Title

Vaping and cardiac disease

Journal

Heart, 107(19)

ISSN

1355-6037

Authors

Shahandeh, Negeen
Chowdhary, Harshika
Middlekauff, Holly R

Publication Date

2021-10-01

DOI

10.1136/heartjnl-2020-318150

Vaping and Cardiac Disease

Negeen Shahandeh[1], MD, Harshika Chowdhary[2], Holly Middlekauff[1], MD

[1]Department of Medicine, Division of Cardiology, David Geffen School of Medicine at UCLA, Los Angeles, California; [2]David Geffen School of Medicine at UCLA, Los Angeles, California

Address for Correspondence:

Holly R. Middlekauff, MD

David Geffen School of Medicine at UCLA

Department of Medicine, Division of Cardiology

A2-237 CHS, 650 Charles Young Drive South

Los Angeles, California 90025

Phone 310-206-6672

Fax 310-206-9133

hmiddlekauff@mednet.ucla.edu

Funding resources: This work was supported by the Tobacco-Related Disease Research Program (TRDRP) under the contract numbers TRDRP 28IR-0065 (HRM), TRDRP T29IP0319 (HRM), and TRDRP T31IP1813 (HRM).

Word Count: ~3000

Key words: vaping, electronic cigarettes, cardiovascular disease, nicotine

Abstract

Tobacco cigarette smoking is the most prevalent reversible risk factor for cardiovascular disease in the United States. Electronic cigarettes, invented as an alternative nicotine source for smokers unable or unwilling to stop smoking, have gained skyrocketing popularity, but their cardiovascular risk remains uncertain. Although data recently analyzed in a Cochran report does support their superior effectiveness to other forms of nicotine replacement therapies for smoking cessation, electronic cigarettes are also frequently used by non-smokers –especially high school students. There are no long-term outcome studies of the cardiovascular risks of vaping electronic cigarettes, but the effects of electronic cigarettes on known risk factors for cardiovascular disease, including neurohumoral activation, oxidative stress and inflammation, endothelial function and thrombosis, have been studied. In this review, we summarize evidence in humans that supports the notion that while electronic cigarettes may be less harmful than traditional cigarettes, they are not harmless. Additionally, the increasing popularity of vaping marijuana with its unknown cardiovascular risks, as well as the outbreak in 2019 of Electronic-cigarette, or Vaping, product use Associated Lung Injury (EVALI) related to bootlegged vaping products, raise further concerns. Before physicians can confidently advise their smoking patients about the role of electronic cigarettes as a means for smoking cessation to lower cardiovascular risk, improved regulation and quality control is necessary.

Introduction

Electronic cigarette (ECIG) use has increased dramatically in the United States since the products first entered the market in the United States in 2007. The prevalence of current ECIG vaping among US adults was recently estimated at 2.3% (5.66 million adults)[1]. ECIGs are handheld devices composed of a battery, a heating element, and a cartridge filled with e-liquid. When the user activates the ECIG, typically by puffing on the mouthpiece, the e-liquid is heated without combustion, and released as an aerosol into the user's mouth to inhale. E-liquids contain a mixture of solvents, typically vegetable glycerol and propylene glycol, flavorings, and nicotine, although nicotine is not obligatory. Over time, the design of the ECIG device has evolved to promote more efficient nicotine delivery (**Figure 1**)[2]. The most recent, and popular, iteration, the fourth-generation pod-like device (e.g. Juul) utilizes nicotine salts, and is able to deliver nicotine into the alveoli with pharmacokinetics mimicking tobacco cigarette (TCIG) smoking[3]. ECIG use has been promoted as an effective TCIG smoking cessation aid as part of a harm reduction strategy. However, since their introduction, ECIGs have found an expansive user-base among teenagers and young adults, raising public health concerns about the long-term health risks associated with ECIG vaping in never-smokers, and their potential to act as a gateway to TCIG smoking.

Greater than 1 in every 10 deaths from cardiovascular disease are attributed to TCIG smoking each year[4]. Given this strong association between TCIG smoking and cardiovascular disease, concerns about the cardiovascular effects of ECIGs are warranted. The purpose of this article is to review the acute and chronic effects of ECIG vaping on cardiovascular risk, and in comparison to TCIG smoking.

Who is using electronic cigarettes?

Of the 5.66 million Americans adults who use ECIGs, the majority are current (39.1% [95% CI, 36.8%-41.4%]) or former 37.9% [95% CI, 35.6%-40.1%]) TCIG smokers[1]. Amongst dual users of TCIGs and ECIGs, the majority (69.3% [95% CI, 65.7% -72.7%]) reported using ECIGs to try to quit smoking. Importantly, of former smokers who currently used ECIGs, 80.7% (95% CI, 77.4%-83.5%) reported using ECIGs to quit smoking. Of concern, however, is that while most adults report using ECIGs for smoking cessation, almost a quarter of current ECIG vapers, 23.1% (95% CI. 20.8%-25.4%), were never-smokers[1].

