# 5 Epidemiology of Atherosclerotic Cardiovascular Disease

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## Atherosclerotic Cardiovascular Disease in the USA

Atherosclerotic cardiovascular disease (ASCVD) encompasses a range of conditions resulting from atherosclerotic plaques in arterial beds, including those in the heart (coronary heart disease [CHD]), legs (peripheral arterial disease), aorta, carotid, cerebral, and renal arteries. In the United States, estimated lifetime risk for total cardiovascular disease (CVD) (fatal and nonfatal CHD, atherosclerotic and hemorrhagic stroke, congestive heart failure, and other CVD death) is >50% [1]. Data from 5 population-based cohorts included in The Cardiovascular Disease Lifetime Risk Pooling Project indicated that lifetime risk for total CVD among men and women free of CVD at 55 years of age is 60.2% and 56.3%, respectively [1]. According to a recent report by the American Heart Association (AHA), 121.5 million American adults had some form of CVD (CHD, stroke, heart failure, and hypertension) between 2013 and 2015, and over one million adults in the USA were expected to experience coronary events in 2019 [2]. In addition, approximately 795,000 Americans suffer a new or recurrent stroke annually. The incidence of stroke increases with advancing age in both men and women and is a leading cause of serious long-term disability; 3% of men and 2% of women in the USA report disability due to stroke [2, 3].

Direct and indirect costs associated with ASCVD represent a significant economic burden in the USA. Between 2014 and 2015, CVD and stroke accounted for 14% of health-related expenditures with an estimated total cost of $351.2 billion ($213.8 billion in direct costs and $137.4 billion in lost productivity/mortality) [2]. According to a 2016 report [4], total direct medical costs of CVD are projected to increase to $749 billion by 2035. Although the death rate from CVD in the USA decreased over the last decade, it remains the leading cause of death among adults and accounted for 840,768 (approximately 1 in 3) deaths in 2016 [3]. Of deaths attributable to CVD, CHD accounted for 43.2% and stroke 16.9%. Globally, CVD is also the leading cause of death and, according to the World Health Organization, accounted for more than 17.6 million deaths in 2016.

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## Atherothrombotic Process

The current understanding of the pathophysiology of atherothrombotic disease derives from the descriptive pathology of human autopsies and experimental studies in animal models. A detailed description of the atherothrombotic process is beyond the scope of this chapter but will be briefly described for context and depicted in Fig. 5.1. The process begins when cholesterol-rich, apolipoprotein (apo)B-containing lipoproteins penetrate and accumulate in lesion-prone areas of the arterial wall, where they are modified (e.g., oxidized, acetylated); this triggers unregulated uptake by macrophages and an inflammatory cascade. Low-density lipoprotein (LDL) cholesterol is the primary driver of this process, though recent evidence suggests that most apoB-containing lipoproteins (up to ~70 nm in diameter) are capable of promoting plaque formation, i.e., all but the largest very-low-density lipoprotein (VLDL) and chylomicron particles [5]. The accumulation of modified apoB lipoprotein particles in the arterial wall leads to an immune-inflammatory response characterized by increased secretion of adhesion molecules and

