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Dr. Haddad is a cardiologist trained at the University of Montreal, currently pursuing an Interventional Cardiology Fellowship at New York-Presbyterian/Columbia University Irving Medical Center. He has been actively involved in cardiology research with a focus on complex coronary interventions, CTO PCI, and secondary prevention. Dr. Haddad also completed formal training in epidemiology and clinical research at Harvard University. He has amassed more than 20 publications, either as the primary author or co-author, presented more than 15 scientific abstracts both in oral or poster formats, moderated several conference sessions, and been involved in nearly 20 distinct research projects within the field of cardiology. Dr. Haddad was additionally engaged in administrative and educational responsibilities within Quebec and across Canada. He is planning to return to the University of Montreal Hospital Center (CHUM) upon completion of his fellowship.

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Secondary Prevention After Myocardial Infarction: Bridging Evidence to Practice

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Introduction

Management of acute coronary syndrome (ACS) has advanced significantly over the past years, with various strategies shown to improve patient survival and reduce cardiovascular (CV) adverse events. An expanding body of literature supports the efficacy of both pharmacologic and non-pharmacologic approaches after acute myocardial infarction (MI). This review aims to provide a comprehensive overview of the secondary prevention strategies after acute MI in the modern era, with a particular focus on recent guidelines and their application in Canadian healthcare practice.

The Non-Pharmacological Path After Acute MI

Cardiac rehabilitation (CR) remains the cornerstone of secondary prevention after MI. It is currently recommended prior to hospital discharge after an ACS event, as it has been shown to reduce death, MI, and hospital readmission. CR's multifaceted approach also aims to enhance functional capacity and patients' quality of life, whether delivered through a centre-based or home-based program.[1]

Lifestyle modification with a personalized and team-based approach is also an essential part of secondary prevention.[2] It is grounded in the following principles, designed to improve CV outcomes and reduce mortality.[2]

- The importance of complete abstinence from tobacco, using behavioural and/or pharmacologic approaches when necessary. E-cigarettes are not considered a first-line therapy for tobacco abstinence, due to unknown long-term effects.
- Limitation of alcohol intake to ≤1 drink/day for women and ≤2 drinks/day for men, as alcohol use offers no CV benefit.
- Physical activity counselling to encourage patients to engage in ≥150 minutes/week of moderate-intensity aerobic activities, and ≥2 days/week resistance training.
- Weight management in overweight or obese patients.
- Dietary modification with the adoption of a Mediterranean diet. The use of omega-3 fatty acids or dietary supplements has not shown additional CV benefit.
- Stress management and mental health counselling.

Cardiovascular risk factors should also be managed in accordance with major society guidelines, including optimal control of hypertension,[3] hypercholesterolemia and hypertriglyceridemia management,[4] and aggressive treatment of diabetes.[5]

Electrical complications should also be managed appropriately, including the use of an implantable cardioverter-defibrillator for ventricular arrhythmias when indicated, and a permanent pacemaker for irreversible advanced bradyarrhythmia.[1]

Last but not least, influenza vaccination has demonstrated a survival benefit at one year after MI and is therefore recommended to reduce death and major adverse cardiovascular events (MACE).[1] Other vaccines, such as the COVID-19 and pneumococcal polysaccharide vaccines, may also help lower the risk of post-infection complications and MACE in high-risk populations, particularly in patients with established coronary artery disease.[2]

Rewiring Recovery: Pharmacologic Approaches to ACS Care after MI

Antithrombotic therapy

Dual antiplatelet therapy (DAPT) with low-dose acetylsalicylic acid (ASA) and a P2Y12

inhibitor (clopidogrel, ticagrelor, or prasugrel) is recommended for patients undergoing percutaneous coronary intervention (PCI), coronary bypass surgery, as well as for those managed medically without revascularization for ACS. The duration of DAPT may range from 1 month to up to 3 years, depending on individual risk profiles, to reduce the risk of recurrent ischemic events.[6] In patients managed without revascularization, only ticagrelor and clopidogrel are recommended as part of the DAPT strategy. Selection and duration of DAPT therapy should be guided by a careful assessment of the patient's individual bleeding and ischemic risks.[6] Once DAPT is discontinued, lifelong single antiplatelet therapy (SAPT) with either ASA or clopidogrel is recommended, although emerging evidence suggests a potential benefit of clopidogrel over ASA for reducing recurrent ischemic events.[7]

In the COMPASS trial, combining low-dose rivaroxaban (2.5 mg twice daily) with low-dose ASA reduced the risk of MACE in patients with stable atherosclerotic cardiovascular disease (ASCVD)—including those with remote PCI—at the expense of an increased bleeding risk.[8] As such, its use may be considered for secondary prevention of ASCVD.[9]

A more detailed approach to the management and choice of antithrombotic therapy in both the acute and chronic phases following ACS is presented in **Figure 1**, incorporating the most recent evidence and guideline recommendations.

