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JACC FOCUS SEMINAR: CV HEALTH PROMOTION

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Impact of Lipids on Cardiovascular Health

JACC Health Promotion Series

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ABSTRACT

People who maintain ideal cardiovascular heath have a low lifetime risk of cardiovascular disease. Therefore, encouraging people to achieve ideal cardiovascular health represents an important opportunity to improve the prevention of cardiovascular disease. However, preventing cardiovascular disease by promoting ideal cardiovascular health requires shifting the focus from treating disease after it develops to preventing cardiovascular events before they happen by slowing the progression of atherosclerosis. Because atherogenic lipoproteins play a central causal role in the initiation and progression of atherosclerosis, maintaining optimal lipid levels is necessary to achieve ideal cardiovascular health. This review describes the cumulative effect of lipid-carrying lipoproteins on the risk of cardiovascular disease, estimates the magnitude of the clinical benefit that can be achieved by maintaining optimal lipid levels, identifies the most effective timing for implementing strategies designed to achieve optimal lipid levels, and provides a clinical pathway to help people achieve the lipid levels necessary for ideal cardiovascular health. (J Am Coll Cardiol 2018;72:1141–56)

The Strategic Planning Task Force of the American Heart Association recently introduced the concept of ideal cardiovascular health. They defined it as engaging in specific behaviors—including not smoking, eating a diet low in saturated fats and refined carbohydrates, and engaging in regular physical exercise—as a strategy to prevent cardiovascular disease by avoiding the noxious effects of tobacco smoke and achieving optimal levels of 4 cardiovascular disease risk factors including an untreated total cholesterol level <200 mg/dl, untreated blood pressure <120/80 mm Hg, serum glucose concentration <100 mg/dl, and a body mass index <25 kg/m^2 (1). These 7 metrics of ideal cardiovascular health define the American Heart Association's national goals for cardiovascular health promotion and disease reduction. Observational epidemiological studies suggest that people who maintain these measures of ideal cardiovascular health throughout adulthood have a very low lifetime risk of developing cardiovascular disease (2). Unfortunately, fewer than 5% of people maintain all 7 measures of ideal cardiovascular health throughout adulthood (2). As a result, engaging physicians and other health care providers to help people achieve ideal cardiovascular health represents an important opportunity to improve the prevention of cardiovascular disease substantially.

Low-density lipoprotein (LDL) and other apolipoprotein B (apo B)-containing lipoproteins transport cholesterol and other lipids throughout the body and play a central role in the initiation and progression of atherosclerosis (3). Therefore, maintaining optimal lipid levels is an important component of ideal cardiovascular health. In this review, we describe the cumulative effect of lipid carrying lipoproteins on the risk of cardiovascular disease, estimate the magnitude of the potential clinical benefit that can be achieved by maintaining optimal lipid levels, identify the most effective timing for implementing strategies designed to achieve and maintain optimal lipid levels, and suggest specific strategies to help people

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ABBREVIATIONS AND ACRONYMS

apo B = apolipoprotein B

FH = familial hypercholesterolemia

LDL = low-density lipoprotein

LDL-C = low-density lipoprotein cholesterol

NNT = number needed to treat

achieve optimal lipid levels. In doing so, we suggest a new threshold for optimal lipid levels necessary for ideal cardiovascular health, introduce a new definition for the primordial prevention of suboptimal lipid levels, refine the definition of primary prevention of cardiovascular disease, and provide a clinical pathway that physicians and other health care providers can use to help their patients achieve and maintain the optimal lipid levels necessary for ideal cardiovascular health.

PATHOPHYSIOLOGY OF LIPIDS IN ATHEROSCLEROSIS

Circulating LDL and other apo B-containing lipoproteins <70 nm in diameter, including smaller triglyceride-rich very low-density lipoproteins and their remnant particles, freely flux across the endothelial barrier, where they can interact with extracellular structures such as proteoglycans to become retained in the extracellular matrix (4). According to the response-to-retention model of atherosclerosis, the retention of apo B-containing lipoprotein particles in the subintimal arterial wall provokes a complex, maladaptive inflammatory process that leads to the initiation of an atheroma (5). As additional lipoprotein particles become retained in the artery wall over time the nascent atheroma gradually enlarges, leading to the formation of increasingly larger and more complex atherosclerotic plaques.

MECHANISTIC TRIGGERS OF DISEASE

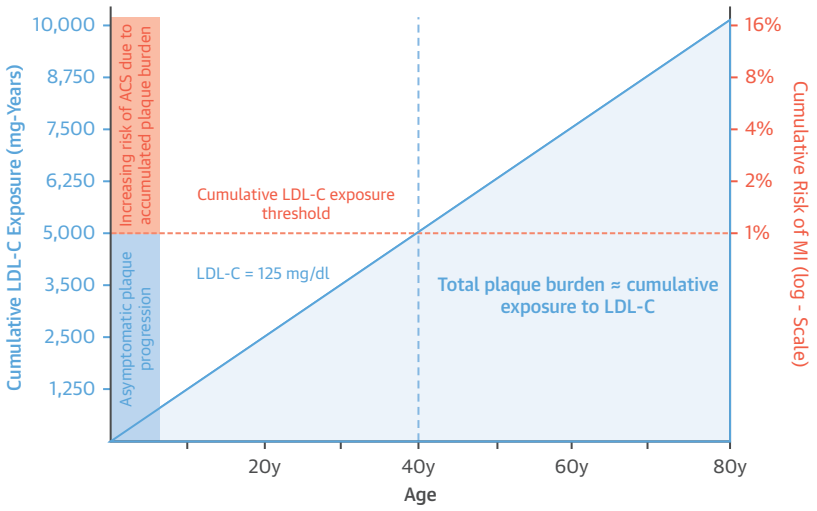
Under most conditions, >90% of circulating plasma apo B-containing lipoproteins are LDL particles. However, for historical reasons, LDL particles (and other apo B-containing lipoproteins) are not measured directly. Instead, plasma LDL cholesterol (LDL-C) concentration, an estimate of the total cholesterol mass carried by LDL particles, is commonly used to estimate the concentration of circulating LDL particles. At any given LDL-C concentration, the likelihood that an LDL particle will be retained in the artery wall is low. With continued exposure to the same LDL-C concentration, however, additional LDL particles become retained over time and accumulate in the artery wall, thus leading to the growth and progression of atherosclerotic plaques. Intravascular ultrasound studies consistently demonstrate that the rate of atherosclerotic plaque progression is directly proportional to the absolute plasma LDL levels (6,7). Because atherosclerotic plaques grow over time as additional lipoprotein particles become retained, the size of the total atherosclerotic plaque burden is determined by both the concentration of circulating LDLs (and other apo B-containing lipoproteins) and by the total duration of exposure to these lipoproteins. Therefore, a person's total atherosclerotic plaque burden is approximately proportional to his or her cumulative exposure to LDL and other apo B-containing lipoproteins, and it can be roughly approximated by multiplying a person's age by the LDL concentration to obtain an estimate of cumulative LDL exposure measured in either mg-years (age × LDL-C measured in mg/dl) or mmol-years (age × LDL-C measured in mmol/l).

As atherogenic lipoproteins slowly accumulate in the artery wall during young adulthood and middle age, the cumulative exposure to LDL and other apo B-containing lipoproteins is not usually high enough during this time to result in a sufficiently large total atherosclerotic plaque burden to obstruct blood flow to cause exertional symptoms or to result in an acute coronary syndrome if a plaque disrupts. Therefore, during young adulthood and middle age a person's short-term risk of experiencing a cardiovascular event is low, but total atherosclerotic burden is slowly increasingly as more LDL particles are retained during this time. Eventually, however, the enlarging atherosclerotic plaque burden reaches a critical mass beyond which the disruption of a plaque can lead to an overlying thrombus that acutely obstructs blood flow resulting in unstable angina, myocardial infarction, or death. Once the size of the total plaque burden exceeds this threshold, a person is at risk of experiencing an acute cardiovascular event.

