Smoke and Heart Should Stay Apart: A Look at E Cigarettes and Other Alternatives to Conventional Cigarettes, and Their Impact on Cardiovascular Health

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Abstract: The leading cause of preventable death in the world is smoking; leading to 7 million deaths attributable to tobacco use per year worldwide and 480,000 deaths per year in the United States. Though the actual rates of smoking in the United States have been on the decline, the advent of electronic cigarettes (E cigs) in 2007 was met with immense reception especially among the youth. Though initially thought to be a means to facilitate smoking cessation, recent evidence and the E cigs epidemic suggest its implications in significant morbidity and mortality. The other alternatives for conventional tobacco cigarettes have also been implicated in cardiovascular diseases. This manuscript aims to review E cigarettes and other alternatives to conventional cigarettes, and their impact on cardiovascular health. We conducted a Medline search using various combinations of "Cigarettes," "E cigarettes," "Smokeless tobacco," "hookah", and "cardiovascular risk" to identify pivotal trials published before May 10, 2020, for inclusion in this review. Concurrently, major practice guidelines, trial bibliographies, and pertinent reviews were examined to ensure inclusion of relevant trials. A consensus among

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the authors was used to choose items for narrative inclusion. The following section reviews data from pivotal trials to review the effects of E cigarettes, smokeless tobacco, hookah, nicotine replacement therapy on cardiovascular mortality and morbidity. There are many alternatives to conventional tobacco cigarette smoking, but none can be attributed as absolutely safe from a cardiovascular health perspective. The abundance of evidence regarding its impact on cardiovascular mortality and morbidity does not position it as a safe alternative, but an alternative means of smoking nicotine. The humongous rise in popularity and its gain in favor among the younger population poses a serious threat to the cardiovascular well-being of the exposed. Thus, E cigs and other alternatives of cigarette smoking do impart differing risks in cardiovascular mortality and morbidity, with the possible exception of nicotine replacement therapy. (Curr Probl Cardiol 2021;46:100640.)

Introduction

The leading cause of preventable death in the world is smoking leading to 7 million deaths attributable to tobacco per year world wide and 480,000 deaths per year in the United States.[1-2] Smoking also leads to significant morbidity, affecting almost every organ in the body.[2] Heart disease, chronic obstructive pulmonary disease, cancer, stroke, etc are caused by cigarette smoking. Approximately, 16 million Americans live with a smoking-associated disease.[2] The economic burden in terms of health care spending is approximately $170 billion and in terms of loss of productivity due to secondhand smoke expenditure and premature death is approximately $156 billion.[2-3]

Though cigarette smoking pose a public health problem, the actual rates of smoking in the United States have been on the decline.[4] The advent of electronic cigarettes (E cigs) in 2007 was met with immense reception especially among the youth.[5] In 2019, over 5 million US middle and high school students used E cigs in the past 30 days.[6] About 40% of E cigs users aged 18-24 years had never tried regular cigarettes, hence this serves as the gateway to tobacco products in younger population.[7] Though initially thought to be a means to facilitate smoking cessation, recent evidence and the E cigs epidemic suggests its implications in

TABLE 1. Cardiovascular impact by conventional tobacco cigarettes alternative

Tobacco cigarette alternative	Cardiovascular impact
E cigarettes	Myocardial infarction, stroke
Alzahrani et al., 2018	Arrhythmias
Vindhyal et al., 2019	
Moheimani et al., 2017	
Hookah	Increased risk of CAD
Selim et al., 2013	
Smokeless tobacco	No association with increased cardiovascular mortality
Huhtasaari et al., 1992	Association with MI and increased cardiovascular mortality
Huhtasaari et al., 1999	
Hergens et al., 2005	
Hansson et al., 2012	
Bolinder et al., 1994	
Henley et al., 2005	
Interheart study 2006	
Boffetta et al., 2009	
ARIC study, 2010	
Arefalk et al., 2014	
Nicotine replacement therapy	Imparts no additional cardiovascular risk
NRT RCT, 1994	
Joseph et al.,1996	
Mills et al., 2014	

significant morbidity and mortality. The other alternatives for conventional tobacco cigarettes have also been implicated in cardiovascular diseases (Table 1).

