LA TUNISIE MEDICALE

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Heart Connections

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SYSTEMATIC- REVIEW

Effects of Heated Tobacco Products compared to Conventional Cigarettes on Cardiovascular System: A Systematic Review

Comparaison entre l'impact du tabac chauffé et celui des cigarettes conventionnelles sur le système cardio-vasculaire : Une revue systématique

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Abstract

Introduction: Heated tobacco products (HTPs) are marketed as reduced-risk alternatives to conventional cigarettes, yet their true cardiovascular safety profile remains unclear. This systematic review aimed to evaluate the acute and short-term cardiovascular effects of HTPs compared to traditional cigarettes.

Methods: A comprehensive literature search was conducted in PubMed, Embase, Cochrane Library, and Embase from inception to March 2024. Eligible studies included randomized controlled trials and observational studies reporting on cardiovascular outcomes in adult users of HTPs compared to conventional smokers. Risk of bias was assessed using RoB 2 and ROBINS-I tools. Data were synthesized qualitatively; a meta-analysis was not feasible due to heterogeneity.

Results: Five studies (n = 460 participants) met the inclusion criteria. Risk of bias ranged from low to serious, with one industry-sponsored study. Acute HTP exposure induced hemodynamic and vascular changes comparable to those observed with conventional cigarettes. Endothelial dysfunction and persistent oxidative stress were reported across studies. One study (Ikonomidis et al.) suggested a minor reduction in oxidative biomarkers with HTP use, though clinical significance was uncertain. No study assessed mid- or long-term outcomes.

Conclusions: HTPs do not appear to offer meaningful cardiovascular benefit over conventional cigarettes in the short term. The similarity in acute harmful effects raises concern over their widespread use and marketing. These findings underscore the urgent need for independent, long-term studies assessing clinically relevant cardiovascular endpoints.

PROSPERO registration: CRD42023453900

Key words: adult, smoker, heated tobacco products, cigarettes, cardiovascular complications, blood pressure, biomarker

Résumé

Introduction: Les produits du tabac chauffé (HTP) sont commercialisés comme des alternatives à risque réduit par rapport aux cigarettes conventionnelles, mais leur véritable profil de sécurité cardiovasculaire demeure flou. Cette revue systématique vise à évaluer les effets cardiovasculaires aigus et à court terme des HTP par rapport aux cigarettes traditionnelles.

Méthodes: Une recherche bibliographique exhaustive a été réalisée dans PubMed, Embase, Cochrane Library et Embase depuis leur création jusqu'en mars 2024. Les études éligibles comprenaient des essais contrôlés randomisés et des études d'observation rapportant les résultats cardiovasculaires chez des utilisateurs adultes de HTP comparés aux fumeurs conventionnels. Le risque de biais a été évalué à l'aide des outils RoB 2 et ROBINS-I. Les données ont été synthétisées qualitativement; une méta-analyse n'était pas faisable en raison de l'hétérogénéité.

Résultats: Cinq études (n = 460 participants) ont satisfait aux critères d'inclusion. Le risque de biais variait de faible à élevé, avec une étude sponsorisée par l'industrie. L'exposition aiguë aux HTP a induit des changements hémodynamiques et vasculaires comparables à ceux observés avec les cigarettes conventionnelles. Une dysfonction endothéliale et un stress oxydatif persistant ont été rapportés dans plusieurs études. Une étude (Ikonomidis et al.) a suggéré une réduction mineure des biomarqueurs oxydatifs avec l'utilisation des HTP, bien que la signification clinique soit incertaine. Aucune étude n'a évalué les résultats à moyen ou long terme.

Conclusions: Les HTP ne semblent pas offrir de bénéfice cardiovasculaire significatif par rapport aux cigarettes conventionnelles à court terme. La similitude des effets néfastes aigus soulève des inquiétudes quant à leur utilisation et leur commercialisation généralisées. Ces résultats soulignent le besoin urgent d'études indépendantes à long terme évaluant des critères d'évaluation cardiovasculaire cliniquement pertinents.

