

*SuperSaturated Oxygen (SSO₂) Therapy:
A Data Compendium*

Summary

SSO₂ Therapy (TherOx, Inc), the latest FDA-approved treatment for the management of ST-segment elevation myocardial infarction (STEMI), delivers an infusion of the patient's superoxygenated blood to the left main coronary artery (LMCA) following successful percutaneous coronary intervention (PCI) within 6 hours of symptom onset. Pre-clinical studies show that SSO₂ Therapy works by improving impaired blood flow in the capillary beds and at-risk myocardium with no toxicity to the coronaries, myocardium, or end organs. SSO₂ Therapy has been clinically evaluated in a series of FDA-sanctioned IDE clinical trials demonstrating safety and effectiveness. Collective data have demonstrated significant reductions in infarct size and preservation of left ventricular (LV) function.

Key Takeaways

1. Even with prompt restoration of blood flow via PCI, many patients still suffer poor outcomes such as heart failure, resulting in reduced life expectancy and high healthcare costs.^{1, 2, 3} Up to 30% of MI patients develop heart failure² and of those, 50% will die within 5 years.³
2. SSO₂ Therapy is a one-time, 60-minute infusion of autologous superoxygenated (hyperbaric) blood to the left main coronary artery immediately post-PCI for qualifying anterior wall LAD STEMI patients. SSO₂ Therapy has demonstrated a relative median infarct size reduction of 26% compared to PCI alone.⁴ Infarct size has been associated with heart failure and mortality.⁵
3. A series of FDA-sanctioned IDE clinical trials (AMIHOT I, AMIHOT II, IC-HOT) demonstrated repeated safety and effectiveness with significant reduction in infarct size and improvements in left ventricular (LV) function.^{4, 6, 7, 8} AMIHOT II (n=301) shows significance with a 6.5% absolute and 26% relative reduction in infarct size.⁴ Other summarized analyses further support conclusions towards safety and effectiveness.

Background

Acute Myocardial Infarction (AMI) is a leading cause of death in the United States, affecting roughly 790,000 patients each year.⁹ Even with timely recognition and prompt restoration of coronary blood flow using PCI or pharmacological treatments, microvascular damage and tissue necrosis still persist and may lead to heart failure, reinfarction, and death. Up to 30% of MI patients develop heart failure² and of those, 50% will die within 5 years.³ Heart failure dramatically impacts patient quality of life¹⁰ and carries high healthcare costs.

SSO₂ Therapy: How it Works

Indicated for qualifying anterior LAD STEMI patients who receive successful PCI and stenting within 6 hours of symptom onset, SSO₂ Therapy is a one-time, 60-minute infusion performed in the cardiac catheterization laboratory immediately following successful PCI. Autologous arterial blood is mixed with oxygen-rich saline in a low-priming volume (50 ml) blood loop to achieve hyperbaric levels of oxygen ($pO_2=1000\text{mmHg}$). The superoxygenated infusate is returned to the patient via a 5F angiographic-style delivery catheter placed in the ostium of the LMCA (Figure 1). The hyperbaric level of dissolved oxygen (7-10x normal) creates a large concentration gradient for oxygen to diffuse into ischemic tissue even when blood flow is compromised. Pre-clinical studies have demonstrated that the effect of this high level of oxygen transfer to the ischemic myocardium is to resolve endothelial cell edema and restore capillary patency, improving microcirculatory flow and tissue level perfusion (Figure 2).^{11,12} Ultimately, this improvement leads to significant reductions in infarct size. Since SSO₂ Therapy is an adjunctive treatment performed after successful PCI, it complements the current standard of care, without delays in treatment or door-to-balloon time.

