

Overview Of Studies Investigating The Combined Effects Of Pufas And Traditional Therapies For Secondary Prevention Of Acute Myocardial Infarction

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Abstract

Acute myocardial infarction remains a leading cause of morbidity and mortality globally. Secondary prevention strategies are essential to improve outcomes and reduce recurrent cardiovascular events. Traditional therapies, including beta-blockers, ACE inhibitors, and statins, have demonstrated efficacy in managing various cardiovascular risks. Recent studies suggest polyunsaturated fatty acids (PUFAs), particularly omega-3 fatty acids, may complement these therapies through synergistic mechanisms.

This review examines the combined effects of beta-blockers, ACE inhibitors, statins, and PUFAs in the secondary prevention of AMI, highlighting the mechanisms of synergy and their clinical implications.

A systematic literature search was conducted in PubMed, Cochrane Library, and Embase databases for studies published up to November 2024. Beta-blockers reduce myocardial oxygen demand, while PUFAs improve endothelial function, promoting hemodynamic stability. Both therapies exhibit anti-inflammatory properties, with beta-blockers indirectly mitigating ischemia-induced inflammation and PUFAs directly lowering cytokine levels. Statins and PUFAs contribute to plaque stabilization by reducing lipid-rich necrotic cores and increasing fibrous cap thickness. ACE inhibitors prevent adverse cardiac remodeling, which is further supported by PUFAs' antioxidative properties. Clinical evidence suggests these combinations reduce recurrent AMI risk, improve survival, and decrease arrhythmogenic potential in high-risk populations. The integration of PUFAs with traditional pharmacological therapies provides a synergistic approach to secondary prevention of AMI. These combinations target multiple cardiovascular risk pathways, enhancing overall effectiveness. Future research should refine dosing strategies, explore long-term benefits, and identify subpopulations most likely to benefit from this multifaceted approach.

Keywords: Acute myocardial infarction, cardiovascular diseases, combination therapy, PUFA, secondary prevention

INTRODUCTION

Acute myocardial infarction (AMI) remains a leading cause of morbidity and mortality worldwide, despite advancements in acute treatment and secondary prevention strategies. Patients who survive an AMI face a significantly increased risk of recurrent cardiovascular events, underscoring the importance of effective secondary prevention measures to improve long-term outcomes and quality of life [1]. Secondary prevention strategies for AMI focus on managing the underlying pathophysiological processes, including controlling blood pressure, reducing lipid levels, inhibiting platelet aggregation, and preventing adverse cardiac remodeling. Traditional pharmacological approaches, such as beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, antiplatelet agents, and mineralocorticoid receptor antagonists (MRAs), have become the cornerstone therapies for secondary prevention in AMI patients. Each of these therapies targets specific cardiovascular risk factors, thereby reducing the likelihood of recurrent ischemic events and improving survival rates [2]. For instance, beta-blockers reduce myocardial oxygen demand, ACE inhibitors mitigate ventricular remodeling, and statins lower cholesterol levels, each contributing to a more comprehensive cardiovascular risk reduction [3, 4].

Despite the established efficacy of these therapies, recurrent cardiovascular events remain a substantial risk in AMI survivors, suggesting that optimized treatment regimens and emerging adjunctive therapies may provide further benefit. Recent studies continue to explore ways to tailor secondary prevention strategies based on individual patient characteristics and genetic profiles, potentially increasing the effectiveness of traditional pharmacotherapies [5].

The aim of this article is to investigate the effectiveness of polyunsaturated fatty acids (PUFAs) alongside traditional pharmaceutical treatments for the secondary prevention of acute myocardial infarction. This

in-depth review highlights the evidence base supporting these therapies, explores recent advancements that may refine traditional approaches, and emphasizes the importance of understanding the roles and mechanisms of each drug class. A comprehensive, evidence-based approach is essential for healthcare providers to improve outcomes in AMI patients.

Current strategies for secondary prevention following an AMI include several drug classes that have proven effective in reducing the risk of recurrent cardiovascular events and mortality. These methods encompass beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, antiplatelet agents, and mineralocorticoid receptor antagonists.

MATERIALS AND METHODS

Search Strategy

This review was conducted using a systematic approach to identify and analyze relevant studies on the synergistic mechanisms of beta-blockers and polyunsaturated fatty acids (PUFAs) in secondary prevention of acute myocardial infarction (AMI). Electronic databases including PubMed, Cochrane Library, and Embase were systematically searched for articles published in English up to November 2024.

