# Chapter 1
# Cardiovascular Disease Epidemiology and Risk Factors: General Concepts


**Peter P. Toth**

## Introduction

Cardiovascular disease (CVD) is epidemic throughout the world and includes atherosclerotic disease in its various forms (coronary artery disease [CAD], peripheral arterial disease, carotid artery disease), hypertension, stroke, and heart failure, among others. CVD is the leading etiology for global mortality and the most important source of morbidity. The most significant clinical sequelae of CVD include myocardial infarction (MI), both hemorrhagic and ischemic stroke, claudication and lower limb loss, chronic kidney disease and end-stage renal disease, heart failure, arterial aneurysm formation in the aorta and its tributaries, and, especially for patients with diabetes mellitus (DM) and/or hypertension (HTN), retinopathy and nephropathy. The diagnosis and management of CVD incurs enormous economic costs upon society worldwide and is responsible for considerable disability throughout all regions of the world [1, 2]. The World Heart Federation estimates that over 17.3 million people die of CVD annually, and by 2030 that number is expected to increase to 23 million people [3]. This represents 31% of all deaths annually. The World Health Organization estimates that 85% of deaths due to CV occur from MI and stroke [4].

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In the United States, the American Heart Association estimates that: [1] CVD accounted for 840,678 deaths in the US in 2016, equal to approximately 1 of every 3 deaths [2]. CVD mortality exceeded all forms of cancer and chronic lower respiratory disease combined [3]. Between 2013 and 2016, 121.5 million American adults were afflicted with some form of CVD. [4] Between 2014 and 2015, direct and indirect costs of CVD and stroke amounted to $351.2 billion ($213.8 billion in direct costs and $137.4 billion in lost productivity/mortality) [5]. In 2016, CAD was the leading cause (43.2%) of deaths attributable to cardiovascular disease in the US, followed by stroke (16.9%), HTN (9.8%), heart failure (9.3%), diseases of the arteries (3.0%), and other cardiovascular diseases (17.7%) [6]. CVD and stroke accounted for 14% of total health expenditures in 2014–2015. This is more than any major diagnostic group [7]. In addition, total direct medical costs of CVD are estimated to increase to $749 billion in 2035, according to a 2016 study [5].

This chapter focuses on cardiovascular epidemiology. Epidemiology quantifies the distribution and determinants of health and disease. More specifically, epidemiologic investigation evaluates associations between exposures to specific genetic, environmental, and behavioral features and the risk for developing disease or maintaining health. After seven decades of research conducted within large prospective longitudinal cohorts around the world, risk factors for the development of CVD are biologically plausible and have been firmly established. Prospective, double-blind, randomized clinical trials testing specific interventions to treat these risk factors have also established that they are either treatable or reversible, and that these actions reduce risk for CVD. Cardiovascular epidemiology has made possible the prevention of some types of CVD events in the primordial, primary, and secondary prevention settings.

## Global Perspective of Cardiovascular Disease

Subsequent to World War II, it became clear that efforts to reduce the incidence of CVD were urgently needed. In the United States the Framingham Heart Study (FSH) was initiated in 1948 with the inclusion of 5209 men and women in the original cohort that was free of CVD at baseline [6, 7]. Being a prospective, longitudinal cohort observed over many years, the temporal relationship between numerous risk factors and the incidence (new cases of specific forms of CVD within a defined time frame) as well as causation of disease could be established in a study such as the FHS. The FHS established dyslipidemia, hypertension, diabetes, smoking, and other genetic and behavioral features as risk factors for the development of CVD. In subsequent decades the FHS also evolved an Offspring cohort, a Third-Generation cohort, and a Spouses cohort, all which continue to yield novel insight into the genesis of CVD.

The Seven Countries Study lent support to many of the most important conclusions reached by the FHS [8, 9]. In the US numerous other cohorts exploring features that predispose to CVD were also introduced, including the Cardiovascular Health Study, [10] the Atherosclerosis Risk in Communities Study (ARIC), [11] the Multiethnic Study of Atherosclerosis (MESA), [12] Reasons for Geographic and Racial Differences in Stroke Study (REGARDS), [13] and the Jackson Heart Study

(JHS), [14] among others. Similar cohorts were recruited in Europe, [15, 16] South America, [17] Asia, [2, 18–20] India, [21] Africa, [22] and elsewhere [23, 24]. The INTERHEART Study evaluated CVD risk factors in 52 countries and affirmed that nearly 92% of risk for an MI is attributable to treatable/preventable risk factors and that risk factors behave similarly in peoples from around the world [25]. The pooling of data has allowed for the generation of global maps depicting the prevalence of specific forms of CVD, such as ischemic heart disease (IHD. (Fig. 1.1). It is

