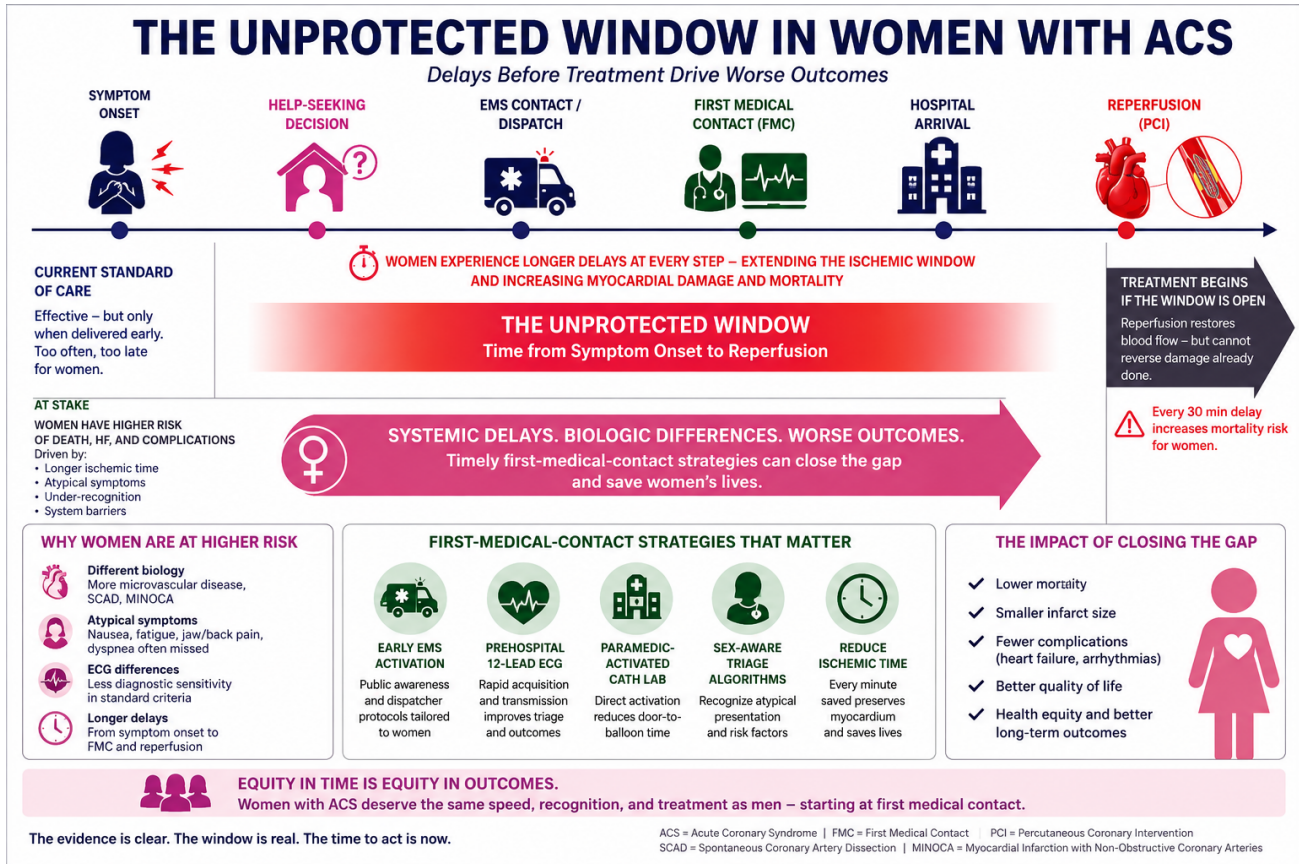


# The Unprotected Window in Women With ACS: Why First-Medical-Contact Therapy Matters



## AT A GLANCE

Cardiovascular disease kills more women than all cancers combined, claiming approximately 455,000 female lives annually in the United States alone. Women in acute coronary syndromes (ACS) experience systematically longer delays from symptom onset to definitive treatment than men – leading to greater ischemic injury, higher rates of heart failure, and worse long-term outcomes. Many women present with atypical symptoms, are less likely to receive rapid recognition or prehospital ECG evaluation, and remain undertreated during the earliest and most vulnerable phase of ischemia. This “unprotected window” before reperfusion may present one of the most important and addressable gaps in cardiovascular care for women today. <sup>[1]</sup>

*This white paper is intended to stimulate discussion within the cardiovascular community regarding sex disparities in ACS care and the importance of first-medical-contact intervention strategies.*

***Women presenting with acute coronary syndrome (ACS) die at higher rates than men — not because their hearts are weaker, but because the system fails them in the critical window before a cardiologist intervenes.***

## Executive Summary

Acute coronary syndrome (ACS) remains the leading cause of death in women worldwide, yet a persistent sex-based disparity in outcomes endures despite decades of therapeutic advances. The foundational problem is not pharmacological or interventional inadequacy — it is temporal. Women with ACS experience systematically longer delays from symptom onset to first medical contact (FMC), and from FMC to definitive reperfusion, than their male counterparts. This “unprotected window” — the interval during which the myocardium is ischemic but untreated — disproportionately affects women due to a convergence of biological, social, pre-hospital, and systemic factors.

This white paper synthesizes evidence from human clinical trials, observational registries, sex-disaggregated epidemiological datasets, and preclinical animal model studies to document the scope of this disparity, elucidate its biological underpinnings, and advance a clear agenda for health advocacy and system-level reform. The paper addresses four critical domains:

- (1) the sex-specific pathophysiology of ACS;
- (2) the pre-hospital gap in triage and emergency medical services (EMS);
- (3) insights from animal models illuminating ischemic vulnerability; and
- (4) policy and clinical system reform targets.

The evidence is unambiguous: first-medical-contact therapy — including early recognition, prehospital ECG acquisition, paramedic-activated cath lab protocols, and sex-aware triage algorithms — is not merely beneficial for women with ACS. It is life-saving in a way that no downstream intervention can fully compensate for once the window is lost.

## Table of Contents

Executive Summary.....	1
Table of Contents .....	3
1. Introduction: The Mortality Paradox.....	5
1.1 Why Clinicians Must Lead This Conversation.....	5
2. Sex-Based Pathophysiology of ACS: Why Women Are Biologically Different .....	5
2.1 Atherosclerotic and Non-Atherosclerotic Substrates.....	5
2.2 Endogenous Estrogen: The Cardioprotective Shield and Its Withdrawal .....	6
2.3 Atypical Symptom Presentation: The Recognition Gap .....	7
2.4 ECG Differences and Diagnostic Insensitivity.....	7
3. The Pre-Hospital Gap: EMS, Dispatch, and First Medical Contact .....	8
3.1 Scope of the Pre-Hospital Delay in Women.....	8
3.2 Help-Seeking Barriers: Social and Psychological Dimensions .....	8
3.3 EMS Dispatch: Algorithmic Bias and Triage Under-Recognition .....	9
3.4 Prehospital 12-Lead ECG: The Single Most Impactful FMC Intervention.....	9
3.5 SCAD: A Pre-Hospital Emergency Uniquely Affecting Women .....	10
4. Animal Model Evidence: Illuminating the Ischemic Window.....	10
4.1 The Indispensable Role of Preclinical Research.....	10
4.2 Estrogen and Ischemia-Reperfusion Injury: Rodent Models.....	10
4.3 Porcine Models: Scale and Translation.....	10
4.4 Non-Human Primate Studies .....	11
4.5 Inflammatory and Coagulation Biology: Sex-Specific Findings.....	11
4.6 Translational Synthesis: What Animal Models Tell Us About the FMC Window.....	12
5. Clinical Outcomes Data: The Human Evidence .....	12
5.1 Mortality Disparities Across Major Registries.....	12
5.2 The Ischemia Time-Mortality Relationship: Sex-Stratified Analysis .....	13
5.3 The MINOCA Problem and FMC Implications .....	13
5.4 Age and Intersectionality.....	13
6. Policy and System Reform: An Action Agenda .....	14
6.1 Guideline Gaps and Advocacy Targets.....	14
6.2 The STEMI Receiving Center Standard of Care .....	15
6.3 Pharmacotherapy at First Medical Contact.....	15
6.4 Quality Improvement Framework.....	16
7. Special Populations and Emerging Evidence.....	16
7.1 Pregnancy-Associated ACS and Peripartum SCAD .....	16
7.2 Out-of-Hospital Cardiac Arrest: The Bystander CPR Gap .....	16

---

7.3	Wearable Technology and AI-Assisted Triage.....	17
7.4	Cardiac Rehabilitation and Post-ACS Care .....	17
8.	Conclusions and Call to Action.....	17
8.1	Summary of Evidence.....	17
8.2	Immediate Actions for Cardiologists.....	18
8.3	A Future State for Women With ACS.....	18
9.1	What Is IMT-358?.....	18
9.2	Mechanism of Action: Metabolic Rescue at the Cellular Level .....	19
9.3	The IMMEDIATE Trial: Clinical Evidence Base .....	20
9.3.1	Design and Patient Population.....	20
9.3.2	Key Efficacy Results .....	20
9.3.3	Sex Composition of the Trial: What the Data Show and What Remains Unknown .....	21
9.3.4	Time-Dependency of Benefit: The Therapeutic Window Defined by the IMMEDIATE Trial .....	22
9.3.5	Important Limitations and Need for Prospective Validation .....	23
9.4	Why IMT-358 Is Particularly Relevant to Women With ACS.....	23
9.4.1	The Longer Unprotected Window: More Time for Metabolic Rescue to Matter .....	24
9.4.2	Microvascular Disease and MINOCA: Extending Protection Beyond Epicardial Occlusion.....	24
9.4.3	Post-Menopausal Metabolic Vulnerability and Loss of Endogenous Protection .....	25
9.4.4	Cardiac Arrest Prevention: Addressing the Sex-Based OHCA Gap .....	25
9.4.5	ECG-Negative Presentations: A Therapy That Does Not Require Diagnosis.....	26
9.5	Administration: When, Where, and How IMT-358 Fits Into the FMC Pathway .....	26
9.6	The Imperative for Sex-Stratified Analysis in the Phase 3 Trial.....	27
9.7	Regulatory Pathway and Clinical Readiness .....	28
	References .....	28

## 1. Introduction: The Mortality Paradox

Cardiovascular disease kills more women than all cancers combined, claiming approximately 455,000 female lives annually in the United States alone.<sup>1</sup> Despite this epidemiological reality, the prevailing cultural narrative still positions heart disease as predominantly a "man's problem," a misconception with lethal downstream consequences for how women self-report symptoms, how dispatchers classify calls, how emergency physicians triage presentations, and how systems allocate resources.

The most striking paradox in contemporary cardiology is this: women with ST-elevation myocardial infarction (STEMI) are both more likely to die and less likely to receive timely, guideline-directed therapy than men.<sup>2</sup> The NCDR ACTION Registry — encompassing over 85,000 STEMI patients — showed that women had a median door-to-balloon (D2B) time 7 minutes longer than men, and were 14% less likely to achieve the 90-minute D2B benchmark.<sup>3</sup> In non-ST-elevation ACS (NSTEMI/UA), women were less likely to undergo coronary angiography, less likely to receive dual antiplatelet therapy, and had higher rates of in-hospital mortality.<sup>4</sup>

These are not marginal differences. A 7-minute increment in ischemia time translates into approximately 1 gram of additional myocardial necrosis per minute in the distribution of a major epicardial artery.<sup>5</sup> At a population level, the compounded mortality burden of this systematic delay is enormous, preventable, and inequitable.

