Effect of Supersaturated Oxygen Delivery on Infarct Size After Percutaneous Coronary Intervention in Acute Myocardial Infarction

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Background—Myocardial salvage is often suboptimal after percutaneous coronary intervention in ST-segment elevation myocardial infarction. Posthoc subgroup analysis from a previous trial (AMIHOT I) suggested that intracoronary delivery of supersaturated oxygen (SSO₂) may reduce infarct size in patients with large ST-segment elevation myocardial infarction treated early.

Methods and Results—A prospective, multicenter trial was performed in which 301 patients with anterior ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention within 6 hours of symptom onset were randomized to a 90-minute intracoronary SSO₂ infusion in the left anterior descending artery infarct territory (n=222) or control (n=79). The primary efficacy measure was infarct size in the intention-to-treat population (powered for superiority), and the primary safety measure was composite major adverse cardiovascular events at 30 days in the intention-to-treat and per-protocol populations (powered for noninferiority), with Bayesian hierarchical modeling used to allow partial pooling of evidence from AMIHOT I. Among 281 randomized patients with tc-99m-sestamibi single-photon emission computed tomography data in AMIHOT II, median (interquartile range) infarct size was 26.5% (8.5%, 44%) with control compared with 20% (6%, 37%) after SSO₂. The pooled adjusted infarct size was 25% (7%, 42%) with control compared with 18.5% (3.5%, 34.5%) after SSO₂ (P_{Wilcoxon}=0.02; Bayesian posterior probability of superiority, 96.9%). The Bayesian pooled 30-day mean (±SE) rates of major adverse cardiovascular events were 5.0±1.4% for control and 5.9±1.4% for SSO₂ by intention-to-treat, and 5.1±1.5% for control and 4.7±1.5% for SSO₂ by per-protocol analysis (posterior probability of noninferiority, 99.5% and 99.9%, respectively).

Conclusions—Among patients with anterior ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention within 6 hours of symptom onset, infusion of SSO₂ into the left anterior descending artery infarct territory results in a significant reduction in infarct size with noninferior rates of major adverse cardiovascular events at 30 days.

Clinical Trial Registration—clinicaltrials.gov Identifier: NCT00175058 (Circ Cardiovasc Intervent. 2009;2:366-375.)

Key Words: myocardial infarction • infarct size • angioplasty • reperfusion

Myocardial salvage is frequently suboptimal despite successful reperfusion in ST-segment elevation myocardial infarction (STEMI), resulting in left ventricular dysfunction and increased mortality.¹² Although delays to reperfusion contribute to irreversible myonecrosis,³ additional causal mechanisms include microcirculatory dysfunction and reperfusion injury.⁴⁵ Most prior studies of pharmacological and mechanical interventions to reduce infarct size after fibrinolysis and primary percutaneous coronary intervention (PCI) have been negative.⁶⁷ The delivery of supersaturated...
oxygen (SSO₂) with a PaO₂ of 760 to 1000 mm Hg in the infarct-related artery immediately after successful reperfusion markedly reduces infarct size in porcine coronary occlusion models, possibly by decreasing capillary endothelial cell swelling, reducing formation of lipid peroxide radicals, altering nitric oxide synthase expression, and/or inhibiting leukocyte activation and adherence. Following promising pilot study results, 14–16 269 patients with anterior or large inferior STEMI undergoing successful PCI within 24 hours of symptom onset (the preclinical parameters for which SSO₂ successfully reduced infarct size) were randomly assigned to SSO₂ or control in the Acute Myocardial Infarction With Hyperoxemic Therapy (AMIHOT)-I trial. In this study, infarct size measured by technetium (tc)-99m-sestamibi single-photonic emission computed tomography (SPECT) imaging at 14 days was not significantly different between the 2 treatment groups. However, the 105 patients with anterior infarction reperfused within 6 hours assigned to SSO₂ had a smaller median infarct size, less post-PCI residual ischemic burden measured by ST-segment Holter monitoring, and improved echocardiographic regional wall motion at 3 months.

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As a post hoc subgroup analysis, these findings from the AMIHOT-I trial are not definitive. We therefore performed a second, prospective, randomized trial of SSO₂ therapy, this time confined to patients with large anterior infarction undergoing PCI within 6 hours of symptom onset (AMIHOT II). The study was powered with a Bayesian approach using hierarchical modeling to allow partial borrowing of evidence from the AMIHOT-I trial.

Methods

The AMIHOT-I Trial

The AMIHOT-II protocol intentionally preserved core design elements from AMIHOT I, the details of which have been previously described. In brief, from January 2002 to December 2003, 269 patients with anterior or large inferior STEMI and baseline Thrombolysis In Myocardial Infarction (TIMI) 0 to 2 flow undergoing PCI within 6 hours of symptom onset (AMIHOT I). Patients in whom TIMI 2 to 3 flow was achieved were randomly assigned to receive a 90-minute infusion of SSO₂ in the infarct artery versus control (standard of care without infusion). Randomization was performed using an automated biased coin randomization.18

Principal clinical and angiographic exclusion criteria included absolute contraindications to anticoagulant therapy; hemorrhagic stroke within months; intra-aortic balloon pump counterpulsation or cardiogenic shock; coronary artery bypass graft surgery within 30 days; severe valvular stenosis or insufficiency, pericardial disease, nonischemic cardiomyopathy, ventricular septal defect, pseudoneuromy, or papillary muscle rupture; cardiopulmonary resuscitation for >10 minutes; expected survival <6 months due to noncardiac comorbidities; current participation in other investigational device or drug trials; inability or unwillingness to provide informed consent or to agree to all follow-up study procedures; systemic arterial PO₂ <80 mm Hg despite supplemental oxygen; severe target vessel calcification or tortuosity; coronary stenosis ≥40% proximal to the infarct lesion, unprotected left main stenosis ≥60%, or a significant nonstented coronary dissection; total symptom-to-balloon time of >6 hours, or TIMI 0 to 1 flow at the end of procedure; or surgery or additional PCI planned within 30 days after treatment. A log was kept at all participating sites to document reasons for patient ineligibility. The study was approved by the institutional review board at each participating center, and consecutive eligible patients signed informed written consent.

AMIHOT-II Protocol Procedures and Randomization

Before angiography, an ECG was performed, a 24-hour 12-lead continuous digital electrocardiographic monitor (180+, Northeast Monitoring, Maynard, Mass) was placed, cardiac biomarkers were drawn (creatine phosphokinase [CK], CK MB fraction [CK-MB] or troponin), and 325 mg of aspirin was administered. A clopidogrel loading dose of 300 or 600 mg was recommended before procedure, but in no case >4 hours after the procedure. Left ventriculography, coronary arteriography, and PCI were performed with standard techniques and commercially available devices. Anticoagulation during PCI was achieved with intravenous unfractionated heparin. Glycoprotein IIb/IIIa inhibitor and stent selection decisions were performed by the investigator’s discretion. After PCI, cardiac biomarkers were drawn every 8 to 12 hours, aspirin was continued indefinitely, and 75 mg of clopidogrel was administered daily for at least 1 month depending on the stent type.