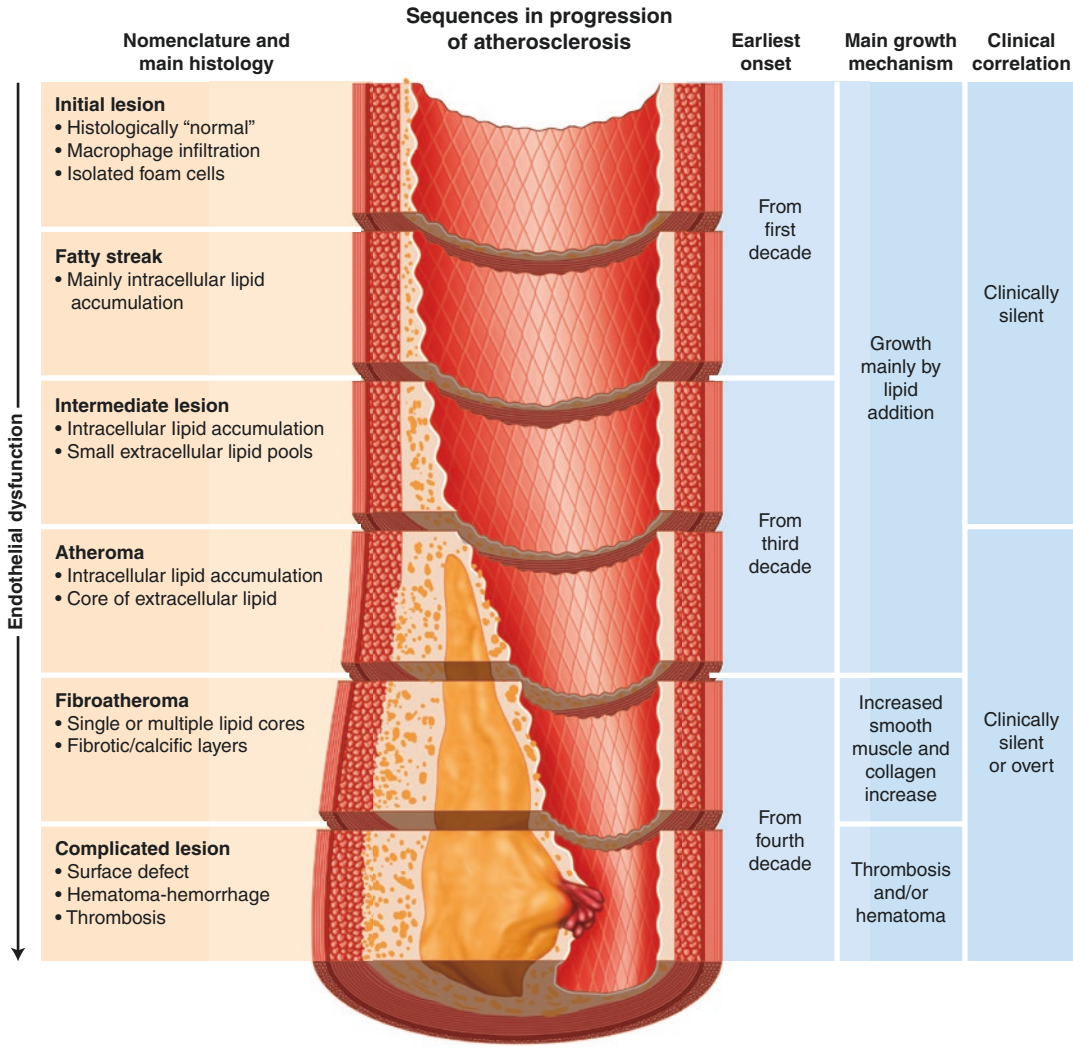


**Fig. 5.1** Progression of the atherosclerotic lesion. (Anonymous, Stages of Endothelial Dysfunction in Atherosclerosis, CC BY-SA 3.0)

the recruitment of monocytes and leukocytes to the arterial lesion. In this inflammatory state, monocytes penetrate the arterial wall and differentiate into phagocytic macrophages that take up the oxidized apoB particles, forming lipid-rich foam cells that coalesce to form a fatty streak. Arterial smooth muscle cells simultaneously secrete extracellular matrix proteoglycans, collagen, and elastin fibers that form a fibrous cap over the growing lesion. Over time, the death of endothelial, smooth muscle, and foam cells leads to the formation of a soft and destabilizing lipid-rich core under the fibrous cap of the growing plaque. In the later stages of atherosclerosis, plaque progression and thickening of the arterial wall can lead to a significant narrowing of the lumen of the artery, limiting blood flow to the affected organ.

In the presence of abundant circulating atherogenic lipoprotein particles, the ongoing cycle of lipoprotein oxidation, foam cell formation, and cell death perpetuate the inflammatory state. Inflammatory processes are important in the development of plaque instability because inflammation can produce thinning of the fibrous cap, enhancing the probability of fissure formation, or frank rupture. Over time, hemodynamic stresses and degradation of the cellular matrix also increase the risk of plaque rupture. A ruptured plaque may result in the formation of a thrombus on the plaque's surface, or a piece of the plaque (or thrombus) may break off and become lodged in a different part of the artery. Either scenario can result in a partial or complete blockage of the arterial lumen, leading to downstream tissue ischemia. The main acute clinical complications of atherothrombotic disease are myocardial infarction (MI) and ischemic stroke, caused by a blockage in an artery of the heart or brain, respectively, from a ruptured plaque [6, 7].

## Cardiovascular Epidemiology

Epidemiology is the study of the distribution and determinants of disease frequency in human populations and the application of that knowledge to evaluate interventions intended to reduce morbidity and mortality. Epidemiologists systematically investigate the associations between endogenous (e.g., cholesterol level) and exogenous (e.g., cigarette smoking) exposures and disease outcomes in populations, or subgroups of individuals within populations, to generate hypotheses about potential causal factors that increase or reduce the risk for human disease. Causal hypotheses generated through observational research may subsequently undergo evaluation in clinical intervention trials, which provide the strongest evidence in favor of an exposure being causally related to disease incidence. Historically, epidemiological methods were employed primarily in the study of infectious disease outbreaks or "epidemics." As the twentieth century progressed, there was a marked shift in the USA and other developed countries from infectious diseases to chronic diseases (characterized by latency periods of 10–20 years or more) as the major causes of mortality. As a result of these changes in disease distribution, the term "epidemic" was broadened to include any disease, infectious or chronic, occurring at an increased frequency in a population [8].

The fundamental measures of disease frequency in epidemiology are incidence and prevalence. Incidence quantifies the number of new occurrences of a disease in a population of at-risk individuals within a specified period of time. Two commonly used incidence measures are cumulative incidence (CInc) and incidence rate (IR).

CInc is defined as the proportion of individuals who become diseased during a specified period of time and is calculated as follows: CInc = number of individuals who develop a disease during a given time period/total number of individuals in the population at risk. It provides an estimate of the probability, or risk, that an individual will develop a disease during this time period. However, CInc assumes that the entire population is at risk for the duration of the specified time period and does not account for circumstances such as loss to follow-up or death from causes other than the disease of interest (competing risk). IR, on the other hand, accounts for the actual amount of follow-up time contributed by all individuals in the study population

(person-time units of observation). IR can be thought of as an instantaneous rate of disease development in a population and is calculated as follows: IR = number of individuals who develop a disease during a given time period/total observation time for all individuals followed. In contrast, prevalence measures the proportion of individuals in a population who have a disease at a given point in time. Using the formula prevalence = number of existing cases of a disease/total population, prevalence can be used to estimate the probability that an individual will have the disease at a specific point in time [8].

