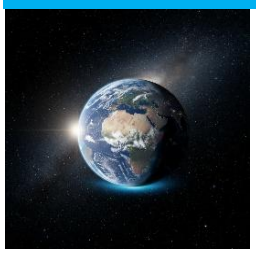
NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ



Quality in Sport. eISSN 2450-3118.

Journal Home Page
https://apcz.umk.pl/QS/index

DZIEMIAŃCZUK, Jakub, DRYL-JARMOC, Ewa, ŚLINKO, Izabela, KULIŚ, Gabriela, PANAS, Zuzanna, KRAWCZUK, Kacper, ZIMOWSKI, Mateusz, KADYSZ, Piotr, KOLANEK, Agata and CZAJKOWSKI, Mateusz. The Effect of Different Nicotine Delivery Systems on Cardiovascular Health and Hemodynamic Load: A Literature Review. Quality in Sport. 2026;54:70308. eISSN 2450-3118. https://doi.org/10.12775/QS.2026.54.70308

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 l.p. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 26.03.2026. Revised: 30.03.2026. Accepted: 30.03.2026. Published: 05.04.2026.

THE EFFECT OF DIFFERENT NICOTINE DELIVERY SYSTEMS ON CARDIOVASCULAR HEALTH AND HEMODYNAMIC LOAD: A LITERATURE REVIEW

Authors

Jakub Dziemiańczuk[1], ORCID https://orcid.org/0009-0007-7454-3111
E-mail: dziemianczukjakub@gmail.com
[1]University Clinical Hospital in Bialystok, Marii Skłodowskiej-Curie 24A, 15-276 Bialystok, Poland

Ewa Dryl-Jarmoc[2], ORCID https://orcid.org/0009-0007-2946-0800
E-mail: ewa.dryl96@gmail.com
[2]University Clinical Hospital in Bialystok, Marii Skłodowskiej-Curie 24A, 15-276 Bialystok, Poland

Izabela Ślinko[3], ORCID https://orcid.org/0009-0002-5953-5168
E-mail: izabelaslinkoo@gmail.com
[3]University Clinical Hospital in Bialystok, Marii Skłodowskiej-Curie 24A, 15-276 Bialystok, Poland

Gabriela Kuliś[4], ORCID https://orcid.org/0009-0006-8136-2661
E-mail: gabriela.kulis1356@gmail.com
[4]University Clinical Hospital in Bialystok, Marii Skłodowskiej-Curie 24A, 15-276 Bialystok, Poland

Zuzanna Panas[5], ORCID https://orcid.org/0009-0009-6850-4110
E-mail: zuzia.panas@wp.pl
[5]University Clinical Hospital in Bialystok, Marii Skłodowskiej-Curie 24A, 15-276 Bialystok, Poland

Kacper Krawczuk[6], ORCID https://orcid.org/0009-0009-3089-6323
E-mail: kacperkrawczuk@gmail.com
[6]University Clinical Hospital in Bialystok, Marii Skłodowskiej-Curie 24A, 15-276 Bialystok, Poland

Mateusz Zimowski[7], ORCID https://orcid.org/0009-0003-0280-343X
E-mail: mateuszzimowski@icloud.com
[7]University Clinical Hospital in Bialystok, Marii Skłodowskiej-Curie 24A, 15-276 Bialystok, Poland

Piotr Kadysz[8], ORCID https://orcid.org/0009-0004-8952-3103
E-mail: lek.kadysz.piotr@gmail.com
[8]Faculty of Medicine, Medical University of Białystok, Jana Kilińskiego 1, 15-089 Białystok, Poland

Agata Kolanek[9], ORCID https://orcid.org/0009-0002-0937-2938
E-mail: agkolanek@gmail.com
[9]Faculty of Medicine, Medical University of Białystok, Jana Kilińskiego 1, 15-089 Białystok, Poland

Mateusz Czajkowski[10], ORCID https://orcid.org/0009-0001-2924-694X
E-mail: matczajkowski24@gmail.com
[10]University Clinical Hospital in Bialystok, Marii Skłodowskiej-Curie 24A, 15-276 Bialystok, Poland

Corresponding Author
Jakub Dziemiańczuk, E-mail dziemianczukjakub@gmail.com

Abstract

Introduction: Active and passive smoking are leading global causes of cardiovascular (CVD) mortality, accounting for 2.25 million deaths annually (2021 data). Alternative nicotine delivery systems (e-cigarettes, heated tobacco products [HTP], snus, nicotine pouches) have surged in popularity, driven by aggressive marketing, 15,000 known flavor additives, and misconceptions of negligible harm, especially among youth. This study assesses how eliminating combustion in these products modifies CVD risk. Nicotine's independent role in atherosclerosis pathogenesis remains under investigation. It strongly stimulates the sympathetic nervous system, increasing plasma adrenaline up to 2.5-fold. This heightens hemodynamic load, potentially triggering acute CVD events, particularly in patients with existing cardiac conditions.

Materials and methods: A PubMed literature review was conducted using keywords: "Nicotine pharmacokinetics", "Cardiovascular risk", "E-cigarettes", "Heated tobacco products", "Snus", "Nicotine pouches", "Endothelial dysfunction".

Conclusions: Eliminating combustion (pyrolysis) significantly reduces released toxins compared to tobacco smoke. HTP aerosols contain >90% fewer harmful substances, and e-cigarettes release <2 µg of HPHC versus 3000 µg in tobacco. However, these products remain unsafe for the CV system. Nicotine's sympathomimetic

effects increase blood pressure and heart rate, and exacerbate insulin resistance; animal studies indicate up to a 57% decrease in insulin-dependent glucose uptake. Furthermore, HTP and ENDS aerosols induce inflammation (increased IL-6, TNF-α, hsCRP), oxidative stress, and secondary vascular endothelial dysfunction. Popular flavor additives (cinnamaldehyde, eugenol, diacetyl) also demonstrate proven cytotoxic effects. Alternative nicotine products have high addictive potential and an undeniably negative CV impact, highlighting an urgent need for long-term health outcome studies.

