



# Vaping Cardiovascular Health Risks: an Updated Umbrella Review

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## Abstract

**Purpose of Review** Modified risk products (MRP) such as electronic vaping cigarettes (EVC) and heat-not-burn cigarettes (HNBC) are alternatives to traditional combustion cigarettes (TCC) with an expanding consumer base. Yet, their cardiovascular health risks are still unclear. We aimed to summarize the evidence base on this topic by conducting an updated umbrella review.

**Recent Findings** We identified 7 systematic reviews, totaling 183 studies and reports, ranging from in vitro and in animal studies to clinical studies in apparently healthy volunteers and patients at risk of cardiovascular disease. Overall, acute EVC use was associated with several toxic effects at molecular, cellular, tissue, organ, and system level. In addition, EVC impacted adversely on blood pressure (BP) management, caused tachycardia, and worsened arterial stiffness. Finally, EVC use was associated with an increased risk of adverse clinical events, including atrial fibrillation and myocardial infarction, even if the causal link is still debated. Most reviews highlighted that the detrimental impact of EVC was of lesser magnitude of that of TCC. In addition, the differential impact of liquids and nicotine was not clearly disentangled. Finally, no review included studies on HNBC.

**Summary** The present umbrella review suggests that EVC, and likely HNBC, despite clearly causing an increase in overall cardiovascular risk, may represent a temporary lesser evil than TCC in a risk-reduction or risk-modification strategy, aiming for eventual abstinence from all tobacco or nicotine products.

**Keywords** Cardiovascular disease · Electronic cigarette · Electronic vaping cigarette · Heat-not-burn cigarette · Smoking

## Introduction

Giving up smoking is the easiest thing in the world. I know because I've done it thousands of times.  
Mark Twain

Smoking represents one of the leading causes of preventable morbidity and mortality worldwide, causing a plethora of adverse medical conditions, including coronary artery disease, stroke, chronic obstructive pulmonary disease, and cancer, and its detrimental effects impact also on passive smokers [1•, 2–5]. Even in the current coronavirus-associated disease 2019 (COVID-19) pandemic, smokers, especially the elderly, appear to have an increased risk of getting infected, progressing toward severely symptomatic disease, and dying due to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection [6–9].

Abstinence is easy to preach but harder to achieve, and several strategies have been proposed to ensure smokers can discontinue and abstain from their habit, ranging from telemedicine, nicotine replacement therapy, varenicline, and bupropion [10••]. Most recently, novel forms of smoking have been developed, which differ from traditional combustion cigarettes (TCC) as smoking is not due to combustion but vaporization of nicotine-containing liquids, i.e., electronic vaping cigarettes (EVC), or heating of tobacco products without combustion,

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i.e. heat-not-burn cigarettes (HNBC) [11–12]. Collectively, these alternative ways to smoke are called modified risk products (MRP) or, more optimistically, reduced risk products (RRP) [13, 14•, 15–17].

Substantial evidence continues to accrue on MRP, including results of randomized controlled trials (RCT), and several systematic reviews have already been published on this topic [18•]. However, the interplay between MRP, cardiovascular physiology, and cardiovascular disease is still uncertain, with conflicting results provided by different scholarly sources [19]. We thus aimed at conducting an updated umbrella review of systematic reviews on the cardiovascular effects, in terms of both pathophysiology and symptomatic disease, of EVC and HNBC [20•].

## Methods

In keeping with prior similar projects led by our group, this work was designed as an umbrella review (i.e., overview of systematic reviews) following established recommendations for evidence synthesis [20•, 21–22]. Specifically, we searched PubMed in order to find pertinent systematic reviews on the cardiovascular safety of MPR using the following string: (vaping OR vapes OR e-cigarette OR ecigarette OR (electronic AND cigarette) OR iqos OR juul) AND (heart OR cardiac OR coronary OR vascular OR venous OR cardiovascular OR artery OR arterial OR myocardial OR thrombosis OR atherosclerosis OR atherothrombosis) AND systematic[sb], restricting our search to studies published until May 5, 2020. Citations were first screened at the title/abstract level. Then, full texts were sought if potentially pertinent. We extracted salient features of included reviews, as well as corresponding original studies when appropriate. Review quality was appraised using the Oxman-Guyatt index [20•].