Discussion

E Cigarettes Effects on Cardiovascular Health

The components of E cigs are a battery, heating element, and the liquid container. In E cigs, aerosol is generated by heating liquids which consists of flavoring agent, solvent, water, and nicotine.[8] Nicotine causes sympathetic activation and is an addictive psychoactive substance. The amount of nicotine delivered by E Cigs depends on the generation of the device. The newer generation delivers nicotine more efficiently, although slower compared to traditional cigarettes.[8] Although the introduction of Juul, mod-pods, where nicotine salts are used, leads to time of delivery of nicotine closer to cigarettes, with a single pod housing as much nicotine as 20 cigarettes.[8] Apart from the nicotine, the solvents like acrolein, formaldehyde, acetaldehyde, the toxic chemicals in the flavorings, lead to additive adverse health effects.[9-10]

Cigarettes are known to activate inflammatory processes including atherosclerosis. There is evidence of E cigs causing inflammation of the pulmonary system.[11] Evidence of E cigs producing oxidative stress also demonstrates the propensity of the E cigs leading to atherosclerosis and major vascular disease, though at a lesser capacity compared to conventional cigarettes.[12-13] Furthermore, E cigs use can lead to stiffening of arteries, as demonstrated by decrease in flow-mediated dilatation, increase in pulse wave velocity, and circulating endothelial progenitor cells.[14-16] E cigs also have been shown to cause aggregation of platelets which can result in cardiovascular disease.[17-18] All these point to E cigs, though to a lesser extent compared to cigarettes, can lead to adverse effects on cardiovascular health through their effects on the vasculature.

A cross-sectional analysis of the National Health Interview Survey data revealed E cigs use was associated with higher odds of myocardial infarction (MI), stroke, and circulatory derangements.[19] Association with MI was also seen in daily use of E cigs when the National Health Interview Survey 2014 and 2016 data was adjusted for risk factors and smoking cigarettes.[20] E cigs can also be arrhythmogenic through sympathetic activation in chronic users which is similar to conventional cigarette use; which can lead to atrial and ventricular arrhythmias and even sudden cardiac death, with abnormalities in heart rate variability after acute use.[21-22] Thus, chronic E cigs use is associated with similar cardiovascular risk factors as cigarette use.

E Cigarettes Help in Smoking Cessation

E cigarettes had a rise in popularity as a relatively safer tool for smoking cessation. A pragmatic randomized-controlled superiority trial of 657 people was conducted to assess the efficacy of E cigs in cessation of smoking. The E cigs with or without nicotine did show a small effect in cessation of smoking which was similar to the results achieved with nicotine patches.[23] ECLAT trial was a prospective randomized-controlled trial where 300 cigarette smokers not intending to quit were divided into a high dose nicotine, lower dose nicotine, and nicotine free E cigs group.[24] It came to the conclusion that E cigs with or without nicotine helped in cessation of smoking with no significant adverse effects.[24] Another small randomized-controlled superiority trial of 48 smokers, who were unwilling to quit, revealed that E cigs, in both naive and prior users, decreased withdrawal symptoms and cravings of smoking cessation.[25] These trials pointed toward the possible use of E cigs as a tool in smoking cessation.

Since the prior evidence of E cigs was pretty much in par with the currently available nicotine patches, a larger randomized-controlled trial of 886 participants was conducted where E cigs and nicotine replacement therapy (NRT) were compared. The study showed statistically significant 1-year abstinence in the E cigs group compared to the NRT group when both groups were accompanied by behavioral therapy.[26] The common adverse effects were cough and phlegm. This study however had limitations; where people who failed to quit ended up with increased risk of double smoking exposure with E cigs on top of cigarettes. With the data indicating the cardiovascular as well as the pulmonary risk factors associated with E cigs, it is unclear whether E cigs should be utilized as the first line in smoking cessation.