Key words: Nicotine pharmacokinetics, Cardiovascular risk, E-cigarettes, Heated tobacco products, Snus, Nicotine pouches, Endothelial dysfunction, Hemodynamic load, Health

Content:

1. Introduction

Smoking traditional cigarettes and passive exposure to tobacco smoke are known risk factors for cardiovascular disease (CVD) morbidity and mortality [1]. Regardless of sex, they cause an increase in the incidence of, among others, myocardial infarction, coronary artery disease, and stroke by affecting all stages of atherosclerosis development, starting with vascular endothelial dysfunction. Tobacco smoke aspirated into the smoker's

respiratory tract consists of a gas phase and a particulate (tar) phase. It is nicotine, a component of the particulate phase, that is associated with the development of addiction [2].

According to the GBD 2021 study, in 2021, smoking-related cardiovascular diseases caused 2.25 million deaths and 3.09 million years lived with disability (YLDs) worldwide, representing an increase of 26.16% and 59.73% compared to 1990. During the same period, the global age-standardized mortality rate (ASMR) and the age-standardized YLD rate (ASYR) for smoking-related cardiovascular diseases decreased by 1.94 and 0.92, respectively [3].

Recently, due to the misconception of their negligible harm, widespread marketing campaigns by nicotine product manufacturers, and the appeal associated with flavor additives, other nicotine-delivering stimulants have gained popularity. These products include electronic nicotine delivery systems (ENDS), heated tobacco products (HTPs), snus, and nicotine pouches. The frequency of using these types of products is also growing among adolescents and young adults [4].

The nicotine contained in the aforementioned products exerts a strong addictive effect associated with the stimulation of nAChR receptors in the mesolimbic pathway and the increased release of dopamine, which is linked to feelings of pleasure [5, 6]. Through its receptors, it significantly affects the cardiovascular system, primarily via the activation of the sympathetic nervous system (SNS). This leads to an increased release of catecholamines (norepinephrine, epinephrine), causing, among other effects, an increase in heart rate and blood pressure [7]. It exerts a vasoconstrictive effect on multiple vascular beds [8]. The exact extent to which nicotine acts as an independent factor in inducing vascular endothelial dysfunction and the development of atherosclerosis remains uncertain. However, due to its mechanism of action, it may contribute to the induction of acute cardiovascular events in individuals with pre-existing cardiovascular diseases [8].

The route of nicotine administration plays a crucial role in its absorption rate, maximum plasma concentration, and the time required to reach this peak concentration, which in turn significantly influences its systemic impact on the body and its addictive potential [9]. The core of the research problem is to analyze how the elimination of the combustion process in alternative nicotine delivery systems modifies cardiovascular risk.

2. Research results

2.1. Pharmacokinetics and pharmacodynamics of nicotine

Nicotine is a naturally occurring alkaloid in tobacco leaves. Currently, nicotine obtained through chemical synthesis is increasingly being used. Its absorption is influenced by the pH of its environment and the route of administration (respiratory tract, mucous membranes, skin). In an alkaline environment, nicotine exists in a non-ionized form (it is a weak base, pKa = 8); in this form, it easily penetrates biological membranes. After absorption, it is distributed throughout the body, binding to plasma proteins only to a small extent [9]. The parameters used to assess nicotine absorption are Cmax, representing the maximum concentration in venous or arterial blood plasma, and Tmax, which is the time required to reach Cmax. On average, a cigarette contains about 10-14 mg of nicotine [10], of which an average of 1-1.5 mg is absorbed into the body; the remaining part undergoes pyrolysis, escapes into the environment with smoke, or remains in the cigarette filter. The Cmax achieved in venous blood within 5 minutes of smoking one cigarette is approximately 15-30 ng/ml of nicotine, and the time to reach this concentration is about 5-8 minutes, with an 80-90% bioavailability of the nicotine inhaled with the smoke [9, 11].

The tissues of the liver, kidneys, spleen, and lungs exhibit the highest affinity for nicotine. The affinity for nicotinic receptors located in the central nervous system is also high, being even higher in smokers [9]. This is associated with a greater density of nAChR receptors in certain brain regions of these individuals, mainly the cerebellum, midbrain, and pons. The predominant nAChR receptor subtype in the brain is the $\alpha4\beta2$ type, featuring an ion channel structure composed of five subunits [12]. It is considered the primary central nervous system (CNS) receptor involved in the development of addiction. After crossing the blood-brain barrier (BBB) and binding to receptors, nicotine induces—both directly and indirectly, involving other neurotransmitters such as glutamate—an increase in the concentration of other neurotransmitters. This primarily involves dopamine in the mesolimbic system, released by dopaminergic neurons in the ventral tegmental area of the midbrain and in the nucleus accumbens, thereby stimulating the reward system [6]. Repeated exposure leads to the desensitization of nAChR receptors and the aforementioned increase in their density (upregulation). A drop in nicotine concentration in an addicted individual can lead to unpleasant sensations associated with a decrease in dopamine levels [13]. Another receptor type, the $\alpha3\beta4$ nAChR, mediates the systemic cardiovascular responses of the body. Nicotinic receptors are also present in the peripheral nervous system, muscles, and many other tissues [6].

Nicotine is a substance with sympathomimetic effects; by influencing the cardiovascular system through its receptors, it causes an increase in heart rate and myocardial contractility, vasoconstriction of coronary and cutaneous vessels, an elevation in blood pressure, and an increase in myocardial oxygen demand [14].