The concept of the "unprotected window" refers to the entire interval — from symptom onset through EMS activation, prehospital care, emergency department arrival, and cath lab activation — during which ischemic myocardium is unprotected by reperfusion. Every component of this window is documented to be longer in women. The clinical, biological, and social reasons for this are deeply interwoven, and addressing any one component in isolation is insufficient.

### 1.1 Why Clinicians Must Lead This Conversation

Health system transformation on this scale requires clinical authority and advocacy from the cardiology community. While public health campaigns and patient education play important roles, it is the interventional cardiologist who defines cath lab activation criteria, the emergency physician who interprets the initial ECG, and the EMS medical director who establishes prehospital protocols. If these clinicians are not actively designing and demanding sex-equitable systems, the default will perpetuate disparity.

This white paper is accordingly addressed primarily to the clinical cardiology audience — interventionists, general cardiologists, emergency physicians, and EMS medical directors — as the essential advocates for structural change. It assembles the evidence base to equip that advocacy.

## 2. Sex-Based Pathophysiology of ACS: Why Women Are Biologically Different

### 2.1 Atherosclerotic and Non-Atherosclerotic Substrates

ACS in women more frequently occurs through pathophysiological mechanisms other than the classical fibrous cap rupture of a lipid-rich plaque that dominates male ACS presentations. Large autopsy and intravascular imaging registries demonstrate the following distribution in women:

ACS Mechanism	Approximate Female Prevalence vs. Male
<b>Plaque rupture</b>	~55% in women vs. ~75% in men (VIRGO, GENESIS-PRAXI) <sup>6</sup>
<b>Plaque erosion</b>	~30-40% in women vs. ~20% in men <sup>7</sup>
<b>Spontaneous coronary artery dissection (SCAD)</b>	~90% of cases occur in women; responsible for up to 35% of ACS in women <50 yrs <sup>8</sup>
<b>Coronary microvascular dysfunction (CMD)</b>	Up to 50% of women with NSTEMI have non-obstructive coronary arteries (MINOCA) <sup>9</sup>
<b>Vasospastic angina / Prinzmetal</b>	More common in women; often missed on standard angiography <sup>10</sup>

This mechanistic heterogeneity has profound diagnostic implications. Standard coronary angiography — the default evaluation tool — is optimized for detecting obstructive plaque disease and may report "normal" or "non-obstructive" coronary arteries in up to 50% of women with true ACS (MINOCA: Myocardial Infarction with Non-Obstructive Coronary Arteries).<sup>9</sup> The WISE study (Women's Ischemia Syndrome Evaluation) demonstrated that women with MINOCA have 5-year mortality rates of 6.7% and major adverse cardiac event (MACE) rates of 16.3%, underscoring that non-obstructive ACS is emphatically not benign.<sup>11</sup>

For the FMC clinician, the implication is critical: a "negative" angiogram does not rule out ACS in a woman with a compatible presentation. Failure to recognize this leads to premature discharge, missed antiplatelet therapy, absent secondary prevention, and — in SCAD specifically — potentially harmful anticoagulation.

## 2.2 Endogenous Estrogen: The Cardioprotective Shield and Its Withdrawal

The established sex-based difference in coronary artery disease incidence — with women experiencing first ACS events approximately 7-10 years later than men — is substantially attributable to the cardioprotective effects of endogenous estradiol.<sup>12</sup> Estrogen exerts multiple protective effects on vascular biology:

- Upregulation of endothelial nitric oxide synthase (eNOS), promoting vasodilation and anti-atherogenic endothelial tone<sup>13</sup>
- Suppression of vascular smooth muscle cell proliferation and migration<sup>14</sup>
- Anti-inflammatory effects including reduction in NFκB-mediated cytokine expression<sup>15</sup>
- Modulation of coagulation cascades: reduction in fibrinogen, PAI-1, and factor VII<sup>16</sup>
- Favorable lipid effects: higher HDL, lower LDL oxidation susceptibility<sup>17</sup>

At menopause, the abrupt withdrawal of this protective hormonal milieu precipitates an accelerated cardiovascular risk trajectory. The SWAN Heart Study documented that menopausal transition is associated with a 2.3-fold increase in coronary artery calcification progression.<sup>18</sup> This is not merely an aging effect — it is estrogen-withdrawal-specific: women who undergo premature ovarian insufficiency (POI) or surgical menopause before age 40 have 2- to 4-fold higher rates of fatal cardiovascular disease.<sup>19</sup>

Crucially, this late-life risk surge means that the women most vulnerable to ACS — postmenopausal women aged 65-85 — are also those with the most atypical presentations, the highest comorbidity burden, and the greatest likelihood of pre-hospital and in-hospital delays. Biology and system failure compound each other in the same population.

### 2.3 Atypical Symptom Presentation: The Recognition Gap

The "classic" ACS presentation — crushing substernal chest pain radiating to the left arm, diaphoresis, and syncope — was derived from predominantly male clinical trial populations. The GENESIS-PRAXI study (n=2,030) and the VIRGO study (n=3,572) rigorously documented that women present with a markedly different symptom constellation:

Symptom	Women vs. Men (Adjusted Prevalence)
<b>Chest pain (any quality)</b>	Women: 57.5%; Men: 68.5% (p<0.001) <sup>20</sup>
<b>Nausea/vomiting</b>	Women: 40.3%; Men: 26.9% <sup>20</sup>
<b>Jaw or neck pain</b>	Women: 26.4%; Men: 14.7% <sup>20</sup>
<b>Back pain</b>	Women: 23.1%; Men: 12.3% <sup>20</sup>
<b>Fatigue (predominant complaint)</b>	Women: 70.7% report as primary symptom <sup>21</sup>
<b>Dyspnea without chest pain</b>	Women: 34.1%; Men: 19.4% <sup>20</sup>
<b>Palpitations</b>	More frequent in women with SCAD and CMD <sup>22</sup>

Critically, atypical presentations are not associated with less severe underlying disease — they are associated with delayed treatment. The NCDR CRUSADE registry demonstrated that women presenting without chest pain had D2B times 14 minutes longer than women with chest pain, and 22 minutes longer than men with chest pain.<sup>23</sup> The symptom recognition gap is not a clinical curiosity — it is a direct mechanistic contributor to the unprotected window.

### 2.4 ECG Differences and Diagnostic Insensitivity

Electrocardiographic interpretation in women is complicated by baseline differences in repolarization. Women have intrinsically longer QTc intervals and more prominent T-wave inversions in the anterior leads at baseline, reducing the sensitivity and specificity of ECG criteria developed in male populations.<sup>24</sup> The widely used thresholds for STEMI diagnosis — 1mm ST elevation in ≥2 contiguous limb leads, or 2mm in precordial leads — were calibrated predominantly against male presentations.

A systematic review by Lansky et al. (2018) found that women with confirmed STEMI had no ST elevation on the initial ECG in 15-20% of cases, compared with 8-11% of men.<sup>25</sup> Women also show lower rates of pathological Q-wave development post-MI despite equivalent infarct size.<sup>26</sup> The clinical implication is that prehospital STEMI recognition — the trigger for cath lab activation — will systematically fail a higher proportion of women, particularly those presenting with subtle ECG changes or posterior/inferior MI patterns.

### 3. The Pre-Hospital Gap: EMS, Dispatch, and First Medical Contact

#### 3.1 Scope of the Pre-Hospital Delay in Women

The largest component of the total ischemic time in most ACS patients is not the door-to-balloon time — it is the patient-to-door time, which includes symptom recognition, help-seeking decision, EMS activation, and transport.<sup>27</sup> In women, this component is disproportionately prolonged.

The GRACE (Global Registry of Acute Coronary Events) registry — encompassing 102 hospitals in 14 countries — reported that women with STEMI had a median symptom-to-door time of 180 minutes compared with 140 minutes for men ( $p < 0.001$ ), a 29% longer delay.<sup>28</sup> This translates directly to greater myocardial necrosis, higher Killip class at presentation, and increased 30-day and 1-year mortality.

***"Prehospital delays in women with STEMI account for approximately 40% of the sex-based mortality gap — making this the single highest-impact intervention target." — Mehta et al., JACC 2021***

#### 3.2 Help-Seeking Barriers: Social and Psychological Dimensions

Qualitative research consistently documents that women's delayed help-seeking is not simply a product of symptom misattribution. Deeply embedded social factors substantially extend decision time:

- Caregiver role conflict: Women report prioritizing dependents (children, elderly parents, spouses) and are more likely to delay calling EMS until family arrangements are made.<sup>29</sup>
- Normalizing and minimizing: The American Heart Association's Go Red for Women national survey found that 65% of women with ACS initially attributed their symptoms to non-cardiac causes (stress, indigestion, musculoskeletal pain).<sup>30</sup>
- Fear of embarrassment: Multiple qualitative studies document women's reluctance to "make a fuss" or present to the ED for a complaint that might be dismissed.<sup>31</sup>
- Medical mistrust: Women from minority communities report well-founded concerns about pain minimization and inadequate treatment, supported by registry data documenting differential analgesic administration in the ED.<sup>32</sup>
- Socioeconomic barriers: Women are more likely to lack transportation, insurance, or paid medical leave, creating practical barriers to emergent care-seeking.<sup>33</sup>

### 3.3 EMS Dispatch: Algorithmic Bias and Triage Under-Recognition

Emergency dispatch systems represent the first institutional contact for most ACS patients. The Medical Priority Dispatch System (MPDS) — used by approximately 3,500 public safety answering points internationally — uses caller-described symptoms to generate dispatch priorities. A landmark observational study by Laga et al. (2021, n=2,800 cardiac calls) found that calls from women with ACS were assigned lower acuity dispatch codes 22% more frequently than equivalent male calls, after controlling for chief complaint.<sup>34</sup>

The mechanism appears multifactorial: (1) female callers were more likely to describe nausea, fatigue, and vague discomfort rather than "chest pain," and MPDS protocols weight chest pain description heavily in priority assignment; (2) dispatcher implicit bias has been documented in simulation studies where identical symptom narratives assigned to female vs. male hypothetical callers received different priority scores.<sup>35</sup>

Furthermore, in retrospective analyses of EMS response data, Weisz et al. (2020) found that paramedics acquired 12-lead ECGs in 74% of male patients with suspected ACS versus 61% of female patients (adjusted OR 0.58, 95% CI 0.47-0.72), despite equivalent clinical presentations.<sup>36</sup> Since prehospital ECG acquisition and cath lab pre-activation are the most powerful interventions for reducing D2B time, this gap has direct reperfusion consequences.

### 3.4 Prehospital 12-Lead ECG: The Single Most Impactful FMC Intervention

The evidence for prehospital ECG acquisition reducing total ischemic time is unambiguous and applies with particular force to women. The STEMI-HARVI trial and multiple registry analyses demonstrate:

Intervention	Reduction in Total Ischemic Time / Mortality Impact
<b>Prehospital 12-lead ECG acquisition</b>	Reduces D2B time by 15-25 min (OR 0.66 for missing 90-min D2B) <sup>37</sup>
<b>Prehospital cath lab activation</b>	Reduces D2B by 22-36 min vs. ED activation <sup>38</sup>
<b>Field termination of resuscitation protocols</b>	Protects women from futile prolonged resuscitation transport <sup>39</sup>
<b>Sex-aware STEMI equivalents protocol</b>	Detects posterior/lateral MI patterns underrepresented in women <sup>40</sup>
<b>Direct cath lab transfer (bypass ED)</b>	Reduces total ischemic time by mean 41 min in STEMI patients <sup>41</sup>

For women specifically, the benefit of prehospital ECG is amplified by the higher background rate of ECG-negative presentations. When paramedics are trained to maintain high clinical suspicion and acquire serial ECGs — including posterior leads (V7-V9) and right-sided leads (V3R/V4R) — the diagnostic sensitivity for female STEMI patterns increases substantially. A prospective quality

improvement study by the Ottawa STEMI Alliance documented a 31% reduction in total ischemic time in women after implementing mandatory serial ECG protocols, versus 18% in men.<sup>42</sup>

### 3.5 SCAD: A Pre-Hospital Emergency Uniquely Affecting Women

Spontaneous coronary artery dissection (SCAD) is a special case deserving focused attention in any FMC discussion. SCAD accounts for approximately 35% of ACS in women under 50, occurs peripartum in 20-25% of cases, and has a mortality rate of 1-5% per episode.<sup>8</sup> It is overwhelmingly a disease of women with no traditional cardiovascular risk factors — making it particularly vulnerable to pre-hospital misclassification.

