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Vaping Instead of Cigarette Smoking: A Panacea or Just Another form of Cardiovascular Risk?

Running title: Cardiovascular Risks of Electronic Cigarettes

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Brief Summary

Indicators cardiovascular risk, including oxidative stress, inflammation, and sympathetic excitation, are associated with electronic cigarette(EC) vaping, but are generally less than tobacco cigarette(TC) smoking. While ECs may once have held promise as part of a harm reduction strategy, this role has been offset by the unconscionable marketing to our youth, and a failure of regulation and enforcement. ECs may yet have a role in smoking cessation, but only if these significant drawbacks can be addressed.

Abstract:

Since 2007, the electronic cigarette(EC) with its increasingly diverse array of device options has gained popularity, both among long-term tobacco cigarette(TC) smokers and among never-smoking youth. The absence of a number of known toxic byproducts of TC smoking has helped cultivate the perception that ECs are healthy. However, an expanding literature has provided concerning evidence that a number of EC constituents, including nicotine, and their thermal degradation byproducts, may have adverse effects, including cardiovascular effects. In this review, we discuss the cardiovascular risks associated with EC vaping, and compare this risk profile to TC smoking. Acknowledging the dynamic nature of EC vaping, we will focus on the latest developments, including the introduction of the pod-like device, which is the most popular EC device used today. We will discuss the implications of a new, unique nicotine chemistry, which mimics the efficient and addictive nicotine delivery of TCs. Further, we will touch on the outbreak of the lethal lung disease associated with ECs, which exposed the lack of quality control in the EC “industry”. Along the way, we will identify the limitations of current knowledge and provide suggestions for future research. Overall, we conclude that although ECs may once have held promise as part of a harm reduction strategy in people who smoke lethal TCs, this role has been offset, largely by the unconscionable marketing to our youth, in addition to a failure of regulation and enforcement, leading to significant harm, especially in never-smokers who use them.

Keywords: Tobacco cigarette; electronic cigarette; smoking; vaping; cardiovascular risk; cardiotoxicity.

Introduction

Tobacco cigarette (TC) smoking remains a leading cause of preventable cardiovascular morbidity and mortality around the globe. In fact, by 2030, TC smoking is projected to account for an estimated 8 million deaths annually worldwide, and the majority of these deaths will be from cardiovascular disease[1]. In the United States and Canada, due to strong legislation that limits and heavily taxes TC sales, ongoing public health campaigns, and several pharmaceutical and behavioral interventions to help smokers quit, TC smoking prevalence has never been lower. Nonetheless, up to 16% of adults in North America still smoke, a proportion that has not decreased in recent years [2, 3]. Thus, additional, effective, anti-smoking strategies are needed [4, 5].

In 2007, the electronic cigarette (EC) was introduced to North American consumers as an alternative to TC smoking [6]. Although EC devices have evolved dramatically since the introduction of the very first EC device that resembled a TC, all ECs have several features in common. All ECs are handheld gadgets comprised of a battery, a cartridge containing an e-liquid, and an atomizer, which contains the heating element. When the user activates the heating element – usually by puffing on the mouthpiece, the e-liquid is heated, without combustion, converting it to an aerosol, which the user then inhales [7]. The e-liquid typically consists of solvents – usually

propylene glycol (PG) and vegetable glycerin (VG), flavorings and nicotine, although this is not obligatory [8]. Since there is no combustion, EC emissions do not contain carbon monoxide. In fact, as detailed below, constituents in EC emissions contain far lower levels of toxicants compared to TC smoke, and thus could be perceived as a less harmful alternative to TCs for chronic smokers unable or unwilling to quit. Unfortunately, far from serving as a panacea used only as a smoking cessation device, ECs are mostly used by TC smokers who continue to smoke TCs ("dual users"); 55% of EC users are dual users[9]. Alarmingly ECs are also used in epidemic numbers by our youth, who are never-TC smokers[10, 11]. The question remains, what are the long-term cardiovascular risks associated with EC vaping, and how do these risks compare to TC smoking?

Since our last review [12], there have been several developments making this review especially necessary and timely. We will briefly summarize the findings from our earlier review, and will then emphasize the latest scientific studies that shed light on the relative cardiovascular risks attributable to EC vaping and TC smoking. Additional new topics to be covered include: 1) The introduction and skyrocketing popularity of pod-like EC devices (e.g. JUUL) with their tremendous appeal to our youth. 2) The potential implications of nicotine salts, which allow the delivery of nicotine into the alveoli of the EC user, where it is rapidly absorbed and delivered within seconds to the brain, mimicking the efficient and especially addictive nicotine delivery profile of TCs. 3) The emergence of "Electronic-cigarette, or Vaping, product use

Associated Lung Injury" (EVALI), the life-threatening pulmonary disease which led to significant morbidity in almost 3000 people including 68 deaths in the US[13].