## Observational Study Designs

Unlike clinical intervention studies, where individuals are allocated to the exposure of interest by study investigators, observational investigations examine the relationships between exposures occurring within a free-living population and disease outcomes. Observational studies have important limitations, such as the potential for residual confounding, and can be subject to biases that must be considered in the study design, analysis, and interpretation. Rigorously conducted observational studies, however, are capable of providing valuable insights that can be used to estimate disease risk, predict disease occurrence, and provide insights into potential causes of disease.

The two main types of observational study designs are the case-control study and the cohort study. A case-control study enrolls participants on the basis of whether they do or do not have the disease under study, defined as cases and controls, respectively. The proportion of individuals within each group with a history of exposure or characteristic of interest is then compared and used to assess the association between the exposure and disease. Case-control studies are particularly useful for studying rare diseases and diseases with very long latency periods, as well as for studying multiple potential etiologic exposures that might be associated with a specific disease, such as in the early investigation of a disease. A major advantage of case-control studies is that they can be conducted more quickly and less-expensively than studies requiring extended follow-up periods. A notable limitation of case-control studies, however, is the fact that both the exposure and the disease have already occurred at the time subjects are enrolled, making them susceptible to bias from participant selection and recall bias, and limiting inference regarding the temporal association between the exposure and disease.

In cohort studies, participants at risk, but (usually) free of the disease under study, are classified on the basis of exposure status, such as the presence or absence (exposed vs. unexposed) of a factor hypothesized to be related to a disease, or into categories of exposure such as quartiles, and followed over time to assess the relationship between exposure and disease incidence. An important advantage of the prospective cohort study design is the ability to more clearly establish a temporal relationship between exposure and disease. Since eligible participants are typically free from the disease or condition under investigation at the time exposure status is defined, direct calculation of IRs of the outcome in the exposed and non-exposed groups is also possible. Cohort studies are optimal for studying the effects of rare exposures since participants are selected based on their exposure status to ensure an adequate sample size for statistical analysis. In addition, cohort studies can be used to examine multiple health effects of a single exposure, providing a more comprehensive understanding of the range of potential health outcomes related to an exposure of interest. Limitations of the cohort study design include the time, personnel, and financial burdens associated with large sample sizes and often long duration of follow-up, and the potential impact that losses to follow-up of participants can have on the validity of the results.

## Bias and Confounding in Observational Studies

The findings from all observational studies are susceptible to the influence of biases and residual confounding that, at times, no amount of statisti-

cal analysis can fully address. Bias can be broadly defined as any systematic error that results in an inaccurate estimate of the association between exposure and disease. Two main classes of bias found in epidemiological studies are selection bias and information bias. Selection bias occurs when the sample of individuals chosen for inclusion into a study differs from the target population it is intended to represent. This can occur as a result of procedures used to select participants, as well as from factors that influence study participation. Information bias arises when data on the exposure or outcome are obtained differently from different study groups. A common type of information bias present in observational studies is recall bias, defined as the tendency for individuals with a particular adverse health outcome to remember and report previous exposures differently from those who are not affected, or when those who have been exposed to a potential hazard report subsequent events with a different degree of completeness and accuracy than those who were not exposed. One particularly problematic type of information bias is misclassification, which occurs when individuals are incorrectly categorized with respect to exposure or disease status. The most effective way to minimize bias in observational studies is through thoughtful and meticulous study design. Analytical methods can also be used to evaluate and address some sources of bias from observational study results.

In addition to bias, confounding may also impact the validity of statistical associations from observational studies. Confounding is a mixing of effects, where the observed association between the exposure and disease outcome is fully or partially due to the effect of a third (confounding) factor. A confounding factor must be associated with the exposure and with the disease, but not lie on the causal pathway from exposure to disease. Imbalance of a known or unknown confounding factor between exposure groups can lead to an over- or underestimation of the true association between exposure and disease. In observational studies, confounding can be controlled through study design and/or statistical analysis. Two approaches to control confounding through study design are restriction, such as including only individuals within prespecified categories of a confounder, and matching, i.e., selecting subjects in a way that distributes potential confounding factors equally among exposure groups. Stratification is an analytical approach to control for confounding that evaluates the association between the exposure and disease within homogenous categories or strata of the confounding variable. For example, if sex is a confounding factor, estimates of the association should be calculated separately for men and women. Confounding is also addressed statistically through multivariable regression by including known and measured factors thought to be potential confounders in regression models.

Because some confounders may be unknown, or if known, be only crudely measured, residual confounding can occur. For example, numerous observational studies showed a strong, consistent and statistically significant association between vitamin E intake (including from dietary supplements) and risk for CHD [9–13]. However, randomized controlled trials (RCTs) of vitamin E supplements failed to demonstrate a significant protective effect of vitamin E supplementation against CHD risk, suggesting that the associations reported in observational studies were attributable to residual confounding. Thus, other behaviors associated with vitamin E supplement use, such as higher diet quality and physical activity, which may have been measured with low precision, likely confounded the association between vitamin E supplement use and CHD risk, despite attempts to adjust statistically for these factors [14].

