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Cardiovascular effects of electronic cigarettes

Neal L. Benowitz^{1,2} and Joseph B. Fraiman³

¹Division of Clinical Pharmacology and Experimental Therapeutics, Medical Service, Departments of Medicine and Biopharmaceutical Sciences, University of California, 1001 Potrero Avenue #3316, San Francisco, California 94110, USA

²Center for Tobacco Control Research and Education, University of California, 530 Parnassus Avenue, San Francisco, California 94117, USA

³Louisiana State University School of Medicine, Department of Emergency Medicine, Lallie Kemp Regional Medical Center, 52579 US-51, Independence, Louisiana 70443, USA

Abstract

Cardiovascular safety is an important consideration in the debate on the benefits versus the risks of electronic cigarette (EC) use. EC emissions that might have adverse effects on cardiovascular health include nicotine, oxidants, aldehydes, particulates, and flavourants. To date, most of the cardiovascular effects of ECs demonstrated in humans are consistent with the known effects of nicotine. Pharmacological and toxicological studies support the biological plausibility that nicotine contributes to acute cardiovascular events and accelerated atherogenesis. However, epidemiological studies assessing Swedish smokeless tobacco, which exposes users to nicotine without combustion products, generally have not found an increased risk of myocardial infarction or stroke among users, but suggest that nicotine might contribute to acute cardiovascular events, especially in those with underlying coronary heart disease. The effects of aldehydes, particulates, and flavourants derived from ECs on cardiovascular health have not been determined. Although ECs might pose some cardiovascular risk to users, particularly those with existing cardiovascular disease, the risk is thought to be less than that of cigarette smoking based on qualitative and quantitative comparisons of EC aerosol versus cigarette smoke constituents. The adoption of ECs rather than cigarette smoking might, therefore, result in an overall benefit for public health.

Electronic cigarettes (ECs) have been marketed since 2007, with a tremendous increase in use since 2010, particularly in Europe and the USA. Epidemiological studies have reported the prevalence of ever and current use of ECs in the European Union of 11.6% and 1.8%, respectively, and 3.8% prevalence of current use in the USA^{1,2}. The vast majority of users are current or former cigarette smokers, but a small percentage of EC users reported never having smoked cigarettes. Considerable debate about whether ECs will provide benefit or

Correspondence: to N.L.B. neal.benowitz@ucsf.edu.

Author contributions

Both authors researched data for the article, discussed the content, wrote the manuscript, and reviewed/edited it before submission.

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N.L.B. has been a consultant to GlaxoSmithKline and Pfizer, pharmaceutical companies that market medications to aid smoking cessation, and has served as a paid expert witness in litigation against tobacco companies. J.B.F. declares no competing interests.

harm to overall public health is still ongoing, with different opinions prevailing in different countries^{3,4}.

Most of the harm caused by tobacco use is derived from exposure to combustion products of tobacco (FIG. 1). Sustained tobacco use is driven by addiction to nicotine. The most important goal in decreasing the harmful effects of tobacco use should be the reduction or elimination of the use of combusted tobacco, a concept that has been embraced by many leading tobacco control researchers and policy makers^{5,6}. ECs provide nicotine without harmful combustion products and have the potential to help tobacco smokers to quit. For individuals who cannot or do not want to quit, ECs can at least help to reduce exposure to various combustion-generated toxicants, resulting in less harm to health, particularly if smokers can completely replace combusted nicotine products with noncombusted products. In 2016, the promotion of EC use for harm reduction was recommended by the Royal College of Physicians in the UK³. Several clinical trials and longitudinal epidemiological studies suggest that ECs can promote smoking cessation, but high-quality clinical trials using modern EC devices are not yet available⁷. However, replacing tobacco cigarettes with ECs has been shown to decrease user exposure to the toxicants and carcinogens that are present in tobacco cigarettes, as determined by measuring numerous metabolite biomarker levels⁸. Despite these preliminary studies showing a benefit of EC use, others argue against the promotion of ECs, citing numerous concerns, including long-term adverse health effects; dual use with tobacco cigarettes, which might result in lower rates of cigarette smoking cessation; normalization of nicotine and cigarette smoking; disregard for smoke-free air legislation; diversion of smokers from proven smoking cessation treatment services; and its potential to serve as a gateway to cigarette smoking among young individuals^{4,9,10}.

Analyses of the public health burden of ECs need to consider both effects of EC use on smoking uptake and cessation, and direct effects of ECs on health¹¹. In this Review, we provide an overview of the potential adverse effects of ECs on cardiovascular health by describing the constituents, level of exposure of toxicants, and potential mechanisms of cardiovascular toxicity of ECs compared with tobacco cigarettes. Furthermore, we review available human data on cardiovascular effects of ECs to assess likely cardiovascular harm, and provide relevant advice for clinicians treating patients with cardiovascular disease (CVD) who are seeking to use ECs to aid in smoking cessation.

