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THE PRESENT AND FUTURE

COUNCIL PERSPECTIVES

Cardiovascular Effects of Exposure to Cigarette Smoke and Electronic Cigarettes

Clinical Perspectives From the Prevention of Cardiovascular Disease Section Leadership Council and Early Career Councils of the American College of Cardiology

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ABSTRACT

Cardiovascular morbidity and mortality as a result of inhaled tobacco products continues to be a global healthcare crisis, particularly in low- and middle-income nations lacking the infrastructure to develop and implement effective public health policies limiting tobacco use. Following initiation of public awareness campaigns 50 years ago in the United States, considerable success has been achieved in reducing the prevalence of cigarette smoking and exposure to secondhand smoke. However, there has been a slowing of cessation rates in the United States during recent years, possibly caused by high residual addiction or fatigue from cessation messaging. Furthermore, tobacco products have continued to evolve faster than the scientific understanding of their biological effects. This review considers selected updates on the genetics and epigenetics of smoking behavior and associated cardiovascular risk, mechanisms of atherogenesis and thrombosis, clinical effects of smoking and benefits of cessation, and potential impact of electronic cigarettes on cardiovascular health. (J Am Coll Cardiol 2015;66:1378–91) © 2015 by the American College of Cardiology Foundation.

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Inhaled tobacco products are highly engineered, pleasurable, and rapid delivery systems for nicotine, a highly addictive substance, in addition to numerous harmful toxicants and carcinogens (1,2). When tobacco is burned, a complex chemical mixture of more than 7,000 compounds is produced, many of which are causally associated with premature deaths and diseases affecting nearly every organ system in the body (2–4). Cigarette smoking is the predominant form of tobacco exposure throughout the world (5,6). Global estimates demonstrate a significant reduction in the prevalence of daily smoking in both men and women between 1980 and 2012 (7,8). However, the total number of smokers worldwide has increased during this period, from approximately 721 million to 967 million, largely because of population growth. The burden of disease attributable to cigarette smoke exposure (CSE) and secondhand smoke (SHS) is substantial, causing 6.3 million deaths annually and 6.3% of disability-adjusted life-years (8). In Western Europe and high-income North America, CSE and SHS are the leading risk factors for morbidity and mortality, and globally only high blood pressure is associated with a higher burden of disease.

One-third of deaths from CSE are secondary to cardiovascular disease (CVD) and 11.1% of these deaths occur in people with exposed to SHS (9). Extensive epidemiological research on SHS spanning several decades supports a strong causal relationship with a 25% to 30% increase in coronary heart disease (CHD) (10–12). CSE has a nonlinear dose effect on CVD and risk is increased at all levels of CSE, even among persons smoking fewer than 5 cigarettes per day and with exposure to SHS (13,14). Evidence also suggests that the cardiovascular effects of CSE may have a low threshold effect, with a marked increase in risk at even low levels of exposure (**Figure 1**) (15). Thus, the 2014 report of the U.S. Surgeon General states "there is no safe level of exposure to tobacco smoke" (3).

Although there have been significant advances in the understanding of the pathophysiology of tobacco-related CVD, the pace of new research has slowed in recent years. In addition, tobacco-related products have continued to evolve more quickly than scientific knowledge of their biological effects. There has been a slowing of cessation rates in the United States during recent years, possibly caused by high residual addiction or fatigue from cessation messaging. Tobacco control policies to protect persons from SHS in public places are not universal and nearly one-third of nonsmokers in the United States are passively exposed to cigarette smoke. Tobacco products are featured on the Internet and in media, and cigarettes remain remarkably affordable. Finally, despite well-documented and devastating health consequences, tobacco use continues to be undertreated in the healthcare environment with suboptimal implementation of evidence-based intervention (16).

This review focuses on selected tobacco-related issues since the JACC review by Ambrose and Barua in 2004 (17), including mechanisms of CSE-related atherogenesis, recent research on the genetics and epigenetics of smoking behavior and the causal link between tobacco use and CVD, the clinical impacts of CSE/SHS and benefits of legislation to reduce SHS exposure, and consideration of the potential cardiovascular effects of electronic cigarettes (ECs). The cardiovascular effects of involuntary exposure to tobacco smoke are not specifically addressed in this paper, because this topic has been comprehensively reviewed in the report of the U.S. Surgeon General (18). The authors' purpose is to reinvigorate commitment to advance the scientific understanding of smoking behavior and the cardiovascular effects of tobacco products and newer forms of nicotine exposure, to encourage advocacy efforts to more broadly implement smoke-free policies, and to make cessation counseling a clinical imperative for every patient.

