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Safety and efficacy of e-cigarettes in those with atherosclerotic disease: a review

Conor James McCaughey ,[1] Greg Murphy,[1] Jennifer Jones,[2] Kaumal Baig Mirza,[3] Mark Hensey[1]

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[1]Cardiology, St James Hospital, Dublin, Ireland
[2]National Institute of Preventive Cardiology, National University of Ireland Galway, Galway, Ireland
[3]School of Medicine, Trinity College Dublin, Dublin, Ireland

Correspondence to
Dr Conor James McCaughey; cmccaugh@tcd.ie

ABSTRACT

Smoking cessation is the most effective intervention to reduce mortality in patients with established atherosclerotic cardiovascular disease (ASCVD), with 'e-cigarettes' becoming an increasingly used intervention to achieve smoking cessation. The current review aims to summarise the current evidence base for their efficacy and safety in the ASCVD cohort. A search of the PUBMED and MEDLINE databases using the terms 'e-cigarette', 'cessation', 'safety' and 'efficacy' since 2012 yielded 706 results. Both observational and experimental studies were included, while those with an unavailable full text, non-English or duplicates were excluded, yielding 78 relevant articles, with 13 subsequent additional articles included from a search of reference lists, for a total of 91 included papers. E-cigarette vapour contains many known pro-atherosclerotic substances and has been demonstrated to potentiate traditional atherosclerotic mechanisms. While e-cigarettes may be more effective in promoting smoking cessation in the general population over a medium term (>6 months), when compared with nicotine replacement therapy (NRT), few studies specifically examined those with ASCVD, despite the latter having a higher baseline quit rate (52% vs 2%). Most studies compare e-cigarettes with NRT alone and do not include pharmacotherapy, which may be more effective in the ASCVD cohort.
The single randomised controlled trial addressing the research question favoured traditional methods. Those that successfully quit smoking using e-cigarettes are more likely to continue to use the intervention at 1 year (90% vs 9%). Conflicting advice exists regarding the utilisation of e-cigarettes for smoking cessation. E-cigarettes may be inferior to standard care for smoking cessation in those with ASCVD, and their use is likely to promote the key drivers of the atherosclerotic process already active in this cohort.

INTRODUCTION

Smoking cessation is the most effective intervention to reduce mortality in patients with established atherosclerotic cardiovascular disease (ASCVD).[1] The approximately 45% relative risk reduction (RRR) in cardiovascular mortality[2–4] is greater than that of high-intensity statin therapy (approximately 35% RRR[5 6]), or achieving a blood pressure reduction of 10 mm Hg (15% RRR[7]), and yet over half of patients presenting with myocardial infarction (MI) continue to smoke.[8] With such scope for therapeutic benefit, clinicians are having to consider the use of 'electronic cigarettes' (e-cigarettes), a device which has been marketed as both a smoking cessation tool and a method of harm reduction in those who smoke traditional tobacco cigarettes. With an evidence base which is still rapidly evolving and conflicting advice from regulatory bodies, the decision if, and to what degree, their use should be endorsed by clinicians is fraught. Fears of underusing a potentially effective smoking cessation tool must be balanced with the risk of promoting a potentially harmful nicotine-containing product to a vulnerable, high-risk population. The aim of the current review is to provide clarity to clinicians who may be considering recommending e-cigarettes to those with ASCVD, by outlining the rationale and latest evidence base for their use as a smoking cessation aid, addressing concerns regarding their safety and reviewing the current recommendations of varying health authorities. Finally, the review will highlight gaps in current evidence and outline recommendations for future practice.

METHODS

A search of the PUBMED and MEDLINE databases using the terms 'e-cigarette', 'cessation', 'safety' and 'efficacy' since 2012 yielded 706 results. Titles and abstracts were reviewed for relevancy to the research question. Both observational and experimental studies were included, while those with an unavailable full text, non-English or duplicates were excluded, yielding 78 relevant articles. A search of reference lists yielded a further 13 additional papers for inclusion for a total of 91 included papers (figure 1).

