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Cardiovascular Impact of Electronic-Cigarette Use

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Abstract

The majority of premature deaths related to tobacco cigarettes (TCs) are attributable to cardiovascular disease, so it is fitting and timely to review the overall cardiovascular impact of electronic cigarettes (ECs), which have recently exploded onto the tobacco product market. Longitudinal studies of EC users are necessary, but not yet available, to answer the question whether cardiovascular disease is lower in chronic EC users compared to TC smokers, so we must rely on biomarker studies. Several biomarkers that portend increased cardiovascular risk, including markers of increased sympathetic nerve activity, oxidative stress and inflammation, vascular dysfunction, and thrombosis, have been reported to be abnormal after EC use, although often not to the degree found in TC smokers. We conclude that if all FDA-certified strategies for TC smoking cessation have been tried without success, then ECs may be a reasonable strategy for TC smoking cessation, but the message to non-TC smokers must be clear and unwavering: non TC-smokers should not use ECs – they are not harmless.

Electronic cigarettes (ECs) have exploded onto the tobacco product market, accounting for 3.6 billion dollars in sales in the United States in 2018. An estimated 10.8 million (4.5%) adults and 3.05 million (20.8%) high school students in the United States are current EC users, a prevalence that has been described as by the FDA as “an epidemic”(1, 2). ECs have incited impassioned and dramatically divergent reactions among the public and health care communities. On the one hand, ECs have been embraced as a potential lifesaving replacement for lethal tobacco cigarettes (TCs), which kill half of the people who use them. On the other hand, ECs have been vilified as a stealth means, promoted by Big Tobacco, of addicting the next generation to nicotine just when the endgame to TC smoking was in sight. The majority of premature deaths related to TCs are attributable to cardiovascular disease, so it is fitting and timely to review the overall cardiovascular impact of EC use, and to do this encompassing both perspectives. Afterall, the impact of ECs on cardiovascular risk may be vastly different in the middle-aged breadwinner addicted to TCs who is unable to quit, compared to the young, never-smoking high school student, who “Juuls” in the high school bathroom and sometimes, daringly, even in the classroom.

TC smoking is the most prevalent, preventable risk factor for cardiovascular disease in the United States, thus the impact of *any* strategy to decrease TC use is likely to have a favorable impact on cardiovascular mortality. Using sophisticated statistical modeling techniques to develop

"pessimistic and optimistic e-cigarette substitution scenarios," in which the estimates of the relative cardiovascular risk of ECs compared to TCs is varied, Levy *et al.* (3) estimated that replacement of TCs by ECs in the United States could yield *1.6 to 6.6 million fewer premature deaths* over 10 years(3). In Great Britain, since the introduction of ECs, the number of TC quit attempts, and importantly, *successful* TC quit attempts, has significantly increased (4).

Should physicians recommend electronic cigarettes to their patients as an effective smoking cessation strategy?

Until recently, only a few small randomized controlled trials (RCTs), using first generation ECs (less effective nicotine delivery devices compared to 2nd and 3rd generation devices), tested the effectiveness of ECs in smoking cessation. In the one available RCT in TC smokers trying to quit, 657 adult TC smokers were randomly assigned to 3 different groups: 1) nicotine (16 mg) EC, 2) placebo EC (no nicotine) and 3) nicotine (21 mg) patch. During the trial, ECs were well tolerated. At six months, verified abstinence rates in the EC groups, with and without nicotine, were similar to those achieved with the nicotine patch (range 4.1 to 7.3%, verified abstinence). In another RCT of ECs as a cessation device, 300 TC smokers not intending to quit were randomized to: 1) 12 weeks of 7.2 mg nicotine ECs, 2) 6 weeks of 7.2 mg nicotine ECs followed by 6 weeks of 5.4 mg nicotine ECs, and 3) 12 weeks of no-nicotine ECs. After 1-year follow-up the investigators reported that ECs were well-tolerated, overall TC quitting was 8.7%, and daily TC consumption

was decreased, without significant differences among the groups. Rahman *et al*. (5) performed a meta-analysis of 7,551 TC smokers using ECs for smoking cessation in 6 studies, including these 2 RCT, 2 cross-sectional studies, and 2 prospective cohort studies. Although the meta-analysis was limited by the heterogeneity of the studies, the authors concluded that ECs with nicotine were more effective than no-nicotine ECs in achieving TC quitting, and that there was insufficient data to compare ECs to certified, U.S. Food and Drug Administration (FDA)-approved cessation strategies.

Only recently have data become available consistent with the superiority of ECs with nicotine over certified nicotine replacement therapies(NRTs), each accompanied by behavioral support, for TC smoking cessation. In this multicenter, pragmatic randomized trial in which almost 900 TC smokers were enrolled, ECs were almost twice as effect as NRTs (18.0% vs 9.9%) in achieving smoking abstinence at one year, confirmed by exhaled carbon monoxide testing(6). Importantly, however, 80% of those successfully quitting TC smoking were still using ECs at 1 year, whereas only 4% in the NRT group were still using nicotine replacement products.