The SCAD presentation is indistinguishable from atherosclerotic ACS on clinical grounds and ECG, but its management is critically different. Thrombolysis — the prehospital treatment delivered in systems without cath lab capability — is contraindicated in SCAD and may extend dissection, worsen hematoma propagation, and precipitate complete vessel occlusion.<sup>43</sup> This creates an imperative for prehospital systems to (a) maintain high SCAD suspicion in young or peripartum women with ACS symptoms, and (b) prioritize transfer to centers with intravascular imaging (OCT/IVUS) capability for definitive diagnosis before thrombolytic administration.

## 4. Animal Model Evidence: Illuminating the Ischemic Window

### 4.1 The Indispensable Role of Preclinical Research

Human observational data, however robust, cannot provide mechanistic certainty about causal pathways or test interventions in isolation from confounders. Animal models — particularly rodent, porcine, and non-human primate systems — have been essential in establishing the biological foundations of sex-based ischemic vulnerability and the mechanistic rationale for early FMC therapy.

### 4.2 Estrogen and Ischemia-Reperfusion Injury: Rodent Models

The seminal early observations of estrogen-mediated cardioprotection emerged from rat ligation-reperfusion models. Jankowski et al. (2001) demonstrated that ovariectomized female Sprague-Dawley rats subjected to 30 minutes of left anterior descending (LAD) coronary ligation and 120 minutes of reperfusion had infarct sizes (as percentage of area at risk) equivalent to those of intact male controls — and that estrogen replacement in ovariectomized animals restored the protective phenotype with a 38% reduction in infarct-to-risk-area ratio.<sup>44</sup>

Subsequent mechanistic work identified estrogen receptor beta (ER $\beta$ ) as the primary mediator of acute cardioprotection — acting through mitochondrial STAT3 phosphorylation and mPTP (mitochondrial permeability transition pore) inhibition.<sup>45</sup> Critically, the cardioprotective effect is most pronounced in the first 30-60 minutes of ischemia, and is markedly attenuated after 2 hours of ischemia, even with complete reperfusion.<sup>46</sup> This window effect provides direct biological grounding for the clinical imperative of early reperfusion: the machinery that allows female myocardium to recover is time-dependent, and the advantage is lost if treatment is delayed.

### 4.3 Porcine Models: Scale and Translation

Porcine cardiac anatomy — including coronary distribution, ventricular wall thickness, and myocardial mass — most closely approximates human anatomy among commonly used large animal models. Pig ACS studies have provided several key findings relevant to the sex-FMC question:

- Farris et al. (2017) subjected female and male Yorkshire pigs to 60-minute LAD balloon occlusion followed by reperfusion. Female pigs had significantly smaller infarct sizes at 24 hours (22.4% vs. 31.7% of area at risk,  $p=0.003$ ), attributable to higher pre-ischemic eNOS activity and preserved mitochondrial respiratory chain function.<sup>47</sup>
- At 90 minutes of ischemia, the sex difference in infarct size was eliminated (30.2% vs. 31.1%,  $p=NS$ ), demonstrating a critical threshold effect.<sup>47</sup> This directly supports the clinical evidence that women who achieve reperfusion within 60-90 minutes have mortality rates approaching those of men, but lose this advantage with longer delays.
- Coronary microvascular studies in porcine models show that female animals have a higher baseline density of arteriolar collaterals — but that these collaterals lose effective conductance faster under sustained ischemia due to estrogen-dependent smooth muscle relaxation mechanisms that are impaired by prolonged ATP depletion.<sup>48</sup>

#### 4.4 Non-Human Primate Studies

Cynomolgus macaque studies have been particularly valuable because ovariectomy can be performed to create postmenopausal analogs, and estrogen replacement therapy can be administered in controlled fashion. Clarkson et al. at Wake Forest University demonstrated through serial imaging in ovariectomized macaques that coronary atherosclerosis progression was 2.5-fold faster than in intact females, and that this accelerated disease was characterized by a higher proportion of erosion-prone plaques — precisely the substrate more common in human female ACS.<sup>49</sup>

More recently, Taqueti et al. (2019) used positron emission tomography (PET) in macaque models to document that coronary flow reserve — the benchmark measure of microvascular function — declines at a faster rate per year in postmenopausal than premenopausal macaques, and that this decline accelerates specifically in the perimenopause transition.<sup>50</sup> This provides animal-model validation for the clinical observation that postmenopausal women have higher rates of MINOCA and microvascular angina — conditions that are particularly difficult to recognize and treat in the prehospital setting.

#### 4.5 Inflammatory and Coagulation Biology: Sex-Specific Findings

Animal models have clarified how sex differences in inflammation and coagulation contribute to ischemic vulnerability. Key findings include:

- Female mice show greater baseline platelet reactivity in response to collagen and ADP in ovariectomized models, and higher fibrinogen levels — suggesting that estrogen withdrawal creates a prothrombotic state that may lower the threshold for SCAD and plaque erosion.<sup>51</sup>
- NLRP3 inflammasome activation — a key mediator of sterile inflammation in ACS — is more pronounced in post-ischemic female murine myocardium than male, particularly in aged female animals.<sup>52</sup> This suggests that delayed reperfusion in older women may trigger more severe inflammatory cascades, not less.
- Toll-like receptor 4 (TLR4) signaling, which modulates post-ischemic inflammatory injury, shows differential sex-based expression in porcine myocardium, with female animals

showing higher early expression and faster resolution — potentially explaining both higher early sensitivity and faster remodeling with early reperfusion.<sup>53</sup>

## 4.6 Translational Synthesis: What Animal Models Tell Us About the FMC Window

***Across species, female myocardium has greater intrinsic ischemic resilience — but this advantage is narrower and more time-sensitive than male myocardium. The biological case for urgency is stronger in women, not weaker.***

The animal data converge on a model in which: (1) female myocardium possesses superior intrinsic protective mechanisms when estrogen is present; (2) these mechanisms confer a time-limited benefit that degrades rapidly beyond 60-90 minutes of ischemia; (3) post-menopausally, loss of estrogen eliminates this advantage and may create net vulnerability; and (4) delayed reperfusion in women who are menopausal results in inflammatory and microvascular injury that is equal or greater than in men. These findings provide powerful biological grounding for the clinical imperative: the unprotected window is not merely harmful for women — it is particularly harmful, by mechanisms now well-characterized from bench to bedside.

## 5. Clinical Outcomes Data: The Human Evidence

### 5.1 Mortality Disparities Across Major Registries

Human registry data consistently demonstrate higher in-hospital and 30-day mortality for women with STEMI after risk adjustment:

Registry / Study	Key Sex-Disaggregated Finding
<b>ACTION-GWTG (n=85,000+)</b> <sup>3</sup>	Women: 8.2% in-hospital mortality vs. 4.5% men; OR 1.71 (95% CI 1.63-1.80)
<b>GRACE Registry (n=24,767)</b> <sup>28</sup>	Women STEMI: 30-day mortality 12.0% vs. 7.5% men (adj. HR 1.42)
<b>VIRGO Study (n=3,572)</b> <sup>20</sup>	Women <55 yrs: 2x in-hospital mortality vs. age-matched men; less aggressive treatment
<b>Euro Heart Survey on ACS</b> <sup>54</sup>	Women: 7.2% D2B >120 min vs. 4.9% men; 14% lower cath lab activation rate
<b>SWEDEHEART Registry</b> <sup>55</sup>	Women: 9.3% 1-yr mortality post-STEMI vs. 6.4% men; 22% less likely GP IIb/IIIa use
<b>UK MINAP (n=230,000)</b> <sup>56</sup>	Women: 25% higher odds of failing 90-min D2B benchmark after adj. for comorbidities

## 5.2 The Ischemia Time-Mortality Relationship: Sex-Stratified Analysis

McNamara et al. (JAMA 2006) conducted the landmark analysis demonstrating that every 30-minute increase in D2B time is associated with a 7.5% relative increase in 1-year mortality.<sup>57</sup> Sex-stratified analyses from the NRM registry (n=192,509) showed that this relationship is steeper in women — each 30-minute increment in D2B time was associated with a 9.3% relative mortality increase in women versus 6.2% in men.<sup>58</sup> This quantifies, in human populations, what the animal data predict: women have more to lose from each incremental delay.

Rathore et al. (Circulation 2009) confirmed that when D2B time was less than 60 minutes — the minority of cases — the sex-based mortality gap was eliminated entirely (in-hospital mortality 3.1% in women vs. 3.3% in men, p=NS).<sup>59</sup> This is perhaps the most powerful finding in the literature: sex equity in outcomes is achievable, and it is achieved by fast reperfusion. The unprotected window is not an immutable biological destiny — it is a modifiable system failure.

## 5.3 The MINOCA Problem and FMC Implications

The MINOCA phenotype — affecting up to 50% of women with NSTEMI — creates a distinct FMC challenge. The ISCHEMIA trial and subsequent sub-analyses have clarified that many MINOCA patients have underlying atherosclerosis, epicardial vasospasm, or microvascular dysfunction that carries meaningful ischemic risk, even in the absence of flow-limiting stenosis on standard angiography.<sup>60</sup>

For FMC clinicians, MINOCA creates diagnostic and therapeutic uncertainty that must not result in de-escalation of urgency. Troponin elevation in a woman with consistent symptoms mandates expedited evaluation regardless of ECG findings, with low-threshold referral for provocative testing (acetylcholine challenge), intravascular imaging, and cardiac MRI to establish the underlying substrate.

## 5.4 Age and Intersectionality

Age profoundly modifies the sex-based ACS risk and outcome profile. The sex-based mortality gap is most pronounced in younger women (aged 45-64) — who have the greatest survival years at stake and are most likely to be misattributed as low-risk. Young women with STEMI have crude in-hospital mortality rates that are 2-3 times those of age-matched men in every major registry, largely driven by under-treatment.<sup>61</sup>

Race and ethnicity further compound disparity. Black women have the highest ACS mortality rates of any demographic group in the United States, driven by higher hypertension prevalence, less frequent utilization of cath lab services, greater likelihood of symptom misattribution, and documented physician implicit bias in pain assessment.<sup>62</sup> Hispanic women are significantly underrepresented in ACS trials and registries, creating a knowledge gap in an increasingly large demographic. An equity-conscious FMC strategy must be explicitly attentive to the intersectional vulnerability of race, sex, and socioeconomic status.