Lipid-Lowering Therapies

The treatment of dyslipidemia is considered a fundamental part of pharmacologic care after MI. Patients should all be treated with maximally tolerated dose of statins with add on therapy considered when low-density lipoprotein cholesterol (LDL-C) of ≥1.8 mmol/L, non-high-density lipoprotein cholesterol (non-HDL-C) of ≥2.4 mmol/L, and/or apolipoprotein B (ApoB) of ≥0.7 g/L.4 The European Society of Cardiology (ESC) recommends even more stringent targets, advising an LDL-C level of <1.4 mmol/L with a reduction of ≥50% after an ACS, and potentially lowering the target to an LDL-C of <1.0 mmol/L in patients who experience a second event within 2 years.[10]

Besides health-behaviour modifications, early initiation of high-intensity potent statin therapy (atorvastatin or rosuvastatin) is recommended as first-line treatment to achieve these targets and reduce MACE.[1,4] The evidence supporting their use is robust, with demonstrated benefits during both the acute and chronic phases following MI.[11,12] In both the European and American Guidelines, early reassessment of lipids post ACS and adjustment of therapy until desired lipid levels are achieved (every 4-8 weeks) are emphasized.[1,10]

In addition to high-dose statin therapy, second-line treatments include ezetimibe (if LDL-C levels remain between 1.8 and 2.2 mmol/L) or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in patients whose lipid parameters are further away from threshold levels (if LDL-C remains >2.2 mmol/L, ApoB >0.8 g/L or non-HDL-C >2.9 g/L). Other high-benefit patients for initiating PCSK9 inhibitors upfront after high-dose statin therapy include, among others, those within 52 weeks of index hospitalization for a recent ACS, patients with recurrent acute MI, and those with diabetes.[4]

The FOURIER and ODYSSEY OUTCOMES trials are the key clinical studies evaluating PCSK9 inhibitors for managing hypercholesterolemia in MI,[13,14] and they are cited in recent guidelines.[4] The FOURIER trial evaluated evolocumab in patients with established ASCVD, including those with prior MI, prior stroke, or peripheral artery disease, demonstrating a significant reduction in MACE when added to statin therapy (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.79 to 0.92, P<0.001).[13] The benefits of evolocumab were reinforced in the FOURIER-OLE study which confirmed a long-term sustained reduction in MACE by 15% and CV death by 23% over a follow-up period exceeding 8 years.[15] The ODYSSEY OUTCOMES trial specifically enrolled patients who experienced a recent ACS within the preceding year and had persistent hypercholesterolemia despite receiving maximally tolerated statin therapy. In this population, alirocumab significantly reduced MACE and all-cause mortality compared to placebo, achieving a relative risk reduction of approximately 15% for the primary composite endpoint (HR 0.85, 95% CI 0.78 to 0.93, P<0.001).[14]

Ezetimibe has been demonstrated to be an effective adjunct therapy to statin post ACS. In the IMPROVE-IT trial, adding ezetimibe to statin therapy resulted in a 6.4% relative risk reduction and a 2% absolute risk reduction in MACE over a 7 year period compared to placebo (HR 0.94, 95% CI 0.89 to 0.99, P=0.016).[16]

Recent updates to the American College of Cardiology guidelines for managing hypercholesterolemia post-ACS include the

addition of inclisiran and bempedoic acid. These agents are recommended for patients on maximally tolerated statin therapy or those with statin intolerance.[1] Bempedoic acid is an ATP-citrate lyase inhibitor that provides an additional ~20% reduction in LDL-C, and has demonstrated efficacy in reducing MACE in statin-intolerant patients.[17] In contrast, inclisiran is a small interfering RNA that inhibits PCSK9 synthesis, achieving up to a 50% additional reduction in LDL-C.[18] Its advantage lies in its convenient subcutaneous administration once every 6 months. However, clinical outcome trials with inclisiran in ASCVD are still ongoing.

