Can We Cure Atherosclerosis?

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Cardiovascular disease mortality rates have begun to rise in the United States. Based on the large body of supportive evidence, we propose a proof-of-concept, first-in-human trial to cure atherosclerosis: CURing Early ATHEROsclerosis (CURE ATHERO). This trial is based on a model of intensive induction therapy for extensive, if not complete, plaque regression, followed by intermittent maintenance therapy. An extensive body of evidence has demonstrated the causal role of apolipoprotein B lipoproteins in atherosclerosis progression and data suggest intensive low-density lipoprotein cholesterol (LDL-C) lowering may have a substantial impact on earlier stages of atherosclerosis. Compared with lifetime treatment to prevent atherosclerosis progression, this induction–intermittent treatment model will minimize costs and maximize adherence and safety.

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KEY WORDS

Atherosclerosis • Regression • Primary prevention • Familial hypercholesterolemia • Apolipoprotein B lipoproteins • PCSK9 monoclonal antibodies • Statins

Following three decades of dramatic decline, cardiovascular disease mortality rates have begun to rise in the United States.[1] By 2035, it is projected that nearly 50% of the US population will have some form of cardiovascular disease, and cardiovascular-related healthcare costs will double to $1.1 trillion annually. Systematic approaches to maintaining ideal lifestyles and improving risk factor control are sorely needed, but unlikely to be effectively implemented in the near future. A new paradigm for cardiovascular prevention is needed.

Based on the large body of supportive evidence reviewed herein, we have proposed a proof-of-concept, first-in-human trial to cure atherosclerosis: Curing Early Atherosclerosis (CURE ATHERO). CURE ATHERO will determine if 3 years of intensive low-density lipoprotein cholesterol (LDL-C) lowering will substantially regress early atherosclerotic plaque in obese, high-risk young adults (Figure 1). This trial is based on a model of intensive induction therapy for extensive, if not complete, non-calcified plaque regression, followed by intermittent maintenance therapy (Figure 2).[2] Compared with lifetime treatment to prevent atherosclerosis progression, this induction–intermittent treatment model will minimize costs and potentially maximize adherence and safety.

Key Role of Apolipoprotein B Lipoproteins

Atherosclerosis begins in childhood, and manifests clinically as coronary heart disease, peripheral

