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The Effect of Emerging Tobacco Related Products and Their Toxic Constituents on Thrombosis

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Abstract

Although conventional cigarette smoking is declining, emerging tobacco related products (ETRPs) are currently gaining ground, especially among the youth. These products include electronic cigarettes, waterpipes/hookah, cigars/cigarillo, smokeless tobacco, and heat-not-burn cigarettes. The observed increase in the use of ETRPs is multifactorial and complex but appears to be mainly driven by efforts from the major tobacco companies to reinvent themselves, and present more appealing and allegedly safe(r) tobacco products. However, it is becoming apparent that these products produce substantial amounts of toxic chemicals, many of which have been shown to exert negative health effects, including in the context of the cardiovascular system. Thus, there has been research efforts, albeit limited in general, to characterize the health impact of these products on occlusive/thrombotic cardiovascular diseases (CVD). In this review, we will discuss the potential impact of ETRPs on thrombosis-based CVD. Specifically, we will review how these products and the major chemicals they produce and/or emit can trigger key players in the process of thrombosis, namely inflammation, oxidative stress, platelets, coagulation, and the vascular endothelium, and the relationship between these effects.

Introduction

There is overwhelming evidence that conventional cigarette smoking (CS) is a major risk of cardiovascular disease (CVD), not only to active users, but also individuals within close vicinity [1, 2]. For instance, CS in both men and women increases the incidence of myocardial infarction (MI) and fatal coronary artery disease (CAD) [3]. Similarly, studies also demonstrated that even low-tar cigarettes increase the risk of acute cardiovascular events in comparison to nonsmokers [4]. Along the same lines, passive smoking or

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environmental tobacco exposure- with a smoke exposure about that is only 0.01% that of active CS- was found to be associated with approximately a 30% increase in risk of CAD, compared with an 80% increase in active smokers [1]. It is worth mentioning that the risk of CVD due to CS is both dose and duration dependent [3, 5, 6]. In short, the available set of facts- that took decades to accumulate- document a clear link of CS to major negative health consequences, particularly in the case of CVD. This body of evidence, along with efforts from private and public entities mounted "push back" campaigns against CS use, which is considered a public health problem. Consequently, these efforts have resulted in noticeable decline in CS use in the United States (US) and Europe [7]. Nonetheless, although CS has experienced a declining trend on a global scale [8], emerging tobacco related products (ETRP) are gaining ground [9], especially among the youth [10, 11], and women of childbearing age [12, 13]. The observed increase in the use of ETRPs is multifactorial and complex but appears to be mainly driven by efforts from the major tobacco companies to reinvent themselves, and present more appealing and allegedly safe(r) tobacco products [14–16]. Fortunately, nonetheless, these ETRP are now the focus of rigorous research efforts-including from our team- to understand their safety profile and their effects on health outcomes, including in the context of thrombotic CVD. It is of utmost importance to note that thrombosis is a major mechanism of occlusive CVDs. To this end, thrombosis is defined as the pathological condition in which a blood clot is formed within blood vessels, lead to obstruction of blood flow, and that can manifest as a MI or stroke. Major players in thrombosis include hyperactive platelets, activated coagulation system, and vascular endothelium injury. Therefore, in this review we will discuss the potential impact of ETRPs on thrombotic based CVD. Furthermore, we will review how these products and the major chemicals they produce/emit can trigger inflammation, and oxidative stress, as well as how they impact platelets, coagulation, and the vascular endothelium- all of which are key players in the process of thrombosis- and the relationship between these effects.

Emerging Tobacco Related Products

ETRPs are group of products that include electronic cigarettes, waterpipes/hookah, cigars/cigarillo, smokeless tobacco, and heat-not-burn (HNB) cigarettes (see Table 1). These products emerged on the premise of their safe profile – especially in current smokers trying to quit - in comparison to traditional cigarettes, and this assumption made them very appealing to many including the youth (e.g., high and middle school students; Figure 1A). In the next section, we will describe the different ETRPs and their health impact especially in the context of thrombotic CVDs.

E-cigarettes

Electronic cigarettes, also referred to as "e-cigs", "vapes", and "electronic nicotine delivery systems" (ENDS), are devices that include a power source, a heating element, and a prefilled or e-liquid refillable tank or cartridge (pods). These battery-operated devices exist in different sizes, colors, and shapes, some of which are like cigarettes and pipes. Newer generations on the other hand, are similar to USB flash drives or slim pens [17]. Notably, e-cigarettes contain different percentages of nicotine and flavors [18] that are dissolved in glycerol and propylene glycol. These are the main constituents of the e-liquid, which