The threshold size that the total plaque burden must reach to increase the risk of experiencing an acute coronary syndrome when a plaque disrupts can be inferred by using the cumulative exposure to LDL as an estimate of plaque burden size (**Figure 1**). For example, the cumulative incidence of myocardial infarction among people 40 years old in the United States is approximately 1%, but it is negligible in younger persons (8). If the mean untreated LDL-C level in the United States is 125 mg/dl, then by age 40 years the average person will have been exposed to 5,000 mg-years of LDL (40 × 125 mg/dl) or 125 mmol-years (8). Therefore, on average, 5,000 mg-years or 125 mmol-years appears to be the minimum threshold of cumulative LDL exposure necessary to develop a sufficiently large total atherosclerotic plaque burden to increase the risk of experiencing a myocardial infarction.

After the cumulative LDL exposure threshold has been exceeded, the total atherosclerotic plaque burden continues to enlarge in proportion to the

FIGURE 1 Effect of Cumulative Exposure to LDL on Plaque Burden and Risk of Cardiovascular Disease



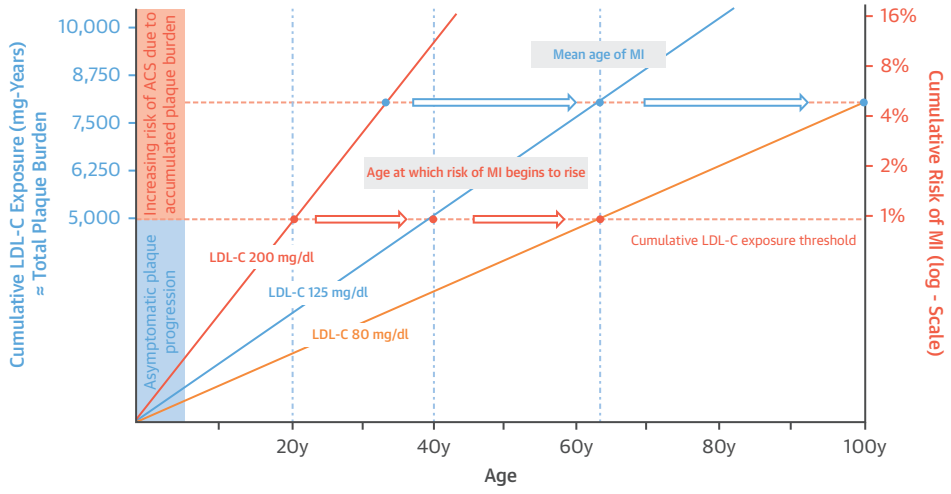
The **solid blue line** represents constant exposure to plasma low-density lipoprotein cholesterol (LDL-C) of 125 mg/dl. Cumulative low-density lipoprotein cholesterol exposure is derived by multiplying age by plasma low-density lipoprotein cholesterol. The **shaded area under the solid blue line** represents the accumulating total plaque burden (which is directly proportional to both age and cumulative exposure to low-density lipoprotein cholesterol). The **horizontal orange dashed line** represents the cumulative low-density lipoprotein cholesterol (and therefore total plaque burden) needed to result in a measurable increase in the risk of myocardial infarction (MI). It is derived by multiplying age 40 years (age at which the cumulative incidence of myocardial infarction exceeds 1%) by 125 mg/dl (plasma low-density lipoprotein cholesterol level). Beyond this threshold, if the plasma low-density lipoprotein cholesterol level remains constant, then both cumulative low-density lipoprotein cholesterol exposure and total plaque burden increase linearly, but the risk of myocardial infarction rises log-linearly (and is shown on the right-hand side y-axis expressed on the log or "doubling scale"). ACS = acute coronary syndrome.

circulating plasma LDL-C concentration as additional LDL particles become retained over time. By contrast, however, once the cumulative LDL threshold has been exceeded, the risk of experiencing an acute coronary syndrome in response to continued plaque growth increases log-linearly (**Figure 1**) (9). Indeed, after the cumulative LDL exposure threshold has been exceeded, the incidence of myocardial infarction appears to double with each increasing decade of exposure to the same plasma level of LDL. For example, the risk of myocardial infarction increases from 1% after 5,000 mg-years (129.2 mmol-years) of cumulative exposure to LDL by age 40 years, to 2% after 6,250 mg-years (156.3 mmol-years) of exposure by age 50 years, to 4% after 7,500 mg-years (187.5 mmol-years) of exposure by age 60 years, to 8% after 8,750 mg-years (218.8 mmol-years) of exposure by age 70 years, and to 16% after 10,000 mg-years (250 mmol-years) of cumulative exposure to LDL by age 80 years (8).

This concept that a person's total atherosclerotic plaque burden is proportional to his or her cumulative exposure to LDL and other apo B-containing lipoproteins explains why younger people are at low risk of experiencing cardiovascular events despite experiencing a progressively increasing atherosclerotic plaque burden. The short-term risk of having a clinical cardiovascular event does not rise materially until after the threshold cumulative exposure to LDL needed to produce a substantial plaque burden has been exceeded. This concept also explains why the short-term risk of atherosclerotic events rises rapidly with continued exposure to LDL after the cumulative LDL exposure and corresponding plaque burden thresholds have been exceeded. The presence of a large underlying atherosclerotic plaque burden means that the "residual" risk of having a clinical cardiovascular event remains high even when LDL-C levels are lowered because 1 or more of the larger underlying plaques can still disrupt to cause an acute coronary syndrome.

Because atherosclerotic plaques grow over time proportional to the concentration of circulating apo B-containing lipoproteins, people with higher LDL levels retain more particles and therefore experience a faster rate of plaque growth. By contrast, people with lower LDL levels retain fewer particles and therefore have a slower rate of plaque growth (**Figure 2**). As a result, people with lower circulating concentrations of LDL and other apo B-containing

FIGURE 2 Cumulative Effect of LDL on Risk of Atherosclerotic Cardiovascular Disease



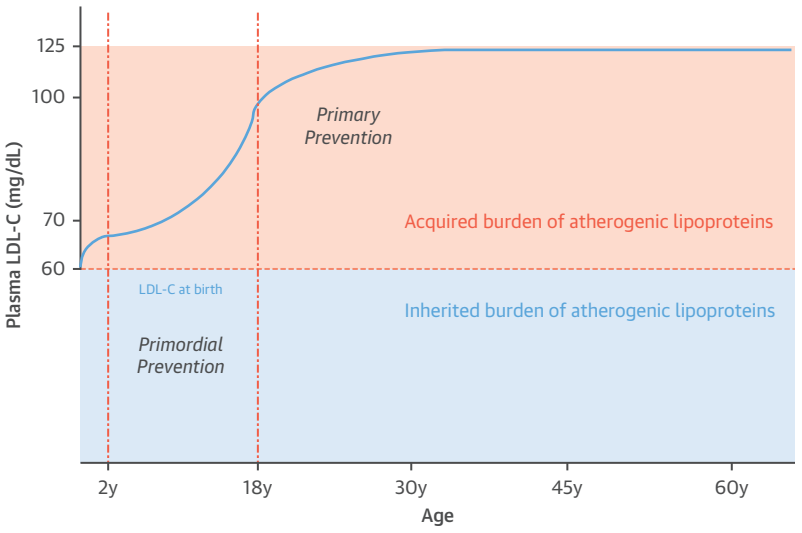
The **solid orange line** represents a low-density lipoprotein cholesterol (LDL-C) level of 200 mg/dl throughout life. The **solid blue line** represents a low-density lipoprotein cholesterol level of 125 mg/dl throughout life. The **yellow line** represents a low-density lipoprotein cholesterol level of 80 mg/dl throughout life. Cumulative low-density lipoprotein cholesterol exposure is derived by multiplying age by plasma low-density lipoprotein cholesterol. Cumulative risk of myocardial infarction (MI) is measured on the log ("doubling") scale. The **orange dots** represent the age at which persons with lifetime exposure to 200 mg/dl, 125 mg/dl, and 80 mg/dl, respectively, exceeds the 5,000 mg-years threshold of cumulative exposure to low-density lipoprotein cholesterol beyond which the cumulative lifetime risk of myocardial infarction exceeds 1%. The **blue dots** represent the average age that persons with lifetime exposure to 200 mg/dl, 125 mg/dl, and 80 mg/dl, respectively, experience a myocardial infarction (or approximately 8,000 mg-years of cumulative low-density lipoprotein cholesterol exposure). The figure shows that lower cumulative exposure to low-density lipoprotein cholesterol can slow plaque progression and delay the onset of myocardial infarction and other acute coronary syndromes (ACS). Abbreviations as in Figure 1.

