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A cautionary note on electronic cigarettes and vascular health

Jessica L Fetterman, Naomi M Hamburg

Evans Department of Medicine and Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston, MA, USA

Electronic cigarettes (e-cigarettes) first became widely available in 2003. E-cigarettes are particularly popular among current and former smokers and youth.¹ Among smokers, many express interest in utilizing e-cigarettes as a smoking cessation device, but the current literature creates an unclear picture as to whether e-cigarettes support complete cessation from tobacco products.² The majority of adult e-cigarette users continue to smoke combustible cigarettes, with reports suggesting close to a quarter are dual users of both electronic and combustible cigarettes.¹ A recent study showed that regular but not occasional e-cigarette use was associated with cessation of combustible cigarette use.² Regular e-cigarette use may help reduce daily consumption of combustible cigarettes, but there are cardiovascular risks associated with even low-intensity combustible cigarette smoking. Thus, the health impact of dual-use smoking patterns is not clear. Additional evidence about the health effects of e-cigarettes is required to ascertain their relative safety to combustible cigarettes and to advise policy makers regarding the risk of youth uptake.

E-cigarettes are electronic nicotine devices that encompass a wide array of products with varying battery sizes, voltage options, designs, nicotine concentrations, solvents, and flavored e-liquids. With thousands of e-cigarette products currently on the market, this diversity creates challenges in evaluating the health effects.³ Because most of the diseases associated with smoking are chronic, requiring years and even decades to develop, the chronic effects of e-cigarettes on human health will likely not be fully appreciated for many years to come. Consequently, intermediate biomarkers of cardiovascular injury must be utilized to begin to understand the potential health consequences of e-cigarette use.

The cardiovascular impact of combustible cigarette smoking is well described and is a major contributor to morbidity and mortality. Measures of arterial stiffness and endothelial function serve as intermediate dynamic biomarkers of cardiovascular injury that are associated with the risk of cardiovascular events.⁴ Prior studies have shown that combustible cigarette smokers have lower flow-mediated dilation (indicative of endothelial dysfunction), and nicotine itself has been shown to reduce flow-mediated vasodilation, albeit to a lesser degree than combustible cigarette smoking.⁵ Antioxidant treatment in smokers improves flow-mediated vasodilation, suggesting that smoking-induced endothelial dysfunction may be the result of increased oxidative stress.⁶

Corresponding author: Jessica L Fetterman, Evans Department of Medicine and Whitaker Cardiovascular Institute, Boston University School of Medicine, Evans Building, Room 748, Boston, MA 02118, USA. jefetter@bu.edu.

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Only a few studies have evaluated the acute impact of e-cigarette use on intermediate cardiovascular biomarkers of injury in people. In a study of young, healthy non-smokers and smokers, a single use of an e-cigarette containing nicotine lowered flow-mediated dilation.⁷ Further, measures of oxidative stress, serum 8-isoprostanes, and soluble NOX2 were shown to increase with acute use of e-cigarettes, suggesting that oxidant scavenging of nitric oxide may be a mechanism for e-cigarette-induced endothelial dysfunction.⁷ Consistent with this, in a study of combustible cigarette smokers, acute use of an e-cigarette containing nicotine increased malondialdehyde (MDA) levels, suggestive of oxidative stress.⁸ This same study found that 30 days of e-cigarette use in smokers was associated with an intermediate level of MDA compared to those who continued to smoke only combustible cigarettes and those who quit smoking completely. Further, smokers who used an e-cigarette device for 30 days had improved augmentation index (corrected for heart rate), suggestive of an improvement in arterial stiffness compared to those who continued to smoke only combustible cigarettes. Collectively, these studies to date have shown that transition to e-cigarettes may improve cardiovascular function among smokers, resulting in an intermediate level of injury compared to complete cessation and ongoing combustible cigarette smoking.

In this issue of *Vascular Medicine*, Franzen and colleagues describe the hemodynamic impact of acute e-cigarette use compared to combustible cigarettes in young healthy smokers.⁹ Smokers were studied three times in random order: following the use of a combustible cigarette, a third-generation e-cigarette with nicotine, and an e-cigarette without nicotine. The primary endpoints were peripheral and central blood pressures and measures of arterial stiffness. Although the number of study participants was small ($n=15$ participants), the e-cigarette exposure used the same device, e-liquid, and settings. Further, the participants received instructions to minimize variability related to differences in vaping topography. Compared to e-cigarette use without nicotine, peripheral systolic blood pressure, heart rate, augmentation index, and pulse-wave velocity were increased following use of an e-cigarette with nicotine or smoking a single combustible cigarette. Vaping an e-cigarette with nicotine or smoking a combustible cigarette resulted in elevated pulse-wave velocity that was independent of mean arterial pressure and heart rate, suggestive of increased vascular stiffness. The effects of nicotine from an e-cigarette and combustible cigarette seemed comparable, though the small sample size limited the ability to detect subtle differences in the health consequences between the two products. Overall, the findings add to prior acute e-cigarette use studies by including the nicotine-free e-cigarette exposure and suggest that the acute hemodynamic effects of e-cigarette use may be attributable to nicotine exposure. However, it remains possible that other components of e-cigarette aerosol have chronic vascular effects not observed in this acute use study. In addition, the effects of e-cigarette use may differ in older smokers with established cardiovascular risk factors or disease. Future studies are needed to evaluate different electronic nicotine delivery devices given the rapid evolution of the technology and changing patterns of use. Such studies would evaluate the cardiovascular health effects of e-cigarettes across multiple product characteristics such as voltage, solvents, device generation, and flavoring additives.

Data on the cardiovascular effects of chronic e-cigarette use are critically needed to develop public health recommendations. E-cigarette aerosol contains volatile organic compounds,

which are known cardiovascular toxicants.¹⁰ Whether e-cigarette users have reduced exposure to toxicants is unclear. Smokers who use e-cigarettes self-titrate in order to obtain the same level of nicotine exposure as they would if smoking combustible cigarettes.¹¹ Self-titration based upon nicotine could lead to a higher exposure to other toxicants, which could negate any harm-reduction effects. The study by Franzen and colleagues adds to the growing evidence that acute e-cigarette use impairs vascular function. The cardiovascular impact of acute e-cigarette use provides a cautionary note on the concept that e-cigarettes are lower risk tobacco products and supports the public health importance of reducing use of all tobacco products.

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