is heated to generate aerosols [19]. An analysis of brands (Figure 1B) websites revealed that there are more than 15,000 flavors and the most common are tobacco, menthol, alcohol/drink, fruit and dessert/candy [20] Since 2015, the popularity of the USB-like device JUUL has grown significantly, becoming the most popular device sold in the US [21]. To this end, and likely due to their success, other companies have also manufactured separate e-cigarette devices containing prefilled e-liquid in pods like JUUL [22]. It is noteworthy that although e-cigarettes do not emit large smoke clouds in comparison with traditional cigarettes, the pods may in fact contain as much nicotine as a pack of 20 regular cigarettes [22]. Indeed, e-cigarettes have the capacity to deliver levels of nicotine similar to traditional cigarettes. Additionally, a vast number of e-cigarette users are dual users, meaning that they use both types of cigarettes (traditional and electronic), and hence are consuming toxic substances from both products [23]. Importantly, e-cigarettes were found to be associated with MI even after adjusting for conventional cigarette use [24]. Furthermore, it was observed that there is an association between some days e-cigarette use and MI (odd ratio: 2.11, 95% CI: 1.14–3.88, $p = 0.017$), as well as between coronary heart disease and daily e-cigarette use (odd ratio: 1.89, 95% CI: 1.01–3.53, $p = 0.047$; [25]). Also, there is evidence that e-cigarette use is associated with stroke, when used with conventional cigarette smoke (dual use), even when compared with current sole conventional cigarette use in young adults [26]. Finally, the use of e-cigarettes is shown to be associated with increase in platelet activity[27], a cell that is known to be a main player in thrombotic CVDs.

Waterpipes

The use of waterpipes, also known as hookah or shisha, has been rising around the world, mainly in young adults [28]. Many factors have been attributed to their popularity, such as the use of flavored tobacco, marketing, and the misperceptions about their adverse health effects [29]. The tobacco used in waterpipes is also called mouassal “honeyed tobacco”, which usually contains 30% tobacco and around 70% honey/sugarcane, as well as glycerol and flavors [30]. Most recently, e-hookah was introduced as a healthier alternative to the regular charcoal operated waterpipes, and it was “picked up” quickly by users [31]. Two types of e-hookahs are available in the market, e-hookah pens (they are mostly disposable) and e-hookah bowls (used in similar manner to the regular hookah or waterpipe). Interestingly, a recent study has shown that e-hookahs have a distinct user profile (common among females and higher prevalence of substance use) when compared to e-cigs [32]. In terms of their negative health effects, indeed, data has shown that smoking waterpipes is associated with MI [33, 34], and we have recently shown that they can directly induce occlusive thrombotic disorders [35]. Nevertheless, data that link waterpipes to negative clinical outcomes are generally limited, and hence more research is needed in this area.

Cigars/Cigarillos

Cigars represent perhaps the simplest form of tobacco products, in which tobacco is wrapped in a “tobacco” leaf, which is different from a cigarette in which tobacco roll is wrapped in paper. Cigarillo is a common and distinct cigar product [36], and is shown to be increasingly used among youth [37] (Figure 1C). In addition, cigarillo users are most likely to also be users of multiple tobacco products[38], and tend to be low income, and represent

racial/ethnic minority youth living in urban centers[39, 40]. Concerningly, studies on the use of cigars, toxicant exposure, and health effects are limited [41]. Nonetheless, cigar smoking has been associated with increased risk of CAD, and aortic aneurysms [42]. This should be reconciled with the rather interesting fact that the use of cigars is becoming more common among youth; primarily because of curiosity, peer influence, and low cost [43].

Heat-Not-Burn tobacco products

The heated tobacco products, also known as heat-not-burn (HNB) tobacco products, represent the most recent “invention” from the tobacco industry, and are claimed to be less harmful. These battery-operated devices heat tobacco to a maximum of 350°C (500°F) to generate an inhalable aerosol [44]. They also contain nicotine, propylene glycol, flavors and other tobacco particles [45, 46]. HNB products contain as much nicotine as traditional cigarettes, although the levels of nicotine in the aerosols may be lower than those in cigarettes [47]. Of note, the heated tobacco products are the least well-characterized products among the ETRP. Nevertheless, it has been indicated that due to the lack of combustion in HNB, less toxicants are formed in the aerosol of these products than in cigarette smoke [48]. However, the aerosol of heated tobacco contains the same acrolein, formaldehyde, benzaldehyde, acenaphthylene, nicotine, carbon monoxide, and particulates that are the harmful constituents of conventional cigarette smoke [45]. Nonetheless, there is limited data on the effects of HNB on general health and cardiovascular endpoints; a knowledge gap that warrants attention.

Smokeless Tobacco

Smokeless tobacco products contain fire-cured tobacco that is powdered for nasal or oral snuff use, and is also grated for chewing use[49]. The effect of smokeless tobacco on the cardiovascular system is controversial. On one hand, a systematic review indicated that there is insufficient data to link smokeless tobacco to CVD, including thrombotic events[50]. On the other hand, data have shown that smokeless tobacco products are not harmless, and that for instance, their long-term use may be associated with an elevated risk of MI and stroke [51]. One main assumption driving the use of smokeless tobacco is that they help in smoking cessation. This assumption was disputed by a randomized trial, which concluded that success of smokeless tobacco products as means of smoking cessation is low, and that they are indeed associated with risks for long-term adverse events [52]. A large case-control study found that smokeless/chewed tobacco increased the risk of MI and the highest increase in the risk of acute MI was in smokers who also chewed tobacco [53].