It also contributes to an increase in insulin resistance. The association between tobacco smoking and the development of diabetes, along with its characteristic vascular complications, is well known. Many of the pathophysiological mechanisms are closely related to the nicotine contained in tobacco smoke itself [15]. There are two known types of muscle-type nAChR receptors, composed of two α1 subunits and one each of the β1, δ, and γ subunits, or β1, δ, and ε subunits, forming pentameric receptors similar to neuronal-type nAChR receptors [16]. A study on the effects of nicotine conducted on rat muscle cell cultures (Rat L6 myotubes) confirmed a 57% decrease in insulin-dependent glucose uptake by cells subjected to a two-hour nicotine exposure. The pathomechanism of this phenomenon was associated with the activation of the mTOR signaling pathway and the secondary phosphorylation of the IRS-1 signaling protein [17]. The onset and exacerbation of insulin resistance in humans are primarily associated with chronic nicotine exposure [18].

The increase in sympathetic nervous system (SNS) activity associated with nicotine intake is linked to the activation of nicotinic receptors located in both the central and peripheral nervous systems, including the chemoreceptors of the carotid bodies [7]. This leads to the release of catecholamines. A 2.5-fold increase in blood plasma epinephrine concentration is observed in cigarette smokers, leading to an increase in heart rate, contractility, and blood pressure, regardless of the route of nicotine administration, thereby increasing myocardial oxygen demand. The release of catecholamines may also contribute to the arrhythmogenic effects of nicotine [7]. Depending on the vascular bed, nicotine can exert vasoconstrictive (coronary vessels, cutaneous vessels) or vasodilatory (skeletal muscle vascular bed) effects. Adverse effects are also noted in the microcirculation of the retina and kidneys; furthermore, nicotine negatively impacts the wound healing process. Secondary intensified beta-adrenergic stimulation of the myocardium can lead to cardiac tissue remodeling associated with fibrosis, ventricular hypertrophy, and the risk of developing heart failure [19]. Despite the proven impact of nicotine on vascular endothelial function, it remains unclear how significant this effect is compared to the effects of oxidative stress and pro-inflammatory factors associated with tobacco smoke inhalation [8, 20].

Nicotine can be particularly dangerous in patients with pre-existing, diagnosed cardiovascular disease. A Swedish study conducted on a cohort of 21,220 individuals, which compared the effects of snus use among post-myocardial infarction patients, found an almost 50% decrease in the risk of death in patients who ceased their use compared to those who continued using snus. Similar benefits were achieved by post-myocardial infarction patients who quit smoking cigarettes, relative to patients who continued smoking [8, 21].

2.2. Conventional cigarettes and combustion products

Cigarette smoking and passive exposure to tobacco smoke are among the most well-known modifiable risk factors for many cardiovascular diseases [1]. Despite decades of unequivocal evidence of its harm, tobacco smoking is, according to the WHO, the cause of over 8 million deaths annually. Tobacco smoke generated during tobacco combustion contains over 9,000 chemical compounds, including 69 with proven carcinogenic effects. The chemical compounds and reactive oxygen species contained therein contribute to an unfavorable pathophysiological profile of smoking-induced changes. Oxidizing compounds induce adverse vascular endothelial changes associated with oxidative stress. This initiates the development of atherosclerosis and its numerous medical implications. Chemical compounds associated with tobacco smoke also exhibit a pro-aggregatory effect on blood platelets while simultaneously limiting the fibrinolytic properties of blood plasma, which is associated with a high prothrombotic potential [8, 22].

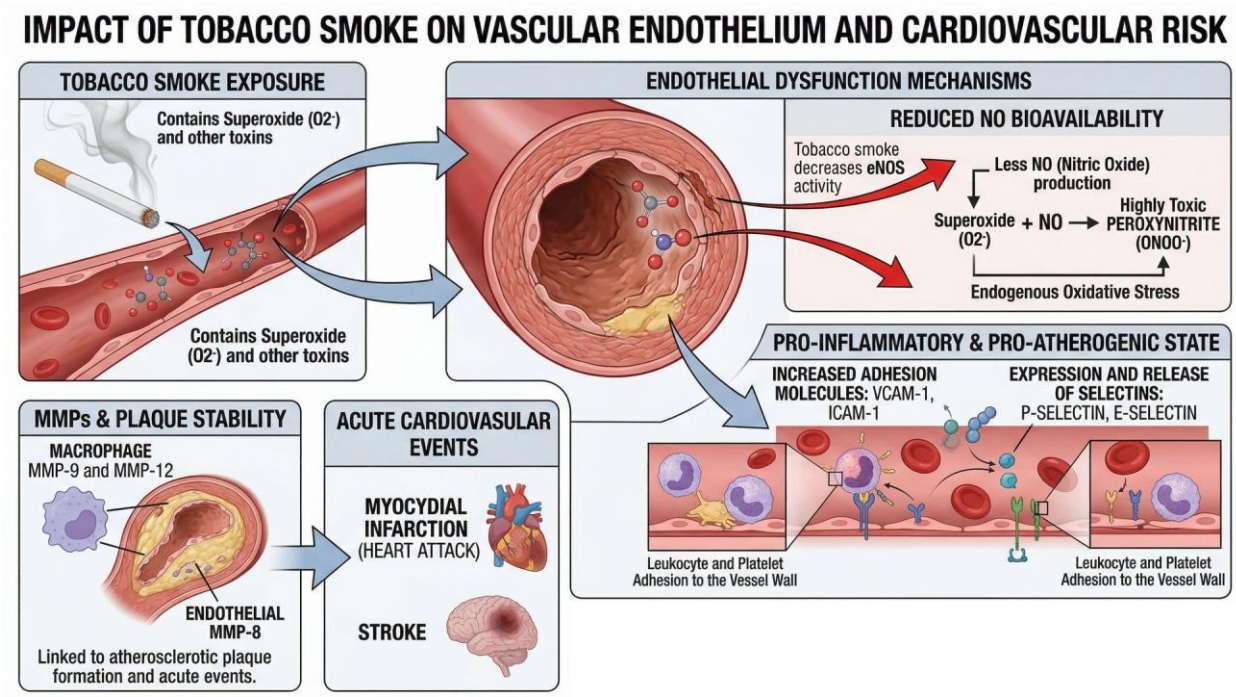
A 2013 American study analyzing data from a cohort of 216,917 adults between 1997 and 2004 found a significant increase in mortality among smokers associated with neoplastic, cardiovascular, respiratory, and other diseases. Overall mortality among smokers aged 25-79 was 300% higher than among non-smokers. Tobacco smokers, compared to those who had never smoked, lost at least 10 years of life. However, smoking cessation at age 25-34 was associated with a gain of 10 years of life, at age 35-44 with a gain of 9 years of life, and at age 45-54 with a gain of 6 years of life [23].

