Chapter 4. Tobacco and Cardiovascular Disease: A Summary of Evidence

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Abstract

Tobacco kills nearly half of the people who use it, making it a serious global public health threat, and it is the single most preventable cause of cardiovascular disease. Research has demonstrated the myriad pathophysiological mechanisms by which tobacco harms the cardiovascular system, and evidence makes clear its adverse effects on cardiovascular morbidity and mortality, accounting for at least 10 percent of global cardiovascular deaths. Tobacco use also has definitive harmful effect on exposed nonsmokers. In response, the United Nations General Assembly agreed to target a 30 percent reduction in tobacco use from 2010 levels as a crucial step toward the goal of reducing premature mortality from no communicable diseases by 25 percent by 2025 (the 25x25 goal). The benefits of quitting tobacco kick in early, with substantial reduction in cardiovascular risk. The need is urgent for proven, cost-effective, individual-level interventions, with support from health providers and interventions agreed by governments in the Framework Convention on Tobacco Control.
I. Introduction
   A. Current and projected burden of tobacco and cardiovascular diseases
   B. Mandate and Opportunity for Action

II. Tobacco Use and Cardiovascular Disease: Pathophysiology and Mechanisms
   A. Endothelial Dysfunction
   B. Prothrombotic Effects of Smoking
   C. Lipid Oxidation and Insulin Resistance
   D. Proinflammatory Effects of Smoking
   E. Oxygen Supply-Demand Mismatch
   F. Role of Genes

III. Tobacco Use and Cardiovascular Risk Factors
   A. Smoking and Dyslipidemia
   B. Smoking and Hypertension
   C. Smoking and Diabetes

IV. Cardiovascular Disease Outcomes and Manifestations of Tobacco Use
   A. Smoking and Cardiovascular Mortality
   B. Smoking and Coronary Heart Disease
   C. Smoking and Heart Failure
   D. Smoking and Carotid and Cerebrovascular Diseases
   E. Smoking and Arrhythmia
   F. Smoking and Aortic and Peripheral Artery Disease
   G. Smoking and Chronic Kidney Disease

V. Cardiovascular Diseases Associated with Other Forms of Tobacco Use
   A. Second-Hand Smoke
   B. Third-Hand Smoke
   C. Other Forms of Tobacco Smoking
      a. Bidi
      b. Waterpipe Tobacco Smoking
      c. Smokeless Tobacco Use
      d. Electronic Nicotine Delivery System

VI. Socioeconomic Dimensions of Tobacco Use-Related Cardiovascular Diseases

VII. Cardiovascular Benefits of Tobacco Use Cessation

VIII. Conclusions
Current and projected burden of tobacco and cardiovascular diseases

Tobacco use is a leading cause of global death, accounting for over 6 million annually or at least 12 percent of deaths among people ages 30 years and above (16 percent for men, 7 percent for women) (WHO 2012; WHO 2013). It is the single most preventable cause of cardiovascular diseases, which comprise a large number of conditions and are the number one cause of death globally, with an estimated 17.3–17.5 million deaths yearly (WHO 2015x; GBD 2013). Tobacco is also the leading cause of premature death from cardiovascular disease (before age 70 years), estimated to be 5.9 million in 2013. Such deaths deprive families of productive members and communities and economies of a productive workforce (Rigotti and Clair 2013; Roth and others 2015). Tobacco use also causes substantial cardiovascular disease morbidity and results in tremendous cardiovascular-disease-related health care costs. While tobacco impacts all countries, regardless of level of economic or health system development, the impact is most profound in low- and middle-income countries (LMICs), which shoulder the largest share of total and premature global cardiovascular disease deaths (WHO 2015x). Future projections are alarming, with LMICs also accounting for much of the future global burden of tobacco use and related cardiovascular disease mortality and morbidity (Ezzati and Lopez 2003). China, with 301 million users followed by India, lead the global league in tobacco use (WHO n.d.).

More generally, high tobacco use rates mean an even higher burden of cardiovascular disease, and this trend is occurring amid population growth and ageing, both major contributors to the absolute numbers of cardiovascular disease sufferers. (Roth and others 2015b).

Reducing tobacco use is thus crucial to averting tobacco deaths, now projected to increase to 10 million annually by 2030 if the current trend continues (WHO 2013; WHO 2015a. This is also true for premature death from cardiovascular diseases, which are projected to increase to 7.8 million in 2025 if “business-as-usual” continues, including in the approach toward tobacco control and control of noncommunicable disease prevention (Roth and others 2015). Urgent action is needed to reverse this course.

MANDATE AND OPPORTUNITY FOR ACTION

The global mandate for reducing tobacco use is now stronger than ever, with the World Health Assembly’s adoption of a 30 percent global target for relative reduction of tobacco use by 2025. This goal is one among several targets to reduce premature mortality from the four
noncommunicable diseases by 25 percent in 2025 (25x25 target), including cardiovascular disease. Unfortunately, many countries are off course to meet this target. (Bilano and others 2015).

Studies clearly show nonetheless that the reduction of tobacco use is key to achieving these targets, including in LMICs (Kontis and others 2014; Kontis and others 2015). Reducing tobacco use would offset some of the rise in the absolute numbers of cardiovascular deaths caused by population growth and ageing, especially in LMICs (Roth and others 2015b). Indeed, several studies demonstrate the need to achieve more ambitious targets for reducing tobacco use (50 percent relative to 2010) if countries are to reach the 25x25 target (Roth and others 2015a; Kontis and others 2014; Kontis and others 2015).

The chapter reviews the literature to synthesize key information on the links between tobacco use and cardiovascular disease. The first section reviews the main pathophysiological mechanisms by which tobacco use causes cardiovascular disease. The focus is on cigarette smoking, but other forms are discussed. The second section highlights the role of tobacco and other cardiovascular disease risk factors, and the third reviews tobacco-related cardiovascular diseases that are most important from a public health and health system perspective. The fourth section looks at the benefit to cardiovascular health of stopping tobacco use, and it calls for enhanced engagement and cooperation of public health and health care providers to stem the rise of tobacco-related cardiovascular diseases, especially in LMICs.