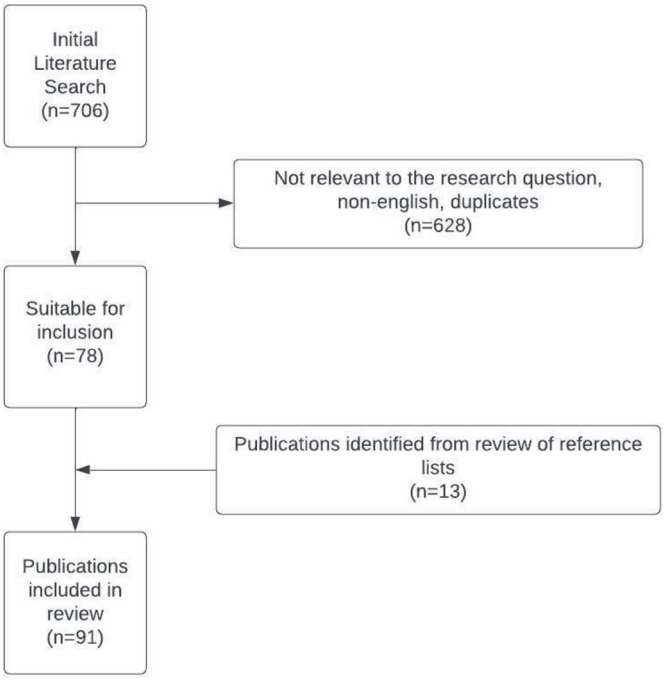

Figure 1 Flow chart detailing the process of literature review, with the number of articles indicated in parenthesis.

RESULTS

An addiction to smoking cigarettes is hard to quit

The primary addictive chemical in tobacco is nicotine.[9] Once absorbed, nicotine triggers the release of stimulatory neurotransmitters which, over time, lead to physical dependence through a process of repeated stimulation, neuroadaptation, tolerance and, eventually, withdrawal.[9] While nicotine has acute, unfavourable effects on blood pressure and heart rate, its role in disease, if any, is controversial.[10] There is consensus, however, that the primary drivers of smoking-related diseases are the over 7000 carcinogenic, atherosclerotic and proinflammatory chemicals found within cigarette smoke- inhaled at temperatures reaching several hundred degrees Celsius.[11] Traditional smoking cessation strategies, therefore, aim to either deliver nicotine through patches, gum or inhalers (nicotine replacement therapy (NRT)); or use non-nicotine-containing pharmacotherapies (eg, varenicline or bupropion) as a means to alleviate the symptoms of withdrawal, while circumventing the harmful effects of cigarette smoke.

As with any addiction, however, an addiction to cigarette smoking is more complex than physical dependence. A habit of smoking is developed around a range of conditioned behaviours, as well as social and environmental factors, which can in turn serve to potentiate withdrawal, reinforce the addiction and decrease the likelihood of a successful quit attempt.[9] For example, an individual may become conditioned to the sensation of inhaled smoke in response to a stressful situation, to holding a cigarette when drinking a cup of coffee, or to smoking in certain social situations. These psychological factors have neurobiological sequelae,[9] and may not be adequately addressed by traditional means of smoking cessation.[12]

Potential role of e-cigarettes in smoking cessation

E-cigarettes have been in mainstream use since 2009, being widely accredited to Chinese inventor Hon Lik.[13] Generally, they consist of a battery-powered heating coil which atomises an 'e-liquid' (a mixture of glycerol, polyethylene glycol and variable amounts of nicotine and flavourings) to generate a vapour, which is then inhaled[14] (figure 2). Proponents argue these devices serve as an NRT strategy and address the aforementioned behavioural aspects of addiction, providing similar tactile and visual feedback as a tobacco cigarette.