The composition of tobacco smoke is complex and varies depending on whether it is mainstream smoke (MS), sidestream smoke (SS), or secondhand smoke (SHS) [2], but the main substances associated with an increased risk of cardiovascular diseases are considered to be carbon monoxide (which binds with hemoglobin to form carboxyhemoglobin), oxygen free radicals, oxidizing compounds, and the extensively discussed nicotine [24]. Tobacco smoke aspirated into the smoker's respiratory tract is primarily mainstream smoke (MS), composed of a particulate (tar) phase—which includes nicotine and constitutes 8% of the smoke—and a gas phase, which constitutes 92% of the smoke [2].

Tobacco smoke induces endothelial dysfunction by reducing nitric oxide (NO) bioavailability, caused by a decrease in eNOS enzyme activity. Superoxide (O2-) present in tobacco smoke reacts with nitric oxide, leading to the formation of highly toxic peroxynitrite (ONOO-). This drives further endogenous processes associated with oxidative stress [25]. Pro-inflammatory and proatherogenic effects, which favor prothrombotic states, are associated with, among other things, the increased expression of adhesion molecules (VCAM-1, ICAM-1) and the

expression and release of selectins (P, E), enabling the adhesion of leukocytes and platelets to the vessel wall. [Figure 1] The relationship between tobacco smoke and an increase in the amount of macrophage metalloproteinases MMP-9 and MMP-12, as well as endothelial MMP-8, which are associated with the formation of atherosclerotic plaques and subsequent acute cardiovascular events, is well known. It should be remembered that any amount of smoked tobacco significantly increases the risk of cardiovascular events, such as myocardial infarction and stroke [24].

Figure 1. Based on: Rahman M, Alatiqi M, Al Jarallah M, et al. Cardiovascular Effects of Smoking and Smoking Cessation: A 2024 Update. Glob Heart. 2025;20(1):15. Published 2025 Feb 19. https://doi.org/10.5334/gh.1399 [24] Barua RS, Ambrose JA, Srivastava S, DeVoe MC, Eales-Reynolds LJ. Reactive oxygen species are involved in smoking-induced dysfunction of nitric oxide biosynthesis and upregulation of endothelial nitric oxide synthase: an in vitro demonstration in human coronary artery endothelial cells. Circulation. 2003;107(18):2342-2347. https://doi.org/10.1161/01.cir.0000066691.52789.be [25]



2.3. Heated Tobacco Products (HTP)

Heated tobacco products (HTPs) are electronic devices used to heat tobacco via heating elements without leading to the combustion process (pyrolysis), unlike traditional cigarettes. The temperature reached is typically below 350 degrees Celsius, and the tobacco heating time is limited by the number of puffs or a specific duration. In the case of conventional cigarettes, the temperature reaches up to 900 degrees Celsius. Unlike tobacco smoke, the aerosol generated during tobacco heating is devoid of a particulate phase, consisting solely of a gas phase. Contrary to popular beliefs suggesting negligible or no harm, the resulting aerosol contains nicotine, free radicals, and many other toxic substances, albeit at lower concentrations than tobacco smoke [26].

For the popular IQOS and Glo devices, a 2020 study found that the amount of nicotine and the total amount of free radicals per puff were 122.2 ± 9.6 micrograms of nicotine, 12.6 ± 1.1 picomoles of free radicals, and 72.1 ± 10.6 micrograms of nicotine, 12.5 ± 0.3 picomoles of free radicals, respectively. The amount of free radicals is significantly lower than in the case of a traditional cigarette (567.6 ± 78.3 picomoles in the gas phase and 73.9 ± 7.5 picomoles in the particulate phase); however, these amounts are clinically significant. The amount of delivered nicotine largely depends on the heating temperature and the device model, reaching values comparable to or much lower than those of conventional cigarettes [27]. Lower nicotine concentrations could hypothetically be associated with a higher number of puffs in order to achieve a nicotine concentration comparable to smoking a conventional cigarette [28].

An analysis of the aerosol generated during tobacco heating indicates a much higher concentration of water and glycerin compared to tobacco smoke. By eliminating the combustion process, the concentration of most harmful and potentially harmful substances was reduced by over 90%. The concentration of aromatic amines, polycyclic aromatic hydrocarbons, aldehydes, and phenols was reduced by approximately 75% [29].

Similar to tobacco smoking, the use of HTPs leads to an exacerbation of oxidative stress and an increase in inflammatory parameters. However, this impact is lesser than in the case of cigarettes [30].

A 2023 study demonstrated the impact of IQOS on an increase in the blood leukocyte count ($p<0.05$), including lymphocytes ($p<0.001$), a significant increase in the concentration of inflammatory parameters IL-6 ($p<0.05$), IL-2 ($p<0.05$), TNF-α ($p<0.01$), hsCRP ($p<0.01$), and an increase in the CO content in exhaled breath ($p<0.001$). In terms of cardiovascular risk, a significant increase in pulse wave velocity (PWV) and the augmentation index (AIx@75) ($p<0.05$) was also noted [31]. The aforementioned changes can be associated with vascular endothelial dysfunction, contributing to the development and progression of atherosclerosis. Platelet activation is also observed [30].

