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Postponing AMI to 100 Years: An Emerging Concept

Prabhash Chand Manoria

Director and Head Department of Cardiology, Heart and Critical Hospital, Bhopal, India
Email: pmanoria@rediffmail.com

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Abstract

Acute myocardial infarction is a deadly disease, and in the Indian context, it occurs at a younger age, even below the age of 40 years, and sometimes even below 30 years. These young MI patients have high mortality rates, and many of them are not able to reach the hospital. The pathophysiology of AMI is very well understood. AMI is a multifactorial disease and has several risk factors, like dyslipidemia, diabetes, hypertension, smoking, diet, etc. However, low-density lipoprotein cholesterol (LDL-C) has a very strong causal relationship with atherosclerosis. Reducing LDL-C to <70 results in the arrest of the progression of atherosclerosis, and slashing its level to below 50 produces the regression of atherosclerosis. The cumulative exposure of LDL-C to the arterial wall is a very strong determinant of atherosclerosis and the development of AMI. The coronary heart disease (CHD) threshold target of LDL-C for the development of AMI is roughly 7000 mg/year. If LDL-C is 100 mg/dL from an early age, the CHD threshold target for the development of AMI will reach 70 years of age. However, if LDL-C target is <70 mg/dL from an early age, the patients will reach the CHD threshold of LDL-C at the age of 100 years. Based on the current science, this is an emerging concept to postpone AMI by several years, even up to 100 years. The goal of LDL-C <70 mg/dL can be achieved by available oral or injectable drugs. Gene editing with CRISPR technology is emerging as a very exciting modality for lowering LDL-C to a very low level for the rest of life.

Keywords

Acute Myocardial Infarction, Cumulative Exposure of LDL-C, Inclisiran, CRISPR Technology

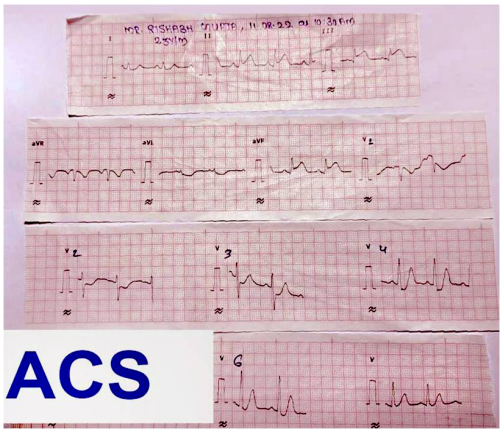
1. Introduction

The last couple of years have witnessed spectacular advances in the field of coro-

nary artery disease (CAD), both in terms of enhanced understanding and in the availability of new therapeutic options. The pathophysiology of acute myocardial infarction (AMI) and atherosclerosis has been demystified. AMI is a multifactorial disease and has several risk factors like dyslipidemia, hypertension, diabetes, smoking, diet, lack of physical activity, stress, etc. It is true that we must adopt a multipronged approach for reducing the risk of myocardial infarction, and no doubt this strategy is useful, but lipids play a very important role in the pathogenesis of AMI. LDL-C is causally related to AMI. Distressingly enough, premature coronary artery disease has emerged as a new entity in the Indian context. Many celebrities in India have died at a young age, and many have not even been able to reach the hospital. 30 percent of heart attacks in Indians occur below the age of 40, and in some cases, they develop even below the age of 30. Therefore, we are very concerned about AMI in India, and based on the current science, we are trying to work on strategies to postpone it for many years. Every month, we see one or two patients with AMI below the age of 30 years, also in females during the childbearing age. Two of the many such examples are summarized below.

2. Case 1

This is the story of a 23-year-old engineering student and heavy smoker who sought consultation with a physician for retrosternal discomfort and burning lasting for two hours. The physician took an electrocardiogram, and it showed ST segment changes (**Figure 1(a)**), so he referred the case to our hospital. He developed a cardiac arrest in our outpatient department. He was revived and sent to our catheterization laboratory. His coronary angiography showed total occlusion of the left anterior descending artery (**Figure 1(b)**). There was a big thrombus in the artery; thrombus aspiration was done. The post-procedure angiogram is shown in (**Figure 1(c)**) and intravascular ultrasound (IVUS) only showed plaque erosion (**Figure 1(d)**), so no stenting was done. Following the procedure, the electrocardiogram (**Figure 1(e)**) and the patient improved, and he is well to date, *i.e.*, after 18 months. So the big question is at what age prevention of ASCVD and AMI should start in India. This is a very complex and unresolved issue.