Yet, despite being widely considered as a safer alternative to cigarette smoking,[15] the long-term safety of e-cigarette use has not been established, and there are growing concerns regarding their safety at both the individual and population levels.[16] Consequently, governmental and non-governmental bodies have adopted their utility as a smoking cessation tool with different degrees of enthusiasm and hesitancy (table 1). The European Society of Cardiology, for example, has stated that while e-cigarettes are 'probably less harmful than tobacco' and 'may be more effective than other methods of smoking cessation', they have stopped short of an explicit endorsement, and have advised against dual use with tobacco cigarettes.[17] They do not make any comment on their use in an ASCVD population.[17]

One point of concern shared by almost all of these agencies is the uptake of e-cigarette use in adolescents and never smokers, with the potential to undo hard-fought public health gains and positive trends in smoking rates; as well as reported cases of vaporiser-associated acute respiratory distress syndrome.[18] While the importance of these concerns to cardiovascular disease prevention more broadly is acknowledged, they are outside the scope of the current review.

Safety of e-cigarettes

It may take decades before robust prospective epidemiological data emerge in habitual e-cigarette smokers examining clinical outcomes, and this is likely to always be confounded by some degree by previous or concurrent cigarette exposure.[16] And yet, many of the known mechanisms by which cigarettes mediate atherosclerotic disease initiation and progression are already well elucidated,[19] and it may be reasonable to assume that in having similar proinflammatory and atherogenic effects in both experimental and animal models (summarised in table 2) that e-cigarettes pose at least some risk to those with ASCVD. E-cigarette vapour, with a litany of harmful or undescribed chemicals, provides further indirect evidence of potential harm,[20] and there are emerging epidemiological data linking e-cigarette use to negative cardiovascular outcomes.[21]

Contents of e-cigarette vapour

The primary chemicals found within e cigarette vapour are carbonyl compounds, including acetaldehyde,

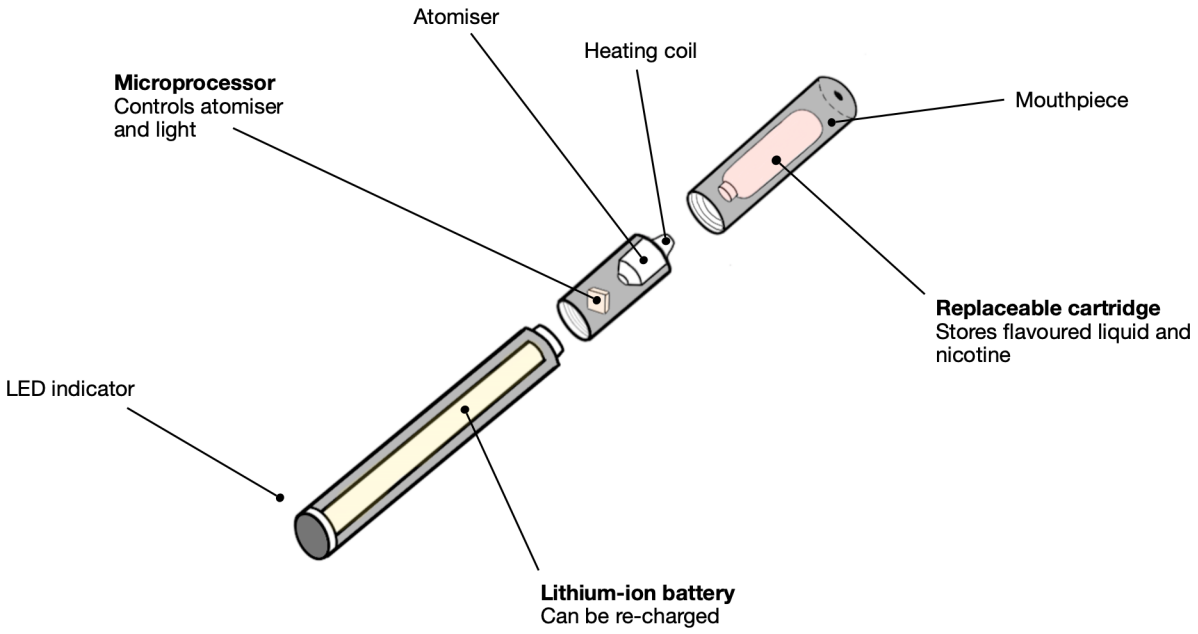

Figure 2 Diagram of a typical electronic cigarette ('e-cigarette').

acrolein and formaldehyde, as well as volatile organic compounds and metals[20]; however, there is marked variation in the analyte profiles of many available e-liquids and their resultant aerosols.[22] A number of studies have implicated the aerosolisation process itself with the formation of harmful chemicals, such as formaldehyde, being derived from solutions in which they were not originally detected.[20 23] This casts doubt on the assertion that the aerosolisation process is a safe alternative to combustion.