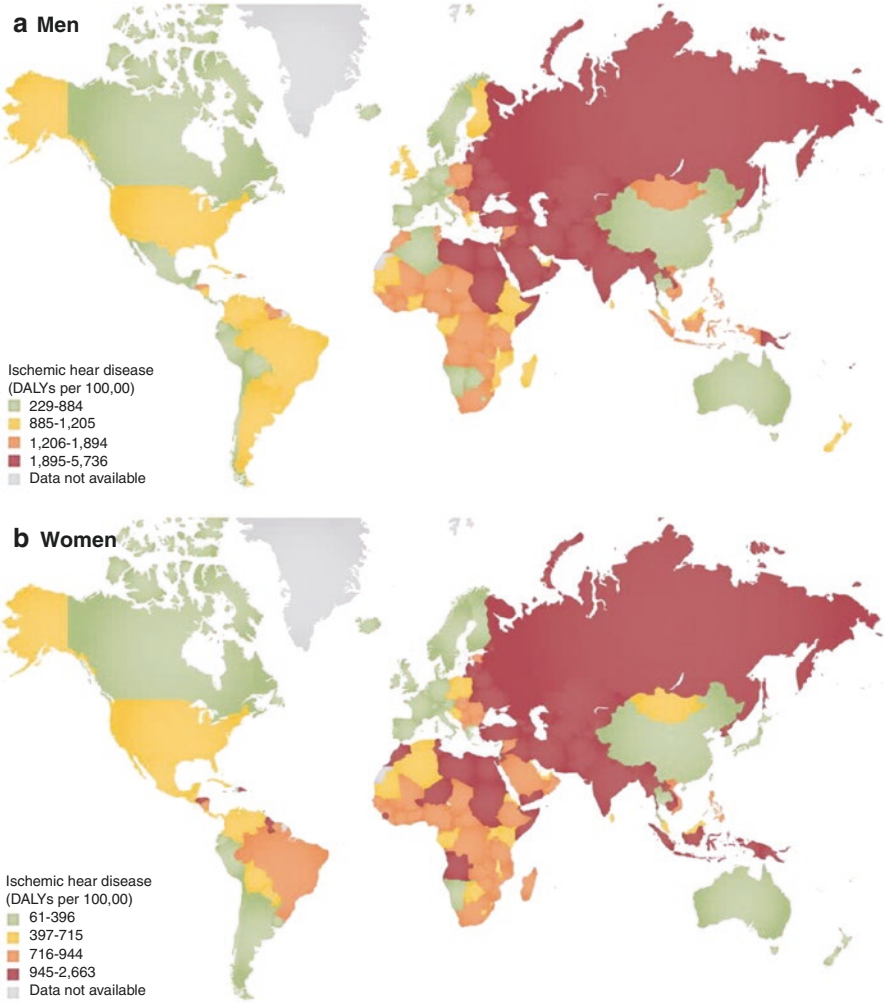


**Fig. 1.1** The Global Distribution of Ischemic Heart Disease for both men and women, in DALYs, in 2011. (**a**)| Men (**b**) |Women. Data are age-standardized per 100,000 of the population. Abbreviation: DALYs, disability-adjusted life years. (Reproduced, with permission from the publisher, from Mendis, S., Puska, P. & Norrving, B. (Eds) Global Atlas on Cardiovascular Disease Prevention and Control. Geneva, World Health Organization, 2011 (Figures 19 & 20, Page12 http://whqlibdoc.who.int.proxy2.cl.msu.edu/publications/2011/9789241564373_eng.pdf?ua=1, accessed 29 December 2019)

easily discerned that IHD is widely prevalent in all nations and continents and that Eastern Europe, the Middle East, the Indian Subcontinent, and Northern Africa are particularly impacted by IHD.

## Risk Factors for Atherosclerotic Disease

### *Dyslipidemia*

#### Low-Density Lipoprotein

After nearly 100 years of experimental investigation, low-density lipoprotein cholesterol (LDL-C) is indisputably established as atherogenic [26]. LDL particles are the most abundant in serum and are scavenged in the subendothelial space by activated macrophages [27]. Lipid-laden macrophages are an important substrate for atheromatous plaque formation and provide pro-inflammatory stimuli to propagate plaque and ultimately render it unstable and prone to rupture, leading to the development of acute tissue ischemia in affected vascular territories [27–29]. There is a log-linear relationship between LDL-C and risk for CAD. (Fig. 1.2.) There is unequivocal evidence that lowering LDL-C with statins (3′-hydroxymethyl-glutaryl coenzyme A inhibitors) [30] and other drugs such as ezetimibe [31] and proprotein convertase/subtilisin kexin type-9 inhibitors [32, 33] beneficially impact risk for acute cardiovascular events (Fig. 1.3).

A relatively novel means by which to view the relationship between LDL-C and risk for CAD-related events is by assessing life years of exposure to specific serum levels of this lipoprotein [34]. The higher the level and the longer the exposure, the higher the risk for developing CHD. By lowering LDL-C earlier and more and more aggressively, the age at which an acute CV event may be expected to occur is extended to older and older ages (Fig. 1.4) [34, 35]. Hence, time is of the essence since limiting exposure to LDL-C is akin to limiting exposure to an established

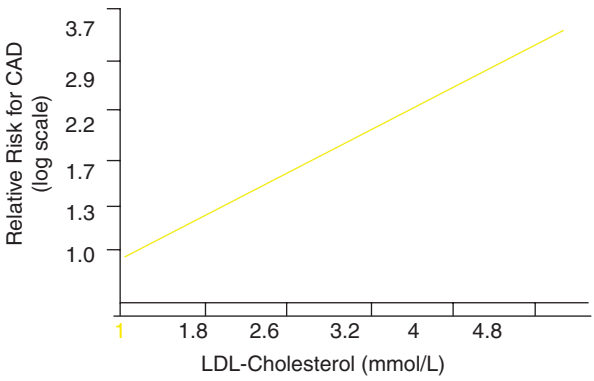


**Fig. 1.2** Log-Linear relationship between LDL-C and Relative Risk for Coronary Artery Disease. (Reproduced with permission from Grundy et al. Circulation 2004; 110: 227–239)