<<II>>TOBACCO AND CARDIOVASCULAR DISEASE: PATHOPHYSIOLOGY AND MECHANISMS

Tobacco use has a myriad of effects on the cardiovascular system that contribute to cardiovascular disease pathophysiology. Box _1 explains some of the terms we use in our explanation of the mechanisms by which tobacco use can cause cardiovascular disease. The effects of cigarette smoking and exposure to its second-hand smoke have been studied most, but many of the effects are common to other forms of use, including smokeless tobacco, as we discuss later.
Burning tobacco products produces two forms of smoke: mainstream and side stream. Mainstream smoke is inhaled and exhaled by the smoker, whereas side-stream smoke comes from the burning end of the cigarette (Ambrose and Barua 2004), and is even more toxic than mainstream smoke (Schick and Glantz 2005). Among the more than 7,000 chemicals known to exist in cigarette smoke, many components are known to mediate the pathophysiology of cardiovascular disease (Borgerding and Klus 2005). Toxic chemicals such as carbon monoxide, polycyclic aromatic hydrocarbons, nicotine, and heavy metals and their oxides have profound effect on vascular endothelium (cells lining the blood vessels), blood lipids (fats), and clotting (thrombotic) factors causing atherosclerosis (plaque build-up). The latter affects arteries (vessels carrying oxygenated blood to organs across various vascular beds. These effects can lead to adverse cardiovascular events such as myocardial infarction (heart attack), stroke (brain attack), and aortic dissection (rupture of the aorta, the main artery emanating from the heart). Figure __.1 illustrates the pathophysiological mechanisms implicated in tobacco-associated atherosclerosis.

**Box_.1  Glossary of terms**

**Atherothrombosis**: Disruption of atherosclerotic plaque with superimposed thrombus formation.

**Coronary vasoconstriction**: Narrowing of the lumen of vessels supplying the heart due to contraction of muscular layer.

**Endothelial dysfunction**: Imbalance between dilating and constricting characteristics of the inner lining of the vessel wall that affect clotting mechanisms.

**Inflammation**: Response of vascular tissues to harmful stimuli to remove the cause and initiate repair.

**Myocardial ischemia**: Reduced oxygen supply to the muscles of the heart.

**Oxidative stress**: Disruption of normal cellular structure due to damage caused to DNA, proteins and lipids by reactive oxygen species.

**Prothrombotic state**: It is the hypercoagulable state induced by vessel injury and other changes in the blood that affects the clotting mechanism.

**Sympathetic stimulation**: Mediated by sympathetic nervous system and the release of catechol amines to increase the rate and force of contraction.
The mechanisms by which cigarette smoking induces and promotes atherogenesis, and consequently atherosclerosis and atherothrombosis, are complex. However, the key ones are inflammation, endothelial dysfunction, prothrombosis, altered lipid metabolism, insulin resistance, and increased demand for but diminished supply of myocardial oxygen and blood (demand-supply mismatch) (U.S. Department of Health 2014). We review some of these mechanisms in more detail and depict them in figure __.2, which also displays the key constituents involved (Salahuddin, Prabhakaran, and Roy 2012).

Briefly, atherogenesis starts with adherence of smoking-activated inflammatory cells to the inner vessel wall (endothelium) that has been damaged by smoking and the accumulation under the vessel surface (sub-endothelium) to cause chronic inflammation. This and other mechanisms contribute to endothelial dysfunction. Sub-endothelial inflammatory cells secrete substances that promote the development and growth of plaques through accumulation of cholesterol-rich cells. Continued inflammation contributes to the destabilization and rupturing of plaques (which could lead to arterial occlusion or impaired flow), causing vasoconstriction (acute narrowing of arteries) and thrombosis (clots made mainly of platelets, or thrombocytes, which are components of blood responsible for stopping bleeding). This can lead to occlusion of blood vessels, causing cardiovascular events such as heart or brain attacks.

**Endothelial Dysfunction**

Healthy vascular endothelium is crucial to cardiovascular functioning and health. The blood vessels normally dilate in response to external or internal stress and increased flow demands caused by the endothelium’s production and release of nitric oxide, a vessel relaxant, thus maintaining blood flow. A healthy endothelium also fights thrombosis and inflammation. Smoking undermines all of these functions, making endothelial dysfunction (decreased dilatation and ability to fight thrombosis and inflammation) a central mechanism in cardiovascular disease pathophysiology.

Nicotine, oxidants, and free radicals in smoke—and free radicals generated by endothelial cells themselves in response to smoke—reduce the availability of nitric oxide; thus either there is no response or vasoconstriction in response to stress (18–24). Vasoconstriction
can, in turn, increase the prothrombic (clotting) response, although this is not the only mechanism for thrombosis. Smoking-induced damage to the endothelium also alters interaction with flowing blood cells, thus increasing the chances of inflammatory substances and platelets sticking to the vessel wall. In addition, the damage decreases the ability of the endothelium to regulate the local levels of clot-forming versus clot-dissolving substances in favor of clotting (U.S. Department of Health 2014; Nowak and others 1987). Smoking also reduces the elasticity of arteries, resulting in stiffening and trauma to their walls and reducing coronary flow reserve (Stefanadis and others 2007; Celermajer and others 1993; Celermajer 1996).

Other smoke components are also implicated in endothelial dysfunction, including heavy metals such as lead, arsenic, and mercury, which catalyze the oxidation of cellular proteins and may lead to structural cellular damage and endothelial dysfunction. In addition to free radicals and oxidants, further endothelial dysfunction may be mediated by polycyclic aromatic hydrocarbons (Salahuddin, Prabhakaran, and Roy 2012, Wolf and Baynes 2007). These compounds also enhance oxidation of low-density lipoprotein (LDL) as we will discuss later.

The adverse effects of smoking on endothelial function occur early, with recent studies showing that even brief exposure (one hour or less) to smoke, including second-hand smoke, results in endothelial damage and can potentially be long lasting (Juonala and others 2012). Fortunately, quitting smoking is associated with improved endothelial function (Johnson and others 2010).

