REVIEW

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A new paradigm to reduce cardiovascular disease based on the pathogenesis of atherosclerosis

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ABSTRACT

Atherosclerotic coronary artery disease is the number one cause of morbidity and mortality in the United States, Europe, and Westernized countries. This review recommends a new paradigm for the reduction of atherosclerotic coronary artery disease, namely prevention and treatment by addressing the pathophysiological basis of atherosclerotic disease. This paradigm utilizes the role of cholesterol transport and inflammatory cytokines to reverse atherosclerosis. There are three principal pathogenic processes involved in the development of atherosclerotic arterial plaque formation: 1) arterial endothelial disruption, 2) cholesterol subendothelial deposition and 3) inflammation. Pharmacological treatment is reserved for individuals with proven atherosclerosis. This targeted approach is both cost-effective and widely available. Using both circulating low density lipoprotein cholesterol (and/or other transport lipids) and C reactive protein to monitor cholesterol flux and inflammation respectively, provides on-going insight into the beneficial effects of therapy. Employing the pathophysiology of atherosclerosis as a guideline to treat coronary artery disease in place of computer-based risk equations will greatly decrease the epidemic of cardiovascular disease and move medical practice forward toward the eradication of this global syndemic.

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KEYWORDS: Atherosclerosis; Atherosclerotic coronary artery disease; Coronary artery calcium scan; Inflammation; Cholesterol transport; Endothelial disruption

Introduction

Why an alternative approach to atherosclerotic disease is urgently needed. Atherosclerotic heart disease (ASHD) is the number one cause of morbidity and mortality in the United States and the Western world, more than all cancers combined.[1] Since 2018, cardiovascular disease has progressively increased secondary to rising rates of obesity and diabetes in the population. By the age of 50 years, asymptomatic atherosclerosis is present in approximately 50% of males and 40% of females in the absence of major cardiovascular risk factors (Fig. 1).[2] This global syndemic continues despite many organizations funding major efforts through health care programs and guidelines directed at reducing ten-year risk, primarily lifestyle changes, weight loss, exercise, and control of cardiovascular risk factors. Computer generated risk equations are used to calculate the ten-year/thirty-year probability of having a major cardiovascular event. Based on the results of these calculations, various treatment options are recommended to reduce the

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risk depending on the risk category into which an individual is placed.[3]

There are several reasons that risk equation recommendations have not resulted in the reduction of cardiovascular disease. However, the primary reason is that these equations only represent a single, limited period of time in which atherosclerosis has progressed since birth. In contrast, atherosclerosis continues at different rates throughout a person's lifetime depending upon the person's variable risk exposure. The study of risk factors was initiated over 75 years ago in a population study in Framingham Massachusetts in 1948. While the concept of using risk factors to inform clinical decisions emerged with these early findings, the first widespread incorporation of quantitative risk equations to directly guide therapy recommendations in clinical guidelines occurred later. Most recently, the American Heart Association released the PREVENT equations in 2023, aiming to provide a more contemporary and accurate assessment of cardiovascular risk.[3] However, problems with these latest equations were rapidly recognized.[4]

CLINICAL SIGNIFICANCE

- Using computer-based risk equations to assess cardiovascular risk and therapy has not reduced the global syndemic of cardiovascular disease.
- A new paradigm addressing the pathophysiology of atherosclerosis promises to significantly reduce this atherosclerotic disease epidemic.
- The underlying causes of atherosclerotic plaque formation and rupture include endothelial injury, cholesterol deposition, and inflammatory cytokine activation.
- The new paradigm is readily acceptable by both physician and patient, can be initiated immediately, and saves national resources and patient lives.