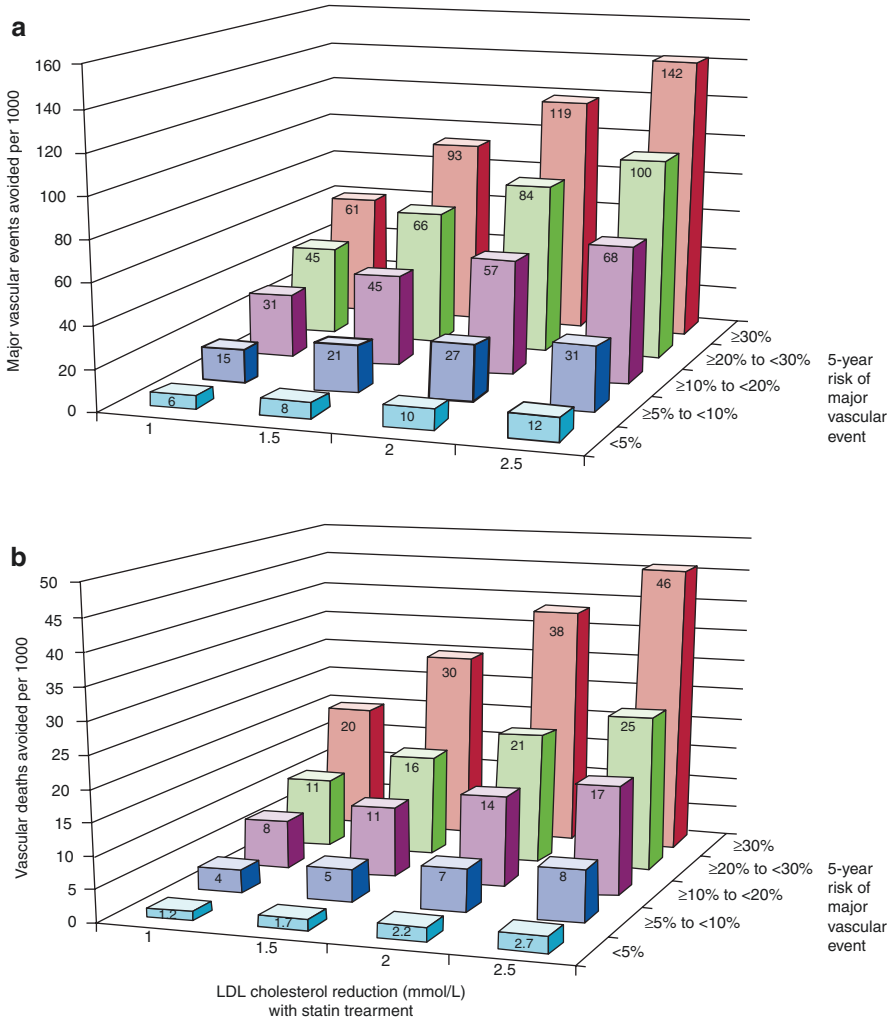


**Fig. 1.3** Predicted 5-year benefits of LDL cholesterol reductions with statin treatment at different levels of risk. (**a**) Major vascular events and (**b**) vascular deaths. Lifetable estimates using major vascular event risk or vascular death risk in the respective risk categories and overall treatment effects per 1.0 mmol/L (38 mg/dL) reduction in LDL cholesterol with statin therapy. (Reproduced from Cholesterol Treatment Trialists, C., et al. (2012). "The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials." Lancet (London, England) **380**(9841): 581–590. This article is open access and free to read and use)

vascular toxin. Thus, when it comes to LDL-C and CVD risk reduction, lower is better, but lowest is best. Guidelines for the management of dyslipidemia continue to emphasize that LDL-C is the primary target of therapy for patients with dyslipidemia [36, 37].

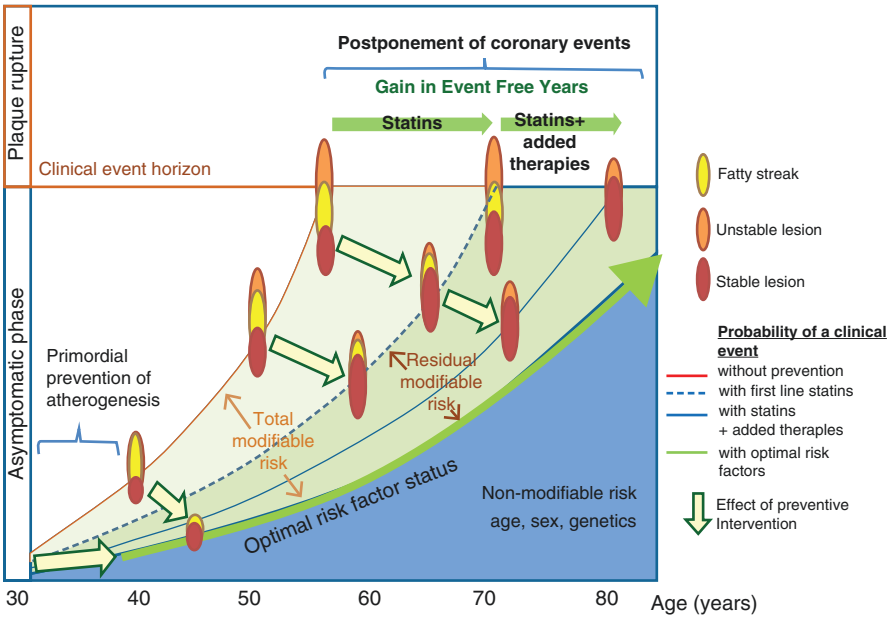


**Fig. 1.4** Disease Trajectories in Coronary Heart Disease Prevention. (Reproduced with permission from Packard, C. J., et al. Vascular Pharmacology 215; 71: 37–39)

## High-Density Lipoprotein

High-density lipoprotein (HDL) is still incompletely characterized and understood [38]. It is characterized by a lipidome and proteome of enormous complexity, and can bind to a variety of cell surface receptors [39]. HDL particles drive reverse cholesterol transport (i.e., the process by which cholesterol is extracted from lipid-enriched macrophages in the subendothelial space and transported back to the liver) and appear to have a variety of antiatherogenic properties, including anti-inflammatory, antithrombotic, and anti-oxidative effects by virtue of their proteomic constituents [40, 41]. Perhaps for these reasons virtually all prospective longitudinal cohorts have shown that HDL-cholesterol (HDL-C) is protective or a "negative risk factor" when its level in serum is elevated [42, 43]. It is an important component of most 10 year and lifetime risk calculators [44–46]. However, current guidelines recommend against making HDL-C a therapeutic target because prospective, randomized clinical trials with agents that raise HDL-C have failed to demonstrate any CV benefit [47–50]. More recent analyses suggest that HDL particles are likely not as protective as once thought [51, 52]. HDL-C tends to decrease in patients with insulin resistance, metabolic syndrome, obesity, chronic kidney disease, and inflammatory disease [53, 54].