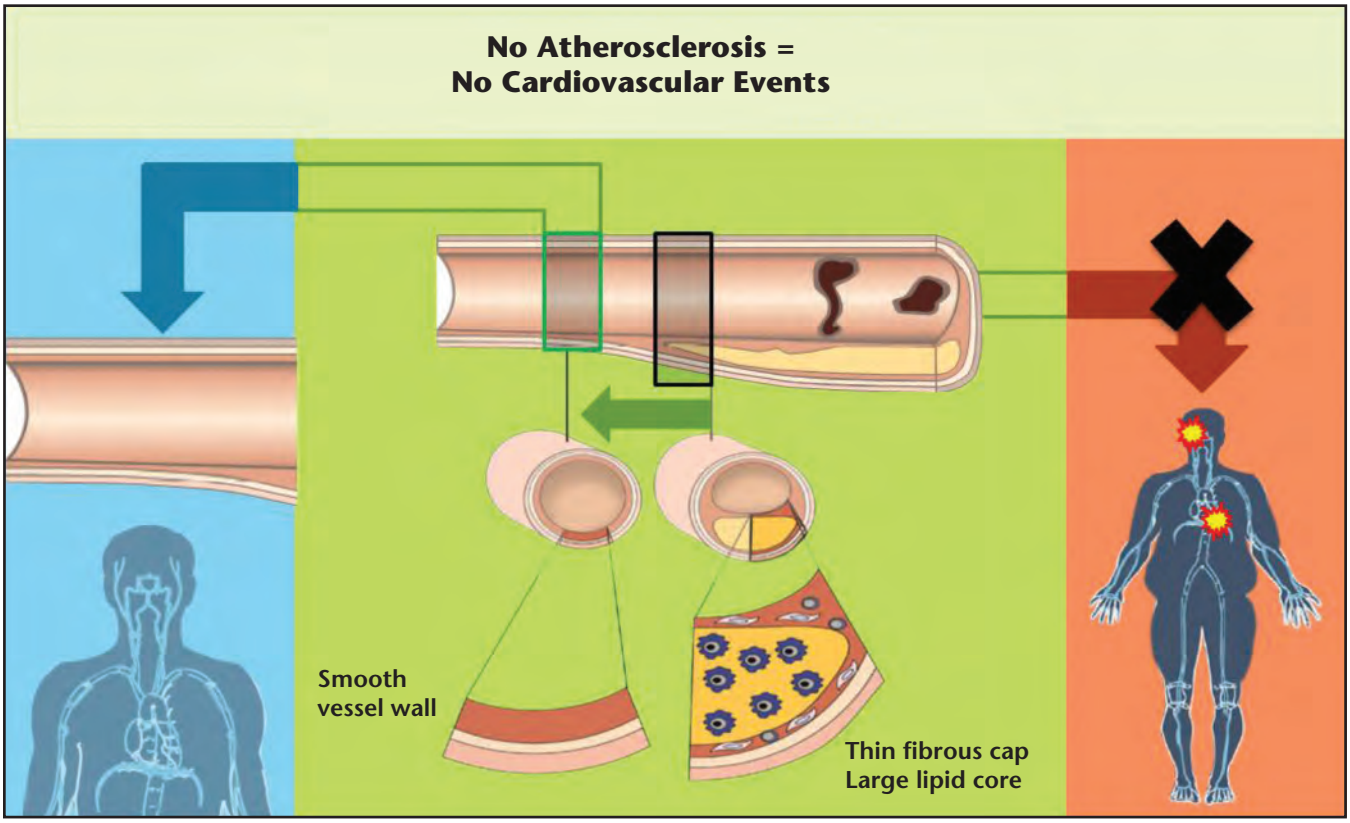

Figure 1. Conceptual model for a greater impact from intensive low-density lipoprotein cholesterol lowering for regression in earlier stages of atherosclerotic plaque.

vascular disease, and stroke in the fifth and sixth decades of life (Figure 1).[3] Multiple lines of evidence have proven the causal role of apolipoprotein B (ApoB) lipoproteins in atherogenesis.[4,5] LDL-C comprises the majority of atherogenic ApoB lipoproteins, whereas non–high-density lipoprotein cholesterol (HDL-C) additionally includes very low-density lipoproteins, intermediate-density lipoproteins, and chylomicron remnants. Animal studies have revealed the fundamental role of ApoB lipoproteins in the initiation and progression of atherosclerosis.[4] Marked reductions in the

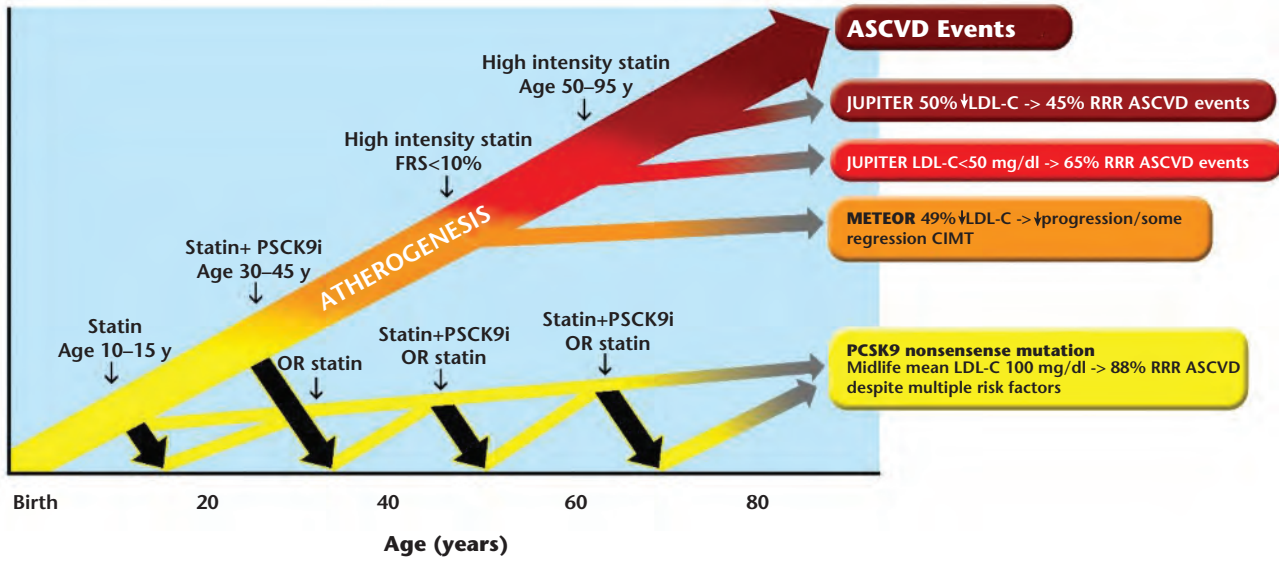

Figure 2. Resetting the vascular aging clock by treating atherosclerosis earlier, and intermittent suppressive therapy though the lifespan. ASCVD, atherosclerotic cardiovascular disease; CIMT, carotid intima-media thickness; FRS, Framingham risk score; JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL-C, low-density lipoprotein cholesterol; METEOR, Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RRR, relative risk reduction. Reprinted with permission from Robinson JG and Gidding SS.[2]