Mechanisms of Cardiovascular Risk Associated with TC Smoking

The pathophysiologic links between TC smoking and clinical cardiovascular disease are well-known, and are summarized in Figure 1 [12, 14]. Decades ago, recognition that nicotine is powerfully addictive led to the insight that "people smoke for the nicotine but die from the tar" – referring to the over 7000 non-nicotine constituents ("tar") in TC smoke that are major contributors to cardiovascular, pulmonary, and oncological pathologies[15]. In the context of comparing TC smoking to EC vaping, cardiovascular risks may be best divided into effects attributable to nicotine and those attributable to non-nicotine constituents in TC smoke.

Nicotine, although not a carcinogen, is sympathomimetic. Increased sympathetic tone is known to increase cardiac risk through many potential mechanisms (Table 1), , including increased heart rate (HR) and blood pressure (BP), vasospasm and arrhythmias, and may contribute to inflammatory atherosclerosis [12, 16] . The sympathomimetic effects of nicotine from TC smoking may contribute to the risk of ischemic events as well as arrhythmias – and even sudden death[17]. Non-nicotine constituents are the primary instigators and drivers of oxidative stress and inflammation, which lead to endothelial dysfunction and damage, atherosclerosis, thrombosis, and lipid abnormalities[18]. These adverse effects interact, precipitating acute

myocardial ischemia and infarction, and sudden cardiac death [17]. Although nicotine replacement therapies (NRTs), including gum and patches, are generally thought to be safe (discussed below), the pharmacokinetics of NRTs are vastly different from the pharmacokinetics of nicotine delivered by TCs. Of concern, the pharmacokinetics of nicotine salts delivered by the latest generation of EC devices mimic the pharmacokinetics in TC smoke. Additionally, ECs, unlike NRTs, do not just deliver nicotine; EC emissions also contain low, but detectable, levels of non-nicotine toxicants. Thus, the cardiovascular risks associated with the nicotine and non-nicotine constituents in EC emissions will be reviewed.

Electronic Cigarette: The Evolution in Devices and Nicotine Delivery

Since their introduction in 2007, the EC device has evolved, and these changes in device features have been categorized into four generations of EC device. The differences in design features between the different generations of ECs are depicted in Figure 2 [19]. Briefly, first generation devices resembled traditional TCs and in fact were called “cigalikes.” However, the bioavailability of nicotine dispensed by these devices, which was largely absorbed through the oral mucosa, was poor, and plasma nicotine levels increased slowly, and peaked at low levels – far below those in TC smokers. Second and third generation devices soon followed, which had two major advances: 1) larger, variable voltage batteries, leading to increased power and temperature, and 2) larger e-liquid reservoirs. Both of

these features resulted in large plumes of EC aerosol per puff, and more efficient, and satisfying, nicotine delivery.

Finally, the fourth generation pod-like EC device has two further advances. First, the pod-like EC device capitalizes on a novel development in nicotine chemistry: alkalinized nicotine salts[20]. Raising the pH permits a very high concentration of nicotine in e-liquid, which, when aerosolized, is absorbed in the alveoli. Thus, it takes only seconds from the time alkalinized nicotine is inhaled to its absorption in the pulmonary circulation, and then its rapid delivery into the central nervous system, mimicking the nicotine pharmacokinetics of TCs that favor addiction. This efficient nicotine pharmacokinetic profile is critical for increasing the acceptance and success of ECs as TC smoking cessation devices compared to other NRTs. Further, this efficient nicotine delivery may be accompanied by a decrease in exposure to non-nicotine toxicants, since smokers titrate tobacco product use to a certain nicotine level [21]. On the downside, this addictive nicotine delivery profile may be more likely to hook young, non-smokers who are experimenting. Further, we must recognize that nicotine, in addition to being addictive, has cardiovascular effects, which must be considered. In summary, the net effects on the cardiovascular system of fourth generation pod ECs in which escalating nicotine delivery is accompanied by diminishing non-nicotine toxicants, remains an opportunity for further research.

Nicotine Effects on the Cardiovascular System

Nicotine delivery systems, including NRTs, smokeless tobacco, ECs and combusted tobacco, can be ranked within a pyramid of cardiovascular harm, stratified by potency of nicotine delivery and the accompanying non-nicotine toxicants (Figure 3) [22]. Our understanding of the impact of nicotine without the confounding effect of non-nicotine combustion products is largely through clinical trials of pharmaceutical NRTs as well as population studies of smokeless tobacco, including both chewing tobacco and snus.