### Triglycerides

Triglycerides constitute an enormously important storage form of energy for systemic tissues. Because triglycerides are not soluble in an aqueous phase, triglycerides are exported from the liver within very low-density lipoprotein (VLDL) particles. Free fatty acid is liberated from triglycerides by lipoprotein lipase. Lipoprotein lipase progressively delipidates VLDL to form, in succession, intermediate-density lipoprotein (IDL) and then LDL. In the setting of insulin resistance or when there are genetic polymorphisms leading to reduced lipoprotein lipase activity (increased apoprotein CIII, reduced apoprotein CII, reduced expression of lipoprotein lipase, etc.), small VLDLs and IDLs accumulate because they are inadequately lipolyzed. Small VLDLs and IDLs together comprise remnant lipoproteins, which are triglyceride rich lipoproteins. In patients with hypertriglyceridemia, remnant lipoproteins are elevated in serum.

A variety of genetic polymorphisms associated with hypertriglyceridemia correlate with increased risk for CV events, increased coronary calcium burden, and accelerated atherogenesis [55]. Hypertriglyceridemia is recognized as an important risk factor and is a defining feature of the metabolic syndrome [56, 57]. Serum levels that exceed 150 mg/dL are considered abnormal in the fasting state. Hypertriglyceridemia correlates with increased risk for acute coronary syndromes, health care costs, renal disease, and heart failure [58–61]. Triglyceride rich lipoproteins strongly correlate with increased risk for CVD events [62–65] and have been shown to be pro-inflammatory [66]. The treatment of high risk hypertriglyceridemic patients with eicosapentaenoic acid has been shown to reduce risk for all major CV endpoints [67].

## *Hypertension*

The World Health Organization Reports that: [1] Worldwide, hypertension (HTN) causes 7.5 million deaths, or approximately 12.8% of the total of all annual deaths [2] HTN is responsible for 57 million disability-adjusted life years (DALYS) or 3.7% of total DALYS [3]. HTN is a major risk factor for CAD and cerebrovascular disease. [4] Blood pressure levels are positively and continuously related to the risk of stroke and CAD [5]. In some age groups, the risk of CVD doubles for each incremental increase of 20/10 mmHg of blood pressure, beginning as low as 115/75 mmHg [6]. In addition to CAD and cerebrovascular disease, poorly controlled blood pressure increases risk for heart failure, chronic kidney disease and end-stage renal disease (ESRD), peripheral vascular disease, as well as retinopathy and blindness [4].

HTN is widely prevalent throughout the world. It is generally accepted that a blood pressure > 140 mm Hg systolic and > 90 mm Hg diastolic constitutes HTN. For adults without HTN, prehypertension is defined by an untreated SBP of 120 to 139 mm Hg or untreated DBP of 80 to 89 mm Hg. The American Heart Association (AHA) notes that: [1] between 2011 and 2014, the prevalence of

hypertension among US adults was 45.6% [2]. Meta-analyses demonstrate that prehypertension correlates with an increased risk for CVD, ESRD, and death. These risks are greater for people in the upper (130–139/85–89 mm Hg) versus lower (120–129/80–84 mm Hg) range of prehypertension [3]. In prospective follow-up of the MESA, REGARDS, and JHS cohorts, 63.0% of incident CVD events occurred in participants with systolic BP (SBP) <140 mm Hg and diastolic BP <90 mm Hg [4]. In the US, the estimated direct and indirect cost of HTN from 2014 to 2015 (annual average) was approximately $55.9 billion [6]. HTN was the fourth-leading risk factor for global disease burden in 1990, as quantified by DALYs, but became the number 1 risk factor in 2010 [68].

As demonstrated in the Multiple Risk Factor Intervention Trial (MRFIT) and other cohorts, risk for CVD increases continuously as both systolic and diastolic blood pressure rise; however, the relationship is substantially steeper for systolic blood pressure elevations [69, 70] (Fig. 1.5). Hypertension is polyfactorial and is strongly influenced by lifestyle, environmental, and genetic factors [71–73]. Guidelines for the diagnosis and management of HTN are available for different regions of the world, and generally state that blood pressure should be reduced to <140/90 mm Hg in patients with HTN [74–76]. It is highly established that blood pressure reduction reduces risk for CV events, mortality, left ventricular hypertrophy (LVH), heart failure, renal injury and proteinuria, and stroke (both hemorrhagic