ABBREVIATIONS AND ACRONYMS

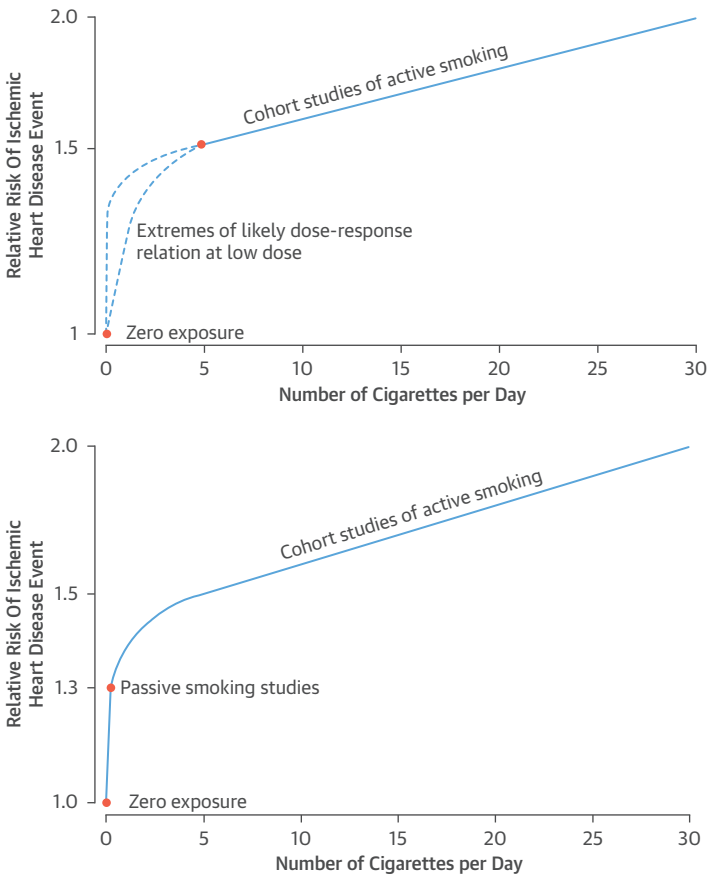
AAA = abdominal aortic aneurysm
AF = atrial fibrillation
BDNF = brain-derived neurotrophic factor
CHD = coronary heart disease
CI = confidence interval
CSE = cigarette smoke exposure
CVD = cardiovascular disease
EC = electronic cigarette
EPC = endothelial progenitor cell
MI = myocardial infarction
MMP = matrix metalloproteinase
NO = nitric oxide
OR = odds ratio
PCI = percutaneous coronary intervention
RR = relative risk
SC = smoking cessation
SHS = secondhand smoke
SNP = single-nucleotide polymorphism
TF = tissue factor

GENETICS AND EPIGENETICS OF TOBACCO-RELATED CVDs

Genomic and epigenomic studies have provided important insights into the risk for initiation of tobacco use, the intensity of smoking behavior, mechanisms of CSE-induced atherogenesis, and evidence to support a causal association between CSE and CVD risk (**Table 1**).

In the recent Tobacco and Genetic Consortium meta-analysis of genome-wide association studies, several common polymorphisms were found to be robustly associated with smoking behavior (19). The strongest evidence for association was a synonymous single-nucleotide polymorphism (SNP) on chromosome 15q25 located in the nicotinic receptor gene CHRNA (rs1051730). Among smokers, each additional copy of the T allele of this SNP was associated with an approximately 1 cigarette per day increase in the intensity of smoking ($p = 2.8 \times 10^{-72}$). Furthermore, a nonsynonymous SNP (rs6265) on chromosome 11 in the brain-derived neurotrophic factor (BDNF) gene (involved in nicotine-related dopamine reward

FIGURE 1 Dose-Response Relationship Between Cigarette Smoke Exposure and Risk for Ischemic Heart Disease Events



Data from studies of environmental tobacco smoke exposure and of active smoking indicate that the relative risk of coronary heart disease events is significantly increased at even low levels of exposure. Adapted with permission from Law et al. (15).

circuits) was associated with increased odds of smoking initiation ($p = 1.8 \times 10^{-8}$). Each additional copy of the C allele of the rs6265 SNP was associated with an approximately 6% greater odds of regular smoking (odds ratio [OR]: 1.06; 95% confidence interval [CI]: 1.04 to 1.08) (20).

In addition to providing important information about genomic vulnerability to smoking behaviors, the discovery of polymorphisms that are associated with smoking intensity and the risk of initiating tobacco smoking may provide a unique opportunity to evaluate the causal effect of smoking on the risk of CVD. Like other polymorphisms, the smoking-associated rs1051730 and rs6265 SNPs are allocated approximately randomly at the time of conception in a process sometimes referred to as mendelian randomization (21). Therefore, inheriting an allele associated with greater smoking intensity is analogous to being randomly allocated to more intense smoking, whereas inheriting the other allele is analogous to being randomly allocated to less intense smoking. Comparing the risk of disease among smokers with and without such an allele should, therefore, provide a naturally randomized and unconfounded estimate of the causal effect of more intense (as compared with less intense) smoking on the risk of disease in a manner analogous to a randomized trial.

A recent mendelian randomization study conducted among 55,568 persons from the Danish general population found that the rs1051730 polymorphism in the nicotinic receptor gene was associated with both more intense smoking and with an increased risk of all-cause mortality (22). These data provide strong evidence that increasing smoking intensity is causally related to an increased risk of all-cause mortality. To date, however, the rs1051730 polymorphism has not been reported to be associated with CVD events.

Another recent mendelian randomization reported that a common SNP in the BDNF gene (rs492361, a SNP in close linkage disequilibrium with rs6265) was associated with a greater risk of ever having smoked and a greater risk of both all-cause mortality and cardiovascular mortality (23). In addition, the BDNF rs6265 SNP was associated with a greater risk of CVD among subjects studied in the CARDIoGRAMplusC4D consortium studies (OR: 1.04; 95% CI: 1.02 to 1.06; $p = 8.3 \times 10^{-4}$) (24,25). Together, these data suggest that exposure to tobacco smoking may be causally associated with an increased risk of both all-cause and cardiovascular mortality, and with an increased risk of CVD events. These data must be interpreted with caution, however, because both BDNF SNPs studied are also associated with increased body mass index (22,24). Because of the pleiotropic effect of these SNPs, it is not possible using the available evidence to determine how much of the association between these BDNF SNPs and the risk of CVD and totality mortality is mediated by smoking and how much, if any, may be mediated by their effect on body mass index.