## RCTs

RCTs avoid many of the methodological challenges faced by observational studies and are therefore widely accepted as the gold standard for supporting causal relationships between exposures and health outcomes. In an RCT, study investigators randomly assign participants to separate groups to compare exposures, typically therapeutic or preventive interventions. Therefore,

each study participant has a pre-defined chance of being assigned to each treatment group, and thus, the groups should have similar prognoses. Importantly, not only will all known confounding variables, theoretically, be randomly distributed between or among groups, but all unmeasured and unknown confounders will also be balanced. Randomization also ensures that the results of the study are not biased by the way participants are assigned to an exposure status, further ensuring that the observed effects of an exposure are not due to other factors. RCTs, however, are not without limitations. Compared with observational studies, RCTs are often more difficult to design and conduct and present challenges related to ethics, feasibility, and costs [15].

## Mendelian Randomization

An observational research method that has provided substantial contributions to the field of cardiovascular epidemiology is Mendelian randomization, which uses genetic variation as a proxy to investigate the relationship between potentially modifiable risk factors and disease outcomes. Mendelian randomization is defined as the random assortment of genes inherited by offspring from parents during meiosis. In Mendelian randomization studies, genetic variants, such as single-nucleotide polymorphisms, are used as "instrumental variables" for modifiable risk factors hypothesized to affect disease outcomes. An instrumental variable is one that is associated with the risk factor (exposure) of interest, not related to confounders, and has no potential effects on the disease under study except through the risk factor modified by the genetic variant. Though observational in nature, Mendelian randomization studies are less likely to be affected by bias, confounding, and reverse causation than traditional observational studies, because exposure-associated genetic variants are randomly allocated to individuals prior to any exposure or disease outcome [16–18]. An important contribution of the Mendelian randomization approach was the finding that individuals with mutations in proprotein convertase subtilisin kexin type 9 (PCSK9) and Niemann-Pick C1-Like 1, both of which result in lower levels of LDL cholesterol throughout life, were associated with lower ASCVD risk [19, 20]. Genetic variants in lipoprotein lipase, apoC3, and apoA5 that result in decreased triglyceride (TG) and TG-rich lipoprotein cholesterol levels have also been shown to be associated with reduced ASCVD risk [21].

## Association vs. Causation

The results of individual observational studies provide evidence for associations between risk factors and health outcomes, but insight on causal relationships must be inferred from the totality of the evidence. In the mid-1960s, Sir Austin Bradford Hill proposed nine criteria that provide a framework for evaluating when there is sufficient evidence to establish causality [22]. The most relevant of these criteria for the investigation of a potentially causal factor in ASCVD include the *strength* and *consistency* of the relationship across studies and populations, *dose-response* (progressively greater exposure associated with progressively higher or lower disease risk), a *biologically plausible mechanism* to explain why the exposure might be causally related to the development of the disease, appropriateness of the *temporal relationship* between the risk factor and the disease (i.e., the risk factor precedes the disease), and the availability of *confirmatory evidence* from laboratory and clinical intervention studies. Epidemiological research has established associations between lifestyle factors and physiological changes that inform testable hypotheses regarding causal pathways that have helped to identify targets for intervention. For example, evidence from population studies showing a strong association between elevated blood cholesterol and ASCVD event and mortality rates, along with studies in animals indicating that experimental elevation in blood cholesterol produced atherosclerosis, laid the foundation for clinical trials that have since demonstrated that lowering elevated atherosclerotic lipoprotein cholesterol levels reduces ASCVD event risk [23, 24].

## Framingham Heart Study

The Framingham Heart Study (FHS) was the first large-scale, prospective population-based investigation of CVD in the USA. In 1948, the FHS was initiated with the goal of identifying common factors or characteristics that contribute to CVD. At the time, little was known about the general causes of heart disease and stroke; the prevailing view was that the hardening of arteries was an unavoidable consequence of aging. The investigators measured characteristics of a group of approximately 5200 men and women between the ages of 30 and 62 from the town of Framingham, MA, and followed them (and eventually 2 generations of offspring) over decades to determine what characteristics were associated with CVD later in life. The FHS provided clear evidence that risk factors, many of which were identifiable years or even decades before clinical events, could predict CVD risk. These findings also suggested that risk factor modification might be helpful for disease prevention. The FHS identified 4 major modifiable risk factors for CVD: high cholesterol, high blood pressure, cigarette smoking, and diabetes mellitus. Building upon the success of the FHS, additional studies of CVD epidemiology both in the USA and internationally have confirmed and expanded these findings.

## ASCVD Risk Factors

The FHS study paved the way for future studies of cardiovascular risk factors, and today, the major established ASCVD risk factors include elevation in cholesterol carried by atherogenic lipoproteins, a premature family history of CHD (defined as CHD in a male first-degree relative <55 years of age or CHD in a female first-degree relative <65 years of age), low high-density lipoprotein (HDL) cholesterol (<40 mg/dL for men and <50 mg/dL for women), age ≥45 years for men and ≥55 years for women, current cigarette smoking, hypertension (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg or use of antihypertensive medication for lowering blood pressure), and diabetes mellitus [25, 26].