In summary, emerging evidence supports the concept that ECs are effective TC cessation devices, and that they are superior to certified NRTSs. However, since the majority of those studied continue to use ECs long-term, the health consequences of long-term EC use is of critical importance, yet remains unknown.

Dual use: Does reduction of the number of daily tobacco cigarettes smoked by substituting electronic cigarettes promote cardiovascular health?

Most adults (~55%) who use ECs are dual users, perhaps replacing some of their daily TCs with ECs, but still continuing to smoke TCs(2). In fact, it has even been reported that EC use perpetuates nicotine addiction and thus TC addiction, rendering dual users *even less likely* to quit TCs (7). On first glance, one might assume that a reduction in the daily TC consumption would promote cardiovascular health. Surprisingly and unfortunately, this may not be the case. Cardiovascular risk associated with TC smoking has a nonlinear relationship. That is, the cardiovascular risk conferred by smoking only 1-3 TCs a day is only slightly lower than the cardiovascular risk conferred by smoking 1-3 *packs* per day (8). (Figure 1) Thus, smoking fewer TCs per day would not be expected to decrease overall cardiovascular risk.

Interestingly, however, after quitting TCs completely, cardiovascular mortality returns to that of a non-smoker (9, 10). Thus, it has been suggested that TC smoke behaves like a drug or toxin that triggers adverse cardiac events – and once this toxin is eliminated from the system, risk of the adverse cardiac events rapidly declines. Many toxins in TC smoke, including carbon monoxide, nicotine, reactive oxygen species, carbonyls and poly aromatic hydrocarbons, may directly trigger myocardial ischemia and contribute to its immediate cardiovascular risk. Levels of all of these toxins have been found to be orders of magnitude lower, if present at all, in EC

emissions compared to TC emissions - all except nicotine. Similarly, toxicant levels in plasma or urine, if detectable at all, have been found to be dramatically lower in chronic EC vs TC users – again, all except nicotine(11). Urinary and salivary nicotine equivalents are not different in chronic TC smokers and chronic EC users (11). Thus, switching from TCs to ECs may be expected to decrease cardiovascular risk since toxicants (potential triggers) are lower in ECs compared to TCs, and may be below a threshold for increasing cardiac risk - that is, *except if the trigger is nicotine*.

What do the available data say about myocardial infarction risk in chronic TC smokers vs EC users?

Although it is widely believed that ECs are less harmful than TCs, the true cardiovascular risk of long-term EC use is not known. One large cross-sectional study purported to support the concept that daily EC use increased the odds of having a myocardial infarction, odds ratio (OR) 1.79, less than that associated with TC smoking (OR 2.72), but still significantly increased (12). The conclusions drawn from these cross-sectional data are limited, of course, since the timing of the myocardial infarction relative to EC use or TC use cannot be determined. It is conceivable that some persons classified as EC users with a myocardial infarction, actually suffered their infarct while smoking TCs, and then switched to ECs as a smoking cessation strategy. Even a 10% misclassification of these TC smokers as EC users would invalidate the conclusions of in this study (13).

In summary, longitudinal studies are necessary, but not yet available, to answer the question whether myocardial infarction incidence is lower in chronic EC users compared to TC smokers.

By what biological mechanisms might electronic cigarettes increase cardiovascular risk? (Figure 2)

Since long-term population data are not yet available to clarify the cardiovascular risk associated with chronic EC use, cardiovascular risk must be approached indirectly, by evaluating biomarkers that are predictive of cardiovascular disease in TC smokers, and then determining if these biomarkers are similarly abnormal in EC users. Increases in cardiac sympathetic activation, oxidative stress and inflammation, endothelial dysfunction, and increased platelet aggregation are examples of such biomarkers. (Figure 2, Table)

Do electronic cigarettes increase sympathetic nerve activity? (Figure 2, Table)

Numerous studies are consistent with a hyperadrenergic state in EC users(14, 15). Heart rate and blood pressure significantly increase following acute EC use(14, 16). The increases are small, however, and their clinical significance is uncertain. Heart rate variability (HRV) is another measure of sympathetic activation and autonomic balance; persistently increased sympathetic nerve activity as measured by HRV is associated with increased cardiovascular mortality (17-20). In fact, abnormal HRV reflecting

sympathetic predominance predicts increased cardiovascular risk in the setting of virtually every known cardiac disease, as well as in patients without known cardiac disease(16). Further, this increased cardiovascular risk has been demonstrated to have a dose-response relationship, with the most severe HRV abnormalities conferring the greatest cardiovascular mortality (21, 22). Abnormal HRV consistent with sympathetic predominance is associated with increased cardiovascular risk in TC smokers (16, 23). We studied a small group of otherwise healthy, chronic EC users compared to age-matched non-smoking controls, to determine if cardiac sympathetic nerve activity was similarly increased in chronic EC users. We found that HRV was abnormal in chronic EC users, consistent with increased sympathetic nerve activity (Figure 3) (15). The abnormal pattern of HRV was the same pattern that has been associated with increased cardiovascular risk in patients with and without known cardiac disease (17-22). In a follow-up study, we compared the effects of nicotine vs the non-nicotine constituents present in EC emissions, and determined that nicotine, not non-nicotine constituents acutely increased sympathetic activated as measured by HRV parameters (14).

