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

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for the Multicentre Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study (MULTISTRATEGY) Investigators

THE USE OF ABCIXIMAB, A POTENT INTRAVENOUS ANTIPLATELET AGENT, AND UNCOATED-STENT IMPLANTATION IN THE INFARCT-RELATED LESION IS A COMPLEMENTARY TREATMENT STRATEGY TO REDUCE MAJOR ADVERSE CARDIAC EVENTS IN PATIENTS UNDERGOING ANGIOPLASTY FOR ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI). IT IS UNCERTAIN WHETHER THERE MAY BE SIMILAR BENEFITS IN REPLACING ABCIXIMAB WITH HIGH-DOSE BOLUS TIROFIBAN. SIMILARLY, THE USE OF DRUG-ELUTING STENTS IN THIS PATIENT POPULATION IS CURRENTLY DISCOURAGED BECAUSE OF CONFLICTING RESULTS ON EFFICACY REPORTED IN RANDOMIZED TRIALS AND SAFETY CONCERNS REPORTED BY REGISTRIES.

OBJECTIVE To evaluate the effect of high-dose bolus tirofiban and of sirolimus-eluting stents as compared with abciximab infusion and uncoated-stent implantation in patients with STEMI undergoing percutaneous coronary intervention.

DESIGN, SETTING, AND PATIENTS An open-label, 2 × 2 factorial trial of 745 patients presenting with STEMI or new left bundle-branch block at 16 referral centers in Italy, Spain, and Argentina between October 2004 and April 2007.

INTERVENTIONS High-dose bolus tirofiban vs abciximab infusion and sirolimus-eluting stent vs uncoated stent implantation.

MAIN OUTCOME MEASURES For drug comparison, at least 50% ST-segment elevation resolution at 90 minutes postintervention with a prespecified noninferiority margin of 9% difference (relative risk, 0.89); for stent comparison, the rate of major adverse cardiac events, defined as the composite of death from any cause, reinfarction, and clinically driven target-vessel revascularization within 8 months.

RESULTS ST-segment resolution occurred in 302 of 361 patients (83.6%) who had received abciximab infusion and 308 of 361 (85.3%) who had received tirofiban infusion (relative risk, 1.020; 97.5% confidence interval, 0.958-1.086; P = .001 for noninferiority). Ischemic and hemorrhagic outcomes were similar in the tirofiban and abciximab groups. At 8 months, major adverse cardiac events occurred in 54 patients (14.5%) with uncoated stents and 29 (7.8%) with sirolimus stents (P = .004), predominantly reflecting a reduction of revascularization rates (10.2% vs 3.2%). The incidence of stent thrombosis was similar in the 2 stent groups.

CONCLUSIONS In patients with STEMI undergoing percutaneous coronary intervention, compared with abciximab, tirofiban therapy was associated with noninferior resolution of ST-segment elevation at 90 minutes following coronary intervention, whereas sirolimus-eluting stent implantation was associated with a significantly lower risk of major adverse cardiac events than uncoated stents within 8 months after intervention.

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Multistrategy Study of Antiplatelet Agents and Stents

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MULTISTRATEGY STUDY OF ANTIPLATELET AGENTS AND STENTS

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evated, further elevation of a marker to greater than 50% of the lowest recovery level from the index myocardial infarction with either ischemic symptoms or other ischemic changes on the electrocardiogram.

Clinically driven target-vessel revascularization is defined as any coronary artery bypass graft surgery, or a second PCI of the original target vessel, driven by clinical symptoms of myocardial ischemia with either a positive stress test or electrocardiographic evidence of ischemic changes at rest attributable to the target vessel and the presence of luminal stenosis of more than 70% of the reference luminal diameter by visual estimate. Stent thrombosis was classified as definite, probable, or possible in keeping with recently proposed Academic Research Consortium classification.

**Data Collection and Management**

Clinical data were prospectively collected at each site by research nurses or treating physicians. Independent study monitors employed by University of Ferrara verified 100% of the data in the case-report forms. The data for all patients with primary end-point events were reviewed by an independent adjudication committee whose members were blinded to treatment assignments. Events adjudication was performed separately by 2 members, and in case of disagreement, the opinion of the third member was obtained and the final decision taken by consensus. The committee was also responsible for the adjudication of all clinical events according to the Academic Research Consortium.

Changes in the ST-segment of the electrocardiogram were evaluated cumulatively before and 90 minutes after intervention. ST-segment elevation was measured to the nearest 0.5 mm at 60 milliseconds after the J point by a single experienced cardiologist who was blinded to treatment assignments. The intraobserver agreement was 94.1% (κ = 0.82) in identifying the recovery by at least 50% of ST-segment elevation in 217 randomly selected patients (30% of all interpretable electrocardiograms).

**Statistical Analysis**

Discrete data were summarized as frequencies, and comparisons were made with the likelihood-ratio χ² test or Fisher exact test. Continuous data were expressed as mean (SD) or median and interquartile range according to their distribution; comparisons were made with a 1-way analysis of variance or the Kruskal-Wallis test.