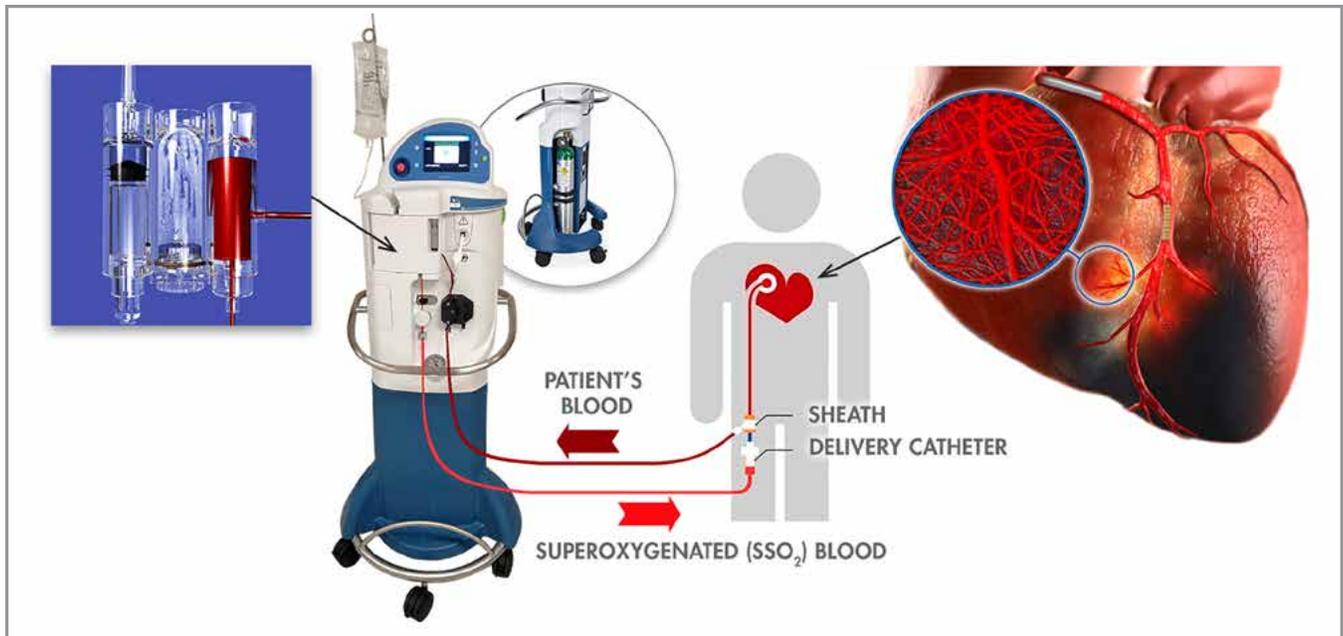


Figure 1. SSO₂ Therapy patient connections and delivery

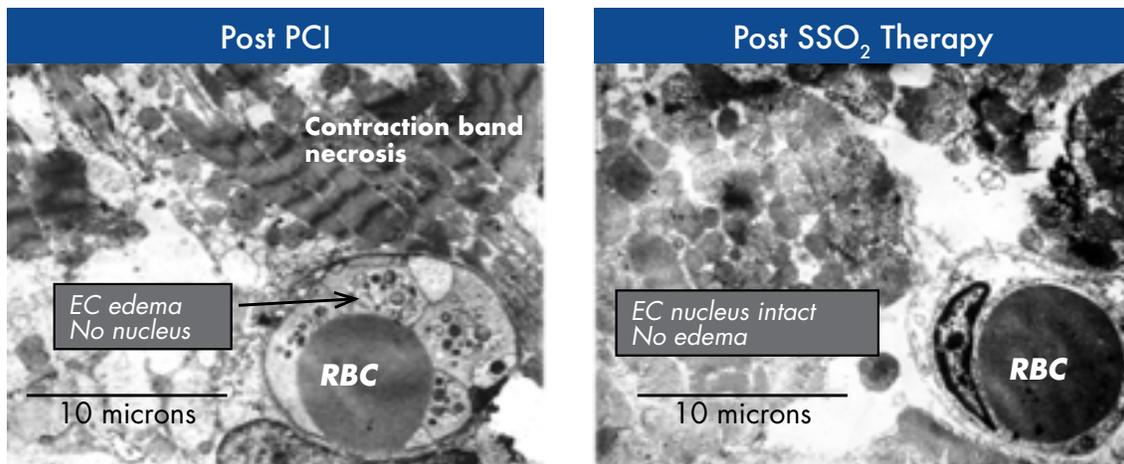


Figure 2. Endothelial edema restoration post SSO₂ Therapy

SSO₂ Therapy: AMIHOT I Trial⁶

AMIHOT I was a prospective, randomized, multicenter IDE trial involving 269 anterior and inferior STEMI patients who received successful PCI with stenting within 24 hours of symptom onset. Patients were randomly selected to receive either normoxemic blood (control group) or hyperoxemic blood (treatment group). The results showed no Major Adverse Cardiac Events (MACE) between the control and SSO₂ group (5.2% vs. 6.7%, p=0.62), demonstrating that SSO₂ Therapy is safe and well-tolerated after PCI. AMIHOT I data (Figure 3) also showed that while the primary end points including infarct size was not significantly different between the study groups for the entire population, a sub-population of anterior AMI patients who were treated within 6 hours of symptom onset (n=105) had a clinically significant relative median infarct size reduction of 61% (23% in controls vs. 9% in SSO₂ patients).

