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A Cardiovascular Perspective of the Promises and Perils of E-Cigarettes

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Even after decades of aggressive anti-smoking campaigns, after banning cigarettes from most public places, after social de-normalization of tobacco use, and after the accumulation of extensive evidence linking tobacco products to early mortality, smoking continues to be the leading cause of preventable death worldwide, killing more than 480,000 American every year, accounting for nearly 5 million premature deaths worldwide, and costing more than \$300 billion in health care costs and lost productivity in the US alone.¹ More than 40 million American still smoke cigarettes, and globally, the number of smokers exceeds 1 billion. While it is well-known that smoking increases the risk of many diseases, cardiovascular disease is the major cause of premature mortality in smokers. The number of cardiovascular deaths due to smoking (1.69 million) far exceeds smoking related deaths from cancer (0.97 million) and pulmonary disease (0.85 million).² Yet, despite this high disease burden, we know little about the mechanisms by which smoking affects cardiovascular health. We do not know how smoking accelerates atherogenesis, promotes negative tissue remodeling or triggers plaque rupture. And we have not yet identified specific cardiovascular targets of smoking or individual constituents of tobacco smoke, responsible for cardiovascular injury in smokers.

Many consider such ignorance inconsequential. Smoking, they argue, is an entirely preventable, unhealthy choice and therefore our efforts should be directed at cessation rather than studying the harmful effects of smoking. However, for many long-term smokers, smoking is not a choice, but a compulsion of their nicotine addiction. Moreover, several risk factors such as hypertension, dyslipidemia, and obesity are linked to unhealthy lifestyle choices such as excessive salt intake, physical inactivity or overeating. Yet, we devote significant resources to studying these largely preventable risk factors. Smoking merits similar consideration. Certainly a phenomenon that affects the cardiovascular health of over 1 billion individuals deserves our utmost attention and interest.

The current exclusion of smoking from in-depth scientific study may be an unintended consequence of our success in de-normalizing smoking. Because we have succeeded in removing smoking from public view and discourse (except for regulatory and cessation-promoting purposes), it may have also contributed to the removal of smoking from serious

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scientific consideration. Few major funding agency support a large portfolio of smoking-related cardiovascular research and the little extant support there is, is far outweighed by the extent and the scope of the problem. Most clinicians and public health advocates, experiencing little smoking in their immediate environment, have paradoxically accepted smoking as an inevitable consequence of an abnormal behavior of derelict individuals at the fringe of an otherwise enlightened society of individuals with admirable self-control. But in the past few years, the tobacco landscape has changed completely. New opportunities and challenges have emerged that could radically redefine the relationship between tobacco use and heart disease, and our perception of smoking and its place in society.

This new scenario was inaugurated with the passing of the Family Smoking Prevention and Control Act in 2009, which gave US Food and Drug Administration (FDA) the authority to regulate the manufacture, distribution, and marketing of tobacco products. The Act is an attempt to prevent and reduce tobacco use in young people, and to prohibit false and misleading labeling and advertising of tobacco products. Importantly, the bill allows provisions to regulate nicotine yields of tobacco products as well as the construction, ingredients, additives, constituents, components, and properties of these products. This Act led to the creation of the FDA Center for Tobacco Products (CTP) to set performance standards, review premarket applications for new and modified risk tobacco products and to establish and enforce advertising and promotion restrictions. The CTP also funds research on topics that are important to the future of tobacco regulation. But many challenges remain. Because of our previous neglect of smoking research, we do not know which constituents, ingredients and additives contribute to the toxicity of tobacco products. As a result, we are not sure what to regulate. Moreover, because we do not know which subclinical processes contribute to the development of tobacco-induced cardiovascular disease, or which biomarkers of exposure or harm are most informative of tobacco-induced cardiovascular injury, we are not even sure how, without waiting for mortality data, which might take years, if not decades to emerge, we will assess whether any potential new regulations have reduced harm or increased injury.

The implications of this paralyzing uncertainty have been made more profound by the advent of new nicotine delivery devices such as electronic cigarettes. E-cigarettes are battery-powered vaporizers in which a heating element atomizes a solution of nicotine in glycerol or propylene glycol. Often flavors are added to increase palatability. Because e-cigarettes aerosolize a solution of nicotine by heating, many tobacco constituents are absent and the generation of combustion products is minimized. They produce no carbon monoxide, little tar, and only trace levels of carcinogenic nitrosamines – such as nicotine-derived nitrosamine (NNK) and N-nitrosornicotine (NNN).³ Bolstered by this favorable profile, and believing that much of the toxicity of conventional cigarettes is derived from combustion products and tobacco constituents other than nicotine, some argue that e-cigarettes are much less harmful than conventional cigarettes.^{4, 5} They believe that the use of e-cigarettes could meaningfully lessen the burden of smoking related death, disease, and disability. Convinced of this view, they encourage current smokers to switch to e-cigarettes. The message seems to be sticking. The sales of e-cigarettes has sky rocketed. All major tobacco companies have started producing e-cigarettes. Vape shops have mushroomed all over the country, covering all market niches. Profits have doubled every year for the last

three years and the industry is expected to be worth \$10 billion by 2017. A fringe phenomenon has become mainstream.

Reasons underlying the successes of the e-cigarette industry remain unclear. Users offer many reasons why they have taken to e-cigarettes. Some use e-cigarettes because they believe that these devices are less harmful than conventional cigarettes, while others use them to circumvent clean air laws, to vape in places where smoking is prohibited, or to prevent secondhand exposure to those near them. Many smokers use e-cigarettes to quit smoking. They believe that e-cigarettes can help them wean-off conventional cigarettes. Weak data from surveys, personal testimony and randomized trials⁶⁻⁸ are cited to support the notion that e-cigarettes are at least as effective as conventional nicotine replacement therapy and could help some individuals kick their smoking habit. E-cigarette manufacture implicitly, and often explicitly, promote this view, marketing their products as potential cessation devices.