Amongst the nicotine delivery systems, NRTs are thought to confer the lowest cardiovascular risk, that is, the tip, of the pyramid of cardiovascular harm (Figure 2) [22]. In a meta-analysis of 21 RCTs comparing NRT to placebo, Mills et al reported an increased risk for all cardiovascular events, but this increase was largely driven by less serious events such as palpitations and tachycardia[23]. Importantly, when only major adverse cardiac events were considered, NRTs did not increase cardiovascular risk even in smokers with known cardiac disease. In contrast, smokeless tobacco (ST), another form of non-combusted nicotine delivery, is thought to confer greater cardiovascular risk, and may best be positioned in the middle of the pyramid of cardiovascular harm (Figure 2). Piano and colleagues performed a meta-analysis of 11 studies in US and Europe, and found a small but significant increased risk for major adverse cardiovascular events, specifically fatal myocardial infarction (RR1.13; 95% CI 1.06-1.21)[24]. Further, continued snus use compared to snus cessation in myocardial infarction survivors conferred a 50% greater 2-year mortality[25]. Combusted tobacco products, with their

high nicotine potency and 7000 non-nicotine constituents are unrivaled as having the greatest cardiovascular risk; TCs kill half the people who smoke them. They reside, unchallenged, at the base of the pyramid of cardiovascular harm.

Finally, we can consider where ECs might fit in this pyramid of cardiovascular risk. Unlike other NRTs, nicotine delivered by ECs is inhaled, and plasma levels increase more quickly and reach higher levels compared to NRTs. Further, ECs, which are used for pleasure, are likely to become a life-long addiction, whereas NRTs are generally recommended for short course of weeks or months. Finally, EC emissions contain non-nicotine constituents as well, and these constituents may confer additional cardiovascular risk. Thus, consistent with the latest human studies comparing TCs with ECs, the cardiovascular risks of EC may be intermediate (Figure 2).

Electronic Cigarettes: Non-Nicotine Constituents & Byproducts

Solvents and flavorings are the chief non-nicotine constituents in EC emissions. Additionally, the process of heating the e-liquid can lead to the production of thermal degradation products including carbonyl compounds, free radicals, and particular matter with additional concerns for cardiotoxic effects. The concentration of these toxicants– if detectable at all in EC emissions - are orders of magnitude lower than in TC smoke[26]. Similarly, when measured in urine and plasma, toxicants are significantly lower in EC vapers compared to TC smokers[27, 28]. While at first glance, this may be

reassuring, it must be recognized that even low levels of toxicants may be sufficient to increase cardiovascular risk. Air pollution and TC smoking burden have a non-linear relationship with cardiovascular risk[29]. For example, it has been reported that smoking 1 to 3 TCs per day increases cardiovascular risk similarly to 1-3 packs per day[29]. After all, we do not tell our TC smoking patients that is “okay” to smoke even one TC each day. The potential cardiovascular toxicity associated with major EC constituents and thermal degradation products is summarized in Table 2.

Interestingly, with the introduction of the highly concentrated nicotine salts dispensed by fourth generation pod-like devices, which do not use high temperatures and do not dispense large plumes of emission, the exposure to free radicals and carbonyls is significantly less compared to other earlier generation ECs[21].

EC Vaping Impacts Biomarkers of Cardiovascular Risk

Long-term outcome studies are needed to answer the question of whether chronic EC vaping increases cardiovascular risk, but there are none. Two cross-sectional studies have been published purporting to show an association between EC vaping and increased risk for myocardial infarction[30, 31]. The first was challenged on the grounds that the temporal relationship between EC vaping and MI was unknown[32]. It was quite plausible that TC smokers had suffered an MI, *then* switched to ECs as a means of smoking cessation, and thus were misclassified as EC vapers with an MI. Even a low incidence of such misclassifications could explain the reported association[32].

The second publication, with overlapping authorship, was required to be retracted by journal editors due to the same underlying methodological issue[31].

In the absence of long-term outcome studies, the effects of ECs on the cardiovascular system may be best understood through their acute and chronic effects on known biomarkers associated with increased cardiovascular risk. Importantly, the effects of ECs will be compared to the effects of TCs on these same biomarkers, in an effort to estimate relative harm.