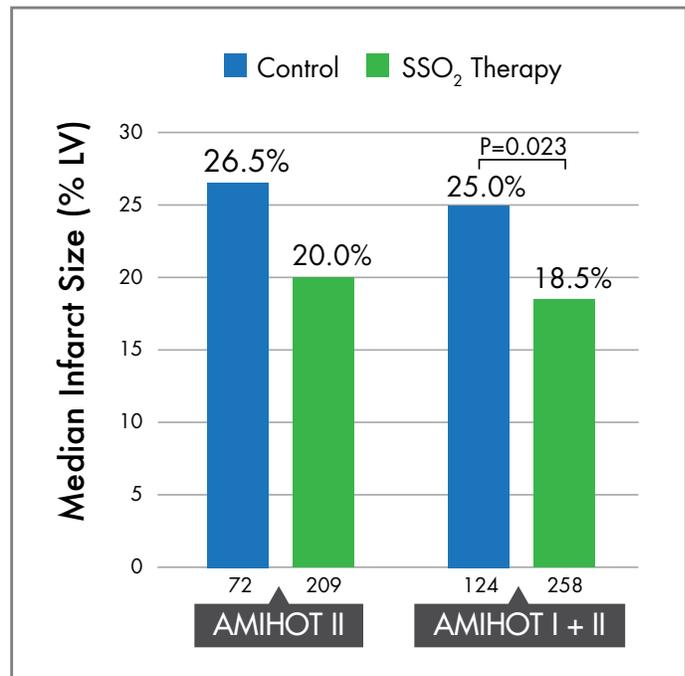


Figure 3. Relative median infarct size reduction with SSO₂ Therapy

SSO₂ Therapy: AMIHOT II Trial⁴

AMIHOT II was a prospective, randomized, multicenter IDE trial (n=301) in patients with anterior STEMI who received successful PCI within 6 hours of symptom onset. Results showed a median LV infarct size of 26.5% in the control group and 20.0% in the treatment group for a median absolute infarct size reduction of 6.5%. The AMIHOT II trial was successful with a 96.9% probability of superiority for infarct size reduction.

Figure 4 illustrates results from a pre-specified pooled analysis of AMIHOT I and II for anterior STEMI patients treated <6 hours was consistent and showed a 6.5% absolute reduction in infarct size from 25.0% to 18.5% for a relative reduction of 26% (p=0.023).

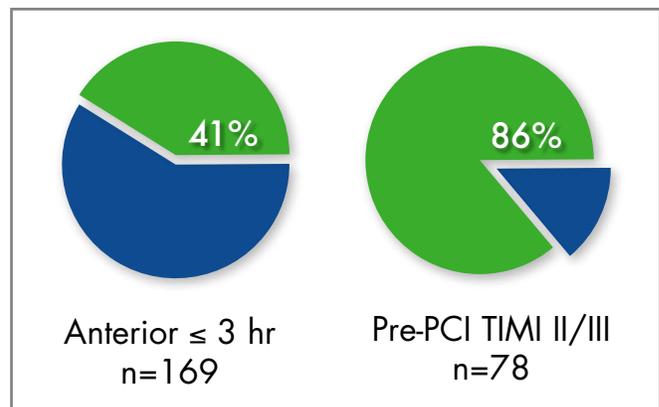


Figure 4. Subgroup analyses demonstrating further infarct size reduction

This magnitude of infarct size reduction is highly correlated with mortality reduction (p=0.002) and heart failure reduction (p<0.0001) at one year in a landmark meta-analysis of over 2600 patients enrolled in ten PCI-era STEMI trials.⁵ For context, PCI was established as the standard of care following demonstration of a more modest absolute infarct size reduction of 5% as compared to administration of thrombolytic therapy.¹³ AMIHOT II further demonstrated safety as SSO₂ Therapy was statistically non-inferior (equivalent) to PCI alone for 30-day MACE¹⁴ with SSO₂ Therapy and Control group observed rates of 5.4% and 3.8%, respectively. The posterior probability of non-inferiority (within the 6% margin) was 99.5%, achieving the study endpoint and further supporting the safety of SSO₂ Therapy.