In fact, use of ECIGs among youth in the United States has increased significantly over the last decade, and in 2019, ECIG use among teens was declared an epidemic. In 2019, almost 30% of high school seniors reported using an ECIG in the previous 30 days (**Figure 2**)[5]. In the first three months of 2020, this percentage of recent ECIG use markedly diminished amongst teenagers[6]. Although the proportion of teens who reported using ECIGs in the last 30 days had decreased, the proportion reporting daily ECIG use had increased, indicative of nicotine addiction[6]. The concern that ECIG vaping may be a gateway to TCIG smoking amongst teens, however, is not supported by the data. In fact, ECIG use seems to be a diversion from TCIG smoking, since smoking rates amongst teams has never been lower (**Figure 2**)[5, 7]. Nonetheless, the cardiovascular effects of lifelong ECIG use in a previous never-smoker are unknown, and remain a major public health concern.

What is the evidence that ECIGs help smokers quit?

Tobacco cigarettes are lethal, killing half the people who use them. It has been estimated that by switching from TCIGs to ECIGs, 1.6 to 6.6 million American lives could be saved over the next ten years[8]. Although the majority of adult ECIG users report using ECIGs to quit smoking, until recently, it has been uncertain that this strategy is effective. Several studies have examined the efficacy of ECIGs as a TCIG cessation aid, and these have recently been summarized in a Cochran report[9]. After analyzing 50 studies (26 RCT), including 12,430 participants, 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). Adverse events associated with ECIG use were uncommon and mild (e.g. throat /mouth irritation). Of note, a large number of former smokers who use ECIGs to stop TCIG smoking continue to use ECIGs at one year[10]. The cardiovascular effects of lifelong ECIG use in former smokers are unknown, and remain a major public health concern.

Cardiovascular Effects of ECIG Use (Figure 3)

Both nicotine and the non-nicotine constituents in TCIG smoke have been implicated in mechanisms of the development of atherosclerosis and adverse cardiovascular effects from TCIGsmoking[11, 12, 13]. Levels of non-nicotine toxicants detectable in emissions from ECIGs, if present at all, are orders of magnitude lower than in smoke from TCIGs[14]. Similarly, toxicant levels present in the urine or saliva from ECIG vapers are also orders of magnitude lower than in TCIG smokers[15]. However, steady state plasma nicotine levels are similar in smokers and vapers, and the pharmacokinetics of nicotine delivery by the 4th generation pod-like devices, which use highly concentrated nicotine salts, mimic the addictive alveolar delivery of

TCIGs. Thus, it is best to consider cardiovascular effects of ECIGs in terms of risks associated with nicotine and non-nicotine constituents (**Figure 3**).

Nicotine is sympathomimetic, which may lead to vasospasm and acute, albeit modest, increases in heart rate (HR) and blood pressure (BP), potentially increasing risk for ischemia[13]. Increases sympathetic tone may also precipitate atrial and ventricular arrhythmias. Non-nicotine constituents generated from combustion of organic materials in TCIG smoke and heating of e-liquid, likely leads to increased oxidative stress and inflammation, which are important mediators of smoking-related cardiovascular disease[16]. Endothelial damage, platelet activation, oxidized lipids and abnormal ventricular repolarization may follow, leading to increased risk for myocardial ischemia and sudden cardiac death. ECIG emissions, which contain nicotine, but lower toxicant levels and no combustion products, may increase sympathetic nerve activity similarly to TCIGs but may only modestly activate other mechanisms, which underlie cardiovascular risk (**Figure 3**). The relative effects of TCIG smoking and ECIG vaping in these risk factors will be discussed below.

Increased Sympathetic Nerve Activity

Cardiac sympathetic nerve activity, as estimated by changes in heart rate variability (HRV), is increased in otherwise healthy chronic ECIG vapers compared to non-smokers[17]. This abnormal pattern of HRV is the same pattern that is associated with increased cardiac risk in populations with and without known cardiac disease[17]. Further, measures of HRV are not different in otherwise healthy ECIG vapers and TCIG smokers[18]. Acutely, increases in sympathetic nerve activity as estimated by abnormal HRV, and hemodynamics, including HR

and BP, are mediated by nicotine, not non-nicotine constituents in ECIG emissions[19]. Acute TCIG smoking leads to significantly greater increases in hemodynamics, specifically HR and BP, compared to ECIG vaping[20]. However, it is important to acknowledge two important limitations in the studies that support this observation[20]. First, changes in plasma nicotine levels were not reported in most studies comparing acute effects of ECIGs and TCIGs, so it is unknown whether the exposures were equivalent. Secondly, most studies to date have not included the 4th generation pod-like devices which deliver nicotine efficiently, replicating the pharmacokinetics of TCIG smoking. Thus, further studies are needed.