The solvent ethylene glycol (the primary ingredient in antifreeze) has been detected in commercially available e-liquids,[23] with detectable levels of its metabolites being found in e-cigarette users.[24] Additionally, many e-liquids listed as 'nicotine free' often contained up to one-quarter of the European Union-mandated maximum level of nicotine.[25]

E-cigarette vapour also contains high levels of fine particulate material (FPM) at a distribution (120–160 nm) comparable to that of tobacco cigarettes,[26 27] with FPM from tobacco cigarettes being a known driver of atherosclerosis.[28]

Experimental studies: indirect evidence for atherosclerosis and toxicity

A range of in vitro, animal and human studies have provided indirect evidence of the role of e-cigarettes in atherosclerosis, which are summarised in table 2. These studies demonstrate that e-cigarettes have unfavourable effects on cardiovascular haemodynamics,[16 29 30] are proinflammatory[31 32] and lead to endothelial dysfunction[30 33 34] and cardiac impairment in animals[35] (figure 3). Toxic metabolites and surrogate markers of oxidative stress have been found at higher levels in those who use e-cigarettes when compared with controls.[24 36]

A prospective cohort study of over 3000 US volunteers found that there was no difference in blood or urine concentrations of known toxicants in those who transitioned from exclusive cigarette use and 'dual' use with both cigarettes and e-cigarettes. There was an observed decrease in toxin concentrations when cigarette smokers or dual users transitioned to smoking exclusively e-cigarettes, however.[37] Given that the harmful effects of smoking on coronary disease risk are non-linear at lower exposures,[38] using e-cigarettes to 'cut down' on tobacco cigarettes through dual use is unlikely to derive significant benefit.

Observational data

The annual US-derived National Health Interview Surveys (NHIS) are some of the largest sources of cross-sectional data which have been used to examine the association between e-cigarette use and cardiovascular disease. Analysis of data derived from almost 70 000 patients enrolled in the 2014 and 2016 NHIS demonstrated an association between daily e-cigarette use and risk of prior MI (OR 1.79, 95% CI 1.20–2.66, p=0.004), although less so when compared with daily tobacco cigarette smoking (OR 2.72, 95% CI 2.29–3.24, p<0.001).[21] This association has not been consistently observed in pooled analysis of the 2016 and 2017 surveys, however.[39]

A similar pooled analysis of over 400 000 people included in the 2016 and 2017 Behavioural Risk Factor Surveillance System surveys demonstrated that dual use of cigarettes and e-cigarettes was associated with a 36%

Table 1 List of the most recent summary statements from governmental and non-governmental organisations on the use of e-cigarettes as a means of smoking cessation

