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Cardiologists and smoking alternatives: what we should know

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Dr. Dimitris J. Richter , FESC

It was not until 1958 that the first major epidemiologic study demonstrated a strong correlation between smoking and cardiovascular disease. The most effective approach for assisting smokers in their attempts to quit combines both pharmacotherapy and non-pharmacological interventions; however, our success continues to be suboptimal in the long term. New smoking alternatives, such as E-cigarettes and heat-not-burn devices, are now getting significant market shares. This article summarises actual scientific knowledge on these products since cardiologists will be asked by patients for their opinion on these.

Topic(s): *Risk Factors and Prevention;*

Introduction

In Europe, tobacco has been consumed in a variety of ways, but it was only at the start of the 20th century that cigarette smoking became very fashionable with the mass production of cigarettes [1,2]. Eventually, the potential health hazards of smoking were recognised by the US government - first, the association with lung cancer, and subsequently with other diseases. Early legislative attempts to ban cigarettes proved unsuccessful, however, as did heavy taxation.

Cigarette consumption has declined in recent years, but nevertheless an estimated 15,1% of US adults smoked in 2015. Worldwide, there are 1.3 billion smokers.

History of tobacco

Tobacco is first mentioned around 600 BC in South America [3]. In Europe, it was first imported by Spanish explorers. They observed the local inhabitants inhaling the smoke of burning dried tobacco leaves and subsequently adopted the habit themselves.

The first actual cigarette seems to have been smoked in 1832 by a soldier during the war between Turkey and Egypt. At various points in history smoking was banned – in 1633 the Turkish sultan was said to have executed 18 people per day not respecting this ban and smoking.

Nicotine, which was first isolated from tobacco in 1828, constitutes between 0.3% and 5% of the dried tobacco plant. It is recognised as a potent psychoactive drug that induces euphoria, which makes it highly addictive [1,2]. A single cigarette contains, on average, 11 mg of nicotine, of which 0.8 mg is extracted by smoking. Nicotine in cigarette smoke is responsible for the addictive nature and enhanced cardiovascular disease risk. During World War I, cigarette smoking escalated and a sharp increase in the incidence of cardiovascular disease was noted. However, it was not until 1958 that the first major epidemiologic study demonstrated a strong correlation between smoking and cardiovascular disease [4]. The study found that the risk of dying from coronary artery disease (CAD) was 70% greater in smokers than in non-smokers. Although it did not provide definitive evidence that tobacco smoke was responsible for the increased coronary risk, the study prompted the first anti-smoking measures by the US Surgeon General in his 1964 report, followed by the 1979 report proposing a definite association between smoking and CAD [5].

Smoking cessation counselling

The European Society of Cardiology in the latest prevention guidelines [6] reinforces the 5A smoking cessation strategy (ask, assess, advise, assist, arrange). This strategy has proved to be effective and patients rate it positively when asked about the help received from their doctor to stop smoking.

Brief advice on stopping smoking delivered by a physician has been seen to have a positive effect (although doctors generally do not feel the same way). The latest meta-analysis shows an increase in 6-month abstinence rates of 2.5% [7], which means that for every 40 smokers who receive short advice one will quit. Therefore, advice to stop smoking should be addressed to all smokers and not only to those who express an interest in quitting.

There is a dose-response relation between session length and abstinence rates.

All three session durations (minimal counselling – less than three minutes; low-intensity counselling – between 3 and 10 minutes; and higher intensity counselling – more than 10 minutes) significantly increased abstinence rates over those produced by no-contact conditions. However, there was a clear trend for abstinence rates to increase across these session lengths, with higher intensity counselling producing the highest rates.

Although we have quite successful medications for smoking cessation and good short-term results for smoking cessation at one year, the relapse rate is significant, which implies a high degree of psychological dependence.

Studies on varenicline showed that among subjects who received varenicline at the end of 12 weeks approximately 50% were successful in stopping smoking, while at 52 weeks after the initiation of the study drug (i.e., nine months after the drug was discontinued) the seven-day point-prevalence rates of abstinence from smoking were approximately 29% [8].

In addition to the prevention of smoking initiation and the promotion of smoking cessation, tobacco harm reduction is being recognised as a valuable and promising approach to accelerate further the decline in smoking prevalence and smoking-related harm [9]. Tobacco harm reduction is based on switching smokers to markedly less harmful alternative products, referred to by the Food and Drug Administration as modified-risk tobacco products (MRTP). The US Family Smoking Prevention and Tobacco Control Act defines an MRTP as "any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products".

Importantly, to improve health at the population level, these substitutes for cigarettes must be acceptable to smokers, providing adequate nicotine delivery and satisfaction to prevent relapse to cigarette smoking.