EC device and e-liquid constituents

EC devices generate a vapour or aerosol that delivers nicotine for inhalation without combusting tobacco. EC devices differ in size and mechanism of action, but all consist of a cartridge or reservoir filled with an e-liquid solution (containing propylene glycol and/or vegetable glycerin, nicotine, and flavourants), a heating element, and a battery¹² (FIG. 2). A wick, usually made of silica or cotton, delivers the e-liquid from the reservoir to the heating element (typically a metal coil). Some devices resemble conventional cigarettes, whereas others mimic pipes, cigars, or water pipes.

ECs are commonly categorized as either first-generation (cigarette-like), second-generation (tanks), or third-generation (mods) devices. Third-generation devices allow the user to alter

the temperature and the voltage or power applied to the atomizer, and are self-assembled. Advanced-generation devices typically have bigger batteries that produce a larger amount of aerosol and deliver much higher doses of nicotine than first-generation devices. Some EC devices have prefilled cartridges, with or without refillable cartridges or tanks, whereas others require the user to drip e-liquid directly onto the wick before use.

E-liquids typically contain nicotine at concentrations of 3–48 mg/ml. When using devices with higher battery voltage and heating temperature, solutions with lower nicotine content are typically used because more aerosol can be generated. Devices usually have one or more heating coils with different resistance characteristics, which can influence the heating temperature, and aerosol quantity and composition. E-liquids are typically flavoured; thousands of different flavours have been marketed, with the most common flavours being fruit-based, candy, coffee, menthol, and tobacco.

An EC is activated either by inhalation or pressing a button, which activates a sensor to begin heating the coils, resulting in vapourization of the liquid in the wick (FIG. 2). A typical puff lasts for 3–4 s (REFS 13,14). Upon reaching the mouth or the air, the vapour condenses into particles to form an aerosol. The pattern of EC use differs from that of tobacco cigarette use. Cigarette smokers typically inhale 10–12 puffs from their cigarette over 5–6 min, and this pattern is repeated with each cigarette every 30–60 min or so throughout the day, depending on their daily cigarette consumption. Because ECs do not burn, EC users can take fewer puffs at one time, which results in them spreading out their puffs more evenly throughout the day. A study in regular EC users reported wide variability in daily puffs, with averages of 120–225 puffs per day¹⁴. The amount of aerosol inhaled by an EC user can also vary depending on the device and nicotine concentration in the e-liquid. Users of third-generation EC devices with low nicotine content take in several-fold higher amounts of aerosol compared with users of earlier generation devices with higher nicotine levels in the e-liquid, suggestive of an attempt to maintain a desired level of nicotine in the body¹⁵. Therefore, ECs cannot be considered as a single device, and the exposure to nicotine and toxicants from one EC cannot be generalized across devices.

Because tobacco is not burned in ECs, they deliver neither carbon monoxide nor most of the thousands of combustion products found in cigarette smoke. The main constituents of e-liquid include propylene glycol and vegetable glycerin as the carrier solvents, nicotine, and flavourings. Low levels of contaminants might be present, either co-extracted with nicotine from tobacco or derived from the EC device. Tobacco-derived contaminants can include tobacco-specific nitrosamines, which are carcinogenic, and minor tobacco alkaloids such as nornicotine, nicotine, anabasine, and anatabine, some of which are psychoactive in high concentrations¹⁶. Contaminants from the device might include metals from the heating coils, solders, and wick, such as cadmium, chromium, lead, nickel, silver, tin, and silicates^{17,18}. These contaminants are generally present in low concentrations and most likely do not confer substantial toxicity to the user. However, the threshold dose for toxicity remains to be determined, and the presence of metals in nanoparticles that can be systemically absorbed is of concern.

Propylene glycol and vegetable glycerin

When heated, propylene glycol can form thermal dehydration products, including acetaldehyde, formaldehyde, propylene oxide, acetol, allyl alcohol, glyoxal, and methylglyoxal^{19–21}. Vegetable glycerin can generate acrolein and glycidol, as well as formaldehyde. As will be discussed later, of most concern with respect to CVD is acrolein, and to a lesser degree, formaldehyde and acetaldehyde. The generation of these aldehydes is highly dependent on temperature, which in turn depends on the power supplied to the atomizer. Increasing the battery voltage from 3.3 V to 4.8 V doubles the amount of e-liquid vapourized and increases the total aldehyde generation more than threefold, with acrolein emission increasing tenfold^{19,22}. Therefore, at low battery voltages, aldehyde emissions are relatively low compared with those generated by cigarettes; however, at high battery voltages, emissions are closer to and could even exceed those generated by cigarettes. Reuse of a device can also increase aldehyde generation, which is thought to be related to a build up of polymerization products that degrade upon heating. An important issue in extrapolating laboratory studies of emissions to human disease risk is to what extent ECs are used in a manner that generates high levels of aldehydes. Farsalinos and colleagues have suggested that at high temperatures, the taste of the emissions becomes unpleasant such that users will not operate their devices at this high setting²³. Studies in humans that assessed exposure to acrolein using urine biomarkers reported that exposures in EC users are much lower than those of smokers, and similar to those of nonsmokers^{8,24–26}. Although the lack of an increase in urinary acrolein metabolites with EC use does not translate to an absence of a biological effect, it does mean that exposure to acrolein from EC is much less than that of tobacco cigarettes, and presumably the harm associated with ECs is also considerably less.