CSE may also cause CVD through epigenetic effects. The best understood epigenetic effect is DNA methylation, a covalent modification that occurs predominantly at cytosines followed by guanines (CpG dinucleotides) (26). CSE is one of the most powerful environmental modifiers of DNA methylation (27), and is strongly associated with a pattern of DNA

methylation at distinct loci that can reliably distinguish between smokers and nonsmokers (18,26,28-30). In recent epigenome-wide association studies, CSE was strongly associated with hypomethylation of a CpG site in the protease-activated receptor 4 gene (F2RL3). The protease-activated receptors (PAR-1 and PAR-4) are important mediators of thrombin-induced platelet aggregation and are the targets of antiplatelet agents that have been shown to reduce acute cardiovascular events or are currently in development (31,32). CSE-related hypomethylation of the F2RL3 gene may lead to overexpression of the PAR-4 receptor, rendering smokers more vulnerable to thrombin-induced platelet aggregation, and thus providing a mechanistic link between CSE and an increased risk of acute thrombotic cardiovascular events. Indeed, F2RL3 hypomethylation was found to be strongly associated with increased cardiovascular and total mortality among smokers with stable CHD (33).

Insights into the genetic and epigenetics of smoking behavior and the cardiovascular effects of tobacco exposure have provided an understanding of the biology and behavioral basis for smoking-attributable disease. Ongoing research is vital for the development of therapies to prevent initiation of tobacco use and for successful tobacco cessation.

TABLE 1 Polymorphisms Associated With Smoking Behavior in Genome-Wide Association Studies

Chromosome	Nearby Genes	SNP	Effect Allele	Sample Size	Effect Size (SE)	p Value
Smoking intensity: cigarettes per day						
15q25	*CHRNA3*	rs1051730	A	73,853	1.02 (0.06)	2.7×10^{-73}
10q23	*LOC100188947* (noncoding RNA)	rs1329650	G	73,853	0.37 (0.06)	5.7×10^{-10}
		rs1028936	A	72,956	0.45 (0.07)	1.9×10^{-9}
8p11	*CHRNB3-CHRNA6*	rs6474412	T	84,956	0.29 (0.05)	1.4×10^{-8}
		rs13280604	A	76,670	0.31 (0.05)	1.3×10^{-8}
9q13	*EGLN2*	rs3733829	G	73,853	0.33 (0.06)	1.0×10^{-8}
	near *CYP2A6*	rs4105144	C	83,317	0.39 (0.06)	2.2×10^{-12}
	CYP2A6 (*2 allele)	rs1801272	A	66,380	0.68 (0.18)	1.1×10^{-4}*
	CYP2B6	rs7260329	G	86,092	0.20 (0.04)	5.5×10^{-6}*
Smoking initiation: odds of starting smoking						
11p14	*BDNF*	rs6265	C	143,023	1.06 (0.01)	1.8×10^{-8}
Smoking cessation: odds of being a former smoker (former vs. current smokers)						
9q34	near *DBH*	rs3025343	G	64,924	1.12 (0.02)	3.6×10^{-8}
Epigenetic effects: DNA hypomethylation among smokers						
9p13	*F2RL3*	cg03636183		493	0.83 v.0.95	2.7×10^{-34}

*p value less than the threshold for genome-wide significance ($p < 5 \times 10^{-8}$).
SNP = single-nucleotide polymorphism.

