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Cardiovascular Effects of Electronic Cigarettes

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Standfirst

Available literature suggests that electronic-cigarettes, although not without risk, may decrease cardiovascular risk in chronic tobacco cigarette smokers who switch. To simultaneously safeguard our youth, laws regulating electronic-cigarettes sales must be strictly enforced with criminal prosecution. Electronic-cigarettes must be required to meet product standards, and all flavors must be banned.

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.
Robert Frost

Not long ago a hand-held device was released on the market that provided aerosolized nicotine. The accompanying literature stated encouragingly that it, “Keeps your hands busy – you can twirl it, tap it, pinch it…[and] use it to stop smoking.” However, smokers and non-smokers alike took little notice of this product, and it never caught on. It was 1997, and the device, of course, was the nicotine inhaler. In clinical trials of the nicotine inhaler, only occasional palpitations, but no serious cardiovascular events, were reported.

Fast forward to 2020. We are faced with two major tobacco-related public health crises. First, the ongoing devastation wrought by tobacco cigarettes (TCs), which kill half a million Americans annually, and second, the rising prevalence of electronic-cigarette (EC) “vaping” among our youth, with 30% of high school seniors reporting EC-vaping in the previous month. We are at a regulatory and legislative crossroads: Should we ban ECs outright, as many public officials and medical societies have advocated? Or, similar to the approach in Britain, should we embrace ECs as a replacement for TCs in a harm-reduction approach? Data and science must inform our decision of which road to take, thus, this review of the science is timely.

It would be naïve to equate emissions from the nicotine inhaler with those from an electronic cigarette, since the former consists of unheated pharmaceutical-grade nicotine particulates and inactive menthol flavoring,

while emissions from ECs consist of particulates generated by heating solvents, flavorings, and contaminants. ECs remain largely unregulated and highly variable. For example, over 7000 different flavors are reportedly on the market. Nonetheless, the toxicants and carcinogens detected in people who use ECs are similar to those who use FDA-certified nicotine replacement therapy (NRT), and are vastly lower than those in TC smokers. That is, except for one – nicotine, the highly addictive constituent in EC aerosol.

Cardiovascular effects of non-combusted nicotine have been studied in smokers using oral or transcutaneous NRTs to quit smoking. Short term NRT use has not been associated with increased risk of major cardiovascular adverse events, except for a rare occurrence of non-ischemic chest pain and palpitations. Smokeless tobacco products are associated with a modest increase in fatal myocardial infarction (MI) and may double mortality risk in those who continue to use them following an MI. Thus, although not as harmful as combusted tobacco, non-combusted nicotine-containing tobacco products are not risk free.

Nicotine is a sympathomimetic drug, increasing norepinephrine release which acutely increases heart rate, contractility, vasoconstriction, and even vasospasm and may trigger acute coronary ischemia and even lethal arrhythmias. Emissions from most ECs, like TCs, also contain nicotine. Of concern, EC-vapers compared to non-smokers have increased cardiac sympathetic nerve activity as estimated by heart rate variability (HRV), and it is the nicotine, not the non-nicotine constituents in EC aerosol, which

underlines acute sympathetic excitation[1]. This pattern of abnormal HRV is the same pattern predictive of increased cardiovascular risk in patients with and without known cardiovascular disease.

Importantly, the pharmacokinetics of inhaled nicotine delivered by early generation ECs is quite different from TCs and more closely resembles the pharmacokinetics of NRTs, which deliver nicotine more benignly. Specifically, plasma nicotine levels rise more slowly and peak at lower levels. In a meta-analysis of autonomic cardiovascular effects of EC use, the increase in heart rate and blood pressure after acute EC vaping was significantly lower compared to acute TC smoking[2]. Importantly, the studies included in this review did not include the latest generation “pod” EC device (aka JUUL) in which nicotine, in the form of nicotine salts, leads to alveolar nicotine delivery. Alveolar nicotine absorption from the pod-EC replicates the pharmacokinetics of nicotine from TCs, and the steep increase in plasma nicotine is likely accompanied by augmented cardiovascular effects.

Not only do TC-smokers compared to non-smokers have increased overall cardiovascular risk, but they have increased sudden death risk. TC smoking prolongs ventricular repolarization, which can increase the likelihood of lethal ventricular arrhythmias, especially in the setting of ischemia. Nicotine has been shown to block potassium channels in ventricular myocytes, which may be the underlying mechanism. Acute TC smoking prolongs key ECG indices of ventricular repolarization, but EC vaping effects on ventricular repolarization were significantly less, despite

similar increases in nicotine[3]. These findings may implicate the non-nicotine toxicants in TC smoke in mediating the acute adverse cardiovascular effects.