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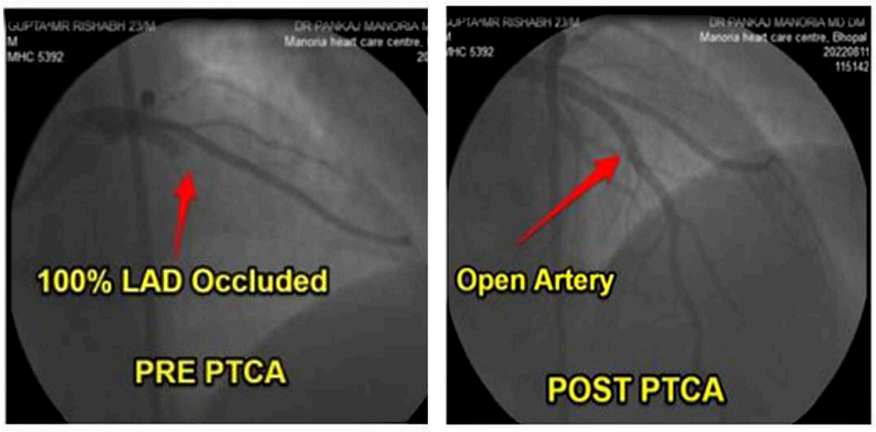

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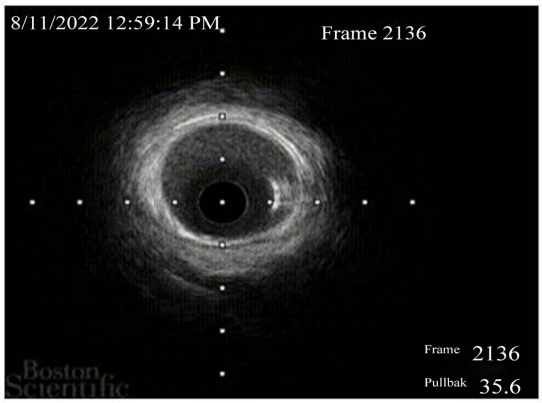

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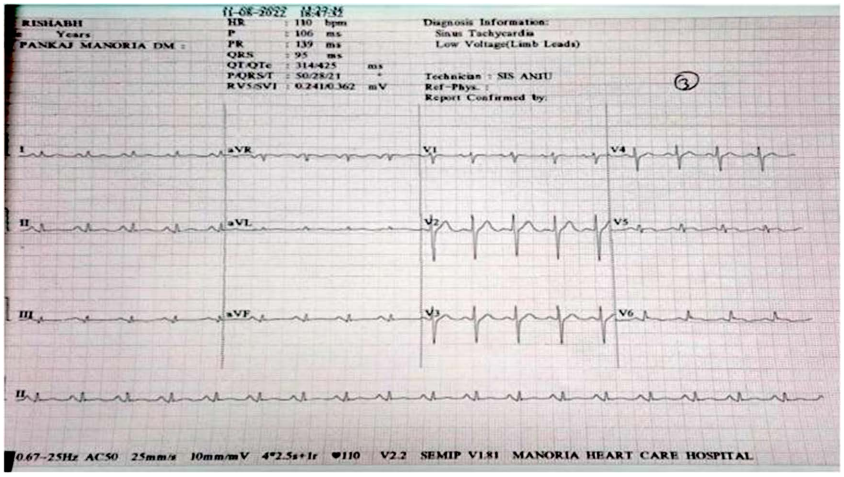


(e)

