Approximately 400,000 coronary artery bypass graft (CABG) surgical procedures are performed annually in the United States. Approximately 12,000 (3%) patients die within 30 days of surgery. The presence of an increased frequency of co-morbid risk factors has led to a 30% increase in predicted operative risk in the past decade. Despite recent advances in myocardial preservation, pharmacological intervention, and modification of cardiopulmonary bypass (CPB) circuits, perioperative myocardial infarction (MI) continues to contribute significantly to postoperative morbidity and mortality.

Inflammation associated with ischemia and reperfusion injury is thought to

Context Inflammation and ischemia-reperfusion injury during coronary artery bypass graft surgery requiring cardiopulmonary bypass are associated with postoperative myocardial infarction (MI) and mortality.

Objective To determine the efficacy and safety of pexelizumab, a C5 complement inhibitor, in reducing perioperative MI and mortality in CABG surgery.

Design, Setting, and Participants A randomized, double-blind, placebo-controlled trial, including 3099 patients (≥18 years) undergoing CABG surgery with or without valve surgery at 205 hospitals in North America and Western Europe from January 2002 to February 2003.

Interventions Patients were randomly assigned to receive intravenous pexelizumab (2.0 mg/kg bolus plus 0.05 mg/kg per hour for 24 hours; n=1553) or placebo (n=1546) 10 minutes before undergoing the procedure.

Main Outcome Measures The primary composite end point was the incidence of death or MI within 30 days of randomization in those undergoing CABG surgery only (n=2746). Secondary analyses included the intent-to-treat analyses of death or MI composite at days 4 and 30 in all 3099 study patients.

Results After 30 days, 134 (9.8%) of 1373 of patients receiving pexelizumab vs 161 (11.8%) of 1359 of patients receiving placebo (relative risk, 0.82; 95% confidence interval, 0.66-1.02; P=0.07) died or experienced MI in the CABG surgery only population. In the intent-to-treat analyses, 178 (11.5%) of 1547 patients receiving pexelizumab vs 215 (14.0%) of 1535 receiving placebo (relative risk, 0.82; 95% confidence interval, 0.68-0.99; P=0.03) died or experienced MI (relative risk, 0.82; 95% confidence interval, 0.68-0.99; P=0.03). The trial was not powered to detect a reduction in mortality alone.

Conclusions Compared with placebo, pexelizumab was not associated with a significant reduction in the risk of the composite end point of death or MI in 2746 patients who had undergone CABG surgery only but was associated with a statistically significant risk reduction 30 days after the procedure among all 3099 patients undergoing CABG with or without valve surgery.

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contribute to myocardial damage via activation of the complement, coagulation and cytokine cascades. These pro-inflammatory pathways facilitate activation of leukocytes, platelets, and endothelial cells resulting in thrombosis, myocardial injury, and subsequent MI. Complement activation during CABG surgery requiring CPB may play a particularly important role in the development of perioperative tissue injury due to the proinflammatory effects of the terminal complement products of C5 cleavage, C5a, and C5b-9. C5a is an extremely potent anaphylatoxin, whereas C5b-9, otherwise known as the membrane attack complex, can directly lyse cells, including cardiomyocytes. Both C5a and C5b-9 exhibit pleiotropic activities that include direct cellular damage, alteration of vascular permeability and tone, leukocyte chemotaxis, initiation of cardiomyocyte apoptosis, initiation of thrombosis and promotion of both cellular activation and adhesion. The generation of C5a and C5b-9 during CABG surgery requiring CPB has been well documented and correlates with clinical morbidity. In preclinical models of CPB-induced inflammation and MI, inhibition of C5 cleavage markedly reduced inflammation, myocardial necrosis, and apoptosis.

The terminal complement inhibitor, pexelizumab, is a recombinant, humanized single-chain antibody fragment that targets and binds to the human C5 complement component with high affinity (100 pmol/L), thereby blocking the cleavage of C5b-9 and vitamin K-dependent enzymes generated from the classical, alternative and lectin pathways. Pexelizumab blocks the generation of C5a and C5b-9 but permits the generation of C3b, the critical mediator of bacterial opsonization and immune complex solubilization. Inhibition of C5 activation and cleavage therefore represents a potentially effective therapeutic strategy for reducing C5a and C5b-9 mediated MI associated with CABG surgery requiring CPB.

