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Achieving the Target Cholesterol After Acute Coronary Syndrome: Fire but not Forget!

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Introduction

Acute coronary syndrome (ACS) continues to be a substantial contributor to both morbidity and mortality, withstanding notable evolutions in its prevention and treatment. (1).

Hypercholesterolemia is a known significant risk factor for coronary artery disease. Increased total cholesterol, LDL cholesterol (LDL-C), and non-HDL-Cholesterol (non-HDL-C) are associated with 20 – 30% risk of premature cardiac damage in youth. Hypertriglyceridemia is associated with two-threefold risk of incident and progressive cardiac and structural damage. (1) Lipid-lowering therapy must be initiated immediately after ACS to reduce the risk of recurrent cardiovascular events and mortality. (2) The approach to managing hypercholesterolemia has evolved significantly over the years, emphasizing the need for an aggressive treatment, akin to firing at a target, while also highlighting the importance of long-term vigilance.

Take Home Messages

- Lowering LDL cholesterol promptly and significantly in the acute phase after an ACS is crucial for preventing further damage and enhancing the chances of a favourable outcome. This forms the foundation of the "fire" approach.
- While the initial aggressive management is crucial, sustained, long-term efforts are required for continued benefits. This is the basis of the "not forget" approach.
- Shared decision-making between healthcare providers and patients is crucial in tailoring therapy to individual needs and promoting long term compliance.

Fire: Aggressive Initiatives in Hypercholesterolemia Management Post-ACS

In recent years, there has been a revolution in the management of hypercholesterolemia. Early and aggressive intervention with statins has become the cornerstone of post-ACS care. High-intensity

statin therapy has demonstrated its efficacy in reducing both LDL-C level and subsequent cardiovascular events. (3, 4)

The PROVE IT-TIMI 22, demonstrated intensive atorvastatin 80mg lowers major adverse cardiovascular events (MACE) in patients with ACS who undergo percutaneous coronary intervention. (5), and the IMPROVE-IT trial exhibited LDL-C level decreased incrementally and provided further cardiovascular benefit by reducing major adverse cardiovascular events, including non-fatal myocardial infarction, unstable angina requiring hospitalization, and non-fatal stroke, by adding ezetimibe to statin therapy following ACS in the early stage. (6) These trials have reinforced the importance of aggressive statin therapy in the early phase after ACS leads to improved outcomes and reduces the risk of recurrent cardiovascular events. (5,6)

In addition to stabilising atherosclerotic plaques, high-intensity statin therapy also produces anti-inflammatory effects by inhibiting isoprenoid synthesis, downregulating inflammatory transcription factors, increasing nitric oxide bioavailability, modulating leukocyte function, and its antioxidant effects which further enhance the overall therapeutic benefits. (7) Treatment with statins, especially when administered at high intensity for prolonged periods, significantly alters the composition of coronary plaque by reduction in fibrous tissue and an elevation in dense calcium volume. (8)

Novel Therapies: Beyond Statins

While statins have been revolutionary in managing hypercholesterolemia, novel therapies have emerged as potent additions.

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

PCSK9 inhibitors represent a breakthrough in cholesterol management. (9) These monoclonal antibodies lower LDL-C levels by inhibiting PCSK9, a protein that plays a crucial role in cholesterol metabolism. (10)

The FOURIER study **(Figure 1)** demonstrated a 59% decrease in LDL-C level and a decrease in cardiovascular events when evolocumab was added to statin. (11)

The FOURIER trial

Evaluated the PCSK9 inhibitor evolocumab in patients with atherosclerotic cardiovascular disease and LDL cholesterol ≥70 mg/dL while on statin therapy.

