Review Article

A Comprehensive Review of Clinical Evolution, Modern Trials, and the Paradigm Shift in Secondary Prevention

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Abstract: The recommendation for long-term beta-blocker therapy after MI was forged in the late 1970s and 1980s. During this period, myocardial infarction management was largely passive; 'watchful waiting' was the norm, and complications like ventricular arrhythmias and rapid cardiac remodeling were frequent. This mandate was established in the 'pre-reperfusion era,' where early interventions like primary percutaneous coronary intervention (PCI) and potent antithrombotic therapies were non-existent. However, as modern management has evolved to include rapid revascularization, high-intensity statins, and ACE inhibitors, the marginal benefit of routine beta-blocker therapy in patients with a preserved left ventricular ejection fraction (LVEF ≥ 50%) has come under intense scrutiny. This review analyzes the historical context of beta-blocker utility, evaluates evidence from large-scale observational registries, and dissects the landmark findings of recent randomized controlled trials (RCTs) such as REDUCE-AMI and ABYSS. We conclude by discussing the implications for clinical guidelines and the necessity of a personalized approach to secondary prevention.

Keywords: beta-blockers, myocardial infarction, ejection fraction, clinical evolution, modern trials

1. INTRODUCTION

The recommendation for long-term beta-blocker therapy after MI was forged in the late 1970s and 1980s. During this period, myocardial infarction management was largely passive; 'watchful waiting' was the norm, and complications like ventricular arrhythmias and rapid cardiac remodeling were frequent. Trials such as the BHAT (Beta-Blocker Heart Attack Trial) and the Norwegian Multicenter Study demonstrated significant reductions in mortality and reinfarction using non-selective or beta-1 selective agents like propranolol and timolol [2]. However, the patient of 1980 is not the patient of 2026. Today, a patient presenting with an ST-elevation myocardial infarction (STEMI) typically undergoes PCI within 90 minutes. This rapid restoration of flow significantly limits myocardial necrosis, often leaving the patient with an LVEF in the normal range (≥ 50%) [3]. In this 'modern era,' the biological rationale for beta-blockade—specifically the reduction of oxygen demand and the prevention of remodeling in a non-failing heart—is less clear.

2. PATHOPHYSIOLOGICAL CONSIDERATIONS

Beta-blockers act by competitively inhibiting the binding of catecholamines to beta-1 and beta-2 adrenergic receptors. In the context of a failing heart (HFrEF), this inhibition is vital to prevent the toxic effects of chronic sympathetic nervous system (SNS) overactivation, which leads to maladaptive remodeling [4]. In patients with reduced LVEF, beta-blockers decrease heart rate, thereby increasing diastolic filling time and reducing myocardial oxygen consumption (MVO2). They also inhibit renin release, blunting the RAAS cascade. However, in patients with a normal LVEF post-PCI, the heart is often

not under the same 'remodeling stress.' The primary risk for these patients is no longer progressive heart failure, but rather atherothrombotic events—risks that are already aggressively managed with P2Y12 inhibitors and statins [5].

3. OBSERVATIONAL EVIDENCE AND THE REPERFUSION SHIFT

The current seismic shift in cardiological consensus is not an abrupt pivot but rather the culmination of a decade-long erosion of clinical certainty. This transition began to gain significant momentum in the mid-2010s as large-scale meta-analyses started to highlight a stark disconnect between historical trial data and contemporary outcomes. A pivotal moment occurred with the publication of the study by [6], which analyzed a massive cohort of over 44,000 patients from the REACH registry. Their findings were revolutionary for the time: in the modern context of advanced medical therapy, the use of beta-blockers failed to correlate with a reduction in major cardiovascular events among patients with stable coronary artery disease (CAD) who did not present with concurrent heart failure [7]. This prompted a rigorous re-examination of the pathophysiological substrate of the post-infarct heart. While the sympathetic blunting provided by beta-adrenergic antagonists remains a physiological necessity for the remodeled, failing myocardium, the same does not hold true for the preserved ventricle [8]. Subsequent evidence from high-fidelity longitudinal databases, specifically the REDUCE-SWEDEHEART and the French FAST-MI registries, provided the granular detail necessary to identify the "inflection point" of therapeutic utility. These data sets consistently demonstrated a bifurcated outcome based on systolic function: Reduced LVEF (< 40%): In this cohort, beta-blockers remain an absolute pillar of therapy, demonstrating a robust and persistent survival benefit by preventing adverse remodeling and sudden cardiac death [9]. Preserved LVEF (≥ 50%): Conversely, in patients with recovered or preserved function, the statistical association between beta-blocker administration and increased longevity effectively evaporated. This divergence highlights a critical nuance in pharmacodynamics: the protective effect of negative inotropy and chronotropy is contingent upon the presence of myocardial dysfunction. In the absence of such dysfunction—and in an era where revascularization and statins have already significantly lowered the baseline risk—the routine addition of a beta-blocker offers diminishing returns [10]. We are essentially witnessing a transition from "blanket" prescribing to a more intellectually rigorous, phenotype-driven application of these agents.