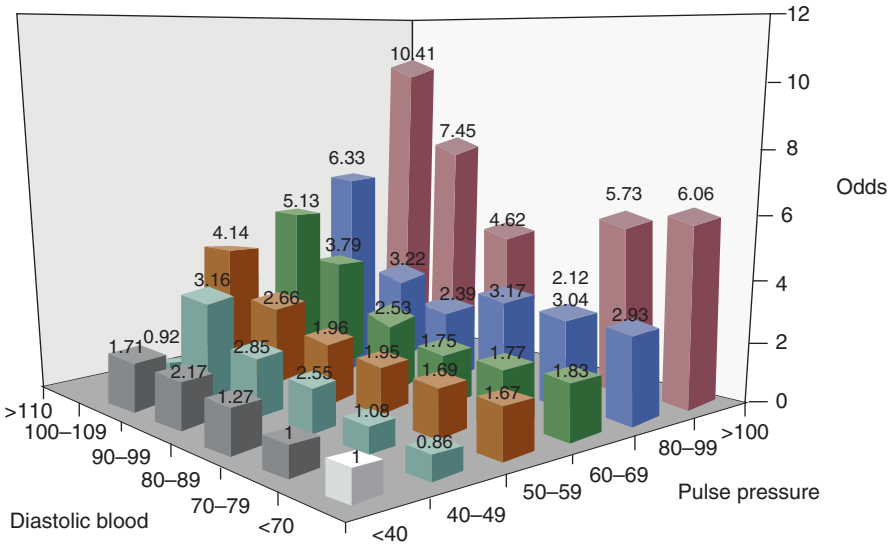


**Fig. 1.5** Odds for the likelihood of a cardiovascular event with combined pulse pressure (PP) and mean arterial pressure (MAP). Data are adjusted for age, sex, total cholesterol, smoking, body mass index, diabetes, and secular trend. (Reproduced with permission from Franklin, S. S. and N. D. Wong. Hypertension and Cardiovascular Disease: Contributions of the Framingham Heart Study." Global Heart 2013; 8 [1]: 49–57)

and ischemic) [77, 78] and novel means for studying HTN are continuously being developed [79]. Blood pressure can be reduced by antagonizing the renin-angiotensin-aldosterone axis, inhibiting α- and β- adrenergic receptors, calcium channel blockade, diuretics, and nitrates, among other approaches. Despite widely recognized benefits of treating HTN, substantial disparities in the prevalence and treatment of HTN have been identified (Fig. 1.6). Based on a global analysis for 2010, 46.5% of adults with HTN knew they had the condition and only 36.9% were taking antihypertensive medication [80]. Despite widespread availability of antihypertensive medications, only 13.8% of hypertensive patients had their blood pressure controlled to guideline specified targets. These investigators further demonstrated that high-income countries had twice the rate of awareness (67.0% versus 37.9%) and treatment (55.6% versus 29.0%) and 4 times the rate of BP control in patients with HTN (28.4% versus 7.7%) when compared to low- and middle-income countries. These treatment and awareness disparities warrant urgent recognition and intervention.

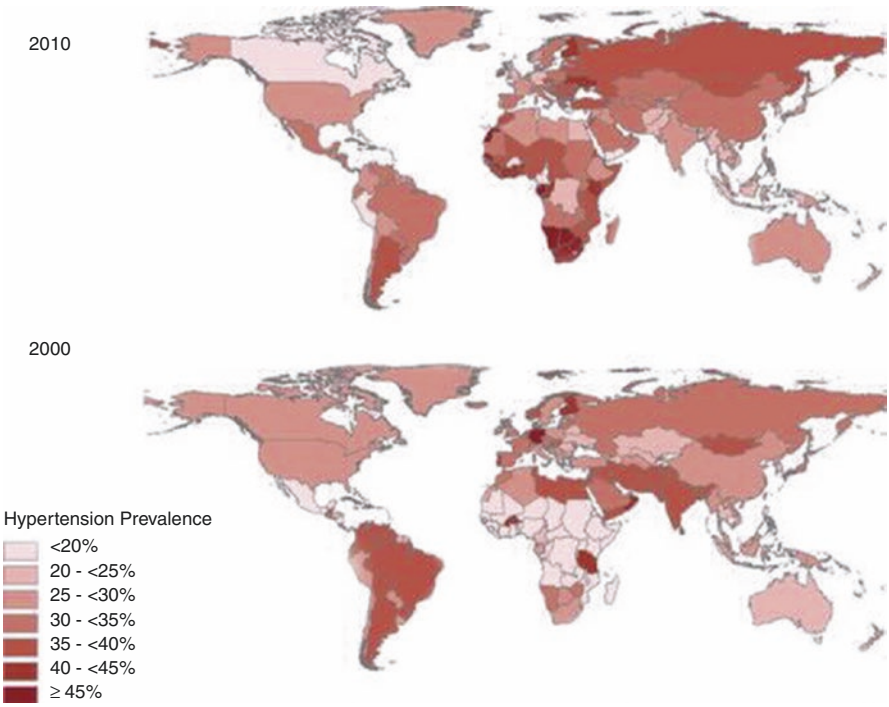


**Fig. 1.6** Worldwide age- and sex-standardized prevalence of hypertension in adults 20 years and older by country. Top, Country-specific prevalence in 2010. Bottom, Country-specific prevalence in 2000. Maps are shaded according to prevalence, from light (lower prevalence) to dark (higher prevalence). (Reproduced with permission from Mills et al. Circulation. 2016;134: 441–450)

## *Metabolic Syndrome*

Metabolic syndrome (MS) represents a constellation of CV risk factors defined by elevations in blood pressure, hypertriglyceridemia, hyperglycemia, obesity, and low HDL-C [81, 82]. (Table 1.1) Insulin resistance is etiologic for MS. [83] Insulin resistance typically develops in the setting of obesity [84]. In the insulin resistant state there is impairment in the transduction of the insulin receptor signal; this results in less nuclear transcription and cell surface expression of glucose transport proteins [85]. As this occurs the capacity to transport glucose from the extracellular milieu into the cytosol is progressively reduced. Hyperglycemia is a manifestation of less cellular glucose uptake.

Insulin resistance induces endothelial cell dysfunction, [86] which leads to reduced nitric oxide and prostacyclin production as well as increased blood pressure secondary to decreased vasodilatory inputs into the arterial wall. This is exacerbated by increased endothelin-1 production, a potent vasoconstrictor [87]. Endothelial dysfunction also increases risk for impaired microvascular responsiveness and microangiopathy [88]. Hyperglycemia potentiates the formation of advanced glycosylated end products which can bind to receptors that trigger development of a prooxidative and proinflammatory milieu [89, 90]. These changes can lead to the intensification of endothelial dysfunction and accelerated atherogenesis. Serum triglyceride levels rise because: [1] Visceral adipose tissue becomes less responsive to insulin, leading to persistent activation of hormone sensitive lipase and continuous hydrolysis of adipocyte triglyceride and release of free fatty acid. The fatty acids can be reassimilated into triglycerides by the liver and secreted into the circulation within VLDL particles [91] [2]. Lipoprotein lipase production decreases and there is increased production of this enzyme's most important natural inhibitor, apoprotein CIII [92]. Serum HDL levels decrease because of reduced biosynthesis and increased catabolism and renal elimination of this lipoprotein [38, 93].