Initial evaluation of pexelizumab in 2 previous clinical trials indicated that pexelizumab reduced the composite end point of death or MI in patients undergoing CABG surgery without concomitant valve surgery, but a significant impact of pexelizumab on myocardial damage in patients undergoing CABG with concomitant valve surgery was not detected. Based on these data, the Pexelizumab for Reduction in Infarction and Mortality in Coronary Artery Bypass Graft surgery (PRIMO-CABG) trial was designed to test the following hypotheses: whether the C5 complement inhibitor pexelizumab would reduce perioperative MI in patients who had undergone CABG surgery and whether the reduction in MI with pexelizumab would be associated with sustained morbidity and mortality benefit.

**METHODS**

**Patient Population**

The PRIMO-CABG trial was conducted at 205 sites in 7 North American and Western European countries. Eligible patients included those scheduled for CABG surgery with or without concurrent valve surgery. Although the primary efficacy analysis was performed for patients undergoing CABG surgery without concomitant valve surgery (the CABG-only subpopulation), patients undergoing concomitant valve surgery were also enrolled (as requested by the US Food and Drug Administration) for the purpose of collecting additional safety and efficacy data for pexelizumab in the broader CABG population. The patients undergoing CABG surgery alone or with valve surgery represents the intent-to-treat cohort.

To be included, patients had to be at least 18 years and had to have met at least 1 of the following baseline risk factors: require urgent intervention defined according to the American College of Cardiology–American Heart Association (ACC/AHA) guidelines as being patients who are required to stay in the hospital due to medical factors but may be scheduled and operated on within a normal scheduling routine; have been diagnosed as having diabetes mellitus; be a woman; have undergone prior CABG procedure; have a history of a neurologic event (cerebrovascular accident, transient ischemic attack, or carotid endarterectomy), congestive heart failure (New York Heart Association class III or IV), at least 2 MIs (excluding patients who have had an MI within 48 hours of undergoing CABG surgery) or experiencing an MI in not less than 48 hours but no more than 4 weeks before CABG surgery. Patients were excluded if they were scheduled to undergo planned aortic dissection repair and/or aortic root reconstruction; required salvaging intervention; had current cardiogenic shock; had acute left ventricular, septic, or acute papillary muscle rupture; had uncontrolled diabetes (plasma blood glucose value >400 mg/dL [>22.2 mmol/L] within 3 days before surgery); had a history of renal failure and a serum creatinine value greater than 3.0 mg/dL (265.2 µmol/L), of chronic hepatic failure and/or hepatic cirrhosis, and of malignancy, excepting basal cell carcinoma and malignancies in remission (>2 years); had known or suspected hereditary complement deficiency, any active infection that was clinically significant in the opinion of the investigator, participated in another investigational drug study, or was exposed to another investigational agent within 30 days; and had a known or suspected pregnancy, was breastfeeding, or intended to become pregnant during the study.

The institutional review boards or equivalent at each site approved the protocol, and all patients provided written informed consent. A 5-member independent data and safety monitoring board, consisting of physicians, statisticians, and other scientists, monitored and assessed unblinded patient safety outcomes throughout the study.

**Study Protocol**

Patients were randomly assigned in a double-blind fashion by a central telephone-based interactive voice randomization system to receive either intravenous pexelizumab (2.0 mg/kg bolus followed by 0.05 mg/kg per hour infusion of pexelizumab for 24 hours) or placebo (placebo bolus followed by 24-hour placebo infusion). Stratification occurred within each site and was based...
on whether valve surgery was planned, the type of valve surgery (whether mitral or other valve), and whether they had previously undergone CABG surgery.

Pexelizumab or placebo bolus was administered as soon as possible after the general anesthesia induction but not later than 10 minutes before CPB. Patients were followed up for in-hospital adverse events and clinical end points. In addition, patients were seen 14, 30, 90, and 180 days after CABG surgery for adverse events, electrocardiograms, and clinical outcomes and were contacted by telephone at 6 months to determine survival status if visits were missed.