In summary, although the available data are in general still preliminary and there is an urgent need for more longitudinal studies, they indicate that ETRPs are instigators of thrombotic events. Thus; in the next section we will focus on what is known regarding the major mechanisms that play a role in ETRF-mediated thrombosis

Emerging Tobacco Related Products and Thrombosis

Thrombosis, which is the formation of blood clots inside blood vessels, can lead to a reduction in the blood supply to organs, and consequently hypoxia and/or tissue damage. Hemostasis on the other hand, is the physiological balanced response to vascular/circulatory injury that results in the formation of a platelet-fibrin clot, which prevents further bleeding. The hemostatic machinery integrates many players, including the endothelium, the clotting factors (e.g., fibrinogen) and importantly platelets, working along the fibrinolytic system [54]. These elements are there to ensure the formation of a stable clot that can seal the damaged blood vessel. Exaggerated responses to endothelial injury can lead to thrombosis [55], a critical event that is associated with MI and stroke [56]. Thrombosis can also lead to venous thromboembolic events, which account for considerable morbidity and mortality [57]. It has been shown that for thrombosis to take place there must be 1) an abnormal pro-thrombotic activity (e.g., hyperactive platelets[58], increase plasma fibrinogen[59]), 2) abnormal antithrombotic activity (e.g., defect in the inhibitory prostaglandin/PGI_2's antiplatelet function[60]), 3) an increase in thrombin generation[61], 4) vascular cell damage[62], 6) and fibrinolysis system failure or inhibition[63]. These processes are shown to be impacted by a number of ETRPs (Table1). These data provide evidence that ETRPs indeed present a risk in developing thrombotic CVDs, through modulating different aspects of hemostasis. Nonetheless, these studies are limited by the sample size used and the observational nature of their design, thereby opening the opportunity for more longitudinal studies, which would be expected to contribute more meaningful results in linking these products to thrombotic CVDs.

In this connection, and much like CS[64, 65], ETRPs are found/shown to produce proinflammatory toxic chemicals and reactive oxygen species [66–70], both of which are instigators/promoters of the thrombotic process, which is essential for development of occlusive CVDs. Surprisingly, there has not yet been any clear model to link these processes together in a manner that would aid not only in understanding the complete picture of the disease conditions, but also how these processes work in an intertwined manner to form a continuous cycle of harm to the users of these products.

Emerging Tobacco Related Products, Inflammation, Oxidative Stress, and Thrombosis

It is inferred from the evidence in the literature that inflammation, oxidative stress, and thrombosis are interconnected processes that can be very detrimental to our cardiovascular system health. Therefore, it is imperative to discuss this process in one framework to appreciate their role in the disease state. To this end, animal and human studies (including data from Population Assessment of Tobacco and Health Study (PATH) indicate that the majority if not all of the tobacco products can induce inflammation and oxidative stress [66–71]. For instance, e-cigarette usage was found-some of which by our group-to be associated with increase in proinflammatory proteins IL6, TNFα, and CXCL8[67], ROS[72] and a heightened risk of thrombosis [27, 73]. These effects are possibly due to the proinflammatory toxic chemicals produced by heating the e-liquid. Similarly, waterpipes

are known to produce many proinflammatory toxic chemicals [66]. In fact, it is now known that waterpipes increase proinflammatory cytokines IL-6, IL-8, IL1β and TNFα, as well as markers of oxidative stress such as 8-isoprostane, myeloperoxidase, and matrix metalloproteinase-9[74], all of which are preconditions for development of CVD [66, 75, 76]. Smokeless tobacco has also been shown to cause inflammation [77] and to produce oxidative stress [78]. Most recently, HNB products were found to induce oxidative stress and inflammation [79–81] in a manner similar to conventional cigarettes. It should be noted that inflammation and oxidative stress are strong instigators of thrombosis, the main pathology of acute occlusive cardiovascular events.