The metabolic syndrome increases risk for CVD, nonalcoholic hepatic steatosis, erectile dysfunction, polycystic ovarian syndrome, and diabetes mellitus [94, 95]. Metabolic syndrome also increases risk for both atrial fibrillation [96] and peripheral vascular disease [97]. Individual components of the metabolic syndrome should be aggressively treated, [98] but two of the most important interventions for this condition should be increased daily exercise and weight loss, both of which relieve insulin resistance and reduce risk factor burden [99, 100]. With increased mechanization, urbanization, sedentary lifestyle, and adverse alterations in dietary habits,

**Table 1.1** Defining features of the metabolic syndrome

| |
|---|
| Abdominal obesity (waist circumference ≥ 40 inches in men, and ≥ 35 inches in women) |
| Triglyceride level of 150 mg/dL or greater |
| HDL-C < 40 mg/dL in men or < 50 mg/dL in women |
| Systolic blood pressure 130 millimeters of mercury (mm Hg) or greater, ***or*** diastolic blood pressure of 85 mm Hg or greater |
| Fasting serum glucose of 100 mg/dL or greater |

there is a worldwide epidemic of MS. [101, 102] In Europe the prevalence of MS is estimated to be 24.3 and 24.6% for men and women, respectively, and its prevalence increases with age [103]. In the United States, the prevalence of MS is approximately 23% and includes just over 50 million persons [104].

## *Diabetes Mellitus*

Diabetes mellitus (DM) is a complex disorder whose principal diagnostic manifestation is the dysregulation of glucose metabolism resulting in hyperglycemia (blood glucose ≥126 mg/dL). Diabetes increases risk for CVD and its clinical sequelae (MI, stroke, mortality, heart failure) and microangiopathy (retinopathy with adult onset blindness, neuropathy and lower extremity amputation, nephropathy with ESRD and need for renal allografting or dialysis).

Diabetes is pathophysiologically devastating to the CV system because it is characterized by the "***ominous octet***," which includes: [105].

A. Decreased β-islet secretion of insulin. In the setting of DM there is increasing loss of β-islet cell mass over time, leading to progressive rises in glucose.
B. Increased α-islet secretion of glucagon. Glucagon stimulates hepatic glucose secretion, exacerbating the hyperglycemia of DM.
C. Reduced incretin effect. The incretins are secreted by the gut in response to glucose exposure. They include glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) and are secreted from K cells and L cells, respectively, in the gastrointestinal tract [106]. They both stimulate pancreatic insulin secretion.
D. Increased adipocyte lipolysis. This was discussed above and is the result of increased triglyceride lipolysis by hormone sensitive lipase visceral adipose tissue secondary to insulin resistance. Insulin resistant visceral adipose tissue is also an important source of adipokines that potentiate systemic inflammation [107].
E. Increased renal reabsorption of glucose by the sodium-glucose cotransport protein (SGLT2) along the proximal tubular epithelium [108]. This also augments the hyperglycemic state observed in DM.
F. Decreased glucose uptake by skeletal muscle. Insulin resistance is associated with reduced cell surface expression of such glucose transport proteins as glut2 and glut4 [109].
G. Increased hepatic glucose production. Insulin resistance is associated with increased activity of phosphoenolpyruvate carboxykinase activity, an enzyme responsible for converting oxaloacetate to phosphoenolpyruvate during gluconeogenesis [110].
H. Central nervous system neurotransmitter dysfunction. There is increased central sympathetic outflow which can lead to HTN, tachycardia, and potentiate hyperglycemia. In addition, this is associated with impaired sensing of satiety.

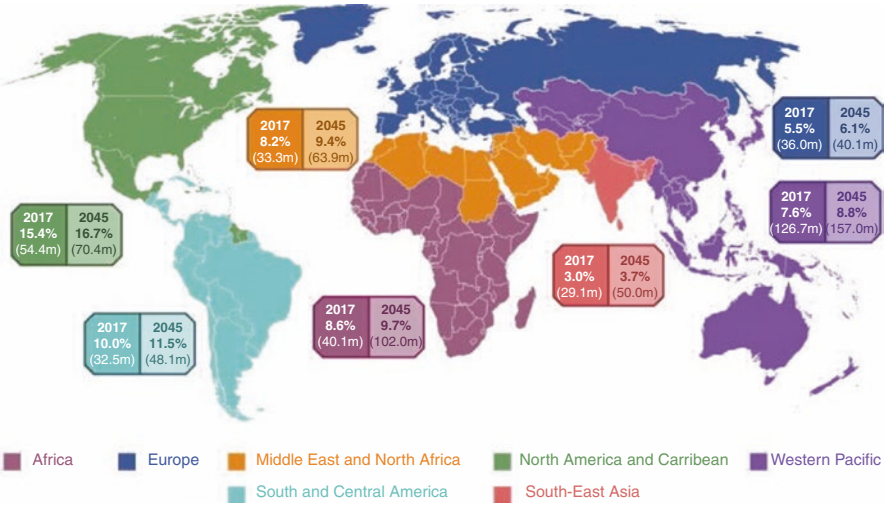


**Fig. 1.7** Global Prevalence of impaired glucose tolerance (IGT) in 2017 and prevalence projected in 2045. Percentages are unadjusted regional prevalence estimates. Numbers in parentheses are the estimated number of persons affected by IGT in each region. (Reproduced with permission from Hostalek. Clinical diabetes and endocrinology. 2019;5:5)