ECs generate both highly reactive, short-lived free radicals, and stable, long-lived free radicals²⁷. The chemical nature of the radicals is unclear. The concentrations of reactive free radicals generated by ECs are 100-fold to 1,000-fold lower than those generated by cigarette smoke, but this value could vary considerably across devices. Daily exposure to free radicals from regular EC use is estimated to be higher than from air pollution, which is known to increase CVD risk^{27,28}. Therefore, although the relative degree of harm induced by free radicals is likely to be lower in ECs versus conventional cigarettes, the possibility of injurious effects from regular EC use cannot be excluded.

Particles generated by ECs are reported to have a bimodal size distribution, including both nanoparticles and submicron particles, the latter similar in size to most cigarette smoke particles²⁹. The nanoparticles are thought to be generated by the heating element or by pyrolysis of compounds in direct contact with the wire surface, and contain metals and low-volatility chemicals. The submicron particles are primarily derived from liquid propylene glycol and vegetable glycerine, and evaporate quickly in the air (half-life of 11 s)³⁰. The chemical nature of particles generated from ECs is different from that found in cigarette smoke. Cigarette smoke particles are made up of a complex mixture of hundreds of potentially toxic, semivolatile organic chemicals (cigarette tar), as well as carbonaceous solid materials⁵. Cigarette smoke, with a half-life of 20 min, persists in the environment for considerable periods of time. Cigarette smoke particles are similar to particles generated from burning of other organic materials such as wood, and have clearly been demonstrated

to have cardiovascular toxicity. The liquid particles in ECs deliver propylene glycol and vegetable glycerine to the lungs, where these solvents are presumed to be rapidly absorbed into the circulation and quickly metabolized. Whether the liquid particles generated by ECs are toxic is not known, but if so, given the simple solvent chemical composition of the EC liquid particles, the toxicity is likely to be less than that of the complex carbonaceous cigarette smoke particles. The toxicity of the EC nanoparticle emissions is unknown.

Flavourings

Most e-liquids are flavoured, and thousands of different flavours are currently available. Flavourings might contain alcohol, mixtures of terpenes and aldehydes, and known toxic chemicals such as diacetyl and benzaldehyde, which can cause pulmonary injury³¹. Cinnamaldehyde, found in cinnamon flavouring, has been shown to be cytotoxic *in vitro*³². No empirical data are available to date on the contribution of e-liquid flavouring to the health of EC users.

Nicotine

Whereas first-generation devices deliver less nicotine than late-generation devices, more advanced devices deliver similar amounts of nicotine compared with conventional cigarettes^{33,34}. The role of nicotine in cardiovascular toxicity of cigarette smoking has been of concern to researchers and clinicians for many years, and is a critical question when assessing potential cardiovascular risks of ECs. The cardiovascular pharmacology and toxicity of nicotine has been discussed in detail previously³⁵.

Basic pharmacology—Nicotine binds to nicotinic cholinergic receptors in the brain, autonomic ganglia, and adrenal medulla. Addiction to nicotine is mediated by $\alpha_4\beta_2$ nicotinic acetylcholine receptors (nAChRs), whereas its cardiovascular effects are mediated primarily by $\alpha_3\beta_4$ nAChRs³⁶. The binding of nicotine to the $\alpha_3\beta_4$ nAChRs results in release of catecholamines, both locally (neuronal) and systemically (adrenal). Nicotine also induces non-neuronal effects that are mediated primarily by homomeric α_7 nAChRs. Non-neuronal nAChRs are found on endothelial cells, inflammatory cells, macrophages, and keratinocytes³⁷.

Sustained exposure to nicotine results in desensitization of nAChRs and the development of acute tolerance. Tolerance must be considered when extrapolating acute effects of nicotine to predict the chronic effects. For example, nicotine leads to augmentation of angiogenesis acutely, whereas chronic exposure impairs angiogenesis, believed to be mediated by desensitization of vascular nAChRs^{38,39}. This tolerance explains, at least in part, the nonlinear cardiovascular dose–response relationship for nicotine, which is reassuring when considering whether there is an increased cardiovascular risk owing to increased nicotine levels when treating smokers with nicotine replacement therapy (NRT), or using ECs while they are still smoking cigarettes⁴⁰.

Pharmacokinetics: tobacco cigarettes versus ECs—Nicotine delivered via cigarette smoke or EC aerosol enters the mouth during the particle phase, and diffuses out of the particles into the vapour phase in the airways. Nicotine delivered through cigarette

smoke is rapidly absorbed, reaching the brain in 15–20 s (REF. 41). Although the nicotine from ECs is thought to be absorbed similarly, the extent of absorption from different sites within the pulmonary system might differ. Since nicotine is a weak base, the partition of nicotine from the particle phase to the vapour phase is dependent on pH levels, with more nicotine being un-ionized and free to diffuse at higher pH. E-liquid typically has a pH 7 (compared with a pH of 5.5 for cigarette smoke), with higher nicotine concentrations producing higher pHs¹⁶. Therefore, nicotine would leave the alkaline EC particulate phase more easily and be absorbed to a greater extent in the upper airway compared with cigarette delivery of nicotine.

