Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: Keystone First Community HealthChoices	**Submission Date**: 11/1/2024
Policy Number: ccp.1499	**Effective Date:** 11/2021 **Revision Date:** October 1, 2024
Policy Name: Transcatheter coronary infusion of supersaturated oxygen therapy in acute myocardial infarction	

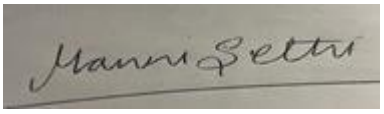
Type of Submission – Check all that apply:

- ☐ **New Policy**
- ☒ **Revised Policy***
- ☐ **Annual Review – No Revisions**
- ☐ **Statewide PDL**

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

See tracked changes below.

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Keystone First
Community HealthChoices

Transcatheter coronary infusion of supersaturated oxygen therapy in acute myocardial infarction

Clinical Policy ID: CCP.1499

Recent review date: 10/2024

Next review date: 2/2026

Policy contains: Acute myocardial infarction; aqueous oxygen therapy; hyperoxemic reperfusion therapy; percutaneous coronary intervention; STEMI; ST-segment elevated myocardial infarction; supersaturated oxygen.

Keystone First Community HealthChoices has developed clinical policies to assist with making coverage determinations. Keystone First Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First Community HealthChoices, on a case by case basis, when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First Community HealthChoices will update its clinical policies as necessary. Keystone First Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

Intracoronary supersaturated oxygen therapy (otherwise known as aqueous oxygen therapy, hyperoxemic reperfusion therapy, or super-oxygenation therapy) is investigational/not clinically proven and, therefore, not medically necessary for the treatment of reperfusion during acute myocardial infarction.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

- Percutaneous coronary intervention.
- Percutaneous transluminal coronary angioplasty with or without atherectomy and/or stent placement.

Background

Following an acute myocardial infarction, early restoration of blood flow through the blocked coronary artery with the use of thrombolytic therapy or primary percutaneous coronary intervention is the most effective approach to

reduce the size of a myocardial injury and improve clinical outcomes. Although early reperfusion therapy in ST-elevation myocardial infarction has reduced mortality overall in the past several decades, reperfusion after ischemia may contribute to additional cell death and increases in infarct size. This, known as myocardial reperfusion injury, culminates in the death of cardiac muscle cells that were viable immediately before reperfusion (Kloner, 2021). It may partly explain why, despite optimal reperfusion to the heart, the mortality after an acute myocardial infarction approaches 12% (Jenca, 2021), and the incidence of cardiac failure after one is almost 25% in Medicare-eligible patients (Krumholz, 2019).

Chen (2021) also noted that despite high rates of epicardial coronary flow restoration to the infarct-related artery, heart muscle salvage is often suboptimal even with sustained patency. This issue has been attributed to late reperfusion, microvascular dysfunction or lack of reflow, reperfusion injury, and other mechanisms which may progress over hours to days.

Noninvasive imaging methods, such as cardiac magnetic resonance imaging and technetium-99m sestamibi single photon emission computed tomography, provide important insights regarding the prognosis of patients who experience problems at the extreme end of the spectrum, such as myocardial regions with no reflow, hemorrhage, and pathologies within the infarcted necrotic core (Spears, 2019). For example, infarct size measured by cardiac magnetic resonance imaging or technetium-99m sestamibi single photon emission computed tomography within one month after primary percutaneous coronary intervention was a strong prognostic indicator of all-cause mortality and heart failure hospitalization within one year (Stone, 2016).

Therapies to further reduce infarct size after timely epicardial reperfusion have been studied over several decades, but many have failed to produce a benefit in clinical trials. Intracoronary supersaturated oxygen therapy is an emerging adjunct to percutaneous coronary intervention for patients with anterior acute myocardial infarction. Intracoronary supersaturated oxygen therapy delivers a super-oxygenated saline solution with the patient's arterial blood to targeted ischemic myocardial regions, thereby increasing oxygen diffusion to the ischemic area, restoring microvascular flow, and protecting the myocardium from further injury (Kloner, 2021).