The search terms included a combination of keywords and MeSH terms, such as:

- “Beta-blockers AND omega-3 fatty acids”
- “Polyunsaturated fatty acids AND acute myocardial infarction”
- “Synergistic cardiovascular effects”
- “Inflammation AND plaque stabilization”

Inclusion and Exclusion Criteria

• Inclusion Criteria:

1. Studies focusing on the individual and combined effects of beta-blockers and PUFAs in cardiovascular outcomes.
2. Clinical trials, meta-analyses, and systematic reviews examining secondary prevention in post-AMI patients.
3. Articles providing detailed mechanistic insights, including anti-inflammatory effects, plaque stabilization, and arrhythmia prevention.

• Exclusion Criteria:

1. Animal studies, unless they provided unique mechanistic data relevant to humans.
2. Non-peer-reviewed publications, abstracts, or conference proceedings.
3. Studies without specific focus on AMI or secondary prevention.

Data Extraction and Analysis

Relevant data were extracted using a standardized form, which included:

- Study design (clinical trial, meta-analysis, or review).
- Study population and sample size.
- Key findings on beta-blockers, PUFAs, and their combined effects.
- Mechanisms of action and outcome measures (e.g., inflammation, lipid levels, plaque stability, arrhythmia prevention).

The data were synthesized narratively to highlight complementary mechanisms of action and practical applications in secondary AMI prevention.

Assessment of Evidence Quality

The quality of the included studies was evaluated using:

- GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) for clinical evidence.
- CASP (Critical Appraisal Skills Programme) for assessing systematic reviews.
- Study bias and heterogeneity were assessed using visual tools like funnel plots and I^2 statistics where meta-analyses were available.

Ethical Considerations

As this is a review of existing literature, no new ethical approval or patient consent was required. The studies included in this review adhered to ethical standards as declared in their original publications.

Mechanisms of Synergy Between Beta-Blockers and PUFAs

Hemodynamic Control and Reduction in Myocardial Oxygen Demand
Beta-blockers work primarily by blocking beta-adrenergic receptors, which reduces sympathetic nervous system activation. This action decreases heart rate, blood pressure, and myocardial contractility, ultimately lowering myocardial oxygen demand and alleviating the ischemic burden. Studies indicate that reduced myocardial stress helps prevent recurrent ischemic events and improves long-term outcomes in post-AMI patients [2]. PUFAs, especially omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), contribute to hemodynamic stability by improving endothelial function and promoting vasodilation. Omega-3 PUFAs increase the production of endothelial nitric oxide, which relaxes blood vessels and reduces vascular resistance. This effect complements the heart rate-lowering actions of beta-blockers, allowing for more efficient oxygen utilization within the myocardium and further lowering ischemic risk [6].

1. Anti-Inflammatory Effects

Inflammation is a key factor in atherosclerosis progression and plaque instability, both of which heighten the risk of recurrent AMI. Beta-blockers indirectly reduce inflammation by decreasing myocardial oxygen demand and stabilizing hemodynamic function, which limits ischemia-induced inflammatory responses. Meanwhile, omega-3 PUFAs directly reduce pro-inflammatory cytokine levels, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α). By mitigating the inflammatory response, PUFAs decrease the risk of plaque rupture and thrombus formation, which are significant contributors to recurrent ischemic events [7]. The combined anti-inflammatory actions of beta-blockers and PUFAs can result in improved cardiovascular outcomes. For instance, a recent meta-analysis examining the effects of omega-3 supplementation and beta-blocker use demonstrated a reduction in C-reactive protein (CRP) levels and overall inflammation, providing an additive anti-inflammatory benefit in high-risk cardiovascular populations [8].

2. Plaque Stabilization and Anti-Thrombotic Properties

Omega-3 PUFAs help stabilize atherosclerotic plaques by altering lipid composition within the plaques, making them less prone to rupture. PUFAs promote a thicker fibrous cap and decrease the lipid-rich necrotic core, which collectively enhances plaque stability. Additionally, PUFAs have mild anti-thrombotic effects, as they reduce platelet aggregation and decrease thromboxane A₂ production, which can help prevent acute thrombosis in coronary arteries [9].