## Recent Findings

From 36 citations, we appraised in detail 17 articles, eventually including 7 systematic reviews, totaling 183 studies and reports (Tables 1, 2 and 3) [18•, 19, 23–28, 29•]. Specifically, Tzortzi et al. overviewed case reports on EVC-related injury reported in several databases including the leading US Center for Disease Control [29•]. From a total of 133 publications, no specific cardiac event was reported, but chest pain was relatively common in such compiled series of cases (22%). Hua and Talbot screened several databases looking for case reports of adverse events associated with EVC use, retrieving two cases (a case of acute myocardial infarction in a young man and a case of atrial fibrillation in an elderly woman) [24]. In both cases reported in this

hypothesis-generating systematic review, nicotine-containing EVC had been used.

Farsalinos and Polosa conducted a systematic review on several different generations of EVC focusing on their comparison versus TCC and nicotine gums, the impact of nicotine, and the risk of active as well as passive smoking [18•]. In particular, they synthesized evidence from 97 different reports, including several chemical studies, toxicological studies, and clinical trials. They concluded that, despite evident safety issues, including the presence of many toxic agents with established multidimensional risk (e.g., acetaldehyde, acrolein, aluminum, amino-tandafafil, copper, diethylene glycol, formaldehyde, iron, lead, nickel, particulate matter, rimonabant, and silica), EVC represent an appealing alternative to TCC in a RRP strategy. In terms of hazards, they highlighted the risk of tachycardia and hypertension, as well as impaired left anterior descending flow reserve, even if it remained unclear whether these effects depended mainly on nicotine. Interestingly, this old review was promising but limited by incomplete reporting and lack of quantitative synthesis.

Garcia and colleagues performed a systematic review and meta-analysis on the effects of EVC on blood pressure (BP), heart rate (HR), and heart rate variability (HRV), pooling data from 19 studies, and using largely explicit and valid methods [23]. They concluded that EVC are associated with acute increases in systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR, and changes in HRV typical of sympathetic prevalence over vagal activity, even if mostly explained by nicotine exposure. Notably, chronic use of EVC still had adverse effects on HRV, but effects on BP and HR were much more diluted, potentially suggesting time-dependent adaptation.

Kennedy and colleagues reviewed several experimental and clinical studies on the cardiovascular safety of EVC, highlighting that they may cause oxidative stress, cardiomyocyte dysfunction and mutagenesis, vascular inflammation, endothelial dysfunction, vasospasm, complement deposition, platelet aggregation, adhesion, and activation, with hypertension, tachycardia, arterial stiffening, atherosclerosis and thrombotic risk, albeit less intensely than TCC [25]. Most importantly, they suggested that studies with conflicts of interest were less likely to report adverse events.

Skotsimara and colleagues reviewed 26 studies, ranging from preclinical to clinical ones, and then performed a formal meta-analysis of 14 trials [28]. Overall, they identified the following as main signs of detrimental effects of EVC: cytotoxicity, oxidative stress, endothelial dysfunction, BP, HR, arterial stiffness, and myocardial infarction. Notably, most of these effects were heterogeneous and quantitatively less intense than those associated with TCC.

Finally, Riley et al. conducted a systematic review originally focused on the interplay between hormonal