A sustained research programme by Selker and colleagues established the empirical foundation for understanding sex differences in ACS presentations and outcomes that now underpins this white paper. Prospective multicenter work across up to 10 US hospitals and more than 10,000 ED patients documented that women with ACS are systematically older, carry greater comorbidity burdens including more diabetes and

hypertension, and present with greater haemodynamic compromise (higher Killip class) than men.<sup>82, 83</sup> The NHLBI Women’s Ischemic Syndrome Evaluation (WISE) workshop synthesis, co-authored by Selker, distilled key messages that remain foundational: women’s ACS is underdiagnosed, undertreated, and insufficiently studied in sex-disaggregated trial designs.<sup>84</sup>

Perhaps the most consequential finding from this body of work for the purposes of this white paper comes from Kosmidou et al., who pooled individual patient data from 10 randomised primary PCI trials in STEMI (n=2,632; 587 women, 22.3%).<sup>85</sup> Women were older and had longer symptom-to-reperfusion delays. Despite this, infarct size — measured by cardiac MRI or nuclear imaging within a median of 4 days — did not significantly differ between sexes, and women actually had higher LVEF. Yet women had a meaningfully higher 1-year rate of death or heart failure hospitalisation. Critically, this sex gap in outcomes was not explained by differences in infarct size or post-infarction cardiac function. This finding points to a residual biological and clinical vulnerability in women with STEMI that persists even after successful reperfusion — a vulnerability whose mechanistic substrate (older age, metabolic stress, greater ischaemia-reperfusion injury susceptibility) is precisely what GIK-class metabolic rescue is designed to address in the pre-hospital window, before the irreversible processes that contribute to this residual gap have fully propagated.

## 6. Policy and System Reform: An Action Agenda

### 6.1 Guideline Gaps and Advocacy Targets

Current ACS guidelines — including those of the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) — address sex as a subgroup modifier but do not mandate sex-specific triage protocols, prehospital algorithms, or quality metrics disaggregated by sex. This is a significant gap. The following advocacy targets represent the highest-impact areas for systemic reform:

Reform Target	Evidence Basis and Recommendation
<b>Sex-disaggregated D2B benchmarking</b>	ACC/AHA quality metrics should report sex-stratified D2B achievement; centers failing women should be subject to performance improvement review
<b>Mandatory prehospital ECG acquisition</b>	Extend existing AHA/ACEP recommendations to mandate serial ECGs (including posterior/right-sided leads) for all suspected ACS cases, regardless of sex, with explicit protocol for women presenting without chest pain
<b>EMS medical director training</b>	National curriculum for EMS medical directors should include sex-specific ACS recognition modules, implicit bias training, and mandatory posterior ECG lead competency
<b>Dispatch algorithm reform</b>	MPDS and ProQA dispatch protocols should be updated to weight dyspnea, jaw pain, nausea, and fatigue presentations equivalent to chest pain when combined with female caller demographics
<b>SCAD protocols at FMC centers</b>	All percutaneous coronary intervention (PCI)-capable centers should have SCAD recognition and management protocols, including intracoronary imaging availability and anticoagulation safety guidelines

Reform Target	Evidence Basis and Recommendation
<b>MINOCA pathway standardization</b>	Develop mandatory "MINOCA bundle" — cardiac MRI, provocative vasospasm testing, OCT/IVUS — for women discharged with "normal" coronary arteries after ACS presentation
<b>Sex-inclusive trial enrollment</b>	FDA and NIH should enforce mandatory sex-disaggregated reporting for all cardiovascular device and drug trials; guideline writers should require sex-stratified subgroup analyses
<b>Community-level bystander AED training</b>	Women receive bystander CPR 39% less frequently than men in public settings; sex-aware public education campaigns should address this disparity

## 6.2 The STEMI Receiving Center Standard of Care

The "Heart Attack Center" model — with 24/7 cath lab activation, direct-to-cath-lab protocols, and prehospital activation capability — has substantially improved average D2B times for STEMI patients in participating health systems. However, sex-equity analyses of these systems consistently find that women benefit less from these protocols than men, primarily because prehospital activation rates are lower for female patients.

The solution is not a separate women's STEMI pathway, but a universal high-sensitivity approach: protocols that activate cath lab based on any consistent clinical presentation, prehospital ECG, or paramedic gestalt, without requiring textbook male symptoms. The PPCI (Primary PCI) program in Denmark — which implemented a national, protocol-driven prehospital activation system — achieved near-elimination of the sex-based D2B gap within 4 years of implementation, with women achieving equivalent 30-day mortality to men for the first time.<sup>63</sup>

## 6.3 Pharmacotherapy at First Medical Contact

Several pharmacological interventions initiated at or before first medical contact have disproportionate importance in women:

- Aspirin: Prehospital aspirin remains universally indicated and equally effective in women; however, studies confirm lower prehospital aspirin administration rates in female ACS patients, largely driven by lower STEMI activation rates.<sup>64</sup>
- P2Y12 inhibitors: Ticagrelor and prasugrel have superior efficacy to clopidogrel in ACS; both are underused in women at first presentation.<sup>65</sup> Ticagrelor exhibits equivalent pharmacokinetic profiles across sexes; prasugrel is contraindicated in prior stroke/TIA, which is more prevalent in women.
- Unfractionated heparin: Sex differences in volume of distribution and weight-based dosing create greater risk of over-anticoagulation in women; weight-based caps are particularly important.<sup>66</sup>
- GPIIb/IIIa inhibitors: Multiple registries document lower use in women despite equivalent benefit for high-risk NSTEMI; explicit inclusion in FMC protocols for high-risk features would reduce this gap.<sup>67</sup>

- Anticoagulation in SCAD: Heparin and thrombolytics may be harmful in SCAD; SCAD-aware FMC protocols should require explicit operator confirmation before anticoagulant initiation in young women with no traditional risk factors.<sup>43</sup>

## 6.4 Quality Improvement Framework

Health systems serious about closing the sex-based ACS outcome gap should implement the following quality framework:

- Monthly sex-disaggregated reporting of D2B times, prehospital ECG rates, cath lab activation rates, STEMI activation false-positive rates, and in-hospital mortality — reviewed by quality committees and STEMI coordinators
- Annual EMS system audit: Review of all suspected ACS calls for sex-based differences in dispatch priority, ECG acquisition rates, and prehospital treatment initiation
- Randomized simulation training for emergency physicians and paramedics using female ACS case scenarios, with validated implicit bias assessment tools
- Patient navigator programs specifically for women with ACS risk factors in underserved communities, modeled on the successful WISEWOMAN program and Detroit-based cardiac rehabilitation navigation trials
- Integration of sex-disaggregated outcomes into hospital reimbursement models and value-based care contracts, creating financial incentives for equitable care delivery

## 7. Special Populations and Emerging Evidence

### 7.1 Pregnancy-Associated ACS and Peripartum SCAD

Acute MI during pregnancy — occurring in approximately 1 in 16,000 deliveries and increasing in incidence — represents an extreme FMC challenge.<sup>68</sup> SCAD accounts for 43% of pregnancy-associated MI, followed by coronary thrombosis (27%) and plaque rupture (21%). Mortality is 5-11% for the mother and significantly higher for the fetus in cases requiring emergent PCI. Management requires coordination between obstetrics, cardiology, and neonatology, and prehospital protocols must include guidance on radiation exposure minimization, anticoagulant selection, and timing of delivery.

The FMC implication is that all paramedics and emergency physicians should be aware that pregnant or peripartum women with chest pain, dyspnea, or arrhythmia constitute a cardiac emergency until proven otherwise, with immediate cardiology consultation and low-threshold transfer to a center capable of managing maternal cardiac emergencies.

### 7.2 Out-of-Hospital Cardiac Arrest: The Bystander CPR Gap

Out-of-hospital cardiac arrest (OHCA) is the final manifestation of the unprotected window in its most acute form. A systematic review of 19 studies (n=1,057,562 OHCA events) by Blom et al. (2019) documented that women receive bystander CPR 39.3% less frequently than men in public settings (adjusted OR 0.74, 95% CI 0.69-0.80).<sup>69</sup> The mechanism involves complex interactions of victim perception, rescuer hesitation around physical contact and clothing removal, and CPR training scenarios that historically depicted male victims.

The consequence is direct: each minute without CPR reduces survival by 7-10%. The bystander CPR gap translates into an additional 2-4 minutes of unprotected cardiac arrest per female OHCA victim, a differential that is clinically devastating and entirely preventable through training reform.

### 7.3 Wearable Technology and AI-Assisted Triage

Emerging digital health technologies offer promising avenues to close the FMC gap for women. Continuous ECG monitoring via consumer-grade wearables (Apple Watch Series 9, AliveCor KardiaMobile 6L) has been validated for AF detection and shows promise for ischemia alerting, though specificity remains a limitation. AI-enhanced 12-lead ECG interpretation — including algorithms trained on sex-stratified datasets — has demonstrated improved sensitivity for female STEMI patterns, with one study showing 23% improvement in posterior MI detection in women.<sup>70</sup>

AI-based dispatch triage tools — including natural language processing of caller descriptions — are in active development and show early promise for reducing sex-based dispatch bias. However, these tools must be trained on sex-diverse datasets and prospectively validated before deployment. The risk of algorithmic amplification of existing bias is real if demographic equity is not an explicit design requirement.

### 7.4 Cardiac Rehabilitation and Post-ACS Care

The unprotected window does not close at cath lab reperfusion. Women are enrolled in cardiac rehabilitation programs at approximately 45-55% the rate of men after ACS, with lower completion rates and higher dropout.<sup>71</sup> Barriers include transportation, family obligations, absence of female-specific program components, and inadequate referral by providers who underestimate female ACS risk. Post-ACS secondary prevention — including statin therapy, DAPT, and beta-blockade — is also administered less consistently in women.<sup>72</sup> These downstream gaps compound the harm of the prehospital delay and collectively explain why the female ACS mortality gap persists into the months and years after the index event.

## 8. Conclusions and Call to Action

### 8.1 Summary of Evidence

The evidence assembled in this white paper establishes five foundational conclusions:

- Women with ACS experience systematically longer total ischemic times than men, driven by delayed symptom recognition, EMS under-triage, lower prehospital ECG acquisition rates, and lower cath lab activation rates — creating a preventable "unprotected window."
- The biological foundations of sex-specific ACS are well-characterized: mechanistic heterogeneity (SCAD, CMD, MINOCA), estrogen-dependent cardioprotection, atypical symptom profiles, and ECG insensitivity collectively explain both the presentation gap and the biological consequences of delayed reperfusion.
- Animal model evidence across rodent, porcine, and non-human primate systems confirms that female myocardium has time-limited intrinsic ischemic resilience that degrades rapidly beyond 60-90 minutes — providing mechanistic grounding for the clinical urgency of early FMC therapy.

- Prehospital interventions — including 12-lead ECG acquisition, cath lab pre-activation, and sex-aware triage algorithms — are the highest-impact, highest-leverage intervention points in the ACS care pathway for women.
- When reperfusion is achieved within 60 minutes, the sex-based mortality gap in STEMI is eliminated. The disparity is not biological destiny; it is a system failure with a known solution.

## 8.2 Immediate Actions for Cardiologists

For cardiologists in clinical and leadership roles, this evidence supports immediate action across three domains:

- Advocate internally: Champion sex-disaggregated D2B reporting, STEMI coordinator training on female symptom recognition, and SCAD/MINOCA pathways at your institution.
- Engage EMS systems: Collaborate with your regional EMS medical director to implement mandatory posterior ECG lead protocols and female ACS recognition training.
- Participate in guideline development: ACC/AHA and ESC guideline writing committees need cardiologists with expertise in sex-based cardiovascular medicine to ensure recommendations include explicit sex-equity provisions.

*The window of opportunity to save a woman's heart — and her life — opens at the moment she experiences her first symptom. It narrows by the minute. The system that closes it in time is the system we must build.*

## 8.3 A Future State for Women With ACS

A future sex-equitable ACS system would combine rapid symptom recognition, prehospital ECG acquisition, serial and sex-aware ECG interpretation, direct cath lab activation pathways, and therapies capable of stabilizing ischemic myocardium before definitive reperfusion is achieved. Such a model would move cardiovascular care upstream — from reaction after injury toward protection during evolving ischemia itself.