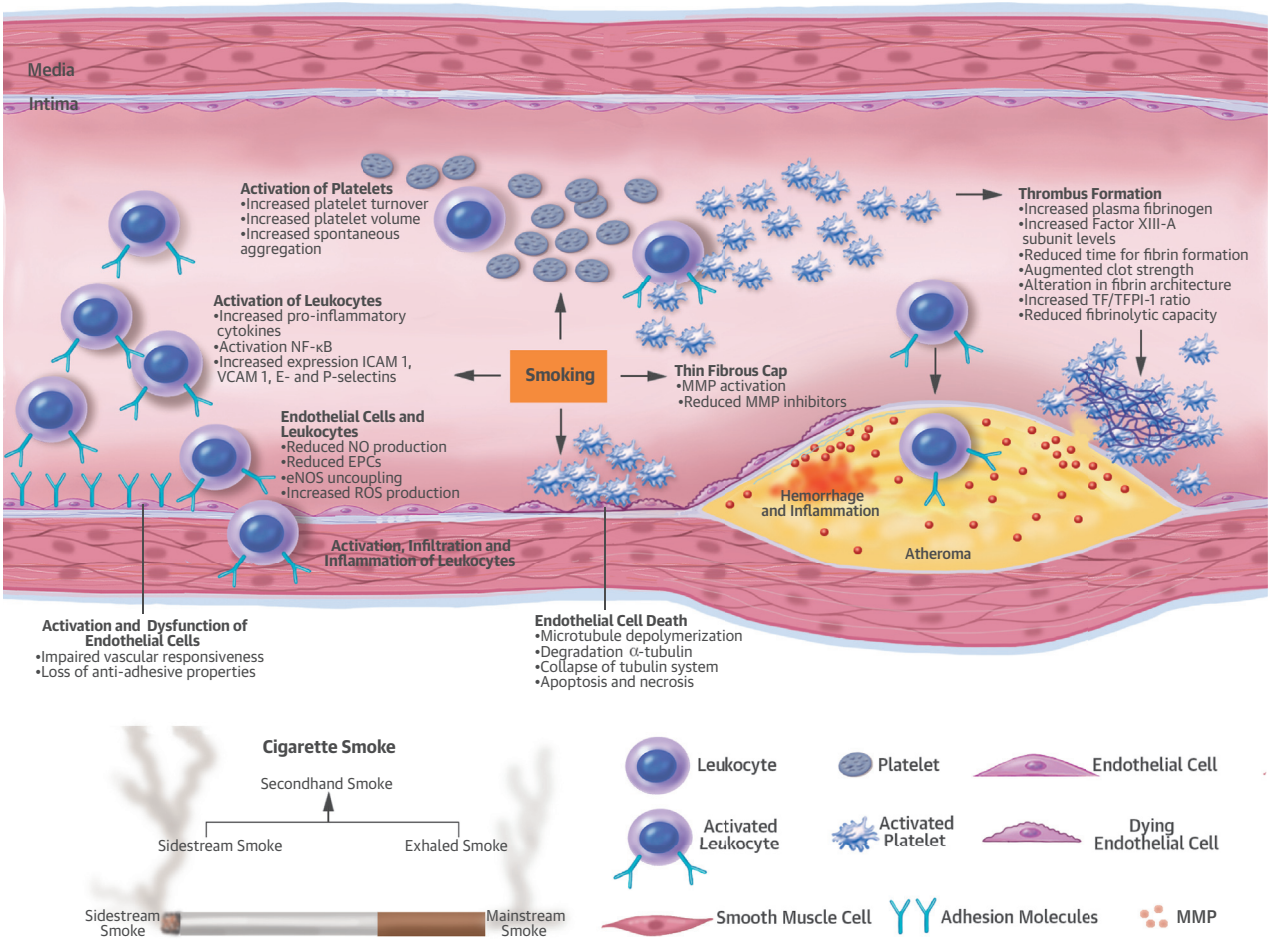
MECHANISMS OF EFFECTS OF TOBACCO PRODUCTS ON THE CARDIOVASCULAR SYSTEM

PROPERTIES OF CIGARETTE SMOKE. The adverse effects of CSE and SHS are mediated by the tar or by the particulate phase and the gas phase, which both contain significant numbers of free radicals, resulting in oxidative stress (**Central Illustration**) (2,34). Mainstream smoke is inhaled by the smoker and is comprised primarily of gaseous components (92%) and some tar components (8%). Sidestream smoke is unfiltered and emitted from the burning end of a cigarette. It contains a higher concentration of toxic gaseous chemicals (polycyclic hydrocarbons and volatile nitrosamines) than mainstream smoke, which is inhaled by the active smoker (35). SHS is the combination of the small amount of exhaled smoke from the smoker (15%) and sidestream smoke (85%) (36).

INITIATION OF ATHEROGENESIS. Both direct CSE and SHS cause vascular endothelial cell activation, dysfunction, and damage. CSE affects the endothelium through an increase in oxidative stress, with effects on endothelial cell function and structure (1). The scavenging activity of increased levels of superoxide and other reactive oxygen species produced by CSE, along with uncoupling of endothelial nitric oxide (NO) synthase, leads to NO inactivation and reduced availability of NO (37,38). CSE-induced NO depletion causes a decrease in vascular responsiveness and a loss of antiadhesive properties of the endothelium (1,36,39). Increases in macrophage and platelet activity, along with impairment in the adhesiveness of monocyte-derived endothelial progenitor cells (EPCs), may also contribute to endothelial cell activation and dysfunction (1,40). CSE induces higher expression and activity of matrix metalloproteinases (MMPs) and lower expression of the MMP inhibitors, thereby increasing the turnover of components of the extracellular matrix (41,42). Deregulation of MMP and MMP inhibitor activity may also impair neovascularization in the diseased vessel wall. Nicotine also acts directly on cellular elements participating in plaque formation via stimulation of nicotinic cholinergic receptors on the endothelium to induce pathological angiogenic processes (43,44).

CSE is also associated with damage to the structural integrity of the endothelium (1). CSE-induced oxidative stress causes microtubule depolymerization and proteasome-dependent degradation of α-tubulin. The breakdown of cytoskeletal structures and intermediate filaments result in collapse of the tubulin system and contraction of vascular endothelial cells (45,46). Furthermore, apoptosis and necrosis can

CENTRAL ILLUSTRATION **Pathogenic Effects of Tobacco: Setting the Stage for Atherosclerotic Plaque Formation**



Morris, P.B. et al. J Am Coll Cardiol. 2015; 66(12):1378–91.

Exposure to cigarette smoke and secondhand smoke (CSE/SHS) causes endothelial cell activation, dysfunction, injury, and death, leading to insudation of lipids and inflammatory cells. The activation of leukocytes results in increased release of inflammatory cytokines, activation of NF-κB, and increased expression of adhesion molecules. Increased inflammation, MMP activation, and reduced MMP inhibitors lead to the formation of rupture-prone plaques. Upon plaque rupture, CSE/SHS shifts the balance toward a pro-thrombotic milieu with platelet activation, increased spontaneous platelet aggregation, increased platelet volume, increased platelet turnover, increased plasma fibrinogen, augmented clot strength, and reduced fibrinolytic capacity. EC = endothelial cell; eNOS = endothelial nitric oxide synthase; EPC = endothelial progenitor cell; ICAM = intercellular adhesion molecule; MMP = matrix metalloproteinase; NF = nuclear factor; NO = nitric oxide; ROS = reactive oxygen species; TF = tissue factor; TFPI = tissue factor pathway inhibitor; VCAM = vascular cell adhesion molecule. Adapted with permission from Messner et al. (1) and Csordas et al. (165).

occur from the impact of reactive oxygen species and other components of cigarette smoke (38,47,48). The necrotic death of endothelial cells leads to proteolysis of extracellular matrix through the release of lysosomal proteases (49).