**Comparisons Between Drug Groups.** A total of 580 patients was included in drug comparison (8-mo clinical outcomes). PCI indicates percutaneous coronary intervention; SES, sirolimus-eluting stent; DES, drug-eluting stent; LBBB, left bundle-branch block; ECG, electrocardiogram; and NSTEMI, non–ST-segment elevation myocardial infarction.

Figure 1. Study Profile

1030 Patients assessed for eligibility

196 Randomized to receive abciximab and uncoated stent
184 Received abciximab
2 Received tirofiban
190 Received PCI
170 Received stent
169 Received uncoated stent
0 Received SES
1 Received other DES

179 Included in drug comparison (ST-segment resolution)
7 Excluded
2 Died during PCI
2 LBBB at ECG
2 NSTEMI
1 ECG not analyzable
186 Included in stent comparison (8-mo clinical outcomes)

187 Randomized to receive abciximab and sirolimus-eluting stent
187 Received abciximab
0 Received tirofiban
184 Received PCI
172 Received stent
6 Received uncoated stent
161 Received SES
5 Received other DES

182 Included in drug comparison (ST-segment resolution)
5 Excluded
1 Withdrew consent
1 Died during PCI
2 LBBB at ECG
1 Pacemaker
186 Included in stent comparison (8-mo clinical outcomes)
1 Excluded (withdrew consent)

186 Randomized to receive tirofiban and uncoated stent
186 Received tirofiban
1 Received abciximab and tirofiban
182 Received PCI
177 Received stent
176 Received uncoated stent
0 Received SES
1 Received other DES

186 Included in stent comparison (8-mo clinical outcomes)
184 Included in drug comparison (ST-segment resolution)
2 Excluded
1 Pacemaker
1 ECG not analyzable
1 NSTEMI
3 ECG not analyzable
186 Included in stent comparison (8-mo clinical outcomes)
177 Included in drug comparison (ST-segment resolution)
9 Excluded
4 LBBB at ECG
1 Pacemaker
1 NSTEMI
3 ECG not analyzable
186 Included in stent comparison (8-mo clinical outcomes)
required for greater than 85% power in detecting a 9% absolute difference, 0.89 in terms of relative risk, between groups in the proportion of patients who attained at least 50% resolution of ST-segment elevation, which corresponds to the 50% previously observed absolute difference between abciximab and placebo, with a 2-sided 2.5% significance level and an 85% expected event rate in the control group based on previous findings. The noninferiority test was computed with the continuity-corrected $\chi^2$ of Dunnett and Gent on the entire patient cohort. This was based on both intention-to-treat and per-protocol principles and was applied to an exploratory analysis across several prespecified subgroups. The Cochran-Mantel-Haenszel $\chi^2$ test was performed to evaluate possible imbalances of the relative risk among different recruiting centers.

