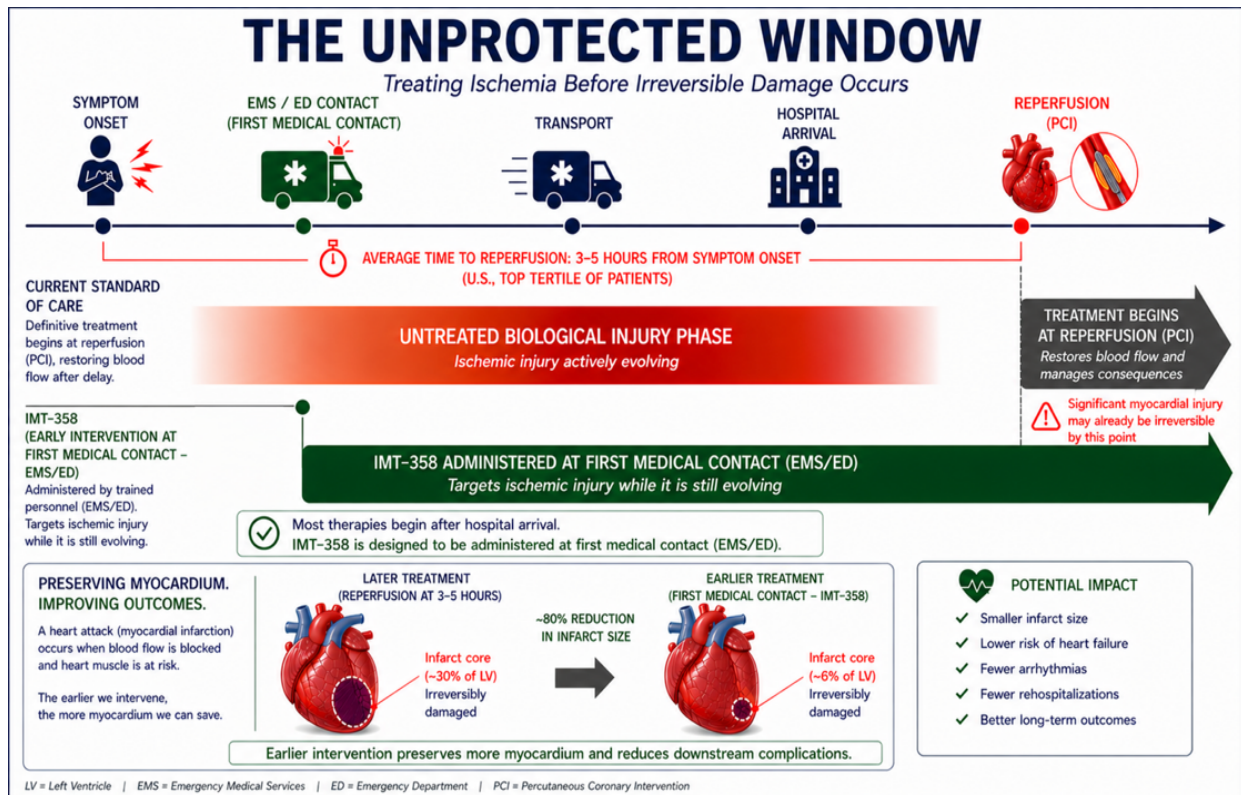


THE UNPROTECTED WINDOW

Why the first hours of ischemia remain untreated — and how that may finally change



AT A GLANCE

Each year, approximately 7.5 million Americans develop symptoms suggestive of acute coronary syndrome (ACS) — and 1.5 million are confirmed to have it. Most will survive the acute event, but a large share will go on to develop heart failure, cognitive impairment, or lasting disability. The defining factor in long-term outcomes is often how much tissue was lost in the first minutes and hours, before hospital treatment began. That window has never had a therapy designed specifically for it.^[1]

The Gap That Modern Medicine Left Open

Over the past three decades, cardiology and neurology have been transformed. Rapid balloon angioplasty (percutaneous coronary intervention, or PCI) has cut the death rate from heart attack by roughly half since the 1990s.^[2] Mechanical thrombectomy has redefined stroke recovery. Advanced critical care has improved survival across the board. Yet for all that progress, there is a phase of acute ischemia that none of these therapies addresses: the period between the moment a blockage occurs and the moment a patient reaches a hospital. For the average heart attack patient, that window is two to four hours. For those in rural areas, it is longer.^[3]

During those hours, the biology of injury runs largely unchecked — and the field's most authoritative voices are now saying so explicitly.