**Table 1** Systematic reviews screened for the present umbrella review

First author (year)	PubMed ID	Studies/reports included	Screening result	Reason for exclusion
Boffetta (2009)	19690343	11	Excluded	Focus on smokeless, snuff, or spit tobacco
Cardenas (2019)	1582941	0	Excluded	Focus on pregnancy
Critchley (2004)	12728167	95	Excluded	Focus on smokeless, snuff, or spit tobacco
Farsalinos (2014)	25083263	97	Included	-
Farsalinos (2018)	29375395	32	Excluded	Focus on carbonyl emissions
Garcia (2020)	32219640	19	Included	-
Hua (2016)	27413679	2	Included	-
Kalkhoran (2016)	26776875	38	Excluded	Focus on smoking cessation
Kennedy (2019)	31344384	24	Included	-
Kozak (2020)	32011186	12	Excluded	Focus on schizophrenia
Leite (2018)	29656920	28	Excluded	Focus on periodontitis
Rahman (2015)	25822251	6	Excluded	Focus on smoking cessation
Riley (2016)	26546021	13	Included	-
Rostron (2018)	30364426	25	Excluded	Focus on smokeless tobacco
Skotsimara (2019)	30823865	26	Included	-
Tzortzi (2020)	32230711	2	Included	-
Vidyasagan (2016)	27256827	20	Excluded	Focus on smokeless tobacco

contraception, EVC, and cardiovascular risk [19]. No study explicitly focused on hormonal contraception was retrieved, and thus they expanded their analysis to the pathophysiologic link between EVC and cardiovascular outcomes. After including a total of 13 studies they concluded that EVC significantly impact of BP and HR, and may be associated with an increased risk of myocardial infarction.

## Implications

Our umbrella review, poignantly synthesizing the evidence accrued so far from *in vitro*, in animal, in human volunteers, healthy subjects, and patients on the cardiovascular risk associated with EVC use, either acute or chronic, shows that data are expanding progressively, but several conclusions can already be made on the

**Table 2** Main features of included systematic reviews

First author (year)	Exposure/intervention	Comparison	Findings
Farsalinos (2014)	EVC with nicotine, EVC without nicotine	Nihil, NRT, sham, TCC	EVC are a less harmful alternative to TCC and significant health benefits are expected in smokers who switch from TCC to EVC.
Garcia (2020)	EVC with nicotine, EVC without nicotine	Nihil, sham, TCC	EVC acutely increase HR and BP but less than TCC. Nicotine but not non-nicotine constituents in EVC aerosol were responsible for the sympathoexcitatory effects. EVC chronically lower HRV
Hua (2016)	EVC with nicotine	NA	EVC use was associated with atrial fibrillation or myocardial infarction in two case reports.
Kennedy (2019)	EVC with nicotine, EVC without nicotine	Nihil, sham, TCC	EVC increased sympathetic nerve activity, platelet hemostatic processes, reactive oxygen species production and endothelial dysfunction. Notably, studies with conflicts of interest or median-high risk of bias were less likely to identify potentially harmful effects.
Riley (2016)	EVC with nicotine, EVC without nicotine	Nihil, sham, TCC	EVC may increase HR and BP less than TCC. CV events are rare among EVC users in the general population.
Skotsimara (2019)	EVC with nicotine	Nihil, sham, TCC	EVC have detrimental effects on endothelial function, arterial stiffness, and risk of coronary events, and also increase HR, SBP, and DBP. However, their impact on HR, SBP, and DBP is less severe than TCC.
Tzortzi (2020)	EVC with nicotine, EVC with cannabinoid and nicotine	NA	EVC use was associated with acute coronary syndromes in two young patients.

BP, blood pressure; DBP, diastolic blood pressure; EVC, electronic vaping cigarette; HR, heart rate; NA, not applicable; NRT, nicotine replacement therapy; TCC, traditional combustion cigarette; SBP, systolic blood pressure

**Table 3** Quality features of included systematic reviews

First author (year)	Explicit search methods	Comprehensive search	Explicit selection criteria	Appropriate selection	Explicit validity criteria	Appropriate validity assessment	Explicit analysis methods	Appropriate analysis methods	Appropriate interpretation
Farsalinos (2014)	No	No	No	No	No	No	NA	NA	NA
Garcia (2020)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Hua (2016)	Yes	Yes	Yes	Yes	No	No	NA	NA	Yes
Kennedy (2019)	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes
Riley (2016)	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes
Skotsimara (2019)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tzortzi (2020)	Yes	Yes	Yes	Yes	No	No	NA	NA	NA