The value of HTPs in assisting smoking cessation is uncertain. Their use for this purpose may have consequences opposite to those intended. A recent Japanese study proved that using HTPs significantly decreases the chances of quitting the addiction and promotes relapse to traditional cigarettes among former smokers. For this reason, these types of devices should be discouraged as support in smoking cessation therapy [32].

2.4. Electronic cigarettes (ENDS)

In the case of electronic cigarettes, the nicotine carrier is an aerosol generated during the vaporization of a liquid by electronic heating elements. This liquid is most commonly a mixture of glycerol, propylene glycol, nicotine, and flavorings [31]. The amount of nicotine delivered depends on the liquid used, reaching 0-35 micrograms of nicotine per puff. The total amount of nicotine delivered to the bloodstream through the respiratory tract depends on how the device is used [33]. The aerosol, formed without the pyrolysis process, consists mainly of propylene glycol (PG) and glycerol (Gly), which upon heating can convert into harmful aldehydes (formaldehyde, acetaldehyde) and acrolein [34].

In a 2023 study, 45 nicotine-addicted users were recruited and divided into 15-person subgroups. Each subgroup was assigned electronic cigarette products (JUUL), HTPs (IQOS 3 Duo), or conventional cigarettes. Over a 90-minute period, their behaviors were assessed, including the number of puffs and puff duration, and the concentration of nicotine and its metabolites in venous blood was evaluated at appropriate time intervals (Table 1). The group assigned electronic cigarettes achieved the highest number of puffs and the longest puff duration: 71.9 puffs and 2.8 seconds, respectively (HTP - 52.2 puffs and 1.9 seconds, traditional cigarette - 42.3 puffs and 1.8 seconds) [28].

The use of electronic cigarettes is associated with lower and more stable concentrations of nicotine absorbed via the respiratory tract over a 24-hour period compared to tobacco smoking. This is associated with a lesser impact of these types of devices on the cardiovascular system and less pronounced nicotine-induced blood pressure spikes [8].

Analysis of the aerosol composition revealed a predominant content of propylene glycol, glycerol, water, and approximately 2% nicotine (about 30 micrograms of nicotine per puff compared to about 200 micrograms for conventional cigarettes). Trace concentrations below 2 micrograms of HPHCs (Harmful and Potentially Harmful Constituents) were also found, compared to 3000 micrograms in the case of tobacco smoke [35].

Flavor additives are a major problem, determining the attractiveness of these types of products among minors and young adults [36]. Over 15,000 flavor additives are known; cytotoxicity has been confirmed, among others, in the case of cinnamon-flavored liquids (cinnamaldehyde, 2-methylcinnamaldehyde). Other flavor additives with confirmed cytotoxicity are O-vanillin, pentanedione, diacetyl, 2,3-pentanedione, and acetoin [37].

The use of electronic cigarettes is less harmful than tobacco smoking; however, this does not imply an absence of negative health impacts. Many human studies have referred to an increase in oxidative stress, vascular endothelial dysfunction, and the activation of leukocytes and blood platelets resulting from the use of such devices, which could potentially be linked to the development of atherosclerosis and its complications [39]. Long-term assessment of health outcomes in the general population is necessary, and the effectiveness of these types of devices in assisting smoking cessation requires further analysis [37].

Table 1 Based on: Rabenstein A, Rahofer A, Vukas J, et al. Usage Pattern and Nicotine Delivery during Ad Libitum Consumption of Pod E-Cigarettes and Heated Tobacco Products. Toxics. 2023;11(5):434. Published 2023 May 5.

	Electronic cigarette	HTP	Traditional cigarette
Cmax (ng/mL)	8.0 (136%*)	17.7 (66%*)	24.0 (45%*)
AUC 0-90 min (ng/mL * h)	8.3 (126%*)	17.3 (68%*)	24.8 (51%*)
Tmax (min)	90	75	75

https://doi.org/10.3390/toxics11050434 [28]

*coefficient of variation (CV)

2.5. Oral products: Snus and Nicotine Pouches

Snus, similarly to traditional cigarettes and HTPs, is a tobacco product, with the difference being the route of administration, which in this case is oral. Snus is a moist product based on ground tobacco and salt, molded with fingers into a single portion or in the form of ready-made cellulose pouches placed under the upper lip [40]. It has been a banned product since 1992 in European Union countries, except for Sweden. It is also available in Norway.

Nicotine pouches, unlike snus, are not tobacco products. Nicotine is suspended in plant fibers and may contain flavor additives, including those with confirmed cytotoxicity, such as cinnamaldehyde and eugenol. The entire content is placed in cellulose pouches. The pouch is placed, similarly to snus, between the lip and the gum [5].

The nicotine contained in these types of stimulants is absorbed directly through the mucous membranes, largely bypassing the first-pass effect in the liver. This form allows for discreet, odorless consumption, in contrast to cigarettes, which are associated with tobacco smoke and exposing individuals in the addicted person's vicinity [41].

In a 2014 study evaluating 12 nicotine products against 14 criteria of harm to the user and their environment, traditional cigarettes achieved a maximum score of 100 points. The scoring system ranged from 0 to 100, where 0 indicates a complete absence of harm to the user and their environment. Snus ranked significantly lower on this scale, scoring 5 points, while electronic cigarettes scored 4 points. Snus was only slightly associated with cancer development and an increased cardiovascular risk [42]. The relationship between snus use and increased cardiovascular risk most likely stems from the nicotine delivered to the body [40].

