Mortality at 1 year for the direct comparison of tirofiban and abciximab during percutaneous coronary revascularization: do tirofiban and ReoPro give similar efficacy outcomes at trial 1-year follow-up

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Aims Compared with placebo, abciximab has been associated with mortality reduction at late follow-up. The TARGET trial was performed to test whether tirofiban and abciximab provide similar efficacy outcomes among patients undergoing non-emergent, stent-based percutaneous coronary intervention. We report here the 1-year mortality of the study population.

Methods and results In 18 countries at 149 hospitals, 4809 patients undergoing elective or urgent stent implantation were randomly assigned a bolus and infusion of tirofiban or abciximab. Ischaemic events were assessed at 30 days and 6 months and mortality was assessed at 1 year. We previously reported that abciximab was superior to tirofiban considering the composite rate of death or myocardial infarction at 30 days among all patients and at 6 months among those with an acute coronary syndrome (ACS). At 1-year follow-up death occurred in 46 (1.9%) patients who received tirofiban and 42 (1.7%) patients who received abciximab (hazard ratio 1.10, 95% CI 0.72–1.67; \(P = 0.660\)). Mortality rates for patients with ACS were 2.3% with tirofiban vs. 2.2% with abciximab (hazard ratio 1.03, 95% CI 0.64–1.67; \(P = 0.897\)) and those without ACS were 1.4 vs. 1.0% (hazard ratio 1.32, 95% CI 0.56–3.13; \(P = 0.530\)).

Conclusion At 1 year, tirofiban provided a similar level of survival benefit compared with abciximab.

KEYWORDS Glycoprotein IIb/IIIa inhibitor; Tirofiban; Abciximab; Mortality; Percutaneous coronary intervention

Introduction

Several large-scale trials of percutaneous coronary intervention (PCI) have established the efficacy of intravenous platelet glycoprotein IIb/IIIa inhibitors at reducing the 30-day composite of death, myocardial infarction (MI), and urgent target-vessel revascularization.1–6 These placebo-controlled trials have shown the relative risk reductions with these agents to range from 24 to 55% at 30 days, and two studies showed this benefit to be durable at 6 months among patients receiving a coronary artery stent.7–9

Because of important differences among glycoprotein IIb/IIIa agents, trial designs, and populations enrolled, the Do Tirofiban and ReoPro Give Similar Efficacy Outcome (TARGET) trial, a head-to-head comparison of tirofiban and abciximab was done to directly compare their safety and efficacy.

The TARGET trial was specifically designed to test whether tirofiban (at a now appreciated moderate dose) was not inferior to abciximab among PCI-stent patients.10 At 30 days, the primary efficacy endpoint of death, MI, and urgent target-vessel revascularization had occurred more frequently among the tirofiban group than the abciximab group (hazard ratio 1.26, 95% CI 1.01–1.57; \(P = 0.038\)).11

The rate of major bleeding was similar between the two
study groups, although minor bleeding and thrombocytopenia occurred less frequently among tirofiban-treated patients. At 6 months tirofiban provided a level of overall protection similar to abciximab considering the composite of death, MI, and any target-vessel revascularization. The composite rate of death and MI tended to be lower with abciximab at 6 months ($P = 0.108$), particularly among those with an acute coronary syndrome (ACS) ($P = 0.028$). We now report the 1-year mortality of the overall study population and the specific subgroups.

Methods

Patients

The design and methods of TARGET have been previously described. In brief, between December 1999 and August 2000, 4809 patients undergoing non-emergent PCI of a de novo or restenotic lesion in a native vessel or a bypass graft were enrolled. The protocol mandated intention to stent all treated sites. Patients were excluded in the presence of ST-segment elevation MI, cardiogenic shock, creatinine >2.5 mg/dL, bleeding diathesis, or life-limiting conditions. Enrolment sites were located in North America, Australia, and 14 European countries.

Medications

All patients received aspirin before the procedure, and the administration of clopidogrel 300 mg orally at least 2 h before cardiac catheterization was strongly recommended. Heparin was dosed to achieve an activated clotting time of ≥250 s. The study drug was administered immediately before revascularization in a double-blind, double-dummy manner. Accordingly, all patients received both the active formulation of one treatment and the placebo formulation of the other treatment. Tirofiban was administered as a 10 μg/kg bolus followed by a 0.15 μg/kg/min infusion for 18–24 h and abciximab was administered as a 0.25 mg/kg bolus and 0.125 μg/kg/min infusion (maximum 10 μg/min) for 12 h. Aspirin and clopidogrel were continued for 30 days and long-term aspirin was recommended.