Organisation	Advice	Recommendation
WHO	'[E-Cigarette] emissions typically contain nicotine and other toxic substances that are harmful to both users and those exposed to the vapours. Evidence reveals that these products are harmful to health and are not safe. However, it is too early to provide a clear answer on the long-term impact of using them or being exposed to them.'	Cautionary[49]
American Heart Association (AHA)	'The American Heart Association is a relentless force against vaping.' 'The AHA supports the inclusion of e-cigarettes in smoke-free air laws.' 'Clinicians should be educated about e-cigarettes and should be prepared to counsel their patients regarding comprehensive tobacco cessation strategies. There is not yet enough evidence for clinicians to counsel their patients who are using combustible tobacco products to use e-cigarettes as a primary cessation aid.'	Advises against[50]
European Association of Preventive Cardiology: Population Science and Public Health Section	'Health professionals should be cautious in recommending the use of e-cigarettes to their patients and the general public as: a. mounting evidence suggests that e-cigarettes are harmful to health, including to the heart; b. smokers might end up using e-cigarettes as a supplement to smoking without cutting back their tobacco consumption; c. there is a lack of robust evidence that e-cigarettes are effective as a smoking cessation tool; d. e-cigarettes seem to be used instead of evidence-based smoking cessation products and smoking cessation clinics.' 'E-cigarette should only be considered to aid tobacco cessation alongside a formal tobacco cessation programme.'	Cautionary[16]
Australian Government(s)	'For people who have tried to achieve smoking cessation with first-line therapy (combination of behavioural support and pharmacotherapy) but failed and are still motivated to quit smoking, [e-cigarettes] may be a reasonable intervention to recommend along with behavioural support. However, this needs to be preceded by an evidence-informed shared-decision making process.' (E-cigarettes are now available only by prescription in Australia.)	Cautionary[51]
Irish Heart Foundation	'While we recognise that some adult smokers may use them to help them quit traditional cigarettes, as they are not harm-free we would not recommend their use. Evidence has indicated that e-cigarettes can harm cardiovascular health and can act as a gateway to traditional tobacco use.'	Advises against[52]
Public Health England	'E-cigarettes are significantly less harmful than smoking. We may encourage smokers to try vaping, but we certainly encourage vapers to stop smoking tobacco completely.'	Advocates[53]

Summary recommendations are inferred as 'cautionary' if no explicit statements of endorsement or opposition could be found. Sources were taken from either official position/policy statements or issued advice to healthcare professionals. Citations are found below recommendation summaries.

higher risk of cardiovascular disease compared with those who just smoked cigarettes (OR 1.36, 95% CI 1.18–1.56, p<0.001), although failed to demonstrate a significantly increased risk among current e-cigarette users who had never smoked cigarettes.[40]

While these findings are certainly cause for concern, it is important to note that such cross-sectional surveys cannot determine a temporal association nor causality. That those who use e-cigarettes may have a higher association with prior ASCVD may simply reflect an increased tendency for those who have suffered an MI to use e-cigarettes to quit smoking, for example.

The large longitudinal Population Assessment of Tobacco and Health study, however, has been following a large cohort of Americans for over 6 years. An analysis of over 24 000 participants compared the rates of incident cardiovascular disease in those who were currently using exclusively e-cigarettes, exclusively cigarettes and dual users. After 4 years of follow-up, there was no significant increase in the rate of incident cardiovascular disease in exclusive e-cigarette users compared with non-users, although the study was limited by low event numbers in those that used exclusively e-cigarettes (41 events in 822 exclusive e-cigarette users).[41] As the majority of the participants in the study were under 35 years and those with pre-existing ASCVD were excluded, the degree to which the results can be applied to those with established ASCVD is unclear.

Efficacy of e-cigarettes as a smoking cessation tool in those with ASCVD

In order to address questions regarding the efficacy and safety of e-cigarettes in smoking, the Irish government commissioned a systematic review and meta-analysis of randomised controlled trials (RCTs), which found no benefit.[42] A subsequent Cochrane review of 61 studies (34 RCTs), however, suggested that there was moderate quality evidence that e-cigarettes were likely more effective than NRT for achieving abstinence in the short to medium term (6 months), equating to an extra three to

Table 2 Summary of a selection of available experimental studies examining the effect of e-cigarette vapour on established mechanisms of atherosclerosis