**<B>Prothrombotic Effects of Smoking**

We have already discussed the prothrombotic state associated with smoking-induced endothelial dysfunction. Smoking also promotes thrombosis through two mechanisms strongly implicated in adverse cardiovascular events: 1. platelet activation and aggregation; and 2. activation of the coagulation system (U.S. Department of Health 2014). Although the latter is important and occurs through increased production of thrombosis factors—such as thrombin, fibrinogen, and von Willebrand factor—and decreased dissolution of blood clots (fibrinolysis), it is platelet activation and aggregation that is especially critical in cardiovascular disease pathophysiology. This mechanism is largely responsible for thrombi that form in coronary arteries following plaque rupture and cause heart attacks by blocking arterial blood supply to the myocardium.
Several mechanisms explain the platelet-activating effects of smoking. This includes elevated levels of platelet-activating substance, which is partly due to oxidation of phospholipids. Impaired release of nitric oxide is another, which inhibits platelet activation, due to oxidative stress and endothelial dysfunction. A third mechanism is increased production of substances that promote platelet aggregation (U.S. Department of Health 2014). Smoking also leads to more binding of platelets to white blood cells, a process that is both proinflammatory and prothrombotic, and changes the structure of platelets to make them more susceptible to aggregation.

**<C>Lipid Oxidation and Insulin Resistance**

While smoking can enhance the endothelial dysfunction caused directly by elevated cholesterol, it is through lipid oxidation that smoking produces its important impact. Cigarette smoking enhances oxidation of plasma LDL cholesterol, the “bad” cholesterol that is pro-atherogenic and known to impair endothelial function (Frei and others 1991; Heitzer and others 1996; Pech-Amsellem and others 1996).

Another product of lipid peroxidation caused by tobacco is acrolein, an aldehyde that reacts with lipoproteins in high-density lipoprotein (HDL), the “good cholesterol,” and modifies them, making them unavailable to remove cholesterol from cells lining the vessels (Shao and others 2005). This undermines a key mechanism that the body uses to fight atherosclerosis.

Smoking is also associated with increased insulin resistance, which has been implicated in the link with diabetes and the acceleration of atherosclerosis.

**<D>Proinflammatory Effects of Smoking**

Cardiovascular disease is now understood as an inflammatory condition, with inflammation playing a major role in initiation and progression of atherosclerosis and cardiovascular events. Inflammatory markers are a harbinger of damage to blood vessels and contribute to all the pathways already mentioned (Kannel, D’Agostino, and Belanger 1987; Matetzky and others 2000; Newby and others 1999).

Well-conducted, large population studies demonstrate that markers of inflammation, including white blood cells, fibrinogens, interleukin-6 and other proteins, are elevated in smokers (38–40). Such markers return to normal baseline levels within five years of quitting
smoking, as demonstrated in the Northwick Park Heart Study and the Monitoring Trends and Determinants in Cardiovascular Disease study (Meade, Imeson, and Stirling 1987; Dobson and others 1991). Using data from 15,489 individuals who participated in the Third National Health and Nutrition Examination Survey, Bakhru and Erlinger (2005) demonstrated that inflammatory markers—including C-reactive protein, fibrinogen, white cell count, and albumin—demonstrated a dose-dependent and temporal relationship to smoking and smoking cessation, with the markers returning to baseline levels five years after smoking cessation. This suggests that the inflammatory pathway of smoking-related cardiovascular disease may be reversible with smoking cessation and reduced exposure to second-hand smoke.

**Oxygen Supply-Demand Mismatch**

Nicotine and carbon monoxide, among other components of tobacco smoke, also contribute to cardiovascular disease by affecting the myocardial (heart muscle) oxygen demand–supply balance (the first two pathways in figure 2). Nicotine exerts its cardio-metabolic effects through sympathetic stimulation (the adrenaline system) (U.S. Department of Health and Human Service 1988). It increases myocardial oxygen demand through increasing heart rate, blood pressure and myocardial contractility (pumping), while reducing myocardial blood supply through vasoconstriction and endothelial dysfunction (Salahuddin, Prabhakaran, and Roy 2012). This produces ischemia (reduced blood and oxygen supply which, when symptomatic, can produce angina or heart attacks). Carbon monoxide also produces ischemia as it competes with oxygen to combine with haemoglobin, the blood component responsible for carrying oxygen to tissues. Due to greater affinity to haemoglobin, carbon monoxide binds more tightly to haemoglobin and compromises oxygen availability to the myocardium (Aronow 1974; Glantz and Parmley 1991).

**Role of Genes**

Most of the harmful cardiovascular disease effects of smoking are attributed to the poisonous substances in cigarette smoke. However, some authors have attributed a role for genes in influencing smoking impact, altering the metabolism of the byproducts of smoke, and playing an intermediate role in other pathophysiologic pathways leading to cardiovascular disease (Winkelmann, von Holt, and Unverdorben 2009). Although the role of genetics needs further study, epigenetic modifications of several cells of the body lead to vessel wall damage, increasing clotting tendency and inflammation, all of which contribute to cardiovascular
disease (Ambrose and Barua 2004; Breitling 2013; Freson, Izzi, and Van Geet 2012; Schleithoff and others 2012; Vinci, Polvani, and Pesce 2013).

Figure __2 Overview of Pathophysiological Mechanisms of Tobacco in the Development of Cardiovascular Disease

In summary, a synergistic interplay of alterations in coronary vasoconstriction, endothelial dysfunction, and altered lipids stimulate a cascade of events leading to athero-thromboembolism (deposition of fats and clot) and, subsequently, heart attack.

<<III>> Tobacco and the Cardiovascular Disease Risk Factors

<A>Smoking and Dyslipidemia</A>

Compared with nonsmokers, smokers have higher levels of bad cholesterol LDL, and lower serum concentrations of good cholesterol HDL. Smokers have 3 percent more cholesterol, 9 percent more triglycerides and 5.7 percent less HDL (Craig, Palomaki, and Haddow 1989). A clinical trial showed that stopping smoking improved total HDL, and large HDL particles, but
did not affect LDL cholesterol levels or LDL size (Gepner and others 2011). Smoking and dyslipidemia both significantly increase the risk of coronary atherosclerotic disease.