In summary, acute and chronic ECIG vaping is associated with increased sympathetic activity, and modest increases in HR and BP[17, 19, 20]. These changes are attributable to nicotine, not non-nicotine constituents in ECIG emissions[19]. Although the acute hemodynamic changes with ECIG vaping are modest, nonetheless, they could contribute to supply-demand mismatch, especially in the setting of vasospasm. Clinical sequelae of increased sympathetic nerve activity could include increased risk of arrhythmias, myocardial ischemia, and sudden arrhythmic death[13]. Increased sympathetic nerve activity also results in increased epinephrine secretion, which may further contribute to an increased risk for arrhythmias and sudden cardiac death. Long-term outcome studies are necessary to determine if these changes in ECIG vapers are clinically relevant.

Oxidative Stress and Inflammation

Increased oxidative stress and inflammation are fundamental mechanisms that underlie the development of atherosclerosis and cardiovascular risk associated with smoking, but reports of oxidative stress and inflammation in ECIG vapers is limited[16]. Carnevale et al was the first to

report an acute increase in plasma markers of oxidative stress (increased soluble NOX2-derived peptide and 8-iso-prostaglandin F2α levels) in TCIG smokers after acutely using an ECIG, but these levels were significant less compared to the acute effects of smoking a TCIG[21]. Biondi-Zoccai et al reported similar findings; specifically, they also found an increase in soluble NOX2-derived peptide levels as well as a significant increase of H_2O_2, a nonradical oxygen species, after use of both ECIGs and TCIGs, with TCIGs resulting in the largest increase [22]. It should be noted that neither study reported changes in nicotine levels following each exposure, so it is unknown of the ECIG and TCIG exposures were comparable We reported increased susceptibility to oxidative stress, as measured by LDL oxidizability, in young, otherwise healthy chronic ECIG vapers, who had not vaped for 12 hours, compared to non-user controls[17].· In a follow-up study, we compared cellular, rather than plasma, markers of oxidative stress in immune cells from otherwise healthy volunteers who were either chronic TCIG smokers or ECIG vapers compared to nonsmokers[23]. Total cellular and cytoplasmic reactive oxygen species in immune cells were elevated to the greatest level in the TCIG smokers and intermediate levels in the ECIG vapers compared to non-smokers[23]. Importantly, smoking burdens were similar between vapers and smokers as estimated by plasma cotinine levels, a metabolite of nicotine. Notably, increases in cellular oxidative stress were most striking in proinflammatory monocytes – which are known to be the culprits in inflammatory atherosclerosis[23].

There are few other reports of inflammation in chronic ECIG vapers. Using FDG-PET/CT imaging to detect increased metabolic activity and inflammation, Boas et al found increased inflammation of the aorta in a small group of otherwise healthy TCIG smokers compared to non-smokers[24]. Chronic ECIG vapers had intermediate levels of aortic inflammation. This vascular inflammation was accompanied by a similar increase in metabolic

activity in the spleen, a source of circulating monocytes that invade the vascular wall and lead to inflammatory atherosclerosis[24, 25]. Nicotine is known to have anti-inflammatory effects via the cholinergic anti-inflammatory pathway[26], but these anti-inflammatory effects are likely offset by pro-inflammatory, non-nicotine constituents present in ECIG emissions.

In summary, these findings are consistent with a continuum of oxidative stress and inflammation associated with tobacco product usage– greatest in TCIG smokers and intermediate in ECIG vapers, compared to non-smokers.

Endothelial Dysfunction

Endothelial dysfunction, as measured by brachial-artery flow mediated dilation (FMD), and arterial stiffness, as measured by pulse wave velocity (PWV) and augmentation index(AI), have all been recognized as predictors of atherosclerosis and markers for increased risk of cardiovascular disease[27]. Impaired FMD has been demonstrated in chronic TCIG smokers and in non-smokers exposed to secondhand smoke[28]. Until recently, acute effects of ECIG vaping on vascular health had only been studied in chronic TCIG smokers, not in chronic ECIG vapers[11]. Further, the effects of chronic ECIG vaping on vascular health, especially compared to chronic TCIG smoking, had not been studied. Overall, these prior studies reported acute decreases in FMD, PWV and AI, in TCIG smokers after using an ECIG, but these abnormalities were significantly greater following smoking a TCIG[11].

