Over the past 8 years large-scale, placebo-controlled trials have established the efficacy of intravenous platelet glycoprotein (GP) IIb/IIIa inhibitors at reducing the 30-day composite of death, myocardial infarction, and urgent target vessel revascularization associated with percutaneous coronary angioplasty, atherectomy, and stent placement[1–6]. Using abciximab, tirofiban, or eptifibatide, each trial showed a pattern of benefit suggesting an element of class effect, however, the relative risk reductions among these studies ranged from 24% to 55%. While it was generally held that percutaneous coronary intervention trials using the monoclonal antibody, abciximab, demonstrated a more consistent and numerically greater benefit than those with small-molecule agents, no direct comparison of trials could be fairly made. Thus, it was uncertain if variability in trial outcomes were related to differences in the study populations, the protocols, or the particular IIb/IIIa inhibitor utilized.

A necessary next step for the field was a head-to-head trial of GP IIb/IIIa inhibitors, using abciximab as the comparator and the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT)[3] trial as the study model. Specifically, inclusion criteria, endpoint definitions, and sample size calculations were based upon EPISTENT. The Do Tirofiban and Reo-Pro Give Similar Efficacy Outcome Trial (TARGET) was designed to test whether tirofiban was not inferior to abciximab among percutaneous coronary intervention–stent patients[7]. Unique to TARGET (as compared with EPISTENT) were patients whose indication for coronary stents. Also, nearly one-third of patients had multi-vessel percutaneous coronary intervention procedures performed. Despite these clearly increased risks, with the use of third generation stents and GP IIb/IIIa inhibitors, death, Q-wave myocardial infarction, need for urgent repeat revascularization, and major bleeding each occurred with a frequency of <1%.

Once it was established that tirofiban as studied was inferior to abciximab at the 30-day follow-up, the natural question was ‘why?’ Was the dose of tirofiban too low? Was the duration of the infusion too short? Is blockade of $\alpha_{\text{IIb}}\beta_3$ (vitronectin) or $\alpha_{\text{IIb}}\beta_3$ (Mac-1) receptors needed? While the study was powered only to look at the composite end-point at 30 days for the main study cohort, it is reasonable to review the individual components of the ischaemic composite, the outcome among particular subgroups, and to look at timepoints other than 30 days to see if patterns emerge. Each of these considerations is to generate hypotheses and to potentially guide future studies. As reported[8], the pattern of inferiority for tirofiban was consistent across the individual ischaemic end-points, with hazard ratios ranging from 1·21 to 1·27. Likewise, the hazard ratios were always >1 when considering patients according to age, gender, presence of diabetes, and geographic regions (hazard ratio range 1·10–2·42). A particularly interesting subgroup, though not pre-specified in the data analysis plan, were patients whose indication for coronary intervention was an acute coronary syndrome. This subgroup alone (n=3025) had a statistically significant difference in outcome, with a ~50% higher rate of adverse events if randomized to tirofiban (hazard ratio 1·49; 95% CI 1·15–1·93).

The fact that acute coronary syndrome patients did particularly worse with tirofiban is consistent with a lack of antiaggregatory potency relative to abciximab, since these patients are known to have heightened platelet aggregability. Considering the
type and timing of ischaemic events reinforces and focuses this concept. Non-fatal myocardial infarctions accounted for >90% of the 30-day end-point events. These infarctions were observed hours following the procedure as creatine kinase levels rose, and nearly all myocardial infarctions were recorded within 24 h of percutaneous coronary intervention. Since it takes several hours for creatine kinase-MB levels to rise, these events occurred while the patients were receiving study drug. Beyond this, examining the slope of the myocardial infarction event curves reveals that the nidus or beginning of the ischaemic event was during the interventional procedure (Fig. 1). If these observations are true, there are two plausible conclusions: (1) the potency of tirofiban bolus at the time of intervention was suboptimal, and (2) the potency and duration of the tirofiban infusion were comparable to abciximab’s effect.