**Smoking and Hypertension**

Smoking unequivocally raises cardiovascular risks associated with hypertension. However, the role of smoking in altering the blood pressure itself remains unclear, as observational studies in diverse populations, mostly in high income countries, have found no association or lower blood pressure among smokers (Brummett and others 2011; Green, Jucha, and Luz 1986). Blood pressure increases abruptly after smoking starts, but it returns to pre-smoking levels within a few hours (Tachmes, Fernandez, and Sackner 1978). Age may modify the smoking-blood-pressure link. One of the largest cross-sectional studies from a nationally representative sample of adults in United Kingdom reported higher systolic blood pressure among older male smokers after adjusting for covariates. This was not the same for young smokers, however, or for diastolic blood pressure levels (Primatesta and others 2001). Ambulatory day time diastolic blood pressure was also significantly higher, by 5 millimeters of Hg among tobacco users over “never-users” ages 45 years and above. When daytime heart rates were compared among users and nonusers, the former were significantly higher. The increase in heart rate associated with smoking may be the key factor in the added cardiovascular risk associated with smoking in people with high blood pressure.

**Smoking and Diabetes**

Smokers have more insulin-resistance and are more hyperinsulinemic (higher levels of insulin is postulated to be a precursor of type 2 diabetes) compared with nonsmokers (Facchini and others 1992). Cigarette smoking is a risk factor for the development of type-2 diabetes through two pathways (Eliasson 2003). The first is mediated directly through hyperinsulinemia and insulin resistance. The second is through visceral fat accumulation, an effect confounded by low physical activity and unhealthy diet (Chiolero and others 2008). Evidence is increasing that smoking causes greater accumulation of visceral fat. Several cross-sectional studies indicate that the waist-to-hip ratio is higher in smokers than in nonsmokers (Bamia and others 2004; Canoy and others 2005). Smokers with diabetes have higher hemoglobin A1C levels (glycated hemoglobin which indicates long-term blood sugar control), require more insulin, and have increased risk of vascular complications of diabetes such as kidney disease, blindness, and cardiovascular disease (Zhu and others 2011).
Insulin resistance, central obesity, and dyslipidemia caused by smoking increases the risk of incident metabolic syndrome—a constellation of metabolic abnormalities that includes high waist circumference, high blood pressure, abnormal blood sugar, and high lipid levels. The mechanistic link between cigarette smoking and insulin resistance is not fully established, but evidence exists for a role for nicotine. Sympathetic activation and release of corticosteroids and growth hormone by nicotine may contribute to insulin resistance. A systematic review comprehensively investigated the association between smoking and diabetes using compiled results from 88 prospective studies with more than five million participants. The pooled Relative Risk (RR) of diabetes was 1.37 (95 percent Confidence Interval [CI]: 1.33–1.42) among current active smokers and 1.22 (95 percent CI: 1.10–1.35) among passive smokers. The study also highlights the long-term benefits of cessation in reducing diabetes risk to the same level as that of nonsmokers after ten or more years of abstinence (RR= 1.11, 95 percent CI:1.02–1.20) (Pan and others 2015).

Smoking adds multiplicative risk of cardiovascular disease in the presence of each of the three main risk factors. For example, the presence of both high blood pressure and smoking result in a striking 15-fold increased risk of stroke. This relationship is graded and consistent across all levels of blood pressure (Neaton and others 1993). Similar effects have been observed with non-cigarette and smokeless forms of tobacco (Boffetta and Straif 2009; Gupta and Asma 2008; Yusuf and others 2004).

Cardiovascular Disease Outcomes and Manifestations of Tobacco Use

Of the conditions included under cardiovascular diseases (Figure_3.), this review focuses on the major ones caused by tobacco use, primarily through atherosclerosis of various vessel beds. These latter include the aorta and vessels originating from it: the coronary arteries (supplying blood to heart muscle), the carotid and cerebral arteries (supplying blood to the head and brain), and the renal and peripheral arteries (supplying blood to the kidneys and limbs, respectively). Box __.2 lists the main cardiovascular diseases and their complications (Ambrose and Barua 2004; Aronow 1974; Borgerding and Klus 2005; Glantz and Parmley 1991; Salahuddin, Prabhakaran, and Roy 2012; U.S. Department of Health and Human Service 1988). Figure_3. Diagram representing Cardiovascular manifestations of tobacco use.
Box 1.2 Major Cardiovascular Diseases Caused by Tobacco Use

- **Coronary (ischemic) heart disease**
  - Myocardial Infarction (heart attacks)
  - Unstable angina/Stable angina (Chest pain due to block in the arteries supplying the heart)
- **Cerebrovascular diseases** including stroke (brain attack), transient ischemic attacks (mini/transient stroke), and dementia (such as Alzheimer’s disease).
- **Arrhythmias** (Electrical disturbances of the heart) including sudden death
- **Heart failure** whether including chronic obstructive pulmonary disease (Bad lungs leading to strain on the heart and fluid retention)
- **Aortic disease** including aneurysm (Ballooning of the largest blood vessel in the thorax or abdomen which can lead to rupture and possibly death)
- **Kidney disease**, including renal artery stenosis (narrowing of arteries to kidneys leading to reduced blood flow), leading to resistant hypertension and progressive renal failure (potentially leading to dialysis)
- **Peripheral arterial disease** (narrowing of arteries to limbs causing claudication or pain in walking, limiting mobility and possibly leading to gangrene and leg amputation)
- **Internal pudendal and penile atherosclerosis** (causing impotence)
Concerns about the harmful effects of smoking initially centered on lung diseases, but vascular diseases occur earlier in life those and contribute to a substantial number of deaths (U.S. Department of Health and Human Service 1983; Lopex 1994). Cigarette smoking is known to increase the risk of cardiovascular disease, as it is known to do for hypertension, hypercholesterolemia, and diabetes (U.S. Department of Health and Human Service 1983).

**Smoking and Cardiovascular Mortality**

Cigarette smoking increases all-cause and cardiovascular death rates (Brummett and others 2011; Qiao and others 2000). The risk among smokers of 35-year all-cause mortality and 35-year heart disease mortality is nearly 60 percent higher than in nonsmokers (Qiao and others 2000). Smoking is an even stronger independent predictor of all-cause and cardiovascular mortality in older adults. Pooled data on over half a million older (than 60 years) adults from 25 cohort studies indicate more than a doubling of risk for current smokers and 37 percent increased risk for former smokers compared with never-smokers (Mons and others 2015).