Recent studies have shown that switching from TCIG smoking to ECIG vaping is associated with improved endothelial function[29]. George et al conducted a randomized controlled trial that showed a significant improvement in FMD within 1 month of switching from TCIG smoking to ECIG vaping, consistent with the notion that vaping is less harmful to the

vascular endothelium[29]. Interestingly, similar improvements were seen when smokers switched to either nicotine-containing ECIGs or nicotine-free ECIGs, implicating non-nicotine constituents in TCIG smoke rather than nicotine. Similarly, Haptonstall et al reported that baseline FMD was not different among otherwise healthy, young chronic TCIG smokers (n=40), chronic ECIG vapers (n=49), and non-smokers (n=47). However, acutely smoking one TCIG significantly decreased FMD compared with sham control[30]. Surprisingly, however, a comparable "dose" of acute ECIG vaping did not significantly affect FMD. Changes in nicotine levels were compared with each exposure, and were similar, consistent with an equivalent exposure of each tobacco product type[30]. A subset of chronic ECIG vapers acutely used a 4th generation pod-like ECIG device, and findings were similar to exposures using earlier generation devices[30]. Fetterman et al measured FMD, PWV and AI in ~400 volunteers in the Cardiovascular Injury to Tobacco Use study, and found only AI, but not FMD or PWV, was abnormal in ECIG smokers compared to non-smokers[31].

Collectively, these findings suggest that the effects of ECIG vaping, although not harmless, may result in less harm to endothelial function compared with TCIG smoking.

Platelet Aggregation

TCIG smoking results in increased platelet activation, which in turn predisposes to platelet aggregation and thrombus formation that may result in myocardial ischemia and infarction[32]. Few studies have investigated the effect of ECIG vaping on platelet activation. Nocella et al found that chronic TCIG smokers exhibit similar degrees of platelet aggregation, as evidenced by increases in soluble CD40-ligand and soluble P-selectin levels, with acute TCIG and ECIG smoking, however non-smokers exhibit increased platelet aggregation when smoking TCIGs as

compared to ECIGs[33]. Ikonomidis et al compared platelet function between chronic TCIG smokers and those who switched to ECIG vaping after four months measuring *in vivo* platelet activation using the Platelet Function Analyzer PFA-100 and Light Transmission Aggregometry. They found that switching to ECIG vaping had a neutral effect on platelet function[34]. In summary, although the chronic effects of TCIG and ECIG use on platelet function remain unknown, there is limited evidence that ECIG use can adversely affect platelets and increase platelet aggregation.

Sudden Arrhythmic Death

Although TCIG smoking is associated with an increased risk of sudden death, the risk associated with ECIGs is unknown. As noted above, increased cardiac sympathetic nerve activity, as detected in chronic ECIG vapers is associated with increased risk of adverse cardiac events, including ventricular arrhythmias and sudden death[13]. Additionally, abnormal ventricular repolarization in TCIG smokers has been reported, a finding that also increases the risk for ventricular arrhythmias[35].Ventricular repolarization is typically represented by the QT interval on the surface electrocardiogram, but this interval includes both ventricular depolarization and repolarization. The Tpeak-end (Tp-e) interval, measured from the peak of the T wave until the end of the T wave, has emerged as a more specific representation of abnormal ventricular repolarization, and has been associated with increased risk of sudden death is many populations[36]. The Tp-e interval is prolonged in TCIG smokers, but it remains unknown if ECIG vaping also is associated with prolonged Tp-e interval. In a study of 145 healthy young people, including 37 chronic TCIG smokers, 43 chronic ECIG vapers, and 65 non-smokers, Ip et al reported that Tp-e alone or corrected for QT interval was not different among the three

groups[37]. However, smoking just one TCIG significantly prolonged all three (Tpe, Tpe/QT and Tpe/QTc) ECG indices abnormal ventricular repolarization. After a similar exposure (as estimated by changes in plasma nicotine) to an ECIG with nicotine, only one of the ECG indices was significantly prolonged. Importantly, the abnormal ventricular repolarization was significantly greater after TCIG smoking compared to ECIG vaping, despite similar increases in plasma nicotine levels with each tobacco product exposure[37]. These findings are consistent with the notion that non-nicotine constituents in TCIG smoke are major contributors to acute changes in ventricular repolarization with smoking.

In summary, changes in ventricular repolarization associated with increased sudden death risk are significantly greater following TCIG smoking compared to ECIG vaping. Although the repolarization changes were less following ECIG vaping, they were still present and significant, and suggest that although ECIG vaping may be less harmful than TCIG smoking, it is not harmless[37].