Secondary to the global epidemic of obesity, the incidence of global diabetes is rising at shocking rates. In 2014 there was an estimated 382 million people with diabetes worldwide; this is projected to increase to 592 million by the year 2035 [111]. Estimates for the prevalence of impaired glucose tolerance (IGT or prediabetes; defined as two-hour glucose levels of 140 to 199 mg per dL (7.8 to 11.0 mmol) on the 75-g oral glucose tolerance test.) are shown in Fig. 1.7 [112]. These data portend a catastrophic rise in global incidence and prevalence of DM. In the US an estimated 26 million adults have diagnosed DM, 9.4 million adults have undiagnosed DM, and 91.8 million adults (37.6% of the population) have prediabetes [68]. In Europe in 2013 it was estimated that 56 million persons have DM with an overall prevalence of 8.5% of the population [113]. As diabetes progresses and hemoglobin a1c values increase, risk for CV events, all-cause mortality, and CVD mortality all increase continuously [114, 115] (Fig. 1.8). Controlling hemoglobin a1c levels especially below 7% is associated with less risk of microangiopathy [116, 117]. Controlling DM with GLP-1 receptor agonists and SGLT2 inhibitors has been shown to reduce risk for CV events [118–121].

## *Inflammation*

It is now highly established that atherosclerosis is an inflammatory disease. There is considerable complexity and built-in redundancy with interconnecting networks of pro-inflammatory cells and biochemical signaling pathways of inflammation regulated by nuclear factor κB, [122] Krüppel-like factors, [123], and activator

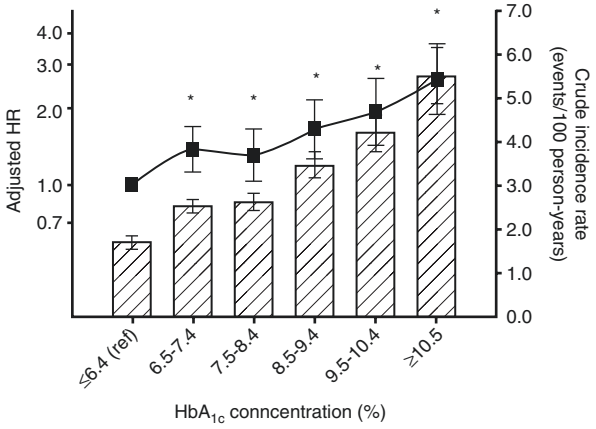


**Fig. 1.8** Adjusted HRs (squares) and crude incidence rates (bars) for primary CV outcome events associated with $HbA_{1c}$ concentrations at baseline. Error bars represent 95% CIs. *$p < 0.05$ for difference between reference group ($HbA_{1c} \leq 6.4\%$) and actual group. Adjusted analysis included sex, age, randomised treatment assignment, diabetes duration, history of arterial hypertension, history of congestive heart failure, history of cardiovascular disease, history of revascularization, ethnicity, tobacco use, systolic and diastolic blood pressure, heart rate, BMI, HDL-cholesterol concentration, LDL-cholesterol concentration, urine albumin/creatinine ratio and use of insulin, metformin, thiazolidinediones and sulfonylureas. (Reproduced with permission from Andersson, C., et al. Diabetologia 2012; 55 [9]: 2348–2355)

protein-1, [124] among others. In the setting of endothelial cell dysfunction, endothelial cells express a variety of cell adhesion molecules (intercellular adhesion molecule-1, vascular cell adhesion molecule-1, selectin P, and others) that promote the binding, rolling, and transmigration of inflammatory white cells into the subendothelial space [125]. The gap junctions holding endothelial cells together can become stressed and leaky, allowing for increased influx of circulating white cells and atherogenic lipoprotein particles [126]. Platelets, neutrophils, mast cells, macrophages, and T helper cells all participate in atherogenesis and can function as delivery vehicles of pro-inflammatory interleukins and cytokines that alter the histologic composition of the vessel wall and potentiate the creation of macrophage foam cells, fatty streaks, atheromatous plaques, and ultimately, unstable plaque that can rupture and lead to the formation of an acute cardiovascular events [127, 128].

C-Reactive protein (CRP) is a pentraxin molecule and a marker of systemic inflammation [129]. It may also directly induce a variety of proatherogenic phenomena and boost the inflammatory response [130]. Increased serum levels of CRP portend heightened risk for CVD, MI, stroke, and death in a variety of cohorts [131–133]. The measurement of CRP levels has been shown to refine 10-year risk prediction for CVD events [134, 135]. As CRP increases at any level of 10-year Framingham risk or any level of LDL-C, risk for CVD increases continuously [136] (Fig. 1.9). Although many inflammatory mediators can be measured, CRP is remarkably stable and can be accurately measured in commercial laboratories. One recent clinical trial showed that lowering systemic inflammatory tone using a monoclonal

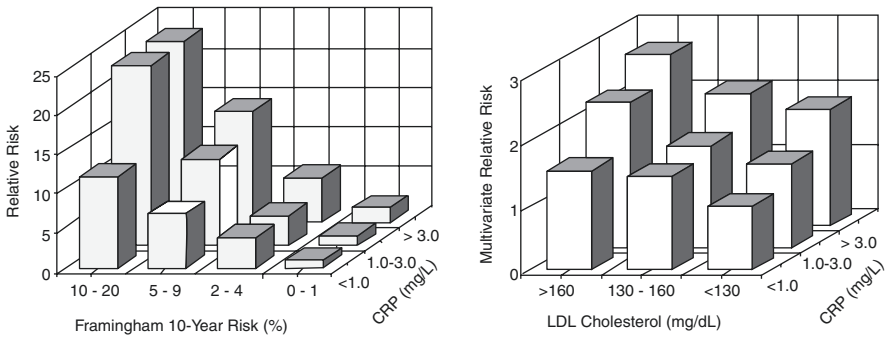


**Fig. 1.9** Relationships between CRP, CVD risk, and Framingham 10-year risk (left) or LDL-C level (right). (Reproduced with permission from Ridker. Circulation. 2003; 107:363–369)

antibody directed against interleukin-1β is associated with significant reductions in risk for CVD events independent of lipid lowering [137].