**Study End Points**

The prespecified primary end point was defined as the incidence of a composite of death or MI within 30 days of randomization in patients undergoing CABG surgery without concomitant valve surgery, representing 2746 patients. Secondary analyses included the death or MI composite within 4 or 30 days of randomization in all 3099 patients, considered the intent-to-treat population, and the death or MI composite through day 4 in the CABG-only population, and the death or MI composite within 4 or 30 days of randomization in all 3099 patients, considered the intent-to-treat population. The pharmacodynamic effect of pexelizumab (inhibition of serum complement activity) was determined using a standard total serum complement assay as previously described.5

**Statistical Analyses**

This trial’s objective was to determine whether pexelizumab and placebo would have different composite end point rates of death or MI 30 days after randomization. To have 90% power for detecting a treatment difference between an expected 12% placebo group event rate and an 8% active group event rate using 2-sided .05 significance testing (χ² test), a sample size of 1250 CABG-only patients per treatment group was needed. To account for intent-to-treat analysis of the data and the additional patients undergoing CABG and valve surgery expected to be entered into the study, an estimated 1500 patients per treatment group were to be randomly assigned.

Primary efficacy analysis was performed on the binary composite end point, death or MI through day 30, using patients in the CABG-only strata. Comparison of incidence rates between the treatment groups was performed via stratified (Mantel-Haenszel) χ² testing, where stratification was defined by type of CABG procedure. Comparison of the incidence rates was made via relative risks and their associated 95% confidence intervals. Patients whose mortality status was unknown at day 30 and who reportedly did not experience an MI by day 30 were considered missing for the primary analysis. We considered them missing because their mortality status was unknown.

Secondary end points included analyzing the individual components of the primary composite end point at the end of days 4 and 30, analyzing the composite at day 4, and the primary end point and its components for the intent-to-treat population at days 4 and 30. Analysis of binary secondary end points was also carried out via stratified χ² testing. Logistic regression was performed to further evaluate treatment differences on the primary end point after adjustment for the following baseline covariates: age, race, valve surgery type, diabetes, female sex, repeat CABG procedure, urgent intervention, history of MI, history of congestive heart failure, and history of neurological event. Additionally, survival analysis was performed on the mortality data and included Kaplan-Meier curve estimation as well as Cox proportional hazard modeling using the above mentioned covariates. SAS version 8.2, S-Plus Version 2000 software (SAS Inc, Cary, NC) was used for all statistical analyses and primary statistical analyses were confirmed by an independent academic statistician.

**RESULTS**

**Randomization, Demographics, Safety, and Pharmacodynamics**

A total of 3099 patients undergoing CABG surgery with or without valve surgery were enrolled between January 2002 and February 2003. The primary analysis was performed on the locked 90-day database. An additional database lock was performed to assess 6-month mortality. The flow diagram of patient disposition through day 90 is shown in FIGURE 1. Baseline characteristics were generally balanced between the 2 treatment groups for both the CABG-only and intent-to-treat populations for each baseline risk inclusion criteria and demographic parameter except that there were more women randomized to pexelizumab treatment than to placebo (TABLE 1).

Adverse events and infection log reporting are shown in TABLE 2. The proportions of adverse events were similar between treatment groups. Serious adverse events were also reported for a similar proportion between groups, except that there were numerical increases in pleural effusions and a numerical decrease in respiratory failure with pexels...
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Compared with placebo, administration of pexelizumab bolus plus infusion resulted in rapid and complete inhibition of total serum complement hemolytic activity that was maintained for 24 hours after the procedure (Figure 2). In this group, total serum complement levels returned to baseline within 72 hours.

Outcomes

The effect of pexelizumab on the death or MI composite end point through days 4 and 30 for the intent-to-treat population and for those who underwent CABG surgery alone is shown in Figure 3. The day 30 death or MI composite in the CABG-only subgroup (n=2746) was reduced by 18% with pexelizumab treatment (P=.07). However, at day 4, pexelizumab reduced death or MI by 24% (P=.008) in the CABG-only group and by 26% (P=.014) in the intent-to-treat population. At day 30, pexelizumab reduced death or MI by 18% (P=.03) in the intent-to-treat population. Although the study was underpowered to detect a reduction in mortality with pexelizumab, the nonsignificant reduction in death was consistent with the reduction in the death or MI composite and MI alone in the CABG-only and intent-to-treat populations.