Enregistrement PROSPERO: CRD42023453900

Mots clé: adulte, fumeur, tabac chauffé, cigarettes, complications cardiovasculaires, pression artérielle, marqueur biologique.

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Introduction

Heated tobacco products (HTPs) have emerged in recent years as a purportedly less harmful alternative to conventional cigarettes (TC) (1). These devices heat processed tobacco at lower temperatures, generating an aerosol that delivers nicotine without combustion. The tobacco heating systems generally operate at 240–350 °C, compared to over 600 °C for TC, theoretically reducing the formation of harmful combustion by products (2,3)
HTPs have rapidly gained popularity worldwide. Evidence suggests they are often used alongside other tobacco or nicotine products, especially among young people and even individuals who have never smoked. This dual use, their appeal among youth, and uptake by non-smokers are concerning trends that highlight the need for vigilant monitoring of HTPs use and its health impacts (4-6).
Industry-sponsored studies have claimed that products like IQOS produce fewer harmful constituents than conventional cigarettes (7-8). However, independent research has shown that HTPs still release toxic substances some of which may even be found in higher concentrations and that the health risks for users may remain significant (3,9,10). In January 2018, the U.S. FDA's Tobacco Products Scientific Advisory Committee examined applications for "Modified Risk Tobacco Products" (MRTPs), ultimately concluding that available evidence did not suffice to support claims of reduced harm compared to combustible cigarettes (8). Among the earliest investigations into the cardiovascular effects of HTPs, Glantz and Bareham argued that although exposure to certain toxicants may be lower, HTPs still pose substantial cardiovascular risks (11). They warned that functional impairments similar to those seen in conventional smokers could occur, urging caution in presenting HTPs as a safer alternative.
Cardiovascular diseases remain the leading cause of mortality among smokers. While preliminary studies have suggested that HTPs may present a reduced cardiovascular risk compared to conventional cigarettes, the current evidence is limited and often conflicting. Key cardiovascular outcomes such as endothelial dysfunction, incidence of cardiovascular events, and inflammatory biomarkers require further investigation through rigorous and independent studies (11).
The underlying aim for this review was to compare cardiovascular effects of using HTPs with those of using TC in adults.

Methods

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (12). The study protocol has been registered in PROSPERO (CRD42024594334).

Information Sources and Search Strategy

Search was performed via databases including PubMed, EMBASE, Clinical Trials. Gov and the Cochrane Library. In addition, we conducted supplementary searches using Google Scholar and by screening the reference lists of included studies.
Search terms included the following keywords and terms : "smokers", "smoking", "Conventional cigarettes", "combustible cigarettes", "traditional cigarettes", "Tobacco products", "tobacco use", "Heated tobacco products", "HTPs", "heat-not-burn", "IQOS", "glo", "Ploom", "Cardiovascular event", "major adverse cardiovascular event", "blood pressure", "myocardial infarction", "stroke", "heart attack", "coronary artery disease" The search strategy was adapted to each database (13). A comprehensive search strategy was developed for each database using a combination of keywords and subject headings related to heated tobacco products, conventional cigarettes, and cardiovascular outcomes. The full search strategies for all databases are provided in supplementary material 1.

Selection criteria

Population – Eligibility Criteria
Inclusion Criteria:
· Adults (aged ≥18 years) who use either heated tobacco products (HTPs) or conventional cigarettes.

Exclusion Criteria:
· Adults using other forms of tobacco or nicotine delivery systems (e.g., electronic cigarettes, nicotine patches, smokeless tobacco).
· Dual users of HTPs and conventional cigarettes.

Study Design – Inclusion and Exclusion Criteria
Included Study Designs:
· Randomized Controlled Trials, cohort studies, and case-control studies comparing the use of HTPs with conventional cigarettes.
· Studies assessing cardiovascular outcomes and reporting at least one clinical parameter (such as blood pressure, heart rate, vascular function). The assessment of biomarkers was considered optional.

