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[Supersaturated oxygen therapy in acute anterior myocardial infarction: Going small is the next big thing](#)

One-year outcomes of supersaturated oxygen therapy in acute anterior myocardial infarction: The IC-HOT study

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Abstract

Background: Supersaturated oxygen (SSO₂) has recently been approved by the U.S. Food and Drug Administration for administration after primary percutaneous coronary intervention (pPCI) in patients with anterior ST-segment elevation myocardial infarction (STEMI) based on its demonstration of infarct size reduction in the IC-HOT study.

Objectives: To describe the 1-year clinical outcomes of intracoronary SSO₂ treatment after pPCI in patients with anterior STEMI.

Methods: IC-HOT was a prospective, open-label, single-arm study in which 100 patients without cardiogenic shock undergoing successful pPCI of an occluded left anterior descending coronary artery were treated with a 60-min SSO₂ infusion. One-year clinical outcomes were compared with a propensity-matched control group of similar patients with anterior STEMI enrolled in the INFUSE-AMI trial.

Results: Baseline and postprocedural characteristics were similar in the two groups except for pre-PCI thrombolysis in myocardial infarction 3 flow, which was less prevalent in patients treated with SSO₂ (9.6% vs. 22.9%, $p = .02$). Treatment with SSO₂ was associated with a lower 1-year rate of the composite endpoint of all-cause death or new-onset heart failure (HF) or hospitalization for HF (0.0% vs. 12.3%, $p = .001$). All-cause mortality, driven by cardiovascular mortality, and new-onset HF or HF hospitalization were each individually lower in SSO₂-treated patients. There were no significant differences between groups in the 1-year rates of reinfarction or clinically driven target vessel revascularization.

Conclusions: Infusion of SSO₂ following pPCI in patients with anterior STEMI was associated with improved 1-year clinical outcomes including lower rates of death and new-onset HF or HF hospitalizations.

KEYWORDS

acute myocardial infarction, infarct size, primary percutaneous coronary intervention, supersaturated oxygen

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1 | INTRODUCTION

Infarct size (IS) measured 1 month after primary percutaneous coronary intervention (pPCI) for ST-segment elevation myocardial infarction (STEMI) by cardiac magnetic resonance imaging or technetium-99 m sestamibi single-photon emission computed tomography has been strongly associated with 1-year clinical outcomes including all-cause mortality and hospitalization for heart failure (HF).¹ Although early reperfusion therapy in STEMI has led to a decline in mortality over the past several decades,² myocardial salvage is often suboptimal despite high rates of restoration of epicardial coronary flow by pPCI and sustained patency of the infarct-related artery.^{3,4} This has been attributed to late reperfusion, microcirculatory dysfunction or no reflow, reperfusion injury, and other mechanisms.

Intracoronary infusion of hyperoxemic blood (supersaturated oxygen [SSO₂] therapy) into the myocardial infarct zone after reperfusion has been shown to reduce endothelial cell edema, induce capillary vasodilatation, and limit IS in experimental animal models.⁵⁻⁷ In the pivotal AMIHOT II trial, treatment of patients with anterior STEMI with SSO₂ infused into the left anterior descending coronary artery (LAD) resulted in a significant reduction in IS measured at 14 days compared with control.⁸ However, hemorrhagic complications were more frequent in the SSO₂ group due to the need for larger or multiple femoral arterial sheaths, and nonsignificant trends were present for increased stent thrombosis and death at 30 days, possibly related to the delivery of the SSO₂ through an indwelling catheter in the stented region of the LAD. As a result, the method of intracoronary SSO₂ delivery was modified so that following pPCI hyperoxemic blood was infused through a diagnostic catheter to the ostium of the left main coronary artery (LMCA), so called "optimized" SSO₂ delivery. The IC-HOT study was a prospective, open-label, single-arm study of 100 patients undergoing successful pPCI of an occluded LAD that found that optimized SSO₂ infusion via the LMCA was feasible and was associated with a favorable 30-day safety profile, with IS at 30 days similar to that observed in the SSO₂ therapy group in the AMIHOT II trial.⁹ On the basis of this study, on April 2, 2019 the U.S. Food and Drug Administration (FDA) approved SSO₂ therapy for treatment of patients with anterior STEMI undergoing primary PCI within 6 hrs of symptom onset.¹⁰