## *Chronic Kidney Disease*

Chronic kidney disease (CKD) is defined as a glomerular filtration rate (GFR) <60 mL/min/1.73 $m^2$), albuminuria (defined ≥30 mg/d), or both. The prevalence of CKD increases with age, and because populations are aging worldwide, the global incidence of CKD is increasing. The current world prevalence of CKD is estimated to be 276 million persons and the majority of people with CKD have stage 3 [138]. DM and HTN are strong risk factors for CKD. Patients with CKD have a greatly magnified risk for developing CAD, stroke, arrhythmias, and congestive heart failure and the uremic state is accompanied by a variety of toxins that can accelerate the rate of progression of each of these disorders [139]. Albuminuria is a strong adverse prognostic indicator for CVD, renal failure, and mortality, and represents injury to renal podocytes and glomeruli [140, 141] (Fig. 1.10).

## *Cigarette Smoking*

The World Health Organization estimates that there are approximately 1 billion smokers in the world [4]. Smoking is the number one cause of preventable death in the United States and throughout the world. It is estimated to account for 7.1 million deaths globally in 2016 [68]. In the US, approximately 17.5% of males and 13.5% of females are smokers [68]. Smoking increases risk for CVD, CAD, MI, stroke, mortality, and a variety of cancers, including lung and transitional cell cancers of the bladder. Compared to lifelong nonsmokers, men and women who smoke on

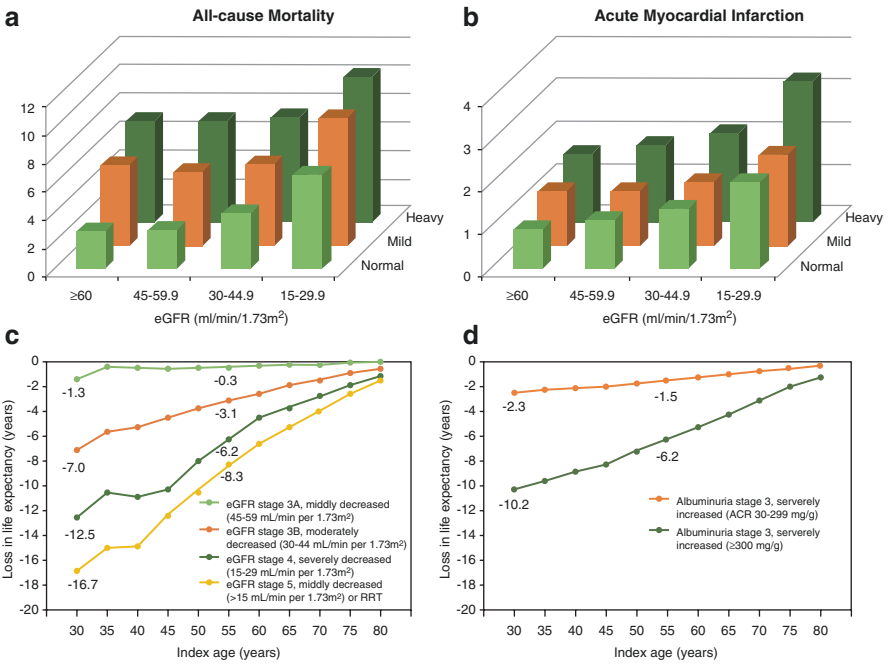


**Fig. 1.10** Relationships between cardiac events and mortality from cardiovascular disease (CVD) by stage of chronic kidney disease (CKD). A and B, The adjusted relative rate of all-cause mortality (ACM) and acute myocardial infarction as a function of glomerular filtration rate and severity of albuminuria as assessed by albumin-to-creatinine ratio (ACR; normal, ACR <30 mg/g; mild, ACR 30–300 mg/g; or heavy, ACR >300 mg/g). C and D, Adjusted mortality resulting from CVD by CKD stage. Loss is compared with life expectancy in people with normal or mildly impaired kidney function (stage 1–2, eGFR ≥60 mL·min$^{-1}$/1.73 m$^2$) and normal or mildly increased albuminuria (stage 1, ACR < 30 mg/g). RRT: renal replacement therapy. (Reproduced with permission from Tonelli et al. Circulation. 2016;133:518–536)

average lose 12 and 11 years of life, respectively [68]. A meta-analysis of 75 studies and including approximately 2.4 million persons showed a 25% higher risk for CHD in female smokers than in male smokers [142]. There is considerable urgency in developing and promoting programs to encourage men and women to engage in lifelong smoking cessation.

## Conclusions

Significant progress has been made in recent decades in identifying risk factors for CVD and in developing safe and efficacious therapies for these disorders. Screening programs are in place in most nations, but more needs to be done. Significant progress has been made in reducing the clinical sequelae of CVD in many nations around

the world, though important deficiencies persist [143]. The global population is aging making it essentially certain that more people will live to develop CVD. It is crucial that global efforts embrace primordial and primary prevention more fully so as to reduce the incidence of disease as well as the costs of treating established disease. It is also important that persons identified with risk factors remain adherent to therapies, as low adherence rates and low guideline directed goal attainment rates are the norm worldwide. There is an urgent need for newer and less costly interventions, and perhaps nutraceuticals will be developed that help to fill some of the gaps for treating risk factors in both the primary and secondary prevention settings.

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