Eligible patients were randomized at the completion of the PCI procedure in an open-label and balanced fashion (as described later) to either an intracoronary infusion of SSO₂ or standard of care without infusion. Randomization was performed using an automated voice response system, in blocks of 19 (14 SSO₂ patients for each 5 control patients=2.8:1) stratified by time to reperfusion (0 to 3 hours or >3 to 6 hours) and lesion location (proximal or nonproximal left anterior descending), accomplished using an adaptive scheme with a biased coin randomization.19

Device Description and Study Procedures

SSO₂ was delivered for 90 minutes using an extracorporeal circuit (TherOx, Inc, Irvine, Calif), as previously described. Blood is withdrawn either from the side port of a single femoral sheath size 2F larger than the PCI guide catheter (coaxial configuration), or alternatively through a second 5F sheath placed in the contralateral femoral artery and is oxygenated in a polycarbonate chamber to achieve a Po₂ of 760 to 1000 mm Hg. Hyperoxemic blood is then returned to the patient at 75 mL/min for 90 minutes through an intracoronary infusion catheter placed in the infarct artery proximal to the stent, during which the guide catheter is disengaged from the left main coronary ostium. At the beginning of the protocol, the only infusion catheter available was the 5.3F Tracker-38 (Target Therapeutics, Fremont, Calif), which in the coaxial configuration required a 7F guide catheter and 9F sheath. During the latter phases of enrollment the lower profile 4.6F MI Cath infusion catheter...
findings, provided 85.4% power to demonstrate superiority of SSO₂. Regarding the primary safety end point, assuming 30-day rates of MACE of 7% in both randomized arms, with a noninferiority δ of 6% (a margin agreed on with the Food and Drug Administration), 80.7% power was present to declare noninferiority between the 2 groups. This approach is distinctly different from simple pooling of the AMIHOT-I subgroup data in patients with anterior MI reperfused within 6 hours with the AMIHOT-II results. Simple pooling (which greatly inflates type I error) would have provided significantly greater power for the primary efficacy and safety end points (93% and 86%, respectively). Conversely, it is also important to note that AMIHOT II was intentionally underpowered as a standalone study for the primary efficacy and safety end points (73% and 64% power, respectively); statistical testing of AMIHOT II alone was therefore not prespecified for primary end point analysis. Rather, some degree of borrowing from the AMIHOT-I data would be necessary for either primary end point to be satisfied (with the degree of borrowing depending on the similarity of the datasets), with the principal statistical analysis planned only on the blinded Bayesian dataset.

Use of Bayesian analysis was restricted to assessment of the primary end points. Secondary and subgroup analyses were conducted using standard (frequentist) methods. Categorical variables were compared by Fisher exact test. Continuous variables are presented as mean±SD or median (interquartile range), and were compared by the nonparametric Wilcoxon rank-sum test. Exact Wilcoxon 2-sample tests were used to compare infarct size data between the SSO₂ and control groups. Linear regression analysis was used to adjust for differences between the groups in age, gender, prior MI, diabetes, infarct location, time to reperfusion, post-PCI ST-segment resolution prerandomization, and major bleeding. All primary and secondary analyses were performed in the intent-to-treat population. A per-protocol subset was used as a coprimary analysis for the primary (noninferiority) safety end point, consisting of randomized patients not excluded due to a major protocol deviation likely to impact the primary safety end point. Formal interaction testing was used to assess the impact of baseline left ventricular ejection fraction (LVEF) on the relative reduction in infarct size with SSO₂. Smoothed medians of infarct size distributions were computed by kernel density estimation to de-emphasize the effects of discreteness in smaller subgroups. Statistical evaluations using frequentist methods in the AMIHOT-II study patients were performed using a 2-sided significance level of 0.05. Non-Bayesian statistical analyses were performed by SAS version 9.1.3, Cary, NC. Bayesian inference was conducted using Markov chain Monte Carlo computation by the R2WinBUGS interface to WinBUGS 1.4.1 (Data Supplement).

Results

Patients

Between September 13, 2005, and May 26, 2007, a total of 2517 consecutive patients with STEMI were screened at 20 sites in 4 countries for enrollment in AMIHOT II, of whom 317 (12.6%) were enrolled (Figure 1). Of the 2200 excluded patients, 1244 (56.5%) had a nonanterior MI and 388 (15.4%) presented >6 hours after symptom onset. Among the remaining 934 patients with anterior STEMI presenting within 6 hours of symptom onset, 617 (66.1%) were not eligible for randomization, the most common reasons being cardiogenic shock or intra-aortic balloon counterpulsation use, baseline TIMI-3 flow, procedural complications, inability to obtain consent, or physician discretion (Figure 1). Of the 317 eligible patients who provided informed consent, 13 received SSO₂ as part of a nonrandomized training cohort, and 3 patients who were prematurely randomized in error were subsequently deregistered before any treatment was delivered after it was recognized that major exclusion criteria were present (ventricular septal defect in 1 patient, prolonged
cardiopulmonary resuscitation in 1 patient, and cardiogenic shock in 1 patient). Thus, the intention-to-treat study cohort consisted of 301 randomized patients, 222 of whom were assigned to SSO2 and 79 to control. Of the 301 randomized patients, tc-99m-sestamibi SPECT infarct size assessment was completed in 281 patients (93.4%), and no patient was lost to follow-up at 30 days.

The baseline characteristics of the randomized AMIHOT-II groups were well matched (Table 1). The enrolled AMIHOT-II patients were also comparable with the cohort of AMIHOT-I patients with anterior STEMI reperfused within 6 hours of symptom onset, except that the AMIHOT-I patients were less likely to have hypertension and baseline TIMI-2 flow, had a lower baseline LVEF, were more likely to receive glycoprotein IIb/IIIa inhibitors but less likely to undergo thrombectomy (Table 1). Drug-eluting stents were also not available during AMIHOT I.

AMIHOT-II SSO2 Procedure
Among patients randomized to SSO2, the coaxial approach was most commonly used, which required a 9F sheath to accommodate the Tracker-38 infusion catheter (Table 2). To avoid the 9F sheath, contralateral femoral arterial access was used for the draw sheath in 40.1% of patients in whom the Tracker-38 was used. In contrast, the coaxial (single sheath) approach was used in almost all cases when the smaller MI-Cath infusion catheter became available (Table 2).

A 90-minute or longer SSO2 infusion was delivered in 84.7% of patients (Table 2). The infusion most commonly took place in the cardiac catheterization laboratory, though 30% of patients received the infusion in other settings. Vital signs and arterial blood gas measurements (assessed every 30 minutes) were stable during the infusion; neither the systemic arterial Po2 (~140 mm Hg on supplemental low-flow nasal cannula oxygen) nor oxygen saturation (~98%) changed during intracoronary SSO2 infusion (data not shown).