An alternative recommended approach based on atherosclerotic pathophysiology and subclinical disease severity

Because of the failure of using risk equation determined therapy to reduce cardiovascular disease morbidity and mortality, an alternative approach is urgently needed. This new approach is based upon the pathological formation of the hazardous unstable atherosclerotic plaque and its subsequent rupture into the arterial lumen.[5] Much has been learned in the last two decades concerning this process and how to reduce its occurrence.[5,6] From a clinical viewpoint, the three main atherogenic processes resulting in unstable atherosclerotic plaques are 1) endothelial disruption, 2) cholesterol transport and subsequent oxidation from the plasma into the arterial vessel wall and 3) the mobilization of macrophages and cytokines which damage the endothelium and initiate thrombogenic events (inflammation). The first process is difficult to directly measure clinically, but the second and third processes can be assessed with the circulating LDL cholesterol concentration (LDL-c) and by the C reactive protein (CRP), respectively. As such, each of these latter circulating measurements help predict the atherosclerotic outcome in the patient.[7] Combining these two latter atherosclerotic biomarkers provides a better predictive outcome than either biomarker alone.[8]

The present article proposes anti-atherosclerosis therapy based on reducing these two circulating biomarkers after the presence of subclinical atherosclerosis has been documented with a coronary artery calcium heart scan (CAC). This noninvasive radiographic technique is superior to all risk equations in predicting future cardiovascular events in several populations.[9] It provides a cumulative assessment of atherosclerotic insults to the arterial wall as assessed by calcified atherosclerotic plaques from birth throughout the lifetime of the individual. Other Westernized countries have already adopted the primacy of CAC measurement in place of risk equations to evaluate future cardiovascular risk.[10]

The pathophysiology of atherosclerosis

The formation and rupture of the atherosclerotic plaque depends upon three related processes—dysfunction of the arterial endothelium, movement of cholesterol into the sub endothelial tissue with subsequent plaque development and the inflammatory environment of the atherosclerotic plaque. Cholesterol is transported in the blood in several forms, primarily by low density lipoprotein (LDL-c), intermediate density lipoprotein, remnant cholesterol during triglyceride metabolism, and Lp(a) cholesterol. However, it is important to appreciate that in non-hypertriglyceridemic individuals, 80% of circulating cholesterol is carried by LDL-c particles. These particles may be part of the inflammatory activation process during the movement of cholesterol into atherosclerotic plaques, although most of these studies have been done in animals. Prior to their uptake by macrophages, they are oxidized forming various species of oxidized LDL-c. Inflammation initiates several atherogenic processes, including 1) mediating endothelial cell injury, 2) activating endothelial cell adhesion molecules, 3) binding to monocytes to transform them into activated macrophages which release a plethora of growth factors, 4) inhibiting endothelial vasodilatation, and 5) activating platelets.[11,12] Damage and apoptosis of the endothelial barrier permits ready passage of cholesterol into the sub endothelial space where it attaches to glycoproteins, becomes oxidized, is translocated into macrophages which form fatty streaks, and which eventually progress into atherosclerotic plaques.[13] In addition, the atherosclerotic plaque's stability can be impaired by several risk factors via inflammation including hypertension, hyperglycemia, and local tissue and circulating cellular cytokines.