Excluded Studies:
• Studies not published in English.
• Non-original papers (reviews, editorials, commentaries).

Study selection

The results of the database search were imported into a reference management software (EndNote) for de-duplication. Study selection was performed independently by two reviewers in three sequential steps:

Excluded Studies:
· Title and abstract screening
. Full-text review of potentially eligible studies
. Final inclusion based on predefined eligibility criteria.
Any discrepancies between reviewers were resolved through discussion or arbitration by a third reviewer.

Data Extraction

Data were extracted using a standardized form and included the following items:
· Study characteristics: first author, year of publication, country, and study design,
· Population characteristics: sample size, age, sex, comorbidities,
· Exposure details: type of tobacco product used, duration of exposure,
· Outcomes: mandatory reporting of at least one clinical cardiovascular parameter (e.g., blood pressure, heart rate); biomarker data were extracted when reported.

Quality Assessment and Risk of Bias

The methodological quality and risk of bias of the included studies were independently assessed by two reviewers. For randomized controlled trials, the Cochrane Risk of Bias tool version 2 (RoB 2) was used, which evaluates five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result. Each domain was judged as having low risk, some concerns, or high risk of bias.
For non-randomized studies, the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool was applied. This tool assesses seven domains, including bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. Each study was categorized as having low, moderate, serious, or critical risk of bias.
Disagreements between reviewers were resolved through discussion or adjudication by a third reviewer.
The results of the risk of bias assessments are summarized in tabular form and visualized using traffic light plots and summary risk graphs.

Data synthesis and analysis

A narrative synthesis of the included studies was performed, structured around study design, population characteristics, type of tobacco product used (HTPs vs. TC), cardiovascular outcomes assessed, and main findings.
No quantitative pooling of data was conducted.

Results

The search strategy yielded 742 records. After de-duplication across the multiple databases, 680 unique records remained. Title and abstract screening led to the exclusion of 663 records. The remaining 17 studies were assessed for eligibility by three reviewers. Four full-text articles could not be retrieved, leaving 13 articles for full-text review. Of these, 8 were excluded based on eligibility criteria. Finally, 5 studies were included in the qualitative synthesis. Figure 1 details the results of the systematic search.

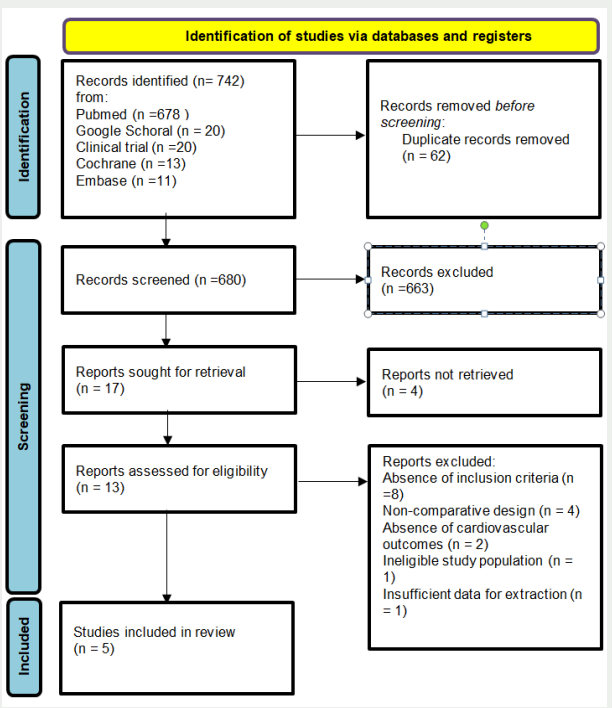

Figure 1. Search strategy for identification of studies.

Description of studies

Table 1 summarizes the main characteristics of the five included studies, which together involved 304 participants meeting the eligibility criteria. For each study, the table presents the authorship, publication year, country of origin, study design, inclusion and exclusion criteria applied, details of the interventions comparing heated tobacco products and conventional cigarettes, and the cardiovascular outcomes assessed, including blood pressure, heart rate, and biomarkers when available.