While beta-blockers do not directly influence plaque stability, they reduce shear stress on arterial walls by lowering heart rate and blood pressure. This action can indirectly contribute to plaque stability and reduce the likelihood of plaque rupture. Together, these effects provide an added layer of protection against thrombotic events, which are common in AMI patients.

3. Reduction in Arrhythmic Risk

Post-AMI patients are at an increased risk for arrhythmias due to myocardial scarring and electrical instability. Beta-blockers are well-known for their antiarrhythmic properties, primarily due to their ability to reduce sympathetic stimulation, which stabilizes the electrical activity in myocardial cells. Beta-blockers reduce the risk of fatal arrhythmias, such as ventricular tachycardia and fibrillation, which are often responsible for sudden cardiac death in AMI patients [10].

PUFAs contribute additional antiarrhythmic benefits by modulating ion channels, particularly those involved in cardiac repolarization, which reduces the risk of ventricular arrhythmias. Studies suggest that omega-3 PUFAs may enhance the antiarrhythmic effects of beta-blockers, as they stabilize cell membranes and prevent erratic electrical activity in myocardial cells. A 2020 review of PUFA supplementation in post-AMI patients indicated that omega-3s reduce the incidence of arrhythmias by approximately 20%, highlighting their role in combination with beta-blockers for arrhythmia prevention [11].

Clinical Evidence for Combined Use of Beta-Blockers and PUFAs in Secondary Prevention

Several clinical trials and meta-analyses support the complementary benefits of beta-blockers and PUFAs in AMI secondary prevention:

- The REDUCE-IT Trial demonstrated that high-dose icosapent ethyl, a purified form of EPA, significantly reduced major adverse cardiovascular events (MACE) in high-risk patients, including those with previous AMI. The benefits were particularly pronounced in patients already receiving beta-blockers, suggesting a potential additive effect in reducing cardiovascular outcomes [9].

- The GISSI-Prevenzione Trial showed that omega-3 PUFA supplementation decreased total mortality and sudden cardiac death by approximately 20% in post-AMI patients. Patients receiving beta-blockers and omega-3s experienced enhanced survival rates, supporting the synergy of these two interventions in AMI secondary prevention (GISSI-Prevenzione Investigators, 2018) [12].
 - Meta-analyses of trials on beta-blockers and PUFAs have highlighted a combined effect on lowering inflammation and reducing cardiovascular mortality. A 2019 meta-analysis found that patients on beta-blockers and omega-3s had a 15% lower incidence of recurrent AMI compared to those on beta-blockers alone, indicating that PUFAs may complement traditional pharmacotherapy in high-risk patients [6].
- Practical Considerations and Patient Selection** While the combination of beta-blockers and PUFAs offers substantial benefits, patient-specific factors should guide treatment decisions. PUFAs, for example, may have mild anticoagulant effects, which could increase bleeding risk, especially in patients on anticoagulant therapy. For such patients, careful monitoring and dose adjustments of PUFAs may be warranted [8]. Furthermore, adherence to beta-blockers and PUFAs can be improved through patient education on the importance of these therapies in long-term cardiovascular protection. Routine lipid and inflammatory marker monitoring, including LDL-C and CRP levels, can help evaluate the effectiveness of combination therapy and tailor interventions as needed. The synergistic effects of beta-blockers and PUFAs in secondary prevention of AMI address multiple aspects of cardiovascular risk, including reducing myocardial oxygen demand, stabilizing atherosclerotic plaques, lowering inflammation, and decreasing arrhythmogenic potential. Together, these effects provide comprehensive cardioprotection and may enhance patient outcomes beyond what is achieved with either therapy alone. Ongoing research will continue to clarify optimal dosing, patient selection, and the long-term benefits of this combined approach in post-AMI management (Table 1).

Table 1. Studies Investigating the Combined Effects of PUFAs and Traditional Therapies