Two key subgroup analyses were performed (Figure 4). For patients with less than three hours from symptom onset to PCI (n=169), a relative reduction in median infarct size of 41% was observed (p=0.055). For patients with a pre-PCI TIMI flow grade of II or III (n=78) the relative reduction in median infarct size was 86% (P=0.001). These results correlate with the mechanism of action of SSO₂ Therapy whereby patients with less compromised flow experience a more complete reversal of ischemia-induced flow dysfunction and have a smaller resultant infarct.

Confirmatory Study: IC-HOT and One-Year Comparative Study⁷

IC-HOT was a single-arm trial evaluating 100 SSO₂-treated patients with an endpoint of achieving a 30-day Net Adverse Clinical Events (NACE¹⁵) of less than 10.7% (this threshold was established based on the INFUSE-AMI trial¹⁶). IC-HOT demonstrated 0.0% 30-day mortality, similar or lower rates of adverse events than other anterior STEMI studies with PCI, and an observed NACE rate of 7.1%. This met the trial endpoint confirming safety. Furthermore, IC-HOT supported the effectiveness established in AMIHOT II with a 30-day median infarct size of 19.4% (as compared to the AMIHOT II SSO₂ group infarct size of 20.0%).

Additionally, cardiac MRI results for IC-HOT subjects demonstrated a reduction in median end left ventricular systolic and diastolic volumes (ESV and EDV) over 30 days, a significant finding that correlates with earlier data obtained via ECHO measurements in the AMIHOT I study. A single-center AMIHOT I sub-study,¹⁷ the Leiden study, examined 42 anterior STEMI patients treated with PCI within six hours. This study observed 30-day mean EDV and ESV changes of -3.0% and -11.0% in SSO₂ Therapy subjects and +14% and +18% in Control subjects. IC-HOT results demonstrating left ventricular stability over 30 days are consistent with these earlier findings and suggest another mechanism of SSO₂ Therapy benefit beyond infarct size reduction. Figure 5 shows these results graphically for ESV changes over 30 days in the Leiden study, as compared to the IC-HOT study. Because the baseline scans for these patients were obtained in the post-treatment recovery period prior to discharge, a reduction in LV volume represents recovery towards the true baseline (pre-STEMI) state, and 30-day LV dilatation for control patients may be underestimated.