Summary of Main Findings

The main results of the included studies are presented in Table 2.

Acute Hemodynamic Effects
All studies reported increases in blood pressure and heart rate following HTP use. In several trials, these acute responses were similar in magnitude to those observed with conventional cigarettes, though some studies found a milder elevation with HTPs.

Oxidative Stress and Inflammation
One study showed a reduction in oxidative stress markers (e.g., malondialdehyde, thromboxane B2) after switching to HTPs, suggesting a potentially lower impact. However, overall differences in inflammatory biomarkers between products were inconsistent.

Lipid Profile and Longer-Term Markers
In longer follow-up (up to 90 days), some improvements in lipid profile and vascular inflammation markers were observed, including reductions in hs-CRP and fibrinogen. Despite these changes, no clear benefit on blood pressure was consistently reported.

Table 1. Characteristics of included studies

Authors (Year/Country) Type of Study	Inclusion and exclusion criteria	Intervention	Outcomes (blood pressure, heart rate, biomarker)
Lokeimidis (14). (2021/Greece) Cross-over randomized trial	**Inclusion criteria:** -Current smokers -No Cardio-vascular risk factors -No medications	-All subjects smoked randomly: (a) HNBC (IQOS) heat stick for 5 min, (b) a standard tobacco cigarette for 5 min and (c) sham cigarette on 3 separate occasions. -The mean nicotine content for both HNBC and TC was 0.5 mg. -Every session took place in the morning, after a minimum 4-h fasting period, while the subjects had not smoked or consumed any caffeinated beverage. -The order of smoking sessions was randomized. -Sessions were conducted at least two days apart from each other. -HR, BP, AIx@75, cfPWV and baPWV were assessed immediately before and after smoking, and then at 5, 10, 20 and 30 min.	-Heart rate -Blood pressure (both brachial and aortic)
Ikonomidis (15) (2021, Greece) Independent, randomised, cross-over trial	**Inclusion criteria:** Current smokers with no intention to quit smoking (≥5 cigarettes per day end exhaled CO ≥10 ppm) **Exclusion criteria:** -Cardiovascular disease -Hepatic or renal failure -Active neoplasia -Alcohol abuse -Psychiatric illness -Pregnancy -Breastfeeding -Cigar smoking -Dyslipidaemia (total cholesterol > 200 mg/dl or the use of cholesterol-lowering agents) -Hypertension (blood pressure> 140/90 mmHg or use of anti-hypertensive drugs) - Diabetes mellitus (fasting plasma glucose > 125 mg/dl or use of antidiabetic drugs).	**Acute phase** -Initial sham smoking session of inhaling on a non-lighted cigarette for 7 min -Participants randomised into either TC smoking session, or a single HEETS stick puffing session - After a washout period of 60 min, the subjects were crossed over to the alternative session - Vascular studies and blood sampling were completed during 20-min at baseline before initiation of smoking and within the wash-out period. **Chronic phase** -All participants replaced TC smoking with HNBC puffing for 1 month and were compared with an external group with no intention to quit smoking, before and after 1 month.	Systolic blood pressure Diastolic blood pressure Heart rate Malondialdehyde Thromboxane B2