circulating levels of ApoB lipoproteins promotes plaque regression by allowing the normal scavenger and phagocytic clearance mechanisms to remove cholesterol and allow outmigration of macrophages and inflammatory cells; enhanced clearance of necrotic cells through efferocytosis, increase smooth cell muscle infiltration, and decrease fibrosis.[6,7] Intensive LDL-C lowering has the greatest impact on early plaque, when it results in complete plaque regression and normalization of vascular function.[8,9] However, the impact on somewhat more advanced stages of earlier plaque is substantial.

Multiple lines of evidence have proven the causal role of apolipoprotein B lipoproteins in atherogenesis.

Studies of individuals with familial hypercholesterolemia (FH) and Mendelian randomization studies have clearly demonstrated that lifetime exposure to genetically determined elevated LDL-C increases the risk of atherosclerotic cardiovascular disease (ASCVD) events (Figure 3).[5] Development of other risk factors, such as smoking, hypertension, and diabetes, accelerates the development of atherosclerosis, especially in genetically susceptible individuals.[10,11]

Three classes of LDL cholesterol-lowering drugs—statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies—have been shown to regress atherosclerosis and reduce cardiovascular events in high-risk individuals with an established burden of clinical ASCVD.

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In the Cholesterol Treatment Trialists meta-analysis of statin trials, greater reductions in the relative risk of cardiovascular disease occurred in lower-risk primary prevention individuals.[20] Because age is the main driver