Table 1. Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Abciximab Plus Uncoated Stent (n = 186)</th>
<th>Abciximab Plus Sirolimus-Eluting Stent (n = 186)</th>
<th>Tirofiban Plus Uncoated Stent (n = 186)</th>
<th>Tirofiban Plus Sirolimus-Eluting Stent (n = 186)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.9 (11.7)</td>
<td>62.7 (11.2)</td>
<td>65.4 (12.1)</td>
<td>63.4 (12)</td>
<td>.29</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>64.1 (54.7-74.0)</td>
<td>63.4 (54.8-70.2)</td>
<td>66.3 (56.7-75.2)</td>
<td>64.1 (53.7-74.2)</td>
<td></td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>136 (73.1)</td>
<td>135 (72.6)</td>
<td>148 (79.5)</td>
<td>146 (78.5)</td>
<td>.44</td>
</tr>
<tr>
<td>Body mass index, median (IQR)</td>
<td>27 (25-29)</td>
<td>27 (25-29)</td>
<td>27 (24-29)</td>
<td>27 (24-29)</td>
<td>.27</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>23 (12.4)</td>
<td>26 (14.0)</td>
<td>32 (17.2)</td>
<td>27 (14.5)</td>
<td>.80</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>112 (60.2)</td>
<td>98 (52.6)</td>
<td>108 (58.0)</td>
<td>108 (58.0)</td>
<td>.84</td>
</tr>
<tr>
<td>Hyperlipidemia, No. (%)</td>
<td>100 (53.7)</td>
<td>95 (51.1)</td>
<td>104 (56)</td>
<td>97 (52.1)</td>
<td>.36</td>
</tr>
<tr>
<td>Creatinine clearance, median (IQR), mL/min</td>
<td>81.3 (63.0-103.1)</td>
<td>81.3 (63.0-103.1)</td>
<td>81.3 (63.0-103.1)</td>
<td>81.3 (63.0-103.1)</td>
<td>.78</td>
</tr>
<tr>
<td>Prior myocardial infarction, No. (%)</td>
<td>12 (6.4)</td>
<td>14 (7.5)</td>
<td>5 (2.7)</td>
<td>9 (4.8)</td>
<td>.18</td>
</tr>
<tr>
<td>Prior coronary bypass surgery, No. (%)</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>4 (2.1)</td>
<td>2 (1)</td>
<td>.42</td>
</tr>
<tr>
<td>Prior stroke or transient ischemic attack, No. (%)</td>
<td>7 (3.8)</td>
<td>5 (2.7)</td>
<td>17 (9.1)</td>
<td>6 (3.2)</td>
<td>.02</td>
</tr>
<tr>
<td>Systolic blood pressure, median (IQR), mm Hg</td>
<td>135 (114-150)</td>
<td>130 (118-153)</td>
<td>135 (118-153)</td>
<td>135 (120-150)</td>
<td>.85</td>
</tr>
<tr>
<td>Heart rate, median (IQR), beats/min</td>
<td>75 (62-88)</td>
<td>75 (62-87)</td>
<td>74 (62-86)</td>
<td>74.5 (62-87)</td>
<td>.70</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, median (IQR), %</td>
<td>45 (40-53)</td>
<td>45 (38-50)</td>
<td>45 (40-50)</td>
<td>45 (40-53)</td>
<td>.51</td>
</tr>
<tr>
<td>Killip class II or higher, No. (%)</td>
<td>22 (11.6)</td>
<td>26 (14.0)</td>
<td>21 (12.4)</td>
<td>14 (12.3)</td>
<td>.20</td>
</tr>
<tr>
<td>Time from onset of symptoms to hospital presentation, median (IQR), min</td>
<td>105 (63-194)</td>
<td>90 (56-177)</td>
<td>107 (59-180)</td>
<td>100 (60-160)</td>
<td>.47</td>
</tr>
<tr>
<td>Time from hospital presentation to angioplasty, median (IQR) min</td>
<td>97 (73-132)</td>
<td>91.5 (74-125)</td>
<td>100 (73-153)</td>
<td>95 (72-121)</td>
<td>.33</td>
</tr>
<tr>
<td>Patients transferred from peripheral hospitals, No. (%)</td>
<td>43 (23.1)</td>
<td>49 (26.3)</td>
<td>57 (30.6)</td>
<td>43 (23.1)</td>
<td>.72</td>
</tr>
<tr>
<td>Creatinine kinase level at peak, median (IQR), U/L</td>
<td>1825 (753-3305)</td>
<td>1405 (678-3027)</td>
<td>1757 (921-2971)</td>
<td>1431 (665-2632)</td>
<td>.43</td>
</tr>
<tr>
<td>Angiographic features, No. (%)</td>
<td>75 (40.3)</td>
<td>85 (45.7)</td>
<td>84 (45.2)</td>
<td>90 (48.4)</td>
<td>.41</td>
</tr>
<tr>
<td>Single-vessel disease</td>
<td>68 (36.6)</td>
<td>65 (34.9)</td>
<td>61 (32.8)</td>
<td>60 (32.2)</td>
<td>.73</td>
</tr>
<tr>
<td>Double-vessel disease</td>
<td>38 (20.4)</td>
<td>34 (18.3)</td>
<td>40 (21.5)</td>
<td>33 (17.7)</td>
<td>.78</td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
<td>79 (43.4)</td>
<td>85 (45.9)</td>
<td>77 (41.8)</td>
<td>79 (43.1)</td>
<td>.88</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>36 (19.8)</td>
<td>24 (13.1)</td>
<td>26 (14.1)</td>
<td>29 (15.8)</td>
<td>.32</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>65 (55.1)</td>
<td>72 (59.3)</td>
<td>70 (42.9)</td>
<td>74 (40.3)</td>
<td>.48</td>
</tr>
<tr>
<td>Left main coronary artery</td>
<td>3 (1.6)</td>
<td>3 (1.6)</td>
<td>0 (0 )</td>
<td>1 (0 )</td>
<td>.14</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

aBody mass index is calculated as weight in kilograms divided by height in meters squared.

bBody mass index is calculated as weight in kilograms divided by height in meters squared.

cAssessed using standard transthoracic echocardiogram at discharge.

dCalculated as the time difference between first hospital contact and first balloon inflation.

Available in 638 patients.

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Comparisons Between Stent Groups. Based on the STRATEGY trial, the tirofiban/sirolimus-eluting stent group experienced a 44% relative risk reduction in the occurrence of MACE at 8 months as compared with the combination of abciximab and uncoated stent, with an absolute risk reduction of 14% (from 32% to 18%). Because this was almost entirely driven by the different rate of reintervention in the 2 groups, we assumed this to be a reasonably good estimate of the effect of sirolimus-eluting stents compared with uncoated stents in the setting of STEMI.

To correct for the “oculostenotic reflex,” which may artificially increase the MACE rate in the study population by affecting the need for target-vessel revascularization, we anticipated a lower event rate in the uncoated-stent group.