With regard to the interconnectedness of these processes, it has been observed that inflammation can shift the hemostasis response toward a prothrombotic state [82]. In fact, data have shown that inflammation may also cause a tendency to develop arterial and venous thrombosis, leading to a wide range of clinical presentations ranging from mild disease to life-threatening situations [82]. It is noteworthy that inflammation is considered one of the main mechanisms by which a host defends itself against external foreign entities, including toxic chemicals[83]. Physiological inflammation is self-limited and beneficial to the host. However, if inappropriately stimulated, excessive inflammation may fail to resolve, thereby creating an environment for “pathogenesis” [84]. One reason that the inflammatory process may fail to resolve is because of continuous exposure to toxic chemicals, including those emitted by tobacco products [85]. The activation of immune cells (e.g., neutrophils, and monocytes)- driven by proinflammatory stimuli- leads to the production of reactive oxygen species (ROS; e.g. hydrogen peroxide, and hydroxyl radical), reactive nitrogen species (e.g., peroxynitrite), and chlorine species (hypochlorous acid), which are the main players of the oxidative stress state [84]. Exaggerated production of ROS predisposes the host to thrombotic state by modulating endothelial function [86], and activating platelets[87] - potentially through leukocyte release of superoxide. Furthermore, ROS impacts polymorphonuclear leukocytes, leading to the production of tissue factor, which is a major trigger of the coagulation system [88, 89]. In fact, a previous study suggested that NAD(P)H oxidase activation and ROS generation are involved in tissue factor upregulation in activated platelets[90]. In addition, superoxide generated in hyperactive platelets might be another mechanism that contributes to the thrombotic state [90]. Oxidative stress also upregulates plasminogen activator inhibitor-1 (PAI-1) and alters the bioavailability of nitric oxide in endothelial cells, which consequently promotes thrombus formation [91]. Interestingly, studies have shown that platelets and coagulation, which are part of the thrombotic state, can augment the inflammatory process by means of modulating proinflammatory cytokines and growth factors[82]. The mechanism by which coagulation modulates inflammation is primarily through binding of thrombin and some other coagulation factors to the protease-activated receptors (PARs)[92]; which are located on the endothelium, platelets, fibroblasts, and smooth muscle cells. While PAR-1, PAR-3, and PAR-4 are mainly interacting with thrombin, PAR-2 is thought to potentially serve as a receptor for both the “TF-factor VIIa” complex and factor Xa. Moreover, thrombin is known to interact with these receptors, which induces the production of growth factors and cytokines (e.g., IL-6 and IL-8), thereby leading to up-regulation of inflammatory responses[93]. Moreover, studies have shown that platelet activation leads to production

of ROS, which becomes a potential source of further oxidative stress[94]. Taken together, the use of ETRPs-in a manner similar to conventional cigarette- can induce inflammation and oxidative stress (through the action of toxic chemicals). Consequently, these activities modulate hemostasis and lead to thrombosis, which can directly potentiate the inflammatory and oxidative stress processes, thereby creating a potentially dangerous, yet vicious cycle (Figure 2)[82, 95, 96].

Toxic Profile of Emerging Tobacco Related Products.

Although the levels of toxic chemicals emitted by ETRPs vary, it is important to note that these tobacco products are not emission free, and the toxic chemicals they emit are hazardous (Table 1), and have the capacity to lead to serious health issues (including CVD), even at low levels [97]. According to accumulating data, tobacco's toxic chemicals that received the greatest scrutiny as possible contributors to CVD, include nicotine[98], particulate matter[99], polyaromatic hydrocarbons (PAHs)[100], and to a lesser extent tobacco-specific nitrosamine (TSNAs). Indeed, some of these chemicals have been proven to profoundly contribute to the cardiovascular hemodynamic instability and thrombotic effects associated with tobacco use[1]. Furthermore, they also participate in the development of a proinflammatory state that is mechanistically involved in "smokers"-associated thrombogenesis [82]. In the next section, we will focus on the specific role of the major toxic components of ETRPs, and the data so far linking them to thrombotic conditions.

Role of various chemical components of emerging tobacco related products in thrombogenesis

Nicotine

Like conventional cigarettes, ETRPs contain considerable amounts of nicotine. For example, e-liquids, which are used in most ENDS such as e-cigs typically contain nicotine at concentrations ranging between 0–87.2 mg/ml[101], albeit some e-liquids are "nicotine free". Furthermore, JUUL, which is one of the popular ENDS, contains e-liquid with nicotine concentrations that could reach as high as 59 mg/mL [102]. With regard to waterpipe, the average nicotine content ranges between 67 – 713 mg per head [103]. Smokeless tobacco also contains considerable amounts of nicotine, which is absorbed more slowly than that of cigarettes. It is noteworthy that the nicotine concentration delivered/inhaled/absorbed by the user depends on a multitude of factors, including frequency of use and puffing patterns (puff number and duration) [104, 105].

Rather interestingly, and perhaps contrary to common beliefs, the majority of published data attached little importance to the role of nicotine as a contributor to tobacco-induced thrombotic diseases[1]. In fact, a significant body of knowledge concluded that nicotine's direct effect on the development of tobacco induced thrombosis is negligible, and its role centers more on hemodynamic instability[106]. Furthermore, these studies suggested that nicotine contributes indirectly to thrombosis, by inducing atherosclerotic plaque development [1, 106–108]. In contrast, other data showed that exposure to nicotine may increase PAI-1, which is a major regulator of fibrinolysis [109]. Also, it was found that

nicotine is a potential modulator of nitric oxide, which normally inhibits platelet activation [110]. It is important to note that some studies found nicotine to be involved in modulating platelet reactivity [111–115], some of which by employing urinary Thromboxane A_2 (TXA_2) metabolite excretion. Of note, while we employed the well-known nicotine metabolite cotinine, we showed that it potentiates platelet aggregation in response to thrombin[35]. This is significant given that platelets are a critical player in the process of thrombosis.