Cannabis and Vaping

Any discussion of the adverse cardiovascular effects of vaping would be remiss in omitting the cardiovascular effects of vaping cannabinoids, since cannabis is the most commonly used illicit substance in the United States, and it is frequently vaped in ECIG devices[38]. The number of youth vaping cannabis increased to record levels in 2018-19, as the 2nd greatest single year increase in any recreational drug in the 49 year history this has been tracked by the National Institute on Drug Abuse (NIDA): Monitoring the Future Survey (**Figure 4**)[39]. A large-scale study showed that almost one third of high school students who use cannabis have tried it in its

vaporized form[40]. Although limited data exist regarding the cardiovascular effects of vaping compared to smoking cannabis, Spindle et al[41] reported that inhaling an equivalent dose of vaporized cannabis led to greater plasma levels of THC, cognitive and psychomotor effects, and significantly greater increases in heart rate, compared to smoked cannabis. Whether these greater physiologic effects of vaporized cannabis lead to greater risk of clinical cardiovascular events remains unknown.

Most of what is known about cardiovascular risks associated with cannabis use stem from events in patients who have smoked it. An increasing number of cardiovascular emergencies temporally-related to smoking cannabis have been reported, but the mechanisms by which cannabis adversely affects the cardiovascular system remain uncertain[42]. The risk of myocardial infarction within 60 minutes of smoking marijuana reportedly is 4.8 times that at baseline, and cannabis use compared with non-use has been associated with a three-fold increase in mortality following survival of an initial myocardial infarction[43, 44]. Potential mechanisms include acute increases in sympathetic nerve activity, HR and BP, thereby contributing to supply demand mismatch[45]. Further, cannabis has been associated with endothelial dysfunction and vasoconstriction of coronary and cerebral arteries, increasing the risk of vasospasm and atherosclerosis[45]. Additionally, cannabis has pro-thrombotic effects which have been noted in multiple cases of young adults suffering acute myocardial infarctions due to coronary thrombosis without underlying atherosclerosis[45, 46]. Research elucidating the effects of vaporized cannabis on cardiovascular health is imperative, since vaporized cannabis use is increasing, and a trend to legalize marijuana for medical and recreational use is spreading across the US.

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

In 2019, thousands of cases of acute lung injury primarily affecting adolescents and young adults who endorsed recent ECIG use were reported across the United States[47]. The disease became known as Electronic-cigarette, or Vaping, product use Associated Lung Injury (EVALI) and was eventually linked to the presence of vitamin E acetate, used as thickener in boot-legged or black market THC-containing ECIG products[48]. Further investigation revealed that a majority of patients reported acquiring the associated THC-containing products from illicit or informal sources[47, 48]. Fortunately, the prevalence of cases has decreased since the recognition of these risk factors. However, the epidemic of EVALI demonstrates the potential for harm from ECIG use and highlights the need for appropriate regulation of the products. Regulation of ECIG products will become increasingly relevant to healthcare providers who are asked by their patients whether the devices are a safe alternative to currently approved smoking cessation aids. Given the cumulative evidence showing that ECIGs have a lower cardiovascular risk profile than TCIGs, regulation and quality control is crucial for minimizing harm to patients.

Pyramid of Cardiovascular Risk (Figure 5)

In considering the effects of vaping on cardiovascular risk, one can place them within the context of other nicotine delivery systems, including nicotine replacement therapies (NRTs) (e.g. gum or patches), smokeless tobacco (e.g. snus or chewing tobacco), and combusted tobacco products. NRTs have been extensively studied and research has been summarized in meta-analyses. NRTs are associated with a slightly but significantly increased risk of minor cardiovascular effects, including palpitations and tachycardia[49]. Serious adverse cardiac events are not significantly increased[49]. Thus, NRTs may be placed at the tip of the pyramid, as conferring the lowest risk

of cardiovascular events (**Figure 5**). Adverse cardiovascular events, including serious cardiac events, associated with smokeless tobacco use are slightly but significantly increased[50]. Thus, smokeless tobacco may be best positioned in the middle of the pyramid of cardiovascular risk. Without controversy, TCIGs and other combusted tobacco products are associated with the greatest cardiovascular risk, and are placed at the large base of the pyramid of cardiovascular risk. Since outcome data are not available to help position ECIGs in this pyramid of risk, we must rely on the effects of ECIGs on known biomarkers and risk factors for cardiovascular disease. The effects of ECIG on markers of oxidative stress, inflammation, endothelial health, thrombogenesis and arrhythmia risk support the placement of ECIGs in the middle of the pyramid, likely less harmful than TCIGs, but with greater risk than NRTs. The uncertainty of this placement, however, is heightened by concern over a lack of regulation and product quality oversight, with the specter of another EVALI- like outbreak lurking.