Late clinical outcomes after optimized SSO₂ infusion in STEMI have not been reported. We thus sought to assess the 1-year clinical outcomes of patients with anterior STEMI treated with SSO₂ infused via the LMCA. To this end, we compared the 1-year outcomes of patients in the IC-HOT study with a propensity-matched control group of similar patients with anterior STEMI enrolled in the INFUSE-AMI (intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction [MI]) trial.¹¹

2 | METHODS

2.1 | Study design and population

The study design, protocol, and primary results of the IC-HOT study have been previously described in detail.⁹ The IC-HOT study was a

prospective, open-label, single-arm study designed with U.S. FDA guidance to assess the safety of an optimized SSO₂ infusion. A total of 100 patients with acute anterior STEMI undergoing pPCI were enrolled between February 2016 and May 2017. In brief, major inclusion criteria included presentation within 6 hrs of symptom onset with ≥ 1 mm ST-segment elevation in ≥ 2 contiguous leads in V1–V4 or new left bundle branch block. Successful PCI of a proximal or mid LAD lesion with commercially available coronary stents and achievement of thrombolysis in myocardial infarction (TIMI) grade 2 or 3 flow were required. Major exclusion criteria included prior coronary artery bypass grafting, prior MI, known prior left ventricular ejection fraction $< 40\%$, use of thrombolytic therapy, any prior LAD PCI, mechanical complications of the STEMI or cardiogenic shock, contraindications to cardiac magnetic resonance imaging, creatinine clearance < 30 ml/min/1.73 m², and postindex PCI planned within 30 days. The local institutional review board at each center approved the study, and informed written consent was obtained from each patient before enrollment.

All patients received 324 mg aspirin and a loading dose of clopidogrel, prasugrel, or ticagrelor prior to angiography. PCI was performed using standard techniques with commercially available bare metal or drug-eluting stents.

2.2 | SSO₂ therapy

SSO₂ therapy was initiated immediately following successful pPCI. Blood was withdrawn from the femoral sheath and circulated via a roller pump through an extracorporeal oxygenator in a polycarbonate chamber (TherOx, Irvine, CA) to achieve a PaO₂ of 760–1,000 mmHg as previously described.⁸ The origin of the LMCA was engaged with a 5-Fr soft-tip JL diagnostic catheter (IMPULSE, Boston Scientific, Marlborough, MA) for the delivery of hyperoxemic blood. The SSO₂ solution of hyperoxemic blood was then delivered at a flow rate of 100 ml/min for 60 min in the cardiac catheterization laboratory. Systemic arterial PaO₂ was measured prior to the SSO₂ infusion, with nasal oxygen adjusted to maintain PaO₂ ≥ 80 mmHg.

2.3 | Definitions and endpoints

The definitions of all endpoints are provided in the original publication.⁹ The primary endpoint of the current study was the composite of all-cause death or new-onset HF or HF hospitalization at 1 year. The definition of HF required 100% oxygen by face mask, documented PaO₂ < 60 mmHg or radiographic evidence of pulmonary edema, intubation, intra-aortic balloon counterpulsation or other mechanical circulatory device support, or HF necessitating rehospitalization. Secondary endpoints included the individual components of the primary endpoint, recurrent MI, clinically driven revascularization, and stent thrombosis. An independent central events committee reviewed and adjudicated all safety and effectiveness endpoints.