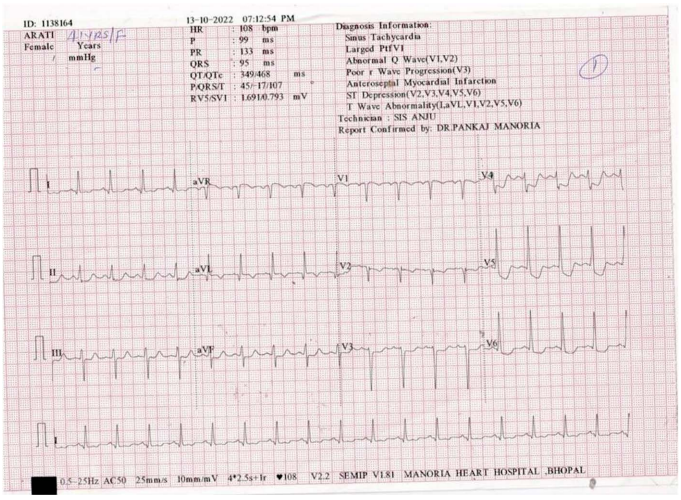
Figure 1. (a) ECG of a 23-year-old male patient with chest pain; (b) Coronary angiography showing total occlusion of the left anterior descending artery; (c) Coronary angiogram following thrombosuction; (d) IVUS of left anterior descending artery showing minimal atherosclerosis; (e) ECG post procedure.

3. Case 2

This is the story of a 41-year-old female who was admitted with prolonged chest

pain. Her electrocardiogram showed ST segment depression in multiple leads and ST segment elevation in lead aVR (**Figure 2(a)**). A diagnosis of left main stem disease was suspected. Coronary angiography showed a left main stem occlusion (**Figure 2(b)**). Coronary angioplasty was performed and the artery was stented (**Figure 2(c)**). Intravascular Ultrasound (IVUS) showed extensive atherosclerosis (**Figure 2(d)**) at this young age. This clearly shows atherosclerosis must have started several years ago and again emphasizes the necessity of applying preventive strategies at an early age in the Indian context. How early it should be initiated is an unresolved issue.

AMI commonly results from disruption of a vulnerable plaque with superimposed thrombus formation, causing an acute occlusion of the culprit artery, which results in necrosis of the myocardium supplied by it. Therefore, if we want to prevent AMI, there are two options. The first is to minimize atherosclerosis and prevent plaque rupture. The second is to utilize potent antithrombotic agents to minimize thrombus formation following plaque rupture, but this is a difficult solution because long-term use of these agents will result in bleeding, which has serious consequences.



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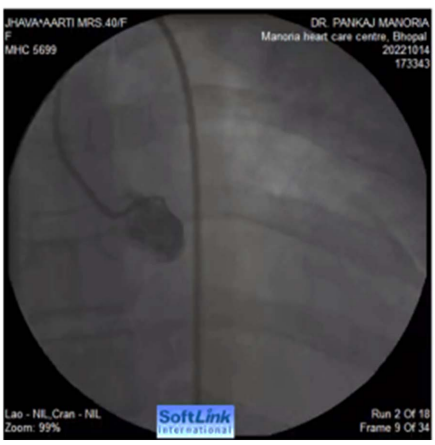

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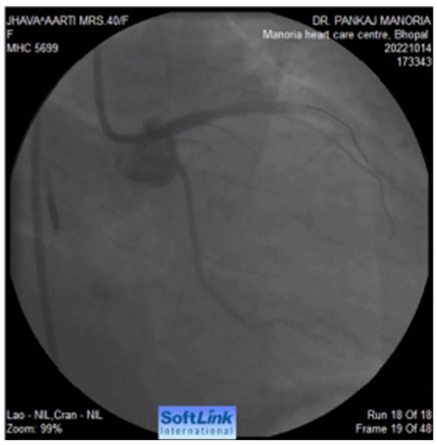

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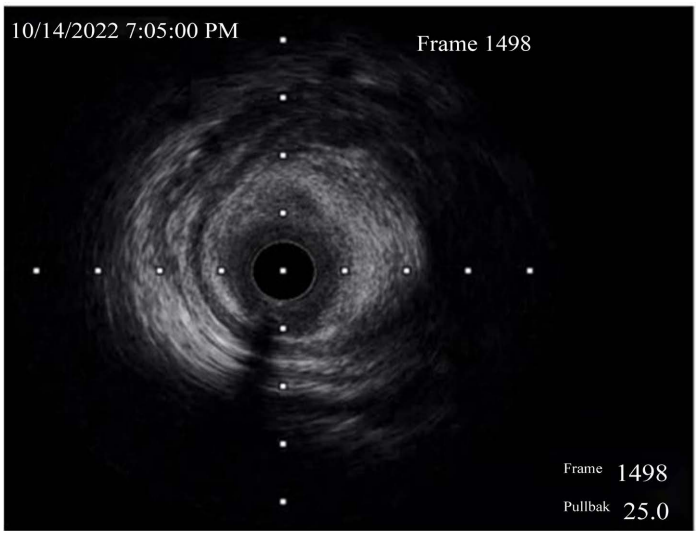

(d)

Figure 2. (a). ECG of a 41-year-old female patient with prolonged retrosternal chest pain (b). Coronary angiogram total occlusion of left main coronary artery (c). Coronary angiogram following successful angioplasty of left main coronary artery (d). IVUS shows extensive atherosclerosis.