Summary

Electronic cigarette (ECIG) use has grown significantly in the United States over the last decade, primarily among TCIG smokers who report using ECIGs as a smoking cessation aid, but also, alarmingly, among adolescents and young adults. Although long-term studies are needed, the evidence available to date suggests that ECIG vaping confers lower cardiovascular risk than TCIG smoking. Furthermore, there is mounting evidence that nicotine-containing ECIGs are effective as a TCIG smoking cessation therapy. Despite the promising results presented above, ECIGs continue to pose potential health risks due to the lack of regulation and quality control. Additionally, the increasing prevalence of ECIG vaping among youth is alarming and raises

appropriate public health concerns about the consequences of their long-term usage and their potential for contributing to cardiovascular disease later in life.

.

References

1 Mayer M, Reyes-Guzman C, Grana R, et al. Demographic Characteristics, Cigarette Smoking, and e-Cigarette Use Among US Adults. *JAMA Netw Open* 2020;**3**:e2020694.
2 Williams M, Talbot P. Design Features in Multiple Generations of Electronic Cigarette Atomizers. *Int J Environ Res Public Health* 2019;**16**.
3 Jackler RK, Ramamurthi D. Nicotine arms race: JUUL and the high-nicotine product market. *Tob Control* 2019;**28**:623-8.
4 Ezzati M, Henley SJ, Thun MJ, et al. Role of smoking in global and regional cardiovascular mortality. *Circulation* 2005;**112**:489-97.
5 FDA. www.fda.gov/tobacco-products/youth-and-tobacco/youth-tobacco-use-results-national-youth-tobacco-survey. 2020.
6 Wang TW, Neff LJ, Park-Lee E, et al. E-cigarette Use Among Middle and High School Students - United States, 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**:1310-2.
7 Ip M, Middlekauff HR. Noncigarette Tobacco Products-Gateway or Diversion? *JAMA Pediatr* 2018;**172**:784.
8 Levy DT, Borland R, Lindblom EN, et al. Potential deaths averted in USA by replacing cigarettes with e-cigarettes. *Tob Control* 2018;**27**:18-25.
9 Hartmann-Boyce J, Chepkin SC, Ye W, et al. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev* 2018;**5**:CD000146.
10 Hajek P, Phillips-Waller A, Przulj D, et al. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. *N Engl J Med* 2019;**380**:629-37.
11 MacDonald A, Middlekauff HR. Electronic cigarettes and cardiovascular health: what do we know so far? *Vasc Health Risk Manag* 2019;**15**:159-74.
12 Kalkhoran S, Benowitz NL, Rigotti NA. Prevention and Treatment of Tobacco Use: JACC Health Promotion Series. *J Am Coll Cardiol* 2018;**72**:1030-45.
13 Middlekauff HR, Park J, Moheimani RS. Adverse effects of cigarette and noncigarette smoke exposure on the autonomic nervous system: mechanisms and implications for cardiovascular risk. *J Am Coll Cardiol* 2014;**64**:1740-50.
14 Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control* 2014;**23**:133-9.
15 Shahab L, Goniewicz ML, Blount BC, et al. Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study. *Ann Intern Med* 2017;**166**:390-400.
16 Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol* 2004;**43**:1731-7.
17 Moheimani RS, Bhetraratana M, Yin F, et al. Increased Cardiac Sympathetic Activity and Oxidative Stress in Habitual Electronic Cigarette Users: Implications for Cardiovascular Risk. *JAMA Cardiol* 2017;**2**:278-84.
18 Arastoo S, Haptonstall KP, Choroomi Y, et al. Acute and chronic sympathomimetic effects of e-cigarette and tobacco cigarette smoking: role of nicotine and non-nicotine constituents. *Am J Physiol Heart Circ Physiol* 2020;**319**:H262-H70.
19 Moheimani RS, Bhetraratana M, Peters KM, et al. Sympathomimetic Effects of Acute E-Cigarette Use: Role of Nicotine and Non-Nicotine Constituents. *J Am Heart Assoc* 2017;**6**.