TABLE 1 Baseline and angiographic characteristics in the propensity-matched cohorts according to treatment with SSO₂

Characteristic	SSO ₂ therapy (IC-HOT) (n = 83)	No SSO ₂ therapy (INFUSE-AMI) (n = 83)	Standardized difference	p value
Age, years	60.0 ± 10.1	60.4 ± 13.2	-0.04	.79
Male	80.7 (67/83)	81.9 (68/83)	-0.03	.13
Body mass index (kg/m ²)	28.9 ± 5.0	27.6 ± 4.2	0.27	.09
Diabetes mellitus	19.3 (16/83)	19.3 (16/83)	0.00	1.00
Insulin-treated	7.2 (6/83)	8.5 (7/83)	-0.05	.76
History of smoking	62.7 (52/83)	59.8 (49/82)	0.06	.70
Current smoker	42.2 (35/83)	47.6 (39/82)	-0.11	.49
Hyperlipidemia	48.2 (40/83)	15.7 (13/83)	0.74	<.0001
Hypertension	50.6 (42/83)	26.5 (22/83)	0.51	.001
Family history of premature coronary artery disease	42.2 (35/83)	21.1 (16/76)	0.47	.004
Congestive heart failure	0.0 (0/83)	1.2 (1/83)	-0.16	.32
Killip class			0.33	.09
I	95.2 (79/83)	85.5 (65/76)	0.33	.04
II	3.6 (3/83)	13.2 (10/76)	-0.35	.03
III	1.2 (1/83)	1.3 (1/76)	-0.01	.95
Time from symptom onset to first device (min)	159.4 ± 70.3	157.7 ± 54.8	0.03	.57
Baseline TIMI flow grade			0.51	.02
0	59.0 (49/83)	54.2 (45/83)	0.10	.53
1	0.0 (0/83)	3.6 (3/83)	-0.27	.25
2	31.2 (26/83)	19.3 (16/83)	0.28	.07
3	9.6 (8/83)	22.9 (19/83)	-0.36	.02
Baseline TIMI flow grade (categorized)			-0.02	.87
0/1	59.0 (49/83)	57.8 (48/83)		
2/3	41.0 (34/83)	42.2 (35/83)		
Post-PCI TIMI flow grade			0.14	.59
0	0.0 (0/83)	0.0 (0/83)	—	—
1	0.0 (0/83)	1.2 (1/83)	-0.16	1.00
2	13.3 (11/83)	12.0 (10/83)	0.04	.82
3	86.7 (72/83)	86.7 (72/83)	0.00	1.00
Location of anterior infarct target lesion			0.05	.75
Proximal LAD	42.2 (35/83)	39.8 (33/83)		
Mid LAD	57.8 (48/83)	60.2 (50/83)		
Propensity score	0.35 ± 0.15	0.35 ± 0.15	0.01	.97

Note: Values are % (n/N) or mean ± SD.

Abbreviations: LAD, left anterior descending coronary artery; PCI, percutaneous coronary intervention; SSO₂, supersaturated oxygen; TIMI, thrombolysis in myocardial infarction.

2.4 | Statistical analysis

Clinical outcomes were compared with a matched set of control arm patients from the randomized INFUSE-AMI trial, a study of very similar entry criteria (STEMI with proximal or mid-LAD occlusion), which enrolled patients between November 2009 and December 2011. Patients from INFUSE-AMI treated with an intralesional infusion of

abciximab, the experimental therapy, were excluded from the propensity score analysis as this therapy was associated with IS reduction. A propensity score model was developed to control for selection bias in the comparison of 1-year clinical outcomes between IC-HOT and INFUSE-AMI patients. The propensity score for an individual is defined as the probability of being included in the IC-HOT (vs. INFUSE-AMI) study conditional on the individual's baseline

TABLE 2 Concomitant medications at baseline and at discharge in the propensity-matched cohorts according to treatment with SSO₂