NA, not applicable

multidimensional hazards of EVC (Fig. 1, Table 4) [30••, 31]. First, acute EVC use is associated with several toxic effects at molecular (e.g., DNA), cellular, tissue, organ, and system level [25, 32]. For instance, oxidative stress, cytotoxicity, and cardiomyocyte dysfunction are established effects of EVC [33]. Second, EVC impact adversely on BP management, cause tachycardia, and worsen arterial stiffness [19, 34]. Third, EVC use has been associated with an increased risk of adverse clinical events, including atrial fibrillation and myocardial infarction, even if the causal link is still debated [24, 35]. Yet, most reviews highlighted that the detrimental impact of EVC was of lesser magnitude of that of TCC. In addition, the differential impact of liquids and nicotine was not clearly disentangled.

Overall, these findings confirm prior reports and support further research on the topic of cardiovascular safety of EVC. Several avenues for research are worth exploring. For instance, translational studies on the precise cellular

mechanisms involved in EVC toxicity are needed, exploring for instance microRNA, inflammatory cascade, autophagy, apoptosis, and regeneration [36–38]. Observational studies on large samples are needed to accurately gauge the short and long-term risks of EVC in apparently healthy subjects and in patients with cardiovascular disease [39]. In addition, randomized trials, from small-sample speculative ones to large pragmatic studies, are direly needed to ensure that the place of EVC in current clinical practice is correctly defined [40]. Indeed, our premise is that EVC should be considered as an over-the-counter medical intervention suitable to support chronic smokers in their journey to eventual cessation. Accordingly, only a comprehensive evidence platform, hopefully summarized in a formal network meta-analysis, will be able to precisely define the place and role, if any, of EVC in a comprehensive approach aiming at smoking cessation and harm minimization [41]. Pragmatically, and based on our personal and professional experience, we may suggest a stepwise use of EVC and HNBC with the eventual aim of total and



**Fig. 1** Key adverse cardiovascular effects of electronic vaping cigarettes and heat-not-burn cigarettes

**Table 4** Key adverse cardiovascular effects and potential clinical impact of electronic vaping cigarettes and heat-not-burn cigarettes

Effect	Potential impact
↑ Arrhythmic risk	Lipothymia, loss of consciousness, syncope, weakness
↑ Arterial stiffness	Ischemia
↑ Blood pressure	Atherothrombosis, myocardial hypertrophy, renal failure
↑ Heart rate	Myocardial ischemia
↑ Oxidative stress	Atherothrombosis, diabetes
↑ Platelet aggregation	Atherothrombosis
↓ Cardiomyocyte function	Decline in left ventricular systolic function
↓ Flow-mediated dilation	Ischemia
↓ Left anterior descending flow reserve	Myocardial ischemia
↓ Vasodilation	Systemic hypertension