Although exocytotic norepinephrine release from peripheral post-ganglionic sympathetic nerve endings is an important mechanism underlying the sympathomimetic effects of nicotine(24), it is unlikely the whole explanation for the hyperadrenergic state in EC users. In our study of chronic EC users in whom sympathetic predominance was present, all EC users had

abstained from EC use on the day of the study, confirmed by non-detectable plasma nicotine levels drawn simultaneously with the HRV recordings (15). This finding of a sustained hyperadrenergic effect, even in the absence of acute nicotine use, mandates that we consider pleomorphic, not just pharmacological effects, of inhaled nicotine.

Nicotinic receptors are present throughout the autonomic nervous system, including the amygdala, a brain area that integrates responses to emotion and stress (25-27). Although studies have not been done in chronic EC users, in chronic TC smokers, dysregulation of the amygdala has been reported (26-28). Amygdalar dysregulation impacts control the sympathetic nervous system, and importantly, amygdalar hyperactivity, as detected by ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET/CT), is associated with future adverse cardiovascular events (29). It is unknown if amygdalar hyperactivity is present in chronic EC users and TC smokers, in whom sympathetic nerve activity is increased, but this area of research is ongoing in our laboratory.

In summary, sympathetic activation, as measured by HRV, is present in chronic EC users, and the pattern of abnormal HRV is the same as that associated with increased cardiovascular risk in patients with and without known cardiac disease. The mechanisms by which heightened sympathetic nerve activity could contribute to adverse cardiac events in EC users include 1) acutely triggering life-threatening arrhythmias, 2) acutely triggering

ischemia, and, as will be discussed below, 3) leading to activation and progression of inflammatory atherosclerosis. (Figure 4)

Do electronic cigarettes increase oxidative stress? (Figure 2, Table)

Tobacco cigarette smoke contains abundant reactive oxygen species (ROS) that overwhelm natural defense systems; oxidative stress is likely a major mechanism by which TC smoking causes atherosclerosis (30). Oxidative stress interferes with nitric oxide generation and bioavailability, increases oxidative modification of LDL particles and therefore their atherosclerotic potential, and induces inflammatory gene activation and amplification(30). Although EC compared to TC emissions have been reported to contain lower levels of pollutants with *carcinogenic* potential(31), and therefore may be safer, EC aerosols may contain heavy metals, aldehydes, and other constituents that also have significant oxidative potential. Lerner *et al.* (32) used a semi-quantitative 2'-7'-dichlorodihydrofluorescein (DCFH) assay to measure oxidants in TC smoke and EC aerosol, and found, unexpectedly, that the range of oxidant activity present in TC and EC emissions were similar; the investigators cautioned that quantitative electron paramagnetic resonance studies are necessary for definitive quantification of radical species. In a cross-over investigation, Carnevale *et al*. (33) measured markers of oxidative stress in non-smokers and chronic TC smokers who smoked either a TC or an EC in random order. Acute TC smoking and EC use each acutely increased oxidative stress as estimated by several biomarkers, although oxidative stress was greatest

following TC smoking. Unfortunately, it is not possible to know if the EC and TC exposures were comparable (1 TC vs 9 puffs of an unspecified EC), since changes in plasma nicotine levels were not measured.

We compared susceptibility to oxidative stress in chronic EC users and non-smoker controls using the biomarker LDL-oxidizability, and found that susceptibility to oxidative stress was significantly greater in chronic EC users compared to non-users (15). Chaumont *et al.* (34) compared oxidative stress levels pre/ post use of an EC with nicotine, an EC without nicotine, or an empty EC (sham control), in order to determine whether the nicotine or non-nicotine constituents in EC emissions were responsible for increased oxidative stress. Only using the nicotine EC, not the no-nicotine EC or sham control, acutely increased plasma myeloperoxidase, a marker of oxidative stress, implicating nicotine as the culprit mediating increased oxidative stress.

In summary, a major mechanism by which TCs promote atherosclerosis is through increased oxidative stress. Although carcinogen levels in EC emissions may be lower than those present in TC smoke, significant, perhaps even comparable, oxidant species are present in EC emissions producing measureable oxidative stress. Potential for adverse cardiovascular sequelae from increased oxidative stress induced by ECs include endothelial dysfunction, inflammatory atherosclerosis, platelet activation, and plaque instability. (Figure 2)

Do electronic cigarettes increase inflammation? (Figure 2, Table)

That atherosclerosis is actually an inflammatory disease has long been accepted. Libby *et al.* (35) have proposed that inflammatory atherosclerosis can be viewed from an integrative biologic perspective, as part of a signaling network called the "Splenocardiac Axis"(35). Evidence supports the concept that the brain, sympathetic nervous system, and hematopoietic tissues (bone marrow and spleen) are linked in the development of atherosclerosis and myocardial infarction (Figure 4). In this model, increased sympathetic nerve activity initiates this Axis by activating bone marrow progenitor cells, which then migrate from the bone marrow to the spleen, where they multiply in response to stem cell factors. Augmented numbers of pro-inflammatory monocytes then enter the circulation, reaching the arterial wall, where increased monocyte recruitment coupled with oxidative stress and prothrombotic factors, promote and accelerate atherosclerosis. Activation of the Splenocardiac Axis may be a mechanism whereby the heightened sympathetic activity that accompanies TC smoking leads to increased cardiovascular risk.