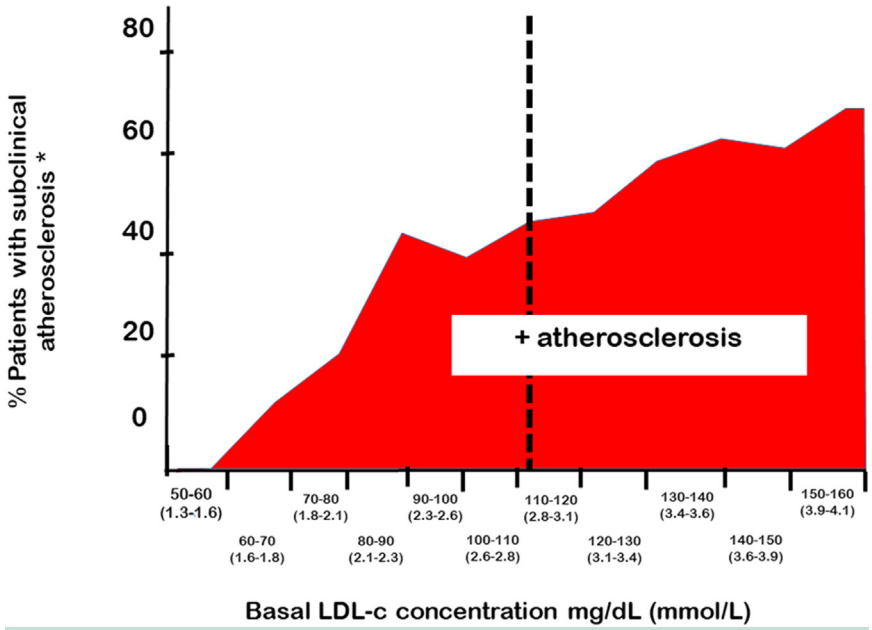

Fig. 1 The percent of asymptomatic middle-aged adults with no major cardiac risk factors (45 +/- 4.1 years of age, 50.3% female) with proven atherosclerosis by non-invasive technology. At LDL cholesterol concentrations between 50 to 60 mg/dL (1.5 to 2.0 mmol//L), no atherosclerosis was present in the infrarenal abdominal aorta, iliofemoral arteries, carotid arteries, or major coronary arteries (when the presence of calcium was used as the surrogate marker in the coronary arteries). In contrast, at LDL cholesterol concentrations between 150 and 160 mg/dL (3.9 to 4.1mmol/L), 62% of individuals demonstrated atherosclerosis in at least one of the locations tested. An approximate linear increase in atherosclerosis was observed when LDL cholesterol progressively increased in this healthy population of 1,779 adults. The dotted line indicates the average LDL cholesterol level in the United States adult population.
* Atherosclerosis was detected by noninvasive technology (two dimensional arterial ultrasound and coronary artery calcium non-contrasted CT). Data derived from ref[2].
LDL-c = low density lipoprotein cholesterol

Targeting the reduction of two of these processes directly (cholesterol accumulation and arterial inflammation) results in prevention and ultimately reversal of atherosclerotic plaques. Proof of this ongoing atherogenic formation and reversal process comes from both human and animal studies. First, vertebrate animals (including nonhuman primates) rarely develop atherosclerosis unless humans intervene experimentally by either feeding animals a high cholesterol atherogenic diet, physically injuring the arterial endothelial layer, or genetically altering their circulating lipoproteins or their cellular receptor proteins.[14] Their LDL-c levels rarely exceed 70 mg/dL (1.8 mmol/L) and are usually much lower. Second, evidence from human studies suggest that atherosclerosis can be prevented and reversed. For example, individuals with familial heterozygous hypobetalipoproteinemia rarely develop atherosclerosis. Familial heterozygous hypobetalipoproteinemia is a genetic partial defect in the synthesis of beta apolipoprotein which is necessary for lipoprotein formation. These patients typically have LDL-c levels below 50 mg/dl (2.8 mmol/L). Autopsy studies in elderly patients who have familial heterozygous hypobetalipoproteinemia have demonstrated no atherosclerosis in any of their vessels.[15] In addition, randomized, controlled atherosclerosis reversal clinical trials in thousands of individuals demonstrate that the lower the LDL-c, the fewer atherosclerotic events occur (Fig. 2).[16-18]

Similar to LDL-c, inflammation is a prime determinant of atherosclerosis initiation, progression, and culmination of atherosclerotic events. Inflammatory cytokines recruit circulating lymphocytes to endothelial walls, mobilize various cell types to plaque locations, and enhance the oxidation of LDL-c for ingestion by lymphocytes turned macrophages in the sub endothelial space. Inflammation causing progressive damage to the unstable atherosclerotic plaque can be caused by many processes including physical (hypertension), chemical (cytokines), molecular (abnormal lipoproteins and receptors), and toxins (smoking). Since atherosclerosis is an inflammatory disease, efforts to reduce this mechanism to normal levels should be part of any strategy to reduce atherosclerosis.[19] In fact, these two