Table 2. Procedural Results and Use of Medications During the Trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Abciximab Plus Uncoated Stent (n = 186)</th>
<th>Abciximab Plus Sirolimus-Eluting Stent (n = 186)</th>
<th>Tirofiban Plus Uncoated Stent (n = 186)</th>
<th>Tirofiban Plus Sirolimus-Eluting Stent (n = 186)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who received coronary intervention, No. (%)</td>
<td>180 (96.8)</td>
<td>183 (98.4)</td>
<td>182 (97.8)</td>
<td>183 (98.4)</td>
<td>.67</td>
</tr>
<tr>
<td>De novo type culprit lesions, No. (%)</td>
<td>180 (96.8)</td>
<td>178 (95.7)</td>
<td>181 (97.3)</td>
<td>180 (96.8)</td>
<td>.79</td>
</tr>
<tr>
<td>Stents implanted, No.</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td>.47</td>
</tr>
<tr>
<td>Range</td>
<td>1-4</td>
<td>1-4</td>
<td>1-4</td>
<td>1-3</td>
<td></td>
</tr>
<tr>
<td>Length of stent, median (IQR), mm</td>
<td>20 (18-28)</td>
<td>23 (18-28)</td>
<td>19 (18-24)</td>
<td>23 (18-28)</td>
<td>.18</td>
</tr>
<tr>
<td>One or more sirolimus-eluting stents implanted, No. (%)</td>
<td>0</td>
<td>161 (93.6)</td>
<td>0</td>
<td>165 (94.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maximal size of stent, mm Mean (SD)</td>
<td>3.07 (0.4)</td>
<td>3.05 (0.4)</td>
<td>3.14 (0.5)</td>
<td>3.05 (0.4)</td>
<td>.06</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3 (2.75-3.5)</td>
<td>3 (2.75-3.5)</td>
<td>3 (2.75-3.5)</td>
<td>3 (2.75-3.5)</td>
<td></td>
</tr>
<tr>
<td>Stent overexpansion, No./total No. (%)</td>
<td>32/169 (18.9)</td>
<td>37/171 (21.6)</td>
<td>36/177 (20.3)</td>
<td>38/175 (21.7)</td>
<td>.91</td>
</tr>
<tr>
<td>Maximal pressure, atm Mean (SD)</td>
<td>14.1 (4.3)</td>
<td>14.6 (3.6)</td>
<td>13.6 (4.4)</td>
<td>14.7 (3.6)</td>
<td>.04</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>14.5 (14-16)</td>
<td>15 (14-16)</td>
<td>14 (14-16)</td>
<td>16 (14-16)</td>
<td></td>
</tr>
<tr>
<td>Abciximab therapy, No. (%)</td>
<td>184 (98.9)</td>
<td>186 (100)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tirofiban therapy, No. (%)</td>
<td>0</td>
<td>0</td>
<td>186 (100)</td>
<td>186 (100)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time from study drug bolus to first balloon inflation, median (IQR), min</td>
<td>40 (25-60)</td>
<td>40 (27-60)</td>
<td>41 (25-60)</td>
<td>45 (25-60)</td>
<td>.52</td>
</tr>
<tr>
<td>Duration of abciximab or tirofiban infusion, median (IQR), h</td>
<td>12 (12-12)</td>
<td>12 (12-12)</td>
<td>24 (16-24)</td>
<td>24 (17-24)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Activated clotting time at peak, median (IQR), s</td>
<td>225 (191-307)</td>
<td>250 (250-303)</td>
<td>229 (194-284)</td>
<td>231 (188-286)</td>
<td>.87</td>
</tr>
<tr>
<td>Quantitative coronary analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombus present, No. (%)</td>
<td>132 (71.0)</td>
<td>140 (75.3)</td>
<td>142 (76.3)</td>
<td>136 (73.6)</td>
<td>.19</td>
</tr>
<tr>
<td>Thrombus possible, No. (%)</td>
<td>25 (13.4)</td>
<td>18 (9.7)</td>
<td>19 (10.6)</td>
<td>34 (18.3)</td>
<td></td>
</tr>
<tr>
<td>TIMI flow, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before procedure Total evaluated, No.</td>
<td>186</td>
<td>186</td>
<td>186</td>
<td>186</td>
<td></td>
</tr>
<tr>
<td>Grade 0 or 1</td>
<td>125 (67.2)</td>
<td>128 (68.8)</td>
<td>127 (68.3)</td>
<td>114 (61.3)</td>
<td>.39</td>
</tr>
<tr>
<td>Grade 2</td>
<td>20 (10.7)</td>
<td>17 (9.14)</td>
<td>23 (12.37)</td>
<td>33 (17.74)</td>
<td>.08</td>
</tr>
<tr>
<td>Grade 3</td>
<td>41 (22.0)</td>
<td>41 (22.0)</td>
<td>36 (19.35)</td>
<td>39 (21.00)</td>
<td>.91</td>
</tr>
<tr>
<td>After procedure Total evaluated, No.</td>
<td>184</td>
<td>186</td>
<td>186</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>Grade 0 or 1</td>
<td>5 (2.7)</td>
<td>2 (1.1)</td>
<td>6 (3.2)</td>
<td>1 (0.5)</td>
<td>.14</td>
</tr>
<tr>
<td>Grade 2</td>
<td>10 (5.4)</td>
<td>5 (2.7)</td>
<td>6 (3.2)</td>
<td>7 (3.8)</td>
<td>.48</td>
</tr>
<tr>
<td>Grade 3</td>
<td>169 (91.8)</td>
<td>177 (95.7)</td>
<td>170 (91.4)</td>
<td>168 (95.7)</td>
<td>.15</td>
</tr>
<tr>
<td>Reference diameter, median (IQR), mm</td>
<td>2.81 (2.52-3.16)</td>
<td>2.88 (2.55-3.14)</td>
<td>2.90 (2.58-3.23)</td>
<td>2.85 (2.61-3.06)</td>
<td>.43</td>
</tr>
<tr>
<td>Final</td>
<td>2.87 (2.57-3.24)</td>
<td>2.91 (2.62-3.17)</td>
<td>2.90 (2.58-3.26)</td>
<td>2.86 (2.61-3.14)</td>
<td>.79</td>
</tr>
<tr>
<td>Minimal lumen diameter, median (IQR), mm</td>
<td>0 (0-0.77)</td>
<td>0 (0-0.56)</td>
<td>0 (0-0.73)</td>
<td>0 (0-1.00)</td>
<td>.34</td>
</tr>
<tr>
<td>Final</td>
<td>2.68 (2.34-2.96)</td>
<td>2.66 (2.42-2.91)</td>
<td>2.65 (2.41-3.00)</td>
<td>2.61 (2.42-2.91)</td>
<td>.64</td>
</tr>
<tr>
<td>Extent of stenosis, median (IQR), %</td>
<td>100 (71-100)</td>
<td>100 (79-100)</td>
<td>100 (76.5-100)</td>
<td>100 (70-100)</td>
<td>.57</td>
</tr>
<tr>
<td>Final</td>
<td>6.5 (2-13)</td>
<td>7 (2-13)</td>
<td>6 (1-13)</td>
<td>8 (2-13.5)</td>
<td>.89</td>
</tr>
</tbody>
</table>