In clinical studies of atherosclerosis using ^{18}F-FDG-PET/CT, increased metabolic activity in hematopoietic tissues, including the bone marrow and spleen, was correlated with vascular inflammation, and has even been shown to confer increased cardiovascular risk (35-37). Importantly, we used ^{18}F-FDG-PET/CT to measure inflammation in hematopoietic and vascular tissues in otherwise healthy chronic EC users, TC smokers, and non-smokers (38).

We found that ^{18}F-FDG uptake was significantly increased in both the spleen and the aorta in a striking linear dose-response relationship from lowest in non-smoking healthy controls, intermediate in chronic EC users, and greatest in chronic TC smokers, consistent with a graded activation of this Splenocardiac Axis. (Figure 5) These findings of increased inflammation in both the spleen and wall of the aorta support the hypothesis that the Splenocardiac Axis is activated in smokers.

In summary, human imaging studies support the concept that EC use leads to activation of inflammatory pathways, with important implications for the development of inflammatory atherosclerosis, plaque progression and instability, and acute myocardial ischemia. (Figure 2)

Do electronic cigarettes promote endothelial dysfunction and arterial stiffness? (Figure 2, Table)

Endothelial dysfunction, as estimated by impaired brachial artery flow-mediated dilatation (FMD), is an independent risk factor for cardiovascular disease. FMD has been found to be impaired in chronic TC smokers, and even non-smokers exposed to secondhand smoke (39, 40). Only one study has measured the effect of EC use on FMD, and this was an acute exposure study in non-smokers and TC smokers. Carnevale *et al*. (33) had chronic TC smokers and non-smokers smoke a single TC or inhale 9 puffs from an EC in a crossover study, and found that both TC and EC acute exposures resulted in a similar impairment in endothelial function as measured by FMD. In another acute exposure study, Chaumont *et al*. (34) compared acute use of

an EC with nicotine, EC without nicotine, and sham control on endothelial function as tested by acetylcholine-mediated dilatation, and found that only ECs with nicotine, not ECs without nicotine, acutely impaired endothelial function. Pharmaceutical-grade nicotine spray administered to TC smokers has also been found to cause acute endothelial dysfunction as measured by FMD(41).

Circulating endothelial progenitor cells (EPCs) are another marker of endothelial damage and dysfunction. Evidence supports the concept that increased oxidative stress overwhelms anti-oxidant defenses in vascular endothelial cells leading to impaired nitric oxide release and endothelial damage. In response to this acute endothelial damage, increased numbers of reparative EPCs are released from the bone marrow, and can be measured in the circulation(42). Smoking even one TC acutely increases the number of circulating EPCs, indicative of endothelial damage(43). Antoniewicz *et al*. (44) recently reported that 10 puffs from an EC similarly increased circulating EPCs, consistent with the concept that ECs, like TCs, acutely damage the endothelium. Whether the nicotine or non-nicotine constituent(s) in the EC emissions is the culprit is not yet known.

Arterial stiffness, as estimated by aortic pulse wave velocity (PWV), is another independent risk factor for cardiovascular disease and all-cause mortality (45). Aortic stiffness is increased by TC smoking, diabetes mellitus, end-stage renal disease, and hypertension, and is a strong predictor of future adverse cardiovascular events, especially in the setting of increased baseline

risk(45). Vlachopoulos *et al.* (46) compared acute changes in PWV following TC smoking and nicotine EC use, and reported both ECs and TCs acutely increased arterial stiffness to a similar degree. Chaumont *et al.* (34) compared ECs with and without nicotine and sham control, and found that only acute exposure to the EC with nicotine increased PWV.

In summary, EC use, especially an EC with nicotine, leads to acute vascular dysfunction (Figure 2). Whether this acute vascular dysfunction translates into sustained vascular dysfunction, and portends the same poor cardiovascular prognosis as chronic vascular dysfunction remains unknown. These vascular studies in chronic EC users are sorely needed.

