The point on the electronic cigarette more than 10 years after its introduction

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Introduction

Smoking is universally recognized as one of the leading causes of premature death in the world. Despite the substantial decline in the prevalence of smoking among adults, it is estimated from studies conducted in the 1980s that it is still responsible for around 200,000 deaths per year for individuals aged 35-69 (around one-quarter of all deaths for this age group).

A prospective study conducted in the USA1 has shown that a person who has never smoked is twice as likely to reach the age of 80 as a smoker. Among women, the probability of reaching the age of 80 is 70% for those who have never smoked and 38% for active smokers; for men, these percentages are 61 and 26%, respectively. The causes for excess mortality in smokers are neoplastic, vascular, and pulmonary in nature. In the same analysis, it was shown that quitting smoking has an advantage in terms of life expectancy, the greater the earlier the cessation occurs. For smokers who quit in the 25-34 age group, the survival curve is practically comparable to those who have never smoked, with a gain of ~10 years in terms of life expectancy; those who quit smoking between the ages of 55 and 64 earn ~4 years.

The most recent European Society of Cardiology (ESC) guidelines for cardiovascular prevention also confirm this finding: the increase in disease-free survival is significant for every age group, and the benefits are even greater when one considers the gain in terms of overall health, not just cardiovascular.

Both active and passive cigarette smoking have a significant impact on cardiovascular risk and, in particular, on the atherosclerotic process. Both have been related to impaired endothelium-dependent vasodilation, both in the macrovascular (which includes the coronary circulation) and microvascular circulation, due to the reduced production of nitric oxide. Furthermore, smoking is associated with an increase in inflammation levels, an essential component in the initiation and maintenance of...
atherosclerosis, as demonstrated by the increase in numerous inflammatory markers, such as CRP, IL-6, and TNF-alpha, and blood leucocyte counts (between 20 and 25% more than in a non-smoker), recruited to the endothelial surface during the plaque formation process. The atherogenicity of cigarette smoke is also linked to an alteration of the lipid profile, with a significant increase in triglyceride and LDL levels and an increase in lipid peroxidation. Nicotine, the most studied active component of smoking, is the causative agent of insulin resistance in smokers (with a higher risk of developing Type II diabetes mellitus and metabolic syndrome) and increases sympathetic activation, with effects on blood pressure, heart rate, and peripheral vasoconstriction.

**Epidemiology**

According to the 2022 edition of the Heart Disease and Stroke Statistics published by the American Heart Association, 23.6% of high school students and 6.7% of middle school students used tobacco (in any form) in 2020. Among the latter, the preference for electronic cigarettes (e-cigarettes) over traditional ones is clear. Among adults, according to 2019 National Health Interview Survey (NHIS) data, 15.3% of men and 12.7% of women report smoking habitually.

As for e-cigarettes, they are the most commonly used tobacco product by young people; among high school students, there was an exponential increase in their use, with 19.6% of smokers using them. Among adults, 4.5% of the population uses it habitually.

In Italy, according to the report of the Istituto Superiore della Sanità (ISS), 24.2% of the population (12.4 million smokes (compared with 22% in 2019), with an average of ~11 cigarettes a day.

Regular and occasional users of e-cigarettes are 2.4% of the population: of these, almost 82% are dual consumers (smoking both traditional and e-cigarettes). Heated tobacco cigarettes, on the other hand, are used routinely or occasionally by 3.3% of the population, with consumption that has tripled compared with the 1.1% recorded in 2019.

**Electronic cigarettes: what are they? What evidence?**

E-cigarettes are devices consisting of a tank (containing a special liquid), an atomizer (which transforms the liquid into vapour), and a battery. The liquid consists of propylene glycol or vegetable glycerin compounds which, when vaporized, act as a vehicle for nicotine, flavours, and other chemical components. To date, four generations of e-cigarettes have been developed (Figure 1). The first two did not allow us to obtain a plasma level of nicotine comparable with that of the combustion products of tobacco. On the contrary, third-
generation devices have similar pharmacokinetics to traditional cigarettes, and in fourth-generation ones (available in refillable or disposable form), the chemical structure of nicotine is modified (from ‘pure’, or free-base, nicotine salt), so that it is more available. The newer devices are more efficient, as they provide a greater amount of nicotine using the less liquid carriers, thus reducing the overall exposure to aerosol from e-cigarettes.

It has been assumed that the use of e-cigarettes increases the rate of smoking cessation. However, a recent review of the literature shows that the available scientific evidence is inadequate to recommend e-cigarettes as a tool for smoking cessation in adults. The World Health Organization and the Food and Drug Administration have not approved them in this regard. Therefore, outside of clinical trials, the use of e-cigarettes should not be recommended to quit smoking. Basically, the positive data come from randomized clinical trials, while the neutral ones from observational studies. In 2020, a Cochrane meta-analysis of 50 intervention studies, half of which were randomized, for a total of over 12,000 subjects, demonstrated modest evidence that nicotine-containing e-cigarettes are more effective in inducing smoking cessation, for at least 6 months, compared with e-cigarettes without nicotine (risk ratio (RR) 1.71 [95% confidence interval (CI), 1.00-2.92]) and replacement therapies such as patches (NRT) (risk ratio 1.69 [95% CI, 1.25-2.27]).