EPCs play an important role in the response to vascular injury and vascular neogenesis (50). The number of circulating EPCs has been shown to be inversely associated with Framingham cardiovascular risk scores (51). In chronic smokers, the numbers of circulating EPCs are significantly lowered as the number of cigarettes consumed is increased, possibly secondary to depletion from ongoing vascular injury, and smoking cessation (SC) leads to a rapid recovery of EPC levels (52). In healthy volunteers, active smoking caused a rapid and significant increase in the number of circulating EPCs, suggestive of an immediate response to CSE-related vascular injury (53).

CSE is associated with increases in inflammatory cells in the peripheral blood; increased

leukocyte recruitment to the vascular endothelium (1,54–56); augmented adhesiveness of leukocytes and platelets to the vascular wall (57); and release of pro-oxidant enzymes, such as myeloperoxidase (**Central Illustration**) (58,59). The increase in reactive oxygen species and oxidant-generating systems induced by CSE leads to both systemic and local immune system activation (60–62). Systemic inflammation is supported by increased expression of MMPs; increased levels of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-1β; and elevated serum C-reactive protein among both active and passive smokers (63–65). Activation of nuclear factor-κB promotes surface expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin, and P-selectin by endothelial cells, as well as by macrophages and platelets (66,67). Tumor necrosis factor-α and interleukin-1β maintain sustained activation of nuclear factor-κB, thereby perpetuating the inflammatory response in smokers.

EFFECTS OF CSE ON COMPONENTS OF HEMOSTASIS AND THROMBOSIS. CSE also plays an important role in shifting the balance toward a prothrombotic cellular and intravascular balance (**Central Illustration**) (68). The turnover, structure, activation, and function of platelets are strongly impacted by CSE, which causes an increase in platelet reactivity and adhesiveness. The number of newly formed reticulated platelets, a measure of platelet turnover, is elevated in smokers and is associated with an increased risk of thrombosis (69). The serum mean platelet volume is also higher in regular smokers compared with control subjects and decreases significantly at 3 months after SC (70).

CSE enhances platelet activation and spontaneous platelet aggregation (71–75). Platelets isolated from smokers exhibit a difference in the globular nature of the platelet membrane visible by electron microscopy, with surface pseudopodia being more pronounced in smokers compared with healthy individuals (76). These structural changes result in decreased platelet membrane fluidity and may cause an increase in platelet activation and aggregation (77).

Plasma fibrinogen levels of smokers are consistently higher than levels in nonsmokers (78). Factor XIII covalently cross-links and stabilizes the fibrin clot and levels of the A subunit of factor XIII are significantly increased in smokers (79). CSE is associated with shortening of the time for fibrin clot formation, augmented clot strength, and an alteration in fibrin architecture (80). Fibrin clots in smokers have thinner fibers on electron microscopy, higher clot turbidity, higher fibrin fiber density, and more uniform fiber distribution.

CSE is associated with an increase in tissue factor (TF)-containing microparticles in the circulation and in the number of tissue macrophages, the predominant source of TF in atherosclerotic plaques (81,82). CSE reduces the expression of TF inhibitor by the endothelium and increases circulating TF activity (83,84). A strong association between the number of cigarettes smoked per day and circulating TF activity is indicative of a possible dose-response relationship. TF pathway inhibitor-1 is a potent regulator of TF factor VIIa-dependent activation of the TF pathway. Smokers have a relative increase of the TF/TF pathway inhibitor-1 ratio and an increase in thrombotic potential (80).

CSE is associated with reduced fibrinolytic capacity and can adversely influence the fibrinolytic balance in the circulation (85). CSE is associated with impaired coronary release of active tissue-type plasminogen activator and a dose-related increase in plasma plasminogen activator inhibitor-1 antigen and activity (86).

CLINICAL EFFECTS OF CSE

Clinical manifestations of CSE can be observed throughout the spectrum of CVD. CSE increases myocardial oxygen demand, resulting in shorter time to the onset of angina (87). The risk of developing CHD and myocardial infarction (MI) is several-fold higher in cigarette smokers compared with nonsmokers (88,89). Compared with lifelong nonsmokers, both prior smoking and current smoking increase the risk of developing heart failure by as much as 33% to 93% (90,91). The risk does not seem to be limited to smoking tobacco products, because moist snuff has also been associated with a higher risk of heart failure (92). Among patients with heart failure, continued smoking increases the risk of multiple hospital admissions (OR: 1.82) (93).

CSE is the most important risk factor for the development and severity of peripheral arterial disease. It increases the risk of peripheral arterial disease by several-fold and is a more influential risk factor for peripheral arterial disease than for CHD (94,95). Abdominal aortic aneurysm (AAA) is the most common form of CSE-related aortic disease and the OR for development of AAA is higher than that for CHD (96,97). CSE has been associated with an increased hazard for AAA incidence among women and men who were current smokers with more than 20 pack-years of exposure (hazard ratio: 10.97 and 6.55, respectively) (98).

The association between stroke and CSE has been demonstrated in multiple studies, in men and

women of multiple ethnicities (99-101). Even exposure to environmental tobacco smoke at home during adulthood is associated with an increased risk of stroke among never-smoking individuals (100).