Table 1. (following) Characteristics of included studies

Authors (Year/Country) Type of Study	Inclusion and exclusion criteria	Intervention	Outcomes (blood pressure, heart rate, biomarker)
Yaman (16) **(2021/Turkey)** **Prospective randomised study**	**Inclusion criteria** Volunteer IQOS users **Exclusion criteria** Chronic cardiac diseases Hypertension Diabetes mellitus Kidney failure Poor image quality High body-mass index (>30 kg/m2) Moderate-severe heart valve disease Systolic dysfunction or diastolic dysfunction High levels of SBP (≥140 mmHg), or DBP ≥90 mmHg History of chronic medical treatment	-Participants were asked to smoke only one IQOS stick Participants were asked to charge their device and smoke only one IQOS stick -All smokers were asked to use one brand of tobacco cigarette -Echocardiography was performed 10 min after IQOS smoking (group 2) and cigarette smoking (group 3) on separate days with random order by a minimum 24 h wash-out period. -10 puff of IQOS or cigarette smoking for 5 min was asked to the participants. SBP and DBP were measured manually at baseline, after IQOS and cigarette smoking immediately before echocardiographic evaluation. HR was recorded during echocardiography for each session.	Blood pressure Heart rate
Biondi-Zoccai (Italy,2019) (17) Independent, cross-over, randomized trial	**Inclusion criteria** - Adult current smokers (≥18 years old) -Habitual use of traditional tobacco cigarettes (at least 1 cigarette per day) -No use of electronic cigarettes or heat-not-burn cigarettes in the previous month -Willingness to abstain from smoking and nicotine products for at least 12 hours before each study visit **Exclusion criteria** - History of cardiovascular disease -Diabetes mellitus -Chronic kidney disease -Use of electronic cigarettes or heat-not-burn cigarettes within the previous month -Use of antioxidant supplements or anti-inflammatory drugs within the previous two weeks -Pregnancy or breastfeeding -Acute illness or infection at the time of enrollment	- Each participant tested the three types of cigarettes (Traditional combustion cigarettes, electronic vaping cigarettes, heat-Not-Burn cigarettes) successively, in a randomized order, with a washout period (one week without smoking) between each session to eliminate residual effects. -In each session, the participant smoked one cigarette of the assigned type. -Measurement of BP, oxidative stress markers, endothelial function, analysis of platelet activation and assessment of antioxidant markers are done Before and after cigarette use.	Systolic blood pressure Diastolic blood pressure Soluble Nox2-derived peptide 8-iso-prostaglandin F2α-III Vitamin E concentration Soluble CD40 ligand Soluble P-selectin

Table 1. (following) Characteristics of included studies

Authors (Year/Country) Type of Study	Inclusion and exclusion criteria	Intervention	Outcomes (blood pressure, heart rate, biomarker)
Ludicke (18) (Japan, 2018) Randomised, three-arm paralell-group	**Inclusion criteria** - Age 23–65 y -Body mass index 18.5–32 kg/m2 -Japanese ethnicity -Healthy smoker - Smoked ≥10 TC per day with a maximum ISO yield of 1 mg for the previous 4 weeks (self-reported) and had smoked for ≥3 consecutive years -No plan to quit smoking in the next 3 months -Ready to stop smoking for up to 90 days and to use the mTHS 2.2 **Exclusion criteria** -Inability to participate for any reason -Legally incompetent, physically or mentally incapable of giving consent -Medical condition requiring smoking cessation, or clinically relevant disease -Medical condition that required or would have required in the course of the study a medical intervention, which would have interfered with study participation and/or study results -Use of nicotine- containing products (other than mCCs) or electronic - Cigarettes/similar devices within 4 weeks prior to enrollment - Administration of drugs likely to affect CYP1A2 or CYP2A6 activity within 14 days or five half-lives of the drug (whichever was longer) before Day −2 - Administration of drugs within 14 days of Day −2 that the principal -Investigator thought was likely to interfere with the study objectives or the participant's safety - Concomitant use of non-steroidal anti-inflammatory drugs or acetylsalicylic acid - Positive alcohol test and/or history of alcohol abuse that could have interfered with participation in the study _ Positive urine drug test - Positive serology test for human immunodeficiency virus 1/2, hepatitis B, or hepatitis C virus - Donation/receipt of whole blood/blood products within 3 months prior to admission - Current or former employee of the tobacco industry, or of their first-degree relatives - Employee of the investigational site, or any other parties involved in the study, or of their first-degree relatives - Participation in a clinical study within 3 months before screening - Participation in the same study at a different time - Pregnant/breast feeding women - Women who were unwilling to use an acceptable method of contraception	**Groups** HNBC (n = 78) TC (n = 42) Smoking abstinence (n = 40) Participants were assigned to one of three groups: switching to HNBC continuing smoking TC, or smoking abstinence. The study period included: 5 days of confinement with controlled product use, followed by 85 days in ambulatory conditions. The primary endpoints were biomarkers of exposure to harmful substances as well as clinically relevant risk markers associated with smoking-related diseases, including indicators of oxidative stress, endothelial function, lipid metabolism, and lung function.	Systolic heart rate Diastolic heart rate White blood cells Hs-CRP Fibrinogen Homocysteine Triglycerides LDL cholesterol HDL cholesterol Total cholesterol sICAM-1 Glucose HbA1c 8-epi-prostaglandin F2α 11-DTX-B2