Hemodynamics

The effects of acute and chronic EC vaping and TC smoking on hemodynamics were recently reported in a systematic review[33]. Acutely, EC vaping increases blood pressure (BP) and heart rate (HR), and this increase is attributable to the nicotine, not non-nicotine constituents in EC emissions[33]. Of note, in studies in which EC vaping was compared head-to-head with TC smoking, the hemodynamic effects were significantly less[33]. Unfortunately, most of the studies available for this review did not measure acute changes in plasma nicotine levels, so it is impossible to know if the "dose" of the tobacco products (ECs and TCs) was equivalent. Further, none of the studies included the fourth generation pod-like device, whose nicotine pharmacokinetics mirror that of TCs, thus further research is needed.

In contrast, chronic hemodynamics, including resting HR and BP, are similar in chronic TC smokers, EC vapers and non-smokers[33]. However in a

recent report, Fetterman et al measured BP and HR in a large group of TC smokers, EC vapers, dual users, and non-smokers[34]. These investigators reported that there was a difference amongst the groups, adjusted for confounders, in systolic BP; systolic BP was highest in dual users, lowest in non-smokers.

In summary, acute increases in HR and BP, although modest in EC vapers, could lead to myocardial supply-demand mismatch, triggering myocardial ischemia. Further, acute increases in HR and BP are indicative of sympathetic nerve activation. Abnormal heart rate variability (HRV) indicative of cardiac sympathetic predominance has also been reported after vaping an EC with, but not without, nicotine[35]. Abrupt increases in cardiac sympathetic nerve activation could in turn lead to atrial and ventricular arrhythmias, platelet activation and thrombosis, and vasospasm (Table 1). Chronically using either ECs or TCs do not seem to lead to hypertension, although further studies are needed.

Arrhythmogenicity

The risk of sudden cardiac death, elevated in TC smokers compared to non-smokers, is unknown in EC vapers. Abnormal HRV, a risk factor for sudden cardiac death in populations with and without known cardiac disease, has been reported in EC vapers compared to non-smokers[36]. Another risk factor for sudden cardiac death is abnormal ventricular repolarization, detectable on the ECG through the measurement of specific indices, including Tpeak-end (Tp-e), (Tp-e)/QT, and (Tp-e)/QTc[37]. In a recent study,

these ECG indices were compared in TC smokers, EC vapers and non-smokers at baseline, and then after acute tobacco product use[38]. There was no difference at baseline, but when TC smokers smoked only one TC, all three ECG indices of ventricular repolarization prolonged significantly. In contrast, when EC vapers vaped an equivalent “dose” of an EC with nicotine (dose estimated by change in plasma nicotine), only one of the three parameters ((Tp-e)/QT) was prolonged. The prolongation in each index of ventricular repolarization was greater after the TC smoking compared to EC vaping[38]. Importantly, the increase in plasma nicotine was similar between exposures, supporting the notion that the non-nicotine constituents in TC smoke were the key mediators of this abnormal ventricular repolarization.

In summary, although it is unknown if EC vaping is associated with increased risk for sudden death, abnormalities in risk factors for sudden death, including HRV and ventricular repolarization, have been reported, and are concerning. Abnormalities in ventricular repolarization appear to be greater after TC smoking compared to EC vaping.

Oxidative stress and Inflammation

Oxidative stress is one the major links between TC smoking and atherosclerotic cardiovascular disease [18]. The assessment of oxidative stress in EC vapers remains much more limited. A small study of otherwise healthy EC vapers compared to non-smokers demonstrated increased low-density lipoprotein oxidizability, which is a known marker for oxidative stress and accelerated atherosclerosis [39]. Carnevale et al compared the effects of acute

TC smoking with acute EC vaping in 20 otherwise healthy TC smokers and 20 non-smokers, and found increases in soluble NOX2-derived peptide and 8-iso-prostaglandin F2α in addition significant decrease vitamin E levels following EC use [40]. Of note, these changes following EC vaping compared to TC smoking were significantly less, although it is unknown if the exposures were similar since changes in plasma nicotine levels before and after smoking were not measured [40] . Finally, Boas et al used 18-fluordeoxyglucose positron emission tomography imaging in young, otherwise healthy chronic TC smokers, EC vapers and non-smokers to compare activation of the splenocardiac axis, which has been previously implicated in the development of atherosclerosis through oxidative stress and inflammation[16]. There was a continuum of increased vascular (aorta) and immune tissue (spleen) inflammation, greatest in chronic TC smokers, intermediate in EC vapers and lowest in non-smokers[16]. Biondi-Zoccai et al compared acute TC smoking, EC vaping, and interestingly, acute heat-not-burn cigarette use, on plasma markers of oxidative stress in chronic TC smokers[41]. All tobacco products increased oxidative stress, but the increases were significantly lower following EC vaping and heat-not-burn cigarette use compared to TC smoking. Unfortunately, plasma nicotine levels were not drawn, so once again, it remains unknown if the exposures were equivalent [41].