Doll and others (2004) did the earliest and seminal work on the relationship of smoking and cardiovascular mortality. They followed a large cohort of doctors from 1951 until 2001 to monitor cause-specific mortality, and attributed 25 percent of excess risk of death to coronary heart disease (in that cohort). Similarly, in a large cohort of construction workers age-adjusted coronary heart disease mortality among smokers was higher than nonsmokers and highest among heavy smokers, with almost a doubling of risk (Bolinder and others 1994). Young smokers (under age 50 years) have five to six times higher death rates than nonsmokers (Parish and others 1995).

**Smoking and Coronary Heart Disease**

Coronary (ischemic) heart disease is the most common form of atherosclerotic cardiovascular disease and is responsible for the largest share of cardiovascular morbidity and mortality. It is also associated with increased risk of sudden death (Aronow 1974; Bolinder and others 1904). Cigarette smoking has been consistently and causally linked to coronary heart disease in prospective studies (Prescott and others 1998; Njolstad, Arnesen, and Lund-Larsen 1996; U.S. Surgeon General 2010). The INTERHEART study (Yusuf and others 2004), a large international case control study showed that smoking increases the risk of heart attack by three times. The risk was highest among younger patients, in whom tobacco use increased risk more than sevenfold. The risk had a dose-response relationship, increasing linearly with an increase in the number of cigarettes smoked per day and duration of use (Yusuf and others 2004). In
addition, women using tobacco lose the gender protection against heart disease noted among those younger than age 50 years (U.S. Surgeon General 2001). In the Nurses’ Health Study (Kawachi and others 1994), heart disease increased more than a fourfold (RR: 4.23; 95 percent CI: 3.6–4.96) among female nurse smokers over never-smokers. This risk was greatest among those who started smoking before age 15 years (Kawachi and others 1994). In a pooled analysis of over 2.4 million people, female smokers were 25 percent more likely to develop coronary heart disease than male smokers (RR: 1.25; 95 percent CI 1.12–1.39) (King 2011).

Smoking and Heart Failure
Heart failure is a rising global public health challenge. It is associated with either reduced myocardial relaxation (stiffness due to ischemia or uncontrolled hypertension) or reduced myocardial pumping (due to prior heart attacks). It may also be associated with smoking-related lung conditions, such as chronic obstructive pulmonary disease. Heart failure is often characterized by dyspnea, fluid retention, and weight gain, and peripheral edema. Coronary (ischemic) heart disease, in which smoking plays a major part, is among the most common causes of heart failure. Heart failure is especially prevalent in the elderly and is associated with significant mortality and morbidity, requiring repeated hospitalization. It ranks among the top causes of health care costs in high-income countries. This portends trouble for LMICs that are currently experiencing a rise in cardiovascular risk factors and diseases known to increase the risk of heart failure.

A systematic review found that smoking is associated with a 60 percent increased risk of incident heart failure (Yang and others 2015). A similar association is found among older people, with current smokers showing highest risk and a dose-effect association among former smokers. The risk of heart failure increases with the number of cigarettes smoked. Men who smoked more than 15 cigarettes per day were at 2.5 times the risk of heart failure over never-smokers (Odds Ratio [OR] = 2.31, 95 percent CI: 1.58–3.37) (Wilhelmsen and others 2008). Continued cigarette smoking is also associated with increased risk of recurrent heart failure. On retrospectively charting the admission status in a veterans administration facility, it was found that noncompliance to smoking cessation interventions was a significant predictor of multiple heart failure readmissions, with 80 percent excess risk (Evangelista, Doering, and Dracup 2000).
Smoking and Carotid and Cerebrovascular Diseases

Similar to heart attacks, cigarette smoking is causally associated with stroke (Ambrose and Barua 2004; U.S. Department of Health 2014). The INTERSTROKE study—a multi-centric study involving 3,000 cases and controls each in 22 countries and designed to establish association between various risk factors and stroke—revealed that the odds of having ischemic stroke (due to occlusion of blood supply to the brain) was 2.3 (99 percent CI: 1.9–2.8) and for hemorrhagic stroke (bleeding into the brain) 1.4 (99 percent CI: 1.1–1.9) higher among smokers than nonsmokers (O’Donnell and others 2010).

Smoking in conjunction with hypertension was the main risk factor identified for stroke, and a dose-response relationship exists with the number of cigarettes smoked per day. A meta-analysis using 32 cohorts and case control studies involving more than 11,000 stroke events showed a 50 percent overall increase in risk of stroke in smokers. This risk appears to be higher among women, young smokers, and heavy smokers (Shinton and Beevers 1989). Smoking is also strongly implicated in transient ischemic attacks, a transient and milder form of stroke with symptoms typically resolving within 24 hours. Smoking has also been shown to increase the risk of dementia, another increasing global health challenge, including dementia caused by Alzheimer’s disease (Cataldo, Prochaska, and Glantz 2010; WHO 2015).

Smoking and Arrhythmia

Although substantial evidence exists on the role of tobacco in the initiation and progression of atherosclerosis, its role in arrhythmias is less defined, and it is likely to be complex (D’Alessandro and others 2011). Two of the most common conditions associated with smoking—coronary heart disease and chronic lung disease—are both strongly associated with arrhythmias, making it difficult to tease out the direct pro-arrhythmic effects of smoking and its components. Nonetheless, D’Alessandro and others (2011) argue strongly that smoking has direct and acute toxic pro-arrhythmia effects. They propose several mechanisms that mediate the risk; this includes nicotine-induced catecholamine release, myocardial pro-fibrotic effects of nicotine which can increase susceptibility to catecholamine, oxidative stress, and ischemia/hypoxia especially associated with carbon monoxide (D’Alessandro and others 2011).