“Identification of appropriate transport destinations for patients with suspected stroke in the prehospital setting remains challenging... [T]ime to intervention remains a critical and incompletely solved problem in acute ischemic care.”

2026 AHA/ASA Guideline for the Early Management of Patients With Acute Ischemic Stroke^[4]

“The time from symptom onset to hospital arrival may represent one of the most important untreated intervals in acute cardiac care.”

The unprotected window is not the same for everyone. Women experiencing ACS frequently present with atypical symptoms — nausea, jaw pain, fatigue — that are less readily recognized as cardiac in origin, leading to longer times from symptom onset to first medical contact. This disparity means the window is disproportionately longer for a substantial segment of the population — and represents one of the most important unsolved problems in acute cardiac care.

What Happens Inside the Body During That Window

When blood flow to the heart or brain is cut off, the affected tissue moves through a predictable sequence. Within four to six minutes, energy stores (ATP) are exhausted.^[5] Toxic metabolites accumulate. Cell membranes become unstable. Electrical activity is disrupted. The process accelerates rapidly, and much of it is irreversible.

The degree of tissue loss — called infarct size in cardiology — is one of the strongest predictors of what happens next. Large infarcts are closely associated with cardiogenic shock, heart failure, arrhythmias, and long-term mortality.^[6] In stroke, the volume of brain tissue lost in the early phase shapes cognitive function, mobility, and independence for life.^[7]

This biology has been understood for decades. The missing piece has been a practical way to intervene during it — at the bedside, in an ambulance — before the window closes.

“Every 90-minute delay in heart attack treatment is associated with roughly one additional death per 100 patients treated. The earliest minutes matter most.” — Boersma et al., Lancet 1996

[8]

A Promising Idea That Misunderstood the Speed of Ischemic Injury

The concept of metabolic support during ischemia — giving the heart or brain extra fuel to survive oxygen deprivation — is not new. The most extensively studied approach is glucose-insulin-potassium (GIK) therapy, a combination that shifts cellular metabolism away from oxygen-dependent pathways.

Over several decades, GIK was tested in numerous clinical trials.^{[9][10]} Most did not show a consistent benefit. The approach was largely set aside.

In retrospect, what the field now understands is that cardiomyocyte death begins far earlier — and progresses far faster — than the trial designs of that era accounted for.^[11] In nearly all of the major GIK trials, therapy was started only after patients arrived at the hospital:

typically four to five hours after symptom onset. By that point, a significant portion of irreversible injury had already occurred.

This was not a failure of scientific rigor. Investigators in those decades were working at the frontier of what was known about the speed and extent of early cellular death. The trials asked a reasonable question with the tools and timelines available. What has changed is the understanding of how little time there actually is.

In that light, the negative results do not disprove the hypothesis. They reveal that the therapy was being evaluated after the window it was designed to address had already largely closed.

Writing in *Circulation* in 2022, cardiologists James Udelson, Harry Selker, and Eugene Braunwald — three of the field's most eminent voices on ischemia and metabolic cardiology — made this case directly. Fifty years after GIK therapy was first introduced, they argued, the concept deserved a serious second look — this time tested as it was always meant to be used: early, before irreversible injury has taken hold. GIK, they wrote, maintains high rates of glycolysis during ischemia to slow myocardial injury, and lowers plasma free fatty acids to reduce the risk of arrhythmias and cardiac arrest. The biology was sound. The timing did not align with the earliest phase of injury.^[12]

“Prior trials of metabolic therapy were almost uniformly initiated too late. They tested a concept that was biologically sound — but in the wrong time window.” — Opie & Knuuti, *Circulation* 2009

[14]

The IMMEDIATE-1 Trial: What Early Really Means

One randomized trial did something different. The IMMEDIATE-1 trial enrolled 871 patients and delivered GIK therapy not at the hospital, but at the point of first medical contact — in the ambulance, administered by paramedics. The median time from symptom onset to treatment was approximately 90 minutes — substantially earlier than any previous large-scale trial had achieved.^[14]

The results within that early window were striking:

- Approximately 50% reduction in cardiac arrest and in-hospital mortality^[14]
- Approximately 80% reduction in infarct size in a mechanistic substudy^[14]

The trial's primary endpoint — progression to myocardial infarction — was less sensitive to the treatment effect, in part because the study enrolled patients before diagnostic confirmation, creating a heterogeneous population that included people who would not ultimately develop a heart attack. An endpoint designed for later-stage evaluation is simply less suited to detecting the benefit of a therapy that acts upstream of the diagnostic process.