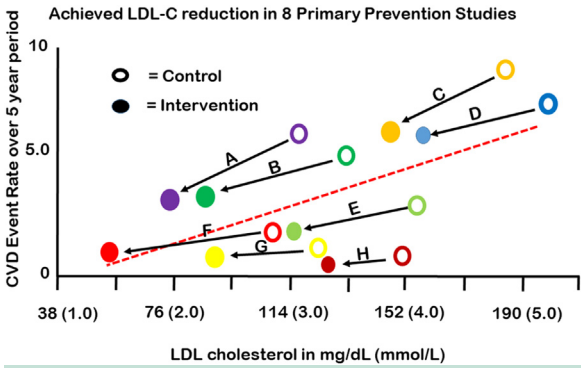

Fig. 2 Change in the cardiovascular event rate associated with the reduction in LDL cholesterol in multiple, randomized, controlled primary prevention studies. In every study, the reduction of LDL cholesterol was associated with a significant reduction in the rate of cardiovascular events. The regression line (red dots) of combining all of these studies approaches zero as the concentration of LDL cholesterol approaches 50 mg/dL (2.8 mmol/L). The capital letter indicates the specific study plotted. Open circles are before intervention, solid circles are post intervention.
A = 10.1016/S0140-6736(04)16895-5., B = 10.1016/S0140-6736(03)12948-0., C = 10.1056/NEJM199511163332001., D = 10.1001/jama.1984.03340270029025., E = 10.1001/jama.279.20.1615, F = 10.1056/NEJMoa0807646., G = 10.1056/NEJMoa1600176., and H = 10.1016/S0140-6736(06)69472-5. Data derived from ref.[17]

atherosclerotic biomarkers (LDL-c and CRP) are closely integrated so the optimal conditions for reversal of atherosclerosis occur when both biomarkers are suppressed to the maximum possible concentration.[8]

Reasons that the atherosclerotic epidemic persists

Based on the above mechanisms of disease, it is concerning that atherosclerosis remains a lethal, epidemic disease. There are at least four reasons for this continuing epidemic. First, the assignment of the degree of risk by quantifying the importance of various risk categories is very imprecise. Its predictions are marginal at best for the young, the aged, and several individual populations.[20] For example, recent data analysis of the PREVENT equations shows that the PREVENT equations lead to under treatment of young adults who experienced a myocardial infarction.[21] Second, the compliance with recommended therapy including medications is poor. Approximately 60 % of the elderly population prescribed statins are no longer adherent after one year.[22] Third, treatment of an LDL-c to <2.8 mmol/L (<55 mg/dL) is often delayed until after an atherosclerotic clinical event occurs. Since atherosclerosis starts in childhood and continues throughout adulthood, delaying the reduction of circulating LDL cholesterol until the middle age or senior years is not an effective preventive strategy. The current average LDL-c of >112 mg/dL (>2.9 mmol) in most adult populations is a principal underlying cause of the atherosclerosis epidemic. Fourth, informing a patient of his/her cardiovascular risk and recommending lifestyle changes without demonstrating that he has coronary artery disease is often not convincing. The fifth reason for this epidemic is the failure of most risk equations to input inflammation as a major risk factor and thus underestimating risk. In some studies, inflammation may surpass LDL-c as a statistical cause of atherosclerosis.[23]

An alternative approach based on pathophysiology

The solution to this conundrum is to replace the goal of percent risk reduction with the goal of reduction of LDL-c and CRP to a level similar to those observed in humans and animals that rarely develop atherosclerosis—i.e., an LDL-c <55 mg/dL (1.4 mmol/L) and a CRP to <1.0 mg/L. This goal can be achieved in almost all patients with a low cholesterol diet and the use of a low statin dose plus ezetimibe.[19,24,25] A low cholesterol diet is extremely important because: 1) many individuals are high gastrointestinal cholesterol absorbers and 2) statin use increases cholesterol gut absorption.[25] The relatively small number of individuals with genetic causes of significantly elevated LDL-c over 190 mg/dL (4.9 mmol/L) will need additional pharmacological therapy which is now available using PCSK9 inhibitors.[26]

Treatment based upon atherosclerotic severity

Improved lifestyle and treatment compliance along with identification of the severity of subclinical atherosclerosis can be obtained with the use of CAC CT scanning. This scan is inexpensive, noninvasive, safe, and widely available. CAC-scanning is superior in predicting cardiovascular events compared to other non-invasive cardiovascular procedures.[27] In fact, the cost of CAC scans (~$150) is offset by reduced numbers of individuals receiving statin treatment recommended by risk equations, with subsequent reductions in lipid panels, other metabolic and hormonal tests, statin costs, and office visits for therapeutic monitoring.[9] Therefore, CAC scanning-directed therapy is cost effective compared to risk equation-directed therapy.[9] No studies have negated CAC's value for noninvasively identifying individuals at risk from subclinical (asymptomatic) atherosclerosis. Treatment addressing other major CVD risk factors (diabetes, obesity, hypertension, and smoking) is also an important component of all treatment strategies and will often result in reductions of LDL-c and CRP.