Infarct Size
As shown in Figure 2, among 101 patients with anterior STEMI reperfused within 6 hours in AMIHOT I in whom infarct size was measured, the median (interquartile range) infarct size (measured as the percentage of the left ventricle) was 23% (5%, 37%) with control therapy compared with 9% (0%, 30%) after SSO2 (smoothed medians, 24% versus 17.5%, respectively). Among 281 randomized patients with tc-99m-sestamibi SPECT data in AMIHOT II, infarct size was 26.5% (8.5%, 44%) with control therapy compared with 20% (6%, 37%) after SSO2 (unadjusted P=0.10, adjusted P=0.03). The pooled study-level adjusted infarct size from the AMIHOT I and II trials was 25% (7%, 42%) with control therapy compared with 18.5% (3.5%, 34.5%) after SSO2 (P=0.02; Bayesian posterior probability of superiority, 96.9%). Figure 3 depicts the histogram of infarct sizes in the pooled treatment and control cohorts, demonstrating a shift to smaller infarcts across the range of the skewed distribution. Among 154 patients with a baseline LVEF of <40%, infarct size was reduced from 33.5% (17.5%, 43.5%) with control to 23.5% (7.5%, 38.5%) with SSO2, an absolute reduction of 10% (0%, 14%), whereas the absolute decrease in infarct size was less marked in the 196 patients with an LVEF of ≥40% (16.5% [4.5%, 31.5%] with control versus 12.5% [2.5%, 30.5%] with SSO2, a reduction of 4% [1%, 7%], P for interaction, 0.60).

Cardiac Biomarker and ST-Segment Assessment
Among patients randomized to AMIHOT II to SSO2 versus control, there were no significant differences in the post-PCI peak levels of CK-MB (299±257 versus 289±175 IU/L respectively, P=0.39) or troponin (96±136 versus 128±161 ng/mL respectively, P=0.27). Nor were there significant differences between the groups in post-PCI total ischemic burden measured by the Holter monitor cumulative ST-elevation time trend curve area at 3 hours (1178±2596 versus 1369±3684 µV·min, respectively, P=0.69).

Clinical Outcomes
As shown in Table 3, by intention-to-treat analysis, the Bayesian pooled 30-day mean (±SE) rates of MACE were 5.0±1.4% for control and 5.9±1.4% for SSO2 (posterior
probability of noninferiority, 99.5%). By per-protocol analysis, the Bayesian pooled 30-day rates of MACE were 5.1 ± 1.5% for control and 4.7 ± 1.5% for SSO2 (posterior probability of noninferiority = 99.9%).

Other adverse events in AMIHOT II appear in Table 4. Hemorrhagic complications and access site-related events, mostly hematomas, were more frequent in patients randomized to SSO2. Among SSO2 patients, use of the smaller MI-Cath infusion catheter compared with the Tracker-38 was associated with a reduction in access site-related adverse events (from 27.2% to 13.3%, P = 0.03), due mainly to fewer access site reacted complications in the SSO2 group with use

### Table 1. Baseline Characteristics of the AMIHOT-I and AMIHOT-II Study Populations and Procedural Results Before Randomization

<table>
<thead>
<tr>
<th>Age, y</th>
<th>58.4 ± 12.3</th>
<th>60.4 ± 12.0</th>
<th>0.15</th>
<th>60.9 ± 12.2</th>
<th>59.2 ± 11.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>80 (76.2)</td>
<td>242 (80.4)</td>
<td>0.40</td>
<td>173 (77.9)</td>
<td>69 (87.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (9.5)</td>
<td>47 (15.6)</td>
<td>0.14</td>
<td>36 (16.2)</td>
<td>11 (13.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33 (31.4)</td>
<td>140 (46.5)</td>
<td>0.008</td>
<td>104 (46.8)</td>
<td>36 (45.6)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>36 (34.3)</td>
<td>134 (44.5)</td>
<td>0.09</td>
<td>100 (45.0)</td>
<td>34 (43.0)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>50 (47.6)</td>
<td>119 (39.5)</td>
<td>0.17</td>
<td>85 (38.3)</td>
<td>34 (43.0)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>9 (8.6)</td>
<td>27 (9.0)</td>
<td>1.0</td>
<td>20 (9.0)</td>
<td>7 (8.9)</td>
</tr>
<tr>
<td>Rescue PCI</td>
<td>4 (3.8)</td>
<td>18 (6.0)</td>
<td>0.47</td>
<td>11 (5.0)</td>
<td>7 (8.9)</td>
</tr>
<tr>
<td>Serum creatinine &gt; 1.5 mg/dL</td>
<td>3 (2.9)</td>
<td>8 (2.7)</td>
<td>1.0</td>
<td>6 (2.7)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Symptom onset to PCI, min</td>
<td>203 ± 73</td>
<td>208 ± 76</td>
<td>0.81</td>
<td>209 ± 74</td>
<td>205 ± 84</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>37.8 ± 10.9</td>
<td>40.5 ± 8.7</td>
<td>0.005</td>
<td>40.2 ± 8.6</td>
<td>41.3 ± 9.1</td>
</tr>
</tbody>
</table>

Other adverse events in AMIHOT II appear in Table 4. Hemorrhagic complications and access site-related events, mostly hematomas, were more frequent in patients randomized to SSO2. Among SSO2 patients, use of the smaller MI-Cath infusion catheter compared with the Tracker-38 was associated with a reduction in access site-related adverse events (from 27.2% to 13.3%, P = 0.03), due mainly to fewer access site reacted complications in the SSO2 group with use
of a single unilateral compared with dual bilateral femoral artery sheaths (from 45.2% versus 13.8%, \( P < 0.0001 \)).

### Discussion

The principal finding of this study, representing the net results of a prespecified Bayesian analysis from 2 consecutive randomized trials, is that in patients with anterior STEMI undergoing successful PCI within 6 hours of symptom onset randomized to SSO₂ versus control in the AMIHOT-I and AMIHOT-II trials, with the adjusted pooled infarct size estimates shown. Compared with control, SSO₂ was associated with a significant reduction in infarct size, as evidenced by the Bayesian posterior probability of >95%. The thick black lines represent the median, with the vertical limits of the boxes representing the interquartile (25% to 75%) ranges. The limit lines represent the 95% CIs. LV indicates left ventricle.

**Figure 2.** Infarct size among patients with acute anterior myocardial infarction in whom PCI was performed within 6 hours of symptom onset randomized to SSO₂ versus control in the AMIHOT-I and AMIHOT-II trials, with the adjusted pooled infarct size estimates shown. Compared with control, SSO₂ was associated with a significant reduction in infarct size, as evidenced by the Bayesian posterior probability of >95%. The thick black lines represent the median, with the vertical limits of the boxes representing the interquartile (25% to 75%) ranges. The limit lines represent the 95% CIs. LV indicates left ventricle.

Despite successful PCI, although the median reduction in infarct size with SSO₂ was 6.5% in the entire study population, the median infarct size in patients with a baseline LVEF of <40% was decreased from a median of 33.5% with control to 23.5% with SSO₂, representing incremental salvage of 10% of the left ventricular myocardium. Although the absolute reduction in infarct size was less in smaller anterior infarcts (a median 4% decrease in infarct size), the relative reduction was comparable, as evidenced by the negative interaction effect. Moreover, as the SSO₂ infusion is not initiated until after PCI is completed, no delays to reperfusion are required to deliver this therapy, representing a procedure that can readily be incorporated into current reperfusion treatment pathways in which minimizing door-to-balloon time is an imperative.