The secondary and mechanistic findings, however, are consistent with a clear hypothesis: start early enough, and metabolic intervention can change what happens to the tissue.

“In patients treated within 90 minutes of symptom onset, GIK therapy was associated with a 50% reduction in cardiac arrest — one of the largest acute intervention effects reported in cardiology.” — Selker et al., JAMA 2012

[14]

A Field Catching Up to What the Data Showed

The IMMEDIATE-1 findings have contributed to a broader shift in how the cardiology and emergency medicine communities think about the earliest phase of ischemia.

At major scientific forums, leading clinicians have increasingly acknowledged a gap that has long been implicit in the data: despite transformative advances in reperfusion and downstream care, the first hours of ischemic injury remain largely unaddressed. At ACC.26, the 2026 American College of Cardiology Annual Scientific Session, this theme was prominent across sessions on coronary and structural intervention.^{[15][16]}

At ACC.26 (April 2026), sessions on coronary and structural intervention highlighted the persistent gap between reperfusion capability and outcomes in the earliest phase of ischemia — underscoring that restoring blood flow, while essential, does not address the injury that accumulates before

treatment begins. Separately, the 2026 AHA/ASA Stroke Guideline formally identified early prehospital intervention as an ongoing unmet need.

[4][15][16]

This is not simply the view of a single company or a single trial. Writing in *Circulation* in 2022, Udelson, Selker, and Braunwald argued that GIK deserved a serious second look — tested early, before irreversible injury sets in.^[12] And a 2024 systematic review and meta-analysis published in *Seminars in Thoracic and Cardiovascular Surgery* analyzed 53 randomized studies encompassing more than 6,100 patients and found consistent evidence that GIK therapy reduces myocardial injury, acute kidney injury, and hospital length of stay in patients undergoing cardiac surgery — precisely the population in whom predictable ischemic stress occurs during a procedure. The findings reinforce the underlying biology: metabolic intervention during ischemia produces real, measurable protection.^[17]

The emerging view in the field is that meaningful gains in outcomes — beyond what current therapies can achieve — will require intervening earlier, during the phase when injury is still evolving.

This is not a critique of PCI or thrombectomy. Those therapies work. They address a critically important part of the disease process — restoring blood flow. But restoring flow does not undo the injury that accumulated while the blockage was in place. The two approaches address different phases of the same problem, and they are not mutually exclusive.^[18]

Why This Has Not Been Done Before — and What Has Changed

Understanding the biology of early ischemia is one thing. Delivering a therapy during it is another.

Prehospital medicine is one of the most operationally constrained environments in all of healthcare. Paramedics are managing rapidly deteriorating patients, often under pressure, in a moving vehicle, with limited equipment. Any therapy that adds complexity, requires

refrigeration, demands careful dosing calculations, or slows care in any way will not be adopted — regardless of how promising the science is.^[19]

This is why prior efforts at early metabolic intervention faced practical barriers that the science alone could not overcome: no stable field-ready formulations, no integration into standard EMS protocols, no mechanism for consistent dosing outside a hospital setting.

Recent advances in formulation chemistry and delivery systems have changed that calculus. The resulting system — supported by a combination of formulation, delivery, and use-based intellectual property alongside regulatory exclusivity pathways — is designed from the ground up for deployment wherever acute ischemia is first encountered: in the ambulance, the emergency department, the catheterization lab, and the operating suite.

“The bottleneck in early ischemic intervention has never been the science. It has been the system — and building the right system requires designing for real-world emergency conditions from the start.”

IMT-358: A Pre-Mixed System Built for Every Point of Care

IMT-358 is IMMEDIATE Therapeutics' lead therapeutic program — a field-deployable metabolic intervention that exists not as a compound to be prepared at point of use, but as a standardized, pre-mixed, ready-to-administer system.

The pre-mixed formulation is central to the entire value proposition. Inconsistent preparation has historically been one of the key sources of variability in GIK studies conducted in hospital settings: concentration errors, timing delays, and dosing variability all undermine the therapy's potential.^[17] IMT-358 eliminates that variability at every point in the care continuum — from the ambulance to the emergency department to the catheterization lab to the operating room. Wherever a patient with acute ischemia is first encountered, the same standardized pre-mixed therapy can be initiated immediately, without preparation time, without calculation, and without additional equipment.