The evidence of acute effects of ECs, summarized thus far, suggests that acute EC vaping induces acute adverse cardiovascular effects, such as increasing sympathetic nerve activity, heart rate and blood pressure, and acutely prolongs ventricular repolarization, thereby potentially triggering adverse acute cardiovascular events. These acute effects with EC vaping are significantly less than those with TC smoking. Importantly, effects of the pod-EC on these adverse effects have not yet been reported.

In addition to acute adverse effects, TC smoking also has chronic adverse cardiovascular effects, for example, premature atherosclerosis mediated by the ongoing, low-grade oxidative stress and inflammation attributed to constituents in TC smoke. When TC smokers use an EC acutely, plasma markers of oxidative stress increase acutely, but this increase is less compared to smoking a TC[4]. However, chronic elevations in plasma markers of oxidative stress and inflammation have not been reported in chronic EC vapers, perhaps reflecting the insensitivity of these biomarkers[1]. With the approach of flow cytometry paired with fluorescent probes to measure immune cell subtypes and their cellular oxidative stress content in otherwise healthy young people, a significant, reproducible, ordered increase in pro-inflammatory monocytes and lymphocytes and their cellular oxidative stress content, was found: lowest in non-smokers, intermediate in EC vapers, and highest in TC smokers[5]. These findings were most striking in pro-

inflammatory monocyte subpopulations that play an important role in the pathogenesis of inflammatory atherosclerosis, and may portend an increased risk of premature atherosclerosis in otherwise healthy young people who chronically vape ECs. However, cellular oxidative stress was lower in EC-vapers compared to TC-smokers, a finding that warrants additional investigation to determine if switching to ECs may be beneficial as part of a harm-reduction strategy.

Atherosclerosis is now recognized to be an inflammatory disease[6]. When viewed from an integrative biological perspective, inflammatory atherosclerosis has been recognized to be part of a signaling network called the “Splenocardiac Axis”[6]. Evidence supports the concept that the brain (amygdala), autonomic nervous system, and hematopoietic tissues (bone marrow and spleen) are linked in the development of atherosclerosis and MI. In this model, norepinephrine released from sympathetic nerves stimulates mesenchymal stem cells to mobilize hematopoietic progenitor cells, which migrate from the bone marrow to the spleen, where they multiply in response to growth factors. Augmented numbers of pro-inflammatory monocytes enter the circulation and reach the arterial wall, where increased monocyte recruitment coupled with pro-oxidative factors promote atherosclerosis[6]. ^{18}F-flurorodeoxyglucose positron emission tomography/computer tomography was used to compare metabolic activity in hematopoietic and vascular tissues in a small cohort of otherwise healthy young people[7]. A significant, ordered increase in inflammation in the spleen

and aorta was found: lowest in non-smokers, intermediate in EC-vapers, and highest in TC-smokers. These findings are again indicative of increased risk for future cardiovascular disease in EC vapers, but this risk may be less than in TC smokers.

Abnormal endothelial function as measured by flow-mediated dilation (FMD) is present in TC smokers and is predictive of future atherosclerosis. George et al[8] conducted a prospective, randomized controlled TC to EC switch study in chronic smokers without known cardiovascular disease, and compared the blinded endpoint of FMD pre/post one month of switching. Remarkably, switching from TCs to ECs was associated with a significant improvement in endothelial function that was largest in those who were most compliant with the switch. Interestingly, similar vascular benefit was observed when the smokers switched to ECs with nicotine and ECs without nicotine, implicating toxic non-nicotine constituents (“tar”), rather than the nicotine, in TC smoke as instigators of endothelial damage. Carnevale[4] was the first to show that acute EC vaping compared to TC smoking was associated with a less severe acute endothelial impairment. We compared endothelial function in otherwise healthy young non-smokers, EC-vapers and TC-smokers and found no difference in baseline FMD[9]. Importantly, acute TC smoking significantly adversely affected acute endothelial function, whereas an equivalent “dose” of EC vaping, as measured by acute changes in plasma nicotine levels, did not. Collectively, these findings suggest that ECs,

although not harmless, may have a role in a harm reduction strategy in chronic TC-smokers.

Decades ago, the FDA approved an inhaled aerosolized menthol-flavored NRT as a smoking cessation strategy. Today we find ourselves in the midst of an epidemic of never-smoking youths vaping highly addictive, nicotine-containing, flavored ECs. ECs have been shown to increase oxidative stress and inflammation, and to increase sympathetic activation, although to levels less than TCs. The potential for future adverse cardiovascular events in this group is alarming. On the other hand, TCs kill half the people who use them, and there is accumulating scientific evidence that switching from TCs to ECs is beneficial, with the potential to avert an estimated 1.6 to 6.6 million American premature deaths in the next decade[10]. The regulatory road we now take will have repercussions for public health for decades to come. A middle road, which includes 1) a requirement that ECs meet product standards and safety requirements, with full disclosure of all ingredients subject to premarketing and postmarketing FDA testing, 2) a complete flavor ban, and 3) strict laws regulating EC sales, enforced by criminal prosecution, may make all the difference.

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