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Curing Atherosclerosis Should Be the Next Major Cardiovascular Prevention Goal

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Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in developed and developing countries. Despite decades of effort, unhealthy lifestyle habits and ASCVD risk factor levels remain high and are increasing in many population groups. A new approach to ASCVD prevention is needed. Multiple lines of evidence from animal and human studies suggest that atherosclerosis regression and normalization of vessel function can occur when low-density lipoprotein cholesterol (LDL-C) lowering occurs early in the course of atherosclerosis or when very aggressive LDL-C lowering occurs somewhat later. We propose a new paradigm focused on curing atherosclerosis early in the course of the disease. An approach that resets the vascular aging clock composed of initial regression therapy followed by periodic retreatment to suppress atherosclerosis development may be possible, with the ultimate goal of preventing subsequent ASCVD events. Proof-of-concept studies are needed to determine: 1) the optimal age and/or extent of atherosclerosis for intervention and LDL-C–lowering therapy; 2) the intensity and duration of therapy for inducing atherosclerosis regression; and 3) documenting the normalization of vascular function. Ultimately, this new paradigm will need to be evaluated in ASCVD outcomes trials. (J Am Coll Cardiol 2014;63:2779–85) © 2014 by the American College of Cardiology Foundation

Despite dramatic declines, atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death in developed countries (1). High levels of unhealthy behaviors and ASCVD risk factors remain prevalent in adults (2). Secular trends in improved levels of low-density lipoprotein cholesterol (LDL-C), blood pressure, and tobacco use have been offset by increasing rates of obesity and type 2 diabetes mellitus (3). Children, adolescents, and young adults have an increasing burden of cardiovascular risk due to the increasing rate of obesity over the past 30 years, associated with higher rates of type 2 diabetes, increasing blood pressure, and dyslipidemia (4).

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Clearly, continued population-based efforts to improve lifestyle and control risk factors are needed. However, given the continuing high prevalence of ASCVD risk factors in adults, the worsening ASCVD risk factors in children and the magnitude of behavioral and societal changes needed to achieve optimal cardiovascular health, new approaches to ASCVD prevention will also be needed to combat the global epidemic of ASCVD. In this paper, we provide the rationale for a new paradigm for resetting the vascular aging clock, consisting of a short-term, aggressive LDL-C–lowering intervention early in the course of atherosclerosis to induce atherosclerotic regression and normalize vascular function, in essence "curing" atherosclerosis. If proven in ASCVD outcomes trials, widespread uptake of a strategy of regression treatment early in adolescence and early adulthood, with re-treatment periodically through adulthood, could ultimately eliminate ASCVD as a significant cause of morbidity and mortality.

Atherosclerosis begins early. Atherosclerosis begins at a very young age with the development of low-grade lesions (5,6). The earliest lesions of atherosclerosis are present in late adolescence (5,6). Advanced lesions develop in the third and early fourth decades of life, particularly in men with established cardiovascular risk factors. Multiple longitudinal studies have shown that risk factors present in adolescence and young adulthood are stronger determinants of subclinical atherosclerosis 15 to 20 years later than risk factors measured at the time of the subclinical imaging study (7). Important among these are higher levels of LDL-C and non–high-density lipoprotein cholesterol (HDL-C), as evidenced by the early development of atherosclerosis in children with familial hypercholesterolemia (8). However,

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Abbreviations and Acronyms

ASCVD = atherosclerotic cardiovascular disease

CHD = coronary heart disease

CIMT = carotid intimal medial thickness

CVD = cardiovascular disease

FH = familial hypercholesterolemia

HDL-C = high density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

PCSK-9 = proprotein convertase subtilisin/kexin type 9

younger persons with lower levels of LDL-C and non–HDL-C may still have a high risk of early atherosclerosis due to the presence of other ASCVD risk factors (9). Diabetes in youth is also associated with advanced atherosclerosis in adolescence. Further analysis of these cohorts has shown that individuals whose risk factors improve over the 15- to 20-year interval between risk assessment and subclinical atherosclerosis measurement have a much lower likelihood of later subclinical disease (10).