lipoproteins exceed the threshold for the cumulative exposure to atherosclerotic lipoproteins later and therefore tend to experience cardiovascular events at older ages, on average, than do people with higher LDL levels. For example, a person who maintains an LDL-C level of 80 mg/dl throughout life would not exceed the 5,000 mg-years of cumulative LDL exposure beyond which cardiovascular events begin to occur until age 62.5 years as compared with a person with an LDL-C level of 125 mg/dl, who would exceed this threshold at age 40 years (Figure 2). Furthermore, beyond this cumulative LDL threshold the plaque burden will continue to grow more slowly for people who maintain lower LDL levels. As a result, the average age at which a myocardial infarction occurs (after 8,000 mg-years of cumulative LDL exposure, on average) will rise from 64 years for a person with an LDL-C of 125 mg/dl to age 100 years for a person who maintains an LDL-C level of 80 mg/dl throughout life (Figure 2). Therefore, maintaining exposure to lower lipid levels throughout life as a strategy to minimize the cumulative exposure to LDL and other apo B-containing lipoproteins has the potential to modify the disease course of atherosclerotic plaque progression dramatically and substantially reduce the lifetime risk of experiencing a cardiovascular event.

ROLE OF PREVENTIVE MEASURES

RATIONALE AND GOALS OF MAINTAINING OPTIMAL LIPID LEVELS TO PROMOTE IDEAL CARDIOVASCULAR HEALTH. The goal of maintaining optimal lipid levels throughout life is to keep the concentration of circulating LDL and other apo B-containing lipoproteins low to minimize the number of particles that become retained in the arterial wall and thereby minimize the rate of progression of atherosclerotic plaques as a strategy to reduce the risk of developing a cardiovascular event. The potential clinical effectiveness of this strategy is supported by the observation that isolated populations that maintain lifetime exposure to low plasma levels of LDL have low lifetime risk of cardiovascular disease. For example, members of the Tsimane, a Bolivian population living a subsistence lifestyle, have a low mean LDL-C level of 91 mg/dl (2.35 mmol/l) and a very low prevalence of coronary atherosclerosis as measured by coronary calcium scoring as compared to populations with higher mean LDL-C levels (10).

FIGURE 3 Life Course Trajectory of LDL and Implications for Primordial Prevention



The **blue line** represents mean low-density lipoprotein cholesterol (LDL-C) level at each age. The **blue shaded area** represents the inherited burden of low-density lipoprotein cholesterol and is equal to the low-density lipoprotein cholesterol level at birth. The **orange shaded area** represents the acquired burden of low-density lipoprotein cholesterol that is equal to the low-density lipoprotein cholesterol level at each age minus the low-density lipoprotein cholesterol level at birth.

In general, there are 2 strategies to prevent cardiovascular events by keeping LDL and other apo B-containing lipoproteins low among people who have not experienced a clinical cardiovascular event: primordial prevention and primary prevention.

REDEFINING PRIMORDIAL PREVENTION AND PRIMARY PREVENTION. *Primordial prevention* is defined as preventing the development of risk factors. To understand the primordial prevention of lipid levels better, it is useful to consider what determines the concentration of circulating atherogenic lipoproteins.

Most people are born with an LDL-C level (a metric used to estimate the concentration of circulating LDL particles) of approximately 40 to 60 mg/dl (11,12). This level rises to approximately 70 mg/dl during the first 2 years of life and then rises more gradually during childhood and the teen years to approximately 110 to 120 mg/dl by early adulthood. Plasma levels of LDL-C then further rise even more gradually during early adulthood before plateauing in middle age and then slightly declining in older age (13,14). On the basis of this life course trajectory, it appears that, on average, approximately one-half of the concentration a person's circulating LDL and other apo B-containing lipoprotein particles is inherited, whereas the other one-half is acquired through diet and lifestyle (Figure 3).

With respect to lipid levels, primordial prevention can be defined as the prevention of suboptimal lipid levels. On the basis of the natural history trajectory of lipid levels, however, it follows therefore that a new, more accurate definition of primordial prevention should be preventing (or minimizing) the *acquired burden* of LDL and other apo B-containing lipoproteins. Furthermore, from the usual trajectory of lipid levels, it appears that most of a person's acquired burden of apo B-containing lipoproteins occurs during childhood and adolescence (13,14). Therefore, strategies for the primordial prevention of suboptimal lipid levels must begin during childhood and adolescence.

By contrast, *primary prevention* is defined as lowering lipid levels to achieve more optimal levels as a strategy to prevent cardiovascular events among people who do not have existing clinical evidence of cardiovascular disease. Because the risk of cardiovascular events depends on the cumulative lifetime exposure to LDL and other apo B-containing lipoproteins, primary prevention strategies designed to lower lipids closer to optimal levels should be initiated in early adulthood to minimize the cumulative lifetime exposure to atherogenic lipoproteins.

The objective of both primordial prevention and primary prevention is not necessarily to prevent the development of atherosclerosis but rather to slow the rate of progression of atherosclerosis to prevent or delay the development of advanced atherosclerotic plaques that can cause clinical cardiovascular events. Under these refined definitions, the benefits of both primordial prevention and primary prevention extend beyond a measure of how well they prevent cardiovascular events to include an assessment of how effectively they slow the progression of atherosclerosis. Therefore, documenting a reduced rate of atherosclerotic plaque burden progression, rather than a reduced incidence of clinical cardiovascular events, may be a more intuitive and accurate metric for assessing the clinical benefit of primordial and primary prevention. Using this metric, nearly every person can assess how much he or she is benefiting from maintaining optimal lipid levels.

REDEFINING OPTIMAL LIPID LEVELS FOR IDEAL CARDIOVASCULAR HEALTH. Currently, the optimal lipid level needed to achieve the American Heart Association's metric for ideal cardiovascular health is defined as an untreated total plasma cholesterol level of <200 mg/dl (2). However, this threshold for optimal lipid levels may not be adequate to achieve ideal cardiovascular health for at least 2 reasons.

First, on average, a total cholesterol level of 200 mg/dl corresponds to an LDL-C level of approximately 120 mg/dl and a non-high-density lipoprotein cholesterol level (an estimate of the circulating concentration of all apo B-containing lipoproteins) of 150 mg/dl. Therefore, on the basis of the natural history of lipoprotein level trajectories, setting a total cholesterol threshold of 200 mg/dl to define ideal cardiovascular health (which is approximately equivalent to a threshold of 120 mg/dl for LDL-C) would miss the opportunity to encourage primordial prevention to limit the acquired burden of LDL and other apo B-containing lipoproteins that occurs during childhood, adolescence, and early adulthood.

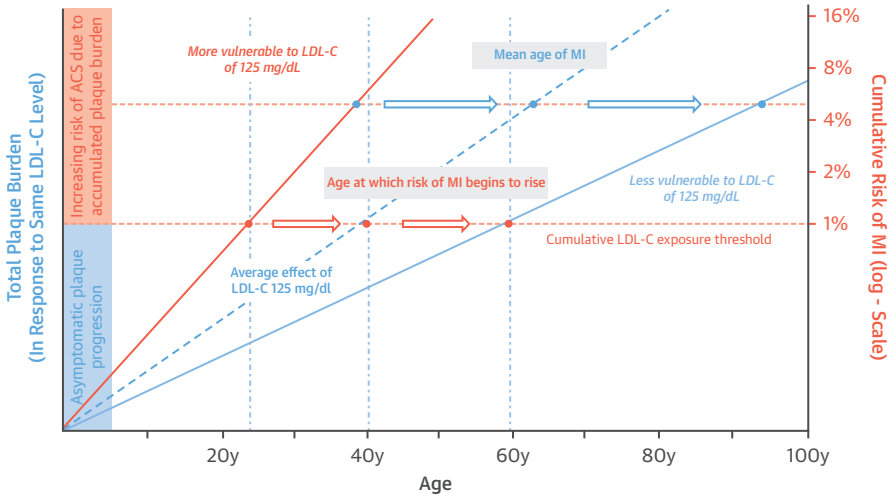
Second, recent evidence has emerged from the PESA (Progression of Early Subclinical Atherosclerosis) studies to suggest that approximately 50% of people with total cholesterol levels lower than 200 mg/dl have evidence of atherosclerotic plaque on noninvasive imaging studies (15,16). Therefore, defining optimal lipid levels as a total cholesterol of <200 mg/dl would imply that these lesions would be permitted to progress unabated over time. As a result, maintaining the current definition of optimal lipid levels would miss the opportunity to lower lipid levels to slow the rate of progression of plaques to prevent cardiovascular events more effectively in one-half of the population of people with a total cholesterol level of <200 mg/dl who have already developed atherosclerosis.