LDL-c as a critical component of atherosclerosis

Support for the LDL-cholesterol treatment goal of LDL-c <55 mg/dL (<2.42 mmol/L) for all CAC-scan positive individuals (scores >0) comes from randomized, controlled trials. An analysis of 8 primary (i.e., subclinical) coronary

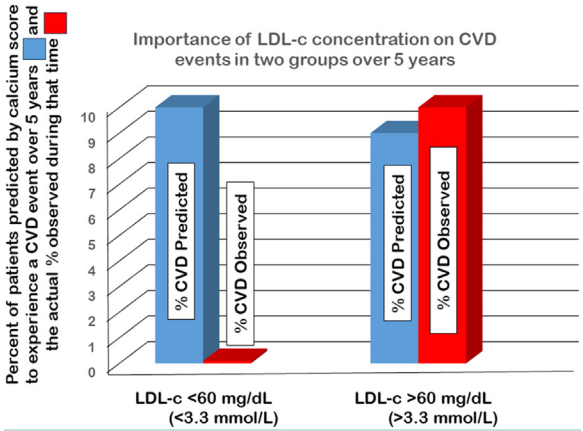

Fig. 3 Clinical experience with preventing cardiovascular events in an observational study over a 5-year period. No cardiovascular events (0%) were observed in a group of 122 individuals with a positive coronary artery calcium scan in spite of a predicted ten cardiovascular events based on their elevated calcium scan score (Left side). In contrast, 20 individuals that refused to follow medical advice and whose LDL-c remained above >60 mg/dl (3.3 mmol/L), 1.8 events were predicted from their calcium scan score and two myocardial infarctions were observed (one was lethal) (Right side). Data obtained from reference.[24] LDL-c = low density lipoprotein, CVD = cardiovascular disease.

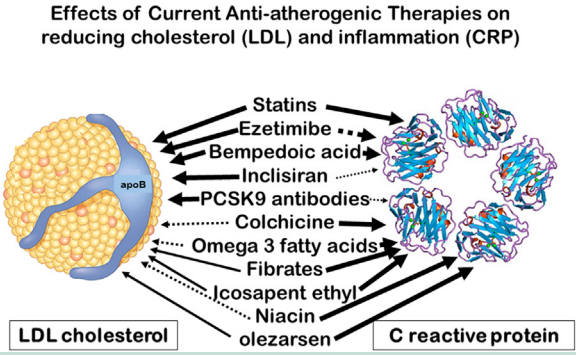

Fig. 4 The effect of current therapies to lower LDL cholesterol and Inflammation (C reactive protein) on the two principal pathophysiological causes of atherosclerosis. A solid wide arrow indicates a major beneficial effect, a narrow solid arrow indicates a minor effect, and a doted arrow indicate no effect under most circumstances. Ezetimibe is unique in that when used alone, it has a minimal effect on CRP, but when used in conjunction with a statin, an additional ~20% decrease in CRP is observed.

heart disease prevention clinical trials using linear regression (LDL cholesterol on abscissa and CVD event rate on the ordinate) estimated that the LDL-cholesterol corresponding to zero events was 57 mg/dL (1.47 mmol/L) (Fig. 2).[17] The implementation, feasibility, and success of a program to reduce LDL-c to <55 mg/dl (<1.4 mmol/L) has been reported in the clinical setting (Fig. 3).[24]