LDL-C Level Reduction at 48 Weeks: Evolocumab group: 59% reduction, Placebo group: 4% reduction, $p < 0.001$ for difference

Primary Endpoint (Composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization): Evolocumab group: 9.8% event rate, Placebo group: 11.3% event rate, Hazard Ratio: 0.85 (95% CI: 0.79-0.92), $p < 0.001$ for superiority

Key Secondary Endpoint (Composite of cardiovascular death, myocardial infarction, or stroke): Evolocumab group: 5.9% event rate, Placebo group: 7.4% event rate, Hazard Ratio: 0.80 (95% CI: 0.73-0.88), $p < 0.001$ for superiority

Figure 1. Summary of the FOURIER trial

Additionally, ODYSSEY study (**Figure 2**) demonstrated that alirocumab reduces the risk of recurrent ischaemic cardiovascular events. (12)

ODYSSEY Trial

Evaluated the PCSK9 inhibitor alirocumab in patients with hypercholesterolemia

LDL-C reduction at 24 weeks:
- Alirocumab group: 61% reduction from baseline
- Placebo group: 0.8% increase from baseline
- $p<0.001$ for difference between groups

MACE (composite of coronary heart disease death, non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization):
- Alirocumab group: 4.6% event rate
- Placebo group: 5.8% event rate
- Hazard Ratio: 0.78, 95% CI: 0.65-0.94, p=0.01

Figure 2. Summary of ODYSSEY Trial

According to the PACMAN-AMI trial (**Figure 3**), adding alirocumab to high-intensity statin resulted in greater coronary plaque regression by measuring maximum lipid core burden index and minimal fibrous cap thickness in non-infarct-related arteries on near-infrared spectroscopy intravascular ultrasonography and optical coherence tomography performed at baseline and after 52 weeks. (13) The benefit of PCSK9 inhibition occurs earlier and is larger in patients with multivessel disease. (14)

PACMAN-AMI Trial

Evaluated the PCSK9 inhibitor evolocumab in patients with recent myocardial infarction (MI)

LDL-C reduction at 12 weeks:
- Evolocumab group: 61% reduction from baseline
- Placebo group: 4.5% increase from baseline
- p<0.001 for difference

MACE (composite of death, MI, stroke, hospitalization for unstable angina or coronary revascularization):
- Evolocumab group: 7.0% event rate
- Placebo group: 15.9% event rate
- Hazard Ratio: 0.43, 95% CI: 0.23-0.80, p=0.007

Figure 3. Summary of PACMAN-AMI Trial

Inclisiran

Inclisiran is a novel small interfering RNA (siRNA) therapeutic agent designed to inhibit PCSK9 protein synthesis. These siRNA molecules are designed to bind to the messenger RNA (mRNA) responsible for PCSK9. Once attached, the siRNA prompts the degradation of PCSK9 mRNA, preventing its translation into functional PCSK9 protein. This reduces the levels of PCSK9 protein in liver cells, leading to an increase in LDL receptors on the cell surface. With more LDL receptors, LDL-C is cleared more efficiently from the bloodstream, resulting in lowered LDL-C levels. (15) LDL-C level can be reduced by 50% when administered via subcutaneous injection twice yearly, following the initial baseline and three-month doses in the ORION-10 and ORION 11trials. (16) Inclisiran has relatively lower cost than PCSK9 monoclonal antibody therapy and is an alternative, and a valuable adjunct to maximally tolerated statin therapy in patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) who require additional therapy. (17)

The "Fire" Approach: Importance of Early Intervention

The urgency of the "fire" approach lies in the fact that the immediate aftermath of ACS is a high-risk period for recurrent cardiovascular events. (18) Lowering LDL-C promptly and significantly in this phase is crucial for preventing further damage and enhancing the chances of a favourable outcome.

The European Society of Cardiology (ESC) advocates for the initiation of high-intensity statin therapy promptly after ACS. (19) The target LDL-C to achieve in risk factor-based patient groups by ESC are listed in (**Table 1**).