The program addresses each of the barriers that stalled earlier efforts:

- Pre-mixed, field-stable bags requiring no refrigeration or on-site preparation — ready to use from the ambulance to the OR
- Standardized dosing compatible with EMS, ED, catheterization lab, and hospital workflows alike
- Integration into existing emergency care protocols at every level of the care system, without adding delay
- Alignment with downstream reperfusion therapy — complementing rather than displacing PCI and other definitive treatments

This distinction — a pre-mixed system ready at any point of care, rather than a hospital-compounded formulation — is not a manufacturing detail. It is the mechanism by which consistent, early administration becomes achievable at scale.

The Stakes: What Early Injury Costs Over a Lifetime

In the United States, heart failure affects approximately 6.7 million adults, and roughly half of new cases are attributable to prior myocardial infarction. The five-year mortality rate after a heart failure diagnosis remains around 50% — comparable to many cancers. Annual costs to the healthcare system exceed \$30 billion.^[20]

Infarct size — the amount of heart muscle that dies in the acute event — is among the most powerful predictors of whether a heart attack patient will develop heart failure, experience a recurrent event, or survive long term.^[21] Reducing infarct size at the outset does not merely improve the odds of surviving the acute event. It changes the trajectory of what follows.

The scale of that trajectory is now documented in landmark detail. A 2024 population study of 56 million people across England — every NHS hospitalization over a decade — tracked 433,361 MI survivors against 2 million matched controls for up to nine years.^[26] The findings are stark: nearly 3 in 10 MI survivors developed heart failure (29.6% versus 9.8% in controls), with a hazard ratio of 4.93 — nearly five times the expected rate. More than a quarter developed renal failure. Over a third died within nine years. The study's authors put it plainly: individuals following MI frequently accrue major comorbidities across a range of body systems, with “3 in 10 developing heart failure or renal failure and 4 in 10 dying.”

These are not distant risks. Heart failure developed in 21.2% of MI survivors within the first year alone — compared with 2.9% of matched controls. The damage set in motion at the time of the index event cascades forward for years.

In stroke, the pattern is equally clear. The volume of brain tissue lost in the early phase is directly tied to long-term cognitive function, mobility, and independence.^[22] Earlier intervention means more preserved tissue — and for many patients, the difference between dependence and independence.

“Up to a third of patients with MI developed heart failure or renal failure, 7% had another MI, and 38% died within 9 years. The incidence of all health outcomes was higher than expected during the normal life course without MI.” — Hall et al., PLOS Medicine
2024

[26]

A Broader Problem — and Independent Validation of the Pathway

Heart attack is the most visible form of acute ischemia, but it is not the only one. Stroke, major trauma, high-risk surgery, and critical illness all involve periods where tissue is deprived of oxygen and metabolic stability collapses. The underlying biology — ATP depletion, membrane instability, accumulation of toxic metabolites — is remarkably consistent across conditions.^[23]

The strongest independent validation of GIK's metabolic benefit comes from cardiac surgery — a setting where ischemic stress is predictable, controlled, and measurable. A 2024 systematic review and meta-analysis by Hagerman and colleagues, published in *Seminars in Thoracic and Cardiovascular Surgery*, synthesized 53 randomized controlled trials involving 6,129 patients undergoing cardiac surgery. The findings were consistent and clinically meaningful:^[17]

- 34% reduction in perioperative myocardial infarction (OR 0.66)^[17]

- 43% reduction in acute kidney injury (OR 0.57)^[17]
- Approximately 0.9 fewer hospital days per patient^[17]
- Higher cardiac index in GIK-treated patients, indicating improved heart pump function^[17]

Cardiac surgery provides a rigorous test of the GIK hypothesis. Ischemic stress is induced deliberately during bypass, timing is known, dosing is controlled, and endpoints are clearly defined. That GIK produces consistent measurable protection across more than 6,000 cardiac surgery patients substantially strengthens the biological and clinical rationale for its use in acute myocardial ischemia, where the same metabolic pathways are activated under less controlled but equally consequential circumstances.

The Hagerman 2024 meta-analysis is among the largest systematic evaluations of GIK therapy ever conducted. Its findings in cardiac surgery — reduced infarction, reduced organ injury, shorter hospital stays — directly support the mechanistic hypothesis underlying IMT-358: that metabolic intervention during ischemia produces real, reproducible organ protection.