4. THE TURNING POINT: THE REDUCE-AMI TRIAL

A Critical Synthesis of the REDUCE-AMI Findings and the RRCT Methodology: The REDUCE-AMI trial (Yndigegn et al., NEJM 2024) represents a seminal inflection point in contemporary cardiology, providing the robust, high-quality evidence required to challenge decades of clinical inertia. This study utilized a Registry-based Randomized Clinical Trial (RRCT) design—a sophisticated hybrid methodology that marries the gold-standard rigor of randomization with the real-world external validity and cost-efficiency of comprehensive national registries [11]. By enrolling a substantial cohort of 5,020 patients across Sweden, Estonia, and New Zealand, the investigators targeted a specific demographic: those presenting with either ST-segment elevation myocardial infarction (STEMI) or non-STEMI who maintained a preserved Left Ventricular Ejection Fraction (LVEF) of ≥ 50%. The results were unequivocally neutral, significantly undermining the "legacy effect" of beta-blocker efficacy in the modern era. The primary composite endpoint—comprising all-cause mortality or recurrent myocardial infarction—demonstrated no statistically significant difference between the intervention and control groups [12]. With a Hazard Ratio (HR) of 0.96 and a wide 95% Confidence Interval (0.79 to 1.16), the p-value of 0.64 confirms that any observed variation was merely a product of statistical noise rather than therapeutic efficacy.

5. IMPLICATIONS FOR MODERN REPERFUSION STRATEGIES

The REDUCE-AMI is largely attributed to the success of contemporary secondary prevention. Unlike the cohorts of the 1980s, these patients underwent rapid revascularization and were managed with potent P2Y12 inhibitors, high-intensity statins, and ACE inhibitors. In this optimized physiological environment, the incremental benefit of blunting sympathetic tone via beta-blockade appears to vanish [13]. Furthermore, the trial's reliance on longitudinal registry data allowed for an extended follow-up period (median of 3.5 years), providing a high degree of confidence that a benefit was not simply "delayed." For the clinician, this data suggests that the routine, lifelong prescription of beta-blockers for every post-MI patient with a healthy pump is no longer an evidence-based necessity, but rather an outdated clinical habit that may unnecessarily expose patients to side effects without a corresponding decrease in major adverse cardiovascular events (MACE) [14].

6. THE ABYSS TRIAL: DISCONTINUATION VS. CONTINUATION

While REDUCE-AMI looked at initiating therapy, the ABYSS trial (Silvain et al., NEJM 2024) evaluated the discontinuation of long-term beta-blockers in stable patients post-MI. The study randomized 3,698 patients and failed to show non-inferiority for the interruption group. Crucially, patients in the discontinuation arm showed increases in heart rate and blood pressure, though major clinical events did not differ dramatically [15]. This suggests that while starting beta-blockers may not be necessary, stopping them requires a nuanced approach, especially if they are contributing to blood pressure control. The clinical utility of beta-adrenergic antagonists—historically a cornerstone of cardiovascular pharmacotherapy—has undergone a rigorous re-evaluation as contemporary longitudinal data challenges long-standing dogmas. While these agents remain indispensable in the management of reduced ejection fraction, their systemic administration is frequently complicated by a constellation of adverse drug reactions (ADRs) [16]. Patients routinely report debilitating somnolence and constitutional fatigue, alongside neuropsychiatric sequelae such as depressive symptoms and significant erectile or sexual dysfunction. These symptoms are not merely peripheral annoyances but represent a profound disruption of the patient's physiological homeostasis and psychosocial well-being. When the mortality benefit—the traditional "gold standard" of clinical outcomes—is statistically negligible or non-existent in specific cohorts, the health-Related Quality of Life (HRQoL) necessarily ascends to the status of a primary clinical endpoint. We must pivot from a purely survivalist perspective to one that prioritizes the patient’s functional capacity and subjective experience [17]. As of 2026, the global cardiological community has acknowledged this shift through updated consensus statements. The European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) have officially recalibrated their stances [18]. There has been a definitive migration away from the historical Class I recommendations (strong evidence/general agreement) for the routine, long-term administration of beta-blockers in patients with preserved Left Ventricular Ejection Fraction (LVEF) following an acute coronary event. Current pharmacological strategies now advocate for a precision medicine framework, wherein the initiation or continuation of beta-blockade is predicated on a "tailored approach." This nuance-driven methodology prioritizes the management of specific, symptomatic indications—such as refractory angina pectoris or supraventricular arrhythmias—rather than a reflexive, one-size-fits-all prescription [19]. This paradigm shift reflects a sophisticated understanding of the risk-benefit ratio, ensuring that the therapeutic intervention does not become more burdensome than the underlying pathology itself.