We have alluded to the increased risk of sudden cardiac death in smokers. Smoking has been linked with ventricular arrhythmias in several studies in people with coronary heart disease (Engström and others 1999; Goldenberg and others 2006; Vlietstra and others 1986).
Smoking is also associated with increasing risk of supraventricular arrhythmias, as documented in the MADIT study (Goldenberg and others 2006). In addition, smoking is associated with atrial fibrillation, the most common form of supraventricular arrhythmia, with a recent review suggesting a doubling of risk of atrial fibrillation in smokers (Morris and others 2015). Both the Atherosclerosis Risk in Communities study (Chamberlain and others 2011), with 15,000 participants, and the Rotterdam study (Heeringa and others 2008), with 5,668 subjects, showed increased incidence in current (RR 2.05, CI 1.71–2.47 and RR 1.51, CI 1.07–2.12) and former smokers (RR 1.32 CI 1.10–1.57 and RR 1.49, CI 1.14–1.97) (Chamberlain and others 2011; Heeringa and others 2008). The risk was dose-dependent. The risk also increased in the Manitoba Follow-Up Study (Krahn 1995). Limitations in older studies may have masked the association between smoking and atrial fibrillation (D’Alessandro 2011). Evidence for the link between smoking and arrhythmias also exists in studies showing less arrhythmia in those who stop smoking (Kinoshita and others 2009; Peters and others 1995;).

**Smoking and Aortic and Peripheral Artery Disease**

It is well-established that various risk factors differ in their association with atherosclerosis disease in various vascular beds. Studies confirm that smoking is more strongly associated with aortic disease, however, particularly abdominal aortic and peripheral arterial disease, than any other risk factor, and the association of smoking with abdominal aortic aneurysm and peripheral arterial disease is much stronger than its association with any other cardiovascular disease. The EPIC-Norfolk prospective population study, with 21,798 participants, showed that smoking was associated with increased risk of abdominal aortic aneurysm (RR 7.66, CI 4.50-13.04) and peripheral arterial disease (RR 4.66, CI 3.29-6.61) (Stoekenbroek and others 2015). In the largest study in United Kingdom involving 1,937,360 people, the corresponding risks were RR 5.18 (CI 4.61–5.82) for abdominal aortic aneurysm and RR 5.16 (CI 4.80–5.54) for peripheral arterial disease (Pujades-Rodriguez 2015). These results are consistent with the findings of a meta-analysis of smoking and peripheral arterial disease involving 55 studies (Lu, Mackay, and Pell 2014). In countries with a high proportion of smokers, nearly 50 percent of peripheral arterial disease can be attributed to smoking (Willigendael and others 2004). Smoking is also strongly associated with the risk of expansion and rupture of abdominal aortic aneurysm, suggesting that screening for abdominal aortic aneurysm should be restricted to smokers (Sweeting and others 2012; Howard and others 2015). Former smokers have reduced risk of both abdominal aortic aneurysm and peripheral arterial disease.
Smoking and Chronic Kidney Disease

Chronic kidney disease, a condition associated with increased mortality, morbidity, and health care costs, is a growing global public health concern. It is strongly linked with cardiovascular disease and its risk factors, including smoking. Smokers have elevated risk of urine-albumin excretion, macro albuminuria (Halimi and others 2000; Pinto-Sietsma and others 2000). The mechanisms underlying the smoking–chronic kidney disease association is affected by several factors; the association between chronic kidney disease, smoking, and heart disease is linked by hemodynamic mechanisms such as cardiorenal syndrome in people with heart failure and increase in blood pressure, which is known to promote progression of chronic kidney disease (Orth 2004). A large population based cohort with a median follow-up of 10.3 years demonstrated that smoking participants younger than age 70 years were at fourfold higher risk of chronic kidney disease than never-smokers (Hallan and Orth 2011). Similarly, greater risk of developing chronic kidney disease was observed among smokers in another large population study in Japan (Yamagata and others 2007). Participants with preexisting chronic kidney disease have a substantial risk of cardiovascular disease mortality. The Cardiovascular Health Study cohort demonstrated that the elderly (over age 65 years) with chronic kidney disease had a cardiovascular disease risk rate of 32 deaths per 1,000 person years, compared to 16 per 1,000 person years in the group without chronic kidney disease, with smoking a major predictor of the same (Shlipak and others 2005).

Cardiovascular Disease Associated with Other Forms of Tobacco Use

Other aspects of cigarette smoking exist, such as second-hand smoke, which have harmful cardiovascular effects. Additionally, tobacco is consumed worldwide in many forms beyond cigarettes, both smoked and smokeless (Saleheen, Zhao, and Rasheed 2014). Although most such forms have been documented to affect cardiovascular health, differences exist either in the magnitude or nature of the cardiovascular impact of various forms (Katsiki and others 2013).

Table __.1 Forms of Tobacco Use

<table>
<thead>
<tr>
<th>Smoked forms of tobacco</th>
<th>Smokeless forms of tobacco</th>
</tr>
</thead>
</table>

19
**Rolled products:** Cigarettes, Bidis, Kretteks, Cheroot, cigars

**Piped tobacco:** Chillum, pipes

**Waterpipes:** Sheesha, Hookah, Goza, Narghile (arghileh)

**Tobacco chewing:** Paan, Gutika, Mawa, Qiwm (khiwm), Zarda, Khaini

**Tobacco sucking:** Naswar (nass), chimo, tommbak

**Tobacco dentifrice:** Masheri (mishri), gul (gudakhu)

**Tobacco sniffing:** Dry snuff (tapkeer)


**<A>Second-Hand Smoke**

Also known as environmental tobacco smoke, second-hand smoke has similar physiological effects to active smoke: oxidized lipids, increased arterial thickening, and decreased coronary flow velocity (Howard and others 1998; Otsuka and others 2001). Many studies have examined the association of second-hand smoke with cardiovascular disease and outcomes and results. An older, influential meta-analysis of 10 cohort studies and 8 case-control studies showed a 25 percent increased risk (1.25, 95 percent CI, 1.17–1.32) of coronary heart disease among nonsmokers exposed to second-hand smoke with dose-response relationship (He and others 1999). An updated meta-analysis comes to a similar conclusion, with 27 percent increased risk (RR 1.27, CI 1.10–1.48) (Fischer and Kraemer 2015). Similarly, the INTERHEART study, which was not included in the updated meta-analysis, found a 24–62 percent increased risk with second-hand smoke, depending on the dose of exposure (Teo and others 2006). In focusing on LMICs, Olasky, Levy, and Moran (2012) show high prevalence of second-hand smoke and increased risk of both ischemic heart disease and stroke. The consistency of these findings after taking account of other (confounding) factors suggests that the association is causal and definitive (Glantz and Parmley 1991). The ill-effects of second-hand smoke can be confirmed by the presence of physiological markers of tobacco smoke. Compared with men not exposed to second-hand smoke, those exposed had higher levels of carbon monoxide and lower pulmonary function (Svendsen and others 1987).
**<B>Third-Hand Smoke**