REVASCULARIZATION. CSE is associated with adverse clinical outcomes following percutaneous coronary intervention (PCI), particularly stent thrombosis (102-104). In the SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) trial, patients who were smoking at baseline and continued to smoke post-PCI had a significantly higher risk of stent thrombosis/graft occlusion and MI compared with those who never smoked (105,106). In the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial, smoking was an independent predictor of reinfarction, and definite stent thrombosis was responsible for 76.3% of reinfarctions occurring within 30 days and 52.0% of reinfarctions within 3 years (107). Current smoking was an independent predictor of late or very late stent thrombosis in the International Drug-Eluting Stent Event Registry of Thrombosis, with events occurring as late as 7.3 years post-PCI (108). Chronic smoking was also associated with a greater risk of definite stent thrombosis in the PLATO (PLATelet inhibition and patient Outcomes) study (109). A recent meta-analysis of 30 studies of drug-eluting stents (4,276 cases of definite stent thrombosis) confirmed that smoking was an important risk factor for stent thrombosis (110). In smokers, acute ST-segment elevation MI secondary to stent thrombosis is associated with fibrin-rich plaque that is more amenable to thrombolytic/fibrinolytic therapy than plaque in nonsmokers (84,111,112). Despite the risks associated with smoking following PCI, approximately two-thirds of patients in a large multicenter cohort of 2,765 patients with PCI remained persistent smokers following intervention and had worse disease-specific and overall health status compared with never-smokers and quitters (113).

Following coronary artery bypass graft surgery, CSE is associated with increased length of hospital stay (114). Percutaneous and/or surgical reintervention following coronary artery bypass graft is more common in smokers compared with nonsmokers (115). Gene expression of MMP-2 and MMP-9 is increased in female coronary artery bypass graft patients who are smokers or are exposed to SHS compared with female nonsmokers, and is associated with a decrease in saphenous vein graft patency (116).

Increased rates of late arterial occlusion following peripheral artery surgical revascularization have been reported in patients who continued smoking postoperatively (117-119). CSE may also be associated with an increased risk of restenosis after lower-limb endovascular interventions (120). Both endovascular and open repair of AAA are associated with poor survival and increased morbidity in patients with pre-intervention CSE (121,122). In octogenarians undergoing urgent open repair of ruptured AAA, a history of CSE was predictive of poor long-term outcomes (123).

ARRHYTHMIAS. CSE increases the incidence of both atrial and ventricular arrhythmias, possibly because of the proarrhythmic increase in sympathetic tone from epinephrine and norepinephrine release associated with nicotine exposure (124,125). The risk is proportional to the quantity and duration of smoking. CSE-induced endothelial dysfunction and inflammation are strongly associated with atrial fibrillation (AF) (126-129). Atrial fibrosis, a profibrillatory condition, has been demonstrated in human atrial tissue slices from nonsmokers cultured in the presence of nicotine base (130,131).

Several observational studies have reported on the incidence of AF in smokers. In the Rotterdam study, the incidence of AF in current and previous smokers was higher than in nonsmokers (51% and 49% increases, respectively), and was not affected by adjustment for AF risk factors (132). The incidence of AF was also higher in current and previous smokers compared with nonsmokers in the Atherosclerosis Risk in Communities study (133). Overall, smoking doubled the incidence of AF. The risk was dose-dependent and the highest smoking tertile was associated with the highest risk of AF. Smoking also increased the incidence of AF in the Manitoba Follow-Up Study (134), whereas in the Framingham study, smoking was associated with higher incidence of AF in women, but not in men (135).

In a secondary analysis from MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II), the incidence of inappropriate shocks was 20% in current smokers, 14% in ex-smokers, and 11% for never-smokers ($p = 0.03$ for the trend) (124,136). CSE also increased the risk of appropriate implantable cardioverter-defibrillator shocks caused by fast ventricular tachycardia (rate >180 beats/min) and ventricular fibrillation. In multivariate analysis, smoking increased the risk of appropriate implantable cardioverter-defibrillator shock 2-fold compared with nonsmokers.

Studies have demonstrated an increase in the risk of sudden cardiac death in smokers. In the Bezafibrate Infarction Prevention trial, the risk of sudden cardiac death was significantly increased (hazard

ratio: 2.47) in smokers compared with nonsmokers (125). Ex-smokers had no increase in the risk of sudden cardiac death compared with nonsmokers. In the Nurses' Health Study, CSE significantly associated with an increased risk of sudden cardiac death (137). This risk increased linearly with the quantity smoked and the duration of smoking. SC reduced this risk over time in a linear fashion.

SMOKING CESSATION AND SMOKE-FREE LEGISLATION

In view of the strong relationship between CSE/SHS and CVD, the elimination of this modifiable risk factor is of particular importance. Overall, there is a robust body of evidence supporting the benefits of SC in reducing cardiovascular events, overall mortality, post-MI mortality, stroke, aortic disease, and peripheral vascular disease (138,139). Considering the significant benefit of SC in reducing the risk of CVD, SC programs are quite cost-effective and have lower cost per net year of life gained compared with management of other risk factors (140,141).

The implementation of smoke-free ordinances has been used as a "natural experiment" and proxy to define the cardiovascular benefits of reduced exposure to SHS. Studies in several countries have shown that smoke-free ordinances are associated with reductions in the incidence and hospitalization rates for acute MI (3). Although there is variation in the extent of smoking restrictions, and differences in study methodology, there is remarkable consistency in results demonstrating reductions in CHD events associated with smoke-free legislation, ranging from 6% to 47%.