In 2013, the American College of Cardiology (ACC) and AHA jointly released the race- (Black/White) and sex-specific (male/female) Pooled Cohort Equations to predict 10-year risk of a first 'hard' ASCVD event (nonfatal MI, fatal CHD, nonfatal or fatal stroke) and guide clinicians in primary prevention. The equations, which have also been used for risk stratification in the 2018 AHA/ACC/Multisociety Cholesterol Guideline [27] estimate 10-year risk based on an individual's age, total cholesterol, HDL cholesterol, systolic blood pressure (including treated or untreated status), diabetes mellitus, and current smoking status [28]. In response to the expanding evidence base of ASCVD epidemiology, current practice guidelines now recommend that clinicians estimate risk by assessing a number of established risk-enhancing factors in addition to the 2013 Pooled Cohort Equations. Collectively, these factors represent comorbid conditions or biomarkers that may not be a part of routine screening, but are effective for refining risk stratification to inform preventive treatment plans [29]. The risk-enhancing factors identified in the 2018 AHA/ACC/Multisociety Cholesterol Guideline are presented in Table 5.1.

Subclinical measures of ASCVD can also be used in addition to traditional risk factors to refine risk stratification and guide treatment. For example, coronary artery calcium (CAC) scoring is a robust marker of the presence and degree of subclinical atherosclerosis that integrates both measured and unmeasured risk factors and is recommended for use as a decision aid for initiating statin therapy when risk status is unclear [29]. Results from the Multi-Ethnic Study of Atherosclerosis which included over 6000 men and women, demonstrated that significant ASCVD risk heterogeneity exists among individuals eligible for statin therapy based on current guidelines [30]. This analysis showed that when considering CAC in risk stratification, a CAC score of zero reclassifies approximately half of primary prevention patients at borderline and intermediate risk, based on the Pooled Cohort Equation estimate, as being at low risk (<5% 10-year risk for an ASCVD event). Conversely, those with a CAC score ≥100 Agatston units consistently have a 10-year

**Table 5.1** Risk-enhancing factors in ASCVD risk assessment[a]

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|---|
| **Family history of premature ASCVD** (males, age <55 years; female, age <65 years) |
| **Primary hypercholesterolemia** (LDL cholesterol, 160–189 mg/dL [4.1–4.8 mmol/L]; non-HDL cholesterol, 190–219 mg/dL [4.9–5.6 mmol/L]) |
| **Metabolic syndrome** (increased waist circumference [by ethnically appropriate cut points], elevated TG [>150 mg/dL, non-fasting], elevated blood pressure, elevated glucose, and low HDL cholesterol [<40 mg/dL in men; <50 mg/dL in women]; a minimum of 3 factors denotes a diagnosis) |
| **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 $m^2$ with or without albuminuria; not treated with dialysis or kidney transplantation)<br>**Chronic inflammatory conditions**, such as psoriasis, rheumatoid arthritis, lupus, or HIV/AIDS |
| **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions such as preeclampsia** |
| **High-risk race/ethnicity** (e.g., South Asian ancestry) |
| **Lipids/biomarkers associated with increased ASCVD risk**<br>Persistently elevated primary hypertriglyceridemia (≥175 mg/dL, non-fasting)<br>If measured:<br>**Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)<br>**Elevated Lp(a)** (≥50 mg/dL or ≥125 mmol/L): indication for measurement is a family history of premature ASCVD<br>**Elevated apoB** (≥130 mg/dL, corresponds to an LDL cholesterol ≥160 mg/dL): indication for measurement is TG ≥200 mg/dL<br>**Ankle-brachial index** (<0.9) |

*AIDS* acquired immunodeficiency syndrome, *apoB* apolipoprotein B, *ASCVD* atherosclerotic cardiovascular disease, *eGFR* estimated glomerular filtration rate, *HDLC* high-density lipoprotein cholesterol, *HIV* human immunodeficiency virus, *LDLC* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein (a), *TG* triglyceride.
[a]Adapted from Grundy et al. [27]

ASCVD event risk ≥7.5%, favoring the use of statin therapy. Such findings have important implications for identifying which patients are likely to have meaningful benefits, or not, of statin therapy and ensuring healthcare resources are allocated accordingly.

Additionally, lifestyle factors such as stress, lack of social support, poor diet quality, and physical inactivity are associated with an increased risk of CVD but do not factor into the current risk stratification guidelines, in part because they operate through effects on other risk factors that are included in the risk stratification process. Nonetheless, these are important for clinicians to assess and address as part of the treatment plan. The focus of the remainder of this chapter will be specifically on lipoprotein-related risk factors.

## Lipoprotein-related Risk Factors

Hypercholesterolemia was one of the first well-established major risk factors for ASCVD. Since the critical role of elevated circulating cholesterol in the formation of atherosclerotic plaques was first identified, the understanding of the relationship between different types of lipoprotein cholesterol and ASCVD risk has evolved enormously. Cholesterol and TGs are not water-soluble and must be transported in the blood in lipoprotein particles. In the fasting state, the three main classes of circulating lipoproteins are LDL cholesterol, TG-rich lipoprotein cholesterol (VLDL cholesterol and a small number of chylomicron remnants), and HDL cholesterol. The main functions of LDL and VLDL are the transport of cholesterol and TGs, respectively, from the liver to peripheral tissues, whereas HDL is primarily involved in the return of cholesterol from peripheral tissues to the liver for excretion. Evidence from epidemiological, genetic, and experimental animal model studies, as well as RCTs, has established the central and causal role of apoB-containing lipoproteins (LDL, VLDL, chylomicron remnants) in the pathogenesis of ASCVD.