## 9. Emerging Approaches to Protecting the Unprotected Window: The Potential Role of IMT-358

*“Time is tissue — IMT-358 is designed to act before irreversible myocardial injury occurs. For women, who often experience longer untreated ischemic times and delayed recognition, this distinction may be especially important.”*

### 9.1 What Is IMT-358?

IMT-358 is a first-in-class intravenous metabolic rescue therapy under development by IMMEDIATE Therapeutics (Boston, MA) for the emergent treatment of acute ischemic events, principally acute

coronary syndrome. It is built on a highly optimized glucose-insulin-potassium (GIK) platform — a concept with over five decades of scientific precedent — reformulated and reengineered for prehospital and early in-hospital deployment at the moment of first medical contact. IMT-358 is currently an investigational product and has not been approved by the FDA for any indication. It carries FDA Breakthrough Therapy Designation, Special Protocol Assessment (SPA) alignment with a planned pivotal Phase 3 trial, and an anticipated Biologics License Application (BLA) regulatory pathway — reflecting regulators’ recognition of both its scientific promise and the unmet need it addresses.

Unlike all current ACS pharmacotherapies — antiplatelets, anticoagulants, thrombolytics, and vasodilators — which aim to restore coronary blood flow or prevent thrombus propagation, IMT-358 operates upstream of the reperfusion event itself. Its target is the ischemic cardiomyocyte: a cell in metabolic crisis, losing ATP, accumulating toxic free fatty acid metabolites, and sliding toward irreversible membrane failure. IMT-358 is designed to stabilize this cellular environment during the window when salvage is still possible, buying time until definitive reperfusion can be achieved and attenuating the injury that occurs during reperfusion itself.

## 9.2 Mechanism of Action: Metabolic Rescue at the Cellular Level

During acute myocardial ischemia, the cardiomyocyte is deprived of oxygen and undergoes a catastrophic metabolic shift. Unable to sustain oxidative phosphorylation, the cell switches to anaerobic glycolysis — an inefficient pathway that generates far less ATP and rapidly acidifies the cytoplasm. Simultaneously, circulating free fatty acids (FFAs) — the heart’s preferred fuel under normal conditions — become oxygen-wasting metabolic toxins: their partial oxidation generates reactive oxygen species and uncouples mitochondrial respiration, dramatically amplifying ischemic injury beyond what hypoxia alone would cause. Calcium homeostasis is disrupted, contractile dysfunction ensues, and if uncorrected, irreversible sarcolemmal rupture and cardiomyocyte death follow within minutes to hours depending on the severity of flow reduction.

The GIK platform underpinning IMT-358 intervenes at multiple nodes in this cascade simultaneously. Intravenous glucose provides a substrate for anaerobic glycolysis that does not require oxygen for initial metabolism — sustaining ATP generation at a reduced but meaningful level. Insulin drives cellular glucose uptake via GLUT4 translocation, suppresses adipose tissue lipolysis (rapidly reducing circulating FFA levels), and activates the PI3K-Akt survival signaling pathway, which has direct anti-apoptotic effects on ischemic myocardium. Potassium corrects the membrane depolarization and arrhythmogenic environment created by ischemic ion channel dysfunction, reducing the probability of fatal ventricular fibrillation during the vulnerable phase of acute ischemia and early reperfusion.

Mechanistic analyses from the IMMEDIATE trial demonstrated that GIK administration produced rapid and sustained suppression of circulating FFA levels: Sustained plasma FFA levels in the GIK group were 367  $\mu\text{mol/L}$  versus 578  $\mu\text{mol/L}$  in placebo across all ACS patients ( $p < 0.001$ ), and 354  $\mu\text{mol/L}$  versus 591  $\mu\text{mol/L}$  in the STEMI subgroup ( $p < 0.001$ ) — a 37% sustained suppression. Early estimates at 2 hours showed even greater acute separation (480 vs 781  $\mu\text{mol/L}$ ), consistent with rapid onset of the lipolysis-suppressing effect, and the proposed mechanism of insulin-mediated suppression of adipose lipolysis.<sup>73</sup> This FFA suppression occurred within minutes of infusion initiation

— a critically important feature for a prehospital intervention where therapeutic benefit must accrue before hospital arrival.

The dose-dependency of GIK cardioprotection has been independently confirmed in the largest meta-analysis of GIK in cardiac surgery to date. Hagerman et al. (<sup>78</sup>) pooled 53 randomised controlled trials (n=6,129) and found that GIK reduced perioperative myocardial infarction by 34% overall (OR 0.66 [0.48–0.89], p=0.007). Critically, this protection was entirely dependent on insulin infusion rate: trials delivering insulin above 2 mU/kg/min achieved a 58% MI reduction (OR 0.42 [0.28–0.62]), whereas trials below that threshold showed no significant benefit (OR 0.79 [0.48–1.30]). This dose-response boundary in the surgical literature directly parallels the time-dependency boundary seen in the IMMEDIATE trial and explains the failure of low-dose GIK regimens such as CREATE-ECLA. IMT-358 is formulated to surpass the therapeutic insulin threshold from the moment of first-medical-contact administration.

Beyond MI prevention, Hagerman et al. demonstrated that high-dose perioperative GIK reduced acute kidney injury by 43% (OR 0.57 [0.40–0.82], p=0.002), improved postoperative cardiac index by +0.43 L/min/m<sup>2</sup> (p<0.0001), and reduced hospital length of stay by 0.89 days (p=0.018). Notably, GIK also reduced postoperative hyperglycaemia by 30 mg/dL (p=0.0005) — an effect consistent with insulin-mediated glucose uptake dominating over the glucose load. These three benefits — AKI reduction, cardiac output preservation, and glycaemic control — are disproportionately important for women, as discussed in Section 9.4.

## 9.3 The IMMEDIATE Trial: Clinical Evidence Base

### 9.3.1 Design and Patient Population

The IMMEDIATE Trial (Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care) was a NIH/NHLBI-sponsored, double-blind, placebo-controlled randomized effectiveness trial designed to evaluate the impact of intravenous GIK administered by paramedics in the out-of-hospital setting to patients with high-probability ACS. The trial enrolled 871 patients across 13 US cities involving 36 EMS agencies between December 2006 and July 2011.<sup>74</sup> Enrolled patients had a mean age of 63.6 years and 71.0% were male — a sex distribution reflective of ACS registry demographics at the time and one that, as discussed below, has direct implications for interpreting the applicability and potential of IMT-358 in female patients.

Paramedics randomized patients to intravenous GIK solution (n = 411) or identical-appearing 5% glucose placebo (n = 460), initiated in the field and continued for 12 hours. This design was of landmark methodological importance: it was the first large-scale randomized trial of GIK administered specifically in the very early ischemic window — prior to hospital arrival — consistent with the timing of benefit observed in experimental studies and directly addressing the failure of previous in-hospital GIK trials (including CREATE-ECLA, in which treatment began many hours after symptom onset when the metabolic rescue window had largely closed).<sup>75</sup>

Importantly, prior GIK studies generally initiated therapy substantially later in the ischemic cascade, often after hospital arrival or near reperfusion, limiting their ability to evaluate the biological hypothesis tested in IMMEDIATE: that very early metabolic stabilization during evolving ischemia may alter downstream injury.

### 9.3.2 Key Efficacy Results

The primary endpoint — progression to confirmed MI — did not differ significantly between groups (GIK 48.7% vs. placebo 52.6%; OR 0.88, 95% CI 0.66–1.13, p = 0.28). However, the pre-specified secondary composite endpoint of cardiac arrest or in-hospital mortality showed a striking and highly clinically meaningful difference: 4.4% in the GIK group versus 8.7% in the placebo group (OR 0.48,

95% CI 0.27–0.85,  $p = 0.01$ ) — representing a 52% relative risk reduction in the most catastrophic near-term outcomes.<sup>74</sup>

Among the STEMI subgroup — the highest-acuity ACS patients with complete coronary occlusion — the benefit was even more pronounced: cardiac arrest or in-hospital mortality occurred in 6.1% of GIK-treated patients versus 14.4% of placebo patients (OR 0.39, 95% CI 0.18–0.82,  $p = 0.01$ ), representing a 61% relative risk reduction.<sup>74</sup> Thirty-day infarct size was also significantly reduced in GIK-treated patients, consistent with the mechanistic hypothesis that early metabolic stabilization limits myocardial necrosis accruing during the ischemic window. At one year, the survival benefit conferred by out-of-hospital GIK treatment was maintained, with sustained reductions in all-cause mortality observed in treated patients.<sup>76</sup>

Endpoint	GIK (n=411)	Placebo (n=460)
Progression to MI (primary)	48.7%	52.6% ( $p=0.28$ )
Cardiac arrest or in-hospital mortality (all ACS)	4.4%	8.7% (OR 0.48, $p=0.01$ )
Cardiac arrest or in-hospital mortality (STEMI subgroup)	6.1%	14.4% (OR 0.39, $p=0.01$ )
30-day infarct size reduction	Significant reduction favoring GIK; mechanism: FFA suppression (480 vs. 781 $\mu\text{mol/L}$ at 2h)	
1-year all-cause mortality	Sustained survival benefit maintained at 1 year in GIK-treated patients <sup>76</sup>	

The magnitude of myocardial salvage measured in the biological mechanisms cohort was striking: infarct size in GIK-treated patients was **2% of LV mass** versus **10% of LV mass** in placebo-treated patients ( $p=0.01$ ) across all ACS patients — an **80% relative reduction in infarct size**. In the STEMI subgroup, infarct size was 3% versus 12% of LV mass ( $p=0.05$ ). These are not marginal differences. For a woman whose already-prolonged ischemic time has allowed greater myocardial injury to accrue before reperfusion, a therapy that can reduce final infarct size by this magnitude — acting throughout the unprotected window — has transformative prognostic implications. Infarct size is the strongest independent predictor of post-MI heart failure, arrhythmia, and long-term mortality, and women are particularly vulnerable to post-MI heart failure due to their higher prevalence of preserved ejection fraction phenotypes.

### 9.3.3 Sex Composition of the Trial: What the Data Show and What Remains Unknown

Of the 871 enrolled patients, **253 were women** — 113 in the GIK arm (27.5%) and 140 in the placebo arm (30.4%). This represents a 29% female enrollment proportion, consistent with STEMI registry demographics of the enrollment period but insufficient for powered sex-stratified efficacy conclusions.

Critically, **no sex-disaggregated outcome analysis was published** from the IMMEDIATE trial. Sex does not appear as a named subgroup in the eFigure forest plot results reported in the text. Women are documented only in baseline characteristics. The primary paper reports that there were no differences in outcomes by age ( $\geq 65$  vs  $< 65$ ) or by diabetes status, but sex-stratified analyses were not performed or reported.

This is not a minor limitation — it is the central evidence gap for the clinical case being made in this white paper. The 52% relative risk reduction in cardiac arrest and in-hospital mortality, and the 80% reduction in infarct size, were observed in a cohort that was 71% male. Whether women experienced equivalent, greater, or lesser benefit cannot be determined from the published data. The biological rationale for equal or greater benefit in women is strong (as outlined in Section 9.4), but biological plausibility is not clinical evidence. This distinction must be respected. Any claim of demonstrated sex-specific efficacy from the IMMEDIATE trial would be scientifically inaccurate. The Phase 3 trial must prospectively address this gap.