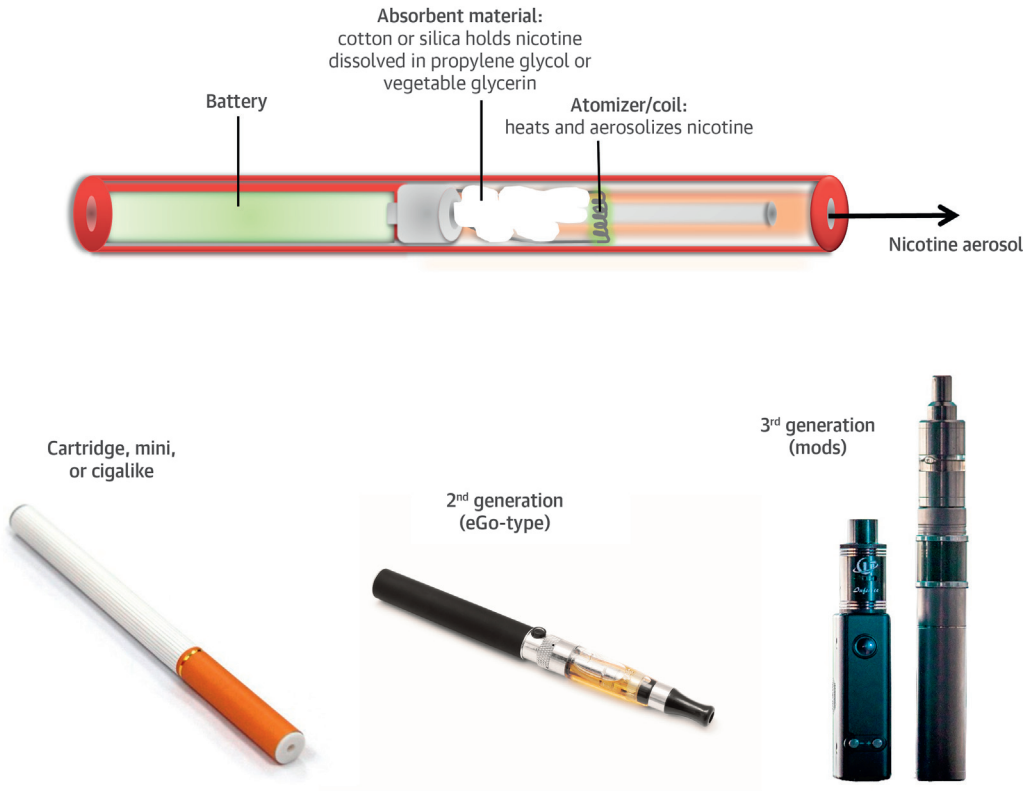
A meta-analysis of 11 reports on smoking bans found a 17% (incidence rate ratio [IRR]: 0.83; 95% CI: 0.75 to 0.92) reduction in incidence of acute MI, with incremental decreases of 26% per each year of the ordinance implementation (142). In this meta-analysis, the greatest benefit was observed among nonsmokers and younger individuals. A second meta-analysis using 35 estimates of effect size from 17 studies found a pooled estimate of 0.9 (95% CI: 0.86 to 0.94) for the relative risk (RR) of acute coronary events following the introduction of smoke-free legislation. This study did not provide analysis by smoking status. The effect was larger in studies with longer follow-up after implementation (143). There was a significant degree of heterogeneity among studies included in this meta-analysis, indicating the challenges of measuring the effects of the smoking bans; however, the results did not significantly change when adjusted for age, sex, population size, and location. A recent meta-analysis of 45 studies examining 33 smoke-free laws demonstrated that comprehensive smoking bans were associated with lower rates of hospitalization or death from coronary events (RR: 0.848; 95% CI: 0.816 to 0.881), cerebrovascular accidents (RR: 0.760; 95% CI: 0.682 to 0.846), and other heart disease (RR: 0.610; 95% CI: 0.440 to 0.847) (144). More comprehensive laws were associated with greater reductions in hospitalizations ($p = 0.001$), but the risk reduction for MI did not increase with longer follow-up ($p = 0.537$). The benefit of more comprehensive legislation was confirmed in the most recent meta-analysis of 31 studies providing estimates for 47 locations (145). Following enactment of smoke-free laws between 1991 and 2010, there was a 12% reduction in hospitalizations for acute CHD events (RR: 0.88; 95% CI: 0.85 to 0.90). Reduction in risk was greatest in locations with comprehensive legislation banning smoking in indoor places and workplaces (14%) compared with locations with only partial restrictions (8%).

CARDIOVASCULAR EFFECTS OF ECs

ECs have rapidly evolved and are marketed with of claims of health benefits compared with smoking cigarettes including for reducing and quitting smoking, for use when a person is forbidden to smoke cigarettes, and for smoking without generating irritating SHS. Despite claims, the primary health effects of concern with EC use are lung disease and CVD. ECs heat a nicotine solution to generate an aerosol that is inhaled without combustion of tobacco and its toxic combustion constituents (146,147). The devices consist of a cartridge containing liquid (propylene glycol, glycerin, nicotine, and flavorings), a heating element (atomizer), a battery, and a microchip (**Figure 2**). The main EC aerosol constituents of concern with respect to CVD are nicotine, carbonyls, and particulates.

