JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 12, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.07.037

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

Pamela B. Morris, MD,* Brian A. Ference, MD, MPHIL, MSC,† Eiman Jahangir, MD, MPH,‡ Dmitriy N. Feldman, MD,§ John J. Ryan, MD,‖ Hossein Bahrami, MD, PHD, MPH,¶ Mikhael F. El-Chami, MD,# Shyam Bhakta, MD,** David E. Winchester, MD,†† Mouaz H. Al-Mallah, MD, MSC,‡‡‡ Monica Sanchez Shields, MD,§§ Prakash Deedwania, MD,‖‖ Laxmi S. Mehta, MD,¶¶ Binh An P. Phan, MD,## Neal L. Benowitz, MD##

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.

The views expressed in this paper by the ACC's Prevention of Cardiovascular Disease and Early Career Councils do not necessarily reflect the views of the *JACC* or of the ACC.

From the *Medical University of South Carolina, Charleston, South Carolina; †Wayne State University School of Medicine, Detroit, Michigan; ‡John Ochsner Heart and Vascular Institute, Ochsner Clinical School-The University of Queensland School of Medicine, New Orleans, Louisiana; §Weill Cornell Medical College, New York, New York; ‖University of Utah Health Science Center, Salt Lake City, Utah; ¶Stanford Cardiovascular Institute, Stanford University, Stanford, California; #Emory University School of Medicine, Atlanta, Georgia; **Northeast Ohio Medical University College of Medicine, Rootstown, Ohio; ††University of Florida College of Medicine, Gainesville, Florida; ‡‡King Abdul-Aziz Cardiac Center, Riyadh, Saudi Arabia; §§Baylor College of Medicine, Gainesville, Florida; ‖‖UCSF Fresno, Fresno, California; ¶¶The Ohio State University, Columbus, Ohio; and the ##University of California, San Francisco, San Francisco, California. Dr. Morris has served on advisory boards for Amgen, AstraZeneca, and Sanofi Regeneron. Dr. Feldman has consulted for and/or received speaker fees from Eli Lilly and Company, Daiichi-Sankyo, Bristol-Myers Squibb, Pfizer, and Abbott Vascular. Dr. El-Chami is a consultant for Boston Scientific; has received institutional research grants from Medtronic. Dr. Benowitz has been a consultant for Pfizer, GlaxoSmithKline, and McNeil; and has been an expert witness in litigation against manufacturers of tobacco products. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Manuscript received March 15, 2015; revised manuscript received July 12, 2015, accepted July 14, 2015.

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