Nicotine pouches are characterized by high variability in parameters such as nicotine content (from <2 mg to 50 mg per pouch), pH (from 5.5 to >10, median 8.8), and flavor additives. These differences affect nicotine absorption and the achieved blood concentration [Table 2], and the potential risk is primarily associated with the pharmacological action of the nicotine itself [5]. Attractive flavor additives, combined with nicotine doses frequently equaling or exceeding those in traditional cigarettes, pose a significant threat. These products effectively attract young people, which drastically increases the risk of developing an addiction [44]. Composition analysis of many tobacco-free products has revealed concentrations of formaldehyde, tobacco-specific nitrosamines (TSNAs), ammonia, chromium, and nickel at levels comparable to or exceeding those found in snus. Although these types of products constitute a less harmful alternative to traditional cigarettes, their long-term health consequences should be the leading topic of further research [41].

Table 2 Based on: Lunell E, Fagerström K, Hughes J, Pendrill R. Pharmacokinetic Comparison of a Novel Non-tobacco-Based Nicotine Pouch (ZYN) With Conventional, Tobacco-Based Swedish Snus and American Moist Snuff. Nicotine Tob Res. 2020;22(10):1757-1763. https://doi.org/10.1093/ntr/ntaa068 [43]

	ZYN 3mg	ZYN 6mg	General snus 8mg
Cmax (ng/mL)	7.7 (6.3-9.0*)	14.7 (12.3-17.1*)	10.6 (8.9-12.3*)
AUC (ng/mL * h)	32.0 (23.3-40.7*)	57.7 (43.9-71.6*)	45.9 (29.8-62.1*)
Tmax (min)	61 (56-66*)	66 (59-72*)	69 (60-78*)

*95% CI

3. Summary and Conclusion

Traditional tobacco smoking remains one of the leading causes of cardiovascular (CVD) mortality, accounting for 2.25 million deaths worldwide annually, according to 2021 data. The primary danger lies in the combustion process (pyrolysis), during which over 9,000 chemical substances are released, including many toxic ones and 69 with proven carcinogenic effects. Among these are, inter alia, highly reactive free radicals that induce oxidative stress. The search for less harmful forms of nicotine delivery has led to a rapid increase in the popularity of alternative systems, such as heated tobacco products (HTPs), electronic nicotine delivery systems (ENDS), and oral products—nicotine pouches and snus. Studies clearly indicate that the elimination of the combustion process results in a significant reduction in the concentration of released toxic substances compared to classic tobacco smoke. For example, the aerosol from HTP devices is characterized by a concentration of harmful and potentially harmful substances that is over 90% lower, while in the case of e-cigarettes, the amount of released HPHC-type compounds is below 2 micrograms, compared to approximately 3,000 micrograms released in the case of cigarette smoke.

This trend, driven by intensive marketing, is largely based on the misconception of the negligible harm of these products, especially among young users. However, it must be firmly emphasized that the aforementioned analytical data regarding harm reduction absolutely do not mean that these products are risk-free. As demonstrated in this literature review, alternative nicotine delivery systems are by no means safe for the cardiovascular system. The sympathomimetic effect of nicotine itself leads to an increase in blood pressure, heart rate, and the exacerbation of insulin resistance. It has been proven that, regardless of the route of administration, this substance stimulates chemoreceptors and receptors in the central and peripheral nervous systems, leading to up to a 2.5-fold increase in blood plasma epinephrine concentration. A direct impact of nicotine on glucose metabolism has also been demonstrated. In animal muscle cell studies, a 57% decrease in insulin-dependent glucose uptake was noted after just two hours of exposure. These phenomena induce a significant hemodynamic load and increase myocardial oxygen demand. Consequently, this may trigger acute cardiovascular events, making these products particularly dangerous for patients with pre-existing, diagnosed cardiovascular diseases.

Moreover, the analysis of aerosols from alternative nicotine delivery systems shows that these devices generate their own dangerous toxicological profile. Despite the absence of pyrolysis, the propylene glycol and glycerol vaporized during vaping convert into toxic aldehydes (e.g., formaldehyde) and acrolein. The aerosol from HTP devices still delivers clinically significant amounts of free radicals (from 12.5 to 12.6 picomoles per puff). This has been proven to induce inflammation, expressed by a significant increase in the concentrations of IL-6, IL-2, TNF-α, and hsCRP, as well as oxidative stress and the activation and adhesion of leukocytes and blood platelets, driving secondary endothelial dysfunction. The presence of flavor additives (over 15,000 are available on the market) is also of considerable importance in assessing the toxicity of ENDS products and nicotine pouches. The most popular of these, such as cinnamaldehyde, eugenol, O-vanillin, or diacetyl, demonstrate proven cytotoxic effects. It is also worth noting significant behavioral differences: the lower nicotine dose per puff from an e-cigarette is associated with a significantly higher total number of puffs (average 71.9) and a longer puff duration (2.8 seconds) compared to traditional smoking (42.3 puffs for 1.8 seconds), which significantly extends the total exposure time.

In conclusion, alternative nicotine products are characterized by a very high addictive potential and exert an undeniably negative impact on the cardiovascular system. This indicates an urgent need for further, long-term studies on their distant health outcomes. It should be emphasized that using products such as HTPs does not increase the chances of successfully quitting the addiction and even promotes a relapse to traditional cigarettes; therefore, recommending them as a form of support in smoking cessation therapy is discouraged.

Disclosure:

Supplementary Materials
Not applicable.

Author's contribution
Conceptualization: Jakub Dziemiańczuk, Gabriela Kuliś
Methodology: Zuzanna Panas, Jakub Dziemiańczuk, Zuzanna Panas
Software: Ewa Dryl-Jarmoc, Izabela Ślinko
Check: Mateusz Czajkowski, Mateusz Zimowski
Formal analysis: Kacper Krawczuk, Mateusz Zimowski, Jakub Dziemiańczuk
Investigation: Agata Kolanek, Piotr Kadysz
Resources: Izabela Ślinko, Jakub Dziemiańczuk
Data Curation: Piotr Kadysz, Kacper Krawczuk
Writing-rough preparation: Mateusz Zimowski, Agata Kolanek, Mateusz Czajkowski
Writing-review and editing: Jakub Dziemiańczuk, Izabela Ślinko
Visualization: Ewa Dryl-Jarmoc, Agata Kolanek
Supervision: Gabriela Kuliś, Izabela Ślinko
Project administration: Jakub Dziemiańczuk, Mateusz Zimowski
Receiving funding: not applicable
All authors have read and agreed with the published version of the manuscript

Funding
The article did not receive any funding.