Pathology	Study	Description	Outcome
Endothelial cell dysfunction	In vitro (Putzhammer *et al*[33])	Human vascular endothelial cells exposed to 11 samples of e-cigarette vapour and cigarette smoke.	Cytotoxicity, inhibition of cell proliferation and alteration in morphology comparable to conventional high-nicotine cigarettes. High variability in vapour content and toxicity.
	In vitro (Hon *et al*, 2016) [32]	Human platelets exposed to tobacco smoke, e-cigarette smoke and controls.	Platelets exposed to e-cigarette vapour exhibited a greater proinflammatory adhesion and prothrombotic activity compared with cigarette smoke.
	In vivo (animal) (Olfert *et al*[35])	35 mice randomised to 8 months of 4 hours/day cigarette smoke, e-cigarette vapour or controls.	Similar increases in aortic arterial stiffness and impairment in endothelial function when compared with cigarettes.
	In vivo (human) (Staudt *et al*, 2018)[54]	Ten healthy volunteers who inhaled e-cigarette vapour assessed for blood levels of endothelial microparticles.	Increased levels of endothelial microparticles when compared with baseline.
	In vivo (human) (Antoniewicz *et al*[34])	Examination of endothelial progenitor cells (EPCs) in 16 healthy volunteers randomised to 10 puffs of e-cigarette vapour or no exposure in a cross-over design.	Increase in EPCs of the same magnitude as smoking one traditional cigarette.
Unfavourable haemodynamic changes	In vivo (human) (Vlachopoulos *et al*, 2016[55])	Effects of e-cigarettes, tobacco cigarettes and sham control on aortic stiffness and blood pressure of 24 smokers examined in a cross-over trial.	E-cigarette smoking over 30 min induces an unfavourable effect on aortic stiffness similar to cigarette smoking.
	In vivo (human) (Franzen *et al*, 2018[56])	Peripheral and central blood pressures of 15 active smokers up to 1 hour after e-cigarette or cigarette use in a cross-over randomised trial.	E-cigarettes were associated with a comparable but more prolonged increase in both central and peripheral arterial stiffness when compared with tobacco cigarettes.
	Cross-sectional (human) (Moheimani *et al*[29])	Cross-sectional case–control study of heart rate variability and oxidative stress of 42 healthy e-cigarette smokers and non-smoking controls.	E-cigarette use was associated with an increase in markers of sympathetic drive and oxidative stress.
Increased oxidative stress	In vitro (Higham *et al*[31])	Human neutrophils exposed to e-cigarette vapour and expression of CD11b, CD66b, MMP-9 and NE.	Increased release of proinflammatory cytokine upregulation of inflammatory signalling pathways.
	Cross-sectional (Rubinstein *et al*[24])	Cross-sectional analysis of urine and saliva of 105 adolescent e-cigarette and tobacco dual users and controls.	Increased levels of volatile organic compounds such as benzene acrylonitrile, acrolein and acrylamide in dual users and e-cigarette-only users.
	In vivo (human) (Carnevale *et al*[36])	A cross-over, single-blind study in 40 healthy subjects (20 smokers and 20 non-smokers, matched for age and sex).	E-cigarettes had an unfavourable effect on markers of oxidative stress and vascular resistance compared with controls, although to a lesser degree than cigarette smoke.

MMP-9, metal metalloprotease-9; NE, neutrophil elastase.

eight successful quit attempts per 100 patients.[43] When applying these findings to an established ASCVD cohort, however, several caveats should be noted.

Primarily, patients in these trials were recruited from a wide range of populations, with most trials not enumerating, and often even excluding, those with ASCVD. As there exists significant heterogeneity in the likelihood of a successful quit attempt between those with different comorbidities,[12] this aggregated finding is unlikely to be directly applicable to an ASCVD cohort, who, it should be noted, tend to have relatively higher rates of abstinence, often even greater than that of NRT or pharmacotherapy (figure 4).[12]

The use of NRT as the comparator arm may also obfuscate the relevance to the ASCVD cohort, as this may not equate to best medical therapy. For example, a meta-analysis of smoking cessation methods in those with ASCVD found that both varenicline (2.64, 95% CI 1.34–5.21) and bupropion (relative risk reductin (RR) 1.42, 95% CI 1.01–2.01) were effective when compared with placebo. The evidence regarding NRT was inconclusive (RR 1.22, 95% CI 0.72–2.06),[44] although it has been found to be safe.[45] The use of these pharmacotherapies varied greatly between studies, with some studies excluding those who had previously or currently used either medication; or allowed their use to varying degrees as an adjunct to NRT; or even as an adjunct to e-cigarette use.[43]