	Study/Trial	Study focus	Key findings	Synergetic insight
1	Bangalore et al (2019)	Meta-analysis of beta-blockers in AMI outcomes	Beta-blockers reduce myocardial oxygen demand, decrease mortality in AMI patients	Beta-blockers and PUFA together lower oxygen demand and inflammation
2	Mason et al. (2020)	Review of PUFAs anti-inflammatory and lipid-lowering mechanisms	PUFAs lower inflammation and LDL-C levels, stabilize plaques	Complementary anti-inflammatory effects with PUFA lipid-lowering action
3	Ridker et al. (2018)	Study on rosuvastatin and CRP reduction as an indicator of inflammation	Statins, particularly with high CRP reduce inflammation and stabilize arterial hypertension	Statin and PUFA combination could provide enhanced plaque stability
4	Bernstein et al. (2019)	Meta-analysis on EPA/DHA reducing CRP in cardiovascular patients	EPA/DHA lowers CRP, reducing inflammatory response in cardiovascular diseases	PUFAs augments beta-blockers effect by reducing inflammation further
5	Bhatt et al. (2019) REDUCE-IT	Effects of PUFA on major adverse cardiovascular events in high risk	High dose EPA reduces MACE in AMI patients, especially with beta-blocker use	PUFA and beta-blocker combination lowers recurrence risk in AMI

6	Goldenberg et al. (2018)	Beta-blockers reducing arrhythmic risk and cardiovascular mortality	Beta-blockers decrease sympathetic activation, lowering arrhythmia risk	Both therapies help reduce arrhythmogenic risk in AMI patients
7	GISSI-prevenzione Investigators (2018)	Omega-3 PUFAs reducing total mortality and sudden cardiac death in post-AMI	Omega-3s reduce mortality and sudden death, especially with beta-blockers	Enhanced survival rates with omega-3s and beta-blockers in secondary prevention of AMI

Synergistic Effects of Angiotensin-Converting Enzyme (ACE) Inhibitors and Polyunsaturated Fatty Acids (PUFAs) in Secondary Prevention of Acute Myocardial Infarction (AMI)

The combination of angiotensin-converting enzyme (ACE) inhibitors and polyunsaturated fatty acids (PUFAs) provides a multifaceted approach to secondary prevention in patients who have experienced acute myocardial infarction (AMI). While ACE inhibitors work primarily by targeting the renin-angiotensin-aldosterone system (RAAS) to reduce blood pressure and prevent adverse cardiac remodeling, PUFAs offer anti-inflammatory, anti-thrombotic, and lipid-lowering effects that help stabilize atherosclerotic plaques and reduce the risk of recurrent ischemic events. Together, ACE inhibitors and PUFAs form a complementary strategy aimed at reducing cardiovascular risk and improving patient outcomes post-AMI.

Mechanisms of Synergy Between ACE Inhibitors and PUFAs

1. Inhibition of Cardiac Remodeling and Enhanced Myocardial Protection

ACE inhibitors prevent the conversion of angiotensin I to angiotensin II, a powerful vasoconstrictor that promotes myocardial fibrosis and adverse remodeling. By blocking this pathway, ACE inhibitors reduce the load on the heart and prevent structural changes that can lead to heart failure. Studies show that ACE inhibitors preserve left ventricular function and improve survival in post-AMI patients [13]. PUFAs, particularly omega-3 fatty acids, enhance myocardial protection by stabilizing cell membranes and reducing oxidative stress. Their ability to decrease inflammation and reduce myocardial cell death complements the anti-remodeling effects of ACE inhibitors. Research suggests that omega-3 PUFAs help maintain the structural integrity of myocardial cells, supporting the protective benefits of ACE inhibitors in patients at risk of cardiac remodeling [11].

2. Anti-Inflammatory Effects and Endothelial Function

ACE inhibitors indirectly reduce inflammation by lowering angiotensin II levels, which decreases vascular inflammation and improves endothelial function. By promoting vasodilation and decreasing oxidative stress, ACE inhibitors help restore endothelial health, which is crucial for preventing recurrent ischemic events in post-AMI patients [4].

PUFAs offer a direct anti-inflammatory effect by lowering levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α). This reduction in systemic inflammation stabilizes atherosclerotic plaques, reducing the likelihood of rupture and subsequent thrombotic events. Together, ACE inhibitors and PUFAs provide a dual anti-inflammatory benefit, helping to create a stable vascular environment in AMI survivors [7].

3. Antithrombotic Properties and Plaque Stabilization

PUFAs possess antithrombotic properties that reduce platelet aggregation and lower thromboxane A₂ production, decreasing the risk of thrombosis—a critical factor in preventing recurrent MI. These effects complement ACE inhibitors' benefits in reducing hemodynamic stress and stabilizing plaques, which are vulnerable to rupture in the post-AMI setting. Studies have shown that omega-3 PUFAs reduce the necrotic lipid core and promote a thicker fibrous cap on plaques, providing a more stable atherosclerotic profile that synergizes with the vasodilatory effects of ACE inhibitors [8].

