

IMT-358 and Women with ACS

Why the IMMEDIATE Trial Design Ensures Women Receive Equal — and Potentially Greater — Benefit from Metabolic Rescue

Immediate Therapeutics | May 2026 |

Women and ACS: The Persistent Gap

Cardiovascular disease remains the leading cause of death in American women, yet women with acute coronary syndrome (ACS) continue to face a documented and persistent gap in recognition, triage speed, and early treatment compared with men.^{1,2} Women tend to present at older ages with greater comorbidity burdens — higher rates of diabetes, hypertension, and prior heart failure — and with symptom profiles that diverge from the ECG-centric diagnostic paradigm built on male-predominant trial populations.^{3,4} Atypical presentations — fatigue, dyspnea, nausea, and jaw or back pain in the absence of classic chest pressure — are more common in women, and the result is a systemic tendency to underestimate ACS probability at first medical contact.⁵

The clinical consequences are measurable. Women with STEMI have median symptom-to-door times approximately 29% longer than men.⁶ Women are less likely to receive timely reperfusion therapy and are more likely to be discharged without appropriate secondary prevention.^{7,8} When women do undergo primary PCI, they have higher 1-year rates of death or heart failure hospitalization compared with men — and this residual mortality gap is not explained by differences in infarct size or post-infarction cardiac function.⁹ That unexplained residual points toward pre-reperfusion metabolic injury as a key contributor: damage that accrues during the unprotected window before the catheterization lab, and that is disproportionately long in women.

Post-menopausal women face an additional metabolic vulnerability. Estrogen loss accelerates insulin resistance and elevates circulating free fatty acids (FFAs) at baseline, amplifying the toxic FFA surge that occurs during myocardial ischemia and worsening ischemia-reperfusion injury.^{10,11} These mechanisms are directly targeted by GIK-class metabolic rescue therapy — and they are more severely dysregulated in women than in age-matched men, providing a strong biological rationale for disproportionate benefit.

Despite this clear epidemiological and biological case, women have historically been enrolled in ACS trials at rates of 19–23% — far below their representation among ACS patients. The IMMEDIATE trial and IMT-358's development program directly address this through two deliberate design features: the ACI-TIPI enrollment instrument, and a treatment threshold based on ACS probability rather than confirmed AMI.

The ACI-TIPI Entry Point: Structural Protection Against Sex Bias

Patient eligibility for the IMMEDIATE trial was determined not by physician gestalt or ECG criteria alone, but by the Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI) — a validated logistic regression algorithm that computes the probability of acute cardiac ischemia from presenting symptoms, ECG findings, age, and sex.^{12,13}

This design choice has a specific and consequential implication for women. The ACI-TIPI formula includes **female sex and age as separate, independent variables**, explicitly calibrated to account for the fact that women tend to present at older ages with different symptom constellations than men. This directly counteracts the systemic bias of ECG-based triage and clinical pattern recognition, both of which were developed predominantly on male populations.^{14,15} In practical terms: a woman whose presentation would not trigger the standard 'classic MI' clinical script — but whose age, sex, symptoms, and ECG together generate a high ACI-TIPI probability — is enrolled and treated. She is not missed.

ACI-TIPI's sex- and age-adjusted formula is not a minor methodological detail. It is the mechanism by which IMMEDIATE enrolled 29% women — meaningfully above the 19–23%

typical of STEMI intervention trials — and why IMT-358's evidence base includes women at a rate that reflects their true burden of disease.

Decades of prospective multicenter research by Selker and colleagues across more than 10,000 ED patients established the empirical foundation for this approach: women with ACS present at older ages, with greater comorbidity burden, and in higher Killip class at the time of diagnosis.^{14,15} Critically, Coronado et al. demonstrated in a prospective cohort of 10,783 patients that once age, diabetes, and Killip class are controlled for, sex is not an independent predictor of hospital mortality.¹⁵ This finding has an important implication: women's excess mortality from ACS is not an immutable biological fate — it is an expression of older age at presentation, greater comorbidity, and more advanced hemodynamic compromise, each of which is a consequence of delayed recognition and treatment. Closing the first-medical-contact gap is the direct mechanism by which IMT-358 addresses these modifiable contributors.

ACS Probability, Not Confirmed AMI: A Second Layer of Inclusivity

Eligibility for IMMEDIATE — and for IMT-358 initiation — is based on the **probability of ACS**, not on a confirmed AMI diagnosis. Treatment is initiated in the ambulance before hospital arrival, before any diagnostic workup is complete. This is clinically important for women because the debate about whether women present differently from men with AMI — while real — becomes largely irrelevant when the threshold for treatment is ACS probability rather than diagnostic certainty.¹⁶ Whether or not a woman's presentation fits the canonical AMI pattern, a sufficiently high ACI-TIPI score triggers treatment.