More recently, in a study using flow cytometry and fluorescent probes, cellular, rather than plasma, oxidative stress was determined in immune cell

subtypes in otherwise healthy young people: nonsmokers (n=12), EC vapers (n=12), and TC smokers (n=9) all of whom had refrained from recent smoking as verified by non-detectable plasma nicotine levels[42]. A dose-response increase in proinflammatory monocytes and lymphocytes, and their cellular oxidative stress content among the 3 study groups was found: lowest in nonsmokers, intermediate in EC vapers, and highest in TC smokers. These findings were most striking in proinflammatory monocytes which have been identified as the culprits in inflammatory atherosclerosis [42].

In summary, increased acute and chronic oxidative stress has been reported in EC-vapers. Although multiple studies support the notion that the oxidative stress burden associated with EC vaping is lower than with TC smoking, these findings collectively portend the development of premature cardiovascular disease in otherwise healthy young people who vape ECs.

Thrombogenesis

There is limited literature assessing the potential impact of ECs on thrombogenesis and potential MI risk. A study of 20 chronic TC smokers found increased platelet activation following EC vaping, which was less than that associated with TC smoking[43]. Similarly, in another study on 40 healthy participants, acute EC vaping was found to have some effect on increasing platelet aggregation, again less so than TCs [44]. Additional studies in chronic EC vapers are sorely needed.

Vascular Health

The effects of ECs on the vascular health has gained significant research interest in the past few years. Typically, endothelial function has been measured non-invasively with brachial artery flow-mediated dilatation (FMD), and arterial stiffness has been estimated with pulse-wave velocity (PWV) and augmentation index (AI). Abnormalities in these indicators of vascular health are associated with increased cardiovascular risk. In our prior review [12], we reported that acute effects of EC vaping had actually only been studied in chronic TC smokers – not chronic EC vapers[40]. Overall, these studies demonstrated abnormal FMD, PWV and AI following acute EC vaping[12]. However, in head-to-head comparison studies, acute TC smoking produced significantly greater abnormalities. Now we are able to report results from recent studies of vascular health performed in chronic EC vapers.

Fetterman et al examined these parameters of vascular health (FMD, PWV and AI) in almost 400 participants who had refrained from smoking for several hours in the Cardiovascular Injury due to Tobacco Use (CITU) cohort, including non-smokers (n=94), EC vapers (n-=36), TC smokers (n=285), and dual users (n=52)[34]. Only AI, but not PWV or FMD, was abnormal in TC smokers compared to non-smokers; importantly AI was not different in TC smokers compared to EC vapers. The authors concluded that EC vaping compared to TC smoking did not confer a lower cardiovascular risk as estimated by these non-invasive parameters [34]. Haptonstall et al compared FMD in otherwise healthy, young chronic TC smokers, EC vapers, and non-smokers, and found no difference in vascular function after refraining from

smoking for several hours[45]. However, the study reported that the FMD of chronic smokers after smoking one TC was acutely blunted, while the FMD was not blunted when chronic EC vapers vaped an equivalent dose of ECs, including the fourth generation pod-like EC (JUUL). Given a similar rise in plasma nicotine in the two arms, this study implicates the non-nicotine constituents of TCs as the culprits in causing endothelial dysfunction [45]. Importantly, in a switch study, chronic TC smokers were asked to switch from smoking combustible TCs to vaping ECs with or without nicotine. At one month, switching from TCs to ECs with or without nicotine resulted in a significant improvement in endothelial function [46].

In summary, these findings are consistent with the notion that the adverse effects on vascular health attributable to EC vaping compared to TC smoking are less, as estimated by non-invasive parameters. Further, these adverse vascular effects may be largely mediated by non-nicotine constituents in TC smoke.

Electronic Cigarettes: Effective Tools to Reduce Tobacco Cigarette Smoking?

In a recent Cochran report[47], 50 studies (26 RCT), including 12,430 participant were examined to determine the efficacy of ECIGs compared to NRTs or behavior support only as a TCIG cessation aid. In this analysis, the authors concluded with moderate certainty that nicotine ECIGs were more effective (risk ratio [RR] 1.69, 95% CI, 1.25-2.27) than certified NRTs for smoking cessation, and more effective than behavioral support (RR 2.50,

95% CI, 1.24-5.04). Additionally, adverse events associated with ECIG use were uncommon and mild. Of note, a large number of former smokers who use ECIGs to stop TCIG smoking continue to use ECIGs at one year[48]. The cardiovascular effects of lifelong ECIG use in former smokers are unknown, and remain a major public health concern. Finally, no EC manufacturer, many with ties to Big Tobacco, has applied for approval to market their device for smoking cessation purposes.