A recent Canadian study using second-generation devices showed that nicotine-containing e-cigarettes, combined with psychological counselling, significantly increased smoking abstinence compared with simple counselling (21.9%, 9.1, respectively) at 12 weeks, but not at 24 weeks. On the other hand, non-nicotine e-cigarettes fared better than counselling alone at 24 but not at 12 weeks. The study, however, did not include NRT treatment and was terminated early due to ‘manufacturing delays’.

However, outside the strictly controlled conditions of clinical trials, the effects of ‘vaping’ on smoking cessation seem less favourable. The most recent meta-analysis that included observational studies on the use of e-cigarettes for smoking cessation was published in 2021 and analysed studies published since January 2020. This meta-analysis included 55 observational studies and 9 randomized clinical trials. The analysis of clinical trials was in line with the Cochrane analysis of 2020, demonstrating an association between the use of the e-cigarette and smoking cessation [OR 1.53 (95% CI, 1.16-2.02)]. Overall, data from observational studies concluded that there was no association between e-cigarette use and smoking cessation in adult smokers [OR 0.95 (95% CI, 0.77-1.16)] or in a subset of adult smokers with the intention to quit smoking [OR 0.85 (95% CI, 0.68-1.06)].

Similar results were obtained from a randomized intervention trial of 6006 smokers: providing free e-cigarettes was no more effective than standard therapy (motivational messages, information on the benefit of quitting). Unlike other randomized trials, the latter was not conducted in a clinical setting and the participants did not have access to psychological-behavioural support. The dichotomy of outcomes, depending on the study design, may in part be due to the behavioural support provided in the randomized clinical trials.

There are also further concerns regarding the effectiveness of e-cigarettes on smoking cessation. While e-cigarettes could be more effective in stopping cigarette smoking, they could be more addictive. A study of 886 subjects in the UK showed that smoking cessation for 1 year was achieved in 18% of subjects using second-generation devices and in 9.9% of subjects using standard nicotine replacement therapies (RR 1.83; 95% CI 1.30-2.58). However, among those who quit smoking tobacco, 80% still used e-cigarettes at 1 year (whereas 9% still used NRT). In addition, 25% of subjects became ‘dual users’ even though the e-cigarette user group reduced the number of tobacco cigarettes.

Some studies have suggested that there are higher relapse rates when e-cigarettes are used to quit smoking. According to a 2021 review, this risk is double that of subjects using other methods.

Finally, there are possible harmful effects of e-cigarette smoking. The combined use of e-cigarettes and traditional cigarettes was associated with higher rates of cardiovascular disease [OR 1.36 (95% CI 1.18-1.56)] compared with the use of traditional cigarettes alone. It has recently been shown that smoking cessation secondary to e-cigarette use exposes individuals to an increased risk of cardiovascular disease compared with those who quit without these alternatives [HR 1.31, (95% CI 1.01-1.70)]. The data would need further validation and longitudinal surveillance since those currently available are derived from cross-sectional studies.

To date, there are no conclusive data relating to the long-term cardiopulmonary effects of the use of e-cigarettes, partly due to their recent marketing and also as they are devices that are constantly evolving from both an engineering and chemical composition point of view.

Electronic cigarettes: cardiovascular and pulmonary effects

As already mentioned, data on the effects of vaping on cardiovascular risk are derived from cross-sectional studies and short-term observational epidemiological studies. The data available to date show a worsening of cardiovascular risk and an increased incidence of myocardial infarction [OR, 1.79 (95% CI, 1.20-2.66)] associated with the use of e-cigarettes. Several studies related to the acute effects of e-smoking demonstrate a pathogenetic mechanism affecting the cardiovascular system similar to traditional smoking, suggesting how ‘vaping’ can determine:

- Increased blood pressure and heart rate in the case of nicotine-containing e-cigarettes.
- Increased arterial stiffness, as documented by the increase in pulse wave velocity (PWV) following inhalation of the aerosol of e-cigarettes. The acute alteration of this parameter is likely secondary to
Endothelial dysfunction or sympathetic activation of the smooth muscle cells of the arterial vessels.

- Endothelial dysfunction due to a reduction in the release of nitric oxide at the level of the vessels, as evidenced by several studies documenting an acute reduction in plasma concentrations of nitric oxide or its metabolites,18,19 and an increase in the indices of endothelial dysfunction18,19 and of oxidative stress18,19 associated with vaping.