Some view such developments with enthusiasm. Convinced of the favorable emission profiles of e-cigarettes, their wide public acceptance, and their potential as cessation devices, they believe that widespread use of these devices might decisively banish the scourge of smoking from our society and ease the heavy toll of misery, disease and death^{9, 10} that cigarettes have extracted from those who succumb to their addictive attraction. They expect that adults and children would use e-cigarettes as a gateway out of smoking, not into it. They imagine a future in which combustible products are obsolete and those addicted to nicotine feed their habit with rather innocuous vaporizers, a future where the rates of heart disease, cancer and COPD have plummeted and even those addicted to nicotine live long, healthy lives.

Others are less persuaded by this utopian view. They point out that direct rigorous evidence showing that e-cigarettes are less harmful than conventional cigarettes is lacking and that better quality data are needed to conclude that e-cigarettes are effective cessation devices. They worry that the e-cigarette emissions contain harmful levels of fine particles¹¹ and toxic aldehydes^{12, 13} that have been linked to a majority of the harmful non-cancer effects of conventional cigarettes.¹⁴ They fear that acceptance of e-cigarettes might renormalize smoking, promote dual use, and increase nicotine dependence by enabling use in places where smoking is banned.¹⁵ They are alarmed by the rapid rise of e-cigarette use in youth, even in those who have not used a nicotine product before^{16, 17} and they are concerned that the use of a plethora of flavors and additives¹⁸, which have not been tested for safety as inhaled chemicals, could lead to new diseases such as the “popcorn lung”¹⁹ or attract children and youth to a dangerous, lifelong addiction to nicotine. They do not believe that nicotine is innocuous and cite extensive literature documenting that nicotine is a strong vasoactive drug, responsible for the variety of hemodynamic effects of smoking such as an increase in blood pressure and heart rate,²⁰ and that it might be responsible for triggering acute cardiovascular events in smokers. They raise the possibility that decreased harm by reduced e-cigarette emissions may be offset by increased use. They point out that the dose-response relationship between smoking and cardiovascular mortality is non-linear, in which most (80%) of the harm is incurred at low dose of exposure (<3 cigarettes per day),²¹ therefore reduction in harmful or potentially harmful substances in e-cigarettes may not

result in proportional harm reduction. While proponents of e-cigarette dismiss the idea, opponents fear that e-cigarette use could act as a gateway to the use of other more harmful drugs. Most importantly, they are wary of Big Tobacco. They refuse to believe that Big Tobacco is manufacturing e-cigarettes for altruistic purposes of reducing nicotine addiction and harm.¹⁴ Moving forward, they are looking back to years of lies, deception and cover ups by the Tobacco industry and their repeated attempts to deny that cigarettes are addictive and to develop “safer” products such as low-tar cigarettes that turned out to be no safer than previous products. They question the newly acquired harm reduction attitude of Big Tobacco when it continues to “offer a cornucopia of child friendly flavors familiar at preschoolers’ birthday parties.”²²

So, is there a path forward? Can opposing camps reconcile and support policies and regulation that would be widely accepted by the public? For now this seems difficult. The field has become increasingly polarized and e-cigarettes have been the subject of many sharp, and sharply contested, debates among public health advocates. In the UK, Public Health England has declared that e-cigarettes are 95% safer than regular cigarettes.²³ Some believe that the promulgation is flawed²⁴ and confusing²⁵ because it replaces opinions with evidence, and that it is deceptive because, by putting a specific number, it conveys a sense of accuracy and knowledge, which are currently lacking. Moreover, it assumes that 95% of the harmful effects of e-cigarettes are due to combustion products, and that nicotine and residuals toxic compounds and particles, present in e-cigarette aerosols, contribute to less than 5% of the toxicity of conventional cigarettes, which is unlikely to be the case. While it is understandable that this is one of the incidences in which we have to adopt a well-reasoned stance, even in the absence of relevant evidence, we cannot abandon our commitment to evidence-based policy making or offer opinions at odds with extant knowledge. Hence, for now, it might be more prudent to acknowledge ignorance, which has resulted from our failure to consider fully the complexities of the health effects of tobacco and tobacco-related disease.

As we wait for the relevant evidence to emerge, we have to find ways to regulate marketing, youth access, and labeling; to prohibit free sampling; and to set standards for contamination.²⁶ At the very least, device characteristics should be regulated to minimize the risk of fires and explosions¹⁴, and bottles containing nicotine should have child proof packaging to prevent accidental swallowing or exposure. Importantly, companies should not be permitted to claim that their devices are cessation aids unless they present rigorous, convincing data supporting their claims.^{14, 26} Such minimal regulations would ensure that the use of e-cigarettes does not result in unintended harm and that manufacturers in their enthusiasm to promote e-cigarette sales, do not compromise safety, overstep the boundaries of currently available evidence, or erode years of public health gains in de-normalizing tobacco use. Going forward, we must reevaluate the relationship between tobacco and disease, understand how tobacco products inflict injury, which ingredients, components and constituents contribute to this risk, and which specific biomarkers can be followed to estimate harm and exposure. We have to resolve these issues, not only for e-cigarettes, but also for other tobacco products such as hookah, cigars, cigarillos and smokeless tobacco as well. We have to locate, with clarity, where e-cigarettes are within the current tobacco landscape and we have to agree on larger, more profound questions regarding the social

acceptance of nicotine addiction and its potential health effects. Whatever we choose to do, we have to proceed urgently, but with care, caution and responsibility, because over the next decades, our actions could impact over a billion lives.

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