E Cigarettes and EVALI

E cigs use among youth is of major concern. Apart from the exposure to addictive substances like nicotine in the adolescent population affecting brain development, the epidemic of E cigs, or vaping, product use-associated lung injury (EVALI) raised concerns about the long-term safety of vaping.[7] As of February 2020, 2807 cases with 68 confirmed deaths of EVALI has been reported.[27] The epidemic saw an acute rise in August, 2019 with its peak in September of 2019, and only a gradual decline since then.[7]

Vitamin E acetate was strongly linked with EVALI with identification of Vitamin E in 48 out of 51 BAL of EVALI patients.[28] This epidemic sparked the conversation of the widespread use of E cigs among youth and the need for regulations. The regulations with increased awareness and removal of Vitamin E acetate from the products has resulted in a steady decline of cases. The centers for disease control and prevention (CDC) and food and drug administration (FDA) recommend against use of E cigs in naive populations, especially the youth and pregnant women, with the use of E cigs as a cessation tool only to be considered if the adult decides to quit cigarettes while vaping.[27]

Other Alternatives for Conventional Tobacco Cigarettes

Nicotine Replacement Therapy

NRT is an FDA-approved smoking cessation tool which is considered safer. Transdermal nicotine, Varenicline, a partial agonist for the $\alpha 4\beta 2$ nicotinic acetylcholine receptor subtype, and bupropion, an atypical antidepressant, are commonly used in smoking cessation therapy. In a study

to test these healthier alternatives involving 584 outpatients that were split into a placebo group and a nicotine group. The subjects were checked for a sum of 14 weeks for the essential end purposes of the examination. After 14 weeks, the rate of abstinence from smoking was 21% in the nicotine group, as compared with 9% in the placebo group ($P = 0.001$), but after 24 weeks the abstinence rates were not significantly different (14% vs 11%, $P = 0.67$). They concluded that transdermal nicotine does not cause a huge increase in cardiovascular events in outpatients with heart ailment.[29]

Another study assessed the safety of transdermal nicotine for smoking cessation with patients who have coronary heart disease. This 5-week, randomized, placebo controlled, multicenter study selected 156 patients with coronary artery disease (CAD) who smoked in any event 1 pack of cigarettes every day. Patients were randomized to get either transdermal nicotine (14 mg/d) or transdermal placebo. Following a week, patients who had smoked in excess of 7 cigarettes had the option to have their portion of blinded investigation drug expanded to 21 mg/d of transdermal nicotine or related placebo. Transdermal nicotine was well tolerated by patients with stable CAD in this trial.[30] A meta-analysis looked at the 3 approved smoking cessation therapies—NRT, bupropion, and varenicline—and their association with an increased risk of cardiovascular disease events. The analysis did not reveal any increase in the risk of serious cardiovascular disease events.[31] Thus, the NRT seems to impart no additional cardiovascular risk, including the medications like varenicline and bupropion.

Hookah

Hookah is another alternative to traditional cigarette smoking that has been around for centuries among the African and Asian population but has recently enjoyed a rise in popularity in the United States. The increase in popularity though has largely stemmed from the introduction of flavored hookah tobacco in the 1990s.[32] The 2019 National Youth Tobacco Survey showed that over 600,000 youth have used hookah in the past month.[33] Hookah is a water pipe which uses charcoal as an external heat source to produce aerosol from tobacco.[34] Also, new forms of electronic hookah products including steam stones and hookah pens have been introduced. These products are battery powered and turn liquid containing nicotine, flavorings, and other chemicals into an aerosol, which is inhaled.