Perhaps the included trial with the greatest applicability to the current review was an RCT of varenicline versus e-cigarette use in 54 patients with a history of acute coronary syndrome, which found that those receiving varenicline were more likely to be abstinent at 24 weeks (47.3% vs 32.5%),[46] although this trial was noted to have

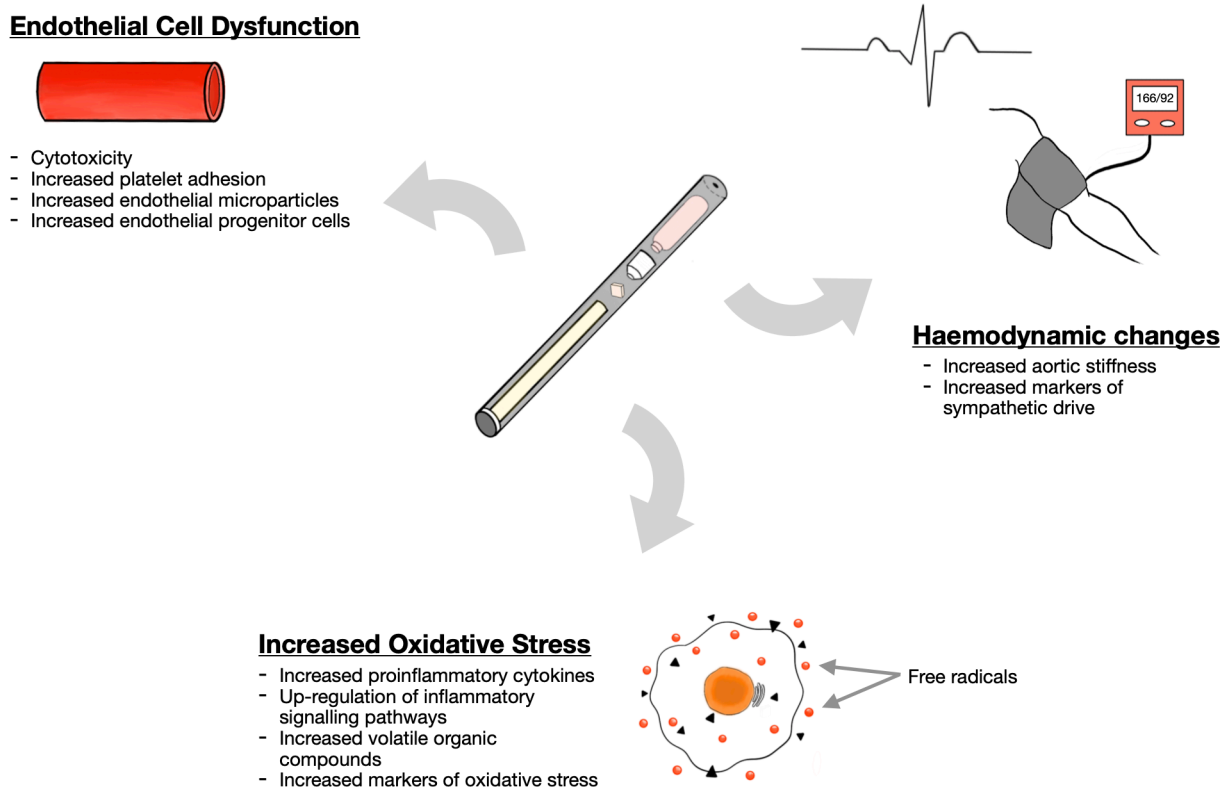

Figure 3 Diagram summarising the proatherosclerotic properties of e-cigarette vapour.

a high risk of bias given its small sample size and single-centre design.[43]

A much larger trial of six methods of smoking cessation offered as part of a company wellness programme to over 6000 participants found no significant increase in smoking cessation rates among those offered free smoking cessation aids (NRT and/or pharmacotherapy) and free e-cigarettes at 6 months. The number of participants with ASCVD was not recorded.[47]