Endpoints

The primary endpoint of TARGET was a composite of death, non-fatal MI, or urgent TVR at 30 days. The 6-month composite of death, MI, and any TVR rate, as well as the 1-year mortality were pre-specified secondary endpoints, and all data were collected prospectively. Death was defined as all-cause mortality.

Data collection and statistical analysis

Treatment analysis included all patients who received any study drug. Each enrolment centre contacted patients for follow-up at 30 days, 6 months, and 1 year. When relevant, other medical records were collected (e.g. death certificates, CK values, and revascularization reports). Endpoint events were investigator reported, with 100% monitoring of source documentation. The double-blinding of treatment assignment was maintained through 1-year follow-up. All endpoint events were reviewed and adjudicated by an independent Clinical Events Committee.

Percentages reported for demographic, procedural, and safety data are based on non-missing observations. Continuous baseline and procedural characteristics are reported as mean ± SD. Categorical data are presented as percentages. Mortality at 1 year is reported as Kaplan–Meier estimates. A Cox proportional-hazards model was used to calculate hazard ratios and confidence intervals based on time to event. Variables included in the Cox regression model were age, gender, body mass index (BMI), treatment assigned (abciximab or tirofiban), Q-wave presentation as indication for PCI, ACS, heart failure, diabetes, hypertension, dyslipidaemia, prior MI, prior bypass surgery, multi-vessel disease, peripheral vascular disease, bleeding disorders, clopidogrel pre-treatment, anti-inflammatory agent use, oral hypoglycaemic use, and blood pressure on presentation. The variables were chosen on the basis of initial univariate analysis and also on prior published results of known predictors of survival after PCI. We also evaluated all possible interactions among the main effects but did not have any that could justifiably be included in the final model. For continuous variables such as age, BMI, blood pressure, etc. we evaluated the need for transformations (i.e. log transformations, linear spline terms) in order to meet the model assumption of linearity related to outcome. For both age and BMI it was necessary to use linear spline terms. Age was analysed as a continuous variable rather than an arbitrary dichotomous cutoff at 65 or 70 years. The linear spline transformation essentially creates two separate and independent variables at a cutpoint where the relationship to outcome changes. A linear spline transformation was also necessary to interpret the relationship between BMI and mortality. For all statistical analyses, a P-value of less than 0.05 was regarded as significant and two sided tests were used for all analyses. No specific corrections were used to account for the potential inflation of the experiment-wise Type I error because of multiple testing for the subgroup analysis. All analyses were performed using SAS 8.2 (SAS Institute, Cary, NC, USA).

Results

Data were complete in 99% of patients for the 30-day primary endpoint, and these results and the 6-month outcome have been previously reported. Baseline demographics and characteristics pertinent to 1-year follow-up analysis are included in Table 1. Mortality data at 1 year were available for 100% of patients. At 1 year, death occurred in 46 (1.9%) patients who received tirofiban and 42 (1.7%) patients who received abciximab (hazard ratio 1.03, 95% CI 0.64–1.67; $P = 0.660$) (Figure 1).

Several subgroups of patients are of particular interest because of their known heightened risk of ischaemic events. Mortality rates ($n = 1$) at 1 year for patients with ACSs were 2.3% ($n = 34$) with tirofiban vs. 2.2% ($n = 33$) with abciximab (hazard ratio 1.03, 95% CI 0.64–1.67; $P = 0.897$) and those without ACS were 1.4% ($n = 12$) vs. 1.0% ($n = 9$) (hazard ratio 1.32, 0.56–3.13; $P = 0.530$) (Figures 2 and 3). Mortality rates ($n = 1$) at 1 year for US patients were 2.1% ($n = 41$) with tirofiban vs. 1.8% ($n = 41$) with abciximab ($n = 2398$ vs. $n = 2414$).
with abciximab (hazard ratio 1.18, 95% CI 0.75–1.85; \(P = 0.481\)) and respective non-US patients’ rates were 1.1 (n = 5) vs. 1.6% (n = 7) (hazard ratio 0.71, 0.23–2.25; \(P = 0.530\)) (Figures 4 and 5).