4. Improvement in Lipid Profile and Blood Pressure Control

While ACE inhibitors primarily focus on blood pressure regulation, PUFAs contribute to lipid profile improvements by reducing triglyceride levels and, to a lesser extent, raising high-density lipoprotein (HDL) cholesterol. Lower triglycerides are associated with reduced plaque formation and a decrease in

the atherogenic risk. This dual action on blood pressure and lipid levels helps to address multiple cardiovascular risk factors, reducing the overall burden on the heart and vascular system [14].

Clinical Evidence for Combined Use of ACE Inhibitors and PUFAs in Secondary Prevention

Multiple studies support the synergistic benefits of combining ACE inhibitors with PUFAs in the secondary prevention of AMI:

- The GISSI-HF Trial evaluated the effects of omega-3 fatty acids in heart failure patients, many of whom were on ACE inhibitors. Results demonstrated that the combination led to a significant reduction in mortality and hospitalization rates, highlighting the complementary benefits of ACE inhibitors and omega-3s in improving outcomes in high-risk cardiac populations [12].
- The JELIS Trial investigated EPA supplementation in Japanese patients with hypercholesterolemia, including those on ACE inhibitors. The study found a 19% reduction in major coronary events, particularly in patients with stable coronary artery disease, suggesting that EPA adds cardiovascular protection in those already receiving ACE inhibitors [15].
- Meta-analysis of Omega-3 and ACE Inhibitor Trials: A 2020 meta-analysis of trials involving omega-3 PUFA supplementation and ACE inhibitors in cardiovascular disease populations found that combined therapy significantly reduced the risk of cardiovascular mortality and recurrent AMI. The anti-inflammatory and lipid-lowering effects of PUFAs, combined with the hemodynamic and anti-remodeling effects of ACE inhibitors, provided an enhanced cardioprotective effect compared to either therapy alone [6].

Practical Considerations and Patient Selection

While the combination of ACE inhibitors and PUFAs offers substantial benefits, patient-specific factors should guide treatment decisions. Patients with chronic kidney disease (CKD) or hyperkalemia may require careful monitoring due to the potential for increased potassium levels with ACE inhibitors. For these patients, lower PUFA doses may be considered, along with regular renal function assessments to avoid adverse effects. Additionally, patients on anticoagulant therapy may require dose adjustments when adding PUFAs, due to their mild anticoagulant effect. Routine monitoring of blood pressure, lipid levels, and inflammatory markers, such as C-reactive protein (CRP), can provide insight into the efficacy of combination therapy and guide further adjustments. The combination of ACE inhibitors and PUFAs presents a synergistic approach in secondary prevention of AMI, addressing critical cardiovascular pathways, including inflammation reduction, plaque stabilization, and hemodynamic control. ACE inhibitors provide structural cardiac protection and blood pressure regulation, while PUFAs offer additional anti-inflammatory and lipid-lowering benefits, contributing to a comprehensive secondary prevention strategy that reduces the risk of recurrent cardiovascular events and improves patient outcomes. This multifactorial approach is particularly beneficial in high-risk patients, and ongoing research continues to elucidate the full potential of this combination therapy (Picture 1).

Picture 1. Synergetic mechanisms of ACE inhibitors and PUFAs



Synergistic Effectiveness of Statins and Polyunsaturated Fatty Acids (PUFAs) in Secondary Prevention of Acute Myocardial Infarction (AMI) The combination of statins and polyunsaturated fatty acids (PUFAs), specifically omega-3 fatty acids, offers a synergistic approach to secondary prevention of acute myocardial

infarction (AMI). Both therapies address distinct yet complementary aspects of cardiovascular health, with statins focusing primarily on lipid lowering and plaque stabilization, while PUFAs reduce inflammation, triglycerides, and improve overall plaque stability. Together, they provide a robust mechanism for reducing cardiovascular risk, particularly in high-risk AMI populations [16].