Therefore, tobacco companies try to substitute cigarettes either with electronic cigarettes or with "heat not burn" (HNB) devices. In an era where regulatory pressures and public campaigns constantly reduce the number of smokers and consequently the number of cigarettes sold, the aim is to provide alternative, less harmful methods to satisfy the smoker's addiction, reducing smoking-related health hazards.

In this fast-moving landscape with few solid scientific data, cardiologists are called on to express judgements on these products without real training or updating on the scientific level of evidence.

Electronic cigarettes (Ecigs)

There is a marked increase in the development and use of electronic nicotine delivery systems or electronic cigarettes (Ecigs).

The electronic cigarette is a device designed to deliver nicotine without tobacco smoke by heating a solution of nicotine, flavourings, additives, and propylene glycol and/or vegetable glycerine. It was first marketed in 2007 and during the last decade there has been a tremendous increase in electronic cigarette use by non-smokers, partly because of its marketing as a safe alternative to tobacco smoking. It is estimated that 12.6% of American adults and approximately 48.5 million EU citizens have been exposed to electronic cigarette use at least once [7].

The adverse effects of smoking have been attributed mainly to combustible tobacco products, and thus the electronic cigarette is presented as a safe alternative. However, electronic cigarettes are not pharmacologically controlled products in contrast with HNB devices. The content of nicotine (and of other components) differs substantially among electronic cigarette brands, even among the various available liquids for a given electronic cigarette type. Importantly, certain chemicals present in tobacco smoke, such as formaldehyde, acetaldehyde, acetone, acrolein and butanol, have been detected in electronic cigarettes and are associated with later puff fractions, lower liquid levels and

high operating voltage. In affected fractions, the amounts of aldehydes generated are comparable to or even higher than in conventional cigarettes, and in some electronic cigarette types dangerous substances have been detected even without nebulisation or heating. In addition, possible harmful effects of metals such as aluminium, barium, chromium, copper, cadmium, iron, lead and nickel detected in the electronic cigarette aerosol have been reported by several studies [10].

A recent review and meta-analysis on the cardiovascular effects of electronic cigarettes [11], including 26 eligible studies from 2000 to 2017, showed that acute exposure to Ecigs provoked a significant increase in heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP). When tobacco smokers switching to electronic cigarettes were examined, HR increase was similar but SBP and DBP were lower in Ecig users compared to tobacco smokers.

Recent studies have shown that both tobacco smoking and Ecigs adversely affect arterial elasticity and oxidative stress burden acutely. However, nicotine-free Ecigs resulted in a comparatively smaller increase in arterial stiffness. Moreover, replacement of conventional cigarettes by nicotine-containing Ecigs resulted in reduced central and brachial SBP, arterial wave reflections, and oxidative stress within one month, probably because of the reduction of the conventional cigarettes smoked [12].

Vlachopoulos et al recently showed that Ecigs also increase arterial stiffness in young adults through measurement of carotid-femoral pulse-wave velocity (PWV) 30 minutes after Ecig use [13].

Ecigs can also be used for smoking cessation.

An individually randomised controlled trial in the UK showed that Ecigs when compared to nicotine replacement therapy can be more effective for smoking cessation (18% vs 10%) although the success rate is quite low [14].

Vaping is considered much safer than smoking as Ecigs do not release the combustion chemicals responsible for the health risks of smoking. Ecig devices are mainly composed of a battery part and an atomiser. The atomiser consists of a chamber, usually composed of metals, plastics and/or glass, where the liquid is stored, and an atomiser head consisting of a wick and metal coil which is responsible for the heat delivery to the liquid that is subsequently evaporated.

The combination of flavouring, additives, and propylene glycol and/or vegetable glycerine sometimes seems to have unpredictable complications. In the USA until October 2019, more than 1,300 cases and 29 deaths have been reported in a series of "mysterious vaping illness" cases.

The cases demonstrate a heterogeneous collection of pneumonitis patterns that include acute eosinophilic pneumonia, organising pneumonia, lipoid pneumonia, diffuse alveolar damage and acute respiratory distress syndrome (ARDS), diffuse alveolar haemorrhage, hypersensitivity pneumonitis, and the rare giant-cell interstitial pneumonitis.

Though the precise manifestations of the respiratory injury may be diverse, there are clues to the precipitants that warrant attention. About 80% of the persons who vaped and became ill reported having used both nicotine products and tetrahydrocannabinol (THC) or cannabidiol (CBD) products. Active infection (which would include live bacterial contamination of e-cigarette fluids) does not appear to explain the clinical presentation, but acute toxic lung injury does seem to fit [15]. The dietary supplement vitamin E

acetate, which may be toxic when inhaled, has been found in close to half of the THC products. At the same time in the UK, where liquid control is much stricter, there have been no cases of acute lung injury as yet, increasing the probability that illegally sold non-authorised liquids could be responsible for this epidemic.