Characteristic	SSO ₂ therapy (IC-HOT) (n = 83)	No SSO ₂ therapy (INFUSE-AMI) (n = 83)	Standardized difference	p value
Baseline				
Aspirin	38.6 (32/83)	10.8 (9/83)	0.67	<.0001
P ₂ Y ₁₂ inhibitor	9.6 (8/83)	0.0 (0/83)	0.46	.007
Clopidogrel	2.4 (2/83)	0.0 (0/83)	0.22	.49
Prasugrel	0.0 (0/83)	0.0 (0/83)	—	—
Ticagrelor	7.2 (6/83)	0.0 (0/83)	0.39	.03
DAPT	9.6 (8/83)	0.0 (0/0)	0.46	.007
Beta blockers	10.0 (8/83)	7.2 (6/83)	0.10	.53
ACEi or ARB	15.7 (13/13)	12.1 (10/83)	0.10	.50
ACEi	10.8 (9/83)	8.4 (7/83)	0.08	.60
ARB	4.8 (4/83)	3.6 (3/83)	0.06	.70
Statin	9.6 (8/83)	10.8 (9/83)	-0.04	.80
Discharge				
Aspirin	96.3 (78/81)	98.8 (82/83)	-0.16	.36
P ₂ Y ₁₂ inhibitor	96.3 (78/81)	98.8 (81/82)	-0.16	.37
Clopidogrel	44.4 (36/81)	67.1 (55/82)	-0.47	.004
Prasugrel	13.6 (11/81)	31.7 (26/82)	-0.44	.006
Ticagrelor	38.3 (31/81)	0.0 (0/82)	1.11	<.0001
DAPT	92.6 (75/81)	97.6 (81/83)	-0.23	.14
Beta blockers	93.8 (75/80)	96.4 (80/83)	-0.12	.49
ACEi or ARB	75.9 (63/83)	94.0 (78/83)	-0.52	.001
ACEi	67.5 (56/83)	80.4 (75/83)	-0.58	.0003
ARB	8.43 (7/83)	6.0 (5/83)	0.09	.55
Statin	60.2 (50/83)	97.6 (81/83)	-1.02	<.0001

Note: Values are % (n/N).

Abbreviations: DAPT, dual antiplatelet therapy; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blockers; SSO₂, supersaturated oxygen.

characteristics. The propensity score was estimated using a logistic regression model in which the study variable (IC-HOT vs. INFUSE-AMI) is the outcome and the baseline characteristics are the covariates. The following covariates were included in the propensity score model: Age, sex, diabetes mellitus, time from symptom onset to first device, baseline (0/1 vs. 2/3) and post-PCI (0/1/2 vs. 3) TIMI flow assessed by the angiographic core laboratory, and target lesion location (proximal- vs. mid-LAD). A greedy nearest neighbor algorithm was used to match (1:1) IC-HOT patients with available control patients from INFUSE-AMI. A caliper of 0.2 times the standard deviation of the propensity score was enforced.

Comparison of baseline and procedural characteristics, medical history, and clinical events were conducted by χ^2 test or Fisher exact test for binary variables, *t* test or Wilcoxon rank sum test for continuous variables, and log-rank test for time-to-event variables. Adjusted comparisons of IS were conducted using linear regression. All *p* values are 2-tailed, and *p* < .05 was deemed statistically significant for all analyses. Statistical analyses were performed using the SAS version 9.4 (SAS Institute Inc., Cary, NC).

3 | RESULTS

The propensity score-matched cohort included 166 patients (83 patients treated with intracoronary SSO₂ from IC-HOT and 83 control patients from INFUSE-AMI). Patients treated with SSO₂ had a higher prevalence of hypertension (50.6 vs. 26.5%, *p* = .001), hyperlipidemia (48.2 vs. 15.7%, *p* < .0001), and family history of premature coronary disease (42.2 vs. 21.1%, *p* = .004) at baseline, while pre-PCI TIMI 3 flow was less common in these patients (9.6 vs. 22.9%, *p* = .02). Otherwise, baseline characteristics, including the rate of TIMI 2 or 3 at baseline and postprocedural characteristics, were similar in the two groups (Table 1). Concomitant medications at baseline and at discharge are presented in Table 2. Treatment with aspirin, a P₂Y₁₂ inhibitor or both (dual antiplatelet therapy; DAPT) was more common among patients treated with SSO₂ at baseline; however, at discharge, rates of treatment with DAPT were similar between the two groups. Treatment with angiotensin converting enzyme inhibitors (ACEi) or with angiotensin-receptor blockers (ARB) at discharge was more common among patients who were not treated with SSO₂.