## HDL Cholesterol Is an ASCVD Risk Factor But Not a Target of Therapy

Although low levels of HDL cholesterol and its main structural protein, apoA1, are strongly associated with an increased risk of ASCVD in observational studies, this relationship has proven to be complicated. Mendelian randomization studies of genetic variants that alter HDL cholesterol levels have not shown significant associations with ASCVD risk, unlike those associated with changes in LDL- and TG-rich lipoprotein cholesterol, as reviewed later in this chapter [31, 32]. While some evidence suggests that therapies that increase HDL cholesterol or apoA1 levels are associated with a reduction in ASCVD risk [33], clinical trials investigating the use of such therapies, such as niacin and cholesteryl ester transfer protein inhibitors, have not demonstrated ASCVD risk reduction. HDL cholesterol levels can be raised through a variety of mechanisms, and it is unclear whether all would produce benefits for CVD risk. Consequently, HDL cholesterol is not currently considered a target of ASCVD risk reduction therapy, although it is used in ASCVD risk assessment and stratification [25].

## Evidence for a Causal Relationship for ApoB-containing Lipoproteins and ASCVD Risk

Genetic variants that alter apoB-containing lipoproteins, and the cholesterol carried by those lipoproteins, provide strong evidence supporting a causal relationship to ASCVD risk. It is well documented that genetically inherited forms of severely elevated LDL cholesterol, such as familial hypercholesterolemia (homozygous and heterozygous), familial defective apoB-100, and polygenic hypercholesterolemia, are associated with a substantially increased risk of premature CHD [34]. Also, prolonged exposure to low LDL cholesterol levels beginning early in life as a result of genetic polymorphisms is associated with a reduction in the risk of ASCVD that is larger than would be anticipated based on results from studies of lowering LDL cholesterol levels later in life with pharmacologic interventions [35]. For example, Cohen et al. examined the effect of DNA-sequence variations in PCSK9 associated with reduced levels of plasma LDL cholesterol throughout the lifespan on incident CHD (MI, fatal CHD, or coronary revascularization) over 15 years in black and white men and women in the Atherosclerosis Risk in Communities prospective cohort study [19]. Loss-of-function mutations in PCSK9 were associated with a 28% reduction in mean LDL cholesterol and an 89% reduction in the risk of ischemic CHD (hazard ratio 0.11, 95% confidence interval [CI] 0.02–0.81; $p = 0.03$).

Mendelian randomization studies also support the causal effects of elevations in plasma TGs and TG-rich lipoproteins for ASCVD risk, independent of LDL cholesterol [31, 32, 36, 37]. The degree of risk reduction associated with each mmol/L (39 mg/dL) lower level of cholesterol carried by LDL or TG-rich lipoprotein particles (VLDL and chylomicron remnants) produced by genetic variants is similar, and roughly twofold greater than would be predicted on the basis of results from RCTs of cholesterol-lowering therapies, which have had an average duration of ~5 years [38].

Non-HDL cholesterol is composed of cholesterol carried by all potentially atherogenic (apoB-containing) particles, including LDL, intermediate-density lipoproteins, Lp(a), VLDL, chylomicron particles, and their remnants. Both components of non-HDL cholesterol (LDL cholesterol and TG-rich lipoprotein cholesterol) independently predict atheroma progression in statin-treated patients with coronary artery disease [39]. A recent meta-regression analysis of data from clinical intervention trials by Marston et al. [40] showed that pharmacologic reduction in non-HDL cholesterol is strongly associated with a lower risk of major cardiovascular events, regardless of the class of lipid-lowering drug employed. For each 1 mmol/L (39 mg/dL) reduction in non-HDL cholesterol, the effect of statin therapy (relative risk 0.80, 95% CI 0.77–0.82), which mainly lowers LDL cholesterol, was similar to that of fibrate therapy (relative

risk 0.79, 95% CI 0.71–0.88), which mainly lowers VLDL cholesterol. There is no apparent threshold in the relationship between non-HDL cholesterol level and ASCVD risk and the available data suggest a continuous relationship down to very low levels [41].