(continued)
of around 27% in keeping with recent data, with a 40% relative risk reduction for MACE in the sirolimus-eluting–stent group (from 27% in the standard-stent to 16% in the active-stent group). Thus, a minimum of 600 patients was required for at least an 80% power to detect the prespecified difference using a 2-sided 2.5% level of significance (with Bonferroni correction).

Event-free survival curves were generated by the Kaplan-Meier method and survival differences between groups were compared using the log-rank test. To test whether initial differences between the 2 treatment groups influenced the difference in outcomes in terms of the primary end point, all variables with a P < .16 in the log-rank test were evaluated with the multivariate Cox proportional hazard model. The assumption of proportionality was tested using Schoenfield residuals. A model selection procedure was applied using the Akaike information criteria linked to a bootstrap approach. An extension of the standard Cox model that allows for random effects was also applied to estimate the heterogeneity between centers. All analyses were performed using Stata version 9.2 (Stata Corp, College Station, Texas).

RESULTS

Patient Population and Baseline Characteristics

Between October 2004 and April 2007, 1030 patients were screened; of these, 745 were enrolled and randomly assigned to the 4 treatment groups (FIGURE 1). After randomization and treatment, 1 patient in the abciximab/sirolimus-stent group withdrew from the study. Patient characteristics were similar among all 4 groups except for a slightly higher prevalence of prior transient ischemic attacks in the tirofiban/uncoated-stent group (TABLE 1).

Procedural Results

The procedural results were similar in the 4 groups with the exception of a slightly smaller maximal stent size in the sirolimus-eluting–stent group—reflecting the limited available range of stent diameters—which was compensated for by a higher pressure of stent deployment (TABLE 2). In the uncoated-stent group, 96% of the implanted stents had less than 0.10 mm strut thickness. Coronary thrombus was unequivocally identified in more than two-thirds of the cases, and flow rates of...
grade 3 were present in 20% of patients before the procedure. Reference vessel and minimal lumen diameters did not differ among the 4 treatment groups. Normal flow grade was achieved in 91.4% to 95.7% of all patients.

**ST-Segment Resolution on the Electrocardiogram**

Among the 722 patients (97%) who had an interpretable electrocardiogram (Figure 1), at least 50% recovery from ST-elevation occurred in 302 of 361 patients (83.6%) and 308 of 361 patients (85.3%) in the abciximab and tirofiban groups, respectively, in the intention-to-treat analysis (relative risk for tirofiban vs abciximab, 1.020; 97.5% confidence interval, 0.958-1.086; P value < .001 for noninferiority). The efficacy of the tirofiban infusion did not show heterogeneity among different recruitment sites (χ², 6.22, P = .72) and was consistent among multiple prespecified subgroups (Figure 2).