Disparities in TC smoking and EC Vaping: Public Health Implications

In the US, TC smoking is most prevalent amongst people of low socioeconomic status. Specifically, adults with low educational attainment, who are unemployed, or living below the poverty line, are more likely to smoke TCs[49]. Interesting, this is not the case for EC vaping. EC vapers are similarly represented across a range of education and household income levels[50]. More importantly, TC smokers with higher educational attainment are more likely to try ECs, and to switch exclusively to EC vaping[50]. Since ECs are believed to be less harmful than TCs, this switch, while expected to decrease TC-related morbidity and mortality overall, will exacerbate disparities in smoking-related diseases [50]. If EC vaping is adopted as part of a harm reduction strategy, care that this strategy is adopted equitably and fairly, is critical. Further, this disparity may pose challenges for observational studies reporting less harm with EC vaping compared to TC smoking, since

lower socioeconomic status is an independent risk factor for increased cardiovascular risk.

Pod-like devices and the 2nd Wave of Vaping Amongst our Youth

According to two large authoritative surveys, Monitoring the Future (MTF) and National Youth Tobacco Survey (NTTS) performed annually in American middle and high school students, vaping nicotine increased dramatically in 2013-14[51, 52]. In 2013 fewer than 5% of high school students reported having used ECs in the prior 30 days, but by the end of 2014, this percentage had tripled. Then, for several potential reasons, including anti-vaping campaigns, tighter controls, and decreasing novelty, the percentage plateaued and even decreased. Then in 2015 a new, pod-like fourth generation EC, the JUUL, was introduced to the market, and by late 2017 had captured over 50% of the market share. A recent cross-sectional survey comparing the prevalence of vaping in youths ages 17-19 in the United States, Canada and England, reported that in 2019, almost 1 in 5 high school students reported vaping nicotine in the last 30 days. The prevalence iwas significantly lower in England, where ECs sales are subject to stricter regulation and marketing[11]

The unique appeal of the fourth generation pod-like device includes its streamlined, distinctly *non-cigarette-like* appearance resembling a USB drive. Called the “i-phone of ECs”, this sleek design appeals to tech-savvy youth, and its non-cigarette-like appearance can fool even seasoned teachers and parents. The perception that ECs are harmless coupled with sweet, dessert flavors further increased appeal and popularity. Fortunately, TC smoking

continues to decline amongst high school students, so ECs appear to be a diversion, rather than a gateway, to TC smoking[53]. Of note, in early 2020 compared to 2019 in the United States, EC vaping declined significantly [52].Before we celebrate, we must realize that this still translates into over 3.6 million American middle and high school students who vape. Of further concern, although the percentage of EC vapers declined significantly in early 2020, the number of students who reported vaping every day increased, signaling an increase in nicotine addiction, likely facilitated by the efficient and addictive nicotine delivery profile in these pod-like devices.

This epidemic reflects an unconscionable marketing strategy directed at children and young adults and a failure in regulation and enforcement. Although EC sales to children under 21 years (under 19 years in Canada) are illegal in most places, this law is only weakly enforced. Again, it should be noted that in England, where EC marketing and sales are more tightly regulated, and maximum nicotine content of ECs is lower than in the United States and Canada, the prevalence of youth vaping is significantly lower[11]. Only recently have restrictions on e-liquids with youth-targeting dessert flavors gone into effect. The long-term outcome of this epidemic in youth vaping remains unclear. Will a large proportion of youths continue to vape beyond high school? What will be the long-term cardiovascular sequelae of chronic EC vaping?

EVALI: Electronic-cigarette, or Vaping, product use Associated Lung Injury

Electronic-cigarette, or Vaping, product use Associated Lung Injury, or "EVALI," is the life-threatening lung disease associated with EC vaping that emerged in the US in the summer of 2019, and which led to the acute lung injury in almost 3000 people, leading to 68 deaths [13]. EVALI ultimately has been largely attributed to boot legged or unregulated THC liquid to which vitamin E acetate was added as a thickener[54]. Inhalation of heated vitamin E acetate within the e-liquid led to severe, often irreversible, and sometimes fatal, lung damage. Although believed to be largely limited to THC liquids, this is not certain, and some EVALI cases may have occurred in persons who vaped only e-liquid with nicotine. Although there are no specific cardiac manifestations of EVALI, that such a life-threatening condition resulted from vaping ECs reminds us that ECs remain unregulated, and without any quality control. Thus, only with great caution and after exhausting all over smoking cessation strategies, should we consider recommending to our TC smoking patients that they switch to ECs. Switching to unregulated ECs, with all their promise as smoking-cessation devices, may lead to unforeseen, potentially fatal consequences. ECs, as currently marketed without quality control, are no panacea.