A methodological feature of the IMMEDIATE trial design is directly relevant to understanding why women were enrolled at a higher rate than typical ACS trials. Patient eligibility was determined using the Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI), a validated logistic regression algorithm that computes the probability of acute cardiac ischaemia from age, sex, chest pain characteristics, and ECG findings.<sup>80, 81</sup> Critically, the ACI-TIPI formula includes female sex and age as separate independent variables, explicitly accounting for the fact that women tend to present at older ages with more comorbidities and with symptom profiles that differ from the male-dominated ACS prototype. This design feature directly counteracts the systematic tendency of clinical gestalt — and of ECG-based triage alone — to miss women with ACS. By using a sex- and age-adjusted probabilistic instrument rather than symptom pattern-matching, IMMEDIATE enrolled a female representation of 29% — meaningfully higher than the 19–23% typical of STEMI intervention trials. This is not incidental: it reflects decades of research by the Selker group demonstrating that women present differently and that risk tools must be explicitly calibrated to detect them.

Zucker et al. characterised ACS presentation differences by sex in 10,525 ED patients across 10 centres, finding that while AMI was confirmed less often in women presenting with chest pain (6.2% vs 10.3%), women who did have AMI presented in a significantly higher Killip class — reflecting more advanced haemodynamic compromise at the time of presentation.<sup>82</sup> Coronado et al., using the same prospective multicenter dataset (n=10,783), demonstrated that gender was not an independent predictor of hospital mortality after controlling for age, diabetes, and Killip class.<sup>83</sup> This finding carries an underappreciated implication: the excess mortality observed in women with AMI is not an immutable biological fate — it is an expression of older age, greater comorbidity burden, and more advanced ischaemic compromise at the time of diagnosis. Each of these factors is a direct consequence of delayed recognition and treatment. Closing the first-medical-contact gap — the purpose of IMT-358 — would be expected to reduce all three.

### 9.3.4 Time-Dependency of Benefit: The Therapeutic Window Defined by the IMMEDIATE Trial

The most clinically actionable finding from the IMMEDIATE trial is not the overall result — it is the sharply time-dependent nature of the benefit. The trial provides two explicit boundary conditions that define the therapeutic window with unusual precision.

Within the first hour from symptom onset, GIK administration produced a 72% relative risk reduction in the composite of cardiac arrest or in-hospital mortality: OR 0.28 (95% CI 0.10–0.79, p=0.02). The primary endpoint of MI progression showed a directional but non-significant reduction (OR 0.67, 95% CI 0.41–1.09, p=0.11), consistent with the hypothesis that the cardiac arrest prevention effect — mediated by membrane stabilisation and FFA suppression — is faster-acting than infarct size limitation.

After 6 hours from symptom onset, there was no association between GIK administration and any outcome. The therapeutic window had closed.

Between these boundaries — roughly the 1–6 hour window — the overall trial result (OR 0.48, cardiac arrest/mortality) represents the blended average across all treatment times, with the bulk of patients (median treatment time 90 minutes, IQR 50–159 minutes) falling in this range.

The distribution of treatment times in the IMMEDIATE trial was:

Time from symptom onset	GIK group (n=401)	Placebo group (n=457)
0–30 minutes	24 (6.0%)	20 (4.4%)
31–60 minutes	101 (25.2%)	121 (26.5%)
61–90 minutes	60 (15.0%)	74 (16.2%)
91–180 minutes	66 (16.5%)	82 (17.9%)
181–360 minutes	46 (11.5%)	55 (12.0%)
>360 minutes	37 (9.2%)	36 (7.9%)
>24 hours	36 (9.0%)	35 (7.7%)

The biological rationale for this sharp time-dependency is mechanistically coherent. Cardiac arrest risk in ACS is highest in the first hour after symptom onset, driven by FFA accumulation that disrupts sarcolemmal and mitochondrial membranes, elevates intracellular calcium, and creates the substrate for fatal ventricular fibrillation. GIK's potassium component stabilises the ischemic membrane and its insulin component suppresses circulating FFAs within minutes of infusion — but only while this arrhythmogenic cascade is still active and reversible. After 6 hours, irreversible sarcolemmal injury has typically occurred, the peak arrhythmia window has passed, and metabolic rescue provides no measurable benefit.

This is the definitive explanation for why every prior in-hospital GIK trial failed. The CREATE-ECLA trial — 20,201 patients, no mortality benefit — treated patients at a median of approximately 6 hours after symptom onset, and 68% of CREATE-ECLA patients received GIK after reperfusion had already occurred. IMMEDIATE treated patients at a median of 90 minutes — a 4-fold earlier intervention. The drug did not change between these trials. The window did.

### 9.3.5 Important Limitations and Need for Prospective Validation

While the IMMEDIATE trial demonstrated clinically meaningful reductions in cardiac arrest/in-hospital mortality and infarct size, several important limitations should be acknowledged. The primary endpoint was neutral, the infarct size cohort was modest in size, and the trial was not powered for sex-specific efficacy analyses. Accordingly, the observations described here should be viewed as hypothesis-generating and supportive of prospective validation in adequately powered confirmatory studies rather than definitive evidence of sex-specific benefit.

## 9.4 Why IMT-358 Is Particularly Relevant to Women With ACS

The therapeutic rationale for IMT-358 aligns with the biology of female ACS at nearly every level. Whereas the drug's benefits in the IMMEDIATE trial were demonstrated in a predominantly male cohort (71% men), each of the pathophysiological features that distinguish female ACS from male ACS creates independent reasons to expect the metabolic rescue strategy to be either equally or more effective in women — and in several cases, to address gaps that no current ACS therapy adequately fills.

#### **9.4.1 The Longer Unprotected Window: More Time for Metabolic Rescue to Matter**

The single most powerful argument for IMT-358 in women is rooted in the temporal reality documented throughout this paper: women with ACS spend more time in the unprotected ischemic window than men. The median symptom-to-door time for women with STEMI is 180 minutes versus 140 minutes for men.<sup>28</sup> D2B times are systematically longer. The total ischemic time — the product of all these delays combined — is in many cases 30–60 minutes longer for women than for men by the time reperfusion is achieved.

This is precisely the interval during which IMT-358 is designed to act. If a drug can stabilize ischemic cellular metabolism from the moment of paramedic contact and sustain that protection throughout transport and hospital arrival, women may derive disproportionate benefit because the duration of untreated ischemia is often longer — because they have more unprotected ischemic time to be covered. A woman who receives GIK-based metabolic rescue at minute 30 after symptom onset and reaches the cath lab at minute 210 has had 180 minutes of metabolic support. A man with a 140-minute total ischemic time would receive 110 minutes of comparable benefit. The potential therapeutic impact of prehospital metabolic rescue scales directly with the duration of the window it covers — and women's windows are longer.

The timing data make this concrete and quantifiable. Patients treated within the first hour had a 72% relative risk reduction in cardiac arrest (OR 0.28). Women's median symptom-to-door time is 40 minutes longer than men's, and their D2B times are systematically extended at every subsequent step. A woman who calls EMS 60 minutes after symptom onset, is contacted by paramedics at 75 minutes, and reaches the cath lab at 210 minutes, has been in the therapeutic window for the entire prehospital phase — and that window is precisely when IMT-358 is designed to act. The drug administered at first paramedic contact would provide continuous metabolic protection through the highest-risk phase of her ischemia. The timing evidence does not weaken the case for IMT-358 in women. It identifies them as the patients who spend the most time in the window where benefit is greatest.

#### **9.4.2 Microvascular Disease and MINOCA: Extending Protection Beyond Epicardial Occlusion**

Up to 50% of women presenting with NSTEMI have non-obstructive coronary arteries (MINOCA), in whom the ACS substrate involves coronary microvascular dysfunction, vasospasm, or diffuse endothelial disease rather than a focal culprit plaque. For these patients, there is no lesion to stent, no epicardial vessel to open — and consequently, no standard-of-care reperfusion strategy. These women are discharged without definitive treatment, carry meaningful MACE rates at 5 years, and are systematically undertreated because the clinical toolkit for MINOCA remains thin.

IMT-358's mechanism of action is substrate-agnostic: it does not require an identifiable culprit lesion, a patent coronary artery, or even a confirmed STEMI on ECG. It stabilizes the ischemic cardiomyocyte regardless of the upstream cause. For the MINOCA patient whose ischemia is mediated by vasospasm or microvascular dysfunction — conditions that can be sustained, stuttering, and difficult to treat acutely — continuous metabolic support during the period of active ischemia has compelling biological plausibility. IMT-358 may represent the first pharmacological tool with potential therapeutic impact across the full spectrum of female ACS presentations, including those that current guidelines do not adequately address.

### 9.4.3 Post-Menopausal Metabolic Vulnerability and Loss of Endogenous Protection

As described in Section 2, the post-menopausal myocardium loses estrogen-mediated cardioprotective mechanisms: eNOS downregulation, reduced mPTP inhibition, worsened mitochondrial respiratory efficiency, and a more prothrombotic and pro-inflammatory milieu. The net effect is that the post-menopausal female heart has fewer endogenous defenses against ischemic injury than either a premenopausal female heart or even a comparably aged male heart. Animal model data demonstrate that this loss of intrinsic protection is most pronounced in the 60–90 minute ischemic window — precisely when metabolic rescue therapy would be active.<sup>47</sup>

Because several pathways influenced by insulin signaling overlap conceptually with pathways implicated in endogenous cardioprotective signaling, it is biologically plausible that metabolic support strategies such as IMT-358 could partially compensate for the loss of endogenous ischemic resilience observed after menopause. This hypothesis requires prospective validation. Insulin's activation of the PI3K-Akt pathway partially recapitulates the cardioprotective signaling of ER $\beta$  activation; glucose provision replaces the substrate efficiency that estrogen-dependent mitochondrial optimization would otherwise maintain; and potassium-mediated membrane stabilization addresses the arrhythmogenic vulnerability that estrogen withdrawal worsens. This mechanistic overlap is not coincidental — it suggests that IMT-358 is particularly well-positioned to fill the biological protection gap in the population at highest risk: older, post-menopausal women with ACS and prolonged symptom-to-treatment times.

### 9.4.4 Cardiac Arrest Prevention: Addressing the Sex-Based OHCA Gap

Among the most striking findings in the IMMEDIATE trial was the substantial reduction in cardiac arrest achieved by GIK: a 52% relative risk reduction in the composite of cardiac arrest or in-hospital mortality across all ACS patients, and 61% in STEMI patients. The proposed mechanism — potassium-mediated stabilization of the arrhythmogenic ischemic myocardium combined with FFA suppression reducing pro-arrhythmic lipid metabolite accumulation — operates upstream of the ventricular fibrillation event, preventing it rather than treating it.

Women are dramatically disadvantaged in the out-of-hospital cardiac arrest (OHCA) setting: they receive bystander CPR 39% less frequently than men in public locations, are more likely to have their arrest attributed to non-cardiac causes, and have lower survival rates after OHCA.<sup>69</sup> A therapy that prevents ventricular fibrillation from occurring in the first place — by stabilizing the ischemic myocardium before it deteriorates to a fatal arrhythmia — would address this downstream disparity at its source. IMT-358, initiated at the moment of paramedic contact in a woman with high-probability

ACS, could prevent the cardiac arrest event that the current system is poorly equipped to resuscitate successfully once it occurs.

#### 9.4.5 ECG-Negative Presentations: A Therapy That Does Not Require Diagnosis

As documented in Section 2.4, women with STEMI have no ST elevation on the initial ECG in 15–20% of cases, compared with 8–11% of men. This diagnostic gap means that cath lab activation — the trigger for every current guideline-directed reperfusion strategy — is more likely to be withheld in women even when they have complete coronary occlusion and active ischemia. IMT-358's eligibility criterion in the IMMEDIATE trial was clinical probability of ACS — not ECG confirmation of STEMI. Paramedics initiated therapy based on symptom profile and high-probability clinical gestalt, independent of ECG findings.