The treatment-independent relationship between adjudicated MI through day 4 and mortality was determined (Figure 4). The population of patients who did not have an MI through day 4 experienced day 30, 90, and 180 mortality of 2.1%, 3.0%, and 4.0%, respectively. Among patients who had a clinically adjudicated MI through day 4, the day 30, 90, and 180 mortality was 10.9%, 14.6%, and 16.3%, respectively. Mortality incidence in the 2 populations was significantly different across the entire 6 months (P<.001, log-rank test). The mortality associated with non–Q wave MI and Q-wave MI through day 4 did not differ from each other (180-day mortality with non–Q wave MI, 16.7%; with Q-wave MI, 14.8%; P=.39, log-rank test).

The impact of pexelizumab on clinically adjudicated MI was determined through days 4 and 30 in the CABG-
only subpopulation and in the intent-to-treat population. Through day 4, pexelizumab reduced MI by 24% \((P = .01)\) in the intent-to-treat population and by 27% \((P = .01)\) in the CABG-only subpopulation (Figure 5). Through day 30, pexelizumab significantly reduced MI by 18% \((P = .04)\) in the intent-to-treat population and by 22% \((P = .04)\) in the CABG-only subpopulation (Figure 3). There were consistent relative reductions in non–Q wave MI and Q-wave MI in both populations at all time points.

Pexelizumab’s effect on long-term morbidity and mortality was further explored in a post hoc analysis of event-free (death or MI) survival through day 180 in the intent-to-treat population (Figure 6). Pexelizumab was associated with a statistically significant reduction in death or MI throughout the entire 6-month period \((P = .03)\), with a 17% relative reduction and a 2.6% absolute reduction in patients experiencing death or MI at 6 months. A Kaplan Meier survival analysis was determined for the intent-to-treat study population through 6 months (Figure 6). Patients treated with pexelizumab showed an improvement in survival that widened from day 4 to day 30 to day 90 and was maintained at day 180, with an absolute 1.0% improvement in 6-month survival in the intent-to-treat population.

**COMMENT**

The PRIMO-CABG trial represents, to the best of our knowledge, the first large prospective study designed to investigate the safety and efficacy of a novel anti-inflammatory agent, the terminal complement inhibitor pexelizumab, for its effect on reducing death or MI in patients undergoing CABG surgery requiring CPB. The primary end point of the study, the incidence of death or MI in the CABG-only subpopulation through day 30 \((n = 2746)\), was nonstatistically significantly reduced by 18%. In the larger intent-to-treat population \((n = 3099)\), which included a broad spectrum of patients with diverse baseline risk factors undergoing CABG surgery with or without valve surgery, pexelizumab statistically sig-