Cigarette smoking results in intermittent peaks and troughs of nicotine in the blood throughout the day. The half-life of nicotine is approximately 2 h, and regular smoking produces a rise in nicotine levels over 6–8 h, with a slow decline overnight⁴². EC users tend to spread out their puffs more evenly throughout the day compared with cigarette smokers, leading to lower blood nicotine levels and lesser magnitude of arterial spikes. This differential pattern in nicotine concentration might be important when considering toxicity because the rate of rise of nicotine concentration in the blood affects the intensity of its pharmacological effects. Therefore, slower absorption and lower peak nicotine levels in users of ECs might result in less pronounced cardiovascular effects than from tobacco cigarettes.

The systemically absorbed dose of nicotine from cigarettes is approximately 1.0–1.5 mg (REF. 43). The absorbed dose of nicotine from ECs is potentially more variable, depending both on the device and how it is used. As mentioned previously, first-generation cigarette-like EC devices produce lower blood nicotine levels compared with conventional cigarettes, whereas more advanced devices with larger liquid reservoirs and higher voltage batteries can deliver as much nicotine as a cigarette^{33,44,45}. The concentration of nicotine in e-liquids typically ranges from 3 mg/ml to 48 mg/ml, but nicotine delivery is strongly influenced by the device and how much e-liquid is vapourized. An individual using an advanced device might absorb an equivalent or higher dose of nicotine from a 3 mg/ml e-liquid as another individual does from a first-generation device with a 30 mg/ml e-liquid¹⁵. Therefore, when interpreting research studies on the cardiovascular effects of ECs, the nature of the device and the concentration of the liquid should be taken into consideration for the optimal measurement of blood nicotine levels.

Cardiovascular effects of nicotine—Activation of nAChRs has been shown to promote haemodynamic changes, endothelial dysfunction, insulin resistance, dyslipidaemia, arrhythmogenesis, inflammation, and changes in the myocardium (TABLE 1). Importantly, epidemiological studies of smoking-related CVD cannot distinguish effects of nicotine from the effects of toxic combustion products from tobacco smoke. However, the cardiovascular risk of nicotine can be evaluated by assessing cardiovascular changes in participants of smoking cessation trials using NRT, and by analysing the epidemiological studies of users of smokeless tobacco.

Several studies have shown that NRT in patients with CVD does not increase cardiovascular event risk compared with placebo^{5,46–49}. Furthermore, a meta-analysis of 21 clinical trials

found that NRT was not associated with an increased risk of major adverse cardiac events compared with placebo, but was associated with an increased risk of less-serious events, such as palpitations and arrhythmia⁵⁰. A drawback of these NRT safety trials is the short study duration, and hence their limited utility in assessing the role of nicotine in atherogenesis.

The use of snus (a form of snuff), a smokeless tobacco product with low levels of carcinogenic nitrosamines that delivers similar amounts of nicotine to users as cigarettes, is widespread in certain parts of the world, such as in Sweden⁵¹. Snus did not increase the risk of myocardial infarction or stroke among a cohort of Swedish users, but was associated with a small increased risk of fatal myocardial infarction^{52,53}. A large US prospective trial found a modest, but significant, increased risk of acute cardiovascular events in current users of smokeless tobacco (snuff and chewing tobacco)⁵⁴. In another Swedish study, snus users who quit after an acute myocardial infarction event experienced a ~50% reduction in mortality in the following 2 years compared with those who continued snus use⁵⁵. In a cross-sectional study, carotid intima-media thickness (a biomarker of degree of atherosclerosis) was increased among cigarette smokers but not in snus users⁵⁶. Snus use has also been associated with a higher risk of heart failure, but not atrial fibrillation^{57,58}.

A 2016 meta-analysis investigating the use of smokeless tobacco and risk of CVD reported an overall increased risk of ischaemic heart disease and stroke deaths among ever-users⁵⁹. However, marked geographical differences were observed, with elevated nonfatal ischaemic heart disease risk seen in Asian countries, but not in European countries. The nature of the smokeless tobacco products can vary across countries, with Asian smokeless tobacco containing higher levels of nitrosamines and other toxic constituents, reflecting differences in preparation and use. The cleanest forms of tobacco, such as Swedish snus, would be most appropriate for examining the isolated effects of nicotine.

Given that the cleanest forms of smokeless tobacco use, unlike cigarette smoking, are generally not associated with an overall increased risk of myocardial infarction or atherosclerosis, nicotine is unlikely to be a major contributor to cigarette-induced atherosclerosis. The association between smokeless tobacco use, increased incidence of fatal myocardial infarction, and increased mortality with continued use after an acute myocardial infarction suggests that nicotine can contribute to acute cardiovascular events and mortality in the presence of ischaemic heart disease. However, a limitation of extrapolating the cardiovascular effects of the use of both NRT and smokeless tobacco to predict the potential harm of ECs is that nicotine is absorbed more slowly from the former delivery systems compared with nicotine that is absorbed rapidly from cigarette smoking and EC use, and thus the vascular effects could be less adverse.