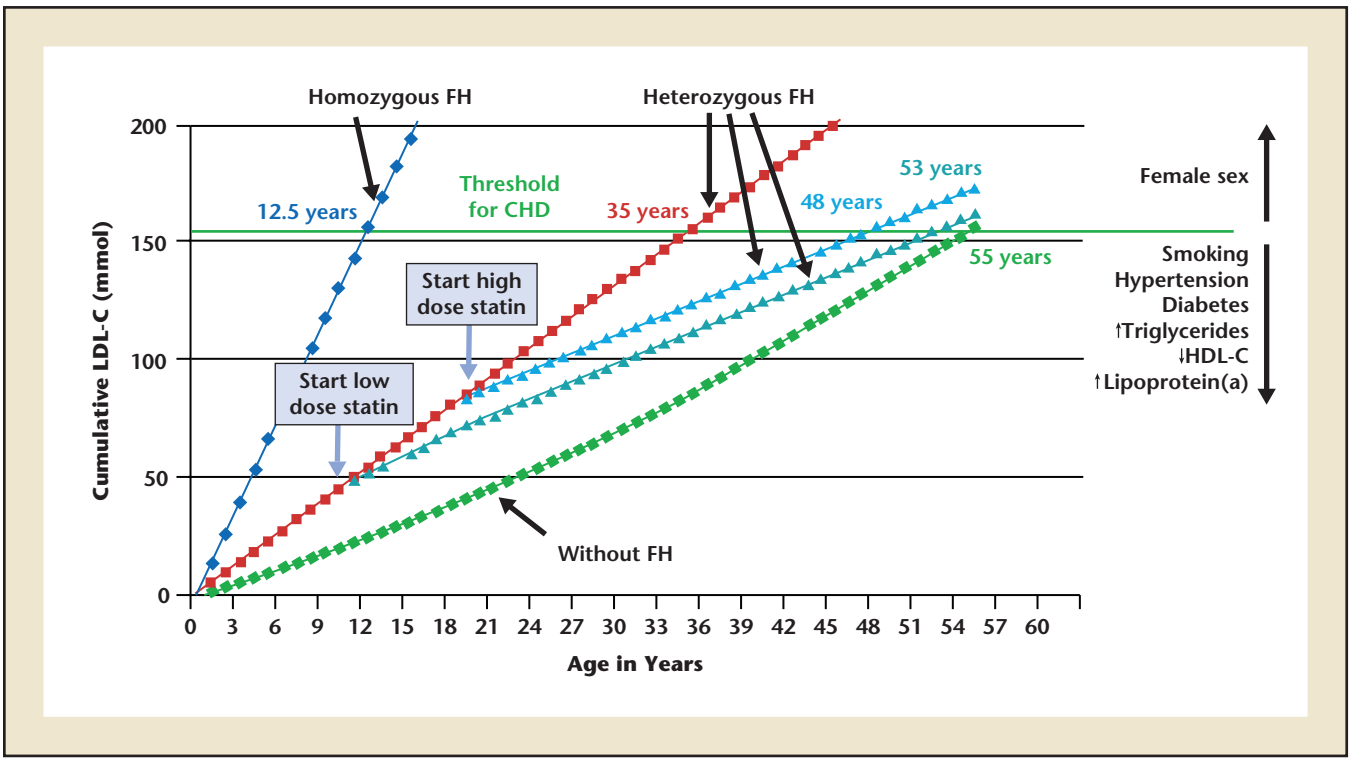

Figure 3. Modeling the impact of starting statin therapy in individuals with and without familial hypercholesterolemia. CHD, coronary heart disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Reprinted with permission from Nordestgaard BG et al.[29]

of cardiovascular risk, this suggests LDL-C lowering may have a greater impact on earlier stages of atherosclerosis when there is a lower burden of plaque and plaque is less fibrotic and calcified.[21]

Long-term follow-up of several statin trials has shown that the relative risk of cardiovascular event rates remains reduced compared with the control groups over periods of up to 20 years.[22] This legacy effect suggests that statin therapy for periods of 3 to 5 years has a lasting impact on atherosclerosis due to plaque stabilization and regression, in essence "resetting" the vascular aging clock. Thus, a legacy effect supports the concept that following a period of intensive LDL-C lowering, less intensive therapy may be sufficient to maintain long-term cardiovascular event reduction.[2] Data from epidemiologic studies show that those whose LDL-C remains <100 mg/dL, or whose non–HDL-C remains <130 mg/dL, through young adulthood do not develop significant atherosclerosis as they age.[23,24] The finding of legacy effects further suggest that no therapy might be sufficient for a period of a decade or more, especially in the setting of healthier lifestyle habits following a period of intensive therapy. In those with atherosclerosis progression, intermittent, and perhaps lower-intensity therapy may be sufficient for a lasting impact on cardiovascular event reduction (Figure 2).

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Special Case of Familial Hypercholesterolemia

FH is an autosomal dominant disorder affecting approximately 1 in 250 individuals, a finding consistent in populations worldwide.[25] Exposure to elevated LDL-C levels from birth increases the risk of cardiovascular events 20-fold, and is a common contributor to premature coronary heart disease events before age 55.[26-28] Exposure to the FH phenotype of LDL-C levels ≥190 mg/dL, which also has a large genetic contribution, increases cardiovascular risk five-fold.

Others have proposed treating individuals with FH earlier in life to better reduce cardiovascular events (Figure 2).[29] A similar treatment model of a period of intensive LDL-C lowering can be used to substantially, if not completely, regress early plaque. However, the maintenance phase would likely require long-term continuous therapy, which would be desirable due to the high genetically determined LDL-C. Less intensive LDL-C–lowering therapy to keep LDL cholesterol <100 mg/dL and non–HD-C levels <130 mg/dL may be sufficient to prevent development of new atherosclerotic plaques.[23] These LDL-C levels can be achieved by many FH patients with generic high-intensity statin and ezetimibe therapy.[30]

Conclusions

An extensive body of evidence has demonstrated the causal role of ApoB lipoproteins in atherosclerosis progression. Data suggest intensive LDL-C lowering may have a substantial impact on earlier stages of atherosclerosis. A paradigm of early and intense lipid reduction with statins and, if necessary, PCSK9 inhibitors for patients with high

MAIN POINTS

- An extensive body of evidence has demonstrated the causal role of apolipoprotein B lipoproteins in atherosclerosis progression and data suggest intensive low-density lipoprotein cholesterol (LDL-C) lowering may have a substantial impact on earlier stages of atherosclerosis.
- Studies of individuals with familial hypercholesterolemia (FH) and Mendelian randomization studies have clearly demonstrated that lifetime exposure to genetically determined elevated LDL-C increases the risk of atherosclerotic cardiovascular disease (ASCVD) events.
- Three classes of LDL-C–lowering drugs—statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies—have been shown to regress atherosclerosis and/or reduce cardiovascular events in high-risk individuals with an established burden of clinical ASCVD.
- Compared with lifetime treatment to prevent atherosclerosis progression, an induction–intermittent treatment model will minimize costs and maximize adherence and safety.

lifetime risk for cardiovascular events may lead to plaque regression and stabilization with a legacy effect followed by maintenance or suppressive therapy holds promise for significantly, and reducing the lifetime risk of ASCVD events. ■

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