Beyond hypercholesterolemia management, icosapent ethyl has emerged as another therapy for cardiovascular risk reduction in high-risk patients with elevated triglycerides. It consists of a high-dose, purified eicosapentaenoic (EPA) omega-3 fatty acid (4 g/day). The REDUCE-IT trial demonstrated its efficacy in reducing CV events in high-risk patients (including those post-MI), with an elevated triglyceride level of 1.52 to 5.63 mmol/L showing a 25% relative risk reduction of MACE compared to placebo. This benefit was independent of the reduction in triglyceride levels.[19] A post hoc subgroup analysis of the REDUCE-IT trial in patients with recent ACS <12 months showed a statistically significant reduction in the primary outcome, of 37% with an absolute risk reduction of 9.3%, which is higher than that of the parent trial, without increased risk of bleeding even in patients receiving DAPT.[20]

Renin-Angiotensin-Aldosterone System inhibitors

Oral Angiotensin converting enzyme (ACE) inhibitors are a cornerstone of pharmacologic therapy for secondary prevention after acute MI, with their efficacy demonstrated in landmark trials such as ISIS-4 and GISSI-3.[21] Their benefits are particularly pronounced in high-risk patients,

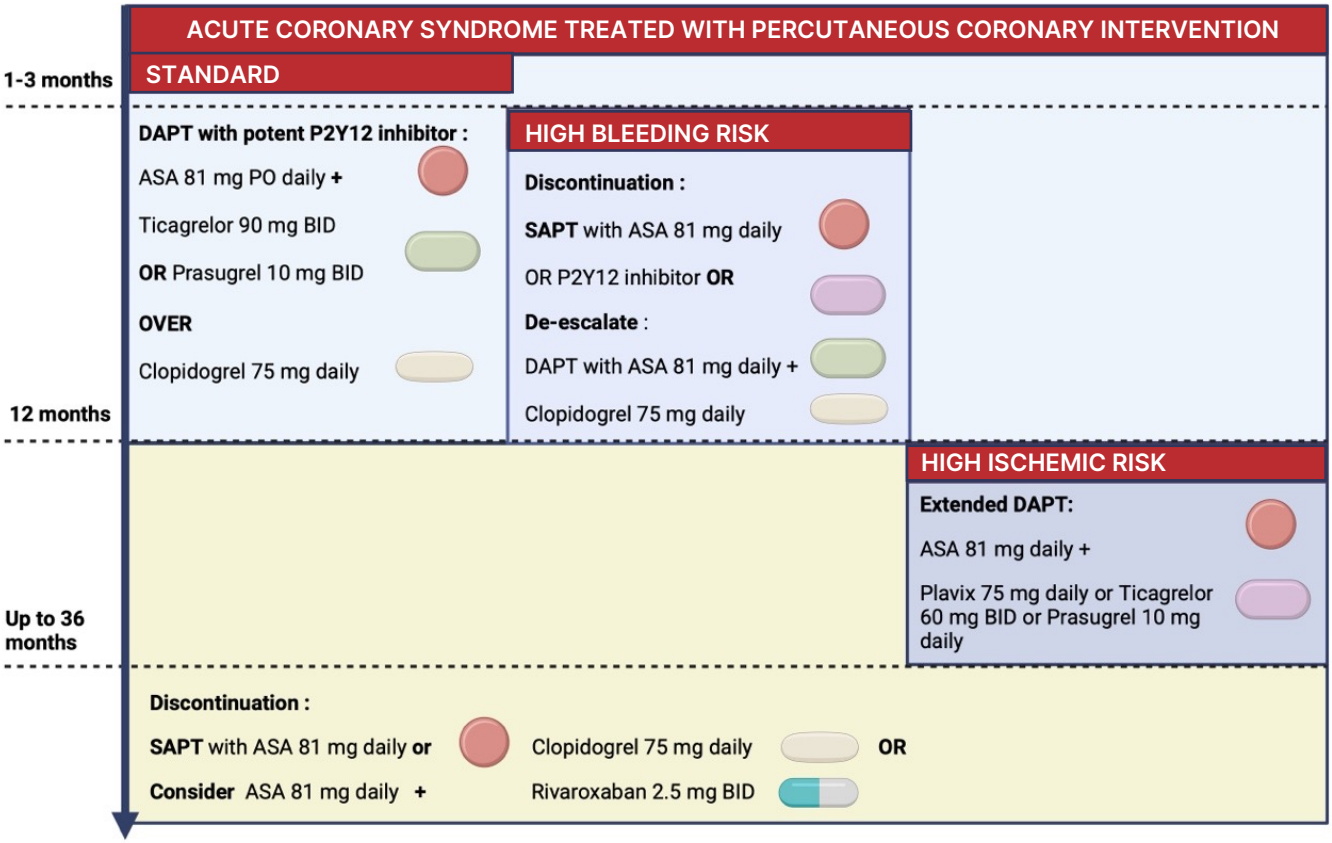

Figure 1. Recommended antithrombotic therapy following acute coronary syndromes treated with percutaneous coronary intervention; *courtesy of Kevin Haddad, MD, MSc and Laurie-Anne Boivin Proulx, MD, MSc*

Abbreviations: ASA: acetylsalicylic acid; **DAPT:** dual antiplatelet therapy; **SAPT:** single antiplatelet therapy.