A revised threshold to define optimal lipid levels necessary to achieve ideal cardiovascular health can be inferred from 2 different lines of evidence. First, intravascular ultrasound studies suggest that, on average, the progression of atherosclerotic plaques stops at approximately 70 mg/dl (6,7). Therefore, an LDL-C level of 70 mg/dl may be a possible definition of the threshold for optimal lipid levels needed to prevent cardiovascular events most effectively. This LDL-C level corresponds to the average plasma LDL-C concentration after 2 years of life, before LDL-C levels begin to rise in childhood and adolescence. Second, alternatively, **Figure 2** suggests that maintaining an LDL-C level of 80 mg/dl (as compared with 125 mg/dl or approximately equivalent to the current threshold of 200 mg/dl for total cholesterol) has the potential to increase the age at which myocardial infarctions begin to occur from 40 years to age 62.5 years and to increase the average age at which a first myocardial infarction occurs from 64 years to approximately 100 years. Thus, an LDL-C level of 80 mg/dl may be another possible definition of the threshold for optimal lipid levels needed to achieve ideal cardiovascular health.

THRESHOLD LIPID LEVELS BELOW WHICH CARDIOVASCULAR DISEASE DOES NOT DEVELOP. Although the retention of apo B-containing lipoproteins within the artery wall is a necessary condition for the initiation and progression of atherosclerotic plaques, it is unknown whether there is a plasma LDL-C concentration below which apo B-containing lipoproteins are not retained within the artery wall. Although intravascular ultrasound studies suggest that, on average, the progression of atherosclerotic plaques stops when plasma LDL-C levels are reduced to less than approximately 70 mg/dl, recent data from the intravascular ultrasound GLAGOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound) trial demonstrated that some people continued to experience progression of atherosclerotic lesions even when their plasma LDL-C level was reduced to <20 to 30 mg/dl during treatment with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (17).

Importantly, the observation that some people continue to experience plaque progression even at

FIGURE 4 **Differential Vulnerability to Retaining LDL and Other Apo B-Containing Lipoproteins**

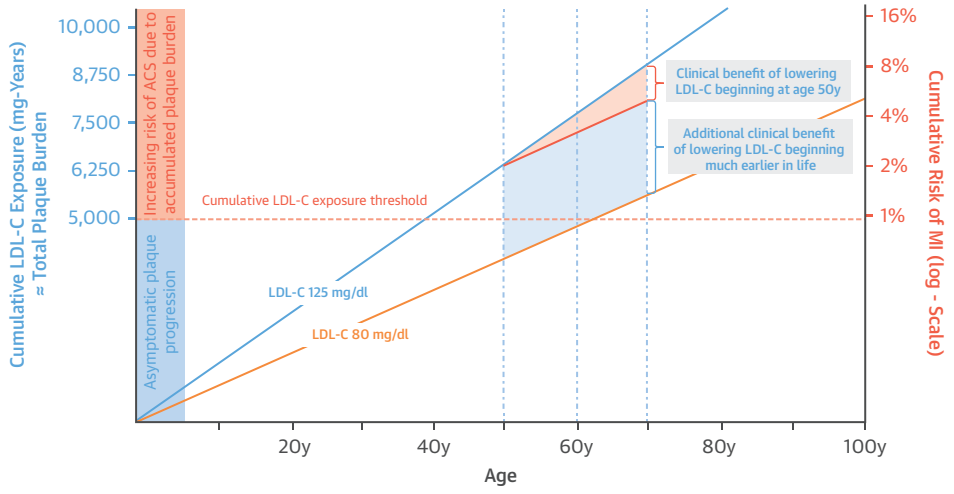


The **dashed blue line** represents the average rate of total plaque burden accumulation in response to a plasma low-density lipoprotein cholesterol (LDL-C) level of 125 mg/dl. The **solid orange line (top)** represents the rate of plaque burden increase for people with a low-density lipoprotein cholesterol level of 125 mg/dl who retain low-density lipoprotein particles in the artery wall more avidly. The **solid light blue line (bottom)** represents the rate of plaque burden increase for people with a low-density lipoprotein cholesterol level of 125 mg/dl who retain low-density lipoprotein particles in the artery wall less avidly. Cumulative risk of myocardial infarction (MI) is measured on the log ("doubling") scale. Figure shows that people who are more vulnerable to retaining low-density lipoprotein particles have more rapid plaque progression and experience cardiovascular events at an earlier age in response to exposure to the same level of circulating low-density lipoprotein particles (as estimated by plasma low-density lipoprotein cholesterol) than people who are less vulnerable to retaining low-density lipoprotein particles. ACS = acute coronary syndrome; Apo B = apolipoprotein B.

very low achieved LDL-C levels while other people cease plaque progression and may even achieve plaque regression at higher LDL-C levels strongly suggests that not everyone retains LDL and other apo B-containing lipoproteins within the artery wall at the same rate. Some people may retain apo B-containing lipoproteins much more avidly than others and therefore may accumulate plaque much more rapidly as compared with other people who retain atherogenic lipoproteins less avidly despite being exposed to the same plasma LDL-C concentration. Such people may be particularly vulnerable to the deleterious effects of LDL and apo B-containing lipoproteins and therefore may benefit from earlier and more aggressive therapy to lower LDL-C than other people who are less vulnerable to retaining apo B-containing lipoproteins (**Figure 4**). This concept of differential vulnerability immediately suggests a strategy to use genomics, biomarkers, and imaging studies to identify people who are the most vulnerable to developing rapidly progressing atherosclerosis and thereby identify people who would benefit most from lipid-lowering therapy at any given LDL-C level. This concept of using genomics and other "-omic" technologies to identify differential vulnerability is an active area of research that may represent a practical strategy to personalize the prevention of cardiovascular disease (18).

TIMING OF STRATEGIES TO PROMOTE OPTIMAL LIPID LEVELS. Because the risk of developing a cardiovascular event is determined by the cumulative exposure to LDL and other apo B-containing lipoproteins, the effectiveness of strategies to achieve optimal lipid levels will depend on the timing of implementation of those strategies. For example, lowering LDL-C from 120 to 80 mg/dl at age 50 years will slow the rate of progression of atherosclerotic plaques and reduce the risk of developing a cardiovascular event (**Figure 5**). However, initiating lipid-lowering therapy after a person has already been exposed to a cumulative burden of 6,250 mg-years of LDL by age 50 years means that person has very likely already developed a large atherosclerotic plaque burden. As a result, lowering LDL after this cumulative exposure to LDL should reduce the risk of cardiovascular events, but this person will remain at relatively high "residual" risk of experiencing an acute cardiovascular event because 1 of the underlying plaques can still disrupt to cause an acute

FIGURE 5 Effect of Primary and Primordial Prevention on Progression of Atherosclerosis and Risk of Acute Cardiovascular Events



The **solid blue line** is a low-density lipoprotein cholesterol (LDL-C) level of 120 mg/dl. The **yellow line** is a low-density lipoprotein cholesterol level of 80 mg/dl. The **solid orange line** represents lowering low-density lipoprotein cholesterol by 40 mg/dl (approximately 1 mmol/l) from 120 to 80 mg/dl beginning at age 50 years and extending to age 70 years. Cumulative low-density lipoprotein cholesterol exposure is derived by multiplying age by plasma low-density lipoprotein cholesterol. Cumulative risk of myocardial infarction (MI) is measured on the log ("doubling") scale. The **orange shaded area** represents a 25% relative risk reduction in myocardial infarction (MI) as a result of lowering low-density lipoprotein cholesterol by 40 mg/dl from 120 to 80 mg/dl from age 50 to 70 years. During this period of treatment, however, the "residual" risk of myocardial infarction remains high because of the high accumulated total plaque burden (as estimated by the cumulative exposure to low-density lipoprotein cholesterol). The **blue shaded area** represents the additional clinical benefit that could be achieved by maintaining low-density lipoprotein cholesterol at 80 mg/dl throughout life (which essentially eliminates the "residual" risk of myocardial infarction). ACS = acute coronary syndrome.