- Prothrombotic effect secondary to the activation of platelet aggregation.18

These evidences on the acute effects of electronic smoking support the hypothesis that chronic use can lead to damage to the vascular system (Table 1). Studies comparing e-smoking to traditional cigarettes suggest a lower cardiovascular risk profile associated with the use of these devices.18 The use of e-smoking as a substitute for traditional smoking does not appear to be beneficial in terms of cardiovascular risk reduction.18,19

Finally, considering the respiratory system, several epidemiological observational studies have shown an association between electronic smoking consumption and asthma [OR, 1.39-3.41 (95% CI, 1.15-6.49)], respiratory diseases [OR, 1.31-2.58 (95% CI, 1.03-4.89)], COVID-19 [OR, 5.05 (95% CI, 1.82-13.96)], and wheezing [OR, 1.67 (95% CI, 1.23-2.15)].7 Due to a lack of data in the long term, it is not currently possible to establish a relationship between e-smoking and slow-developing lung diseases such as chronic obstructive pulmonary disease and lung cancer. The pathogenetic mechanisms of pulmonary toxicity associated with e-cigarette use are similar to those of traditional smoking, such as exposure to carcinogenic nitrosamines derived from nicotine metabolism.7 There are also toxic components unique to e-smoking, such as aldehydes and ketones derived from the degradation of liquids used in some devices.7 Overall, compared with traditional smoking, e-smoking has been seen to expose the user to lesser amounts of toxins.7

A special population: pregnant women

A separate chapter is represented by pregnant women. Traditional smoking in pregnant women increases the risk of unfavourable outcomes, such as low birth weight, placental abruption, premature birth, miscarriage, and neonatal or infant death.20 It is therefore extremely important to identify valid approaches to promote smoking cessation during pregnancy. To date, only two drugs have been tested for this purpose. Nine randomized, placebo-controlled trials investigated the efficacy of nicotine replacement products (NRTs), and only two studies evaluated the effects of bupropion, demonstrating limited effects for NRTs and no benefit for bupropion.20 These results may be explained by poor adherence to treatment and, in the case of NRTs, also by a reduced nicotine intake. Therefore, the standard dose of nicotine contained in NRTs may be too low for this category of smokers.20 E-cigarettes may be more effective than traditional NRTs, such as patches and chewing gum, because they allow adequate titration of the intake of nicotine according to the consumer’s needs. The use of these devices as an aid to traditional smoking cessation has in fact increased in pregnant women, although the efficacy and safety of these devices are not yet adequately known.20

The use of e-cigarettes in pregnant women raises the same perplexities as NRT in terms of the potential harmful effects of nicotine on the development of the foetus.

Conclusions

E-cigarettes have been identified by numerous agencies and professional organizations as a genuine public health problem. The risks associated with these devices are different, especially for adolescents, who have a very high incidence of nicotine addiction, a greater vulnerability to lung damage, and potentially harmful effects on cognitive functioning. The proliferation of new and

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### Table 1. Effects of e-cigarettes on the cardiovascular system (data derived from clinical trials)

| Variable             | Marker     | Change | Device generation | Nicotine concentration (mg/mL) |
|----------------------|------------|--------|-------------------|--------------------------------|
| Sympathetic tone     | Heart rate | +      | 1st, 2nd, 3rd     | Up to 24                       |
|                      | Systolic BP| +      | 1st, 2nd, 3rd     | Up to 24                       |
|                      | Diastolic BP| +     | 1st, 2nd, 3rd     | Up to 24                       |
|                      | Neural tone|        | 2nd               |                                |
| Vascular stiffness   | HRV        | –      | 1st               | 1.8                            |
| Endothelial function | FMD        | +      | 1st, 2nd          | Unclear                        |
| Oxidative stress     | MPO        | +      | 3rd               | Unclear                        |
|                      | H2O2       | +      | 2nd               | Unclear                        |
| Prothrombotic effects| Platelet aggregation | + | Unclear | 19 |
|                      | Platelet microvesicles | + | 2nd, 3rd | |

BP, blood pressure; FMD, flow-mediated dilation; H2O2, hydrogen peroxide; HRV, heart rate variability; MPO, myeloperoxidase; PWV, pulse wave velocity.
innovative devices, which are effectively marketed to young people, has led to an exponential increase in vaping in this population of consumers. Although e-cigarettes contain fewer toxic and carcinogenic substances than traditional cigarettes, there is still exposure to these substances and, in particular, to nicotine.

On the other hand, traditional cigarettes are responsible for very serious diseases, which greatly increase morbidity and mortality. It is therefore essential to promote and encourage smoking cessation. To this end, the use of e-cigarettes could be considered in certain circumstances. In fact, there is growing evidence on the efficacy of e-cigarettes as a tool for smoking cessation in the adult population who have failed traditional methods such as NRTs (patches and gums), psychological support, and drugs (especially varenicline). However, there is much concern about the evidence of the high resumption rate of traditional smoking and the continuous dual use of tobacco and e-cigarettes and the risk of non-smokers who use e-cigarettes to start smoking traditional cigarettes. These public health concerns are very important and require close monitoring and should be discussed with anyone intending to use these smoking cessation devices.

Conflict of interest: None declared.

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