including those with left ventricular ejection fraction (LVEF) ≤40%, diabetes, hypertension, chronic kidney disease, or anterior ST-elevation MI (STEMI).[1] Accordingly, ACE inhibitors or angiotensin II receptor blockers (ARB)s are recommended for patients with high-risk features after ACS, though their use remains reasonable even in lower-risk patients, given their proven benefits in reducing all-cause mortality and MACE.[1] While the angiotensin receptor–neprilysin inhibitor (ARNIs) have an established role in patients with heart failure (HF) with reduced ejection fraction (HFrEF), they have not demonstrated superiority over ACE inhibitors in reducing CV death or incident HF following acute MI.[22]

Mineralocorticoid receptor antagonists (MRA) have also been studied in the post-MI setting. Based on the EPHESUS study, patients with ACS and an LVEF ≤40% with HF and/or diabetes experienced a reduction in the primary endpoint of all-cause mortality with eplerenone, as well as in the composite endpoint of death or hospitalization from CV causes.[23] However, more recent findings from the CLEAR SYNERGY trial showed that spironolactone did not reduce MACE—defined as CV death or new/worsening HF—in an all-comers post-acute MI population.[24] These results support the use of MRAs for secondary prevention in post MI patients specifically with left ventricular dysfunction and/or HF, but not in unselected post-MI populations where no benefit has been demonstrated.

Beta-blockers

Oral beta-blockers (BB) are currently recommended within the first 24 hours after ACS, in the absence of contraindications, to reduce the risk of ventricular arrhythmias and reinfarction.[1]