TABLE 3 One-year clinical outcomes according to treatment with SSO₂

	SSO ₂ therapy (IC-HOT) (n = 83)	No SSO ₂ therapy (INFUSE-AMI) (n = 83)	Hazard ratio (95% CI)	p value
All-cause death, new-onset HF, or HF hospitalization	0.0 (0)	12.3 (10)	–	.001
All-cause death	0.0 (0)	7.6 (6)	–	.01
Cardiovascular death	0.0 (0)	5.1 (4)	–	.04
Cardiac death	0.0 (0)	3.8 (3)	–	.08
Vascular death	0.0 (0)	1.3 (1)	–	.30
Noncardiovascular death	0.0 (0)	2.6 (2)	–	.14
New-onset HF or HF hospitalization	0.0 (0)	7.4 (6)	–	.01
MI	2.4 (2)	2.4 (2)	0.97 (0.14–6.88)	.97
Clinically-driven target vessel revascularization	3.1 (2)	5.1 (4)	0.49 (0.09–2.69)	.40
Composite of death, new-onset HF or readmission for HF, or clinically-driven target vessel revascularization	3.1 (2)	14.8 (12)	0.16 (0.04–0.70)	.005
Composite of death, MI, or clinically-driven target vessel revascularization	5.5 (4)	10.0 (8)	0.49 (0.15–1.61)	.23
Composite of death, MI, clinically-driven target vessel revascularization, or new-onset HF or readmission for HF	5.5 (4)	14.8 (12)	0.32 (0.10–0.98)	.035
Stent thrombosis (ARC definite or probable)	1.2 (1)	4.9 (4)	0.25 (0.03–2.20)	.17

Note: Values are % (n).

Abbreviations: ARC, Academic Research Consortium; CI, confidence interval; HF, heart failure; MI, myocardial infarction; SSO₂, supersaturated oxygen; TIMI, thrombolysis in myocardial infarction.

3.1 | Clinical outcomes

At 1 year the primary composite endpoint of all-cause death or new-onset HF or HF hospitalization had occurred in 0% of SSO₂-treated patients compared with 12.3% of control patients ($p = .001$) (Table 3 and Figure 1). Treatment with SSO₂ was also associated with lower 1-year rates of all-cause death (0 vs. 7.6%, $p = .01$) driven by lower rates of cardiovascular mortality (0 vs. 4.0%, $p = .04$), and lower 1-year rates of new-onset HF or HF hospitalization (0 vs. 7.4%, $p = .01$). There were no significant differences between patients who were treated versus not treated with SSO₂ in the 1-year rates of reinfarction (2.4 vs. 2.4% respectively, $p = .97$) or clinically driven target vessel revascularization (3.1 vs. 5.1% respectively, $p = .40$). The rate of the composite of death, MI, clinically-driven target vessel revascularization, or new-onset HF or readmission for HF was also lower among patients treated with SSO₂ (5.5 vs. 14.8%, $p = .035$). Stent thrombosis rates at 1 year were not significantly different in patients treated with SSO₂ compared with control (1.2 vs. 4.9% respectively, $p = .17$).

4 | DISCUSSION

In the present study, treatment of patients with anterior STEMI after successful pPCI with SSO₂ infused through the LMCA was associated with lower rates of the primary endpoint of all-cause death or

new-onset HF or HF hospitalization at 1 year and its components. The current study is the first to demonstrate an association between intracoronary treatment with SSO₂ after pPCI and improved long-term clinical outcomes in patients with anterior STEMI.