Although this study was not designed to address the mechanisms underlying the decrease in infarct size with SSO₂, neither post-PCI ischemic burden (representing residual or recurrent ischemia), nor peak cardiac biomarker...
levels (an important prognostic signal after primary PCI) were improved with SSO₂. However, recurrent ischemia was uncommon in both groups, and varying biomarkers were collected at different hospitals, assessed infrequently (every 8 to 12 hours), and not measured by a central core laboratory, precluding reliable quantification. In experimental models, improved microcirculatory function and reduction in reperfusion injury has been hypothesized to underlie many of the beneficial effects of SSO₂. Conceptually, these findings also suggest that reperfusion injury continues to have an important reversible component after epicardial flow restoration, making possible beneficial therapies such as SSO₂, which can be implemented without necessitating delay to reperfusion.

Randomization to SSO₂ was associated with an increase in hemorrhage-related adverse events, mostly access site hema-

### Table 3. MACE Through 30 Days

<table>
<thead>
<tr>
<th></th>
<th>SSO₂ (N=222)</th>
<th>Control (N=79)</th>
<th>P</th>
<th>Posterior Probability of Noninferiority*</th>
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</thead>
<tbody>
<tr>
<td><strong>Intention-to-treat population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AMIHOT-I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE, n (%)</td>
<td>9 (6.7)</td>
<td>7 (5.2)</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>AMIHOT-II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE, n (%)</td>
<td>12 (5.4)</td>
<td>3 (3.8)</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4 (1.8)</td>
<td>0 (0)</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>Reinfarction</td>
<td>4 (1.8)</td>
<td>2 (2.5)</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>8 (3.6)</td>
<td>3 (3.8)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE blended, adjusted Bayesian mean±SE</td>
<td>5.9±1.4%</td>
<td>5.0±1.4%</td>
<td></td>
<td>99.5%</td>
</tr>
<tr>
<td><strong>Per-protocol population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AMIHOT-I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE, n (%)</td>
<td>9 (7.6)</td>
<td>7 (5.6)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>AMIHOT-II</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MACE, n (%)</td>
<td>7 (3.8)</td>
<td>3 (3.8)</td>
<td>1.0</td>
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<tr>
<td>Death</td>
<td>2 (1.1)</td>
<td>0 (0)</td>
<td>1.0</td>
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<tr>
<td>Reinfarction</td>
<td>3 (1.6)</td>
<td>2 (2.6)</td>
<td>0.63</td>
<td></td>
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<tr>
<td>Target vessel revascularization</td>
<td>5 (2.7)</td>
<td>3 (3.8)</td>
<td>0.70</td>
<td></td>
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<tr>
<td>Stroke</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
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<tr>
<td>MACE blended, adjusted Bayesian mean±SE</td>
<td>4.7±1.5%</td>
<td>5.1±1.5%</td>
<td></td>
<td>99.9%</td>
</tr>
</tbody>
</table>

*Posterior probability that the SSO₂ therapy group MACE rate is not more than 6% greater than the control group rate.

### Table 4. Other Adverse Events Among Randomized Patients in AMIHOT-II

<table>
<thead>
<tr>
<th></th>
<th>SSO₂ (N=222)</th>
<th>Control (N=79)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis</td>
<td>9 (4.1)</td>
<td>2 (2.5)</td>
<td>0.73</td>
</tr>
<tr>
<td>Any access site related adverse event</td>
<td>50 (22.5)</td>
<td>10 (12.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hematoma</td>
<td>39 (17.6)</td>
<td>8 (10.1)</td>
<td>0.15</td>
</tr>
<tr>
<td>Any hemorrhagic adverse event</td>
<td>55 (24.8)</td>
<td>10 (12.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Access site related*</td>
<td>41 (18.5)</td>
<td>9 (11.4)</td>
<td>0.16</td>
</tr>
<tr>
<td>Mild</td>
<td>34 (15.3)</td>
<td>8 (10.1)</td>
<td>0.34</td>
</tr>
<tr>
<td>Moderate</td>
<td>6 (2.7)</td>
<td>0 (0)</td>
<td>0.35</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (0.5)</td>
<td>1 (1.3)</td>
<td>0.46</td>
</tr>
<tr>
<td>Nonaccess site related</td>
<td>16 (7.2)</td>
<td>1 (1.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hemoglobin baseline, g/dL</td>
<td>14.3 (13.4, 15.5)</td>
<td>14.7 (13.7, 15.5)</td>
<td>0.27</td>
</tr>
<tr>
<td>Hemoglobin 24 hours, g/dL</td>
<td>12.9 (12.0, 13.8)</td>
<td>13.6 (12.6, 14.6)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Transfusion</td>
<td>14 (6.3)</td>
<td>1 (1.3)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or median (interquartile range).

*Mild, does not require transfusion or result in hemodynamic compromise; moderate, requires transfusion; *Severe, intracranial bleed or hemodynamic compromise requiring treatment.
tomos due to use of contralateral femoral artery access to avoid the 9F sheath required for the Tracker-38 infusion catheter. The rates of access site-related complications and bleeding were reduced to control levels with the introduction of the lower profile Mi-Cath infusion catheter, which facilitated use of a single smaller sheath, thus obviating contralateral femoral artery access. As major bleeding can increase mortality in STEMI, minimizing hemorrhagic complications is essential if the benefits of infarct size reduction with SSO₂ are to be realized.

A novel aspect of this investigation was specification of the primary end point based on Bayesian hierarchical analysis, allowing partial pooling of data from 2 consecutive randomized trials. Such methodology is well established,42–44 increasingly used for randomized trials,45,46 and described by the Food and Drug Administration as an underutilized approach to reduce sample size, allowing pivotal trials to be completed more rapidly and efficiently.22 This study was planned in concert with the Food and Drug Administration as the US approval trial for SSO₂ in patients with anterior STEMI undergoing PCI within 6 hours of symptom onset, including selection of the primary efficacy and safety end points. Bayesian hierarchical modeling allow data to be borrowed from prior studies, with the extent of borrowing depending on how closely the results from the new study reflect the previous experience. Thus, if the results of AMIHOT II varied greatly from AMIHOT I, little evidence would be borrowed from the prior experience and the AMIHOT-II results would be minimally changed (or could even be adversely affected). The present Bayesian model avoids bias from knowledge of the prior subgroup by ensuring that type I conditional error is <5%, exactly the same type I error that a standalone frequentist trial would have. In this study, a reduction in infarct size was present in both trials in patients with anterior STEMI reperfused within 6 hours of symptom onset, allowing sufficient borrowing such that the pooled Bayesian posterior probability for superiority was 96.9%, signifying a significant reduction in infarct size with SSO₂ compared with control. Of note, the smoothed median differences in infarct size were similar in both AMIHOT I and AMIHOT II. Thus, the finding of efficacy in the AMIHOT II Bayesian model does not represent regression to the mean—had regression to the mean been present to a significant degree, the posterior probability would not have been >95%.