A pooled analysis by the Cholesterol Treatment Trialists' Collaboration showed that each 1 mmol/L (39 mg/dL) reduction in LDL cholesterol produced by statin therapy was associated with a reduction of 23% (95% CI 20–26%) in risk for a major CHD event. Thus, each 10 mg/dL reduction in LDL cholesterol induced by statin therapy would be expected to lower CHD event risk by 6.5% [$1 - 0.77^{(10/38.7)} = 0.0653$ or 6.5%]. Ference et al. showed that each 10 mg/dL reduction in LDL cholesterol produced by genetic variants that affect LDL cholesterol was associated with a reduction of 13.8% (95% CI 12.5–15.1%) in CHD event risk. Each 10 mg/dL reduction in TG-rich lipoprotein cholesterol (estimated as TG/5) was associated with a similar risk reduction of 12.4% (95% CI 9.8 to 15.9%). Both estimates were from a model that contained the other lipid variable, indicating that the associations of LDL cholesterol and TG-rich lipoprotein cholesterol (the two components of non-HDL cholesterol) were independent of one another. Notably, the estimate for LDL cholesterol of 13.8% is more than twice the 6.5% value from the Cholesterol Treatment Trialists' analysis, suggesting that the full benefit of LDL cholesterol-lowering therapy may not be evident over a period of ~5 years. The findings summarized above support the views that both components of non-HDL cholesterol contribute to risk and that "lower for longer is better" with regard to non-HDL cholesterol and ASCVD risk.

Results of a risk-evaluation and modeling study by Brunner et al. [42] that included approximately 400,000 individuals from 19 countries across Europe, Australia, and North America provide strong evidence for the association of non-HDL cholesterol with ASCVD. Based on their findings, the authors developed a tool specific for age, sex, and cardiovascular risk factors to estimate the long-term probability of a cardiovascular event related to non-HDL cholesterol by age 75. With this tool, they also modeled risk reduction through lipid-lowering therapy, with results providing further support for the potential benefit of beginning lipid-lowering therapy early in life. For example, the tool predicted that a woman <45 years of age with a non-HDL cholesterol concentration of 145–185 mg/dL (3.7 to <4.8 mmol/L) and ≥2 additional risk factors had a 15.6% probability of having a major cardiovascular event by age 75; with a 50% reduction in non-HDL cholesterol levels, this probability could be reduced to 3.6%.

## ApoB Concentration Is an Indicator of Atherogenic Particle Burden

For several decades, the custom in the USA has been to use measurements of lipoprotein cholesterol and TG to assess lipoprotein-related ASCVD risk and responses to interventions. The concentration of apoB reflects the total number of circulating lipoprotein particles with atherogenic potential because each VLDL, LDL, and chylomicron particle contains one molecule of apoB [note that intermediate-density lipoprotein and Lp(a) are typically in the LDL density range and thus included in LDL]. Unless an individual has a very high TG level, nearly all of the apoB is carried by VLDL and LDL particles in the fasting state, and <1% is carried by chylomicron remnants of intestinal origin that contain a truncated 48-amino acid form of apoB rather than the 100-amino acid form of hepatic origin. Using a Mendelian randomization study design, Ference et al. [43] demonstrated that both LDL cholesterol and TG level (a proxy for TG-rich lipoprotein cholesterol) lost statistical significance as predictors of CHD risk after adjustment for the concentration of apoB, suggesting that the clinical benefit of lowering LDL and TG-rich lipoprotein cholesterol levels may be a reflection of the degree of reduction in apoB-containing lipoprotein particles.

There is an ongoing debate about the merits of non-HDL cholesterol versus apoB for predicting ASCVD risk and assessing response to therapy in the clinical setting. Results from

observational studies and RCTs suggest that apoB level is modestly superior to non-HDL cholesterol concentration for these purposes [44–47]. However, the 2018 AHA/ACC/Multisociety Cholesterol Guideline favors the use of non-HDL cholesterol because it is universally available and requires no additional expense to measure compared with a standard lipid profile [25]. In some cases, however, an individual's apoB concentration may remain elevated despite having low levels of non-HDL and LDL cholesterol. For these individuals with discordantly elevated apoB, the circulating atherogenic lipoprotein particle burden is higher than would be predicted based on cholesterol measurements, and there is theoretical residual risk from this that could potentially be modified through efforts to further lower the circulating particle concentration, although this hypothesis has not been tested in prospective RCTs [25]. The National Lipid Association has recommended that consideration be given to measuring apoB (or the LDL particle concentration as an alternative) once desired levels of non-HDL and LDL cholesterol have been achieved, to identify such discordant individuals [25].

## TG Elevation as a Marker for Metabolic Disturbances

When considering lipid-lowering approaches for ASCVD risk reduction, it is important to consider that TG elevation is often just one component of a group of metabolic disturbances and, therefore, some of the risk associated with increased TG levels may be due to non-lipid mechanisms. TG elevation is a component of the metabolic syndrome and is frequently associated with other metabolic disturbances that are not components of the syndrome, such as insulin resistance [48], chronic inflammation [49], and oxidative stress [50]. Thus, TG elevation may be useful for identification of individuals with strong potential to benefit from lifestyle intervention, as well as other interventions such as omega-3 fatty acid concentrates [51–53].

The results of the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) suggest that at least some of the effects of icosapent ethyl (ethyl esters of the omega-3 fatty acid eicosapentaenoic acid) on CVD risk may be explained by mechanisms other than a reduction of TG levels [54]. REDUCE-IT compared the effect of 4 g/day icosapent ethyl versus placebo on a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina in patients with established CVD or with diabetes and other risk factors, who were receiving statin therapy and had a TG level of 135–499 mg/dL (1.52–5.63 mmol/L). Compared with placebo, patients treated with icosapent ethyl had a significantly lower risk of major cardiovascular events regardless of baseline TG levels and TG levels attained after the first year of the trial (≥150 or <150 mg/dL). The 25% relative risk reduction observed with icosapent ethyl far exceeded the ~9% risk reduction that would have been predicted from the 0.41 mmol/L (16 mg/dL) lowering of non-HDL cholesterol [40].