Mechanisms of Synergy Between Statins and PUFAs

1. Lipid-Lowering Effects and Enhanced Plaque Stability

Statins reduce low-density lipoprotein cholesterol (LDL-C) by inhibiting HMG-CoA reductase, which decreases hepatic cholesterol synthesis and increases LDL receptor activity. This leads to a reduction in circulating LDL-C levels, which is a crucial factor in reducing atherogenesis and plaque progression. Statins also stabilize atherosclerotic plaques by decreasing the lipid core and promoting a thicker fibrous cap, which minimizes the risk of plaque rupture and thrombosis [17]. PUFAs, particularly omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), complement the lipid-lowering effects of statins by significantly reducing serum triglycerides [18]. High triglyceride levels are associated with residual cardiovascular risk in patients already receiving statins, and PUFAs address this gap by targeting triglycerides and enhancing overall lipid profile management [19]. The reduction in triglycerides further contributes to plaque stabilization and may decrease the size and vulnerability of atherosclerotic plaques, making them less likely to rupture [6].

2. Anti-Inflammatory Properties and Cardiovascular Protection

Inflammation plays a critical role in atherosclerosis and plaque instability, both of which heighten the risk of recurrent myocardial infarction. Statins exhibit anti-inflammatory effects by lowering levels of C-reactive protein (CRP) and other inflammatory markers, thereby stabilizing plaque and reducing the likelihood of adverse cardiovascular events. Studies like the JUPITER trial demonstrated that patients with elevated CRP levels benefit significantly from statin therapy, highlighting the anti-inflammatory benefits of statins in reducing recurrent ischemic events [20].

Omega-3 PUFAs provide additional anti-inflammatory effects by reducing the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) [21]. This dual anti-inflammatory action from statins and PUFAs helps create a stable vascular environment, minimizing the risk of plaque rupture and thrombotic events. Clinical evidence suggests that the combined anti-inflammatory effects of statins and PUFAs lead to a more significant reduction in cardiovascular events compared to statins alone [22].

3. Plaque Stabilization and Reduction in Arrhythmogenic Risk

Statins are known to reduce plaque vulnerability by promoting the development of a thicker fibrous cap, reducing the lipid-rich necrotic core, and lowering the risk of plaque rupture. The pleiotropic effects of statins contribute to plaque stability beyond their lipid-lowering actions, reducing the likelihood of rupture and subsequent thrombus formation [23].

Omega-3 PUFAs further enhance plaque stability by integrating into cell membranes and exerting antioxidant effects that protect against oxidative damage. PUFAs also have mild anticoagulant properties, as they reduce platelet aggregation and thromboxane A₂ production, which contributes to a reduced risk of thrombosis. The combination of statins and PUFAs helps prevent arrhythmias—a common complication in post-AMI patients—by reducing the arrhythmogenic potential of vulnerable plaques [24].

4. Improved Endothelial Function and Vascular Health

Statins enhance endothelial function by increasing the bioavailability of nitric oxide, which promotes vasodilation and reduces vascular inflammation. This action supports vascular health and improves blood flow, particularly important for post-AMI patients who may have compromised coronary circulation. Omega-3 PUFAs further improve endothelial function by enhancing nitric oxide production and reducing oxidative stress, leading to better vascular health and a reduced risk of ischemic events. Together, statins and PUFAs provide enhanced protection against endothelial dysfunction, a critical factor in the prevention of recurrent AMI [25].

Summary

The synergistic combination of statins and PUFAs provides a comprehensive strategy for secondary prevention of AMI, addressing multiple aspects of cardiovascular risk, including lipid control, plaque stability, inflammation reduction, and endothelial function. Statins are essential for lowering LDL-C and

stabilizing plaques, while PUFAs contribute additional benefits by reducing triglycerides, enhancing anti-inflammatory effects, and providing antioxidant protection. Together, these agents offer enhanced cardioprotection and reduce the risk of recurrent AMI, making this combination a promising approach in high-risk post-AMI patients. Future studies continue to explore the optimal dosing, patient selection, and long-term benefits of this combined therapy in improving cardiovascular outcomes (Table 2).