Conclusions

Lethal TCs are the number one preventable cause of cardiovascular death in North America. With statistical modeling techniques, it has been reported that by switching from TCs to ECs, 1.6 to 6.6 million American lives could be saved over 10 years[55]. The latest, fourth generation, ECs meet several

features desirable in a replacement for TCs, including an appealing device, alveolar nicotine delivery, minimal to absence of non-nicotine toxicants, and no combustion. However, largely due to lax enforcement of EC regulations, and an absence of quality control measures, ECs cannot be regarded as a panacea for lethal TCs. Their role as a potential cure-all has been offset by the presence of contaminants unintentionally and intentionally introduced into the liquids, which have led to significant harm and even death. Further, the direct marketing to young, never smokers, and the development of thousands of dessert and candy flavored liquids, has unconscionably attracted millions of children to try them. The long-term cardiovascular effects of EC vaping are unknown but several indicators of increased risk, including evidence of oxidative stress, inflammation, and sympathetic excitation, have been reported. Nonetheless, although not a panacea for TC smoking that kills millions of people each year, ECs may yet have a role as smoking cessation devices if these significant drawbacks can be satisfactorily addressed.

Disclosures

None

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Table 1
Adverse Effects of Sympathetic Activation on the Cardiovascular System

Ischemia	Arrhythmias
Increased Oxygen Demand	Atrial
↑ Heart rate	Premature atrial complexes
↑ Blood pressure	Atrial fibrillation
↑ Inotropy	Ventricular
Decreased Oxygen Supply	Premature ventricular complexes
Vasospasm	Ventricular fibrillation
Vasoconstriction	
Platelet activation	

Table 2
Non-Nicotine Constituents & Byproducts: Cardiovascular risks

Constituent	Potential Effect	Notes
Propylene glycol Vegetable glycerin	Deemed to be safe for oral intake May precipitate bronchospasm	Prolonged effect unknown
Metals (including lead and nickel)	Lead has known adverse effects on the cardiac conduction system and is linked to cardiovascular mortality Data linking nickel to cardiovascular morbidity is less definitive	Higher levels of metal exposure associated with shoddy workmanship and/or higher voltage battery (heating)
Byproduct	**Potential Effect**	**Notes**
Carbonyl compounds: A. Acrolein B. Acetaldehyde C. Formaldehyde	A. Acrolein has been linked to accelerated atherosclerosis, increased thrombogenicity, arrhythmias, and cardiomyopathy B. Acetaldehyde has been linked to accelerated atherosclerosis, arrhythmias, and cardiomyopathy C. Formaldehyde has been linked to increased thrombogenicity, arrhythmias, and cardiomyopathy	Emissions highly voltage dependent, higher voltage devices can lead to emissions exceeding those of TC Efficiency of nicotine delivery may be inversely related to non-nicotine toxicant exposure, since the user may be attempting to maintain a certain level of nicotine in the body
Free radicals	Accelerated	Exposure is >10x compared to air pollution, <100-1000x

	atherosclerosis	compared to TC use
Particulate matter	Accelerated atherosclerosis Increased thrombogenicity	Emissions highly voltage dependent Higher voltage devices lead to such high emissions as to even allow for passive exposure to bystanders

Figure Legends

Figure 1. Mechanisms of Cardiovascular Risk Associated with Tobacco Cigarette Smoking. In the context of comparing TC smoking to EC vaping, cardiovascular risks may be best divided into effects attributable to nicotine and those attributable to non-nicotine constituents in TC smoke. Nicotine is sympathomimetic, leading to increased heart rate (HR) and blood pressure (BP), vasospasm and arrhythmias, and may contribute to inflammatory atherosclerosis. Non-nicotine constituents are the primary instigators and drivers of oxidative stress and inflammation, which lead to endothelial dysfunction and damage, atherosclerosis, thrombosis, and lipid abnormalities. These adverse effects interact, precipitating acute myocardial ischemia and infarction, and sudden cardiac death.