Do electronic cigarettes promote platelet aggregation? (Figure 2, Table)

Pathological thrombus formation within the coronary artery triggers myocardial ischemia and infarction. Increased platelet activation predisposes to thrombus formation, and anti-platelet therapy with aspirin plays a key role in reducing recurrent myocardial ischemia and infarction. TC smoking increases platelet aggregation, and this increased platelet aggregation is likely a major mechanism by which current TC smoking leads to adverse cardiovascular events (30) (Figure 2). To date, only one *in vivo* study comparing the effects of acute TC smoking and EC use on platelet activation in humans has been published. Nocella *et al.* (47) found that both acute TC smoking and EC use increased platelet aggregation to a similar degree in

chronic TC smokers, but TCs compared with ECs had greater adverse effects on platelets in non-smokers. Since epinephrine induces platelet aggregation, and epinephrine is acutely released by nicotine, perhaps it is not surprising that nicotine ECs increase platelet aggregation in humans. Whether the non-nicotine EC constituents also increase platelet activation is unknown and unstudied.

Is inhaled nicotine delivered by electronic cigarettes "safe"?

Many of the potentially adverse cardiovascular effects of ECs have been found to be attributable to the inhaled nicotine. This a potentially ominous finding since plasma nicotine levels achieved with TCs and ECs are similar(11). On the other hand, since nicotine replacement therapies (NRTs), such as transdermal patches, are FDA-approved and available over-the-counter without a prescription, it is easy to become lulled into the belief that, although addictive, nicotine is relatively "safe." It is important to remember that nicotine delivered by ECs differs from NRTs in several important ways: First, unlike NRTs that are intended for short-term use, ECs are used for pleasure, and due to the powerfully addictive nature of nicotine, are likely to become a life-long habit. This means a life-long exposure to its potentially cardiac toxic effects, such as sympathetic activation. Furthermore, most NRTs use oral or transdermal drug delivery routes, and the few inhaled NRTs, such as the Nicotrol® Inhaler, carry warnings regarding the potential for inhaled nicotine to cause bronchospastic disease – *a warning absent from the patches or gum*. Inhalation of nicotine into the airways and delicate,

epithelial cell-lined alveoli may lead to adverse effects not relevant to transdermal or oral delivery, including local and systemic oxidative stress and inflammation(48). Finally, the pharmacokinetics of nicotine delivery are quite different between popular NRTs and ECs. The nicotine levels increase faster and reach higher levels when inhaled nicotine is delivered by the newer generation ECs compared to NRTs delivered orally(49, 50).

Further casting a shadow over the safety of chronic nicotine use is that non-combustible recreational tobacco products, such as snus, which deliver “clean” nicotine unaccompanied by combustible, non-nicotine toxicants, are associated with increased cardiovascular risk, albeit smaller than that associated with TC smoking. It was recently reported that snus users who have had a myocardial infarction, yet who continue to use snus, are twice as likely to suffer a subsequent myocardial infarction compared to those who quit following infarction (51).

In summary unlike NRTs, inhaled nicotine delivered by ECs, due to the differing pharmacokinetics and highly addictive nature of nicotine, may become a lifelong addiction. This prolonged exposure to inhaled nicotine may lead to unique adverse effects not seen with most certified NRTs, including chronically increased sympathetic activation, oxidative stress, systemic inflammation, with potentially dangerous clinical sequelae (Figure 2).

What are the limitations of the current evidence and what are the remaining knowledge gaps?

It is important to recognize several limitations hindering our full understanding of the cardiovascular impact of EC use. First of all, in reports of EC use as a TC cessation strategy, TC smokers have largely switched to ECs, resulting in long-term EC use, rather than resulting in cessation of all nicotine products(6). It is important to reiterate that we do not know the effects of long-term EC use. Secondly, as pointed out earlier, the data regarding myocardial infarction risk associated with EC use is cross-sectional data, which is severely hampered by insufficient temporal information, a seemingly insurmountable limitation (12, 13). To predict the cardiovascular impact of EC use, then, we are left to determine cardiovascular risk from biomarkers of cardiovascular disease in EC users. Unfortunately, it is very rare that these studies actually report biomarkers in *chronic* EC users(15, 38). Most of these studies(33, 34, 44, 46, 47) report the effects of acute EC use on certain biomarkers in current TC smokers, and thus may be confounded by residual TC effects. Finally, we have treated ECs as if they were a single device, but EC devices, liquids, and, by implication, the characteristics of the inhaled EC emissions, are myriad. Findings from one type of device or liquid may not be applicable to other devices, especially when voltages and resistances can significantly alter the characteristics of the emissions. Additionally, in studies comparing the effects of acute TC smoking with acute EC use, no study has compared the plasma nicotine

levels following acute exposure (an estimate of emission exposure), so it is not possible to know if subjects were exposed to comparable "doses" of EC and TC emissions (33, 46, 47).

What should we tell the middle-aged breadwinner addicted to TCs? And what should we tell her high schooler who is experimenting with ECs at school?

To date, ECs are largely unregulated, may only replace one form of nicotine delivery with another when used as a TC smoking cessation strategy, and have not been shown to decrease cardiovascular risk. Nonetheless, there are not many worse things one can do to oneself (legally) than smoke highly-addictive, lethal tobacco cigarettes. Further, there are signals – although no definitive proof - that switching completely (not dual use) - to ECs may help motivated TC smokers quit, and may decrease cardiovascular risk. If all FDA-certified strategies for smoking cessation have been tried without success, then ECs may be a reasonable strategy for smoking cessation; of course, patients should be advised to use them for the shortest time possible.