**Major Adverse Cardiac Events**

At 30 days, the incidence of the primary clinical end point—a composite of death, reinfarction, or revascularization of the target vessel—was 4.3% vs 4.0% (P = .85) in the abciximab and tirofiban groups, respectively. The incidence of major and minor bleedings did not differ (7.8% in the abciximab vs 7.2% in the tirofiban group, P = .89), but the incidence of severe or moderate thrombocytopenia was more common with abciximab compared with tirofiban (4.0% vs 0.8%, P = .004) (Table 3).

At 8 months, the MACE rate was similar among those who received tirofiban (9.9%) and those who received abciximab (12.4%; P = .30) but was higher among those who were treated with the uncoated stent (54 patients, 14.5%) compared with those who were treated with the sirolimus-eluting stent (29 patients, 7.8%);

---

**Figure 2. Risk Ratios and Rates of the Primary End Point According to Selected Subgroups of Study Patients**

<table>
<thead>
<tr>
<th>Primary Endpoint, No. (%)</th>
<th>Abciximab</th>
<th>Tirofiban</th>
<th>Favor abciximab</th>
<th>Favor tirofiban</th>
<th>Noninferiority</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>302/361 (83.6)</td>
<td>308/361 (85.3)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.53</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>171/202 (84.6)</td>
<td>155/180 (86.1)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.18</td>
</tr>
<tr>
<td>≥65</td>
<td>131/159 (82.4)</td>
<td>153/181 (84.5)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.74</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>217/265 (81.9)</td>
<td>247/287 (86.0)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.37</td>
</tr>
<tr>
<td>Female</td>
<td>85/96 (88.5)</td>
<td>61/74 (82.4)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.66</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36/45 (80.0)</td>
<td>44/52 (84.6)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.86</td>
</tr>
<tr>
<td>No</td>
<td>263/312 (84.2)</td>
<td>260/305 (85.2)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.74</td>
</tr>
<tr>
<td>Killip class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>254/299 (84.9)</td>
<td>270/312 (88.5)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.57</td>
</tr>
<tr>
<td>≥II</td>
<td>46/59 (77.9)</td>
<td>57/48 (75.5)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.22</td>
</tr>
<tr>
<td>Stent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncoated</td>
<td>148/179 (82.7)</td>
<td>156/184 (84.8)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.59</td>
</tr>
<tr>
<td>Sirolimus-eluting</td>
<td>154/182 (84.6)</td>
<td>152/177 (85.9)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.74</td>
</tr>
<tr>
<td>Angiographic features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-vessel disease</td>
<td>134/156 (85.9)</td>
<td>144/169 (85.2)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.96</td>
</tr>
<tr>
<td>Double-vessel disease</td>
<td>111/128 (86.7)</td>
<td>103/118 (87.3)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.89</td>
</tr>
<tr>
<td>Triple-vessel disease</td>
<td>51/70 (72.8)</td>
<td>59/70 (84.3)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.10</td>
</tr>
<tr>
<td>Location of myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>113/157 (71.9)</td>
<td>121/152 (79.6)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.71</td>
</tr>
<tr>
<td>Nonanterior</td>
<td>189/234 (82.1)</td>
<td>187/209 (88.4)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.26</td>
</tr>
<tr>
<td>Time to treatment, h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4</td>
<td>192/227 (86.4)</td>
<td>184/217 (84.7)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.89</td>
</tr>
<tr>
<td>&gt;4</td>
<td>110/134 (82.0)</td>
<td>123/143 (89.0)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.37</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>236/277 (85.1)</td>
<td>226/264 (85.6)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.89</td>
</tr>
<tr>
<td>&lt;60</td>
<td>58/76 (76.3)</td>
<td>79/92 (80.8)</td>
<td>1</td>
<td>0</td>
<td>&lt;.001</td>
<td>.11</td>
</tr>
</tbody>
</table>