Particulate Matter (PM)

Studies have shown that conventional cigarettes expose humans to nearly 40,000 μg of particulate matter (PM) [116]. These particles have a mean diameter of <1 μm, which allows a high degree of deposition inside the human body [117], and thus makes them very hazardous. In fact, studies have shown that PM is associated with increased hospitalization and mortality due to CVD [118]. In a striking similarity, ETRPs emit very comparable levels of PM to conventional cigarettes. Thus, studies have shown that e-cigs and waterpipes produce TPM in the range of 0.87–5.8 mg/puff, and 1.8–9.3 mg/puff, respectively, in comparison to 0.1–1.7 mg/puff from conventional cigarettes [119]. Consequently, in light of the substantial difference in the puffing topography between cigarettes (have an average of 18 puff/cigarette)[120–122] and other products, such as e-cigs (average >150 puff/day) [123] and waterpipe (<171 puff/session)[66, 124], these products are even more dangerous with regard to PM emission. Likewise, there is data showing that HNB tobacco emits an average of 44 mg/cig compared to 36 mg/cig with conventional cigarettes, indicating that heating tobacco might be as “bad” as combustion in generating PM [10, 125]. To this end, accumulating evidence shows that exposure to PM does induce a prothrombotic state, which might involve arterial and venous thrombotic events [126, 127]. Consistent with this notion, exposure to PM triggers the production of fibrinogen, Von Willebrand factor, sP-selectin, and sCD40L, all of which are important players in the processes of hemostasis and thrombosis [128–131]. Furthermore, data have also shown that PM exposure causes a defect in the fibrinolysis mechanisms that normally would help in limiting clot expansion, which is consistent with the prothrombotic state. Specifically, exposure to PM led to inhibition of tissue the plasminogen activator (t-PA) [132]. Additionally, this effect was not only limited to t-PA, as PM exposure was also found to upregulate PAI-1, which is considered a risk factor for thrombosis [133, 134]. Taken together, these reports are in complete accord with previous studies that linked PM exposure with increases in plasma viscosity, platelet activation, and modulation of coagulation [135–138]. Interestingly, evidence appears to suggest that a far greater impact on hemostasis is associated with ultrafine particles (PM0.1) rather than coarse particles (PM10) and fine dust (PM2.5). Thus, in patients with metabolic syndrome, short-term exposure (2 h) to PM0.1 caused a decrease in blood plasminogen and thrombomodulin and increased C-reactive protein (CRP; a biomarker for CVD) [139]. In addition, separate cohort studies (humans) have showed that ultrafine particles are associated with modulation of the hemostatic process and increase in the inflammatory state in exposed in comparison to control [140, 141]. Another study with a large sample size found that mortality from ischemic heart disease was more strongly associated with PM0.1 relative to other PM [142]. Finally, it has been documented that cardiovascular mortality is correlated with particle size, and the correlation tends to

be more profound as the particle size decreases [143, 144]. Collectively, there is ample evidence indicating that PM is indeed a common harmful toxic element across variety of emergent tobacco products, even/including those that claimed to be less harmful than the conventional cigarette. Nevertheless, more studies are needed to investigate the mechanism and pharmacodynamics of all sizes and types of tobacco-derived PM on the various elements of hemostasis and thrombotic mechanisms.

Carbon Monoxide

Carbon monoxide (CO) is a product of partial combustion or oxidation of carbon in tobacco products. It is established that a conventional cigarette produces CO, which is known to be associated with negative health effects[145]. Once generated, CO finds its way to the pulmonary system and gets absorbed into the circulation. With the exception of e-cigs, almost all ETRPs have been shown to produce CO, albeit at varying concentrations [119, 146]. For instance, conventional cigarettes can emit 1–2.3 mg/puff in comparison to 1.15–1.67 mg/puff and 0.531mg/12 puff in case of waterpipe and HNB tobacco, respectively. As for its effect on the hemostasis system, excessive exposure to CO was found to increase the risk of deep venous thrombosis and pulmonary embolism; disease states known to be associated with high mortality [147]. Moreover, CO can enhance the coagulation cascade, inhibit fibrinolysis, and expediate clot growth, all of which favor a prothrombotic state [148]. It was also shown that water-soluble CO-releasing molecules (CORMs) are able to increase the speed by which clot formation happens, as well as inhibit t-PA-based fibrinolysis [149]. Interestingly, CO seems to have an opposite effect on platelets in comparison to coagulation, as it was found to suppress their activation. Thus, it was observed that CORM-3 reduces both collagen- and thrombin-induced platelet aggregation. This effect was mediated by the guanylyl cyclase pathway [150, 151]; albeit other pathways might be also involved [152, 153]. Given the apparent conflicting effects CO exerts with regards to platelets, thrombus formation (and coagulation), further studies are needed to clarify these effects. Taken together, tobacco product users are clearly exposed to a multitude of toxic chemicals at once, and so far, data have shown that the “collective” effect of tobacco on hemostasis is shifted towards thrombosis, rather than the other way around.