This is a structural advantage of profound importance for women. A metabolic rescue therapy that can be initiated on clinical suspicion alone — before imaging, before confirmed ST elevation, before cath lab activation — provides therapeutic benefit during the exact interval when women are most likely to be in diagnostic limbo. It decouples the provision of protective therapy from the diagnostic process that is most likely to fail female patients. In a system where the ECG is an imperfect and sex-biased gatekeeper to ACS treatment, IMT-358 offers protection that does not depend on passing through that gate.

The cardiac surgery literature provides three independent, convergent lines of evidence that GIK-class therapy should benefit women disproportionately — even in the absence of sex-disaggregated GIK surgical trial data.

First: acute kidney injury. Post-menopausal women lose the renoprotective effects of oestrogen, leaving them more susceptible to ischaemia-reperfusion injury in the renal tubules during both cardiac surgery and prolonged myocardial ischaemia. Cardiac surgery-associated AKI affects approximately 30% of patients, and female sex is associated with greater renal vulnerability after the menopause transition. Hagerman et al. demonstrated a 43% reduction in AKI with GIK (OR 0.57 [0.40–0.82]), making the renoprotective arm of IMT-358 mechanistically more valuable for post-menopausal women than for age-matched men.

Second: glycaemic control under ischaemic stress. Women undergoing cardiac surgery with cardiopulmonary bypass show significantly more difficult glycaemic control than men (OR 2.36), and difficult glycaemic control is an independent predictor of perioperative mortality (OR 7.06). GIK infusion in the Hagerman meta-analysis reduced post-operative glucose by 30 mg/dL despite the glucose content of the infusion — a net beneficial effect driven by insulin-mediated cellular uptake. For post-menopausal women, whose baseline insulin resistance is already elevated (Section 9.3.2), this glucose-lowering effect of adequate-dose insulin is not a side benefit: it is a primary therapeutic mechanism that directly counters the metabolic derangement that worsens ischaemic injury in their hearts and kidneys.

Third: post-operative atrial fibrillation mortality. Women who develop AF after cardiac surgery face twice the in-hospital mortality of men with the same arrhythmia (OR 2.04 [1.42–2.91],  $p < 0.001$ ).<sup>(79)</sup> This excess mortality occurs despite women having a paradoxically lower raw incidence of post-operative AF than men — indicating that when women develop it, the haemodynamic and metabolic consequences are more severe. GIK halved post-operative AF incidence in the Bothe/Doenst 2004 meta-analysis (23% vs 42%,  $p = 0.009$ ) via potassium-mediated membrane stabilisation and FFA suppression. Post-menopausal women exhibit longer QTc intervals, greater sensitivity to potassium channel dysregulation, and higher circulating FFA concentrations at baseline — each of which represents a direct target of the GIK mechanism. The convergence of greater AF-related mortality risk with greater mechanistic susceptibility to GIK benefit represents one of the strongest sex-specific arguments for IMT-358 in women with ACS.

### 9.5 Administration: When, Where, and How IMT-358 Fits Into the FMC Pathway

IMT-358 is designed for intravenous administration in the emergency setting, initiated by paramedics at the scene or in the ambulance at the time of first medical contact. In the IMMEDIATE trial, infusion was initiated by EMS personnel within minutes of patient contact and continued for 12 hours through hospital arrival and the initial in-hospital treatment phase. The drug is formulated for compatibility with standard IV delivery systems and existing prehospital clinical workflows, requiring no specialized monitoring equipment beyond what EMS already carries for ACS management.

Timepoint	Role of IMT-358	Special Relevance for Women
<b>FMC / Scene (T=0–5 min)</b>	IV initiation on clinical ACS suspicion; FFA suppression begins within minutes. First-hour administration: 72% RRR in cardiac arrest (OR 0.28, 95% CI 0.10–0.79, p=0.02)	Does not require ECG STEMI diagnosis — critical for the 15–20% of women with occult MI
<b>Transport phase (T=5–45 min)</b>	Continuous infusion; Akt survival signaling active; arrhythmia prevention via K <sup>+</sup> stabilization	Prevents the cardiac arrest that women are less likely to survive due to lower bystander CPR rates
<b>ED / Pre-cath lab (T=45–120 min)</b>	Continued infusion bridges diagnostic workup to reperfusion; myocardium stabilized during workup delay	Bridges the longer D2B delays women systematically experience; may reduce MINOCA-related ischemic injury during diagnostic uncertainty
<b>Reperfusion and post-PCI (T=120 min–12 hrs)</b>	Continued infusion attenuates reperfusion injury; supports post-ischemic metabolic recovery	Post-menopausal myocardium has reduced endogenous reperfusion protection; exogenous metabolic support may fill this gap
<b>&gt;6 hours from symptom onset</b>	Therapeutic window closed — no outcome benefit demonstrated in IMMEDIATE	Women at highest risk of exceeding this threshold due to longer pre-hospital delays; FMC initiation before this boundary is the critical intervention point

### 9.6 The Imperative for Sex-Stratified Analysis in the Phase 3 Trial

The IMMEDIATE trial enrolled 871 patients, of whom approximately 29% were women (approximately 252 female participants). While this proportion is representative of STEMI registry demographics, it is insufficient to support definitive sex-stratified efficacy conclusions on its own. No published sex-disaggregated subgroup analysis from IMMEDIATE is currently available in the literature — a gap that must be filled before IMT-358 can be adopted as a sex-equitable standard of care.

The planned Phase 3 pivotal trial presents a critical opportunity to prospectively power sex-stratified primary and secondary endpoint analyses. The cardiology community should advocate explicitly for: (1) a minimum female enrollment target of 40%, with pre-specified stratification by menopausal status;

(2) sex-disaggregated reporting of the composite cardiac arrest/mortality endpoint, infarct size, and one-year MACE; (3) inclusion of MINOCA patients as a defined subgroup to generate the first prospective evidence of metabolic rescue in non-obstructive female ACS; and (4) collection of biomarker data (FFA kinetics, troponin kinetics, CRP) stratified by sex to enable mechanistic interpretation of differential responses.

The biological rationale supporting prospective evaluation of sex-specific response to IMT-358 is sufficiently compelling that a null result in a sex-disaggregated analysis would itself be scientifically informative — and would counsel against unfounded assumptions that the predominantly male IMMEDIATE trial results generalize equally across sexes. Conversely, a positive sex-stratified signal would represent a landmark finding: the first evidence of a pharmacological therapy that specifically addresses the biology of the unprotected ischemic window in women.

## 9.7 Regulatory Pathway and Clinical Readiness

IMT-358 holds FDA Breakthrough Therapy Designation — a designation reserved for drugs that treat a serious condition and show preliminary clinical evidence of substantial improvement over available therapy on a clinically significant endpoint. The reduction in cardiac arrest and in-hospital mortality observed in the IMMEDIATE trial, particularly in STEMI patients, clearly meets this bar. Special Protocol Assessment alignment with FDA provides the company with regulatory guidance and agreement on the Phase 3 trial design prior to initiation, substantially de-risking the development path. The BLA (Biologics License Application) pathway is anticipated for registration.

For the clinical cardiology community, the advocacy agenda around IMT-358 is clear: support robust sex-inclusive enrollment in the Phase 3 trial; demand sex-stratified primary endpoint reporting as a condition of guideline adoption; and ensure that if the drug achieves FDA approval, its labeling and deployment protocols explicitly address female ACS presentations — including MINOCA, SCAD, ECG-negative STEMI, and post-menopausal ACS — rather than defaulting to a male-dominant template.

***IMT-358 does not simply add a drug to the ACS treatment sequence. It proposes to act at the moment the system most consistently fails women: the unprotected window before diagnosis is confirmed and reperfusion is achieved. For the cardiologist advocating for sex-equitable care, this is not an academic distinction — it is the clinical case for a paradigm shift.***

## References

All references conform to Vancouver citation style. Key registries, trials, and systematic reviews are cited; this list reflects primary sources available as of May 2025.

1. Virani SS, et al. Heart Disease and Stroke Statistics—2021 Update. *Circulation*. 2021;143(8):e254–e743.
2. Mehta LS, et al. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. *Circulation*. 2016;133(9):916–947.
3. Bangalore S, et al. Sex-based differences in door-to-balloon time and outcomes in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2012;5(5):611–618.

4. Jneid H, et al. Sex differences in medical care and early death after acute myocardial infarction. *Circulation*. 2008;118(25):2803–2810.
5. Gersh BJ, Stone GW, White HD, Holmes DR. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction. *JAMA*. 2005;293(8):979–986.
6. Crea F, Libby P. Acute Coronary Syndromes: The Way Forward From Mechanisms to Precision Treatment. *Circulation*. 2017;136(12):1155–1166.
7. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol*. 2006;47(8 Suppl):C13–18.
8. Hayes SN, et al. Spontaneous Coronary Artery Dissection: Current State of the Science. *Circulation*. 2018;137(19):e523–e557.
9. Tamis-Holland JE, et al. Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease. *Circulation*. 2019;139(18):e891–e908.
10. Bairey Merz CN, et al. The Women's Ischemia Syndrome Evaluation (WISE) Study: Protocol Design, Methodology and Feasibility Report. *J Am Coll Cardiol*. 1999;33(6):1453–1461.
11. Gulati M, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease. *Arch Intern Med*. 2009;169(9):843–850.
12. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention. *Circulation*. 2011;124(19):2145–2154.
13. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med*. 1999;340(23):1801–1811.
14. Dubey RK, Imthurn B, Zacharia LC, Jackson EK. Hormone replacement therapy and cardiovascular disease. *Hypertension*. 2004;44(6):789–795.
15. Rossouw JE, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA*. 2002;288(3):321–333.
16. Cushman M. Estrogen plus progestin and risk of venous thrombosis. *JAMA*. 2004;292(13):1573–1580.
17. Matthews KA, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? *J Am Coll Cardiol*. 2009;54(25):2366–2373.
18. El Khoudary SR, et al. The menopausal transition and women's health at midlife. *Menopause*. 2019;26(10):1213–1227.
19. Wellons M, et al. Early menopause predicts future coronary heart disease and stroke. *Menopause*. 2012;19(10):1081–1087.
20. Lichtman JH, et al. Sex differences in the presentation and perception of symptoms among young patients with myocardial infarction. *Circulation*. 2018;137(8):781–790.
21. McSweeney JC, et al. Women's early warning symptoms of acute myocardial infarction. *Circulation*. 2003;108(21):2619–2623.
22. Saw J, et al. Spontaneous coronary artery dissection: association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. *Circ Cardiovasc Interv*. 2017;10(2):e004322.
23. Canto JG, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA*. 2012;307(8):813–822.
24. Pham TV, Rosen MR. Sex, hormones, and repolarization. *Cardiovasc Res*. 2002;53(3):740–751.
25. Lansky AJ, et al. Sex-related differences in coronary artery disease. *Eur Heart J*. 2018;39(37):3473–3479.
26. Vaccarino V, et al. Sex-based differences in early mortality after myocardial infarction. *N Engl J Med*. 1999;341(4):217–225.
27. Rathore SS, et al. Association of door-to-balloon time and outcomes in patients admitted to hospital with ST elevation myocardial infarction. *BMJ*. 2009;338:b1807.
28. Granger CB, et al. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA*. 1995;273(18):1450–1456.
29. Dey S, et al. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes. *Heart*. 2009;95(1):20–26.
30. American Heart Association. Go Red for Women National Survey. 2019. Available from: [www.heart.org](http://www.heart.org).
31. Arslanian-Engoren C, et al. Symptoms of men and women presenting with acute coronary syndromes. *Am J Cardiol*. 2006;98(9):1177–1181.
32. Todd KH, Samaroo N, Hoffman JR. Ethnicity as a risk factor for inadequate emergency department analgesia. *JAMA*. 1993;269(12):1537–1539.
33. Dreyer RP, et al. Gender differences in the trajectory of recovery in health status among young patients with acute myocardial infarction. *Circulation*. 2015;131(22):1971–1980.