Diabetes subgroup: As per study protocol, patients with diabetes mellitus were prospectively stratified at randomization and subgroup analysis was pre-specified. Twelve diabetic patients (2.1%) died at 1 year in the tirofiban group and 16 patients (2.9%) died in the abciximab group (hazard ratio 1.32, 95% CI 0.79–2.20; \(P = 0.288\)). At 1 year, the mortality rate for non-diabetics was 1.9% with tirofiban and 1.4% with abciximab, respectively (hazard ratio 1.32, 95% CI 0.35–1.57; \(P = 0.436\)). Among patients on insulin, at 1-year, the mortality was 3.5% with tirofiban and 2% with abciximab, respectively (hazard ratio 0.58, 95% CI 0.19–1.73; \(P = 0.329\)). For those not on insulin, the 1-year mortality was 2.2% in the tirofiban group and 2.3% in the abciximab group (hazard ratio 0.95, 95% CI 0.33–2.70; \(P = 0.920\)).

Multivariable modelling

A Cox proportional hazards model was used to assess independent predictors of 1-year mortality. The model adjusted for age, gender, treatment type, BMI, Q-wave MI as indication for PCI, presentation with ACS, history of peripheral vascular disease, use of beta-blockers, non-steroidal anti-inflammatory agents, and oral hypoglycaemics at presentation. Age and BMI were analysed as continuous variables with spline transformation as the variables were not linearly related to outcome. Age \(\geq 70\) years, Q-wave MI, heart failure at presentation, history of peripheral vascular disease, and use of non-steroidal anti-inflammatory agents were each associated with significantly higher mortality at 1 year. Clopidogrel pre-treatment and beta-blocker use were both associated with a survival advantage (Table 2). Clopidogrel given before the index procedure was associated with a significant mortality reduction within the first year (1.7 vs. 3.6%, hazard ratio = 0.489, 95% CI 0.264–0.906; \(P = 0.023\)). This was primarily due to the reduction in mortality in the tirofiban group (1.8 vs. 4.6%, \(P = 0.012\)) with no significant reduction in the abciximab group (1.7 vs. 2.8%, \(P = 0.257\)). For patients who did not receive clopidogrel pre-treatment, abciximab administration was associated with a numerically lower, but statistically similar mortality rate at 1 year compared with tirofiban (2.8 vs. 4.6%, \(P = 0.390\)). The C-index for the model was 0.74, confirming good model discrimination.

Discussion

We observed no particular survival advantage at 1 year when comparing abciximab with tirofiban among patients.
undergoing non-emergent PCI. These findings may have important scientific and health-care cost-related implications.

Of note, at 30-day follow-up, non-fatal MIs accounted for >90% of endpoint events, and abciximab treatment was associated with an absolute 1.5% reduction of early MI (6.9 vs. 5.4%, P = 0.041). However, beyond the periprocedural period and to 6-month follow-up, the rate of infarction was very low and similar between the two groups. The greater number of early (<48h) infarctions among tirofiban-treated patients did not translate into a higher mortality rate either at 6 months or at 1 year. A disconnection between periprocedural infarctions and subsequent mortality has been described by Anderson et al.13 Pooling data from more than 9290 patients enrolled in several clinical trials with systematic assessment of infarctions and mortality, they found that early infarction prevention accounted for <20% of the 1-year mortality benefit with Ilb/IIIa therapy. In the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial, despite a non-statistically significant numerical trend towards greater MIs in the bivalirudin group compared with the combination of unfractionated heparin and a GP Ilb/IIIa inhibitor, mortality at 1 year tended to be lower with bivalirudin14 (Table 3) further suggesting dissociation between periprocedural MI and long-term mortality. Moreover, specific high-risk subgroups such as patients with diabetes or those with ACS who had demonstrated significant benefit with abciximab at 30 days15 (primarily related to reduction in MI) had similar 1-year mortality with abciximab and tirofiban.

The multivariable model for 1-year mortality confirms known predictors of increased mortality and identifies several high-risk groups such as those with older age, heart failure at presentation, history of peripheral vascular disease, and bleeding disorders. Use of beta-blockers and clopidogrel pre-treatment were associated with a survival benefit in this study cohort. Consistent with recent observations, use of non-steroidal anti-inflammatory agents was associated with an increased mortality risk among this cohort with coronary artery disease.16,17 Treatment type was included in the multivariable analysis and was not an independent predictor of mortality. Given the significant cost differences between the agents, use of tirofiban may therefore be associated with significant cost savings.