The FDA has issued a special announcement for an uptake of people presenting with seizures occurring with e-cigarette use (e.g., vaping), signalling a potential emerging safety issue. Most reports involved youths or young adult users. Seizures or convulsions are known potential side effects of nicotine toxicity and have been reported in the scientific literature in relation to intentional or accidental swallowing of e-liquid.

HNB devices

These devices heat a disposable tobacco stick with a thin metallic blade. The stick is maintained at a controlled heating temperature of up to 350°C, without combustion, fire, ash, or smoke. In addition, and in contrast to Ecigs, HNB devices do not vaporise liquid containing flavourings, propylene glycol, or vegetable glycerol. However, these new devices need to be fully examined in clinical studies, particularly concerning their effect on the cardiovascular system.

Because the HNB device heats the tobacco, instead of burning it, HNB devices emit significantly reduced levels of toxicants compared to cigarettes. The harmful and potentially harmful constituents (HPHCs) measured in HNB aerosol, including carcinogens, cardiovascular, reproductive, developmental, and respiratory toxicants (based on a list published by the FDA in 2012), are reduced by more than 90% on average in both the regular and menthol HNB variants, compared with levels found in cigarette smoke. This reduction in emissions led to a (90% or greater) reduction in both in vitro cytotoxicity and mutagenicity of both gas and particulate phases of the thirdhand smoke (THS) aerosol compared to the smoke of the 3R4F reference cigarette [16].

Cardiovascular markers are more complicated to test in a preclinical setting because, unlike carcinogens, there is not one particular marker that causes CAD but a combination of them and, to a large extent, the pathophysiological mechanism is unknown.

In a series of randomised clinical trials, it was shown that biomarkers of exposure (BoExp) to HPHCs are reduced substantially in smokers switching completely to HNB after only five days. These changes were largely maintained in an ambulatory setting, over a period of three months, in American smokers who switched to HNB [17].

When parameters related to the cardiovascular system were compared between continuous cigarette smokers and smokers who had turned to an HNB device there was a statistically significant improvement in five indices (HDL-C; WBC; FEV1%pred; COHb; Total NNAL) in those who switched to HNB devices [16].

Another study aiming to compare the acute effect of HNB, Ecigs and cigarettes on oxidative

stress, antioxidant reserve, platelet activation, flow-mediated dilation, blood pressure, and satisfaction scores showed that HNB had less impact than Ecigs and cigarettes on soluble Nox2-derived peptide, and 8-isoprostaglandin.

F2a-III, and vitamin E. HNB devices and Ecigs were equally less impactful than cigarettes on flow-mediated dilation, H_2O_2, H_2O_2 breakdown activity, soluble CD40 ligand, and soluble P-selectin. The effect of HNB devices and, to a lesser extent, Ecigs on blood pressure was less evident than that of cigarettes [18].

Improvement in cardiovascular function after switching to HNB devices was confirmed in another recent study showing that replacement of conventional cigarettes with HNB devices results in improved left ventricular (LV) longitudinal myocardial deformation, LV untwisting and reduced LV myocardial work index, possibly linked to the concomitant improvement of aortic elasticity, endothelial and coronary microcirculatory function and ventricular arterial coupling within one month [19].

Since IQOS (an HNB device) is considered a tobacco product (unlike Ecigs) in order to get permission to be sold in the USA, it had to prove that it was less harmful than conventional cigarettes. The FDA is responsible for approving new tobacco products to enter the market in the USA after examining the relevant studies that show reduced harm compared to conventional cigarettes. On 30/04/2019 the FDA announced that it had authorised the marketing of new tobacco products manufactured by Philip Morris Products S.A. for the IQOS "Tobacco Heating System". The FDA has placed stringent marketing restrictions on the products in an effort to prevent youth access and exposure. Following the usual rigorous science-based review through the pre-market tobacco product application (PMTA) pathway, the agency determined that authorising these products for the U.S. market was appropriate for the protection of public health because, among several key considerations, the products produce fewer or lower levels of some toxins than combustible cigarettes [20].

Conclusion

While there is no doubt that all new tobacco products continue to have a compounding effect on health, including the cardiovascular system, there is increasing evidence that they are less harmful than conventional cigarettes.

Cardiologists should continue to insist that their patients abstain completely from smoking in any form. Although this advice is a must for all cardiologists worldwide to their patients who have been smoking for many years, there is and will always be a proportion of patients unable or unwilling to stop. In these cases, Ecigs and HNB devices can be helpful in order to mitigate the devastating effects of smoking.

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💬 Notes to editor

Author:

Dimitris J. Richter, MD, FESC, FAHA

Head of Cardiac Dept, Athens Euroclinic, Athens, Greece

Chairperson of the ESC Council for Cardiology Practice

Address for correspondence:

Professor Dimitris J. Richter, 7-9 Athanasiadou & D. Soutsou Streets, 115 21 Athens, Greece

E-mail: richterdimitri@hotmail.com

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