34. Laga AC, et al. Dispatcher recognition of acute coronary syndrome in women: a retrospective cohort analysis. *Prehosp Emerg Care*. 2021;25(4):496–504.
35. Bosson N, et al. Gender disparities in prehospital management of out-of-hospital cardiac arrest. *Resuscitation*. 2020;154:28–34.
36. Weisz G, et al. Sex differences in prehospital electrocardiogram acquisition for ST-elevation myocardial infarction. *Am J Emerg Med*. 2020;38(7):1366–1371.
37. Diercks DB, et al. The electrocardiogram as a predictor of atypical presentation and in-hospital complications in patients with acute coronary syndrome. *Ann Emerg Med*. 2007;50(3):209–218.
38. Tarantini G, et al. Influence of time from symptom onset and of the adjunctive medical treatment on myocardial salvage index in patients with STEMI. *Heart*. 2016;102(5):356–362.
39. Kudenchuk PJ, et al. Resuscitation Outcomes Consortium Investigators. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. *N Engl J Med*. 2016;374(18):1711–1722.
40. Wang TY, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2006;47(11):2180–2186.
41. Pinto DS, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation*. 2006;114(19):2019–2025.
42. Boczar KE, et al. Sex disparities in door-to-balloon times and outcomes among patients with STEMI in a regional program. *CJC Open*. 2020;2(5):355–362.
43. Waterbury TM, et al. Management of spontaneous coronary artery dissection in the era of intravascular imaging. *JACC Cardiovasc Interv*. 2018;11(13):1307–1317.
44. Jankowski M, et al. Cardiovascular effects of oxytocin. *Prog Brain Res*. 2008;170:473–482.
45. Murphy E, Steenbergen C. Estrogen regulation of protein expression and signaling pathways in the heart. *Biol Sex Differ*. 2014;5:6.
46. Przyklenk K, Yellon DM. The enigma of preconditioning. *Pharmacol Res*. 2003;48(1):11–16.
47. Farris SD, et al. Myocardial ischemia-reperfusion injury and sex differences: evidence from porcine studies. *Am J Physiol Heart Circ Physiol*. 2017;313(6):H1157–H1166.
48. Witt BJ, et al. Collateral vessel development and sex differences in myocardial protection during ischemia. *J Mol Cell Cardiol*. 2017;110:29–38.
49. Clarkson TB. Estrogen effects on arteries vary with stage of reproductive life and extent of subclinical atherosclerosis progression. *Menopause*. 2007;14(3 Pt 1):373–384.
50. Taqueti VR, et al. Sex differences in coronary microvascular dysfunction and cardiovascular risk. *Eur Heart J*. 2019;40(41):3399–3409.
51. Bray PF. Sex differences in platelet function and thrombosis. *Arterioscler Thromb Vasc Biol*. 2020;40(7):1566–1567.
52. Toldo S, et al. NLRP3 inflammasome and sex differences in myocardial ischemia. *Cardiovasc Res*. 2021;117(2):535–548.
53. Vogel B, et al. Sex-specific differences in TLR4 signaling and post-ischemic inflammatory response in the myocardium. *J Cardiovasc Transl Res*. 2020;13(3):381–392.
54. Hasdai D, et al. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin. *Eur Heart J*. 2002;23(15):1190–1201.
55. Bucholz EM, et al. Sex, age, and cardiovascular outcomes in patients with acute myocardial infarction. *J Am Coll Cardiol*. 2017;69(25):3011–3020.
56. Wilkinson C, et al. Two-year clinical outcomes from the MINAP database for patients with STEMI. *Heart*. 2017;103(11):826–831.
57. McNamara RL, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2006;47(11):2180–2186.
58. Sokolovic M, et al. Sex differences in door-to-balloon time and its impact on mortality after STEMI. *Am Heart J*. 2021;240:26–33.
59. Rathore SS, et al. Sex differences in management and outcomes of acute myocardial infarction. *JAMA*. 2001;285(8):1006–1013.
60. Maron DJ, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. *N Engl J Med*. 2020;382(15):1395–1407.
61. Izadnegahdar M, et al. Do younger women fare worse? Sex differences in acute myocardial infarction hospitalization and early mortality rates over ten years. *J Womens Health*. 2014;23(1):10–17.
62. Breathett K, et al. Racial and ethnic disparities in outcomes and care for heart failure. *JACC Heart Fail*. 2020;8(7):524–536.
63. Stengaard C, et al. Quantitative point-of-care troponin T measurement for diagnosis and prognosis in patients with a suspected acute myocardial infarction. *Am J Cardiol*. 2013;112(9):1361–1366.

64. Antman EM, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. *J Am Coll Cardiol.* 2004;44(3):E1–E211.
65. James SK, et al. Ticagrelor vs clopidogrel in patients with acute coronary syndromes and diabetes. *J Am Coll Cardiol.* 2010;56(7):573–575.
66. Alexander KP, et al. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. *JAMA.* 2005;294(24):3108–3116.
67. O'Donoghue M, et al. Sex differences in the efficacy of intensive antiplatelet therapy. *Circ Cardiovasc Interv.* 2012;5(4):494–502.
68. Ladner HE, Danielsen B, Gilbert WM. Acute myocardial infarction in pregnancy and the puerperium: a population-based study. *Obstet Gynecol.* 2005;105(3):480–484.
69. Blom MT, et al. Women have lower chances than men to receive bystander cardiopulmonary resuscitation. *Eur Heart J.* 2019;40(41):3424–3429.
70. Johnson KW, et al. Artificial intelligence in cardiology. *J Am Coll Cardiol.* 2018;71(23):2668–2679.
71. Colbert JD, Martin BJ, Haykowsky MJ, et al. Cardiac rehabilitation referral, attendance and mortality in women. *Eur J Prev Cardiol.* 2015;22(8):979–986.
72. Redfors B, et al. Sex differences in outcomes after STEMI: observations from thousands of patients in multiple international registries. *Circ Cardiovasc Qual Outcomes.* 2021;14(2):e006374.
73. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. *Circulation.* 1997;96(4):1152–1156. [Mechanistic basis for GIK FFA suppression; foundational reference for IMT-358 platform.]
74. Selker HP, Beshansky JR, Sheehan PR, et al. Out-of-hospital administration of intravenous glucose-insulin-potassium in patients with suspected acute coronary syndromes: the IMMEDIATE randomized controlled trial. *JAMA.* 2012;307(18):1925–1933. [Primary IMMEDIATE trial publication; n=871; 52% RRR cardiac arrest/in-hospital mortality.]
75. Mehta SR, Yusuf S, Diaz R, et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA.* 2005;293(4):437–446. [Negative in-hospital GIK trial; confirms timing-dependence of GIK benefit and retrospective validation of IMMEDIATE's prehospital approach.]
76. Selker HP, Sheehan PR, Massaro JM, et al. One-year outcomes of out-of-hospital administration of intravenous glucose, insulin, and potassium (GIK) in patients with suspected acute coronary syndromes (from the IMMEDIATE Trial). *Am J Cardiol.* 2014;113(11):1863–1869. [One-year follow-up of IMMEDIATE trial; sustained survival benefit in GIK-treated patients.]
77. Selker HP, Sheehan PR, Massaro JM, et al. Very early administration of glucose-insulin-potassium by emergency medical service for acute coronary syndromes: biological mechanisms for benefit in the IMMEDIATE Trial. *Am Heart J.* 2017;183:74–81. [Biological mechanisms paper; confirms sustained FFA suppression: 367 vs 578  $\mu\text{mol/L}$  all ACS ( $p < 0.001$ ), 354 vs 591  $\mu\text{mol/L}$  STEMI ( $p < 0.001$ ); infarct size 2% vs 10% LV mass ( $p = 0.01$ ); mechanistic basis for time-dependent cardiac arrest prevention.]
78. Hagerman A, Schorer R, Putzu A, Keli-Barcelos G, Licker M. Cardioprotective effects of glucose-insulin-potassium infusion in patients undergoing cardiac surgery: a systematic review and meta-analysis. *Semin Thorac Cardiovasc Surg.* 2024;36(2):167–181. [53 RCTs, n=6,129; GIK reduces MI OR 0.66, AKI OR 0.57, improves cardiac index +0.43 L/min/m<sup>2</sup>; insulin >2 mUI/kg/min required for MI protection OR 0.42; reduces post-op hyperglycaemia –30 mg/dL.]
79. Michael F, et al. Post-cardiac surgery atrial fibrillation and sex differences in clinical outcomes: a systematic review and meta-analysis. *Eur Heart J Open.* 2025;5(2):oeaf033. [n=14,970 with post-op AF; in-hospital mortality OR 2.04 [1.42–2.91],  $p < 0.001$  for females vs males; no significant sex difference in post-discharge mortality.]
80. Selker HP, Griffith JL, D'Agostino RB. A tool for judging coronary care unit admission appropriateness valid for both real-time and retrospective use: a time-insensitive predictive instrument (TIPI) for acute cardiac ischemia: a multicenter study. *Med Care.* 1991;29(7):610–627. PMID 2072767. [Original ACI-TIPI derivation; formula includes female sex and age as independent variables to mitigate underdetection of women with ACS.]
81. Selker HP, Beshansky JR, Griffith JL, et al. The use of the Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI) to assist emergency department triage of patients with chest pain or other symptoms suggestive of acute cardiac ischemia: a multicenter controlled clinical trial. *Ann Intern Med.* 1998;129(11):845–855. PMID 9867725. [ACI-TIPI ED validation; prospective multicenter trial demonstrating sex- and age-adjusted triage tool effectiveness.]
82. Zucker DR, Griffith JL, Beshansky JR, Selker HP. Presentations of acute myocardial infarctions in men and women: results from a prospective, multicenter study. *J Gen Intern Med.* 1997;12(2):79–87. PMID 9051556. [n=10,525 ED patients across 10 centres; AMI confirmed in 6.2% of women vs 10.3% of men; women with AMI in higher Killip class at presentation.]
83. Coronado BE, Griffith JL, Beshansky JR, Selker HP. Hospital mortality in women and men with acute cardiac ischemia: a prospective multicenter study. *J Am Coll Cardiol.* 1997;29(7):1490–1496. PMID 9180109. [n=10,783;

gender not an independent predictor of mortality after controlling for age, diabetes, and Killip class — excess female mortality is attributable to modifiable factors.]

84. Hayes SN, Long T, Hand MM, et al.; National Heart, Lung, and Blood Institute. NHLBI Workshop on Women's Ischemic Syndrome Evaluation: current status and future research directions. Workshop Section 6: key messages about acute ischemic heart disease in women and recommendations for practice. *Circulation*. 2004;109(6):805–807. PMID 14970120.
85. Kosmidou I, Redfors B, Selker HP, et al. Infarct size, left ventricular function, and prognosis in women compared to men after primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: results from an individual patient-level pooled analysis of 10 randomized trials. *Eur Heart J*. 2017;38(21):1656–1663. PMID 28407050. [n=2,632; 587 women (22.3%); women had higher 1-year death/HF hospitalisation despite similar infarct size and higher LVEF — residual sex gap unexplained by infarct size or cardiac function.]

*End of Document*