Polycyclic Aromatic Hydrocarbons (PAHs)

The PAHs- compounds that are composed of a minimum of two fused benzenoid rings- are known to be among the numerous toxic chemicals produced by incomplete combustion of tobacco. In addition, one study that analyzed 70 brands in the US market, confirmed the presence of PAHs in smokeless tobacco. It is noteworthy that PAHs do not occur naturally in plants, therefore the presence of PAHs in smokeless tobacco might be due to fire-curing, which is a process employed to transform green wet tobacco into a dry “ready to use” product [154]. PAHs are known to possess mutagenic properties [155], and experimental studies have shown that exposure to them might be associated with negative cardiovascular consequences, including thrombotic events such as MI [156]. Also, PAHs are linked to accelerated development of endothelial atherosclerotic plaques [157]. In addition, it has been suggested that PAHs induce apoptosis of endothelial cells by a mechanism that involves activation of phospholipase A_2 [158]. Separate lines of evidence suggested that exposure to PAHs increases mean platelet volume (MPV) [159], which is linked to hyperactive platelets.

Increases in MPV is also associated with cardiovascular inflammation [160], another risk element for thrombogenesis [161]. Likewise, there is convincing experimental data that appears to positively link PAHs exposure with oxidative stress and inflammation [162, 163], which are strong modulators of hemostasis. Indeed, reports indicate that almost all ETRPs with perhaps the exception of e-cigs (not enough data to support such conclusion) can produce PAHs, but at varying levels. This is of significance from a health standpoint, as these chemicals are not safe and have the potential to participate in the genesis of a host of diseases overtime, even at low concentrations.

Heavy Metals

ETRPs carry a considerable profile of heavy metals such as aluminum, antimony, arsenic, cadmium, cobalt, chromium, copper, iron, lead, manganese, mercury, and zinc[164–167]. These heavy metals are of major concern due to their toxic impact on different body systems, including their potential to cause cardiovascular disease such CAD[168, 169]. Furthermore, animal studies have shown that heavy metals such as cadmium can in fact modulate the coagulation system and increase platelet activation, thereby increasing the risk of thrombosis[170]. Heavy metals are also known to increase proinflammatory cytokines, such as IL-1β, IL- 6, and TNF α as well as ROS in both humans and animals[171]. Nonetheless, more studies are needed to mechanistically address how heavy metals contribute to the thrombotic process, which can consequently lead to cardiovascular events.

Tobacco-Specific Nitrosamines (TSNAs)

TSNAs are one of the carcinogenic chemicals produced by tobacco smoke, but are also among the contents of smokeless tobacco [172]. In fact, like conventional tobacco smoke, almost all ETRPs produce TSNAs, albeit in differing amounts. To this end, there is evidence that tobacco smoke produces significantly higher amounts of TSNAs, in comparison to e-cigs and waterpipe [119]. On the other hand, HNB tobacco shows comparable levels of TSNAs relative to conventional cigarettes [146, 173]; which perhaps is inconsistent with the fact that it is being promoted as a safer option to conventional cigarettes [174]. Notably, studies linking TSNAs to CVD are limited, which makes it difficult to appreciate their harmful effects in this regard. Nonetheless, in term of TSNAs impact on the cardiovascular health, studies have shown that they increase CVD biomarkers such as creatine kinase-MB and lactate dehydrogenase. The same study [175] also concluded that TSNAs increased the levels of free radicals and decreased the activity of antioxidant enzymes; all of which are known to favor a state of thrombotic CVDs. Regarding their direct effect on thrombosis, it does not seem to have been explored yet, but clearly warrants investigation.

In summary, it is evident that ETRPs-emitted toxic substances are an important cause of thrombosis. These toxic substances impact different aspects of hemostatic processes such as platelet activation, coagulation, and endothelial function which predisposes to thrombosis and eventual cardiac events such as MI and stroke. And although it is challenging to characterize the effect of different toxic chemicals on the different aspects of thrombosis, there is a huge need for more rigors studies to address this issue mechanistically.

Conclusion

ETRPs were introduced into the market as safe/safer options, mainly for individuals who would like to transition and quit cigarette smoking. However, the safety of these products is questionable. In fact, in many instances, some of these products appear to exert greater negative health effects than cigarette smoking. This- at least in part- derives from the fact that ETRPs emit considerable and often comparable levels of toxic chemicals, in comparison with conventional cigarettes. A host of these toxic chemicals are known to promote inflammation and oxidative stress, both of which are important instigators of thrombosis-based disease states. Indeed, the link between inflammation, oxidative stress, and thrombosis is well established in the literature. However, this relationship is not merely in one direction, as it involves positive feedback and is more of augmentative in nature. In this mini, yet comprehensive review, we attempted to put these relationships in a model that we hope will better help the readers in not only understanding the big picture, but also appreciating smoke-induced thrombotic diseases. Furthermore, the literature appears to indicate that emerging tobacco products, similar to conventional cigarettes, impact all elements of hemostasis, such as the endothelium, platelets, and the coagulation system, albeit with some variability. These effects are associated with a host of negative health consequences, such as myocardial infraction and stroke.. Finally, this review also revealed that more research is warranted to investigate the mechanistic effects of ETRPs in the context of thrombotic cardiovascular disease, and the pathways involved in such disease processes.