In 2019, the U.S. Food and Drug Administration granted premarket approval to the TherOx Downstream® System (TherOx Inc., Irvine, California). TherOx is indicated for "the preparation and delivery of SuperSaturated Oxygen Therapy to targeted ischemic regions perfused by the patient's left anterior descending coronary artery immediately following revascularization by means of percutaneous coronary intervention with stenting that has been completed within six hours after the onset of anterior acute myocardial infarction symptoms caused by a left anterior descending artery infarct lesion" (U.S. Food and Drug Administration, 2019).

Findings

The evidence of safety and efficacy of intracoronary supersaturated oxygen therapy consists of two randomized controlled trials (O'Neill, 2007; Stone, 2009) and one nonrandomized study (David, 2019; Chen, 2021). Clinical trials sought to determine whether introducing hypoxemic blood and supersaturated oxygen therapy after the percutaneous coronary intervention would decrease the resultant reperfusion injury, improve recovery of the affected myocardium, and decrease the size of the damage sustained.

The Acute Myocardial Infarction with HyperOxemic Reperfusion pivotal trial (AMIHOT-I) was a prospective, multicenter study of 269 patients with acute anterior or large inferior myocardial infarction undergoing primary or rescue percutaneous cardiac intervention less than 24 hours from symptom onset. Subjects were randomly assigned after successful percutaneous cardiac intervention to receive hyperoxemic reperfusion (treatment group) or normoxemic blood auto reperfusion (control group). Hyperoxemic reperfusion was performed for 90 minutes using intracoronary aqueous oxygen to the left anterior descending artery as the target vessel. The

primary endpoints were final infarct size at 14 days, ST-segment resolution, and delta regional wall motion score index of the infarct zone at three months (O'Neill, 2007).

The results at 30 days showed the incidence of major adverse cardiac events was similar between the control and arterial oxygenated groups (5.2% versus 6.7%, *P* = .62). There was no significant difference in the incidence of the primary endpoints between the study groups. In post hoc analysis, participants reperfused less than six hours with supersaturated oxygen had a greater improvement in regional wall motion (delta wall motion score index = 0.54 in control group versus 0.75 in arterial oxygenated group, *P* = .03), smaller infarct size (23% of left ventricle in control group versus 9% of left ventricle in aqueous oxygen group, *P* = .04), and improved ST-segment resolution compared with normoxemic controls (O'Neill, 2007).

As a result of the post hoc analysis, a second prospective randomized trial (AMIHOT-II; ClinicalTrials.gov identifier NCT00175058) focused on patients with large anterior infarction undergoing percutaneous coronary intervention within six hours of symptom onset. The study randomized enrollees to the arterial oxygenation group (n = 222) or controls (n = 79). The investigators modified the procedure to target the ostium of the left coronary artery rather than the left anterior descending artery. The effectiveness endpoint was infarct size reduction as measured by 14-day technetium-99m sestamibi single photon emission computed tomography. The safety endpoint was a non-inferiority comparison of 30-day major adverse cardiac event rates within a 6% safety delta (Stone, 2009).

Infusion of intracoronary supersaturated oxygen resulted in a lower infarct size (median 20% [interquartile range 6% to 37%] versus controls (26.5% [8.5% to 44%]; *P* < .03; n = 281) with noninferior rates of major adverse cardiovascular events at 30 days. In the treatment group, there was an increase in hemorrhage-related adverse events, mostly access site hematomas due to the larger or multiple sheaths for contralateral femoral artery access required for the infusion catheter. The introduction of the lower profile infusion catheter helped reduce the rates of access site-related complications and bleeding to that of controls. There were no significant between-group differences in survival at 30 days, but the study was underpowered for that endpoint (Stone, 2009).

Following positive results from a feasibility study of 20 enrollees (Hanson, 2015), the nonrandomized Intracoronary Hyperoxemic Oxygen Therapy in Acute Anterior Myocardial Infarction (David, 2019; IC-HOT; ClinicalTrials.gov identifier NCT02603835) trial evaluated the feasibility and safety of supersaturated oxygen therapy selectively delivered to the left main coronary artery for 60 minutes after percutaneous cardiac intervention and stent placement. The study enrolled 100 participants with anterior ST-segment elevated myocardial infarction with proximal or mid-left anterior descending occlusion presenting within six hours of symptom onset. The primary endpoint was at the 30-day composite rate of net adverse clinical events (death, reinfarction, clinically driven target vessel revascularization, stent thrombosis, severe heart failure, or thrombosis in myocardial infarction major/minor bleeding) compared against an objective performance goal of 10.7%.