**Table 2. Adverse Events and Infection Log Through 90 Days**

<table>
<thead>
<tr>
<th>Adverse Event*</th>
<th>Placebo (n = 1487)</th>
<th>Pexelizumab (n = 1503)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>284 (19.1)</td>
<td>300 (20.0)</td>
<td>.55</td>
</tr>
<tr>
<td>Nausea</td>
<td>242 (16.3)</td>
<td>251 (16.7)</td>
<td>.75</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>247 (16.6)</td>
<td>245 (16.3)</td>
<td>.82</td>
</tr>
<tr>
<td>Postprocedural pain</td>
<td>147 (9.9)</td>
<td>160 (10.5)</td>
<td>.49</td>
</tr>
<tr>
<td>Anemia NOS</td>
<td>155 (10.4)</td>
<td>160 (10.6)</td>
<td>.84</td>
</tr>
<tr>
<td>Hypotension</td>
<td>150 (10.2)</td>
<td>158 (10.5)</td>
<td>.70</td>
</tr>
<tr>
<td>Postoperative wound infection</td>
<td>139 (9.5)</td>
<td>149 (10.1)</td>
<td>.60</td>
</tr>
<tr>
<td>Constipation</td>
<td>145 (9.8)</td>
<td>136 (9.0)</td>
<td>.51</td>
</tr>
<tr>
<td>Fever</td>
<td>115 (7.7)</td>
<td>116 (7.7)</td>
<td>.99</td>
</tr>
<tr>
<td>Hyperglycemia NOS</td>
<td>78 (5.2)</td>
<td>93 (6.2)</td>
<td>.27</td>
</tr>
<tr>
<td>Vomiting NOS</td>
<td>88 (5.9)</td>
<td>92 (6.1)</td>
<td>.82</td>
</tr>
<tr>
<td>Serious adverse event*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>29 (2.0)</td>
<td>41 (2.7)</td>
<td>.16</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>32 (2.2)</td>
<td>37 (2.5)</td>
<td>.57</td>
</tr>
<tr>
<td>Pneumonia NOS</td>
<td>17 (1.1)</td>
<td>36 (2.4)</td>
<td>.009</td>
</tr>
<tr>
<td>Postoperative wound infection</td>
<td>42 (2.8)</td>
<td>36 (2.4)</td>
<td>.46</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>34 (2.3)</td>
<td>30 (2.0)</td>
<td>.58</td>
</tr>
<tr>
<td>Cardiac failure congestive</td>
<td>33 (2.2)</td>
<td>29 (1.9)</td>
<td>.58</td>
</tr>
<tr>
<td>Cerebrovascular accident NOS</td>
<td>27 (1.6)</td>
<td>30 (2.0)</td>
<td>.72</td>
</tr>
<tr>
<td>Renal failure acute</td>
<td>24 (1.6)</td>
<td>26 (1.7)</td>
<td>.81</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>14 (0.9)</td>
<td>18 (1.2)</td>
<td>.50</td>
</tr>
<tr>
<td>Infection log</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg vein harvest site</td>
<td>103 (7.0)</td>
<td>123 (8.3)</td>
<td>.12</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>53 (3.6)</td>
<td>72 (4.8)</td>
<td>.09</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>79 (5.4)</td>
<td>63 (4.2)</td>
<td>.15</td>
</tr>
<tr>
<td>Superficial sternal wound</td>
<td>29 (2.0)</td>
<td>39 (2.6)</td>
<td>.28</td>
</tr>
<tr>
<td>Deep sternal wound</td>
<td>40 (2.7)</td>
<td>34 (2.3)</td>
<td>.55</td>
</tr>
<tr>
<td>Septicemia</td>
<td>45 (3.1)</td>
<td>28 (1.9)</td>
<td>.03</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>2 (0.1)</td>
<td>1 (0.1)</td>
<td>.50</td>
</tr>
</tbody>
</table>

**Abbreviation:** NOS, not otherwise specified.

*Medical Dictionary for Regulatory Activities preferred term.

†Numbers reflect patients who received study medication.

**Figure 2. Pexelizumab Effect on Serum Complement Activity**

Serum complement levels were determined using a standard complement hemolysis assay as previously described.1
posite observed through day 30. The PRIMO-CABG trial prespecified primary analysis excluded 353 patients who needed valve surgery because pexelizumab had not statistically significantly reduced perioperative MI in about 30 to 35 patients in each treatment group who had undergone CABG surgery as part of a phase 2 trial. When the data from these 353 patients were included for the intent-to-treat analysis, the day 30 death or MI end point was reduced by 18%. Taken together, these observations suggest that the trial may have been underpowered to detect the observed drug effect in the CABG-only subpopulation. Nevertheless, the consistent reductions in the death or MI composite in the intent-to-treat population at days 4 and 30 and the reduction in death or MI in the CABG-only population at day 4 support a positive treatment effect of pexelizumab in CABG patients.

We found that perioperative myocardial damage correlated with 6-month mortality and supports similar findings from previous CABG surgery trials. Through the use of a prespecified adjudication process in this trial, PRIMO-CABG further solidifies the correlation between perioperative MI (both non-Q wave and Q wave) through day 4, with longer-term mortality through 6 months. Patients who experienced an MI through day 4 manifested a 4-fold increase in 6-month mortality. Hence, 1 out of every 6 patients who experienced an MI through day 4 died by 6 months. The trend in mortality incidence through days 30, 90, and 180 among the patients who experienced an
MI by day 4 was somewhat greater than mortality in patients with elevated CK-MB levels following elective percutaneous coronary intervention (2.8%, in-hospital cardiac mortality; 6.6%, cardiac mortality at 1 year). Thus, compared with postpercutaneous coronary intervention MI, post-CABG surgery MI as defined in this study appears to be a stronger predictor of earlier adverse clinical outcomes.