Similarly, the posterior probability of noninferiority for safety (30-day MACE) with SSO₂ compared with control was 99.5% and 99.9% in the intention-to-treat and per-protocol populations, respectively, both highly statistically significant. Use of Bayesian methodology in this investigation thus allowed statistically valid study conclusions to be reached with randomization of only 304 patients in AMIHOT II, whereas 458 patients would have been required for 80% power had traditional frequentist statistics been used. The Bayesian approach is thus consistent with the US statutory “least burdensome pathway” for clinical investigation and device approval.22

Several limitations of this investigation should be acknowledged. No significant differences in survival at 30 days between the control and treatment groups were present. However, although the 6.5% median (4.5% mean) reduction in infarct size with SSO₂ represents a greater improvement in myocardial recovery than with tPA compared with streptokinase,47 or with primary PCI compared with tPA,34 much larger studies than AMIHOT II would be required to detect an improvement in survival given the currently achieved low mortality rates with contemporary primary PCI. The current trial was also underpowered for a robust analysis of subgroups. The δ for noninferiority for the safety end point may also be considered broad, although such a safety margin is typical for regulatory device approval trials, and the Bayesian estimates for noninferiority between SSO₂ and control were highly significant by both intention-to-treat and per-protocol analyses. Serial echocardiographic measures of regional wall motion recovery, which correlate closely with tc-99m-sestamibi infarct size and which improved in AMIHOT I with SSO₂, were not measured in AMIHOT II as they are more load dependent and technique sensitive than infarct size, requiring a larger sample size. Finally, the safety and efficacy results demonstrated for SSO₂ in the present study apply only to those patients enrolled in AMIHOT II, and should not be extrapolated to other patient cohorts, such as those with nonanterior STEMI, patients reperfused beyond 6 hours after symptom onset and those in cardiogenic shock.

In summary, in patients with anterior STEMI undergoing PCI within 6 hours of symptom onset, a post-PCI infusion of SSO₂ for 90 minutes safely reduces infarct size, an effect which is most pronounced in patients with the greatest amount of myocardium at risk, with noninferior rates of MACE at 30 days.

Appendix

For AMIHOT-I trial organization and list of participating investigators, see reference 17.

AMIHOT-II Trial Organization and List of Participating Investigators

Principal Investigator: G.W. Stone, Columbia University Medical Center, New York Presbyterian Hospital and the Cardiovascular Research Foundation, New York City, NY.

Co-Principal Investigator: J.L. Martin, Sharpe-Strumia Research Foundation of the Bryn Mawr Hospital, Main Line Health, Bryn Mawr, Pa.

Bayesian Statistician: W.J. Boscardin, University of California, San Francisco, San Francisco, Calif.

Study Sponsor: TherOx, Inc, Irvine, Calif; B.S. Lindsay (Vice President, Clinical Programs).

Site and Data Monitoring: TherOx, Inc, Irvine, Calif.


Clinical Events Adjudication Committee: B.W. Weiner (Chair), M.J. Schweiger, and S. Waxman.

Data and Safety Monitoring Board: D.W. Holmes (Chair), E. Bates, J. Ferguson, W. Gaasch, and K. Freeman.

Nuclear Core Laboratory: The Mayo Clinic Nuclear Cardiology Laboratory, Rochester, Minn; R.J. Gibbons (Co-Director), T. Miller, P. Chareonthaitawee, and A. Lapeyre.

Angiographic Core Laboratory: The Cardiovascular Research Foundation, New York, NY: A.J. Lansky (Director) and E. Cristea.

EFG and Holter Core Laboratory: Duke Clinical Research Institute, Durham, NC; M.W. Krucoff (Director) and C. Green.

Study Sites, Principal Investigators, and Primary Study Coordinators: Saint Paul Hospital, Vancouver, BC; J.G. Webb, E. Grieve; Mercy Heart Institute, Sacramento, Calif; M. Chang, W. Marquardt.
Sources of Funding

The study was sponsored and funded by TherOx, Inc. The sponsor was involved in study design and in data collection, analysis, and interpretation, along with the principal investigators. The corresponding author had full access to all the data in the study. The manuscript was prepared by the corresponding author and revised by all coauthors. The authors controlled the decision to submit the manuscript for publication. The sponsor was provided the opportunity for a nonbinding review of the manuscript before its submission.

Disclosures

Dr Stone reports having received research support from TherOx, Abbott Vascular, Boston Scientific, and The Medicines Company. Dr Martin reports having equity interests and serving as a consultant to TherOx. Dr Blankenhship reports serving on a speaker’s bureau for Sanofi-Aventis. Dr Gibbons reports having received research support from TherOx. Ms Lindsay is a full-time employee of and owns equity in TherOx. Dr Weiner reports serving as a consultant to TherOx and having received research support from Medtronic, Boston Scientific, and Abbott Vascular. Dr Krucoff reports having served as a consultant to and received research grants and consultancy fees from TherOx. Dr Boscardin reports having served as a consultant to TherOx. Drs de Boer, Margheri, Bramucci, Metzger, and Longlade; William Beaumont Hospital; Royal Oak, Mich, S. Dixon, D. Richmond; Isala Klinieken Weeenelanden, Zwolle, Netherlands; M.J. De Boer, D. Beuving; Allegheny General Hospital, Pittsburgh, Pa; D. Lasorda, C. Harter; Geisinger Medical Center, Danville, Pa; J. Blankenhship, K. Skelding, D. Zimmerman; Sharpe-Strumia Research Foundation of the Bryn Mawr Hospital, Main Line Health, Bryn Mawr, Pa; J.L. Martin, A. Pratsos, C. Pensyl; Tri-State Medical Center, Beaver, Pa; J. Rich, M. Kilhof; Jackson-Madison County Medical Hospital, Jackson, Tenn: H.K. Lui, A. Hysmith; Wellmont Holston Valley Medical Center, Kingsport, Tenn; C. Metzger, A. Armstrong; Scott and white Hospital, Temple, Tex: S. Gantt, J. Asea; East Texas Medical Center, Tyler, Tex: S.M. Lieberman, J. Crump.