The lasting or residual tobacco smoke contamination that persists after the cigarette is extinguished is referred to as third-hand smoke (Winickoff and others 2009). It reflects the contamination of surfaces with tobacco smoke. Surface-mediated reactions of tobacco smoke products (hydrogen cyanide, butane, toluene, polonium-201, and others) may form carcinogenic compounds that accumulate with time to become progressively toxic (Petrick and Dubowski 2011; Sleiman and others 2010). Animal studies found third-hand smoke to be associated with increased lipid levels, inflammatory cytokine production, and collagen stimulation, all of which can potentially contribute to cardiovascular disease (Martins-Green and others 2014). Although preliminary research suggests third-hand smoke may be associated with a risk of heart disease, the magnitude of risk needs further research.

**<C>Other Forms of Tobacco Smoking**

**<a>Bidi Smoking**

Bidi smoking is practiced in India and other countries in South Asia. As it is more commonly used among low socioeconomic status groups, its use and health effects raise equity issues. Tobacco is wrapped in leaves that are then thinly rolled and secured with threads. Bidi rolling has expanded as an unorganized business incorporating households, small workshops, and cooperatives to evade regulations and tax implications (Gupta and Asma 2008). Bidis have a concentration of nicotine, tar, and other toxic ingredients equal to or greater than cigarettes. Given the increased risk of cardiovascular disease at a young age among the Indian population, the adverse effects of this and other tobacco forms have large population level health impact. The INTERHEART study revealed that in addition to cigarette smoking, use of other forms of tobacco such as bidi and chewing tobacco (also common in South Asian countries) was associated with significant increased risk of heart attack. The risk with bidi use was as much as with cigarettes, but that of chewed tobacco was slightly lower. However, the risk was highest (fourfold) in individuals who used both smoked and smokeless forms of tobacco (Yusuf and others 2004). Another hospital-based case-control study confirmed nine times greater risk (RR 9.1, CI 4.7–17.7; p for trend < 0.0001) of myocardial infarction among those who smoked over 10 bidis a day compared with nonsmokers, which was slightly less for those smoking an equal
number of cigarettes per day (RR of 7.3 (95 percent CI 3.9 to 13.8; p for trend < 0.0001) (Rastogi and others 2005).

**<b>Waterpipe Tobacco Smoking**

Waterpipe (hookah/shisha/narghile) smoking has been popular among Asians, Arab and other Middle Eastern and some African countries for a long time, and this mode of tobacco use has seen a global resurgence recently, especially among youth (Maziak and others 2004). It is often misunderstood that as the smoke gets filtered it becomes less toxic after passing through a water receptacle, but this has been proven wrong (Kandela 2000; Varsano and others 2003). Waterpipe smokers also engage in longer smoking sessions, which exposes them to more smoke (Shihadeh 2003). Although the health risks associated with waterpipe smoking have not been fully elucidated, the cardiovascular effects are clear and include increased heart rate, blood pressure, increased serum fibrinogen to ischemic heart disease, angina, aneurysms, and stroke (El-Zaatari, Chami, and Zaatari 2015). Cumulative exposure to waterpipe smoking is also significantly associated with Coronary Artery Disease (CAD). Exposure as high as 40 waterpipe-years (reflecting both duration and dose) was associated with almost a threefold increase in the risk of obstructive coronary disease compared with nonsmokers (Sibai and others 2014). A dose-response relationship exists between heart disease and waterpipe smoking. Among more than 50,000 residents of Golestan, Iran, heavy waterpipe smokers had significantly greater risk of heart disease than nonsmokers (Islami and others 2013).

**<c>Smokeless Tobacco Use**

Commonly used in South and Southeast Asia, Sub-Saharan Africa, and northern Europe, smokeless tobacco has been associated with cardiovascular disease (Gupta, Gupta, and Khedar 2013). A pooled analysis of both cohort and case-control studies estimated a 13 percent higher risk of fatal heart attack and 40 percent higher risk of fatal stroke among users compared with nonusers, with evidence of a dose-response relationship. The increased risk of fatal Myocardial Infarction (MI) in this meta-analysis appears to be small, but the effect is large at the population level, especially given the consistency of results and robust study designs and analysis (Boffetta and Straif 2009). This has prompted strong calls for discouraging use of smokeless tobacco (Gupta, Gupta, and Khedar 2013; Piano and others 2010).
Electronic Nicotine Delivery System

Also known as electronic cigarettes, global growth in the electronic nicotine delivery system has been surging in recent years. Although some have advocated it as a smoking cessation aid, others contest this. Electronic cigarettes typically involve the conversion of a liquid in a small compartment into an aerosol, facilitated by a battery circuit. The liquid contents include nicotine, propylene glycol, flavoring agents, and others. Growing awareness and use of electronic cigarettes has been observed among the young and high-income groups and popularity is growing through advertising (Adkison and others 2013; Regan and others 2013). Electronic cigarettes do not fall under the ambit of regulatory authorities in most countries, with no clarity on their benefits to individuals or the wider population. The risks and benefits associated with their use are unclear and subject to exploration before conclusions can be made. In addition to the proposed benefits, the potential may exist that they induce smoking in nonsmokers or maintain nicotine addiction among users, jeopardizing quitting attempts (Morris and others 2015).

Socioeconomic Dimensions of Tobacco-Use-Related Cardiovascular Diseases

The relationship between tobacco use and cardiovascular disease is modified by many socioeconomic variables. We have alluded to some of these, and their interactions, for example age (young male smokers are at higher risk of sudden death), gender (women have more risk for some cardiovascular diseases such as coronary heart disease), and ethnicity (with South Asians facing greater risks) (Huxley and Woodward 2011). However, it is crucial to consider many other socioeconomic dimensions, such as the impact of heterogeneous macroeconomic and human development, income inequality, and socioeconomic status. Although the links have been well researched between each of these variables and either tobacco use or cardiovascular diseases, their complex interactions as modifiers of the link between tobacco use and cardiovascular diseases have been less studied, especially in LMICs. This is an important agenda for future research.