Cardiovascular toxicity of cigarette smoking

Cigarette smoking accounts for a substantial proportion of CVD events worldwide. An examination of the cardiovascular risks of smoking, and the constituents and mechanisms of disease pathogenesis is important for understanding potential cardiovascular risks of EC use. The risk of acute coronary and cerebrovascular events, including myocardial infarction,

stroke, and sudden death, is markedly increased by smoking^{5,60,61}. Smokers experience accelerated atherogenesis involving the coronary arteries, carotid and cerebral arteries, aorta, and peripheral circulation. Smoking also aggravates angina pectoris and intermittent claudication, and causes vaso-spastic angina and restenosis after revascularization of the coronary or peripheral arteries⁴⁰. Other cardiovascular effects of tobacco cigarette smoking include progression and aggravation of heart failure and hypertensive heart disease. Echocardiographic studies involving cigarette smokers reported increased prevalence of left ventricular hypertrophy and diastolic dysfunction — risk factors for the development of heart failure — independent of coronary artery disease or alcohol consumption⁶². Smoking also causes arrhythmic events, including atrial fibrillation and sudden death^{63–66}. Acute myocardial infarction among smokers is associated with larger thrombus load with less severe atherosclerosis, and earlier onset of disease compared with nonsmokers⁶⁷. Other adverse vascular effects of smoking include impaired wound healing, erectile dysfunction, reproductive disorders, and macular degeneration.

Importantly, the relationship between cigarettes smoked per day and CVD mortality in smokers is nonlinear⁶⁸. Relatively low levels of exposure to cigarette smoke is sufficient to induce a substantial increased risk of CVD mortality; however, the level of risk plateaus at high exposure levels. This nonlinear dose–response has implications both for understanding the potentially limited reduction in cardiovascular damage by cutting down on cigarette smoking in heavy users, and for predicting cardiovascular risk based on levels of exposure to tobacco-derived toxicants.

Mechanisms of smoking-induced CVD

Numerous overlapping mechanisms contribute to smoking-induced cardiovascular damage, including oxidative injury, endothelial damage and dysfunction, enhanced thrombosis, chronic inflammation, haemodynamic stress, adverse effects on blood lipids, insulin resistance and diabetes mellitus, reduced oxygen delivery by red blood cells, and arrhythmogenesis. An in-depth discussion of these pathways to disease is beyond the scope of this Review, and has been extensively reviewed previously^{5,35,60,69–71}.

Cigarette smoke consists of a complex mixture of combustion products, including >7,000 chemicals⁵. The constituents within cigarette smoke that are suspected to contribute to CVD include oxidizing chemicals, volatile organic compounds, particulates, heavy metals, and nicotine (FIG. 1). The oxidizing chemicals within cigarette smoke contain reactive oxygen species and reactive nitrogen species; a single puff of cigarette smoke contains 1×10^{17} free radicals⁷². The oxidants present in the gas phase of tobacco smoke are believed to be the main contributors to atherogenesis and thrombogenesis^{69,70}. Oxidants damage endothelial cells, reduce the bioavailability of nitric oxide, deplete endogenous antioxidants, induce inflammation, and generate highly atherogenic oxidized LDL. Cigarette smoke can also contain high levels of carbon monoxide. Carbon monoxide binds more tightly to haemoglobin than oxygen, producing a functional anaemia. Reduced oxygen availability owing to carbon monoxide exposure can lead to angina pectoris, congestive heart failure, intermittent claudication, and chronic obstructive pulmonary disease, and can increase ventricular ectopy and reduce the ventricular fibrillation threshold⁷³. Thrombocytosis can

occur in response to functional anaemia, which increases blood viscosity and contributes to smoking-related thrombogenesis.

Numerous toxic organic chemicals are also present in cigarette smoke, including reactive aldehydes such as acrolein, and polycyclic hydrocarbons. Acrolein has been shown to cause vascular injury, endothelial dysfunction, platelet activation, dyslipidaemia, and neurogenic inflammation in animal models⁷⁴. Furthermore, acrolein can destabilize atherosclerotic lesions, accelerate atherogenesis, and induce dilated cardiomyopathy. Risk models in animal toxicology studies assessing potency and levels of exposure suggest that acrolein is a major contributor to smoking-induced disease, including CVD⁷⁵. Formaldehyde and acetaldehyde in high doses can also have harmful cardiovascular effects in animals⁷⁴. Furthermore, polycyclic hydrocarbons can accelerate atherosclerosis in some animal models⁷⁶, but their contribution to CVD from smoking is unclear.

Cigarette smoke particulates consist of droplets of water, nicotine, and various organic chemicals that contain solid carbonaceous materials. Exposure to particulates with aerodynamic diameters $<2.5\ \mu\text{m}$ (particulate matter [PM] 2.5), such as those in cigarette smoke, leads to oxidative injury, vascular inflammation, platelet activation, increased blood viscosity, and altered cardiac autonomic function⁷⁷. Exposure to PM 2.5, with sources ranging from ambient air pollution to secondhand smoke to cigarettes smoked per day, is associated with increased CVD risk^{68,77}. Furthermore, metals present in tobacco smoke, including lead, cadmium, and arsenic, can have cardiotoxic effects through oxidation of intracellular proteins, which can contribute to endothelial damage.