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Abbreviations

CS	Cigarette Smoking
CVD	Cardiovascular Disease
CAD	Coronary Artery Disease
E-cig	Electronic Cigarettes
ETRPs	Emerging Tobacco Related Products
ENDS	Electronic Nicotine Delivery System
PAHs	Polyaromatic Hydrocarbons
ROS	Reactive Oxygen Species
TSNAs	Tobacco-Specific Nitrosamines
TXA_2	Thromboxane A_2

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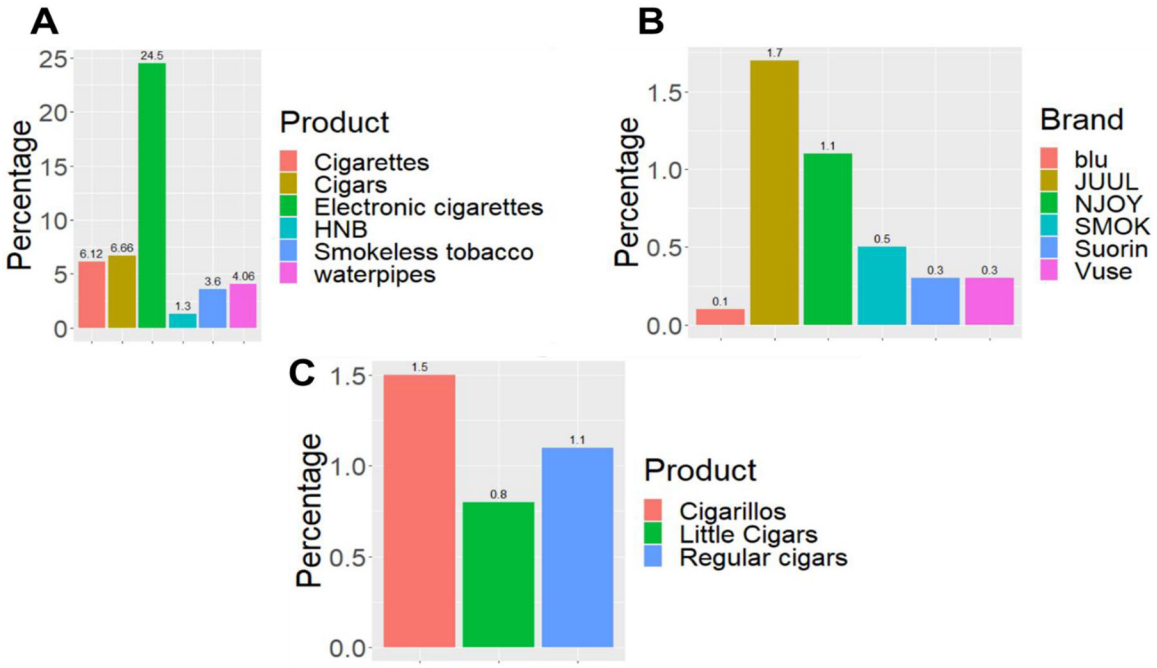


Figure 1:

A) Current Use Estimates for Selected Tobacco Products for Middle and High School Students-United states (2020). Data for the national youth tobacco survey, total population (N=14495). **B)** Percentage of E-cigarette Brands Used Among Middle and High School Students-United states (2020). Data obtained from the national youth tobacco survey, and based on the question (During the past 30 days, what brand of e-cigarettes did you usually use? Choose only one answer). **C)** Percentage of Cigar Products Used Among Middle and High School Students-United states (2020). Data obtained from the national youth tobacco survey. and based on the question (During the past 30 days, which of the following types of cigars, cigarillo, or little cigars have you smoked?)