The primary end point was defined as the proportion of patients that attained at least 50% resolution of ST-segment elevation in a 12-lead electrocardiogram 90 minutes after intervention. The overall treatment effects of tirofiban compared with abciximab are indicated at the top. The dotted vertical line represents the prespecified noninferiority limit. P values for superiority and noninferiority for the whole population and for each subgroup are shown. Superiority P values were sequentially computed for subgroups in which noninferiority testing was satisfied. None of the P values for interactions were significant. CI denotes confidence interval; dashed line indicates the prespecified noninferiority limit.
Table 3. Kaplan-Meier Estimates of the Clinical Outcomes at 30 Days and 8 Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Abciximab Plus Uncoated Stent (n = 186)</th>
<th>Abciximab Plus Sirolimus-Eluting Stent (n = 186)</th>
<th>Tirofiban Plus Uncoated Stent (n = 372)</th>
<th>Tirofiban Plus Sirolimus-Eluting Stent (n = 372)</th>
<th>Uncoated Stent (n = 372)</th>
<th>Sirolimus-Eluting Stent (n = 372)</th>
<th>P Value Between Stents</th>
<th>P Value Between Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At 30 d, No. (%)</td>
<td>At 8 mo, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3 (1.6)</td>
<td>1 (0.5)</td>
<td>4 (2.2)</td>
<td>2 (1.1)</td>
<td>8 (2.2)</td>
<td>2 (1.1)</td>
<td>.79</td>
<td>9 (2.4)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>15 (8.1)</td>
<td>8 (4.3)</td>
<td>11 (5.9)</td>
<td>7 (3.8)</td>
<td>26 (7.0)</td>
<td>15 (4.0)</td>
<td>.09</td>
<td>23 (6.2)</td>
</tr>
<tr>
<td>Red blood cells transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥1 Units: 4 (2.2)</td>
<td>9 (4.8)</td>
<td>.39</td>
<td>8 (2.2)</td>
</tr>
<tr>
<td>Severe thrombocytopenia (&lt;50,000 cells/mm³)</td>
<td>6 (3.2)</td>
<td>3 (1.6)</td>
<td>2 (1.1)</td>
<td>0</td>
<td>8 (2.2)</td>
<td>3 (0.8)</td>
<td>.23</td>
<td>9 (2.4)</td>
</tr>
<tr>
<td>Moderate thrombocytopenia (&lt;100,000 cells/mm³)</td>
<td>2 (1.1)</td>
<td>4 (2.2)</td>
<td>2 (1.1)</td>
<td>0</td>
<td>3 (0.8)</td>
<td>4 (1.1)</td>
<td>.70</td>
<td>6 (1.6)</td>
</tr>
</tbody>
</table>

At 8 mo, No. (%)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Abciximab Plus Uncoated Stent (n = 186)</th>
<th>Abciximab Plus Sirolimus-Eluting Stent (n = 186)</th>
<th>Tirofiban Plus Uncoated Stent (n = 372)</th>
<th>Tirofiban Plus Sirolimus-Eluting Stent (n = 372)</th>
<th>Uncoated Stent (n = 372)</th>
<th>Sirolimus-Eluting Stent (n = 372)</th>
<th>P Value Between Stents</th>
<th>P Value Between Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>8 (4.3)</td>
<td>3 (1.6)</td>
<td>7 (3.8)</td>
<td>13 (7.0)</td>
<td>54 (14.5)</td>
<td>29 (7.8)</td>
<td>.004</td>
<td>46 (12.4)</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>9 (4.8)</td>
<td>4 (2.2)</td>
<td>8 (4.3)</td>
<td>17 (4.6)</td>
<td>12 (3.2)</td>
<td>.34</td>
<td>13 (3.5)</td>
<td>16 (4.3)</td>
</tr>
<tr>
<td>Death or reinfarction</td>
<td>16 (8.6)</td>
<td>11 (5.9)</td>
<td>12 (6.5)</td>
<td>11 (5.9)</td>
<td>28 (7.5)</td>
<td>22 (5.9)</td>
<td>.37</td>
<td>28 (7.5)</td>
</tr>
<tr>
<td>Clinically driven target-vessel revascularization</td>
<td>21 (11.3)</td>
<td>6 (3.2)</td>
<td>17 (9.1)</td>
<td>10 (7.4)</td>
<td>38 (10.2)</td>
<td>12 (3.2)</td>
<td>&lt;.001</td>
<td>27 (7.3)</td>
</tr>
<tr>
<td>Definite stent thrombosis</td>
<td>7 (3.8)</td>
<td>3 (1.6)</td>
<td>4 (2.2)</td>
<td>6 (3.2)</td>
<td>11 (3.0)</td>
<td>9 (2.4)</td>
<td>.65</td>
<td>10 (2.7)</td>
</tr>
<tr>
<td>Possible stent thrombosis</td>
<td>1 (0.5)</td>
<td>3 (1.6)</td>
<td>3 (1.6)</td>
<td>0</td>
<td>4 (1.1)</td>
<td>3 (0.8)</td>
<td>.71</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Definite or probable stent thrombosis</td>
<td>9 (4.8)</td>
<td>4 (2.2)</td>
<td>6 (3.2)</td>
<td>15 (4.0)</td>
<td>10 (2.7)</td>
<td>.31</td>
<td>13 (3.5)</td>
<td>12 (3.2)</td>
</tr>
</tbody>
</table>

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powered based on the preservation of a difference of at least 50% in the effect of abciximab as compared with that of placebo. In that study, abciximab was superior to tirofiban with respect to the prespecified combined end point. This result was driven by a higher rate of periprocedural myocardial infarction in the tirofiban group, suggesting inadequate early platelet inhibition with the bolus regimen (10 µg/kg) used. Subsequent dose-ranging studies showed that increasing the tirofiban bolus dose from 10 to 25 µg/kg provided an optimal level of platelet inhibition, and several independent pharmacokinetics studies suggested that tirofiban, at increased dose, might even lead to a more consistent platelet inhibition than abciximab. To date, 3 small single-center investigations and 1 prematurely stopped multicenter randomized study have compared high-dose tirofiban with abciximab in 719 patients undergoing PCI; however, none of these studies had adequate power to evaluate the comparison between the 2 drugs.