The Juul, a sleek EC that resembles a flash drive, has captured 80% of the EC market in 2018, only 3 years after its introduction in 2015. Juuls have become wildly popular with our youth, who use them at school, and even in the classroom, prompting the FDA to warn of an epidemic of Juuling in teens. Although ECs, including Juuls, remain unregulated and much is unknown about their non-nicotine emissions, much *is known* about nicotine, and it is

disturbing (as reviewed above). Thus, the message should be clear and unwavering: non-TC smokers should not use ECs – they are not harmless.

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Figure Legends

Figure 1. Nonlinear exposure-response function between number of TCs smoked daily and risk of cardiovascular disease. Risk from 1-3 TCs per day is similar to 1-3 packs per day. Adjusted relative risks (and 95% CIs) of ischemic heart disease (orange, light gray) and cardiovascular disease (blue, dark gray) mortality plotted over baseline estimated current TC smoking levels (relative to never smokers). The solid and dotted lines are fitted linear and nonlinear lines illustrating alternative monotonic exposure-response relationships. Adapted from reference 5. TC= tobacco cigarette

Figure 2. Mechanisms of Increased cardiovascular risk with EC use. Inhaled nicotine delivered by ECs, due to the differing pharmacokinetics and highly addictive nature of nicotine, may become a lifelong addiction. This prolonged exposure to inhaled nicotine and other toxicants in ECs may lead to unique adverse effects, including chronical increased sympathetic activation, oxidative stress, systemic inflammation, and with potentially dangerous clinical sequelae. EPCs= endothelial progenitor cells, FDG-PET= ^{18}F-fluorodeoxyglucose positron emission tomography, FMD= flow mediated dilatation, PWV = pulse wave velocity. Other abbreviations the same as for Figure 1.

Figure 3. Heart rate variability in otherwise healthy EC users compared to non-user controls. Vagal tone (HF component) is decreased and sympathetic tone (LF component) is increased resulting in sympathetic predominance (LF/

HF ratio) in otherwise healthy EC users compared to age-match non-user controls. Adapted from reference 17. HF = high frequency, LF= low frequency

Figure 4. The Splenocardiac Axis. Evidence is accumulating that increase sympathetic nerve activity in TC smokers and EC users instigates inflammatory atherosclerosis (please see text for explanation). Reference 34.

Figure 5. FDG-PET/CT results in Non-users, EC users and TC smokers. Inflammation is increased in a graded fashion in the hematopoeitic tissue (spleen) and vascular tissue (aorta), but not in the skeletal muscle (control tissue) in EC users and TC smokers compared to non-users. Reference 34. SUVmax = maximum standardized uptake value

Table

Studies of Electronic Cigarettes vs Tobacco Cigarettes: Impact on Biomarkers

Reference	Biomarker	Study Population	Findings
Boas[38] vs TC	Inflammation	Nonusers vs Chronic EC	
	• FDG-PET		TC > EC > Non-user
Carnevale[33]	Oxidative stress	TC Smokers and Non-smokers 1 TC vs 9 puffs from an EC	
	• NOX2-derived peptide		TC > EC
	• 8-iso-Prostaglandin F2α		TC > EC
	• NO bioavailability		TC > EC
	• Vitamin E level		TC = EC
	Endothelial Function		
	• FMD		TC = EC
Vlachopoulos[46]	Vascular stiffness	TC Smokers	
	• PWV	1 TC vs EC 5 minutes	TC > EC
	• PWV	1 TC vs EC 30 minutes	TC = EC
Nocella[47]	Platelet Function	TC smokers and Non-smokers 1 TC vs 9 puffs from an EC	
	• Platelet aggregation		TC > EC

- sCD40L TC = EC
- sP-selectin TC = EC

Abbreviations for Table. EC = electronic cigarette, FDG-PET = fluorodeoxyglucose positron emission tomography, FMD = flow-mediated dilation, NO Nitric oxide, Pulse wave velocity, sCD40L = soluble CD40 ligand, sP-selectin = soluble P-selectin, TC= tobacco cigarette

