Electronic Cigarettes and Cardiovascular Risk: Science, Policy and the Cost of Certainty

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It often takes time to accumulate enough evidence to deem causal hypotheses plausible truths. Since the introduction of e-cigarettes about a decade ago, studies assessing their potential health effects have resulted in a weak evidence base for causal links to several important clinical outcomes.[1] Specifically, according to the National Academies of Science, Engineering, and Medicine's summary of available evidence on e-cigarettes and their health consequences, there is insufficient evidence to conclude whether e-cigarette use is associated with increased risk of clinical cardiovascular disease (CVD).[1] This lack of evidence, unfortunately, may easily be misconstrued by consumers as an absence of harm. As a result, the direction of e-cigarette regulatory policy and healthcare recommendations remains subject to seemingly endless controversy and debate.

There is one view that e-cigarettes may be less harmful nicotine delivery vehicles than traditional cigarettes, with potential utility for smoking cessation. Their possible use as quit devices is supported by the results of a recent randomised trial that showed e-cigarettes to be more effective for smoking cessation than nicotine-replacement therapy, when both were accompanied by behavioural support.[2]

However, in addition to the need for more trials to ascertain reproducibility of these findings, concerns remain about the safety of e-cigarettes. Because 'safer than cigarettes' does not necessarily mean safe, there are those who hold the opposing precautionary viewpoint that these products should be tightly regulated in view of lingering concerns about their long-term health effects.[3]

The rise in e-cigarette use among people who have never smoked and young people introduces another important piece to the e-cigarette and public health puzzle, extending the conversation from a debate on their utility for smoking cessation to questions about the public health implications of e-cigarette use by an ever-growing population of tobacco-naïve youth and adolescents.[4,5] In the US, for example, a recent study reported there were an estimated 2 million never-smoking e-cigarette users in 2016.[6] With the introduction of JUUL (a sleek, discreet, USB-shaped e-cigarette, especially popular among young people), these estimates are likely to be trending upwards.

In this issue, D'Amario et al. provide a balanced non-systematic narrative review of the e-cigarette evidence base.[6] The authors particularly emphasise the mechanistic, epidemiologic and policy aspects, as well as several important studies that have implications for furthering our understanding of potential relationships between e-cigarette use and CVD.

In examining the relationship between e-cigarette use and CVD risk, the first question that comes to mind is whether a possible relationship between e-cigarette exposure and CVD risk is plausible from a toxicological standpoint. As discussed by D'Amario et al., there is general agreement that e-cigarette vapour contains a range of substances that may be candidates for cardiovascular toxicity, including volatile organic compounds such as acrolein, flavouring derivatives, higher concentrations of nicotine and toxic metals such as lead, nickel and chromium.[6] However, whether these substances increase the risk of CVD at the dose of exposure afforded by e-cigarettes remains the subject of several ongoing studies.

Given the cardiovascular health concerns that exposure to these substances raise, a critical public health question arises over the level of evidence that scientists, clinicians and policymakers should consider sufficient to inform healthcare decisions and regulatory policy.[7] Should e-cigarettes be classified as safe because they contain fewer cardiotoxic compounds than traditional cigarettes?[8,9] Should toxicity findings from *in vitro* and animal studies be directly extrapolated to humans? Are transient changes in haemodynamic parameters, which have been demonstrated in acute exposure studies, sufficient to classify these products as harmful?[10] Should 'evidence' of harm from cross-sectional studies be deemed adequate, despite the possibility of significant confounding?[11] Is it ethical to wait for decades for results of longitudinal studies and an aggregation of evidence akin to that which informed the 1964 US surgeon general's report on smoking and health, while the use of these products by people who have never smoked continues to become more prevalent?

For now, the bulk of evidence is derived – as D'Amario et al. correctly noted – from animal studies, acute exposure human studies and cross-sectional epidemiologic studies.[6] While these studies hint at potential cardiovascular toxicity, they are by no means definitive.

Transient effects on heart rate variability and blood pressure, increased oxidative stress and endothelial dysfunction, toxic effects of flavouring additives on *in vitro* endothelial cells and cross-sectional associations between e-cigarette use and prevalent CVD have all been reported.[10–13] Nevertheless, to be certain of the relationship between e-cigarette use and CVD, more time and large, prospective, epidemiological studies are needed. Initial steps for longitudinal investigation could involve including e-cigarette use assessment in established cardiovascular cohorts. Another strategy may be to establish dedicated cohorts for studying the cardiovascular effects of e-cigarettes and other novel tobacco products.

However, given the rapid evolution of the e-cigarette market, their increasing acceptability and widespread concerns that these products may reverse the gains from many decades of smoking cessation efforts, the stakes are high, and time to strengthen the evidence base may be a luxury. The potential public health cost of certainty must therefore be duly considered in reaching decisions on policy and healthcare recommendations.

Consequently, in line with the position of the American Heart Association,[3] we recommend that, while the health consequences of e-cigarettes continue to be investigated, regulatory bodies must work assiduously to prevent the uptake of e-cigarettes in tobacco-naïve youth and adolescents through flavouring prohibitions, advertising and marketing restrictions, warning labels and robust public health education. ■

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