positive” probability of 36% (21).

Secondary end points listed in the protocol for the PROTECT–TIMI-30 trial included death and myocardial infarction (MI) within 48 h; the composite of death, MI, and occurrence of any ischemia on Holter within 48 h; death within 48 h; MI within 48 h; TIMI major hemorrhage within 48 h; major and minor TIMI bleeding; stroke; intracranial hemorrhage; and thrombocytopenia. Other prespecified end points included total duration of ischemia through 72 h; TIMI myocardial frame count; growth of blush; growth of blush brightness; rise in soluble CD40 ligand and RANTES levels (i.e., regulated upon activation, normal T-cell expressed and secreted); peak troponin level; increase in the level of C-reactive protein; rates of TIMI flow grade 3 and/or TIMI flow grade 2/3; corrected TIMI frame count; TIMI myocardial flow reserve (TIMI myocardial frame count) before and after PCI; digital subtraction angiography flow reserve; thrombus burden after PCI; side-branch occlusion after PCI; an increase in the levels of interleukin-1 and -6; and fragment F1.2 levels. Other statistical provisions were made for adjustments for admission troponin level; normality or non-normality of data allowing transformation; and duration of clopidogrel pre-treatment. In addition to the prespecified end points and adjustments in the protocol, the study listed other secondary analyses and statistical adjustments, such as any increase in creatine kinase-myocardial band from a normal baseline, pre-PCI TIMI myocardial perfusion grade; stent type; pre-PCI corrected TIMI frame count; diabetes; previous coronary artery disease; location of lesion; previous aspirin use; age; and previous PCI.

In the PROTECT–TIMI-30 trial (1), the clinical end point of death or MI did not differ between the treatment groups. No differences in biomarker levels between bivalirudin-treated and eptifibatide-treated patients were observed.

Unexpected bleeding results. The primary safety end point of TIMI major bleeding in the PROTECT–TIMI-30 trial (1) was statistically similar between the bivalirudin and eptifibatide groups (0.0% vs. 0.7%; p = 0.31), which is not surprising, because the occurrence of TIMI major bleeding is so infrequent after PCI that it not a discriminating end point to define treatment safety. The laboratory component of TIMI major bleeding reflects near-catastrophic blood loss. The clinical component of TIMI major bleeding is intracranial hemorrhage, an end point that has guided fibrinolytic practice and trial design (22–24) but occurs 10 times less frequently after high-risk PCI than after fibrinolytic therapy (25). End points in clinical trials should be clinically meaningful (3). Transfusions, vessel repair, and retroperitoneal hemorrhage have been the more important clinical events that define safety differences among treatments in PCI trials.

An unexpected safety finding in the PROTECT–TIMI-30 trial (1) was the 10-fold higher rate of transfusions in the eptifibatide-treated patients with reduced—bolus heparin (4.0%) or enoxaparin (4.6%) than in the bivalirudin-treated patients (0.4%), despite activated clotting time (ACT) values that were 75 s higher in the bivalirudin group than in the heparin group. The effect of postprocedural bleeding on long-term outcome after PCI recently has been emphasized. In the REPLACE-2 trial (26), postprocedural bleeding was more strongly correlated with one-year mortality (odds ratio, 3.5; 95% confidence interval 1.9 to 6.5) than was elevation of creatine kinase-myocardial band enzyme (odds ratio, 2.6; 95% confidence interval 1.5 to 4.5).

Renal risks. A substudy (2) of the PROTECT–TIMI-30 trial was conducted to identify correlates of bleeding. The bivalirudin group was eliminated from the analysis. The overall incidence of major or minor bleeding within 48 h of PCI in the two eptifibatide groups treated with heparin and enoxaparin was 3.2%. All four major bleeds occurred in enoxaparin-treated patients. Although reduced eptifibatide infusions have been recommended when the creatinine clearance is <50 ml/min, 15 of 33 patients (45%) nonetheless received the full dose. The overdosage was associated with an increased risk of bleeding (9.1%).

On univariate analysis, the risk of bleeding was related to age and estimates of creatinine clearance but not to creatinine itself. On multivariate testing, bleeding risk was related to patient age and surprisingly not to estimates of creatinine clearance or to creatinine measurements (2). The lack of correlation between bleeding risk and renal function has not been found in other contemporary studies (27) and raises
statistical concerns. Conclusions made from well-conducted multivariate analyses are unambiguous when all the independent variables (e.g., age and creatinine clearance) are statistically independent of each other. Because creatinine clearance was not measured directly but was calculated from the Cockgroft-Gault formula in the PROTECT–TIMI-30 trial (2), an equation that contains the term (140 – age), redundant information inserted into the multivariate model may be a source of multicollinearity. This may lead to unreasonable coefficients for variables, inflated standard errors, or signs different from the expected results in multivariate models. Multicollinearity may thus lead to erroneous elimination of variables that otherwise are otherwise related to outcomes (28).

The authors emphasized the importance of reduced dosing of GP IIb/IIIa blockers in patients with advanced age or renal impairment, but they should reconsider bivalirudin as an alternative associated with greater absolute treatment benefit in patients with impaired renal function than in those with normal renal function (29).

**Activated clotting time (ACT) fallacies.** The counterintuitive relation between transfusions and ACT was more pronounced in the PROTECT–TIMI-30 trial (1,2) than it was in the REPLACE-2 trial (5). If the bivalirudin patients had been included in the multivariate model for bleeding in the PROTECT–TIMI-30 trial (2), increased rates of bleeding might have been associated with lower ACT values.

Several studies have questioned the ability of ACT measurements to predict bleeding or ischemic complications in contemporary PCI practice. No relation between bleeding and ACT measurements was observed in the PROTECT–TIMI-30 trial (1,2), the REPLACE-2 trial (5), or in a meta-analysis of several other randomized trials performed over the course of a decade (30). Repeat measurements of ACTs have a high coefficient of variation (31) and might simply document qualitatively whether or not an anticoagulant has been given (32).

**Synthesis.** Scientific knowledge from clinical trials is tentative (33). Concerns about end points, concomitant medications, bias, or chance influence the veracity of trial results and their ability to change clinical practice. Resistance to change is great when results threaten a company’s product (3), contradict the beliefs of the investigators, or run contrary to the wishful thinking that underlies all human endeavors (4).

The authors of the PROTECT–TIMI-30 trial (1) and editors have squarely reported the unexpected outcome for the primary end point of coronary flow reserve, eliminated excessive claims based on secondary end points, and concluded that bivalirudin monotherapy was at least physiologically equivalent to and safer than the eptifibatide combinations.

The report of the PROTECT–TIMI-30 trial (1) will likely have a polemic effect in clinical practice. Users of bivalirudin will defend their choice by pointing to reduced bleeding and the theoretical advantage of improved coronary flow reserve. Users of eptifibatide will emphasize the trends in secondary end points. Any remaining users of enoxaparin will wish for an improved safety profile and lower bleeding. The forthcoming publication of the ACUITY (Catheterization and Urgent Intervention Triage Strategy) trial, another industry-sponsored trial comparing bivalirudin with enoxaparin during PCI, will generate more provisional results to challenge existing illusions about marginal superiority of one treatment over another.

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**REFERENCES**