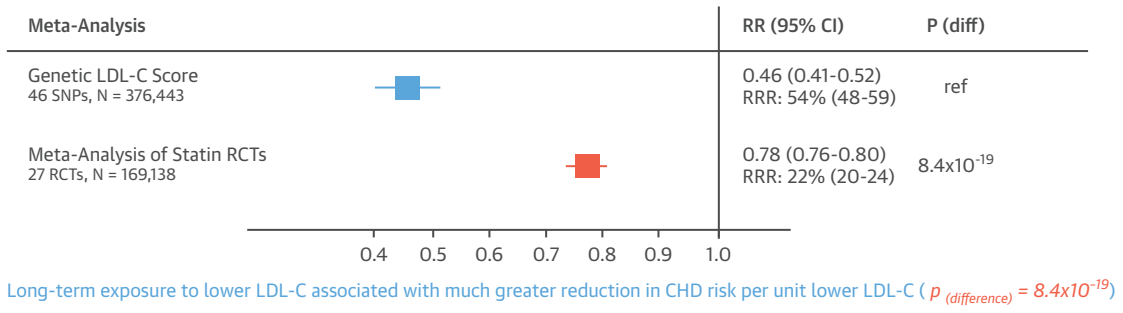
coronary syndrome (Figure 5). Indeed, this continued risk of cardiovascular events despite lipid-lowering therapy initiated after a large total atherosclerotic plaque burden has already developed may explain much of the high residual risk of cardiovascular events observed among people enrolled in lipid-lowering randomized trials (19). By contrast, lowering LDL-C from 120 to 80 mg/dl at age 20 years would begin to slow the progression of atherosclerotic plaques at a stage when these plaques are still too small and lipid poor to produce acute cardiovascular events even if they disrupt and therefore could potentially reduce the risk of cardiovascular events much more effectively than the same reduction in LDL starting at age 50 years (Figure 5).

It is important to recognize that atherosclerosis is a chronic progressive disease that begins early in life and slowly progresses over several decades before becoming clinically manifest. Autopsy and invasive angiographic studies demonstrate that the earliest stages of the atherosclerotic process can be detected in adolescence and early adulthood (20–23). Therefore, the most effective strategy to prevent cardiovascular events by slowing the rate of atherosclerotic plaque progression would be to achieve optimal lipid levels as early in life as possible and maintain those optimal lipid levels throughout life.

ESTIMATING THE POTENTIAL CLINICAL BENEFIT OF MAINTAINING OPTIMAL LIPID LEVELS. Intravascular ultrasound studies demonstrate that lipid-lowering therapies slow the rate of progression of atherosclerotic plaques, and randomized trials of lipid-lowering therapies demonstrate that this reduced rate of atherosclerotic plaque progression translates into improved clinical outcomes. Indeed, numerous randomized trials evaluating multiple different therapies that lower LDL and other apo B-containing lipoproteins have consistently demonstrated that reducing these particles lowers the risk of incident cardiovascular events by approximately 20% per mmol/l reduction in LDL-C (19,24–26).

However, the mean age of participants enrolled in the lipid-lowering trials was 63 years (19). Therefore, participants in these trials had already been exposed to 6,000 to 8,000 mg-years of cumulative exposure to LDL (depending on the mean LDL level and age of participants enrolled in each trial) and thus had

FIGURE 6 Comparison of Proportional Risk Reduction in Cardiovascular Events per mmol/l Lower LDL by Duration of Exposure to Lower LDL



The **blue box** is the odds ratio for coronary heart disease (CHD), defined as CHD death or nonfatal myocardial infarction, per 38.67 mg/dl (1 mmol/l) lower lifetime exposure to lower low-density lipoprotein cholesterol (LDL-C) as estimated from a meta-analysis of Mendelian randomization studies using a genetic low-density lipoprotein cholesterol score consisting of 46 genetic variants associated with low-density lipoprotein cholesterol at a p value threshold of $\leq 5.0 \times 10^{-8}$ (and with at least an 80% concordant effect on apolipoprotein B levels). The **orange box** is the relative risk (RR) for major coronary events per 38.67 mg/dl (1 mmol/l) lower low-density lipoprotein cholesterol derived from the Cholesterol Treatment Trialists meta-analysis of statin trials. The **lines across the boxes** represent 95% confidence intervals (CI). P (diff) = $p_{(difference)}$; RCT = randomized controlled trial; ref = reference; RRR = relative risk reduction.

already developed a substantial burden of atherosclerotic disease including complex atherosclerotic plaques prone to disruption. As a result, these studies almost certainly underestimate the magnitude of the potential clinical benefit that can be achieved by maintaining long-term exposure to low levels of apo B-containing lipoproteins throughout adulthood as a strategy to minimize the rate of progression of atherosclerosis to prevent cardiovascular events by preventing the development of advanced complex atherosclerotic plaques.

Ideally, the magnitude of the potential clinical benefit of maintaining optimal lipid levels throughout adulthood would be tested in a long-term randomized trial. However, such a trial may not be logistically feasible because it would take several decades to complete and because adherence to the allocated treatment over such a prolonged follow-up period would be difficult to maintain. As a result, such a trial is unlikely ever to be conducted.

Fortunately, however, nature may have already conducted this trial for us. Numerous genetic variants are associated with lower LDL and other apo B-containing lipoproteins (27,28). Each of these variants is inherited randomly in a process sometimes referred to as Mendelian randomization (29,30). Therefore, inheriting an allele associated with lower LDL is analogous to being randomly allocated to an LDL-lowering therapy beginning early in life, whereas inheriting the other allele is analogous to being randomly allocated to usual care. If allocation is indeed random, and if the genetic variants used as the instrument of randomization do not have any other pleiotropic effects, then the only difference between the 2 groups will be that 1 group will have a lower lifetime exposure to LDL than the other group. As a result, comparing the lifetime risk of cardiovascular disease in these 2 groups should provide a naturally randomized and unconfounded estimate of the magnitude of the potential clinical benefit of long-term exposure to lower LDL in a manner analogous to a long-term randomized trial (31,32).

Several such Mendelian randomization studies designed as "naturally randomized trials" have been conducted (32–35). These studies consistently demonstrate that long-term exposure to lower LDL and other apo B-containing particles reduces the long-term risk of cardiovascular events by approximately 50% per mmol/l reduction in LDL (36). The magnitude of this estimate of the clinical benefit of long-term exposure to lower LDL is approximately 3-fold greater (on the log-risk scale) than the effect of short-term exposure to LDL observed in randomized trials of lipid-lowering therapies when measured per unit change in LDL (**Figure 6**). These naturally randomized data thus provide powerful evidence not only that LDL and other apo B-containing lipoproteins cause atherosclerosis, but that these particles also have a cumulative effect on the risk of cardiovascular disease over time. This finding is consistent with the hypothesis that plaque progression is caused by the retention and accumulation of LDL particles in the artery wall over time.

TABLE 1 Proportional Reduction in Lifetime Risk of Cardiovascular Disease From Maintaining Lower Lipid Levels

Baseline LDL-C mg/dl (mmol/l)	LDL-C mg/dl (mmol/l) After 50% Reduction	Relative Risk for CHD*	Proportional Reduction in Lifetime Risk of CHD (%)
250 (6.5)	125 (3.2)	0.08	92
190 (4.9)	95 (2.5)	0.15	85
160 (4.1)	80 (2.1)	0.20	80
140 (3.6)	70 (1.8)	0.25	75
120 (3.1)	60 (1.6)	0.30	70
100 (2.6)	50 (1.3)	0.37	65

*Relative risk for CHD is based on 54% relative risk reduction per mmol/l lifetime exposure to lower LDL-C and is calculated as $RR = 0.46^{(\Delta \text{ LDL-C in mmol/l})}$. The proportional reduction in lifetime risk is calculated: (1 − RR for CHD) × 100, where RR is relative risk.

CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol.

The Mendelian randomization studies thus provide strong quantitative evidence to support the claim that maintaining ideal lipid levels throughout adulthood should be an effective strategy to slow the progression of atherosclerotic plaques and therefore should much more effectively prevent cardiovascular events as compared with the current strategy of waiting to lower LDL until much later in life after advanced atherosclerotic plaques have already developed. Indeed, all the major clinical guidelines endorse lowering LDL as early in life as possible to prevent cardiovascular events among people with a high inherited burden of LDL (37-39). As can be seen in **Table 1**, the naturally randomized genetic evidence strongly suggests that this strategy should substantially reduce the lifetime risk of cardiovascular events among people with very high LDL levels. However, the same naturally randomized genetic evidence also suggests that most people can substantially reduce their lifetime risk of cardiovascular disease by two-thirds or more, regardless of their baseline plasma LDL-C level, simply by maintaining prolonged exposure to lower LDL and other apo B-containing lipoproteins beginning much earlier than is currently recommended (3,36). Presumably this benefit is caused by slowing the progression of atherosclerotic lesions by preventing the retention of LDL and apo B-containing lipoproteins in the arterial wall.

Although long-term exposure to lower LDL and other apo B-containing lipoproteins is associated with large proportional reductions in the long-term risk of cardiovascular disease, a more complete evaluation of the potential clinical benefit of maintaining optimal lipid levels throughout adulthood also requires an evaluation of the potential absolute reduction in the risk of cardiovascular events that can be achieved with this strategy. Importantly, just as the proportional reduction in cardiovascular events in response to short-term exposure to lower LDL observed in the lipid-lowering trials cannot be used to estimate the proportional reduction in cardiovascular events in response to long-term exposure to lower LDL, risk equations that estimate the relatively short-term 10-year absolute risk of cardiovascular events cannot be used to estimate the expected reduction in lifetime absolute risk that can be achieved with long-term exposure to lower LDL and other apo B-containing lipoproteins.

All current risk-estimating equations that are used to inform treatment decisions by estimating the absolute risk of experiencing a cardiovascular event over the next 10 years are dominated by age (40-43). Because these risk equations focus on short-term risk and are dominated by age, all young people, including people with familial hypercholesterolemia (FH) who have an extremely high cumulative lifetime exposure to LDL and therefore have an extremely high lifetime risk of developing cardiovascular disease (**Figure 2**), will have a low estimated risk of experiencing a cardiovascular event over the next 10 years. Indeed, risk equations that are dominated by age have the practical effect of recommending that lipid-lowering therapies should not be initiated until a person has developed a sufficiently large underlying plaque burden that they are at a high risk of experiencing an acute cardiovascular event over the next 10 years caused by the disruption of an advanced atherosclerotic plaque. In a sense, using current risk estimating equations to guide treatment decisions is antithetical to prevention because these equations ignore the opportunity to modify the course of the atherosclerotic cardiovascular disease process by lowering LDL among younger people who are at a low short-term absolute risk of having an acute cardiovascular event but who are slowly developing an increasing total plaque burden over time. Therefore, because the lifetime risk of developing a cardiovascular event is determined by the cumulative exposure to apo B-containing lipoproteins rather than by age, current risk estimating equations cannot be used to estimate the potential clinical benefit of maintaining optimal lipid levels throughout adulthood.

Instead, estimating the potential clinical benefit of maintaining ideal lipid levels throughout adulthood requires the use of risk equations that estimate the lifetime risk of cardiovascular events (44). For example, a 25-year-old man with an LDL-C of 140 mg/dl but no other risk factors will have a <1% risk experiencing a cardiovascular event over the next 10 years but a 46% lifetime risk of developing clinically manifest cardiovascular disease. Lowering LDL by 1 mmol/l in this person at age 25 years should

reduce the lifetime risk of cardiovascular events by 50%, from 46% to 23%, resulting in a 23% absolute risk reduction, which translates into a number needed to treat (NNT) of 4 (Table 2). By contrast, if left untreated until age 60 years, this same person would have a 10% absolute risk of experiencing a cardiovascular event over the next 10 years. Lowering LDL by 1 mmol/l at age 60 years would reduce the risk of cardiovascular events by 20%, from 10% to 8%, thus resulting in a 2% absolute risk reduction and an NNT of 50. Therefore, exposure to the same 1 mmol/l lower LDL can potentially produce a 10-fold greater absolute reduction in the risk of cardiovascular events simply by beginning exposure to lower LDL earlier in life, presumably by slowing the progression of a person's total atherosclerotic plaque burden.

The available evidence from Mendelian randomization studies framed as naturally randomized trials, randomized lipid-lowering trials, and intravascular ultrasound studies of randomized trials all suggest that maintaining optimal lipid levels throughout adulthood (or lowering lipids to achieve optimal levels beginning in early adulthood) can substantially slow the rate of progression of atherosclerotic plaques. These data also suggest that slowing the rate of atherosclerotic plaque progression has the potential to result in a 3-fold greater proportional reduction and a 10-fold greater absolute reduction in the lifetime risk of cardiovascular events as compared with the current practice of initiating lipid-lowering therapy much later in life after a person has already developed complex atherosclerotic plaques in response to a high lifetime cumulative exposure to LDL and other apo B-containing lipoproteins.

TABLE 2 Comparison of Expected Absolute Reduction in Risk of Cardiovascular Disease for a 38.67 mg/dl (1 mmol/l) Lower LDL-C by Duration of Exposure*

Age (yrs)	10-yr Risk (%)	Expected 10-yr ARR (%)	NNT	Lifetime Risk (%)	Expected Lifetime ARR (%)	Lifetime NNT
40	1.3	0.3	384	46	23	4.3
50	4	0.8	125	46	23	4.3
60	10	2.0	50	46	23	4.3
70	20.8	4.2	24	46	23	4.3

*Estimates of 10-year risk and lifetime risk for a man with total cholesterol 200 mg/dl, high-density lipoprotein 50 mg/dl, systolic blood pressure 140 mm Hg, nonsmoker, and no history of diabetes or treatment for hypertension. Using these parameters, the 10-yr risk of experiencing an atherosclerotic cardiovascular event is calculated for this person at age 40, 50, 60, and 70 yrs by using the American College of Cardiology/American Heart Association Pooled Cohort Equation. The lifetime risk of atherosclerotic cardiovascular events at each age is calculated using the lifetime risk estimate using the same equation (at age 40 years). A 38.67 mg/dl (1 mmol/l) reduction in LDL-C is assumed to reduce 10-year risk by 20%; and to reduce lifetime risk by 50%. The lifetime NNT is the number of people who would need to maintain optimal lipid levels throughout life to prevent 1 atherosclerotic cardiovascular event. This number remains constant and is always far lower than the NNT to prevent 1 event by starting lipid-lowering therapy later in life.

ARR = absolute risk reduction; LDL = low-density lipoprotein; NNT = number needed to treat.