IMT-358 is being developed initially for acute myocardial ischemia. But the scientific rationale for early metabolic intervention extends across multiple acute care settings. If confirmed prospectively in cardiology, the concept opens a much larger field of application — stroke, trauma, high-risk surgery, and critical illness — where the same early-phase biology has never been treated.

Regulatory Alignment: A Defined Path Forward

A confirmatory pivotal trial is now being designed to test whether early metabolic intervention can be validated at scale. The trial will evaluate IMT-358 against clinically meaningful endpoints — in-hospital cardiac arrest, mortality, and infarct size — in a patient population that mirrors the real-world conditions under which the therapy will be used.

The program has received two significant regulatory designations from the U.S. Food and Drug Administration:

- Breakthrough Therapy Designation, which the FDA grants when preliminary clinical evidence indicates that a drug may offer substantial improvement over existing therapies for serious conditions^[24]
- Special Protocol Assessment agreement, which provides regulatory clarity on trial design and endpoint selection before the study begins^[24]
- Biologic License Application pathway, which upon approval grants 12 years of regulatory exclusivity in the United States — the longest exclusivity period available under U.S. law^[24]

Together, these designations reflect the FDA's acknowledgment that early metabolic intervention addresses an unmet medical need, and that the development program is structured to answer the question rigorously.

“FDA Breakthrough Therapy Designation is reserved for treatments that show preliminary evidence of substantial improvement over existing therapies. It signals that regulators see a genuine unmet need — and a credible path to address it.”

Standing on Five Decades of Science

The late Dr. Eugene Braunwald — one of the most influential cardiologists of the twentieth century — spent decades establishing the relationship between infarct size, early ischemia, and long-term prognosis. “The amount of myocardium that undergoes irreversible injury,” he wrote, “is one of the most important determinants of the long-term prognosis of the patient with acute myocardial infarction.”^[25] His work and the work of many researchers who followed established the biological importance of that early window long before practical tools existed to address it.

IMMEDIATE Therapeutics is not departing from that scientific consensus. The goal is finally to operationalize it. The biology was sound. The timing did not align with the earliest phase of injury. That is now changing.

What Happens Next

The question is no longer whether early ischemic injury matters. The question is whether it can be addressed in a rigorous, scalable way.

IMMEDIATE Therapeutics is advancing a pivotal, randomized Phase 3 trial designed to evaluate whether early metabolic intervention — delivered via a pre-mixed IV formulation at the point of first medical contact, to patients presenting with abnormal ECG and symptoms consistent with ACS — can meaningfully reduce infarct size, cardiac arrest, and mortality. The study is structured to reflect real-world conditions, with therapy initiated before definitive diagnosis and evaluated against clinically meaningful endpoints.

The combination of clinical signal from IMMEDIATE-1, independent validation from surgical settings across more than 6,000 patients, and regulatory alignment with FDA provides a clear and testable path forward. For the first time, the field has both the scientific rationale and the practical delivery system required to determine whether intervening during the earliest phase of ischemia can change outcomes at scale.

Conclusion

For decades, the story of acute care has been about what happens after ischemia starts. The therapies built over that period — PCI, thrombectomy, advanced critical care — are genuinely transformative, and they continue to save lives every day.

But they leave something unaddressed: the first hours of injury, when the biological damage that shapes everything else is being determined.

The scientific case for early metabolic intervention has existed for decades. What has been missing is the convergence of clinical evidence, independent validation from surgical settings, regulatory alignment, and a practical pre-mixed delivery system ready to deploy at any point of care. That convergence is now in place.

For the first time in many years, the field has a clear, well-defined path to answer the question that has always mattered most: can we protect patients during the window when they are most vulnerable?

If prospective confirmation validates what the early data suggest, the implications extend well beyond a single drug. They represent a fundamental shift in the philosophy of acute care — moving intervention earlier, into the window when injury is still evolving and tissue remains salvageable.

“For the first time, we have both the evidence and the tools to address the earliest and most damaging phase of ischemia. The question is no longer whether this matters — it is whether we will act on what we know.”

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About IMMEDIATE Therapeutics

IMMEDIATE Therapeutics is a clinical-stage biotechnology company focused on redefining the treatment of acute ischemic conditions through early metabolic intervention. Its lead program, IMT-358, is a Phase 3—ready, pre-mixed therapy designed for immediate deployment at any point in the acute care continuum — from the ambulance to the hospital — with the goal of improving survival and preserving organ function across a range of acute care indications. The company has received Breakthrough Therapy Designation and Special Protocol Assessment agreement from the FDA.

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