Cardiac magnetic resonance imaging was performed at four and 30 days to evaluate infarct size. Supersaturated oxygen delivery was successful in 98% of patients. The net adverse clinical events at 30 days occurred in 7.1% of patients (meeting the primary safety endpoint of the study); there were zero deaths, only one stent thrombosis and one case of severe heart failure. Median infarct size was 24.1% (interquartile range 14.4% to 31.6%) at four days and 19.4% (8.8% to 28.9%) at 30 days (David, 2019).

At one year follow up, the primary composite endpoint of all-cause death or new-onset heart failure or heart failure hospitalization had occurred in 0% of supersaturated oxygen-treated patients compared with 12.3% of control patients (*P* = .001). Treatment with supersaturated oxygen was also associated with lower one-year rates of all-cause death (zero vs. 7.6%, *P* = .01) driven by lower rates of cardiovascular mortality (zero versus 4.0%, *P* = .04), and lower one-year rates of new-onset heart failure or heart failure hospitalization (zero versus 7.4%, *P* = .01). The rate of the composite of death, myocardial infarction, clinically-driven target vessel revascularization, or new-onset heart failure or readmission for heart failure was also lower among patients

treated with supersaturated oxygen (5.5% versus 14.8%, *P* = .035). There were no significant between-group differences in the one-year rates of reinfarction (2.4% versus 2.4% respectively, *P* = .97), clinically driven target vessel revascularization (3.1% versus 5.1% respectively, *P* = .40), or stent thrombosis rates (1.2% versus 4.9% respectively, *P* = .17) (Chen, 2021).

While the findings of several published reports appear to be encouraging, the available evidence regarding intracoronary hyperoxemic therapy for the treatment of acute myocardial infarction is insufficient to provide an adequate conclusion of its effectiveness. Although supersaturated oxygen infusion following primary percutaneous coronary intervention in acute anterior ST-elevation myocardial infarction via the left main coronary artery was easily performed and associated with a favorable early safety profile, these findings need to be investigated further with long-term follow-up. More studies are still needed. Other potential applications of this treatment include carbon monoxide poisoning, cardiogenic shock, radiocontrast nephropathy, and stroke. There is a lack of published evidence to support the use of intracoronary hyperoxemic therapy for these indications as well.

In 2022, we added a recent American College of Cardiology/American Heart Association guideline on coronary artery revascularization, which does not mention intracoronary supersaturated oxygen therapy as a treatment alternative (Lawton, 2021). No policy changes are warranted.

In 2023, we identified no newly published relevant literature to add to the policy. No policy changes are warranted.

In 2024, we found two studies though no policy changes are warranted. A review of the efficacy of transcatheter coronary infusion of supersaturated oxygen therapy in acute myocardial infarction suggests potential benefits, particularly when therapy is administered early. Zhang (2024) analyzed two pivotal trials that collectively had (n = 570) participants. The first trial (n= 269) showed no significant reduction in infarct size overall, but a benefit was observed in patients with anterior infarcts when treated within six hours of symptom onset. The second trial (n = 301) demonstrated a significant reduction in infarct size among those treated within the same time frame. Similarly, the IC-HOT study, (n = 100), reported improved one-year outcomes, including lower rates of death and heart failure. These findings indicate that early intervention and careful patient selection may enhance the therapy's effectiveness in reducing infarct size and improving clinical outcomes in certain subgroups of myocardial infarction patients (Hsieh, 2023).

References

On September 10, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were super oxygenated, supersaturated oxygen, oxygen delivery, percutaneous coronary intervention, angioplasty, reperfusion, and acute myocardial infarction. We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

10/2021: initial review date and clinical policy effective date: 11/2021

10/2022: Policy references updated.

10/2023: Policy references updated.
10/2024: Policy references updated.