Inflammation as a critical component of atherosclerosis

Atherosclerosis is an inflammatory state and its assessment is critical for reducing cardiovascular events. In fact, in some randomized clinical trials, its relative importance exceeds that of LDL-c.[28] Inflammation affects many of the processes that are necessary for the generation of the unstable plaque and its subsequent rupture into the arterial vessel. For example, inflammation impairs the integrity of the endothelial vascular lining, stimulates the recruitment of lymphocytes to vessel walls, increases oxidation of LDL-c, activates the movement of myocytes into the plaque, stimulates the production of cytokines, and enhances the dissolution of the fibrous cap permitting the rupture of the plaque's thrombogenic contents into the arterial lumen. The ability of statins to reduce acute coronary syndromes is often attributed to their profound reduction of inflammation.[8] Since CRP is increased by inflammatory cytokines, particularly IL-6, it is a good biomarker for an individual's ambient inflammatory level. When choosing a therapy for reduction in atherosclerosis, the effect on inflammation should be an important consideration (Fig. 4).[29]

Assessing the severity of subclinical atherosclerosis

This review recommends starting to treat individuals to an LDL-c of <55 mg/dl (<1.42 mmol/L) and a CRP <1.0 with proven subclinical cardiovascular disease by documenting its presence with a positive CAC scan. This inexpensive, noninvasive test has (for practical purposes) no false positive results. False negative tests are possible (because of the presence of non-calcified plaques) but the cardiovascular disease event rate in patients with zero calcium scores is minimal.[30] Large observational cohorts emphasize that the absence of CAC is associated with an extremely low cardiovascular event rate of 0.027%/year.[31,32]

Other important cardiovascular risk factors

Recent data implicate Lipoprotein(a), and remnant cholesterol (cholesterol remaining during triglycerides removal from chylomicrons and VLDL) as significant additional risk factors for atherosclerosis.[33] Lipoprotein(a) is a genetically determined circulating lipid particle that has atherogenic properties and can be causally related to thrombosis and plaque formation.[34] Remnant cholesterol is a major issue in patients with hypertriglyceridemia and its importance in atherosclerosis may exceed that of LDL-c.[35] Monitoring and addressing these risk factors is important and should be part of any treatment plan. However, the risk from these factors may also be reduced by lowering LDL cholesterol, thereby minimizing the formation of atherosclerotic plaques.[36]

Limitations to a pathophysiological approach

Utilizing LDL-c and CRP goals of 55 mg/dl (2.4 mmol/L) and <1.0 mg/L respectively will not be sufficient in some individuals to prevent or reverse atherosclerosis if other uncontrolled risk factors including severe hypertension, intense smoking, uncontrolled diabetes, renal failure, or non-traditional pathogenic processes are directly involved in plaque formation. In addition, plaque rupture is not always the mechanism of acute coronary syndromes.[37] Furthermore, non-calcified plaques that are not visualized on CAC scanning exist, particularly in young males.[38] If an asymptomatic patient develops signs and/or symptoms of cardiovascular disease, CT angiography (or other radiographic techniques) may be utilized to exclude obstructive disease.[39] However, because the majority of individuals are not in these categories and are candidates for statin therapy, reducing atherosclerotic disease by 90% using the above pathophysiological approach is far superior to the ineffective current percent risk equation reduction goal.

Conclusion

There are several clinical reasons for utilizing atherosclerosis pathophysiology in place of risk equations for reducing cardiovascular disease. First, it provides caregivers and patients with specific measurable treatment goals. Second, it increases patient compliance when coronary artery calcium scoring is used to recommend therapy. Third, it will save billions of dollars in health care costs that may be used for other health related needs.[40] Fourth, it uses proven radiographic technology and generic medications with minimal side effects and cost. Fifth, this approach is relatively simple and the rationale is readily understood by both the patient and the physician. This article's approach is consistent with the recent publication of the Lancet Commission's focusing on the atherogenic plaque as the pathophysiological basis for reducing cardiovascular disease.[5] Our approach to reducing atherosclerotic cardiovascular disease is in agreement with their statement that "atherosclerotic coronary artery disease is an acquired and preventable condition." Making a change in assessing and treatment of subclinical cardiovascular disease is long overdue. It can be initiated immediately and is essential for significantly reducing the epidemic of a preventable disease.

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Declaration of competing interest

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