Cardiovascular toxicity of ECs

Caveats of current EC studies on CVD

ECs are highly variable with regard to the nature of the vapour and aerosol generated. As mentioned above, certain EC devices, particularly the first-generation devices, deliver very little nicotine, whereas more advanced devices can deliver as much as, or more than, a conventional cigarette. The cardiovascular effects of ECs that relate to nicotine are, therefore, dependent on the device. An optimal study of the cardiovascular effects of EC use would involve the measurement of nicotine concentration in blood; however, few studies have reported this method of data collection.

Other potential cardiovascular toxicants, such as acrolein and metals, as well as particle number and size distribution, vary according the device design, composition and resistance of coils, battery voltage, and how the device is used. An EC with high battery voltage and coil resistance generates high temperatures that can have a large effect on aldehyde exposure as well as total volume of aerosol exposure, resulting in increased exposure to oxidants and particulates, and potentially greater cardiovascular-related effects. Optimally, detailed information on EC design and emissions, use patterns, and biomarkers of toxicant exposure should be provided in cardiovascular studies, but so far, no available studies have included these data.

Preclinical studies on the effects of EC aerosols often expose cell cultures or animals to very high levels of aerosol, which do not accurately replicate intermittent human puffing, in either dose or duration. In cell studies, the exposure levels and time course of EC aerosol that is relevant to humans are difficult or impossible to determine. In animal studies, measurement of nicotine levels is feasible, but exposure to free radicals and the particle size distribution will be highly influenced by the exposure conditions (that is, how the aerosol or vapour is generated and delivered to the animal, given that aerosol characteristics change quickly with time, and free radicals are highly reactive and unstable).

The acute effects of ECs on biomarkers of CVD risk might not be useful predictors of future CVD. For example, whereas abnormal flow-mediated dilatation or aortic stiffness are strong markers of future cardiovascular events, an acute stimulus mediated by EC use that produces transient abnormalities might not be a relevant marker, particularly if ECs are used only intermittently. Nicotine can constrict blood vessels leading to a temporary increase in aortic pulse wave velocity, which is not equivalent to stiff vessels owing to chronic vascular disease. Likewise, reduced heart rate variability is a predictor of future cardiovascular events, as it reflects sympathetic neural tone, which is higher in the presence of underlying CVD⁷⁸. Nicotine increases sympathetic tone and is known to reduce heart rate variability⁷⁹, but a drug-induced change in sympathetic tone is not equivalent to increased sympathetic tone that is a manifestation of underlying disease.

Epidemiological studies of EC-related CVD risks are difficult to design and interpret because the overwhelming majority of EC users are either current or former cigarette smokers³⁵. Smokers who have switched completely to ECs can be assessed for future risks of acute cardiovascular events by comparing them with smokers who have quit without ECs, but the number of EC-only users who are in the age range when most acute cardiovascular events occur is small.

Given these limitations, any conclusions drawn from current EC studies must be interpreted with care. The cardiovascular effects mediated by ECs are described by their mechanisms of potential toxicity below. FIG. 3 depicts hypothetical mechanisms of EC-induced acute cardiovascular events.

Haemodynamic effects

The haemodynamic effects of EC are consistent with what is expected from effects of nicotine, as discussed previously. Any variability in effects across studies is likely to be related to differences in device-specific delivery of nicotine. ECs can cause an acute increase in heart rate, although the extent of this increase varies between studies⁸⁰. In addition, numerous EC studies have also reported an acute increase in blood pressure among users^{45,81–83}. However, several other studies have reported no changes in resting heart rate and resting blood pressure observed in daily users of ECs for 14 days up to 1 year^{84–86}. A *post-hoc* analysis of a study that provided ECs to smokers with no intention to quit found that EC users with hypertension who reduced or quit cigarette smoking experienced a significant reduction in resting systolic blood pressure⁸⁶. Cigarette smokers who quit tobacco smoking but continued to use ECs showed a larger reduction in blood pressure compared with those who only reduced tobacco smoking.

Cardiovascular structure and function

Several studies have examined the acute effects of ECs on arterial stiffness and myocardial function. Vlachopoulos and colleagues reported an increase in aortic stiffness with EC use in a cohort of 24 individuals who were free from cardiovascular risk factors, an effect that was delayed and of lesser magnitude compared with cigarette smokers⁸⁷. However, another study ($n = 15$) found no changes in arterial stiffness with EC use⁸⁸. In an electrocardiographic study, diastolic relaxation was impaired after smoking one cigarette (increased isovolumetric relaxation time), whereas *ad libitum* EC use for 7 min, similar to the time it takes to smoke a cigarette, had no effect on diastolic function⁸¹. Furthermore, only conventional cigarettes led to an increase in heart rate and blood pressure, suggesting that ECs users were exposed to less nicotine.

Both *in vitro* and human studies have described changes in endothelial cell function with EC use. In human cultured coronary endothelial cells, tobacco smoke, but not EC aerosol, induced a change in gene expression consistent with a stress response⁸⁹. A study that assessed human cultured vein endothelial cell cytotoxicity in cigarette smoke and 11 different e-liquid vapours reported that five e-liquid vapours were cytotoxic, causing cell death and reduced cell proliferation, but most were less toxic than cigarette smoke⁹⁰. Importantly, e-liquid cytotoxicity was observed with three e-liquids that did not contain nicotine.