Several pharmacologic strategies have been utilized in the past to improve microcirculatory function, prevent reperfusion injury, and reduce IS in patients with STEMI, including intracoronary adenosine, nitroprusside, and abciximab infusions^{12,13}; however, none of these treatments have been shown to improve clinical outcomes.¹⁴ In the AMIHOT II trial, the intracoronary delivery of SSO₂ significantly reduced IS after pPCI in patients with large anterior MI,⁸ a parameter that is strongly predictive of subsequent death and HF rehospitalizations.¹ SSO₂ thus became the first therapy demonstrated in a pivotal adequately powered randomized trial to enhance myocardial salvage and reduce IS.

While the AMIHOT II trial met its primary composite safety endpoint, bleeding complications were more frequent, and there were signals for higher 30-day rates of stent thrombosis, myocardial rupture, and death in patients treated with SSO₂.⁸ Given these concerns, SSO₂ delivery was "optimized" in the IC-HOT study to be selectively infused to the origin of the LMCA rather than to the LAD at the stent site. In the IC-HOT study, SSO₂ administered via LMCA was found to be feasible and was associated with a favorable early safety profile and IS consistent with that seen in earlier studies, which led to the approval of intracoronary treatment with SSO₂ by the FDA for administration after pPCI in patients with anterior STEMI.⁸