AIx@75: augmentation index corrected for heart rate; **ba PWV**: brachial-ankle pulse wave velocity; **BP**: blood pressure; **cfPWV**: carotid femoral pulse wave velocity; **CFR**: coronary flow reserve, **DBP** : diastolic blood pressure, **HbA1c** = hemoglobin A1c; **HDL** = high-density lipoprotein; **HNBC**: heat-not-burn cigarette, hs-**CRP** = high-sensitivity C-reactive protein; **HR**: Heart rate, **ISO** = International Organization for Standardization; **LDL** = low-density lipo protein; **SBP**: systolic blood pressure, **sICAM-1** = soluble intercellular adhesion molecule-1; **TC**: tobacco cigarette; **8-epi-PGF2α** = 8-epi-prostaglandin F2α; 11-DTX-B2 = 11-dehydro-thromboxane B2

Table 2. Results of included studies

Authors, Year Number of participants	Results	Conclusion
Lokeimidis, 2021 (14). 22 participants	- Both HNBC use and conventional cigarette smoking led to a significant acute increase in HR and BP among young smokers. -Specifically, after smoking either product, participants exhibited elevated SBP and DBP as well as an increased pulse rate compared to baseline measurements. - The magnitude of these increases was similar between HNBC product use and TC smoking	-Acute exposure to heat-not-burn tobacco products results in immediate increases in arterial stiffness, HR, and BP, mirroring the adverse hemodynamic effects observed with TC smoking. -These findings suggest that HNBC products are not a harmless alternative to TC in terms of their short-term impact on vascular health.
Ikonomidis, 2021 (15). 75 participants	-HNBC has a much milder effect on BP, with only slight or no increases in the short term. -After one month of switching from TC to HNBC, systolic and diastolic blood pressure tend to decrease or normalize, indicating a relative benefit for vascular function. -No significant variation in overall heart rate was observed after acute exposure to either a TC or a HNBC. -After 1 month of switching from TC to HNBC), there was no notable change in HR among participants. -TC caused a significant MDA increase, in contrast with the lack of increase of MDA levels after HNBC puffing -MDA levels were found lower after HBNC than after TC - Acute TC smoking significantly increased TxB2 concentration; TxB2 levels did not change significantly following HNBC puffing - TXB2 levels were found lower after HBNC than after TC -Switching from TC to HBNC significantly improves these biomarkers after one month of use.	-HNBC has a less harmful acute cardiovascular impact than TC, especially regarding BP. -Completely switching from conventional cigarettes to HNBC can reduce BP - HBNC has a markedly less harmful impact than TC on oxidative stress and platelet activation biomarkers. -Switching from traditional smoking to HNBC significantly improves these biomarkers after one month of use. .
Yaman, 2021 (16) 27 participants	-The rise in BP (both systolic and diastolic) is significantly lower with HBNC than with TC. -The increase in HR is lower with HBNC than with TC	Both CT and IQOS use acutely increase blood pressure and heart rate, but the effect is significantly greater with TC than with HBNC.
Biondi-Zoccai, 2019 (17) 20 participants	HNBC induces - Smaller increase of BP compared to TC -Significantly lower increase of Soluble Nox2-derived Peptide than TC -Smaller increase of 8-iso-prostaglandin F2α-III compared to TC -Less pronounced decrease of Vitamin E concentration than TC -Moderate increase of Soluble CD40 Ligand, lower than TC	TC have a more harmful acute effect than HNBC on BP, oxidative stress markers, antioxidant reserves, and platelet activation
Ludick, 2018 (18) 160 participants	After 90 days of Switching from TC to HNBC: BP: does not lead to a clear benefit White blood cell count: significant reduction Hs-CRP: significant reduction Fibrinogen: decrease observed Triglycerides: moderate improvement, with a relative decrease in heated tobacco users. LDL cholesterol: slight decrease in the heated tobacco group. HDL cholesterol: significant increase Total cholesterol: trend toward reduction in the heated tobacco group. sICAM-1: significant reduction Glucose and HbA1c: no precise data reported. 8-epi-PGF2α: significant decrease 11-DTX-B2: notable decrease	-Switching from TC to HNBC does not lead to a clear benefit on BP These results demonstrate an improvement in cardiovascular risk-related biomarkers among participants who replaced TC with HNBC