Other indications that the bolus dose of tirofiban during percutaneous coronary intervention was suboptimal include the relatively greater gap between the two drugs (hazard ratio=1·50) for patients not treated with clopidogrel in advance of the procedure. Clopidogrel is known to potentiate the effect of other antiplatelet agents. Given the current dosing strategy of tirofiban before undergoing percutaneous coronary intervention, the so-called two-compartment model of treatment before percutaneous coronary intervention was suboptimal include the relatively greater gap between the two drugs (hazard ratio=1·50) for patients not treated with clopidogrel in advance of the procedure. Clopidogrel is known to potentiate the effect of other antiplatelet agents, and receiving clopidogrel in advance may have relatively narrowed the difference between the study drugs (hazard ratio=1·24). That bleeding events occurred more commonly in the abciximab group also suggests more potent antiplatelet effects. Finally, data continue to emerge showing that the bolus dose of tirofiban used in TARGET may have been inadequate to maintain platelet inhibition during the interval while the infusion reached steady state. While early clinical studies found that the 10 µg·kg⁻¹ bolus of tirofiban inhibited light transmission of platelet aggregometry >90%, these data were primarily limited to observations at 5 min and 2 h, with samples collected into citrated tubes, and assays using 5 µM ADP as the agonist. Each of these may have led to suboptimal tirofiban dosing. Subsequent analysis has shown that citrate causes overestimation of aggregation inhibition by tirofiban, as does using 5 µM ADP (as opposed to 20 µM ADP used for testing most antiplatelet agents). More importantly, evolving data with eptifibatide and tirofiban suggest there is a window of vulnerability following the drug bolus and before the drug infusion can maintain high enough plasma levels. This trough appears to occur around 15 to 30 min following the bolus—at the time most crucial for percutaneous coronary intervention. Finally, the data from the Assessing Ultegra-AU (GOLD) study suggest that the best outcome occurs for percutaneous coronary intervention patients achieving 95% inhibition of platelet aggregation 10 min after the initiation of therapy. Hence, giving only 5% of the cumulative tirofiban dose in the bolus and not reaching steady state levels of inhibition for 2 h, may be too little too late.

How should the results of TARGET affect clinical practice and are the above interpretations of TARGET compatible with the strong benefits of tirofiban seen in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) trial? Perhaps the biggest difference between acute coronary syndrome patients treated in TARGET versus TACTICS was the duration of tirofiban treatment before percutaneous coronary intervention. Whereas patients in the invasive strategy of TACTICS underwent percutaneous coronary intervention after 22 h of tirofiban, the acute coronary syndrome group in TARGET received only minutes of therapy in advance. The period of ‘cooling off’ for TACTICS patients probably does not alone explain any difference between the trials since patients undergoing percutaneous coronary intervention sooner in TACTICS had better outcomes. Rather, there may be an obligatory interval of hours needed with the current dosing strategy of tirofiban before maximal steady state platelet inhibition is achieved. As such, the so-called two-compartment model of treating acute coronary syndrome patients—‘upstream’ versus ‘in-lab’—may only remain separated by the adequacy of the bolus dose or the time allowed for steady state plasma levels of small molecule agents to be reached before performing percutaneous coronary intervention.
optimal care. The underlying hope for the TARGET trial was to prove that a less expensive, small-molecule IIb/IIIa inhibitor could provide a similarly good percutaneous coronary intervention outcome. If tirofiban had provided outcome similar to abciximab, choices, decisions, and arguments would have been simplified. On the one hand, TARGET showed tirofiban to be inferior to abciximab and not better than a putative placebo; on the other hand, the cost of preventing an event with abciximab just rose. Given there were 1-6% fewer ischaemic events with abciximab at 30 days, but treatment with abciximab is approximately $1000 greater per patient vs tirofiban, a conjectured estimate of the cost of preventing an end-point event in TARGET — usually a peri-procedural myocardial infarction — might be in excess of $50,000. This estimated cost per event is prevented is higher than that from the placebo-controlled trials.

For the future, further analysis of the TARGET data is needed. Multivariable modelling is required to understand subgroup outcome, such as why diabetic patients fared relatively better than non-diabetic patients. Presumably selection bias could be present, whereby diabetic patients were more often referred for bypass surgery unless coronary anatomy was particularly favourable for percutaneous coronary intervention. Likewise, multivariable analysis will be needed to understand why European patients treated with abciximab had an especially low event rate. Was this cohort particularly unique or was this observation a play of chance? Also, that non-acute coronary syndrome patients tended to do better with tirofiban is intriguing but not biologically intuitive. What is certain is that head-to-head trials of pharmacological therapies are needed and informative. Whether studied alone, or with emboli protective therapies are needed and informative. What is certain is that head-to-head trials of pharmacological therapies are needed and informative. Whether studied alone, or with emboli protective therapies are needed and informative.

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