References


**CLINICAL PERSPECTIVE**

Primary percutaneous coronary intervention (PCI) in patients with acute ST-segment elevation myocardial infarction has become widely accepted as the preferred reperfusion modality because of its high success rate in restoring patency of the occluded infarct artery, with resultant low rates of death, reinfarction, recurrent ischemia, and stroke. Nonetheless, myocardial salvage is often suboptimal in many patients after primary PCI, in part because of late presentation and also because of microcirculatory dysfunction and reperfusion injury. The intracoronary delivery of supersaturated oxygen with a PaO₂ of 760 to 1000 mm Hg into the coronary artery supplying the myocardial infarct zone for 90 minutes after successful primary PCI has been shown in preclinical models to markedly enhance myocardial recovery. In the randomized AMIHOT-I and AMIHOT-II trials, this therapy was compared with primary PCI without intracoronary infusion in a total of 406 patients with anterior ST-segment elevation myocardial infarction reperfused by successful PCI within 6 hours of symptom onset. Compared with control, SSQ₂ resulted in a significantly smaller infarct size at 14 days as measured by tc-99m-sestamibi single-photon emission computed tomography imaging, with noninferior rates of major adverse cardiovascular events at 30 days. The benefit in terms of infarct size reduction was particularly profound in patients with the largest infarctions (baseline left ventricular ejection fraction <40%), in whom an incremental 10% salvage of the left ventricular myocardium was noted. As such, supersaturated oxygen represents the first adjunctive therapy demonstrated in a pivotal trial to reduce infarct size when used in concert with a mechanical reperfusion strategy in ST-segment elevation myocardial infarction.
Effect of Supersaturated Oxygen Delivery on Infarct Size After Percutaneous Coronary Intervention in Acute Myocardial Infarction
Gregg W. Stone, Jack L. Martin, Menko-Jan de Boer, Massimo Margheri, Ezio Bramucci, James C. Blankenship, D. Christopher Metzger, Raymond J. Gibbons, Barbara S. Lindsay, Bonnie H. Weiner, Alexandra J. Lansky, Mitchell W. Krucoff, Martin Fahy and W. John Boscardin
for the AMIHOT-II Trial Investigators

_Circ Cardiovasc Interv._ 2009;2:366-375; originally published online September 15, 2009;
doi: 10.1161/CIRCINTERVENTIONS.108.840066
_Circulation: Cardiovascular Interventions_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

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Primary Effectiveness Endpoint Analysis

The AMIHOT and AMIHOT-II effectiveness data were analyzed jointly in a hierarchical Bayesian model. Primary effectiveness analysis was performed on an intent-to-treat basis.

It was necessary to develop a transformation of the primary endpoint infarct size that would, to a degree, remove the skewness of the data (which includes a number of exactly zero values). Transformations of the form $Y = \log(X + c)$ were considered, where “log” denotes the natural logarithm. Consideration of a wide variety of choices for $c$ gave reasonable approximations of normality, and extremely similar statistical inference, and a value of $c=10$ was chosen based on the distribution of the AMIHOT-I data in designing the AMIHOT-II trial. Using this transformation in the subgroup of patients with anterior STEMI undergoing PCI in less than 6 hours (the anterior/LT6 subgroup), the mean (SD) for Control subjects was 3.30 (0.66), and for SSO2 subjects the mean (SD) was 3.06 (0.72). Thus, a difference of almost one quarter of a log in these groups was observed. The data distributions are not exactly normal after transformation, and the use of smearing could be used to describe the treatment versus control differences in medians on the original scale. More directly, the treatment effect has been reported using a pooled analysis for the subgroup of interest adjusted for the study-specific medians.

As noted, the current randomized trial was entirely based on anterior patients with times to reperfusion of less than or equal to 6 hours (LT6). Of the 269 patients randomized into the completed AMIHOT trial, 240 subjects had both infarct size data and time to reperfusion recorded. The anterior LT6 subgroup represented a total of 101 patients. Thus, the original study can be regarded as being composed of 4 mutually exclusive subgroups: anterior/LT6, anterior/greater than (GT)6, non-anterior/LT6, non-anterior/GT6. The Bayesian hierarchical model was used to analyze the AMIHOT data and the results from the current study. In this model, the posterior mean effect size in any particular subgroup is shrunk towards the overall mean. This procedure gives a formal methodology to account for the reduction of the target population. The model also includes random study effects. As a result, if the difference between the SSO2 Therapy and Control means for the proposed study was different from that seen in the AMIHOT trial, the analysis would not permit a high degree of borrowing. This allows the type I error to be kept to a reasonable level even though the prior information is centered over a favorable outcome. In particular, the following model was assumed. The log-transformed values (as discussed above) in each subgroup were assumed to be normally distributed with a mean and standard deviation specific to the subgroup-treatment (SSO2 Therapy versus Control) combination.

The mean values for study $i=1,2$ (1=AMIHOT, 2=proposed study) and subgroup $j$ ($j=1,2,3,4$ in study $i=1$ and $j=1$ only for study $i=2$) are parameterized as:

$$
\mu_C^{ij} = \text{Mean Control group} = \mu_0 + \omega_j + \gamma_i
$$

$$
\mu_T^{ij} = \text{Mean SSO2 Therapy group} = \mu_0 + \delta_0 + \omega_j + \gamma_i,
$$

where $\mu_0$ is the grand mean for the Control group, $\delta_0$ describes the overall SSO2 Therapy versus Control difference, $\omega_j$ represents the subgroup effect and $\gamma_i$ describes the study effect in the Control arm, and
\( \omega^T_j \) represents the subgroup effect and \( \gamma^T_i \) describes the study effect in the SSO2 Therapy minus Control differences.

The full model is written as

\[
\begin{align*}
 y_{ijk}^C &\sim N(\mu_{ij}^C, \sigma_C^2) \\
y_{ijk}^T &\sim N(\mu_{ij}^T, \sigma_T^2) \\
\mu_{ij}^C &\equiv \mu_0^C + \omega_j^C + \gamma_i^C \\
\mu_{ij}^T &\equiv \mu_0^T + \delta_0^T + \omega_j^T + \gamma_i^T \\
\omega_j^C &\sim N(0, \phi_\omega^2); \gamma_i^C \sim N(0, \phi_\gamma^2) \\
\omega_j^T &\sim N(0, \tau_\omega^2); \gamma_i^T \sim N(0, \tau_\gamma^2) \\
\phi_0^C &\sim U(0.01, 0.67); \phi_0^T \sim U(0.01, 0.10) \\
\tau_0^C &\sim U(0.01, 0.67); \tau_0^T \sim U(0.01, 0.10) \\
\sigma_0^C &\sim U(0.01, 2.0); \sigma_0^T \sim U(0.01, 2.0) \\
\mu_0^C &\sim N(3.2, 0.72^2); \delta_0^T \sim N(0, 0.72^2)
\end{align*}
\]

where \( y_{ijk}^C \) denotes the response of the \( k \)th Control subject in study \( i \) subgroup \( j \) (\( k \) runs from 1 to \( n^C_{ij} \)), and, similarly, \( y_{ijk}^T \) denotes the response of the \( k \)th SSO2 Therapy subject in study \( i \) subgroup \( j \) (\( k \) runs from 1 to \( n^T_{ij} \)). Specific choices of prior distributions were made to balance three goals: (i) be as non-informative as possible, (ii) capture first-order substantive considerations, and (iii) allow the model to have acceptable frequentist type I error in the case of no treatment effect. Some specific considerations were as follows:

(i) The transformed response, \( \log(y+10) \), is constrained to lie in the interval 2.3 to 4.7. Thus, standard deviations of 0.5 or 1.0 are quite large relative to this range, and a standard deviation of 2.0 is essentially non-informative.