BP: blood pressure; **DBP** : diastolic blood pressure, **HNBC**: heat-not-burn cigarette, **HR**: Heart rate, **MDA**: malondialdéhyde, **SBP** systolic blood pressure, **sICAM-1** = soluble intercellular adhesion molecule-1; **TC**: tobacco cigarette; **TxB2**: plasma thromboxane B2, **8-epi-PGF2α** = 8-epi-prostaglandin F2α; **11-DTX-B2** = 11-dehydro-thromboxane B2

Assessment of risk of bias of includes studies

Risk of bias was assessed using the Cochrane RoB 2 tool for the four included randomized controlled trials (RCTs) and the ROBINS-I tool for the non-randomized interventional study Yaman (16).

Among the RCTs, one study of Ikonomidis was judged to be at low risk of bias across all domains (15).The other three trials showed some concerns, mainly related to randomization procedures and blinding of outcome assessment. No RCT was considered to be at high risk of bias overall

The non-randomized study of Yaman et al. was rated as having an overall serious risk of bias (16). The main concerns were a lack of control for confounding variables (e.g., smoking history, cardiovascular risk) and selection bias, due to non-random sampling of habitual IQOS users. Other domains showed moderate risk, particularly in outcome measurement and reporting, while classification of interventions and handling of missing data were considered at low risk

A visual summary of these assessments is provided in Figure 2 and 3 (traffic light plot) and detailed domain-level justifications are available in Supplementary Material 2.

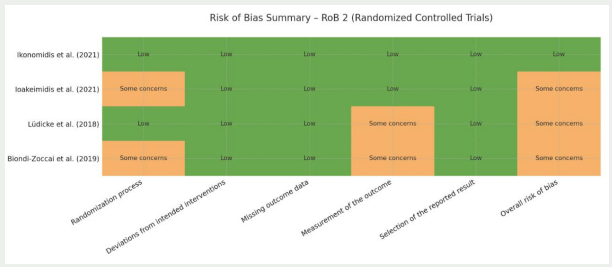

Figure 2. Risk of bias summary of randomised controlled trials included

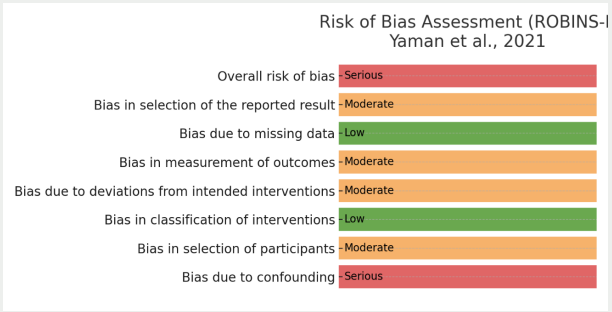

Figure 3. Risk of Bias Assessment – Non-Randomized Study (ROBINS-I)

Discussion

This systematic review provides a comprehensive analysis of the cardiovascular effects of HTPs compared to TC based on five high-quality studies. While HTPs are marketed as reduced-risk alternatives due to the absence of combustion, our findings challenge this narrative by highlighting that HTPs produce acute cardiovascular effects that are largely comparable to those of TC. By synthesizing the current evidence, this study also aims to provide a clearer understanding of the cardiovascular effects of HTPs. This is particularly critical given the rapid adoption of these products worldwide, including among younger and non-smoking populations.