4. Benefits of Lowering LDL-C

LDL-C is casually related to atherosclerosis. Over the last two to three decades, lowering LDL-C has shown exciting results. LDL-C lowering with statins has documented the stabilization of plaques so that plaque rupture and acute coronary syndrome can be minimized. The arrest of the progression of atherosclerosis by high-intensity statins like atorvastatin has been documented. [1] This usually occurs when the LDL-C is lowered below 65 mg/dL. The regression of atherosclerosis has also been documented. [2] A combination of statins and evolocumab resulted in regression of atherosclerosis [2], and this occurred when the LDL-C levels were reduced to <50 mg/dL. It is therefore important to realize that all levels of LDL-C above the normal range at birth are atherogenic, and lowering LDL-C levels to the normal range at birth is safe. The mean ± SD values for LDL-C at neonatal age are 23.8 ± 10.62 mg/dL in males and 25.5 ± 9.29 mg/dL in females. Interestingly, the safety of lowering LDL-C up to 10 mg/dL has been shown in subgroup analyses of Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease (FOURIER trial). [3] It showed that lowering LDL-C levels up to 10 mg/dL is associated with incremental benefits without any side effects.

5. The Concept of Cumulative Exposure of LDL-C to the Arterial Wall

The cumulative LDL-C burden can be easily calculated by the formula LDL-C mg/dL X year's exposure, and the coronary heart disease (CHD) threshold target is 7000 mg-years (**Figure 3**). [4]

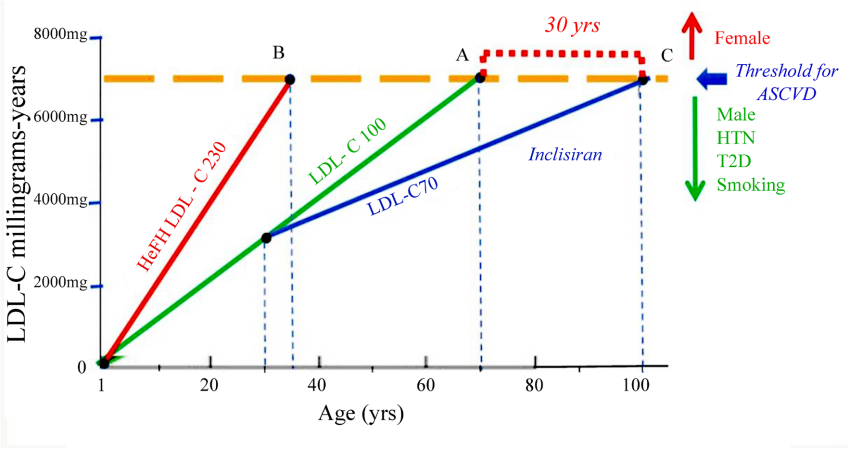

Figure 3. Concept of cumulative exposure of LDL-C and coronary heart disease threshold for developing acute myocardial infarction.

AMI does not randomly hit any individual. It only afflicts individuals who have reached the CHD threshold target of 7000 mg-years. Therefore, if an individual has a LDL-C level of 100 mg from an early age, he will develop AMI at the age of 70. On the other hand, if the LDL-C level is 70 mg from early life, he will develop AMI at the age of 100.

It is important to bear in mind that the CHD threshold target of 7000 mg/year can be lowered by various risk factors for AMI *i.e.* hypertension, diabetes, smokers, stress, and sedentary lifestyle etc. and therefore, along with LDL-C, all other risk factors should also be targeted.