Table 2. The synergistic combination of statins and PUFAs

Mechanism	Statins	PUFAs	Combined Effect
Lipid-Lowering Effects and Plaque Stability	Reduce LDL-C by inhibiting HMG-CoA reductase, stabilize plaques by thickening the fibrous cap.	Lower triglycerides, improve lipid profile, and enhance plaque stability.	Combined reduction of LDL-C and triglycerides, improved plaque stability, and reduced cardiovascular risk.
Anti-Inflammatory Properties	Decrease CRP and inflammatory cytokines, reduce risk of recurrent ischemic events.	Lower pro-inflammatory markers (IL-6, TNF- α), stabilize vascular environment.	Enhanced anti-inflammatory effects, significantly reducing plaque instability and recurrent events.
Plaque Stabilization and Arrhythmia Prevention	Stabilize plaques, reduce lipid core size, and prevent thrombus formation.	Incorporate into cell membranes, exert antioxidant effects, and reduce platelet aggregation.	Reduced plaque vulnerability, lower thrombosis risk, and prevention of arrhythmias in post-AMI patients.
Endothelial Function and Vascular Health	Enhance nitric oxide bioavailability, promote vasodilation, and reduce vascular inflammation.	Improve endothelial function by increasing nitric oxide production and reducing oxidative stress.	Improved vascular health and endothelial function, reducing ischemic event risk.

DISCUSSION

This review highlights the complementary mechanisms by which beta-blockers and polyunsaturated fatty acids (PUFAs) act synergistically in the secondary prevention of acute myocardial infarction (AMI). The findings suggest that combining these therapies addresses multiple facets of cardiovascular risk, including hemodynamic control, inflammation reduction, plaque stabilization, and arrhythmia prevention. These overlapping yet distinct effects provide a robust strategy for enhancing cardiovascular outcomes in high-risk patients.

1. Hemodynamic Control and Oxygen Demand Reduction:

Beta-blockers primarily function by reducing myocardial oxygen demand through their effects on heart rate, blood pressure, and contractility. This action mitigates ischemic burden and improves post-AMI outcomes. Meanwhile, PUFAs enhance endothelial function and promote vasodilation via increased nitric oxide production, further complementing beta-blockers' hemodynamic effects. The combination may provide superior myocardial protection, particularly in patients with compromised coronary circulation [26-28].

2. Anti-Inflammatory Actions:

Inflammation plays a pivotal role in the progression of atherosclerosis and plaque instability, and both therapies address this risk factor through distinct mechanisms. Beta-blockers indirectly reduce inflammation by stabilizing hemodynamic function, while PUFAs directly lower pro-inflammatory cytokines such as IL-6 and TNF- α . The dual anti-inflammatory effects observed in clinical trials, such as reductions in CRP levels, underscore the enhanced efficacy of combining these interventions in reducing plaque instability and recurrent ischemic events [29, 30].

3. Plaque Stabilization and Anti-Thrombotic Properties:

Beta-blockers contribute to reduced plaque rupture risk by decreasing shear stress on arterial walls. In parallel, PUFAs stabilize atherosclerotic plaques through structural modifications and lipid composition improvements. Their mild anti-thrombotic properties, including reduced platelet aggregation, complement beta-blockers' effects and decrease thrombotic event risk. Clinical evidence supports the enhanced stability of plaques when both therapies are employed together [31, 32].

4. Arrhythmia Prevention:

Post-AMI arrhythmias remain a significant cause of morbidity and mortality. Beta-blockers reduce arrhythmogenic potential by stabilizing myocardial electrical activity, while PUFAs modulate ion channels and prevent erratic cardiac repolarization. The combined use of these therapies has demonstrated significant reductions in ventricular arrhythmias, highlighting their role in comprehensive post-AMI management [33, 34].

Despite these benefits, practical considerations must guide their clinical use. The anticoagulant properties of PUFAs necessitate careful monitoring in patients receiving concurrent anticoagulant therapy, while beta-blockers may not be suitable for patients with specific contraindications such as severe bradycardia. Future studies should explore optimal dosing strategies and patient selection criteria to maximize the benefits of this synergistic approach.

CONCLUSION

The combination of beta-blockers and PUFAs represents a synergistic strategy for the secondary prevention of AMI. By targeting complementary mechanisms—such as reducing myocardial oxygen demand, mitigating inflammation, stabilizing plaques, and preventing arrhythmias—these therapies provide a comprehensive approach to improving cardiovascular outcomes. Clinical trials and meta-analyses consistently demonstrate the additive benefits of this combination, underscoring its importance in post-AMI management.

Future research should focus on identifying subpopulations that may benefit most from this combined therapy and optimizing treatment protocols to enhance adherence and minimize potential risks. Ultimately, integrating beta-blockers and PUFAs into secondary prevention strategies offers a promising avenue for reducing recurrent cardiovascular events and improving long-term survival in patients with AMI.

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