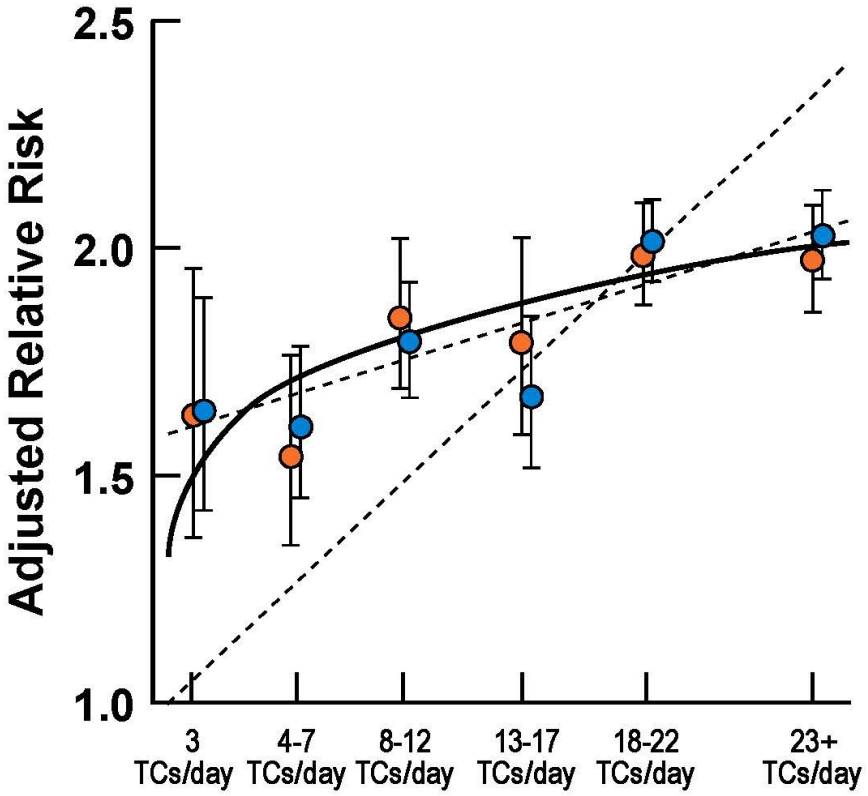

Figure 1. Cardiovascular risk from smoking TCs. Adapted from reference 5.

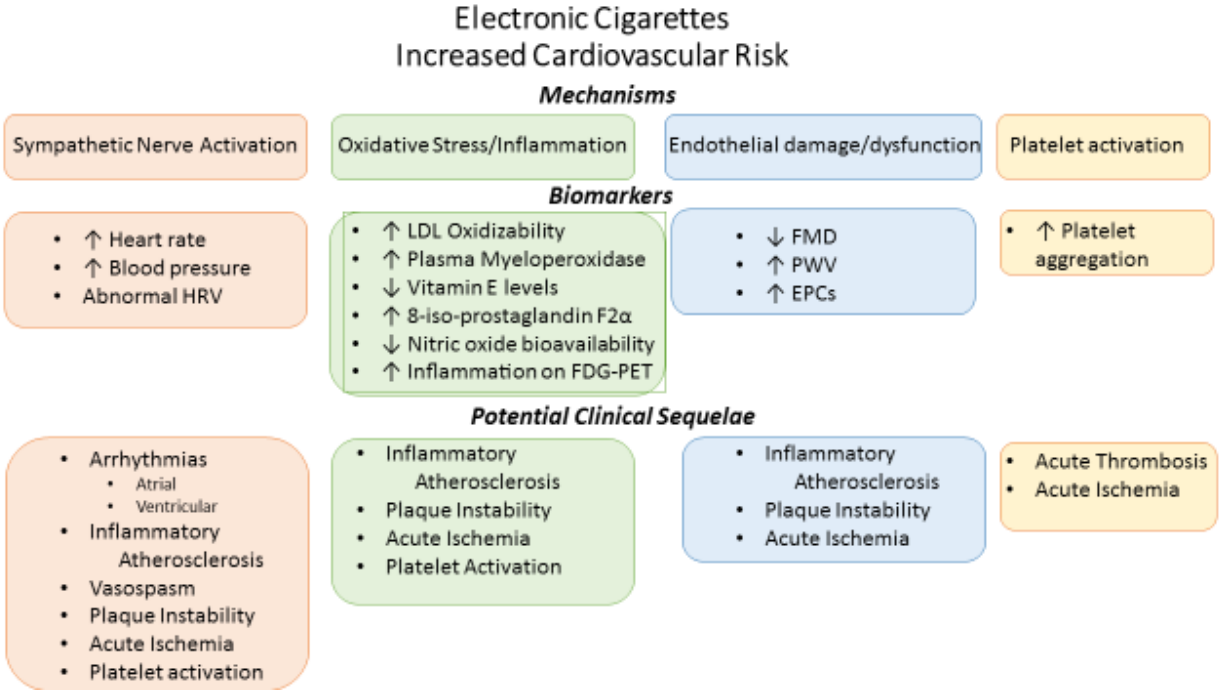

Figure 2. Mechanisms of Increased Cardiovascular risk.

Figure 3. Heart rate variability in EC users compared to non-user controls.