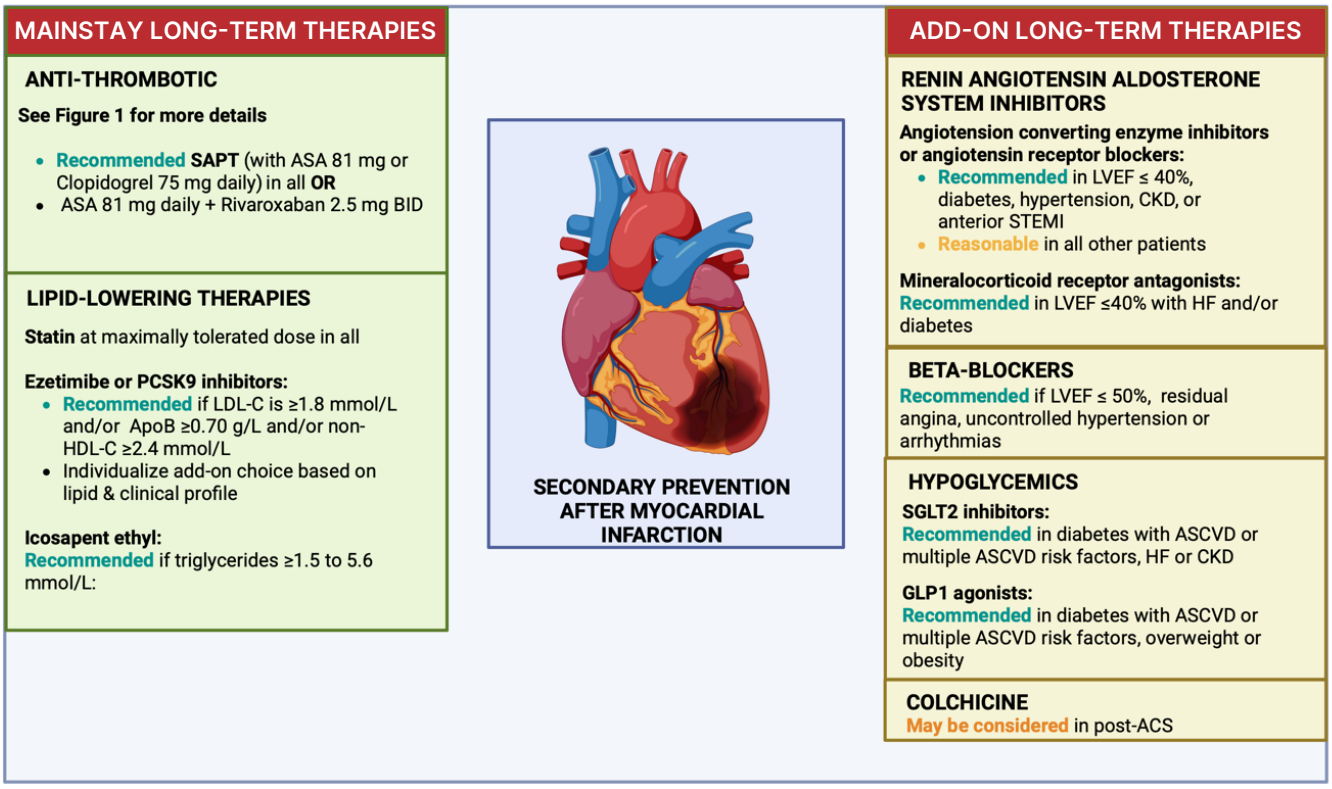

Figure 2. Recommended pharmacological treatment for long-term secondary prevention of myocardial infarction; *courtesy of Kevin Haddad, MD, MSc and Laurie-Anne Boivin Proulx, MD, MSc*

Abbreviations: ACS: acute coronary syndrome; **ApoB:** apolipoprotein B; **ASA:** acetylsalicylic acid; **ASCVD:** atherosclerotic cardiovascular disease; **CKD:** chronic kidney disease; **DAPT:** dual antiplatelet therapy; **GLP1:** glucagon-like peptide-1 receptor agonist; **HF:** heart failure; **HDL-c:** high-density lipoprotein cholesterol; **LDL-c:** low-density lipoprotein cholesterol; **LVEF:** left ventricular ejection fraction; **PCSK9:** proprotein convertase subtilisin/kexin type 9; **SAPT:** single antiplatelet therapy; **STEMI:** ST-elevation myocardial infarction.

They remain a fundamental treatment in patients with compelling and robust indications such as left ventricular dysfunction, HF, ventricular arrhythmias, and anginal symptoms. On the other hand, the benefit of using BB in patients with MI and preserved LVEF (>50%) who have undergone successful reperfusion therapy is less well established.

In the REDUCE-AMI trial, conducted in the contemporary era of early revascularization and optimal medical therapy, routine long-term BB use (median follow-up of 3.5 years) provided no additional benefit in reducing all-cause death or nonfatal MI in patients with preserved LVEF and no other indication for BB (HR 0.96, 95% CI 0.79 to 1.16, P=0.64).[25] The ABYSS trial evaluated the impact of discontinuing BB therapy in stable patients in the chronic phase following MI (median time from MI to randomization of 2.9 years), with an LVEF ≥40% and no CV events in the preceding 6 months. The study failed to demonstrate that discontinuation of BB therapy was non-inferior to continuation for the composite outcome of death, nonfatal MI, nonfatal stroke, or CV hospitalization (HR 1.16, 95% CI 1.01 to 1.33, P=0.44 for non-inferiority).[26] Additionally, interrupting BB did not lead to an improvement in quality of life.[26]

Based on recent guidelines and contemporary data, the use of BB post-MI appears to offer limited benefit in the absence of significant left ventricular dysfunction, HF, or other compelling indications such as a high arrhythmic burden, uncontrolled hypertension, or persistent anginal symptoms. However, for patients with uncomplicated MI who are already receiving chronic BB treatment, continuing BB therapy is currently recommended until new evidence emerges to guide changes in clinical practice.