Flow-mediated dilatation, studied in both smokers and nonsmokers, was acutely reduced in response to EC use and cigarette smoking⁹¹. Furthermore, both cigarette smoking and EC use acutely increased oxidative stress and decreased nitric oxide bioavailability, with EC having a significantly smaller effect on both measures. The mechanism underlying the effect of EC on endothelial function is unclear, but might be related to oxidative stress, or exposure to nicotine or particulates.

The effects of EC use on circulating levels of endothelial progenitor cells (EPCs) and microvesicles have also been examined⁹². Ten puffs from an EC increased levels of EPCs, thought to indicate a response to endothelial injury. However, nicotine itself can directly stimulate EPC release in the absence of endothelial injury, and in general, low rather than high EPC levels were associated with increased CVD risk^{93,94}. Antoniewicz and co-workers found minimal or no effect of EC use on levels of microvesicles that are released during endothelial cell injury or activation of leukocytes or platelets, indicating that EC use did not cause substantial endothelial cell damage, an inflammatory response, or platelet activation. Therefore, although ECs can have an effect on EPCs, given the other study findings, little evidence exists that this effect is predictive of future CVD risk.

Heart rate variability and oxidative stress were assessed in a cross-sectional study of 16 self-reported EC-only users and 19 nonsmokers⁹⁵. The EC users reported substantial use, but cotinine levels (a biomarker of nicotine exposure) were much lower than that typically reported in regular EC users, and specific biomarkers to exclude cigarette smoking were not measured. Study participants were instructed not to use ECs on the day of study. Frequency analysis of heart rate variation found a shift in sympathovagal balance towards sympathetic predominance, similar to what is seen in cigarette smokers⁹⁵. LDL oxidizability was

increased, consistent with elevated oxidative stress. C-reactive protein and fibrinogen levels, markers of inflammation, were not different between EC users and controls. The researchers suggest that EC use has effects on cardiac autonomic regulation even in the absence of acute nicotine-induced effects, and that these effects might indicate increased cardiovascular risk. However, study limitations including very light EC use among participants, failure to measure sensitive and specific biomarkers of cigarette smoking to exclude dual users, and a marked sex-specific imbalance between EC users and controls raise questions about the generalizability of the observations.

Inflammation

Chronic inflammation can accelerate atherosclerosis and induce plaque instability, contributing to acute cardio-vascular events. Cigarette smoking, but not acute EC use, increased white blood cells, lymphocytes, and granulocytes for 1 h after use⁹⁶. As noted previously, acute use of ECs is not associated with inflammation-induced microvesicle release, and a small cross-sectional study found no effects of EC use on C-reactive protein or fibrinogen levels, which are biomarkers of chronic inflammation^{92,95}. Preclinical studies assessing inflammation in response to EC use have focused largely on pulmonary effects⁹⁷. Exposure of human airway epithelial cells to EC aerosol led to increased secretion of inflammatory cytokines and elevated markers of oxidative stress⁹⁸. By contrast, a study of mRNA expression in nasal epithelial tissue of EC users found evidence of immune suppression⁹⁹. Any EC-related effects on chronic pulmonary inflammation is relevant to CVD risk, because systemic inflammation is known to increase CVD risk.

Observational studies

Longitudinal and survey studies have assessed adverse events and measures of physical health among EC users, but few reports of cardiovascular events exist^{100,101}. A case report described a patient aged 70 years with multiple medical issues who developed episodes of paroxysmal atrial fibrillation that were preceded by EC use¹⁰². Furthermore, two randomized, controlled trials investigated the long-term efficacy of ECs as a cessation tool for up to 1 year, with both reporting no significant increase in adverse events associated with EC use^{84,103}.

Conclusions

Cardiovascular safety is an important consideration in the debate on the benefits versus the risks of EC use, in particular for the use of ECs for smoking cessation in those with CVD. Given that no empirical data are available on cardiovascular events in EC users, the probability of CVD risk needs to be assessed from data on toxicity of constituents, levels of exposure, mechanisms, and studies using experimental models, placed in the context of available data on cardiovascular harm from conventional cigarettes. With the exception of nicotine and particulates, potentially toxic constituents are generally present in much lower levels in EC aerosol compared with cigarette smoke. Notably, EC particles are different from cigarette smoke particles, and their toxicity is unknown. Most of the cardiovascular effects demonstrated with EC use in humans are consistent with the known sympathomimetic effects of nicotine. Therefore, we believe that although ECs might pose some cardiovascular

risk, particularly in people with pre-existing CVD, the risk is less than that of cigarette smoking. If the adoption of ECs with appropriate design and safety regulations can reduce the prevalence of smoking, cardiovascular health is likely to improve in this population. A possible disadvantage of increased EC use is persistent dual use with tobacco cigarettes, which might result in lower rates of smoking cessation, and thus an adverse effect on cardiovascular health^{4,9,10}. The net effect of EC use on smoking prevalence is likely to be influenced by public health messaging and consumer perceptions, and vary between countries.