## Lp(a) and ASCVD Risk

The biological plausibility of Lp(a) as a causal factor in ASCVD risk is two-fold. First, Lp(a) particles contain a large glycoprotein and an apo(a) protein bound to apoB by a disulfide bridge, making them structurally similar to plasminogen. As a result, Lp(a) competes with plasminogen for binding, impairing plasmin activation and hindering fibrinolysis. Second, the binding of Lp(a) to macrophages promotes the formation of foam cells and the deposition of cholesterol in atherosclerotic plaques. Meta-analyses of prospective observational studies have consistently shown that higher plasma concentrations of Lp(a) are associated with dose-dependent increases in the risk of CHD and stroke [55].

Results of a Mendelian randomization study that combined data from both the Copenhagen City Heart Study and Copenhagen General Population Study to include over 77,000 partici-

pants demonstrated a stepwise increase in MI risk with increasing levels of Lp(a) [56] and confirmed that elevated Lp(a) levels were associated with increased ASCVD risk in the general population, with levels >90 mg/dL predicting a threefold increase in risk [57]. Although Mendelian randomization studies collectively indicate that plasma Lp(a) is causally associated with CHD risk, RCTs of therapies that specifically target Lp(a) reduction are not yet available. Burgess et al. [58] conducted a Mendelian randomization analysis to estimate the magnitude of change in plasma Lp(a) levels that would be needed to produce a reduction in CHD risk similar to a ~39 mg/dL (1 mmol/L) decrease in LDL cholesterol levels, the amount shown in clinical trials to produce a clinically meaningful 20–23% reduction in the risk of cardiovascular events. Their results suggested that Lp(a) would need to be lowered by ~100 mg/dL to achieve the same CHD risk benefit attained by lowering LDL cholesterol levels by ~39 mg/dL. The practical implications of these findings are complicated by the fact the distribution of individual plasma Lp(a) concentrations are highly skewed, varying by up to 1000-fold among individuals in a given population [56]. The National Lipid Association has issued a Scientific Statement concluding that Lp(a) is an independent predictor of ASCVD risk that is additive to other risk factors including LDL and non-HDL cholesterol concentrations [25]. Current guidelines recommend that an Lp(a) concentration ≥50 mg/dL [or 125 nmol/L for Lp(a) particle concentration] be considered as a risk-enhancing factor (see Table 5.1) when considering pharmacotherapy for ASCVD risk management.

Statin therapy lowers LDL cholesterol and particle concentrations but has little effect on Lp(a) concentration. At the time of this writing, an antisense oligonucleotide agent is in development that will target Lp(a) reduction, but RCT data on cardiovascular outcomes are not available [59]. PCSK9 inhibitor therapy lowers the Lp(a) concentration by ~25%. Post hoc analyses from two secondary prevention trials with PCSK9 inhibitor therapy have provided suggestive evidence that the benefit of therapy may be greater in patients with higher baseline levels of Lp(a), consistent with the possibility that Lp(a) lowering contributes to ASCVD risk reduction [60, 61].

### LDL Particle Size and ASCVD Risk

A large body of observational evidence has established an association of the small, dense LDL phenotype (known as LDL pattern B) with increased ASCVD risk [62, 63]. The biologic plausibility of this association is supported by atherogenic characteristics of small, dense LDL particles, such as extended time in circulation, enhanced susceptibility to oxidation, arterial proteoglycan binding, and ease of permeability through the endothelial barrier [64]. However, the pattern B phenotype is often associated with other high-risk characteristics such as elevated TGs; low HDL cholesterol and particle concentration; increased LDL particle and apoB concentrations; insulin resistance; diabetes; obesity; and metabolic syndrome [63]. Moreover, the association of the small, dense LDL particle or cholesterol concentration with ASCVD event risk typically loses statistical significance after adjustment for the number of circulating LDL particles or the apoB concentration [65]. Therefore, current guidelines do not recommend the use of LDL particle size or the LDL pattern B phenotype in ASCVD risk assessment.

## Conclusions

The application of epidemiological methods of investigation has contributed immensely to the understanding of ASCVD etiology and led to the identification and testing of numerous therapeutic measures. Since the FHS first identified major risk factors associated with CVD, the understanding of ASCVD risk has expanded tremendously. The expanded knowledge of lipid-related risk factors, in particular, has contributed to major advances in the treatment of ASCVD. As a key driver of the atherothrombotic process, apoB-containing lipoprotein levels are used for risk

stratification and represent important therapeutic targets. Over the years, a large body of evidence has also demonstrated the important role of apoB particle number and Lp(a) in ASCVD risk. The relationship between some ASCVD risk factors, such as HDL cholesterol and TGs, has proven to be more complex and further research on how these factors should be addressed in the current treatment paradigm is warranted. In light of the growing epidemic of CVD worldwide, population and genetic studies continue to play an important role in advancing the field of cardiology. Additional investigation of lipid-related risk factors and interactions between risk factors will provide more effective means through which ASCVD can be effectively treated and ultimately prevented.

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