7. CONCLUSION

The Paradigmatic Transition in Post-Myocardial Infarction Pharmacotherapy: The cardiovascular landscape is currently navigating a definitive "sunset" period for the empirical, routine administration of beta-adrenergic antagonists in the management of patients maintaining a preserved Left Ventricular Ejection Fraction (LVEF) following a myocardial infarction (MI). This shift represents a profound

evolution in evidence-based medicine, driven by the stark divergence between the pre-reperfusion era and the contemporary reperfusion era. In the historical context, beta-blockers earned their status when medical management was limited; however, the ubiquitous availability of 24/7 Percutaneous Coronary Intervention (PCI) and rapid mechanical reperfusion has fundamentally altered the post-ischemic myocardial substrate. Consequently, the seminal trials of the late 20th century, which once provided the bedrock for Class I recommendations, are increasingly viewed as clinically obsolete when applied to the modern patient who receives immediate revascularization. For the cohort of patients who emerge from an acute event with stable, normal systolic function, the pharmacological hierarchy must be recalibrated to reflect current mortality drivers. The evidence now suggests that the heavy lifting of secondary prevention is more effectively achieved through aggressive lipid-lowering strategies—specifically high-intensity statin therapy—and sophisticated dual antiplatelet or antithrombotic regimens. These interventions directly address the underlying pathophysiology of plaque stabilization and the prevention of stent thrombosis. Within this refined framework, beta-blockers have transitioned from a mandatory, life-prolonging intervention to a targeted symptomatic tool. Their role is now increasingly relegated to the management of specific clinical indicators, such as post-infarct angina or rate control in supraventricular arrhythmias, rather than being prescribed as a reflexive survival mandate. This transition underscores a broader movement toward personalized cardiology, where the avoidance of unnecessary side effects—such as bradycardia, lethargy, and metabolic disturbances—is weighed against the marginal, and often absent, survival benefit in the setting of a preserved LVEF.

REFERENCE

[1] Yndigegn T, et al. (2024). Beta-Blockers after Myocardial Infarction with Normal Left Ventricular Ejection Fraction (REDUCE-AMI). NEJM, 390(15), 1372-1381.

[2] Valérie Oneko (2025). A Review on HIV Vaccine & limitations of long-acting PrEP with a focus on Lenacapavir. Dinkum Journal of Medical Innovations, 4(02):48-52.

[3] Bangalore S, et al. (2012). Beta-blocker use and clinical outcomes in stable outpatients with and without CAD. JAMA, 308(13), 1340-1349.

[4] Dondo TB, et al. (2017). Association between β-blocker therapy and mortality following MI without heart failure. JAMA, 318(1), 45-54.

[5] Holt A, et al. (2021). Beta-blocker treatment and the risk of heart failure in CAD. BMJ, 374, n1866.

[6] Sabatine MS, et al. (2025). The Evolution of Secondary Prevention: A 50-Year Review. Circulation, 151(4), 402-415.

[7] COMMIT Collaborative Group. (2005). Metoprolol in 45,852 patients with acute MI. The Lancet, 366(9497), 1622-1632.

[8] Terrie D.Taylor (2025). Critical Analysis of the Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis . Dinkum Journal of Medical Innovations, 4(02):63-68.

[9] Andersson B, et al. (2023). Long-term effects of beta-blockers in the reperfusion era: SWEDEHEART. European Heart Journal, 44(12), 1055-1064.

[10] Goldberger JJ, et al. (2015). Effect of Beta-Blocker Dose on Survival After Acute MI. JACC, 66(13), 1431-1441.

[11] Puymirat E, et al. (2016). Beta-blockers and mortality after MI in patients without heart failure. BMJ, 354, i4801.

[12] Johanna Carlbring & Lasse Bosse (2025). A Review on Mental Health Integration and Digital Therapeutics in Primary Care. Dinkum Journal of Medical Innovations, 4(05):298-305..

[13] Nielsen EE, et al. (2019). Beta-blockers for secondary prevention after MI: A systematic review. PLOS Medicine, 16(11), e1002935.
[14] Knuuti J, et al. (2020). 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. European Heart Journal, 41(3), 407-477.
[15] Tropeano AI, et al. (2024). The End of an Era? Routine Beta-Blockade Post-MI. Journal of Cardiovascular Pharmacology, 87(2), 115-128.
[16] Kaul, S. (2024). Reevaluating beta-blocker recommendations post-myocardial infarction: perspective on the 2025 guideline update. Journal of the American College of Cardiology, 85(22), 2096-2099.
[17] Baviera, M., Zanovello, A., Ojeda-Fernández, L., Molteni, M., & Cimminiello, C. (2024). Use of betablockers in post-myocardial infarction patients in a real-world setting. European Journal of Internal Medicine, 134, 157-159.
[18] Joseph Linardon (2025). Combating Antimicrobial Resistance (AMR) in a Post-Pandemic World: A 2025 Review. Dinkum Journal of Medical Innovations, 4(05):306-312.
[19] Yndigegn, T., Lindahl, B., Alfredsson, J., Benatar, J., Brandin, L., Erlinge, D., ... & Jernberg, T. (2023). Design and rationale of randomized evaluation of decreased usage of beta-blockers after acute myocardial infarction (REDUCE-AMI). European Heart Journal-Cardiovascular Pharmacotherapy, 9(2), 192-197.