Cardiovascular Benefits of Tobacco Cessation

The profound cardiovascular harm of tobacco and its global toll, especially in LMICs, indicate that prevention of tobacco initiation and lifelong avoidance of all tobacco products are the best strategies. This has prompted calls for a tobacco-free world (Beaglehole and others 2015). The
evidence for the cardiovascular benefits of tobacco cessation, particularly cigarette smoking, is compelling. Smoking cessation benefits all users, irrespective of form, frequency, and age. Cardiovascular benefits are consistent and set in early after tobacco cessation (Box __.3) (Bakhru and Erlinger 2005; Gratziou 2009; Hatsukami and others 2005).

<table>
<thead>
<tr>
<th>Box __.3 Time to Cardiovascular Benefit of Smoking Cessation after Last Cigarette</th>
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<tbody>
<tr>
<td>• <em>Within 20 minutes:</em>) Blood pressure decreases and body temperature and pulse</td>
</tr>
<tr>
<td>rate return to normal.</td>
</tr>
<tr>
<td>• <em>Within 24 hours:</em>) Risk of MI decreases.</td>
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<tr>
<td>• <em>Within 1 year:</em>) Excess risk of coronary heart disease is half that of a person</td>
</tr>
<tr>
<td>who smokes.</td>
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<tr>
<td>• <em>At 5 years:</em>) Stroke risk is reduced to that of someone who has never smoked.</td>
</tr>
<tr>
<td>• <em>Within 15 years:</em>) Coronary heart disease risk is the same as a person who has</td>
</tr>
<tr>
<td>never smoked.</td>
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</tbody>
</table>

In general population studies, smoking cessation has clearly been shown to prolong life and more so when it occurs early in life. For example, in a cohort of doctors followed for 50 years, smokers who continued to smoke lost on an average 10 years of life (Doll and others 2004). The years of life gained was three, six, and nine for those who stopped at ages 60, 50, 40 years, respectively. However, this does not set a threshold age for quitting, and age should not be a refraining factor for quitting, with even the elderly benefiting from smoking cessation (Burns 2000).

In people diagnosed with cardiovascular disease, persistent smoking confers a significant increase in cardiovascular events and mortality (Buckley and others 2009; Simpson and others 2011). This mandates tobacco cessation as a key secondary measure to prevent further cardiovascular events, particularly heart attacks, and to prolong survival. In a meta-analysis of 12 cohort studies, all reported a reduction in mortality, irrespective of gender, duration of follow-up, or time of assessment of smoking status after the cardiovascular event. The overall reduction in mortality after a mean follow-up of 4.8 years was nearly 50 percent (OR 0.54; CI 0.46–0.62) (Wilson and others 2000). The systematic review by Critchley and Capewell (2003)
of 20 cohort studies of patients with coronary heart disease, with at least two years of follow-up, estimated that one-third of cardiovascular disease outcomes—such as coronary artery bypass surgery, angioplasty, and recurrent heart attacks—can be prevented by quitting smoking (Critchley and Capewell 2003). Unfortunately, numerous studies in diverse populations in high-income countries and LMICs document persistent smoking in people who have been diagnosed with cardiovascular disease, including those who have suffered heart attacks. This indicates a tremendous missed opportunity for secondary prevention. As strong advice by health care providers, particularly physicians, leads to more quitting, there have been calls for cardiovascular specialists to pay greater attention to smoking cessation (Jabbour and others 2002).

Although interventions targeted at individual smokers are important policy interventions, particularly those at high risk of or with existing cardiovascular disease, it is also crucial to reduce overall tobacco use rates at the population level. The World Health Organization (WHO) Framework Convention on Tobacco Control is a comprehensive, binding convention that provides party countries, now 180, with measures and corresponding guidelines to reduce both demand and supply (see also chapter 8 for a more detailed discussion of strategies of tobacco control). The cardiovascular impact of implementing various policy measures in the framework have been variably studied with smoke-free legislation and policies banning smoking in public spaces receiving the most attention. The most recent meta-analysis of 31 studies of cardiovascular impact in 47 locations showed a 12 percent reduction in hospitalization for acute coronary events and 14 percent with comprehensive legislation and with greater reduction in smoking prevalence post legislation (Jones and others 2014). This impact translates into large benefits at the population level. Although it is difficult to know with certainty what proportion of the benefit comes from reduced exposure to second-hand smoke in nonsmokers, as opposed to reduced consumption or more quitting among smokers, studies suggest that both smokers and nonsmokers benefit (Seo and Torabi 2007).

<<VIII>>CONCLUSIONS

Robust evidence indicates that tobacco use causes atherosclerotic cardiovascular disease. The link is strong, with various forms of tobacco use and the magnitude substantial and consistent across all cardiovascular manifestations.
Tobacco use acts both independently and synergistically with other risk factors common to cardiovascular disease. Complex mechanisms underlie the pathophysiology of tobacco attributed cardiovascular disease. The risk appears to be higher among younger age groups smoking more cigarettes per day, among women compared with men, and in certain ethnicities such as South Asians.

The most common tobacco-related cardiovascular disease manifestations include MI, angina, stroke, aortic aneurysm, and peripheral artery disease. However, heart failure, chronic kidney disease, and atrial fibrillation are emerging as global health issues. These manifestations lead to premature morbidity, mortality, loss of productive years of life and tremendous health care costs burdening already stretched health systems especially in LMICs.

Tobacco cessation protects against cardiovascular disease at all ages and adds years to life. Population- and individual-level interventions to reduce the number of people starting to smoke and getting more to quit have great promise, especially for those with or at high risk of cardiovascular disease. The implementation of the full provisions of the Framework Convention on Tobacco Control provides a clear path toward a world free of tobacco use and where tobacco-related cardiovascular disease becomes a thing of the past.

Acknowledgment
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NOTE
<<unnumbered>>World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income per capita for 2013:
• Low-income countries = US$1,045 or less
• Middle-income countries are subdivided:
  a) lower-middle-income = US$1,046 to US$4,125
  b) upper-middle-income = US$4,126 to US$12,745
• High-income countries = US$12,746 or more.
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