Figure 2. The Evolution of E-Cigarette Devices. Since its introduction, the electronic cigarette has evolved through four generations. Major changes include increasing battery power and temperature, and more efficient nicotine delivery. In the 4th generation device, novel nicotine chemistry is used, allowing the most efficient nicotine delivery at lower temperatures, with significantly lower exposure to non-nicotine toxicants. See text for discussion.

Figure 3.The Pyramid of Cardiovascular Risk. Nicotine delivery systems, including nicotine replacement therapies (NRTs), smokeless tobacco, ECs and combusted tobacco, can be ranked within a pyramid of cardiovascular harm, stratified by potency of nicotine delivery and the accompanying non-

nicotine toxicants. NRTs have the least cardiovascular risk, and combustible tobacco products have the greatest risk. Smokeless tobacco produces and ECs likely have intermediate cardiovascular risk.

Figure 1. Mechanisms of Cardiovascular Risk Associated with Tobacco Cigarette Smoking

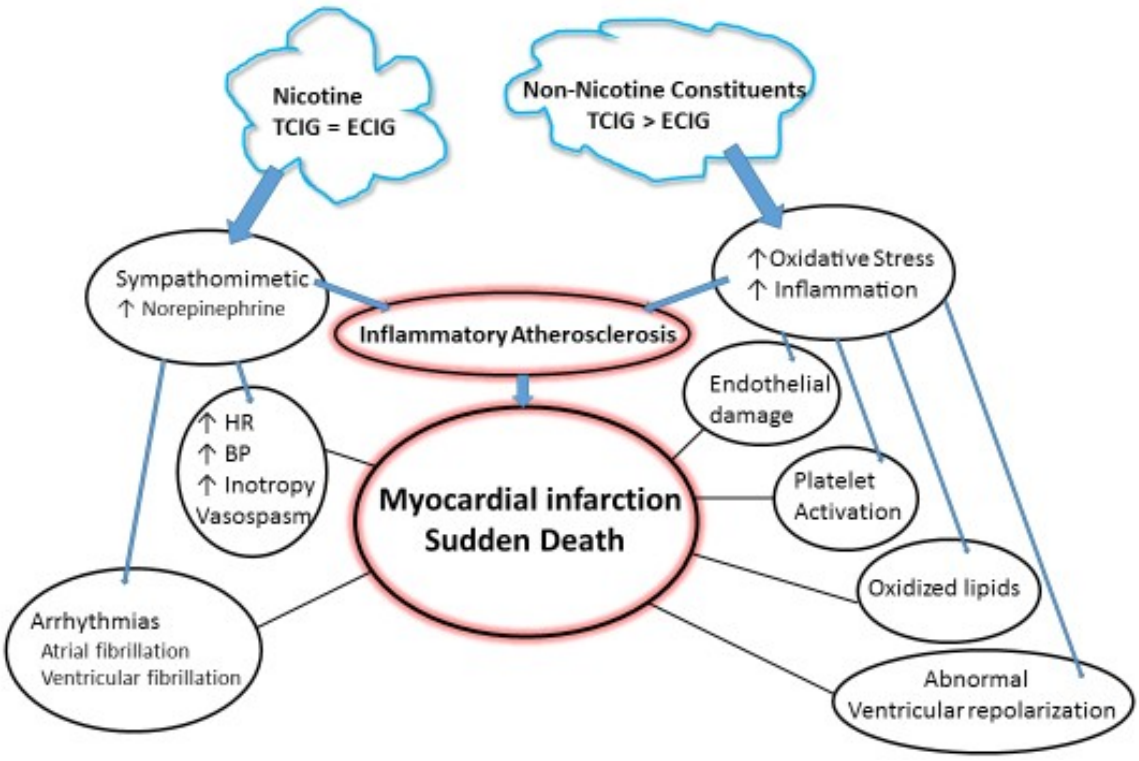

Figure 2. The Evolution of E-Cigarette Devices

Generation	Examples	Battery	Cartridge	Nicotine Delivery
1st Cigalike	 Greensmoke, Blu	Disposable or Rechargeable	Small Closed system	Poor Mucosal absorption
2nd Penlike	 eGo	Higher capacity Rechargeable	Larger Refillable	Better than cigalike Mucosal absorption
3rd Mod or Tank	 Volcano	Highest capacity Rechargeable Modifiable	Largest Refillable	Better than penlike Mucosal absorption
4th Pod	 JUUL, Puff	Disposable or Rechargeable *Not* modifiable	Small Closed system	Mimics tobacco cigarette Alveolar absorption

Figure 3. The Pyramid of Cardiovascular Risk