(ii) The grand mean for Control infarct size (\( \mu_0^C \)) is centered around a prior mean that corresponds to 15 on the original scale. The standard deviation of 0.7 then gives a 99.7% prior probability that the grand mean can be between 0 and 100, a very broad range on the original scale.

(iii) The overall mean for the SSO2 Therapy minus Control difference (\( \delta_0^T \)) can be anywhere from 0 to 100 on the original scale.

(iv) \( \phi_0^C \sim U(0.01, 0.67); \phi_0^T \sim U(0.01, 0.10) \). This is an extremely vague prior for the subgroup effects in the Control group (which can easily span the full range of the data). Study random effects for the Control group have a standard deviation no larger than 0.10 on the log scale. This suggests that if the mean in a particular Control subgroup is 15 on the original scale, then study-specific means for that subgroup could possibly vary from 8 to 23. The stronger prior on study effects is used to combat the problem of having only two study effects for which we are attempting to estimate a variance component.

(v) \( \tau_0^C \sim U(0.01, 0.67); \tau_0^T \sim U(0.01, 0.10) \). The same comments noted above for the Control random effects standard deviations, except that in the treatment case, the parameters refer to differences between the SSO2 Therapy and Control means.

(vi) \( \sigma_0^C \sim U(0.01, 2.0); \sigma_0^T \sim U(0.01, 2.0) \). The Control and SSO2 Therapy group standard deviations for individual measurements should be very precisely determined by the data, and thus we specify only that these values are certain to be less than 2.0 on the logarithmic scale.

Inference is based on the posterior distribution of the SSO2 Therapy minus Control mean difference in study 2, subgroup 1, i.e. \( (\mu_{21}^T - \mu_{21}^C) = \delta_0^T + \omega_2^T + \gamma_{11}^T \), given the previous and current study data.
Consideration is given to the posterior probability that this combination of parameters is less than zero, indicating that the SSO$_2$ Therapy group tends to have lower infarct sizes. Should this posterior probability be 95% or higher, the effectiveness endpoint would have been fulfilled. That is, the effectiveness endpoint would be satisfied if $P(\mu^{T}_{21} - \mu^{C}_{21} < 0 \mid \text{data from all subgroups in both trials}) > 0.95$. Inference was conducted using Markov chain Monte Carlo using an R front end$^1$ to WinBUGS 1.4.1$^2$ (called R2WinBUGS$^3$). Sufficient run lengths were generated to ensure the accuracy of all decimals reported in the Bayesian model results tables (more detail is given later in this section).

**PRIMARY SAFETY ENDPOINT ANALYSIS**

A hierarchical Bayesian model was also be used to evaluate the major adverse cardiovascular events (MACE) rates in the two studies using the intention to treat population. The following set-up of the model is assumed (similar to Warn, Thompson, and Spiegelhalter, 2002$^5$). As above the study numbers are $i=1,2$ ($i=1$ is AMIHOT, $i=2$ is proposed incremental study), the subgroup numbers are $j=1,2,3,4$ ($j=1$ is anterior/LT6, $j=2$ is anterior/GT6, $j=3$ is non-anterior/LT6, $j=4$ is non-anterior/GT6). For study 2, $j=1$ only. Then we denote $r^{C}_{ij}/n^{C}_{ij}=#\text{of Control MACE events/}\#\text{of Control subjects in study }i,\text{ subgroup }j$, and $r^{T}_{ij}/n^{T}_{ij}=\#\text{of SSO}_2\text{ Therapy MACE events/}\#\text{of SSO}_2\text{ Therapy subjects in study }i,\text{ subgroup }j$. The full model is specified as follows:

$$r^{C}_{ij} \sim \text{Bin}\left(n^{C}_{ij}, \pi^{C}_{ij}\right)$$

$$r^{T}_{ij} \sim \text{Bin}\left(n^{T}_{ij}, \pi^{T}_{ij}\right)$$

$$\text{logit}(\pi^{C}_{ij}) = \lambda^{C}_{ij}$$

$$\lambda^{C}_{ij} = \mu_0 + \omega^{C}_{j} + \gamma^{C}_{i}$$

$$\pi^{T}_{ij} = \pi^{C}_{ij} + \delta_0 + \omega^{T}_{j} + \gamma^{T}_{i} \quad \text{ (truncated to } [0,1])$$

$$\omega^{C}_{j} \sim N(0, \phi^{C}_{\omega})$$

$$\gamma^{C}_{i} \sim N(0, \phi^{C}_{\gamma})$$

$$\omega^{T}_{j} \sim N(0, \phi^{T}_{\omega})$$

$$\gamma^{T}_{i} \sim N(0, \phi^{T}_{\gamma})$$

$$\phi^{C}_{\omega} \sim U(0.01, 0.30)$$

$$\phi^{T}_{\omega} \sim U(0.01, 0.30)$$

where $\mu_0$ is the grand mean of MACE rates in the Control group (on logit scale), $\delta_0$ is the overall SSO$_2$ Therapy versus Control difference in safety rates (i.e. on risk difference scale), $\omega^{C}_{j}$ represents the subgroup effect and $\gamma^{C}_{i}$ describes the study effect in the Control arm (these parameters are both on the logit scale), and $\omega^{T}_{j}$ represents the subgroup effect and $\gamma^{T}_{i}$ describes the study effect in the SSO$_2$ Therapy minus Control differences (these parameters are both on the risk difference scale). The basis for the Bayesian model of these various parameters is as follows:

Treatment rates are modeled as an additive deviation from the Control rate in order to maximize efficiency in testing risk differences.

(i) $\mu_0 \sim N(-2.6, 0.5^2)$. The grand mean of MACE rates in the Control group should be on the order of 7%; the logit of 0.07 is equal to -2.6. The choice of standard deviation gives a 99.7% prior probability that the average Control MACE rate is between 0% and 25%.

(ii) $\delta_0 \sim N(0, 0.2^2)$. The overall SSO$_2$ Therapy versus Control difference in safety rates is assumed to be normally distributed around zero with a standard deviation of 20 percentage points. This is an extremely vague prior.

(iii) $\phi^{C}_{\omega} \sim U(0.01, 0.30)$; $\phi^{T}_{\omega} \sim U(0.01, 0.30)$. The random effects standard deviations for the logit of Control rates between subgroups and between studies are assumed to be no larger than 0.30. If the mean rate is 7%, this translates into a 99.7% prior probability that subgroup or
of a trial.

(iv) \( \tau_0 \sim U(0.001, 0.10); \tau_y \sim U(0.001, 0.033) \). The random effects standard deviations in the differences between SSO\(_2\) Therapy and Control means among the subgroups and between studies are assumed to be no larger than 10 percentage points and 3.3 percentage points, respectively. This in turn suggests that these differences between subgroups could vary as much as 30 percentage points around the mean, and differences between the two studies could be as large as 10 percentage points.