This approach is further supported by the safety profile of GIK. The therapy has no effect on hemostasis, carries no prothrombotic or antithrombotic risk, requires no complex titration, and can be stopped at any point if ACS is no longer suspected. The extreme safety of the platform enables a low threshold for initiation, and that low threshold removes one of the most consequential barriers to early treatment in women.

GIK's safety profile means the cost of treating a woman who turns out not to have ACS is effectively nil. The cost of not treating a woman who does — measured in myocardium saved and lives extended — can be substantial.

The Biological Case: Why Women May Benefit Disproportionately

IMT-358 works by suppressing the surge of circulating FFAs during ischemia, preserving glucose oxidation, and activating PI3K-Akt myocardial survival signaling — mechanisms that are more critically engaged in post-menopausal women than in age-matched men.^{10,17}

The IMMEDIATE trial's biological mechanisms substudy confirmed rapid, sustained FFA suppression with GIK administration: sustained plasma FFA levels of 367 vs. 578 $\mu\text{mol/L}$ in controls across all ACS patients ($p < 0.001$), with a corresponding reduction in infarct size from 10% to 2% of LV mass ($p = 0.01$) in the first hour of treatment.¹⁷ Post-menopausal women — who constitute the majority of women presenting with ACS — enter the ischemic event with higher baseline FFA concentrations and greater insulin resistance, making the GIK-mediated FFA suppression mechanistically more valuable for them than for age-matched men.^{10,11}

The time-dependency of this benefit is also relevant to women specifically. The IMMEDIATE trial demonstrated an odds ratio of 0.28 for cardiac arrest or mortality when GIK was administered within the first hour of symptoms — a benefit that attenuated with time and disappeared after six hours.¹⁶ Women with ACS experience median pre-hospital delays approximately 29% longer than men.⁶ A therapy that acts within minutes of EMS contact — before hospitalization — compresses the window during which the female patient is most vulnerable to irreversible metabolic injury, converting a structural disadvantage into an opportunity for early intervention.

Summary

The IMMEDIATE trial's enrollment design, through ACI-TIPI's sex- and age-adjusted probability formula, actively counteracts the mechanisms by which women are systematically underrepresented and undertreated in ACS trials and in clinical practice.^{12,13,14} IMT-358 is initiated on the basis of ACS probability — not ECG pattern-matching or physician gestalt — removing the diagnostic barrier that most frequently disadvantages women.¹⁶ Its exceptional safety profile supports the lowest possible treatment threshold, ensuring that women benefit from the same early window of metabolic rescue as men.

The residual mortality gap in women after primary PCI,⁹ the greater metabolic vulnerability of the post-menopausal myocardium,^{10,11} and the longer unprotected ischemic window that women experience⁶ collectively make this population not merely included in the IMT-358 development program — but among those with the most to gain from it.

References

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. Lichtman JH, et al. Sex differences in the presentation and perception of symptoms among young patients with myocardial infarction. *Circulation*. 2008;118(25):2551–2559.
4. Canto JG, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA*. 2012;307(8):813–822.
5. McSweeney JC, et al. Women's early warning symptoms of acute myocardial infarction. *Circulation*. 2003;108(21):2619–2623.
6. Bugiardini R, et al. Factors influencing underutilization of evidence-based therapies in women. *Eur Heart J Acute Cardiovasc Care*. 2017;6(1):28–38.
7. Bangalore S, et al. Sex-based differences in door-to-balloon time and outcomes in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2012;59(24):2180–2186.
8. Vaccarino V, et al. Sex-based differences in early mortality after myocardial infarction. *N Engl J Med*. 1999;341(4):217–225.
9. Kosmidou I, Redfors B, Selker HP, et al. Infarct size, left ventricular function, and prognosis in women compared to men after primary PCI in STEMI: results from an individual patient-level pooled analysis of 10 randomized trials. *Eur Heart J*. 2017;38(21):1656–1663. PMID 28407050.
10. El Khoudary SR, et al. The menopausal transition and women's health at midlife. *Menopause*. 2019;26(10):1213–1227.
11. Murphy E, Steenbergen C. Estrogen regulation of protein expression and signaling pathways in the heart. *Biol Sex Differ*. 2014;5:6.
12. 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.
13. Selker HP, Beshansky JR, Griffith JL, et al. The use of the 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.
14. 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.
15. 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.
16. 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.
17. 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.