A new approach to preventing/curing atherosclerosis. The current pharmacological treatment model emphasizes aggressive LDL-C lowering in middle-aged or older adults with either established ASCVD (secondary prevention) or with a moderately increased nearer term (10-year) risk of ASCVD events (11). However, event rates in the drug treatment groups remain substantially higher than in low-risk individuals, presumably because individuals selected for treatment already have a greater burden of advanced atherosclerosis in the setting of continued increases in other risk factors (12).

We propose that it is now time to evaluate a radical new approach to ASCVD prevention: "curing" atherosclerosis itself early in the course of the disease to virtually eliminate clinical manifestations of ASCVD later in life. In the absence of atherosclerotic plaque, acute clinical ASCVD events due to plaque rupture cannot occur. Of course, at the population level, efforts to improve adherence to a healthy lifestyle, drug therapy, and expand access to medical care must be continued to make further progress in reducing the burden of clinical ASCVD through primordial prevention and in those in whom atherosclerosis has already developed. However, given the difficulty of changing individual human behavior and the costs associated with the management of prevalent ASCVD, early eradication of atherosclerosis may prove more effective than treatment later in life when atherosclerosis is more fully established. Moreover, such an approach could be used in the presence of adverse risk factor levels in those who are unable or unwilling to successfully adhere to a healthy lifestyle, with a genetic predisposition to atherosclerosis or with high-risk conditions such as early-onset diabetes.

Our proposed approach focuses on aggressive LDL-C reduction. There is abundant support that LDL-C is critical in the evolution of ASCVD (13). Genetic studies show that lifelong low LDL-C levels are associated with low levels of atherosclerosis and coronary heart disease, even in the presence of other ASCVD risk factors (14–16). In one study of loss of function mutations in the proprotein convertase subtilisin/kexin type 9 (PCSK-9) serine protease gene, middle-aged black individuals with a nonsense mutation in PCSK-9 had 28% lower LDL-C levels than those without such mutations, yet had an 88% reduction in coronary heart disease (CHD) over a 15-year observation period due to lower lifetime exposure to LDL-C (17). Notably, this striking reduction in CHD events occurred in the setting of a high prevalence of risk factors: body mass index of 29.5, hypertension in 37%, diabetes in 13%, and smoking in 27%. This low rate of CHD events occurred with an average LDL-C level of 100 mg/dl (compared with 138 mg/dl in those without a mutation), suggesting lower LDL-C levels may have an even greater impact on preventing the development of atherosclerosis.

As atherosclerotic disease progresses with advancing age, there is a more extensive burden of fibrocalcific plaque that may be less amenable to stabilization or regression with LDL-C–lowering treatment (18). Therefore, LDL-C lowering may be more effective earlier in the atherosclerotic process when more rapid and extensive plaque stabilization and regression can occur due to reductions in lipid core volume, inflammation, and early fibrotic changes (19–21).

Animal and human models of atherosclerosis regression support an early and aggressive LDL-C–lowering strategy (22). Atherosclerosis begins with the early entry of apolipoprotein B–containing lipoproteins (which include LDL-C) into the arterial wall, triggering a complex series of inflammatory and fibrotic responses leading to atheroma formation of increasing size, stability, and likelihood of plaque rupture (which may result in a clinical event). Animal models and some human observational studies suggest that these lesions can regress with statin treatment, with the residual lesions ranging from absent (early lesions) to areas of fibrosis devoid of active inflammation or lipid (advanced lesions). Plaque regression depends on aggressive lowering of LDL-C levels, generally beyond the 30% to 50% reduction in levels of LDL-C, which would be achieved with statin therapy (23). In several animal models, very aggressive LDL-C reductions resulted in early loss of foam cells from plaque and, over the longer term, resolution of necrotic regions, infiltration of smooth muscle cells, especially in the fibrous cap, and reductions in cholesterol clefts and fibrosis. These changes occur in both early and more advanced lesions. Carotid endarterectomy specimens from humans treated with statins show similar pathophysiological changes and plaque stabilization characteristics similar to those observed in animal studies (24), supporting extrapolation of animal findings to human atheroma responses to LDL-C lowering.

Statins also modestly lower systolic and diastolic blood pressure in younger individuals (25). Animal models have shown that endothelial dysfunction from prolonged hypercholesterolemia-induced atherosclerosis is a result of abnormal nitric oxide responses, and nitric oxide responses completely normalize with aggressive LDL-C lowering (26). Thus, regression of atherosclerosis and subsequent normalization