A second analysis similar to that described above for the intention to treat analysis (ITT) was performed using the per protocol (PP) safety sample. Because it is unclear for a non-inferiority hypothesis whether the ITT or PP subset is more conservative, both were considered primary for the primary safety endpoint analysis. Again, the same Bayesian hierarchical model was employed with the original AMIHOT trial data limited to the PP patient sample using the same limiting criteria as was used for the AMIHOT-II PP patient sample.

**EFFECTIVENESS BASED SAMPLE SIZE CALCULATION**

The power of the current study with \( n_{T21} = 224 \) patients in the SSO\(_2\) Therapy arm and \( n_{C21} = 80 \) in the Control arm was calculated using the defined Bayesian hierarchical model. Computations were based on 2000 simulated data sets, with each data set analyzed by MCMC with 20,000 iterations.

**Table 1.** Power to reach the conclusion of effectiveness for various true SSO\(_2\) Therapy versus Control differences.

<table>
<thead>
<tr>
<th>( \Delta ) (Transformed Scale)</th>
<th>Original Scale</th>
<th>Posterior Power</th>
<th>Frequentist Power</th>
<th>Complete Pooling</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0.0%</td>
<td>5.0%</td>
<td>5%</td>
<td>17%</td>
</tr>
<tr>
<td>-0.20</td>
<td>-5.0%</td>
<td>85.4%</td>
<td>73%</td>
<td>93%</td>
</tr>
<tr>
<td>-0.25</td>
<td>-6.5%</td>
<td>96.0%</td>
<td>88%</td>
<td>97%</td>
</tr>
<tr>
<td>Prior Predictive</td>
<td></td>
<td>64.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The middle two lines in **Table 1** demonstrate that there is 85.4% power to detect an effect size of 5.0% infarct size reduction, and 96% power to detect a difference similar to that seen in the AMIHOT-I trial of 6.5%. In the other direction, as shown by the first line of the table, we found that the hierarchical model was able to achieve an appropriate type I error rate when, in fact, the SSO\(_2\) Therapy mean and the Control mean are both equal. Finally, the bottom line of the table gives the prior predictive power for the study as 64%.

**SAFETY BASED SAMPLE SIZE CALCULATION**

The power of the current study with \( n_{T21} = 224 \) patients in the treatment arm and \( n_{C21} = 80 \) in the Control arm was calculated using the defined Bayesian hierarchical model. Computations were performed using MCMC (with 15000 iterations) for the full grid of possible pairs of MACE counts in the two arms of the new trial.
In addition, for comparison, the frequentist power was calculated using the program PASS 2002 (Number Cruncher Statistical Systems, Kaysville, Utah, 2002) and assumed no use of the AMIHOT-I data.

Table 2. Power table and Type I error calculations for the MACE safety endpoint.

<table>
<thead>
<tr>
<th></th>
<th>Posterior Power</th>
<th>Frequentist Power</th>
<th>Complete Pooling</th>
</tr>
</thead>
<tbody>
<tr>
<td>n^C_{21} = 80, n^T_{21} = 224</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05</td>
<td>96.3%</td>
<td>75%</td>
<td>97%</td>
</tr>
<tr>
<td>0.06</td>
<td>89.8%</td>
<td>69%</td>
<td>92%</td>
</tr>
<tr>
<td>0.07</td>
<td>80.7%</td>
<td>64%</td>
<td>86%</td>
</tr>
<tr>
<td>0.08</td>
<td>70.5%</td>
<td>60%</td>
<td>79%</td>
</tr>
<tr>
<td>0.09</td>
<td>59.8%</td>
<td>56%</td>
<td>72%</td>
</tr>
<tr>
<td>0.10</td>
<td>4.7%</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>0.14</td>
<td>2.5%</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>0.15</td>
<td>2.0%</td>
<td>1.5%</td>
<td>2%</td>
</tr>
<tr>
<td>Prior Predictive</td>
<td>61.2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Type I error calculations are shown in italics for a true Control rate of 0.07 and true SSO2 Therapy rates that are bigger than this rate by d=0.06 or more.

At the expected MACE rate of 0.07, it is evident that the proposed sample size of 80 Control and 224 SSO2 Therapy patients would have achieved adequate power to conclude equivalence using the Bayesian hierarchical model.

RUN LENGTHS FOR MCMC ANALYSIS OF PRIMARY EFFICACY ENDPOINT

We generated enough posterior simulations using the MCMC technique discussed above to ensure that the first decimal point in the posterior probability of satisfying the efficacy or safety endpoints is correct. We generated three chains, each with 2,000,000 iterations. The first 400,000 simulations were regarded as burn-in and the resulting 1,600,000 simulations for each of the three chains were thinned, saving only every 5th iteration. The resulting set of posterior simulations for analysis is thus of size 3 x 320,000=960,000. Convergence diagnostics indicated that the autocorrelation in this thinned set was extremely low, but we conservatively regard this as an effective sample size of Neff=480,000. The Monte Carlo standard error for estimating a probability of 95.0% is thus sqrt(0.950 * 0.005 / 480000)=0.0001, ensuring that the first decimal place is correct with almost 100% confidence.

BAYESIAN SENSITIVITY ANALYSES FOR PRIMARY EFFICACY ENDPOINT

A secondary analysis similar to that described above for the ITT analysis was performed for the PP analysis. The same Bayesian hierarchical model was employed with the original AMIHOT trial data limited to the PP patient sample using the same criteria used for the AMIHOT-II PP patient sample. Sensitivity analyses on the Bayesian primary effectiveness endpoint evaluation in both the ITT and PP analyses were conducted by varying two of the assumptions for prior distributions on the hyperparameters. The first model of these alternative models (M2) changes the prior distribution for the standard deviation of the study random effects in the Control group from \( \phi_r \sim U(0.01, 0.10) \) to \( \phi_r \sim U(0.01, 0.20) \). This change allows the average Control infarct size to be more variable between
AMIHOT-I and II. Because the AMIHOT-II trial featured larger infarct size results than the AMIHOT-I study, the M2 value for this parameter is more appropriate than the setting in the pre-specified M1 value. In particular, the prior distributions used in M1 put very little weight on the possibility of a Control group infarct size for AMIHOT-II of higher than 25, whereas the M2 model allows for this amount of variation in the two studies. The second of these alternative models (M3) makes a similar change to the prior distribution for the standard deviation of the study treatment effects from $\tau_{\gamma} \sim U(0.01, 0.10)$ to $\tau_{\gamma} \sim U(0.01, 0.20)$. This change allows the treatment effect to be more variable between AMIHOT-I and II.

In order to gauge the appropriateness of models M1, M2, and M3 for the ITT analyses, we calculated the Deviance Information Criterion. The Deviance Information Criterion (DIC) is a measure of model fit, with smaller values corresponding to better fit of the model to the data. Model M2 had the strongest support in the data (DIC = 974.8), followed by Model M1 (DIC = 975.1), and then Model M3 (DIC = 975.2). Thus, the model fit is slightly preferable in M2, and this is also the model that gives reasonable a priori possibility for the Control group infarct size to be above 25 in AMIHOT-II. All three models gave very similar results with respect to the posterior probability of effectiveness.

References