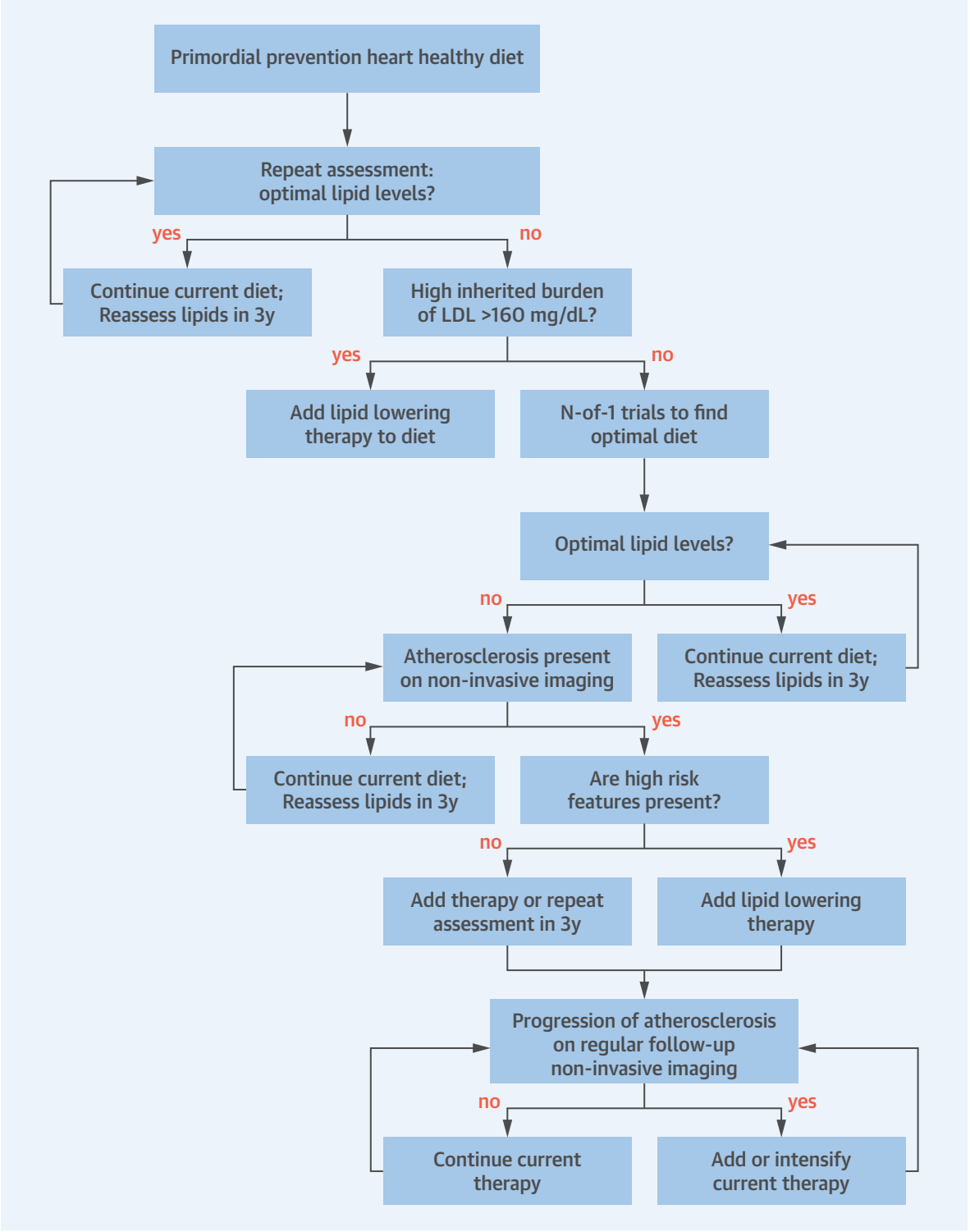
GUIDANCE FOR CLINICIANS

SAFEST AND MOST EFFECTIVE METHODS TO ACHIEVE OPTIMAL LIPID LEVELS. The safest method to achieve and maintain optimal lipid levels throughout adulthood without the risk of medication induced side effects is by engaging in the behaviors that lead to ideal cardiovascular health. Although exercise has a relatively minor impact on circulating levels of LDL and other apo B-containing lipoproteins, diet can have a relatively large impact (45–47). Randomized trials involving total food replacement have consistently demonstrated that reducing saturated fats can reduce plasma LDL-C levels. In the DASH (Dietary Approaches to Stop Hypertension) and DASH-Sodium trials, replacing saturated fats with carbohydrates reduced plasma levels of LDL-C but increased levels of triglycerides (48–49). In the OMNIHeart (Optimal Macro-Nutrient Intake Heart Trial to Prevent Heart Disease), maintaining a DASH-like diet low in saturated fats but replacing carbohydrates with either unsaturated fats or protein further reduced LDL-C levels and eliminated the increased triglyceride levels that occur when carbohydrates are used to replace saturated fats (50).

Furthermore, other randomized trials have demonstrated that eating nuts, plant phytosterols, and foods rich in fiber can also reduce LDL-C (51,52). Combining evidence from these randomized trials suggests that a diet that is low in saturated fats, low in refined carbohydrates, and relatively rich in unsaturated fats (particularly polyunsaturated fats) and protein (particularly plant-based protein), enriched with nuts, plant phytosterols, and high-fiber foods can potentially reduce plasma LDL levels by up to 30 to 40 mg/dl or approximately 0.75-1 mmol/l. The magnitude of this diet-induced reduction in LDL may be enough to eliminate most of the acquired burden of LDL that accumulates during childhood and adolescence and therefore represents the ideal strategy to promote the primordial prevention of suboptimal lipid levels safely, particularly among children.

A CLINICAL PATHWAY TO ACHIEVE OPTIMAL LIPID LEVELS. For many people, however, diet and other lifestyle changes may not be enough to maintain optimal lipid levels throughout life. Among people who cannot maintain optimal lipid levels with diet alone, the question arises whether and when to add lipid-lowering therapy, such as a low-dose statin (e.g., 10 to 20 mg of atorvastatin) or ezetimibe, as an adjunct to healthy diet to achieve optimal lipid levels. The Central Illustration provides a suggested clinical pathway that physicians and other health care providers can use to guide therapeutic decisions and

CENTRAL ILLUSTRATION **Clinical Pathway to Achieve Optimal Lipid Levels**



Ference, B.A. et al. J Am Coll Cardiol. 2018;72(10):1141–56.

A proposed clinical stepwise pathway to apply the evidence proposed in the text. This approach recapitulates the evidence discussed in this paper and aims at optimizing the time for prevention and intervention.

help patients to achieve the optimal lipid levels necessary for ideal cardiovascular health.

The proposed clinical pathway recommends a strong focus on a healthy diet designed to lower LDL and other apo B-containing lipoproteins beginning in childhood and continuing throughout life as a primordial prevention strategy to prevent or minimize the acquired burden of apo B-containing lipoproteins for everyone. Lipid levels should be measured at birth and throughout early life at ages 2, 6, 10, 14, and 18 years to quantify both the inherited and acquired burdens of apo B-containing lipoproteins and to assess the success of the LDL-lowering diet for primordial prevention. Measuring lipid levels at birth and 2 years of age is needed to quantify the inherited burden of LDL and other apo B-containing lipoproteins, and it should serve to identify people with a high inherited burden of LDL who will likely need to initiate lipid-lowering therapy early in life because of a very high lifetime risk of cardiovascular disease. By contrast, measuring lipid levels at regular intervals throughout childhood and adolescence is needed to quantify each person's acquired burden of lipoproteins and thus provide an estimate of how much that person can lower plasma levels of apo B-containing lipoproteins with lifestyle changes alone. This information can help inform the decision about whether and when to recommend lipid-lowering therapy later in life for people with suboptimal lipid levels.

In early adulthood, lipid levels should be assessed once again. If lipid levels are at optimal levels, then that person should be continued on the current diet, and lipid levels should be assessed every 3 to 5 years to ensure that these levels remain lower than the optimal threshold. If lipid levels are higher than the optimal threshold, then physicians (in consultation with dietitians and other health care providers) should consider conducting a series of n-of-1 trials to discover the diet that most effectively reduces apo B-containing lipoproteins for each person. The optimal diet for each person will be the diet that a person can adhere to and that also maximizes the reduction in LDL within the larger context of maintaining normal blood pressure and body mass index. At all times, such advice should be combined with help to avoid smoking and maintain optimal blood pressure levels.

After identifying the diet to which a person can adhere, lipid levels should be reassessed once more. If they are lower than the optimal threshold, then that diet should be continued, and lipid levels should be reassessed every 3 years to ensure that they remain at optimal levels. By contrast, if lipid levels are higher than the optimal threshold, then the decision must be made whether to add lipid-lowering therapy to achieve optimal lipid levels.