20 Garcia PD, Gornbein JA, Middlekauff HR. Cardiovascular autonomic effects of electronic cigarette use: a systematic review. *Clin Auton Res* 2020.
21 Carnevale R, Sciarretta S, Violi F, et al. Acute Impact of Tobacco vs Electronic Cigarette Smoking on Oxidative Stress and Vascular Function. *Chest* 2016;**150**:606-12.
22 Biondi-Zoccai G, Sciarretta S, Bullen C, et al. Acute Effects of Heat-Not-Burn, Electronic Vaping, and Traditional Tobacco Combustion Cigarettes: The Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR - VAPES) 2 Randomized Trial. *J Am Heart Assoc* 2019;**8**:e010455.
23 Kelesidis T, Tran E, Arastoo S, et al. Elevated Cellular Oxidative Stress in Circulating Immune Cells in Otherwise Healthy Young People Who Use Electronic Cigarettes in a Cross-Sectional Single-Center Study: Implications for Future Cardiovascular Risk. *J Am Heart Assoc* 2020;**9**:e016983.
24 Boas Z, Gupta P, Moheimani RS, et al. Activation of the "Splenocardiac Axis" by electronic and tobacco cigarettes in otherwise healthy young adults. *Physiol Rep* 2017;**5**.
25 Libby P, Nahrendorf M, Swirski FK. Leukocytes Link Local and Systemic Inflammation in Ischemic Cardiovascular Disease: An Expanded "Cardiovascular Continuum". *J Am Coll Cardiol* 2016;**67**:1091-103.
26 Ulloa L. The vagus nerve and the nicotinic anti-inflammatory pathway. *Nat Rev Drug Discov* 2005;**4**:673-84.
27 Ras RT, Streppel MT, Draijer R, et al. Flow-mediated dilation and cardiovascular risk prediction: a systematic review with meta-analysis. *Int J Cardiol* 2013;**168**:344-51.
28 Celermajer DS, Sorensen KE, Georgakopoulos D, et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation* 1993;**88**:2149-55.
29 George J, Hussain M, Vadiveloo T, et al. Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes. *J Am Coll Cardiol* 2019;**74**:3112-20.
30 Haptonstall KP, Choroomi Y, Moheimani R, et al. Differential effects of tobacco cigarettes and electronic cigarettes on endothelial function in healthy young people. *Am J Physiol Heart Circ Physiol* 2020;**319**:H547-H56.
31 Fetterman JL, Keith RJ, Palmisano JN, et al. Alterations in Vascular Function Associated With the Use of Combustible and Electronic Cigarettes. *J Am Heart Assoc* 2020;**9**:e014570.
32 Csordas A, Bernhard D. The biology behind the atherothrombotic effects of cigarette smoke. *Nat Rev Cardiol* 2013;**10**:219-30.
33 Nocella C, Biondi-Zoccai G, Sciarretta S, et al. Impact of Tobacco Versus Electronic Cigarette Smoking on Platelet Function. *Am J Cardiol* 2018;**122**:1477-81.
34 Ikonomidis I, Katogiannis K, Kostelli G, et al. Effects of electronic cigarette on platelet and vascular function after four months of use. *Food Chem Toxicol* 2020;**141**:111389.
35 Tasolar H, Balli M, Bayramoglu A, et al. Effect of smoking on Tp-e interval, Tp-e/QT and Tp-e/QTc ratios as indices of ventricular arrhythmogenesis. *Heart Lung Circ* 2014;**23**:827-32.
36 Panikkath R, Reinier K, Uy-Evanado A, et al. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol* 2011;**4**:441-7.

37 Ip M, Diamantakos E, Haptonstall K, et al. Tobacco and electronic cigarettes adversely impact ECG indexes of ventricular repolarization: implication for sudden death risk. *Am J Physiol Heart Circ Physiol* 2020;**318**:H1176-H84.
38 Miech RA, Patrick ME, O'Malley PM, et al. Trends in Reported Marijuana Vaping Among US Adolescents, 2017-2019. *JAMA* 2019.
39 NIDA. Monitoring the Future Survey: High School and Youth Trends DrugFacts. *National Institute on Drug Abuse website* *https://wwwdrugabusegov/publications/drugfacts/monitoring-future-survey-high-school-youth-trends* 2019.
40 Morean ME, Kong G, Camenga DR, et al. High School Students' Use of Electronic Cigarettes to Vaporize Cannabis. *Pediatrics* 2015;**136**:611-6.
41 Spindle TR, Cone EJ, Schlienz NJ, et al. Acute Effects of Smoked and Vaporized Cannabis in Healthy Adults Who Infrequently Use Cannabis: A Crossover Trial. *JAMA Netw Open* 2018;**1**:e184841.
42 Jouanjus E, Lapeyre-Mestre M, Micallef J, et al. Cannabis use: signal of increasing risk of serious cardiovascular disorders. *J Am Heart Assoc* 2014;**3**:e000638.
43 Mittleman MA, Lewis RA, Maclure M, et al. Triggering myocardial infarction by marijuana. *Circulation* 2001;**103**:2805-9.
44 Mukamal KJ, Maclure M, Muller JE, et al. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. *Am Heart J* 2008;**155**:465-70.
45 DeFilippis EM, Bajaj NS, Singh A, et al. Marijuana Use in Patients With Cardiovascular Disease: JACC Review Topic of the Week. *J Am Coll Cardiol* 2020;**75**:320-32.
46 Patel RS, Kamil SH, Bachu R, et al. Marijuana use and acute myocardial infarction: A systematic review of published cases in the literature. *Trends Cardiovasc Med* 2020;**30**:298-307.
47 Ellington S, Salvatore PP, Ko J, et al. Update: Product, Substance-Use, and Demographic Characteristics of Hospitalized Patients in a Nationwide Outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injury - United States, August 2019-January 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**:44-9.
48 Duffy B, Li L, Lu S, et al. Analysis of Cannabinoid-Containing Fluids in Illicit Vaping Cartridges Recovered from Pulmonary Injury Patients: Identification of Vitamin E Acetate as a Major Diluent. *Toxics* 2020;**8**.
49 Mills EJ, Thorlund K, Eapen S, et al. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. *Circulation* 2014;**129**:28-41.
50 Piano MR, Benowitz NL, Fitzgerald GA, et al. Impact of smokeless tobacco products on cardiovascular disease: implications for policy, prevention, and treatment: a policy statement from the American Heart Association. *Circulation* 2010;**122**:1520-44.