6. How to Lower LDL-C to 70 mg/dL or Less from Early Years of Life to Prevent Reaching LDL-C to Threshold Target

6.1. PCSK9 Gene Editing by CRISPR Technology

This is the most exciting development for lowering LDL-C and is a single-shot treatment, and the patient has not to come again. Gene editing seems to be the future of cardiology, but its high cost may preclude its widespread use in the future.

The CRISPR-Cas9 system has two components: gRNA and the Cas9 protein. The gRNA unit guides the Cas9 protein to a specific genomic locus, *i.e.*, PCSK9, whereas the Cas9 nuclease induces a double-stranded break at the specific genomic target sequence. After this, when healing occurs, PCSK9 loses its function, and the PCSK9 and LDL-C levels are reduced to very low levels. The HEART-1 trial in patients with heterozygous familial hypercholesterolemia with VERVE-101 is ongoing. [5] The trial enrolled 10 patients (8 men and 2 women) from the UK or New Zealand. The average LDL-C was 201 mg/dL. Most of the patients had pre-existing severe CAD and had undergone coronary revascularization. In the past, 50% of the participants had experienced at least one AMI. All the participants were on statins, and no patient enrolled in the study was taking PCSK9 inhibitors. All patients were given a single intravenous infusion of VERVE 101, with the first three patients receiving a low dose of 0.1 mg/kg and the other pa-

tients receiving escalating doses. The highest dose was 0.6 mg/kg. The three patients receiving the highest two VERVE 101 doses (0.45 and 0.6 mg/kg) showed the greatest reductions in LDL-C and PCSK9 levels. The two patients in the 0.45 mg/kg group showed reductions in LDL-C by 39% and 48%, respectively, and in PCSK9 by 47% and 59%. The single patient in the 0.6 mg/kg group showed a reduction in LDL-C of 55% and in PCSK9 of 84%. The changes were durable up to a six-month follow-up, and further follow-up is ongoing.

6.2. Drugs

We have several effective oral drugs like high-intensity statins, ezetimibe, and bempedoic acid to lower LDL-C and reach the target. PCSK9 monoclonal antibodies like evolocumab and alirocumab are utilized in patients who have failed to reach the LDL target or are intolerant to oral drugs. But compliance is a big problem with all these drugs because they have to be regularly taken over the years. Inclisiran in this respect seems to be a magic bullet because a single injection of 300 mg every six months decreases LDL-C levels by 50%, and this remains there for the next six months. [6] The protocol of inclisiran is 300 mg administered subcutaneously on day 1, month 3 (day 90), and then every 6 months.

The VictORION-1 trial, a randomized, double-blind, placebo-controlled study, is ongoing to see the effect of inclisiran in preventing major adverse cardiovascular events in high-risk primary prevention patients. The primary endpoint of the study was a 4-Point Major Adverse Cardiovascular Events (4P-MACE) defined as a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, and urgent coronary revascularization, compared to placebo.

The trial is an event-driven study, and therefore, the study will continue until the required number of clinical events have occurred across both treatment arms and all participants have a minimum of 3 years of follow-up during the study.

The VictORION-2-Prevent, a phase-3 trial, is ongoing to assess the effect of inclisiran in 16,500 patients 40 years of age or older with established ASCVD on well-tolerated high-intensity statins to see the effect of a 3-point MACE, *i.e.* a composite of cardiovascular death, non-fatal MI and non-fatal ischemic stroke. The placebo group will receive well tolerated high intensity statins with or without ezetimibe. The trials started on Nov 23, 2021 and the expected completion date is Oct 13, 2027.

We have excellent modalities to treat patients with AMI, and no doubt they decrease morbidity and mortality, but they do not decrease the number of patients with the disease. The number of patients with AMI can only be minimized by primordial prevention, which is useful but difficult to implement on a population basis. The other way is to lower LDL-C to less than 70 for the whole community by using drugs from an early age.

7. Conclusion

Cumulative exposure of LDL-C to the arterial valve is an important determinant

for the development of AMI. Lowering LDL-C to < 70 mg/dL from an early age will prevent LDL-C from reaching the threshold limit (7000 mg-year) for AMI. Based on the current science, this is an emerging concept to postpone AMI up to 100 years. Long-term use of high-intensity statins with or without other oral drugs or subcutaneous inclisiran twice a year are solutions to achieve the above goal. PCSK9 gene editing with CRISPR technology is a one-time treatment to lower LDL-C for the rest of life, but this is still in the process of evolution

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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