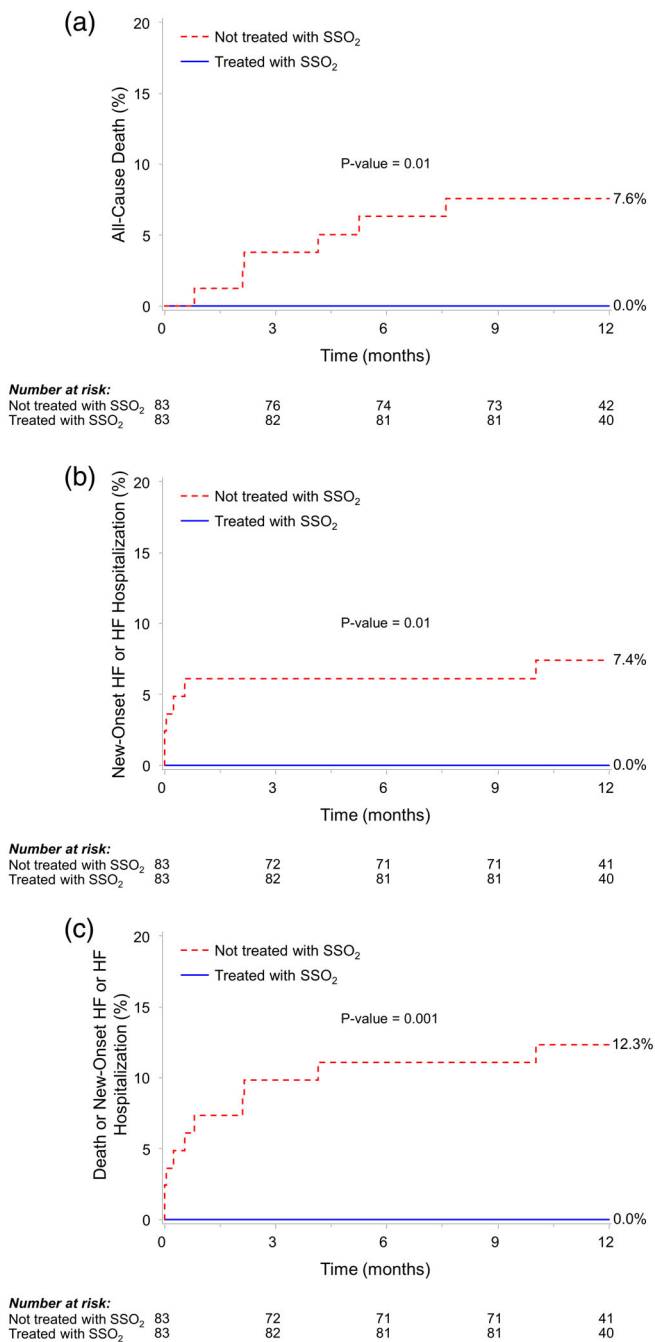


FIGURE Kaplan–Meier time to first event rates in patients with anterior ST-segment elevation myocardial infarction according to treatment with SSO₂. (a) All-cause death; (b) new-onset heart failure (HF) or HF hospitalization; and (c) death, new-onset HF, or HF hospitalization. SSO₂, supersaturated oxygen [Color figure can be viewed at wileyonlinelibrary.com]

The present study was not designed to elucidate the potential mechanisms for the observed improvements in death and HF after SSO₂ treatment observed in the IC-HOT study compared with similar patients with anterior STEMI treated in INFUSE-AMI. The AMIHOT II trial established the utility of intracoronary SSO₂ delivery to reduce IS,⁸ a critical determinant of prognosis.¹ In addition, the observed

extent of microvascular obstruction (MVO) after SSO₂ therapy in IC-HOT was only 0.30% of the left ventricular mass, which is low compared with historical controls.¹⁵ Compromised microvascular flow after epicardial coronary artery reperfusion has been associated with reduced myocardial salvage and adverse cardiovascular outcomes,¹⁶ and has been reported to be an independent predictor of mortality, even after accounting for IS.¹⁵ The pathophysiology of MVO is multifactorial and includes a variety of contributing mechanisms such as distal embolization, ischemia-induced vasoconstriction, and reperfusion injury. Thus, SSO₂, which has been shown to decrease endothelial cell swelling and improve microcirculatory blood flow,^{5–7} may decrease MVO. In addition, SSO₂ administered to the LMCA in anterior STEMI is also delivered to the nonoccluded left circumflex myocardial territory, which could theoretically improve collateral flow to the infarct zone, given the vasodilatory properties of SSO₂. Further study is required to examine the salutary benefits of SSO₂ delivery following pPCI in patients with anterior STEMI.

4.1 | Limitations

First, the present study represents an analysis from a modest-sized propensity-matched cohort rather than a large randomized controlled trial and should thus be considered hypothesis generating. Second, the study population represents a selected cohort of patients; therefore, findings of this study may not apply to all patients with STEMI, such as those with cardiogenic shock, nonanterior MI, and others who did not undergo pPCI with stenting within 6 hrs of symptom onset. In addition, patients from the comparator control group were drawn from the randomized INFUSE-AMI trial; as such, there may be variability from the types of patients enrolled in a single-arm registry such as IC-HOT. Third, in the propensity-matched groups the baseline TIMI 3 flow was less prevalent in the SSO₂ arm, which if anything might have biased the outcomes against SSO₂. Nonetheless, despite propensity-score matching, we cannot rule out the possibility that the analysis is confounded by other unmeasured factors that are correlated with SSO₂ treatment. However, the fact that in the current study reinfarction and revascularization rates did not differ between the groups suggests that the beneficial effects of SSO₂ in reducing mortality and HF hospitalization are specific rather than confounded, as reinfarction and revascularization endpoints would not be expected to be affected by SSO₂. Finally, some details regarding the clinical presentation such as hemodynamic instability and HF symptoms and the completeness of revascularization were not available.

5 | CONCLUSIONS

In the present nonrandomized but propensity-matched controlled study, intracoronary treatment with SSO₂ in patients with anterior STEMI after successful pPCI was associated with improved 1-year clinical outcomes compared to standard treatment without SSO₂, including lower rates of death and new-onset HF or HF

hospitalizations. Appropriately powered randomized trials are warranted to demonstrate the effect of SSO₂ treatment on outcomes in patients with anterior STEMI after successful pPCI.

CONFLICT OF INTEREST

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STUDY REGISTRATION

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