JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 10, 2018

PUBLISHED BY ELSEVIER

JACC FOCUS SEMINAR: CV HEALTH PROMOTION

JACC FOCUS SEMINAR

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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Manuscript received February 19, 2018; revised manuscript received June 3, 2018, accepted June 26, 2018.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.06.046

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