Institutional Review and Board Statement
Not applicable.

Informed Consent Statement
Not applicable.

Data Availability Statement
Not applicable.

Conflict of Interest Statement
Authors declare no conflicts of interest.

Declaration of the use of generative AI and AI-assisted technologies in the writing process.
In preparing this work, the authors used Google Gemini for the purpose of language editing and improvement of text clarity. After using this tool/service, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

References:
[1] National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014. https://www.ncbi.nlm.nih.gov/books/NBK179276/
[2] Ambrose, J, Barua, R. The pathophysiology of cigarette smoking and cardiovascular disease: An update. JACC. 2004 May, 43 (10) 1731–1737. https://doi.org/10.1016/j.jacc.2003.12.047
[3] Zhu S, Gao J, Zhang L, et al. Global, regional, and national cardiovascular disease burden attributable to smoking from 1990 to 2021: Findings from the GBD 2021 Study. Tob Induc Dis. 2025;23:10.18332/tid/200072. Published 2025 Jan 31. https://doi.org/10.18332/tid/200072

[4] Corsello A, Ferraro VA, Reali L, et al. Novel nicotine and tobacco products in pediatric age: a joint position paper. Ital J Pediatr. 2025;51(1):270. Published 2025 Sep 24. https://doi.org/10.1186/s13052-025-02116-2
[5] Abid S, Aggarwal A, Duarte F, Sethi S, Iyengar S, Zarich S. Nicotine pouches and youth: emerging patterns and potential cardiovascular risks. Front Public Health. 2025;13:1632313. Published 2025 Nov 20. https://doi.org/10.3389/fpubh.2025.1632313
[6] Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annu Rev Pharmacol Toxicol. 2009;49:57-71. https://doi.org/10.1146/annurev.pharmtox.48.113006.094742
[7] Najem B, Houssière A, Pathak A, et al. Acute cardiovascular and sympathetic effects of nicotine replacement therapy. Hypertension. 2006;47(6):1162-1167. https://doi.org/10.1161/01.hyp.0000219284.47970.34
[8] Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. Trends Cardiovasc Med. 2016;26(6):515-523. https://doi.org/10.1016/j.tcm.2016.03.001
[9] Benowitz NL, Hukkanen J, Jacob P 3rd. Nicotine chemistry, metabolism, kinetics and biomarkers. Handb Exp Pharmacol. 2009;(192):29-60. https://doi.org/10.1007/978-3-540-69248-5_2
[10] Kozlowski LT, Mehta NY, Sweeney CT, et alFilter ventilation and nicotine content of tobacco in cigarettes from Canada, the United Kingdom, and the United StatesTobacco Control 1998;7:369-375.https://doi.org/10.1136/tc.7.4.369
[11] Hukkanen J, Jacob P 3rd, Benowitz NL. Metabolism and disposition kinetics of nicotine. Pharmacol Rev. 2005;57(1):79-115. https://doi.org/10.1124/pr.57.1.3
[12] Mukhin AG, Kimes AS, Chefer SI, et al. Greater nicotinic acetylcholine receptor density in smokers than in nonsmokers: a PET study with 2-18F-FA-85380. J Nucl Med. 2008;49(10):1628-1635. https://doi.org/10.2967/jnumed.108.050716
[13] Dani JA, Heinemann S. Molecular and cellular aspects of nicotine abuse. Neuron. 1996;16(5):905-908. https://doi.org/10.1016/s0896-6273(00)80112-9
[14] Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. Prog Cardiovasc Dis. 2003;46(1):91-111. https://doi.org/10.1016/s0033-0620(03)00087-2
[15] Eliasson B. Cigarette smoking and diabetes. Prog Cardiovasc Dis. 2003;45(5):405-413. https://doi.org/10.1053/pcad.2003.00103
[16] Albuquerque EX, Pereira EF, Alkondon M, Rogers SW. Mammalian nicotinic acetylcholine receptors: from structure to function. Physiol Rev. 2009;89(1):73-120. https://doi.org/10.1152/physrev.00015.2008
[17] Bergman BC, Perreault L, Hunerdosse D, et al. Novel and reversible mechanisms of smoking-induced insulin resistance in humans. Diabetes. 2012;61(12):3156-3166.https://doi.org/10.2337/db12-0418
[18] Artese A, Stamford BA, Moffatt RJ. Cigarette Smoking: An Accessory to the Development of Insulin Resistance. Am J Lifestyle Med. 2017;13(6):602-605. Published 2017 Aug 23.https://doi.org/10.1177/1559827617726516
[19] van Berlo JH, Maillet M, Molkentin JD. Signaling effectors underlying pathologic growth and remodeling of the heart. J Clin Invest. 2013;123(1):37-45. https://doi.org/10.1172/JCI62839
[20] Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. Arterioscler Thromb Vasc Biol. 2014;34(3):509-515. https://doi.org/10.1161/atvbaha.113.300156
[21] Arefalk G, Hambraeus K, Lind L, Michaëlsson K, Lindahl B, Sundström J. Discontinuation of smokeless tobacco and mortality risk after myocardial infarction. Circulation. 2014;130(4):325-332. https://doi.org/10.1161/circulationaha.113.007252
[22] Csordas A, Bernhard D. The biology behind the atherothrombotic effects of cigarette smoke. Nat Rev Cardiol. 2013;10(4):219-230. https://doi.org/10.1038/nrcardio.2013.8
[23] Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med. 2013;368(4):341-350. https://doi.org/10.1056/nejmsa1211128
[24] Rahman M, Alatiqi M, Al Jarallah M, et al. Cardiovascular Effects of Smoking and Smoking Cessation: A 2024 Update. Glob Heart. 2025;20(1):15. Published 2025 Feb 19. https://doi.org/10.5334/gh.1399
[25] Barua RS, Ambrose JA, Srivastava S, DeVoe MC, Eales-Reynolds LJ. Reactive oxygen species are involved in smoking-induced dysfunction of nitric oxide biosynthesis and upregulation of endothelial nitric oxide synthase: an in vitro demonstration in human coronary artery endothelial cells. Circulation. 2003;107(18):2342-2347. https://doi.org/10.1161/01.cir.0000066691.52789.be