The results, which demonstrated pexelizumab’s impact on early improvements through day 4, are further supported by the mortality data that showed a widening of the absolute reduction in death between pexelizumab and placebo from days 4 to 90, with a 1% absolute reduction measured at day 180. Furthermore, in a post hoc analysis, event-free (death or MI) survival remained significantly improved through day 180. The data suggest that a reduction in early perioperative MI with pexelizumab affords a sustained reduction in clinical morbidity and mortality through day 180.

The reduction in death or MI among patients treated with pexelizumab may be mediated through an amelioration of ischemia-reperfusion-injury-induced inflammation via terminal complement inhibition. However, in 2 other phase 2 trials on acute MI that used angioplasty and thrombolysis, it is of interest to note that although pexelizumab treatment did not significantly reduce CK-MB levels, it did significantly reduce mortality in patients who had undergone angioplasty in the Complement Inhibition in Myocardial Infarction Treated with Angioplasty (COMMA) trial but not in patients who had undergone thrombolysis in the Complement Inhibition in Myocardial Infarction Treated with Thrombolitics (COMPLY) trial. One possible explanation for this apparent discrepancy is that pexelizumab treatment in patients undergoing CABG surgery is initiated prior to ischemia or reperfusion while pexelizumab is administered well after the onset of ischemia for patients experiencing acute MI and therefore may not significantly affect the assessment of acute myocardial damage as measured by CK-MB release. Nevertheless, the anti-inflammatory effect of pexelizumab was correlated with the mortality benefit in the COMMA trial because the severity of post–acute MI inflammation predicted mortality and pexelizumab administration significantly reduced IL-6 and C-reactive protein levels compared with placebo. Additionally, pexelizumab has shown a consistent and significant reduction in 30-day mortality in a pooled analysis of 4986 patients across multiple acute car-

![Figure 5. Pexelizumab Effect on Perioperative Myocardial Infarction](image_url)

<table>
<thead>
<tr>
<th>Population</th>
<th>Outcome</th>
<th>Placebo No./Total (%)</th>
<th>Pexelizumab No./Total (%)</th>
<th>Risk Reduction, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG Surgery Only</td>
<td>MI</td>
<td>127/1368 (9.3)</td>
<td>93/1378 (6.7)</td>
<td>27</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>Non–Q Wave MI</td>
<td>101/1368 (7.4)</td>
<td>76/1378 (5.5)</td>
<td>25</td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td>Q-Wave MI</td>
<td>26/1368 (1.9)</td>
<td>17/1378 (1.2)</td>
<td>36</td>
<td>.15</td>
</tr>
<tr>
<td>All Participants</td>
<td>MI</td>
<td>171/1546 (11.1)</td>
<td>131/1553 (8.4)</td>
<td>24</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>Non–Q Wave MI</td>
<td>140/1546 (9.1)</td>
<td>107/1553 (6.9)</td>
<td>24</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Q-Wave MI</td>
<td>31/1546 (2.0)</td>
<td>24/1553 (1.5)</td>
<td>23</td>
<td>.32</td>
</tr>
</tbody>
</table>

![Figure 6. Event-Free and 6-Month Survival](image_url)

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diovascular disease trials for patients undergoing both CABG surgery and who experience acute MI, suggesting that terminal complement activation plays an important role in cardiac ischemic outcomes in multiple settings.29

In summary, the PRIMO-CABG trial, a prospective, randomized controlled cardiac surgery trial, demonstrated a reduction in perioperative MI with a novel anti-inflammatory drug that has a favorable safety profile. Our primary analysis demonstrated a nonstatistically significant reduction in the composite of death or MI, and our intent-to-treat analysis, which included all patients undergoing CABG, demonstrated a statistically significant reduction in the composite. In addition, both analyses showed a durable effect through day 180. Pexelizumab represents a novel therapeutic approach for CABG surgery with potential for sustained beneficial effects on morbidity and mortality.