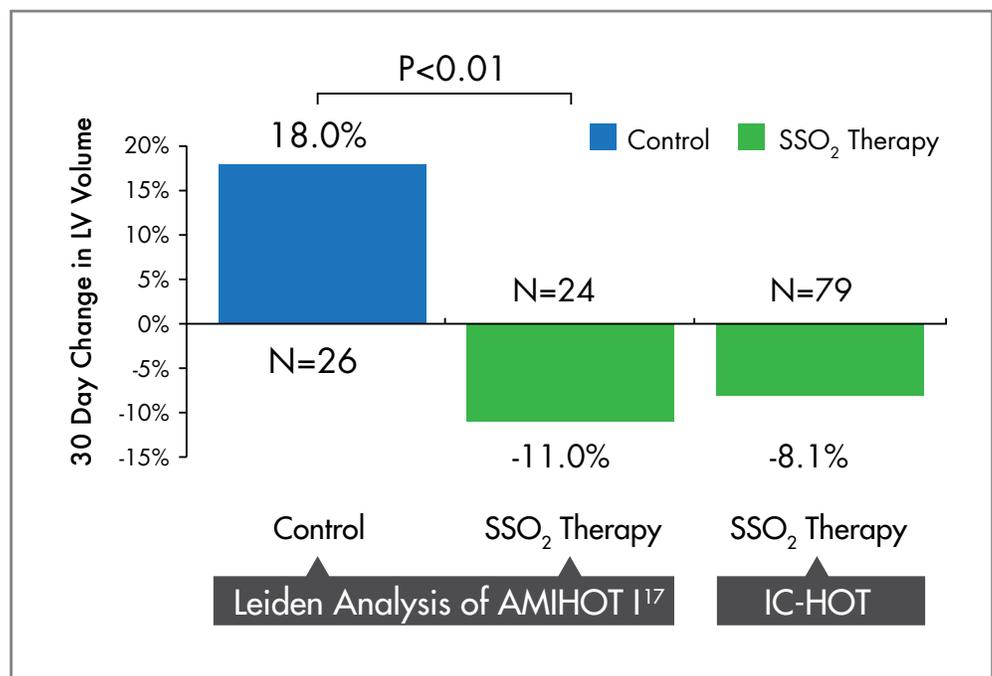


Figure 5. Left Ventricular ESV Recovery in SSO₂ Patients at 30 Days

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Adverse event data was collected through one year after the IC-HOT study and adjudicated by an independent Clinical Events Committee (CEC) with oversight by an independent Data and Safety Monitoring Board (DSMB). Event definitions for the trial were aligned prospectively with those used in the INFUSE-AMI study,¹⁶ which had a very similar patient population. A propensity-score matched analysis comparing similar patients from INFUSE-AMI and IC-HOT was performed to evaluate 1-yr clinical outcomes.¹⁸ Results indicate that adverse events occurred at much lower rates in the IC-HOT study as compared to the similar INFUSE-AMI study. This further confirms safety for SSO₂ Therapy. Table 1 presents one year comparative outcome data.

Event	Statistic	IC-HOT (n=83)	INFUSE-AMI (n=83)	Hazard Ratio (95% CI)	P-value
Death	KM (%)	0.0%	7.6%	NA	0.012
Heart Failure (HF)	KM (%)	0.0%	7.4%	NA	0.012
Death + HF	KM (%)	0.0%	12.3%	NA	0.001
Reinfarction	KM (%)	0.0%	2.4%	0.97 [0.14, 6.88]	0.97
Target Vessel Revascularization (TVR)	KM (%)	2.4%	5.1%	0.97 [0.14, 2.69]	0.4
Death + HF + Reinfarction + TVR	KM (%)	3.1%	14.8%	0.16 [0.04, 0.7]	0.005

Table 1. Reduced mortality and heart failure at one year in SSO₂ Therapy treated patients compared to propensity score-matched controls

Pooled Analysis¹⁹

A pooled analysis of Hanson, Stone, and Khan includes SSO₂ Therapy treated patients (n=526) presenting with anterior STEMI within 6 hours of symptom onset. Control patients (n=132) from Stone et al. were used for comparison. The analysis shows consistent outcomes demonstrated across multiple studies with a slight improvement from a 6.5% absolute decrease in infarct size to 6.6% (p=0.019 for the pooled comparison).

Conclusion

Patients who have acute myocardial infarction (AMI) and receive successful PCI with stenting are still at risk for reinfarction, heart failure, and death. SSO₂ Therapy has been proven through a series of FDA-sanctioned, IDE trials – AMIHOT I, AMIHOT II, and IC-HOT – as safe and effective in significantly reducing infarct size for patients with anterior LAD STEMI presenting within 6 hours of symptoms. Infarct size reduction is associated with long-term reductions in mortality and heart failure. In addition, SSO₂ Therapy is adjunctively administered following PCI with stenting and fits into the cardiac catheterization lab treatment for STEMI patients without impacting rapid primary PCI treatment. For qualifying anterior LAD STEMI patients, SSO₂ Therapy should be considered as part of STEMI treatment protocol in optimizing infarct size reduction, improving microvascular flow and preserving LV function.

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19. Data compiled by TTI Health Research and Economics for TherOx, Inc. Data on File at TherOx, Inc.

Indications For Use:

The TherOx DownStream System is indicated for the preparation and delivery of SuperSaturated Oxygen Therapy (SSO₂ Therapy) to targeted ischemic regions perfused by the patient's left anterior descending coronary artery immediately following revascularization by means of percutaneous coronary intervention (PCI) with stenting that has been completed within 6 hours after the onset of anterior acute myocardial infarction (AMI) symptoms caused by a left anterior descending artery infarct lesion.

Caution: Federal (USA) Law restricts this device to the sale by or on the order of a physician.

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