SGLT2 Inhibitors and GLP1 Agonists

In addition to their established benefits in the treatment of HF and chronic kidney disease (CKD), sodium-glucose co-transporter 2 inhibitors (SGLT2is) are recommended to optimize the prevention of cardiorenal morbidity and mortality in patients with type 2 diabetes with ASCVD or multiple risk factors.[27] In this population, SGLT2is are recommended to reduce the risk of all-cause mortality, CV mortality and MACE.[27,28] Additionally, SGLT2is contribute to lowering the risk of hospitalizations for HF and to reducing the composite risk of significant decline in estimated glomerular filtration rate, progression to end-stage kidney disease, or kidney-related death.[28]

Meanwhile, glucagon-like peptide-1 receptor agonist (GLP-1RAs) are particularly recommended for reducing CV events in patients with diabetes with ASCVD or multiple risk factors. These agents have been shown to reduce all-cause and CV mortality, MACE, and may also reduce the risk of nonfatal stroke.[28] More recently, the SELECT trial demonstrated that subcutaneous semaglutide, a GLP-1RA significantly reduced MACE in patients with overweight or obesity and established ASCVD, even in the absence of diabetes.[29] Oral semaglutide was also shown to reduce MACE in patients with type 2 diabetes with ASCVD, CKD, or both.[30]

Anti-Inflammatory Therapy

Colchicine represents another class of medication that may be used in post-MI management, functioning as an anti-inflammatory agent that interferes with microtubule formation and potentially reducing the atherogenic plaque burden. Evidence supporting its use in the post-ACS setting is derived, in part, from the COLCOT trial, which showed that initiating colchicine 0.5 mg daily within 30 days of MI significantly reduced the primary composite endpoint (CV death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring revascularization) over a median follow-up of 22.6 months. These benefits were mainly driven by reductions in stroke and urgent revascularization.[31] According to the most recent guidelines, colchicine may be considered a reasonable option to reduce MACE.[1] However, more recent data from the CLEAR SYNERGY trial failed to demonstrate a reduction in the incidence of MACE with colchicine compared to placebo at a median follow-up of 3 years in patients with acute MI undergoing PCI.[32]

Future Directions

The current molecular approach to secondary prevention post-MI is presented in **Figure 2**. Nonetheless, many unanswered questions remain to be addressed in the coming decade, requiring a concerted and active effort to clarify how best to improve patient outcomes through various secondary prevention strategies.

As recommended post-MI therapies continue to evolve, new strategies are being explored to mitigate the thrombotic and bleeding risks. One such approach involves a new class of anticoagulants—selective factor XIa inhibitors (e.g., milvexian)—which are being evaluated in

the LIBREXIA-ACS trial. These agents serve as an adjunct to antiplatelet therapy post-MI by targeting a pathway considered dispensable for hemostasis, thereby potentially offering thrombotic risk reduction while minimizing bleeding risk.[33]

In parallel, therapeutic strategies targeting other residual risks are being investigated. While no approved therapy specifically targets lipoprotein(a)—a genetic risk factor for atherosclerosis—research is ongoing. Pelacarsen, an antisense oligonucleotide that lowers lipoprotein(a) levels, is being evaluated in the ongoing HORIZON trial to determine its potential to reduce CV events in patients with established ASCVD including previous MI.[34]

Additionally, finerenone, a novel nonsteroidal MRA, has shown a reduction in HF events and CV death in patients with HF and an LVEF ≥40%.[35] However, its specific role in the post-acute MI population remains to be established.

Ongoing investigations are exploring the potential of certain anti-inflammatory and immunomodulation molecules to reduce atherosclerosis progression. These agents could offer new targets for secondary prevention in patients with a high atherosclerotic risk. The ARTEMIS trial is currently evaluating ziltivekimab, a monoclonal antibody targeting interleukin-6, for its potential to reduce recurrent events in patients post-MI.[36]

Conclusion

The journey after an ACS extends beyond discharge. Through a combination of effective medical therapies and sustained non-pharmacological approaches, secondary prevention transforms recovery into resilience—reducing CV risk, improving survival, and empowering patients to reclaim their health. Achieving this goal requires aggressive risk factor management, delivered through a personalized, team-based approach, while targeting the full spectrum of mechanisms involved in plaque disruption and disease progression.

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Financial Disclosures

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