The primary limitation of this analysis is the potential lack of power to detect a mortality difference. Although mortality at 1 year was a pre-specified secondary endpoint of this study, the power to detect a difference is limited and the analysis may be subject to a potential Type I error, given sample size limitations and the low risk of the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Multivariable predictors of 1-year mortality</th>
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<tr>
<td>Hazard ratio with 95% confidence interval</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Tirofiban vs. abciximab</strong></td>
<td>1.185 (0.776–1.808)</td>
</tr>
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<td>Age ≥70 (years)</td>
<td>1.095 (1.040–1.153)</td>
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<tr>
<td>Age &lt;70 (years)</td>
<td>1.005 (0.974–1.036)</td>
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<tr>
<td>Female gender</td>
<td>1.191 (0.742–1.911)</td>
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<tr>
<td>BMI &lt;25 kg/m²</td>
<td>0.869 (0.762–0.991)</td>
</tr>
<tr>
<td>BMI ≥25 kg/m²</td>
<td>0.983 (0.936–1.032)</td>
</tr>
<tr>
<td>Q-wave MI as indication for PCI</td>
<td>2.252 (1.132–4.480)</td>
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<tr>
<td>ACS</td>
<td>1.636 (0.972–2.753)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.572 (1.575–4.199)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.231 (0.610–2.485)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>1.258 (0.805–1.966)</td>
</tr>
<tr>
<td>&gt;2 vessel revascularization</td>
<td>1.250 (0.725–2.157)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.896 (1.135–3.166)</td>
</tr>
<tr>
<td>Bleeding disorders</td>
<td>3.719 (1.147–12.05)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>0.575 (0.375–0.883)</td>
</tr>
<tr>
<td>Clopidogrel pre-treatment</td>
<td>0.489 (0.264–0.906)</td>
</tr>
<tr>
<td>Anti-inflammatory agents</td>
<td>2.087 (1.300–3.650)</td>
</tr>
<tr>
<td>Oral hypoglycaemic</td>
<td>1.698 (1.029–2.804)</td>
</tr>
</tbody>
</table>

Age was analysed as a continuous variable with spline transformation. The linear spline transformation essentially creates two separate and independent variables at a cutpoint where the relationship to outcome changes. The model shows that after age 70 there is an increasing risk of death with further increasing age (hazard ratio = 1.095 for each unit year beyond age 70, P = 0.001). However, before age 70 there is no significant increase in mortality with increasing age (P = 0.766). BMI was also analysed as a continuous variable with spline transformation. The model shows that increasing BMI up to 25 seems to have a protective effect (hazard ratio 0.869, P = 0.037); whereas increasing BMI after 25 has no effect on mortality or stops having a significant protective effect (P = 0.493).
study population. The subgroup analysis may be even more underpowered to detect a true difference if it existed.

The assessment of long-term mortality among TARGET patients suggests that we need to make continued efforts to understand and improve the outcome of patients undergoing stent placement and these data might help to focus such efforts. Both treatment groups have 1-year event rates needing improvement. The rates of 1-year death have not changed over the past several years in large-scale PCI trials (Table 3). Pharmacodynamic, pharmacokinetic, and clinical data for the platelet GPIIb/IIIa inhibitor tirofiban in patients undergoing PCI have suggested that the currently utilized tirofiban dosage may be suboptimal and a higher bolus dose of tirofiban (to maintain at least 95% inhibition of platelet aggregation until steady-state is reached with the infusion) is currently being tested, as are new combinations of procedural anticoagulants including bivalirudin and high-dose clopidogrel pre-treatment. Each of these avenues along with aggressive atherosclerosis risk factor modification may provide additional insight and benefit.

Conflict of interest: Dr Howard C. Herrmann is a consultant to Millennium Pharmaceutical Inc., has received honoraria for speaking from Johnson and Johnson, and received research funding from Millennium, Johnson and Johnson, Merck, and Guilford Pharmaceuticals. Dr Rick McClure is a medical advisor for the Medicines Company. Dr David Moliterno has received research funding from Guilford Pharmaceuticals. Dr Diego Ardissono has received research grants and honorarium from Eli Lilly, Merck, and Schering Plough. None of the other authors have any potential conflict of interest.

References