Because the goal of maintaining optimal lipid levels is to slow the progression of atherosclerotic lesions to prevent the development of complex atherosclerotic plaques, this decision can be informed by noninvasive imaging to detect the presence of atherosclerotic plaque. If no plaque is present, that person is unlikely to benefit from lowering lipid levels to slow the rate of progression of the underlying total plaque burden (which is too small to be detectable by imaging studies). Therefore, that person should be continued on the current diet, and both lipid levels and imaging to detect the development of atherosclerotic plaque can be repeated every 3 years.

By contrast, when atherosclerosis is present on noninvasive imaging, then that person may benefit from lowering LDL to slow the progression of the detected atherosclerotic plaque burden. The decision whether to add lipid-lowering therapy can be further informed by whether the person has 1 or more "high-risk" features that could portend the rapid progression of atherosclerotic plaque or the development of plaques vulnerable to disruption. These "high-risk" features may include the presence of a large burden of atherosclerosis on noninvasive imaging (indicating that this person avidly retains apo B-containing lipoproteins within the artery walls at the current LDL-C level); a family history of early cardiovascular events (indicating that this person may be at risk for the rapid progression of atherosclerotic lesions that are prone to disruption, leading to acute cardiovascular events); and a high total concentration of circulating apo B-containing lipoproteins (indicating the potential for a large absolute reductions in LDL and other apo B-containing lipoproteins with treatment that should, in turn, translate into large reductions in the lifetime risk of developing a cardiovascular event). If none of these "high-risk" features are present, then it would be reasonable either to initiate treatment with a lipid-lowering therapy as a strategy to slow the progression of the existing atherosclerotic plaque burden or to measure lipid levels and repeat noninvasive imaging yearly for 3 years to document the rate of atherosclerotic plaque progression before initiating lipid-lowering therapy, depending on the patient's preference. However, if 1 or more "high-risk" features are present at the time that atherosclerosis is detected on noninvasive imaging, then lipid-lowering therapy should be added to slow plaque progression in an attempt to modify the atherosclerotic disease course.

The proposed clinical pathway prioritizes recommending a healthy diet designed to reduce LDL and

other apo B-containing lipoproteins beginning in childhood and extending throughout life for everyone. The addition of lipid-lowering therapy beginning early in adulthood to slow the progression of atherosclerosis is reserved for people with a high inherited burden of LDL (including patients with FH) or patients with lipid levels higher than the optimal threshold who also have evidence of a large atherosclerosis plaque burden or a rapidly progressing atherosclerotic plaque burden on noninvasive imaging. Indeed, the "optimal lipid level" for any individual person is likely to be the lipid level that is associated with the absence of atherosclerotic plaque progression for that person. This focused and individualized approach has the potential to improve the prevention of cardiovascular disease substantially while reserving the recommendation for long-term pharmacological lipid-lowering therapy only for those people who have already developed atherosclerosis at their current LDL-C level and therefore are most likely to benefit from additional reductions in LDL and other apo B-containing lipoproteins.

OVERCOMING BARRIERS TO ACHIEVING OPTIMAL LIPID LEVELS. Increasing the proportion of people who achieve the optimal lipid levels needed for ideal cardiovascular health has the potential to improve the prevention of cardiovascular disease substantially. However, to achieve this goal multiple barriers must be overcome among various stakeholders. Barriers to guideline implementation have been defined. These include the complexity of guidelines, time constraints, a lack of training in cardiovascular disease prevention, a lack of remuneration for preventive as opposed to therapeutic medicine, and burdensome government policies (53).

Policymakers play a pivotal role in the potential success of prevention strategies. From a societal perspective, health care resources are finite, and numerous different programs compete for limited funding. Therefore, the cost effectiveness of maintaining optimal lipid levels to prevent cardiovascular disease must be clearly established. Clinical cost effectiveness can be thought of as the cost to prevent 1 event and is calculated as the yearly cost of a therapy or strategy multiplied by the duration of treatment divided by the expected absolute risk reduction in events. Because LDL and other apo B-containing lipoproteins have both causal and cumulative effects on the risk of cardiovascular disease over time, the naturally randomized genetic evidence presented in this review suggests that the absolute risk reduction in cardiovascular events can be improved by a factor of up to 10-fold simply by maintaining lower lipid levels beginning earlier in the atherosclerotic disease process. This dramatic improvement in the expected absolute reduction in the lifetime risk of cardiovascular events can fundamentally transform the cost effectiveness of maintaining ideal lipid levels as a strategy to reduce cardiovascular events such that this strategy is likely to lead to substantial cost savings in all scenarios. Indeed, improved prevention of cardiovascular disease may be an approach that contributes to solving the crisis of rapidly rising health care costs by potentially introducing cost savings.

Communities and schools also play critical roles in promoting both optimal lipid levels and other components of ideal cardiovascular health. Almost all the acquired burden of LDL and other apo B-containing lipoproteins occurs during childhood and adolescence. Therefore, schools must assume the primary role in promoting primordial prevention programs designed to minimize the acquired burden of LDL. Communities and local school districts must make providing heart-healthy meals to children a public health priority. Schools must teach children from a young age about the role of LDL and other apo B-containing lipoproteins in the development of atherosclerosis and the power of a healthy diet to prevent atherosclerosis by maintaining optimal lipid levels (and other components of ideal cardiovascular health) throughout life to reduce dramatically the lifetime risk of cardiovascular events.

Cardiovascular professional societies and organizations also play important roles in preventing cardiovascular disease. Unfortunately, professional societies have not placed sufficient emphasis on the transformative power of maintaining optimal lipid levels throughout life or on strategies designed to help people to achieve ideal cardiovascular health. Professional cardiovascular societies should elevate the role of cardiovascular prevention by creating a new subspecialty of Precision Cardiovascular Prevention that attempts to integrate and harness the explosion of information from genomics, information science, "big data," computational biology, machine learning, and artificial intelligence to refocus medicine on preventing disease by promoting health rather than diagnosing and treating disease.

Cardiovascular medicine professional societies can also help clinicians to develop the new clinical competencies needed to promote optimal lipid levels and ideal cardiovascular health. The required new clinical competencies needed to promote

cardiovascular health more effectively as a strategy to prevent cardiovascular disease may include additional education and training about the role of nutrition and healthy diets in promoting cardiovascular health and about how to conduct n-of-1 trials, how to use genomic information to assess risk, and how to use the power of "big data" to monitor longitudinal trends in lipids levels, biomarkers, imaging studies, and other risk factors to monitor the progression of atherosclerotic lesions more effectively over time.

Finally, the individual person must be empowered to understand that maintaining optimal lipid levels throughout life can dramatically reduce his or her lifetime risk of developing cardiovascular disease. Public health messages should emphasize that each person has the power to control his or her health destiny by engaging in the behaviors that promote ideal cardiovascular health. The public must be given clear advice on which diets can most effectively lower lipid levels and must be provided with easy access to affordable healthful food choices. Evidence is emerging to suggest that lifelong dietary patterns begin in childhood (54,55). Therefore, it is critically important for federal authorities, local communities, professional societies, and health care providers to work together to create a culture among children that encourages eating a heart-healthy diet as a normal part of everyday life, a habit that will then hopefully persist throughout adulthood and into subsequent generations.

CONCLUSIONS

The causal effect of LDL and other apo B-containing lipoproteins on the risk of cardiovascular disease is determined by both the magnitude and the cumulative duration of exposure to these lipoproteins. The goal of maintaining optimal lipid levels throughout life is to keep the concentration of circulating LDL and other apo B-containing lipoproteins low to minimize the number of particles that become retained in the arterial wall and thereby minimize the rate of progression of atherosclerotic plaques. Because apo B-containing lipoproteins have both causal and cumulative effects on the risk of atherosclerotic cardiovascular disease, the most effective strategy to prevent cardiovascular events by slowing the rate of atherosclerotic plaque progression would be to achieve optimal lipid levels as early in life as possible and maintain those optimal lipid levels throughout life. Therefore, maintaining optimal lipid levels throughout life is a necessary component of ideal cardiovascular health and has the potential to reduce dramatically the lifetime risk of developing atherosclerotic cardiovascular disease.

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