[26] Upadhyay S, Rahman M, Johanson G, Palmberg L, Ganguly K. Heated Tobacco Products: Insights into Composition and Toxicity. Toxics. 2023;11(8):667. Published 2023 Aug 2.https://doi.org/10.3390/toxics11080667
[27] Bitzer ZT, Goel R, Trushin N, Muscat J, Richie JP Jr. Free Radical Production and Characterization of Heat-Not-Burn Cigarettes in Comparison to Conventional and Electronic Cigarettes. Chem Res Toxicol. 2020;33(7):1882-1887.https://doi.org/10.1021/acs.chemrestox.0c00088
[28] Rabenstein A, Rahofer A, Vukas J, et al. Usage Pattern and Nicotine Delivery during Ad Libitum Consumption of Pod E-Cigarettes and Heated Tobacco Products. Toxics. 2023;11(5):434. Published 2023 May 5. https://doi.org/10.3390/toxics11050434
[29] Schaller JP, Keller D, Poget L, et al. Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. Regul Toxicol Pharmacol. 2016;81 Suppl 2:S27-S47. https://doi.org/10.1016/j.yrtph.2016.10.001
[30] Morosini C, Vivarelli F, Paolini M, Canistro D. Heated Tobacco Products: Emerging Health Outcomes and Insights into Oxidative Stress and Pro-Inflammatory-Driving Mechanisms. Antioxidants (Basel). 2025;15(1):8. Published 2025 Dec 20. https://doi.org/10.3390/antiox15010008
[31] Belkin S, Benthien J, Axt PN, et al. Impact of Heated Tobacco Products, E-Cigarettes, and Cigarettes on Inflammation and Endothelial Dysfunction. Int J Mol Sci. 2023;24(11):9432. Published 2023 May 29.https://doi.org/10.3390/ijms24119432
[32] Odani S, Tsuno K, Agaku IT, Tabuchi T. Heated tobacco products do not help smokers quit or prevent relapse: a longitudinal study in Japan. Tob Control. Published online February 27, 2023. https://doi.org/10.1136/tc-2022-057613
[33] Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. Circulation. 2014;129(19):1972-1986. https://doi.org/10.1161/CIRCULATIONAHA.114.007667
[34] Komura M, Sato T, Yoshikawa H, et al. Propylene glycol, a component of electronic cigarette liquid, damages epithelial cells in human small airways. Respir Res. 2022;23(1):216. Published 2022 Aug 23. https://doi.org/10.1186/s12931-022-02142-2
[35] Tayyarah R, Long GA. Comparison of select analytes in aerosol from e-cigarettes with smoke from conventional cigarettes and with ambient air. Regul Toxicol Pharmacol. 2014;70(3):704-710. https://doi.org/10.1016/j.yrtph.2014.10.010
[36] Villanti AC, Johnson AL, Ambrose BK, et al. Flavored Tobacco Product Use in Youth and Adults: Findings From the First Wave of the PATH Study (2013-2014). Am J Prev Med. 2017;53(2):139-151. https://doi.org/10.1016/j.amepre.2017.01.026
[37] Marques P, Piqueras L, Sanz MJ. An updated overview of e-cigarette impact on human health. Respir Res. 2021;22(1):151. Published 2021 May 18. https://doi.org/10.1186/s12931-021-01737-5
[38] Bianco E, Skipalskyi A, Goma F, et al. E-Cigarettes: A New Threat to Cardiovascular Health - A World Heart Federation Policy Brief. Glob Heart. 2021;16(1):72. Published 2021 Oct 18. https://doi.org/10.5334/gh.1076
[39] von Hundelshausen P, Schmitt MM. Platelets and their chemokines in atherosclerosis-clinical applications. Front Physiol. 2014;5:294. Published 2014 Aug 8. https://doi.org/10.3389/fphys.2014.00294
[40] Clarke E, Thompson K, Weaver S, Thompson J, O'Connell G. Snus: a compelling harm reduction alternative to cigarettes. Harm Reduct J. 2019;16(1):62. Published 2019 Nov 27. https://doi.org/10.1186/s12954-019-0335-1
[41] Al-Otaibi HM, Althobiani MA. Nicotine pouches: a narrative review of the existing literature. Front Public Health. 2025;13:1641308. Published 2025 https://doi.org/10.3389/fpubh.2025.1641308
[42] Nutt DJ, Phillips LD, Balfour D, et al. Estimating the harms of nicotine-containing products using the MCDA approach. Eur Addict Res. 2014;20(5):218-225. https://doi.org/10.1159/000360220
[43] Lunell E, Fagerström K, Hughes J, Pendrill R. Pharmacokinetic Comparison of a Novel Non-tobacco-Based Nicotine Pouch (ZYN) With Conventional, Tobacco-Based Swedish Snus and American Moist Snuff. Nicotine Tob Res. 2020;22(10):1757-1763. https://doi.org/10.1093/ntr/ntaa068
[44] Duan Z, Henriksen L, Vallone D, et al. Nicotine pouch marketing strategies in the USA: an analysis of Zyn, On! and Velo. Tob Control. 2024;33(2):154-163. Published 2024 Feb 20. https://doi.org/10.1136/tc-2022-057360