The general utility of ECs for cigarette smoking cessation has not yet been determined, but some cigarette smokers do successfully quit using ECs¹⁰⁴. In this context, we support the statement from the AHA: “if a patient has failed initial treatment, has been intolerant to or refuses to use conventional smoking cessation medications, and wishes to use [ECs] to aid quitting, it is reasonable to support the attempt” (REF. 105). For cigarette smokers with known CVD who quit smoking by using ECs, we recommend that they discontinue EC use when they are confident that they will not return to cigarette smoking.

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Key points

- The population risk versus benefit for use of electronic cigarettes (ECs) is strongly influenced by the relative safety of ECs compared with conventional cigarettes
- The exposure of EC users to potentially toxic chemical emissions is difficult to quantify, given the numerous types of EC devices, different e-liquids, and disparities in individual use patterns
- EC emissions of concern for cardiovascular health include nicotine, oxidizing chemicals, aldehydes (especially acrolein), and particulates
- Nicotine might contribute to acute cardiovascular events, particularly in people with underlying cardiovascular disease, primarily by sympathetic neural stimulation and systemic release of catecholamines
- The cardiovascular risk of EC use is likely to be much less than that of cigarette smoking

Figure 1. Tobacco combustion products present in a conventional cigarette

Cigarette smoke consists of a complex mixture of combustion products, including >7,000 chemicals. A single puff of cigarette smoke contains 1×10^{17} free radicals. The oxidizing chemicals present in the gas phase of tobacco smoke are believed to be the main contributors to atherogenesis and thrombogenesis.

Figure 2. Components of an electronic cigarette (EC)

The cartridge holds the e-liquid, which contains propylene glycol or vegetable glycerine, nicotine, and flavourings. When heated to high temperatures, as can occur with the use of advanced EC devices, propylene glycol can form thermal dehydration products such as acetaldehyde, formaldehyde, and propylene oxide, whereas vegetable glycerine can generate acrolein and glycidol.

Figure 3. Overview of mechanisms by which electronic cigarette use might cause acute cardiovascular events

Solid lines indicate known pathways. Dashed lines indicate pathways of concern, but for which there are no empirical data for confirmation.

Table 1

Cardiovascular effects of nicotine and mechanisms of action

Cardiovascular effects	Mechanisms	Contribution to smoking-induced CVD pathogenesis
Haemodynamic effects ^{73,106} : <ul style="list-style-type: none"> • ↑ Heart rate • ↑ Blood pressure • ↑ Myocardial contractility • ↑ Myocardial work • Cutaneous and coronary vasoconstriction • ↑ CBF/↓ CBF reserve 	Sympathetic neural stimulation	Probable
Endothelial dysfunction ^{107,108} : <ul style="list-style-type: none"> • Impaired flow-mediated dilatation with local intravenous infusion and nicotine nasal spray 	Unknown	Possible
Thrombogenesis ^{109,111} : <ul style="list-style-type: none"> • No effect or reduced platelet activation with long-term use in animals or with NRT 	Desensitization of adrenergic receptors	Unlikely
Inflammation ^{37,112} : <ul style="list-style-type: none"> • Direct anti-inflammatory effect • Possible indirect proinflammatory effect 	α ₇ AChR activation; β-adrenergic stimulation	Unlikely
Ventricular arrhythmogenesis ^{66,113,114} : <ul style="list-style-type: none"> • ↓ Ventricular fibrillation threshold in animals • ↑ Ventricular ectopy, ↑ ICD shocks, and sudden death in smokers 	Catecholamine release	Probable
Atrial arrhythmogenesis ⁶⁴ : <ul style="list-style-type: none"> • AF in animal models • ↑ Incidence of AF in smokers, but not smokeless tobacco users 	Altered atrial myocyte ion channel conductance; fibrosis	Probable
Lipid abnormalities ^{115,116} : <ul style="list-style-type: none"> • Lower HDL and higher triglyceride levels in smokers, but effect was minimal or absent in NRT and smokeless tobacco users 	Catecholamine-induced lipolysis with free fatty acid release	Possible
Insulin resistance and diabetes mellitus ^{117,119} : <ul style="list-style-type: none"> • ↑ Incidence of type 2 diabetes and insulin resistance in smokers • ↑ Insulin sensitivity in smokers • Conflicting evidence with NRT and smokeless tobacco use 	Catecholamine release; activation of AMP-activated protein kinase in adipose tissue	Possible
Myocardial effects ⁵⁷ : <ul style="list-style-type: none"> • Promotes remodelling and fibrosis, and causes dysfunction after ischaemia 	β-Adrenergic stimulation; oxidative stress	Possible

Cardiovascular effects	Mechanisms	Contribution to smoking-induced CVD pathogenesis
•	↑ Risk and/or aggravation of heart failure	

AF, atrial fibrillation; CBF, coronary blood flow; CVD, cardiovascular disease; ICD, implantable cardioverter–defibrillator; nAChR, nicotinic acetylcholine receptor; NRT, nicotine replacement therapy.