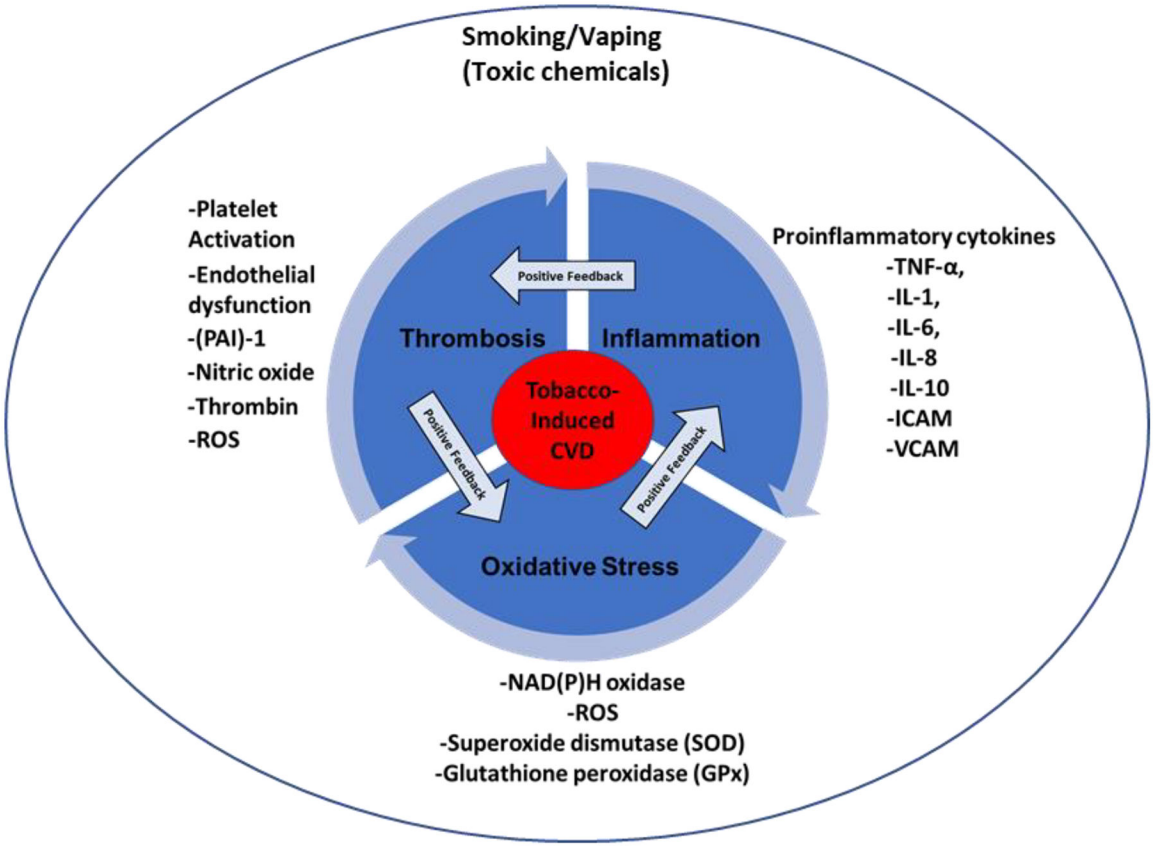
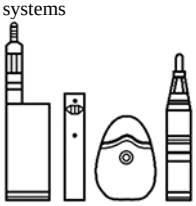
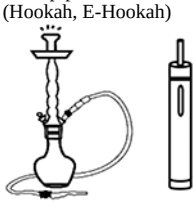
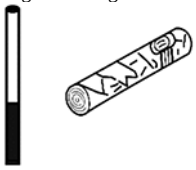
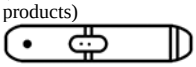
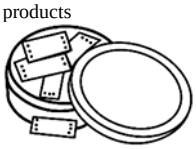


Figure 2: The vicious cycle of thrombotic disease.

Inflammation instigates oxidative stress through the release of ROS from excessively activated immune cells and the consequent production of proinflammatory cytokines. Oxidative stress impacts different aspects of hemostatic process, which consequently leads to thrombosis. Thrombosis participates in increasing the inflammatory process through different mechanisms including thrombin-induced proinflammatory production.

Table 1:

different type of emerging tobacco products and the impact on different aspect of hemostasis.

Product	Common brand	Common Flavors	Common Thrombosis-Dependent Mechanisms	Toxicant / Chemical
Electronic cigarettes (e-cigarettes, vapes) Open and Close systems 	NJOY, JUUL, Vuse, Mart Ten, Blu, Logic	• Fruits, mint, menthol[176]	• Endothelial dysfunction[177–179] • Platelet activation[27] • Coagulation[180–182] • Oxidative stress[178, 183]	• Nicotine[184, 185] • Aldehydes[186–188] • Heavy metals[189, 190] • PAHs[191] • TSNA[192] • ROS[193] • Furans[194] • Phthalates[195]
Waterpipes (Hookah, E-Hookah) 	Starbuzz, Tangiers, Al-Fakher tobacco brands*	• Fruits, Mint/ menthol[66]	• Platelet activation[35] • Endothelial dysfunction[196–198] • coagulation[199]	• Nicotine[200] • TSNA [200, 201] • PAHs[202] • Heavy metals[190, 203] • TPM[204] • CO[205]
Cigars and cigarillo 	• Black & Mild • Swisher Sweets • Cohiba	• Mint/menthol • Fruits • sweet[206]	No sufficient data available	• Nicotine[207] • Heavy metals[167] • TSNA[208]
Heat-not-burn tobacco product (Heated tobacco products) 	iQos, Plom	Tobacco, menthol, bubble gum and lime[209]	• Endothelial dysfunction[210] • Platelet function[211, 212] • Oxidative stress[211, 212]	• Nicotine[47] • TSNAs[213] • CO[10] • Tar[10] • TPM[214]
Smokeless tobacco products 	Pouches: ZYN, DRYFT, On! Snus: Swedish Snus	• Mint[215] • Wintergreen[215]	• Platelets[216] (no effects) • Endothelial effects[217, 218] • Coagulation[219] (no effects) • Oxidative stress[220]	• Nicotine[221] • TSNAs [222] • PAHs[222] • Heavy metals[220]