Figure Legends

Figure 1 – The evolution of electronic cigarette devices. Since their invention in China in 2003, electronic cigarettes (ECIGs) have changed in both appearance and features. The first generation ECIG, called the "cigalike," physically resembled a tobacco cigarette. Initially equipped with a small, disposable battery, cigalikes were inefficient nicotine delivery devices. Over successive 3rd and 4th generation devices, the "vape-pens" and "mods", the ECIG battery has become more powerful, is re-chargeable, and adjustable and modifiable. Additionally, the cartridge that holds the e-liquid has greater capacity. This combination of features has the capability of generating large plumes of aerosol, resulting in greater nicotine delivery, accompanied by a greater level of non-nicotine constituents and toxicants. The latest, 4th generation device, the "podlike" device, takes advantage of novel nicotine chemistry to deliver addictive nicotine at lower temperatures, and perhaps with fewer non-nicotine toxicants, into the alveoli, replicating the pharmacokinetics of tobacco cigarettes.

Figure 2 – Trends in electronic cigarette use among US youth. Data from 2011 through March 16, 2020 from the National Youth Tobacco Survey, a cross-sectional school-based, self-administered survey of middle and high school students across the United States, have been analyzed [5]. These data demonstrate that a large proportion of high school students report using electronic cigarettes (ECIGs) , as defined by use in the last 30 days. Usage seems to have peaked in 2019, with the caveat that less than 3 months of data were available for 2020. However, despite this epidemic in ECIG use, tobacco cigarette use has declined during this period, supporting the notion that ECIGs are a diversion, rather than a gateway to tobacco cigarette smoking.

Figure 3 – Cardiovascular effects of tobacco cigarettes and electronic cigarettes. In considering the cardiovascular risks of tobacco cigarettes and electronic cigarettes, it is best to divide the risks into those largely attributable to nicotine, and those largely attributable to non-nicotine constituents in their respective emissions. Cardiovascular effects associated with nicotine are attributable to nicotine's sympathomimetic effects including increases in heart rate, blood pressure and inotropy, potentially accompanied by vasospasm, leading to ischemia. Additionally, increased sympathetic tone is linked to heightened risk of arrhythmias, both atrial and ventricular. Increased sympathetic tone may be the instigator of activation of the splenocardiac axis, increasing inflammation, and once again increasing risk for inflammatory atherosclerosis and ischemia[25]. Potential cardiovascular effects of non-nicotine constituents include increased oxidative stress and inflammation, leading to endothelial damage, platelet activation, and lipid oxidation, increasing risk for inflammatory atherosclerosis and ischemia. Further, non-nicotine constituents may have adverse effects on ventricular repolarization, once again increasing risk for arrhythmias. See text for discussion.

Figure 4 –Marijuana vaping trends among US teens. Data from the Monitoring the Future Study, a cross-sectional, school-based, self-administered survey of middle and high school students across the United States that has been collecting data for 49 years, has been analyzed[39]. The increase in vaping in 2018 to 2019 amongst high school students was the 2nd biggest increase in recreational drug use ever recorded by the study (the 1st greatest was the year before, the 2017-2018 increase in vaping nicotine products). The prevalence of vaping marijuana has surpassed tobacco cigarette smoking among high school students.

Figure 5- The pyramid of cardiovascular risk. Nicotine delivery products, including nicotine replacement therapies (NRTs), smokeless tobacco, electronic cigarettes, and combustible tobacco cigarette products, can be arranged relative to one another in a pyramid, according to current knowledge of their relative cardiovascular risks. At the tip of the pyramid, with the least risk, reside NRTs[49]. At the broad base lie combustible tobacco products, which, without a doubt carry the greatest cardiovascular risk. Based on available outcome data, smokeless tobacco carries intermediate risk[50]; based on emerging data from their effects on biological risk factors – but no outcome studies, electronic-cigarettes reside next to smokeless tobacco, also carrying an intermediate risk.