In the present study, we sought to determine whether tirofiban, at proper dosing, would achieve at least 50% of the anticipated effect of abciximab on the recovery of ST-segment elevation. Tirofiban yielded noninferior recovery from ST-segment elevation after coronary intervention in comparison with abciximab; this result was consistent across different recruiting centers and multiple prespecified subgroups. Similarly, the rate of MACE or bleeding events did not differ between the tirofiban or abciximab groups, but the incidence of se-

Figure 3. Cumulative Kaplan-Meier Estimates of the Rates of the Primary End Points During the Follow-up Period

Cumulative risk of events at 240 days for the primary end point, consisting of the composite of overall mortality, reinfarction, and reintervention in the target vessel. Comparisons shown are with the abciximab group vs tirofiban group (A); uncoated-stent group vs sirolimus-eluting–stent group (B); and all 4 groups (C): abciximab and uncoated stent, tirofiban and uncoated stent, abciximab and sirolimus-eluting stent, and tirofiban and sirolimus-eluting stent.
vere or moderate thrombocytopenia was lower in the tirofiban group compared with the abciximab group, a finding of potential clinical relevance. This may be related to lower propensity of tirofiban to elicit an antibody response.

Similar to abciximab, tirofiban inhibits platelet activity through glycoprotein IIb/IIIa platelet receptor blockade, but unlike abciximab, tirofiban exerts a competitive and rapidly reversible antagonism and does not inhibit other β3 integrins, such as the vitronectin receptor, at the surface of vascular cells or the activated Mac-1 receptor on leukocytes. These have traditionally been regarded as crucial targets to explain abciximab effects especially on microcirculation in the setting of ongoing myocardial infarction. The results of our study may question this paradigm while emphasizing the possibility of the potency and consistency of platelet inhibition in explaining the differential clinical effects of different antiplatelet agents, which is in keeping with the findings from a recent comparison between 2 oral P2Y12 receptor antagonists.

Two medium-sized multicenter studies have compared drug-eluting vs uncoated stents in patients with STEMI. In the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON), the use of sirolimus-eluting stents improved outcomes compared with uncoated stents in terms of the prespecified primary end point in 712 patients. That study, however, recruited a highly selected patient population based on findings in coronary angiography and mandated angiographic follow-up in a large proportion of patients. In contrast, the Paclitaxel-Eluting Stent vs Conventional Stent in Myocardial Infarction with ST-Segment Elevation (PASSION) trial had less stringent angiographic exclusion criteria and mandated clinical follow-up only. In that trial, use of paclitaxel-eluting stents in 619 patients failed to provide a significant benefit compared with uncoated stents at 6 or 12 months. The present study was designed to avoid confounders driven by findings in coronary angiography; we recruited patients before coronary angiography to avoid selection biases, and our protocol mandated clinical follow-up to circumvent the artificial increase in reinterventions due to the "oculostenotic reflex."

With this approach, we were able to recruit 72% of consecutive patients presenting with STEMI at study sites during enrollment, which favorably compares with the previous 2 studies. We observed a significantly lower rate of MACE at 8 months in patients assigned to sirolimus-eluting stent as compared with uncoated stent. This finding was driven by an almost 70% reduction in the incidence of target-vessel revascularization. Our protocol mandated dual antiplatelet treatment for at least 3 months after stent placement. Accordingly, more than 60% of patients in the sirolimus-eluting stent group were no longer taking thienopyridines by 8 months. Yet, there were no differences between the 2 stent groups in the overall mortality rate, the composite incidences of death or reinfarction, or the cumulative incidence of stent thrombosis.

Our randomized controlled data complement recent observational findings on the use of drug-eluting stents in patients with STEMI.
stents for off-label indications and indicate that sirolimus-eluting stent implantation in the context of largely thrombotic lesions, such as those observed in consecutive patients with ongoing myocardial infarction, may be as safe as, and possibly more effective than, the use of uncoated stents at mid-term follow-up.

Several limitations of the present study deserve comment. First, the open-label design may have introduced the potential for bias. We attempted to minimize this potential with the requirement that all ischemic and hemorrhagic events were adjudicated by independent committees unaware of the treatment assignments. Second, the section of ST-segment resolution as a primary end point for the drug comparison may be regarded as suboptimal compared with clinical outcomes. The recovery from ST-segment elevation, however, represents a crucial target for managing this patient population because this finding reflects myocardial salvage, may guide the selection of ST-segment resolution as a treatment assignment. Second, the selection of thrombotic lesions, such as those observed in consecutive patients with ongoing myocardial infarction, may be as safe as, and possibly more effective than, the use of uncoated stents at mid-term follow-up.

In summary, our study provides evidence that in a broad population of largely unselected patients undergoing PCI for STEMI, tirofiban therapy is associated with a noninferior resolution from ST-segment elevation at 90 minutes postintervention compared with abciximab, and at 8-month follow-up, MACE are approximately halved by sirolimus-eluting stent implantation compared with uncoated stents.

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