A further RCT published in the *New England Journal of Medicine* examined patient-selected NRT versus an e-cigarette starter pack containing 18 ng/mL of nicotine (tobacco cigarette equivalent to 20 ng/mL) along with weekly behavioural support for 1 month. Exhaled carbon monoxide confirmed abstinence at 1 year favoured e-cigarettes, at 18% vs 9.9%, with an RR for successful quit attempt of 1.83 (95% CI 1.30 to 2.58, p<0.001).[48] Again, however, this study did not include the use of varenicline or bupropion, and history of ASCVD was not disclosed. Noteworthy, however, was that at 1 year, 90% of the e-cigarette arm still reported using the product, compared with 9% using NRT. This

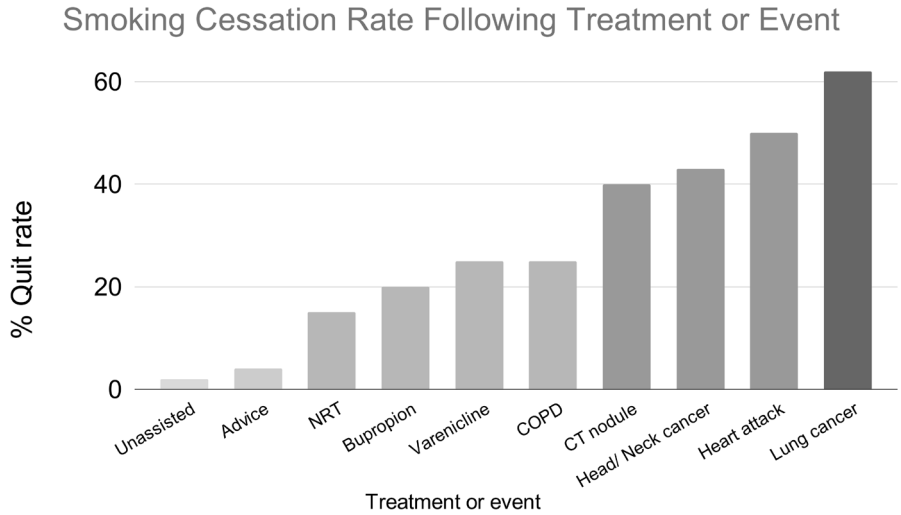

Figure 4 Approximate smoking cessation 1-year quit rates among smokers according to intervention or disease status (adapted from Young *et al* [12]). NRT, nicotine replacement therapy; COPD, chronic obstructive pulmonary disease.

seems to suggest that users simply switched one addiction for another, in a model closer to harm reduction rather than cessation,[48] and yet was considered in the Cochrane review as abstinence.

It may be surmised then, that while it may be the case that e-cigarettes may be more effective in promoting smoking cessation in the medium term when compared with NRT in a general population, the applicability of these studies to the ASCVD cohort is limited. Those with ASCVD may derive the greatest benefit from pharmacotherapy, compared with whom e-cigarettes have yet to demonstrate superiority. Additionally, given the reported propensity for e-cigarette users to continue using the product long term, and therefore likely remain addicted to nicotine, it is not clear what proportion will eventually return to cigarette smoking, casting doubts on their efficacy in the longer term.

CONCLUSION

Clinicians and patients attempting to weigh the evidence may reach varying conclusions regarding the efficacy of e-cigarettes in smoking cessation, with many reputable organisations and publications providing conflicting guidance on their endorsement. It should be remembered that while those with ASCVD are a high-risk population who may derive the greatest absolute risk reductions from smoking cessation, they are also much more likely to quit than the general population and may also be most likely to quit using traditional means. The efficacy of e-cigarettes in this group has yet to be demonstrated, and there is sufficient evidence to suggest at least some degree of harm, particularly in a group in whom the atherosclerotic process is already established. For those who are unable or unwilling to quit using traditional methods, it may be reasonable to frame e-cigarettes as a means of harm reduction, following an informed discussion regarding the risks and benefits, both unknown and known, and dual use with cigarettes should be discouraged.

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ORCID iD

Conor James McCaughey http://orcid.org/0000-0003-2593-6940

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