Recommendations	Evidence Class
In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level ≥10%) the LDL-C goal is <1.8 mmol/L (less than ~70 mg/dL) and/or ≥50% LDL-C reduction when target level cannot be reached.	I
In patients at HIGH CV risk (markedly elevated single risk factors, a SCORE level ≥5 to <10%) an LDL-C goal <2.5 mmol/L (less than ~100 mg/dL) should be considered.	II
In subjects at MODERATE risk (SCORE level >1 to ≤5%) an LDL-C goal <3.0 mmol/L (less than ~115 mg/dL) should be considered.	II

Table 1. European Society of Cardiology guideline on target LDL-C goals

If target LDL-C goal is not achieved by maximum tolerated statin therapy, PCSK9 monoclonal antibody inhibitors can be introduced early in certain groups. This aggressive strategy is an effective technique for "firing" at the cholesterol target while reducing the risk of recurrent cardiovascular events. (20) Current NICE guidance (**Figure 4**) endorses the indications of evolocumab based on the LDL-C and the risks stratifications.

Patient Group	Without CVD	With CVD
Primary non-familial hypercholesterolemia or mixed dyslipidemia	Not recommended at any LDL-C concentration	High Risk of CVD*: Recommended if LDL-C > 4.0 mmol/L persistently Very High Risk of CVD**: Recommended if LDL-C > 3.5 mmol/L persistently
Primary heterozygous-familial hypercholesterolemia	Recommended if LDL-C > 5.0 mmol/L persistently	Recommended if LDL-C > 3.5 mmol/L persistently

* High Risk of CVD is defined as a history of acute coronary syndrome, coronary revascularization, coronary heart disease, ischemic stroke, or peripheral arterial disease.
** Very High Risk of CVD is defined as recurrent cardiovascular events or polyvascular disease (cardiovascular events in more than one vascular bed).

Abbreviations: CVD: Cardiovascular Disease LDL-C: Low-Density Lipoprotein Cholesterol

Figure 4. Indication for evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia: NICE guidance (21)

Inclisiran is an alternative therapy adjunct to diet for treating primary hypercholesterolaemia or mixed dyslipidaemia in adults with a history of cardiovascular events, and persistently high LDL-C levels despite maximum tolerated therapy. The key criteria are: (i) The patient with a history of

any cardiovascular event, such as acute coronary syndrome, coronary/arterial revascularization, coronary heart disease, ischemic stroke, or peripheral arterial disease. (ii) The patient's LDL-C level remains ≥ 2.6 mmol/l despite receiving maximum tolerated lipid-lowering therapy, which includes statins and other lipid-lowering therapies, or other lipid-lowering therapies when statins are not tolerated or contraindicated. If both conditions are met, inclisiran is recommended as an adjunct to diet for further lowering of LDL-C levels in this high-risk patient population. (22)

Not Forget: Long-Term Management and Patient Adherence

While the initial aggressive management is crucial, the "not forget" aspect emphasizes the importance of sustained, long-term efforts in managing hypercholesterolemia as a chronic condition. (23) Patient adherence to prescribed medications and lifestyle modifications is paramount in maintaining the achieved reduction in cholesterol levels and preventing further events. (22)

Healthcare practitioners play an important role in educating patients. The "not forget" method includes regular follow-ups, lipid profile monitoring, and medication strategy adjustments based on individual responses. Combining pharmacological therapies with lifestyle adjustments ensures a comprehensive and long-term decrease in cardiovascular risk. (24)

Shared Decision-Making: Tailoring Therapy to Individual Patients

The treatment of hypercholesterolemia after ACS is not one-size-fits-all. Shared decision-making between healthcare practitioners and patients is critical for adapting therapy to individual needs, considering age, comorbidities, and medication tolerance. (25, 26)

Conclusion

In the management of hypercholesterolemia following ACS, the dual approach of "fire but not forget" emphasizes the urgency of early and aggressive intervention while also acknowledging the chronic nature of the condition. Aggressive statin therapy and the integration of novel agents like PCSK9 inhibitors have transformed the landscape of post-ACS care. However, the long-term

commitment to patient education, adherence, and personalized care is essential to ensure sustained benefits and a lasting impact on cardiovascular outcomes.

Disclosures

None

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