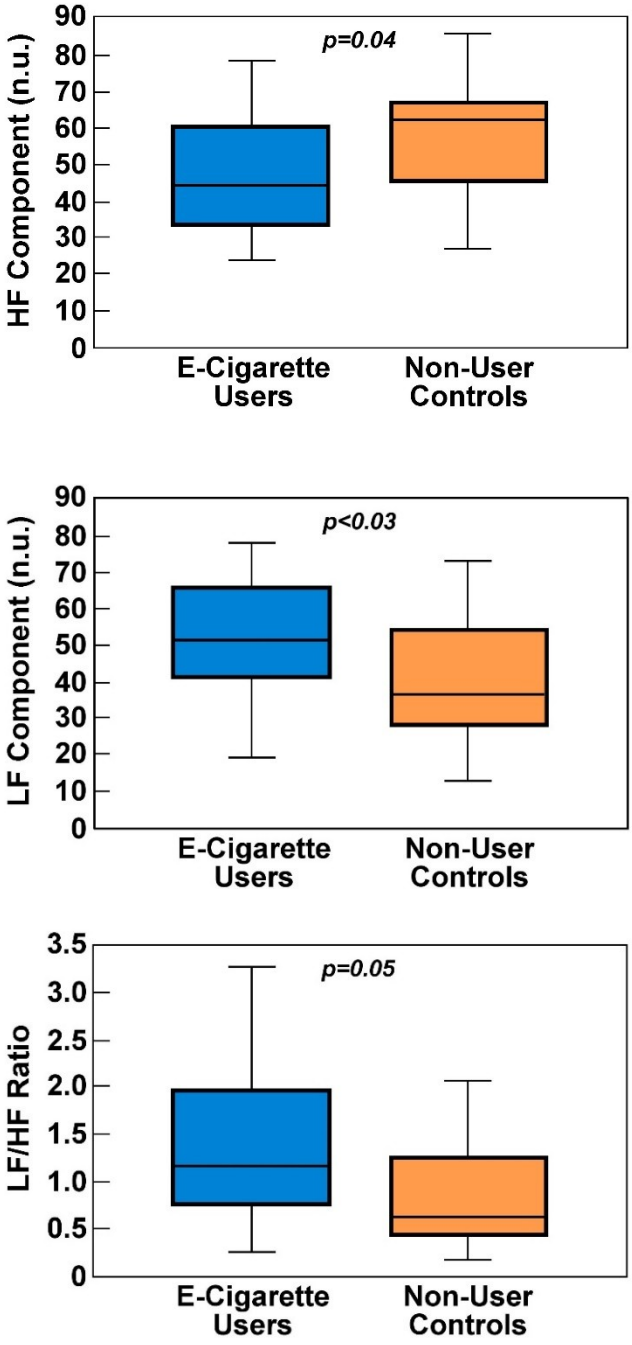

Figure 4. The Splenocardiac Axis.

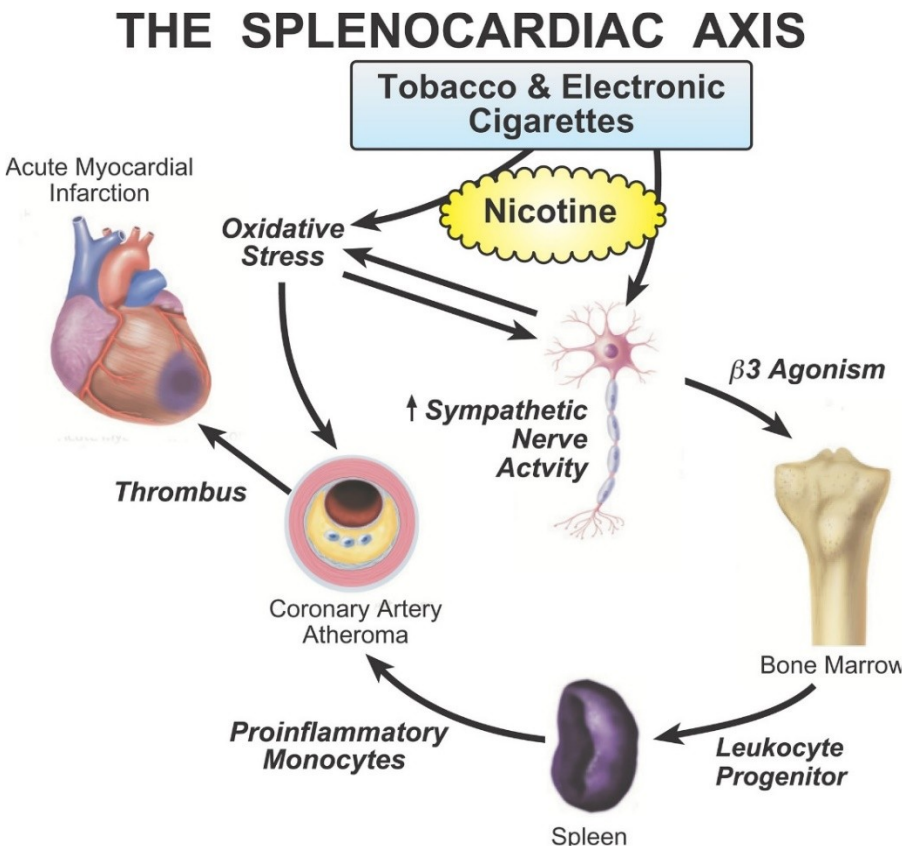

Figure 5. FDG-PET results in Non-users, EC users and TC smokers.