Author Contributions: Dr Verrier had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Verrier, Taylor, Newman, Chen, Carrier, Haverich, Malloy, Adams, Todaro, Mojicé, Rolls, Levy.

Acquisition of data: Verrier, Sherman, Taylor, Adams, Mojicé.


Critical revision of the manuscript for important intellectual content: Verrier, Sherman, Taylor, Van de Werve, Newman, Carrier, Haverich, Malloy, Adams, Todaro, Mojicé, Rolls, Levy.

Statistical expertise: Verrier.

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Role of the Sponsor: The PRIMO-CABG Steering Committee, Alexion Pharmaceuticals, and Procter & Gamble Pharmaceuticals designed the study, developed the protocol, and determined a statistical analysis plan by consensus. Procter & Gamble Pharmaceuticals and Alexion Pharmaceuticals also provided the study drug and placebo and hired a contract research organization to collect the data from the study sites. Data were collected on electronic case report forms managed by Quintiles and Procter & Gamble, which housed the blinded trial database. The data analyses were conducted at Procter & Gamble, and the data analyses results were then given to Dr Verrier and the PRIMO-CABG Steering Committee. Final decision on the content of the manuscript rested with the corresponding author in consultation with the steering committee. No formal approval of the manuscript from Procter & Gamble and Alexion; however, Alexion and Procter & Gamble authors contributed to writing the manuscript.

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(SD, 16%; range, 35%-85%) (FIGURE). Between 21 and 61 minutes of wakefulness, the mean cognitive performance ranged from 83% to 86% of peak performance and was not significantly different from performance at subsequent points. The results for the female participant were not significantly different from the results for the male participants.

Comment. Cognitive performance immediately on waking was worse than performance during subsequent sleep deprivation. We observed severe impairments within the first 3 minutes of awakening, and others have reported severe performance impairments lasting up to 10 minutes following awakening, with effects on performance detectable for at least 2 hours. The degree of impairment is likely to be clinically important, given that changes in cognitive performance following 24 hours of sleep deprivation are reported to be comparable with those due to alcohol intoxication.

Our performance test required cognitive operations that use short-term memory, counting skills, speed of cognitive processing, and number fact and lexical retrieval. These skills are critical for many occupational tasks; however, the test did not simulate a specific operational task or indicate the effects of sleep inertia on performance in an operational setting. Further studies should measure this and should include more participants and broader populations. To extrapolate to medical personnel, such studies should measure the effects of interruption of naps and recovery sleep in on-call sleep-deprived individuals.

However, given that sleep inertia increases with the depth of prior sleep, the present results may have important implications for occupations in which sleep-deprived personnel are expected to perform immediately on awakening from deep sleep, including physicians, truck drivers and pilots arising from on-board sleeper berths, and public safety and military personnel.

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CORRECTIONS
Incorrect Data: In the Original Contribution entitled “Terminal Complement Blockade With Pexelizumab During Coronary Artery Bypass Graft Surgery Requiring Cardio-pulmonary Bypass: A Randomized Trial” published in the May 19, 2004, issue of JAMA (2004;291:2319-2327), there were incorrect data in Table 1 and Table 2. In Table 2, in the “Cerebrovascular accident, not other specified,” row of the “Placebo” column, the percentage should read “1.8.” The corrected rows in Table 1 are as follows:

Table 1. Baseline and Procedural Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intent to Treat</th>
<th>Coronary Artery Bypass Graft Surgery Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 1546)</td>
<td>Pexelizumab (n = 1553)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>625 (40.4)</td>
<td>644 (41.5)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>304 (19.7)</td>
<td>326 (21.0)</td>
</tr>
<tr>
<td>Prior congestive heart failure</td>
<td>473 (30.6)</td>
<td>470 (30.3)</td>
</tr>
</tbody>
</table>

Incorrect Data in Abstract: In the Original Contribution entitled “The Long Road to Patient Safety: A Status Report on Patient Safety Systems” published in the December 14, 2005, issue of JAMA (2005;294:2858-2865), incorrect data were reported in the “Results” section of the abstract. In the sentence that reads “... only 3% reported full implementation at survey 2 of computerized physician order entry systems for medications...”, the 3% should have been 34.1%.

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