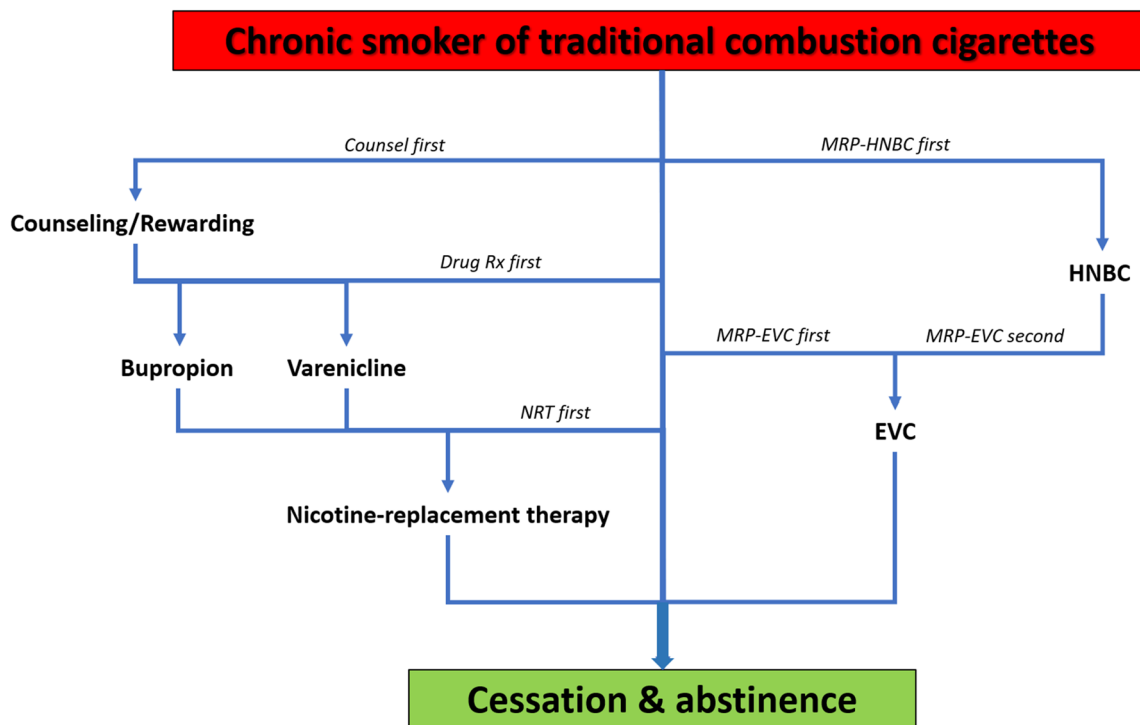
continued abstinence (Fig. 2). Yet, practitioners should be aware of the potential interactions between MRP and pharmacologic therapy in patients with or at risk of cardiovascular disease, ranging from atherothrombosis to heart failure and valvular heart disease [42–46], as indeed it is plausible that many of the adverse cardiovascular effects of MRP depend on nicotine, thus raising the evident risk of cumulative toxicity if NRT and MRP are inadvertently combined.

### Limitations

This umbrella review has several drawbacks, on top of those typical of this research design [20•]. First, studies and reviews discussed hereby are mostly of small size and limited follow-up, and often focus on apparently healthy subjects. Second, data on long-term pulmonary and cancer risk are absent, but this cannot be considered proof of absence of oncologic risk, as only longitudinal studies will be able to inform on this safety dimension. Another elephant in the room is the lack of comprehensive data on HNBC, which are a mainstay in the MRP arena, and can be considered for some aspects as safe or safer than EVC, and for others worse (e.g., because of small but measurable combustion) [47•]. Accordingly, we expect that additional research synthesis efforts will be needed in the future, including updated umbrella reviews.

### Future Directions

The information accrued in this umbrella review, coherently showing multidimensional adverse effects of HNBC and EVC, highlights the evident risk of adverse cardiovascular events associated with MRP. Accordingly, further restrictions to their usage could be considered, including equating them to over-the-counter or even prescription drugs. Indeed, the best perspective is considering HNBC and EVC as another



**Fig. 2** Potential algorithm to exploit modified risk products (MRP) such as electronic vaping cigarettes (EVC) and heat-not-burn cigarettes (HNBC), on top of counseling, drug therapy, and nicotine replacement therapy (NRT), to promote smoking cessation and abstinence

management strategy to promote smoking cessation and maintain abstinence (Fig. 2).

Moreover, their usage should be monitored, minimized in intensity and duration, aiming for clear timelines to switch from HNBC to EVC and then stop them altogether if a HNBC-first approach is chosen, or instead having a goal of EVC usage followed by cessation if an EVC-first approach is adopted. An apparently banal but potentially useful framework could indeed be considering MRP as a novel and more palatable NRT, maintaining many of the rituals of TCC without the abundance of combustion byproducts.

Nonetheless, dedicated large-scale and pragmatic randomized trials are needed to test the above strategy before recommending it to individuals and patients at large.

## Conclusions

The present umbrella review suggests that EVC, despite clearly causing an increase in overall cardiovascular risk, may represent a temporary lesser evil than TCC in a risk-reduction or risk-modification strategy, aiming for eventual abstinence from all tobacco or nicotine products.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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