NICOTINE. Early studies of nicotine absorption from older devices found that ECs delivered much lower levels of plasma nicotine than conventional cigarettes (148). More recent studies in more experienced users using tank-type devices with larger batteries demonstrate nicotine absorption similar to that of conventional cigarettes (149). The main health concern for nicotine in cigarette smokers is maintenance of addiction. Tobacco combustion products cause most of the adverse health effects of smoking, but some health concerns are related to nicotine per se. Many of these concerns are related to the ability of nicotine to release catecholamines, including hemodynamic effects, adverse effects on lipids, and inducing endothelial dysfunction and insulin resistance (2). Nicotine in vitro and in animal models can inhibit apoptosis

FIGURE 2 Schematic Diagram of the Elements of an Electronic Cigarette and Pictures of 3 Generations of Electronic Cigarette Devices



Electronic cigarettes consist of a cartridge containing liquid (propylene glycol, glycerine, nicotine, and flavorings), a heating element (atomizer), a battery, and a microchip. Cigalikes emulate the look of real cigarettes, although they may be slightly bigger and heavier. Second-generation electronic cigarettes resemble a pen, are bigger and heavier, and have a larger battery capacity. These allow the user to customize the e-liquid by varying flavors and nicotine strengths. Third-generation devices include mechanical mods and variable voltage devices, using larger batteries that can hold larger tanks of e-liquid. Courtesy of Dr. Gideon St. Helen, University of California-San Francisco.

and enhance angiogenesis, effects that raise concerns about the role of nicotine in promoting the acceleration of atherosclerotic disease (42,43). Nicotine in ECs has been shown to increase heart rate after overnight abstinence (150). Short-term EC use was reported to result in a small increase in diastolic blood pressure, but unlike cigarette smoking, resulted in no diastolic dysfunction and no reduction in coronary flow velocity reserve, although the devices were low-nicotine delivery devices (151,152).

The health effects of prolonged exposure to pure nicotine, as experienced in the ongoing use of ECs, are of concern. Evidence is available from studies of prolonged exposure during nicotine-replacement therapy in smokers who have quit smoking. No adverse effects were reported when nicotine medication was administered for months to several years (153). Patients with known CVD tolerate nicotine-replacement therapy well for periods up to 12 weeks (154).

The health effects of smokeless tobacco have been examined to assess potential long-term adverse effects of nicotine without exposure to combustion products. Smokeless tobacco users take in as much nicotine as cigarette smokers, although not by the pulmonary route (155). The most extensive and rigorous epidemiological studies on smokeless tobacco use comes from Scandinavia, where a large percentage of men use snus, a smokeless tobacco product that contains nicotine, but has relatively low levels of carcinogens and other toxins. Most studies report only a very small CVD risk in snus users compared with tobacco smokers (156,157). A pooled analysis of 8 prospective observational studies found that current snus use was not associated with risk of MI (hazard ratio: 1.04; 95% CI: 0.93 to 1.17). However,

the short-term case fatality rate was increased in snus users (OR: 1.28; 95% CI: 0.99 to 1.68). A recent study did find that quitting smokeless tobacco use after a MI substantially reduces mortality, suggesting a harmful effect in people with CHD (158). Thus, although adverse health effects of nicotine from ECs cannot be ignored, they are likely to be much less than those of CSE, which exposes the smoker to both nicotine and to thousands of combustion-generated toxins.

CARBONYLS. Thermal degradation of propylene glycol can generate propylene oxide, which is classified by the International Agency for Research on Cancer as a class 2B carcinogen. Heating glycerol can result in formation of acrolein, an irritant and oxidizing agent that is thought to contribute to the adverse cardiovascular effects of CSE (159). Analyses of emissions from cigarettes have found primarily formaldehyde, acetaldehyde, and acrolein, along with low levels of toluene, xylene, benzene, and butadiene (160). Although these compounds are potentially toxic, the levels in EC emissions are many-fold lower than those found in CSE. The risk of exposure to low levels of these compounds is unknown. The intense heating of tank-model ECs with large batteries results in generation of higher amounts of formaldehyde and acetaldehyde, in some cases similar to levels found in CSE (161). Formaldehyde is a carcinogen and irritant, but the cardiovascular risks of prolonged inhalation of formaldehyde at the levels found in EC aerosols are unknown.

PARTICULATES. ECs generate an aerosol consisting of fine and ultrafine particles in a gas phase. In a few reports involving a limited number of devices and liquids, the particle number and size distribution of the mainstream aerosol generated by ECs was similar to that of conventional tobacco cigarettes (162,163). The number of particles in EC aerosol is influenced by the liquid nicotine content and by puffing time, and higher levels of particles were generated by ECs containing higher nicotine concentrations (162). Particles, such as those generated by ECs, can reach deep into the lungs and potentially cross into the systemic circulation. Particles present in CSE and ambient air pollution, which have a different composition than EC particles, have been demonstrated to have adverse cardiovascular and respiratory effects in human and animal models (164). It is not known whether the type of particles generated by ECs have the same toxicity as particles present in ambient air or those generated by conventional cigarettes, but this is an important question for determining the long-term safety of ECs.

CONCLUSIONS

Since the publication of the first U.S. Surgeon General's Report in 1964, there have been significant advances in the mechanistic understanding of the effects of CSE on the function of the cardiovascular system, atherogenesis, vascular inflammation, and thrombosis, although the pace of new scientific research in this area has slowed in recent years (2). There remains great potential for further insights into individualized genetic and epigenetic components of smoking behavior and CSE-related CVDs. Public awareness campaigns and comprehensive smoke-free legislation have achieved success in reducing the initiation of smoking, increasing cessation, and reducing passive exposure to SHS in public places in the United States. However, rates of cessation have slowed in recent years and there has been an overall increase in the number of people who smoke worldwide. To further reduce global morbidity and mortality from tobacco use, it is essential to pursue knowledge of the effects of CSE on the cardiovascular system at a molecular level, to use genetic/epigenetic and mechanistic insights to develop effective therapeutic and preventive modalities for treatment of smoking behavior, and to continue development of effective and targeted public health strategies to discourage smoking initiation and encourage SC.

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