Though the process by which tobacco is heated in hookah is different, it is not much safer than cigarettes. A typical hour-long hookah session

equates to 200 puffs when compared to 20 puffs on average smoking a conventional cigarette, and the amount of smoke inhaled is 90,000 mL compared to 500-600 mL while smoking cigarettes.[35-36] Hookahs, which produce high levels of carbon monoxide, metals, and other cancer-causing chemicals, can lead to lung and oral cancers.[37] Short-term hookah use has been associated with sympathomimetic effects of increase in heart rate and blood pressure, while long-term use increasing the risk of CAD.[38-39] There is also evidence that suggests risk of CAD is higher in hookah smokers compared to conventional cigarette smokers.[40] Thus, the misconception of hookah being safer than cigarette needs to be addressed with evidence of increased harm compared to conventional cigarette smoking.

Smokeless Tobacco

Smokeless tobacco like "snuff," "snus," or chewing tobacco are some alternatives to smoking tobacco cigarettes. Snuff is an inhaled form of dry, ground tobacco leaves, whereas snus is a moist powder variant of the former consumed orally like chewing tobacco. There has been conflicting evidence about the cardiovascular effects of these smokeless tobacco products. One of the earlier studies in 1992 which looked at middle aged men, 35-64 years, concluded that compared to smoking cigarette snuff was associated with lower risk of MI.[41] In a population-based study within the framework of the Northern Sweden center of the World Health Organization Multinational Monitoring of Trend and Determinants in Cardiovascular Disease Project, the risk of MI among snuff dippers aged 25-64 years was not increased.[42] In regards to snus, a case control study with 1760 men, aged 45-70 years, failed to show an association with snus and MI.[43] A meta-analysis pooling data from 8 prospective cohort studies set in Sweden also failed to support any association with snus and MI, though a case fatality after MI was higher in this group, but no conclusions were drawn.[44] From this evidence it appeared from a cardiovascular perspective that smokeless tobacco was a satisfactory alternative to smoking cigarettes.

On the other side of the spectrum, there was also evidence supporting the hypothesis of smokeless tobacco contributing to cardiovascular morbidity and mortality. A prospective study of 135,036 Swedish construction workers revealed increased cardiovascular mortality noted in both users of smokeless tobacco and smokers.[45] An analysis of 2 prospective studies comparing smokeless tobacco users to nonusers, derived at an association with increased mortality from MI and stroke in the smokeless tobacco using population.[46] Furthermore, evidence from INTERHEART

and ARIC studies pointed at an association with increased risk of CAD and MI in smokeless tobacco population.[47-48] A meta-analysis of the studies conducted in Sweden and USA also showed an association of smokeless tobacco use with MI and stroke.[49] Further discontinuation of smokeless tobacco nearly halved the cardiovascular mortality risk, similar to cigarette smoking.[50] Though in the presence of conflicting data, the presence of significant evidence of smokeless tobacco use with cardiovascular mortality advises caution.

Conclusion

There are many alternatives to conventional tobacco cigarette smoking, but none can be attributed as absolutely safe from a cardiovascular health perspective. E cigs initial introduction was poised as a safe alternative to cigarette smoking. The abundance of evidence of its impact on cardiovascular mortality and morbidity does not position it as a safe alternative, but an alternative means of smoking nicotine. The humongous rise in popularity and its gain in favor among the younger population poses a serious threat to the cardiovascular well-being of the exposed. E cigs may have a place as a means of smoking cessation but restricted to adults who are willing to give up cigarettes while using E cigs, and who plan to quit E cigs as well, since smoking E cigs long term will result in similar cardiovascular outcomes.

In terms of other alternatives, the FDA-approved NRT provides a satisfactory safety profile in regard to cardiovascular health while helping to cut down on cigarette cravings. The notion of hookah being safer is false, with available evidence of even more cardiovascular harm compared to conventional cigarettes. Smokeless tobacco apart from the inherent increase in risk of oral cancers, also has some evidence of increase in cardiovascular mortality. Further research is warranted. Thus, E cigs and other alternatives of cigarette smoking do impart differing risks in cardiovascular mortality and morbidity, with the possible exception of NRT.

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