Anticipation of Results

It is anticipated that HTPs may show a reduction in exposure to certain harmful chemicals. For instance, a narrative review highlighted that HTPs produce lower levels of toxicants such as nicotine, particulate matter, benzene, acrolein, and tobacco-specific nitrosamines compared to traditional cigarettes (19). However, despite these reductions, HTPs still emit harmful chemicals that are potentially detrimental to cardiovascular health. A position paper by the European Heart Network emphasized that HTPs produce mainstream and second-hand emissions of harmful chemicals, including nicotine and particulate matter, which are potentially harmful to cardiovascular health (20). Therefore, the overall cardiovascular impact of HTPs remains uncertain, and it is possible that this review will find no significant difference in cardiovascular outcomes between HTPs and conventional cigarettes.

The findings of this review could have significant implications for public health policies and clinical practice. If HTPs are found to have a reduced cardiovascular risk profile compared to TC, this could support harm reduction strategies and inform regulatory policies. Conversely, if no significant differences are found, it may challenge current marketing claims by manufacturers and reinforce the need for stricter oversight (21). Additionally, the findings could highlight gaps in evidence, emphasizing the need for further high-quality randomized trials on this subject.

Similarity in Acute Cardiovascular Effects

Across the included studies, consistent evidence was found for similar acute physiological responses between HTP and cigarette use. These include impairments in endothelial function, alterations in hemodynamic parameters, and sympathetic nervous system activation. Both **Ioakeimidis et al. and Biondi-Zoccai et al**. demonstrated that acute HTP exposure reduced flow-mediated dilation (FMD) and increased heart rate and blood pressure to levels observed with conventional cigarette use (14,17).The similarity in acute endothelial dysfunction, a recognized early marker of atherosclerosis, is particularly concerning.

Oxidative Stress: A Distinctive Signal?

Among the included studies, only **Ikonomidis et al.** provided moderate evidence suggesting a possible reduction in oxidative stress markers with HTP use (15). However, this reduction was neither robust nor consistent across biomarkers (Plasma Malondialdehyde, Protein Carbonyls concentration and Carbon monoxide), and no study reported complete restoration of oxidative balance. Importantly, oxidative stress, even if slightly attenuated, was still present in HTP users, raising the hypothesis that

despite reduced combustion by products, these products remain biologically active and potentially harmful.

Emerging Signal of Myocardial Impairment

There is a strong and long-standing evidence from both experimental and clinical studies that cigarettes have harmful effects on myocardial function (22,23). **Yaman et al.** observed acute impairment in left ventricular longitudinal strain in IQOS users, pointing to a possible subclinical myocardial dysfunction (16). This is a novel and critical observation that suggests HTP use may impact cardiac performance even after brief exposures. Combined with data on endothelial and autonomic dysfunction, this supports a model in which HTPs are not harmless substitutes but may contribute to cardiovascular strain through multiple pathways.

What Remains Untested: A Clinical and Research Perspective

As impressive as these acute findings may be, they paint only part of the picture. If we were to step into the shoes of the original investigators, we would urgently seek to extend the clinical evaluation of HTPs beyond their surface. For instance, none of the studies explored **biomarkers of myocardial injury** such as high-sensitivity cardiac troponins (hs-cTn), N-terminal pro-BNP, or galectin-3, which are now routinely used to assess subclinical cardiac stress even in asymptomatic individuals (24,35). Their inclusion would help determine whether myocardial strain observed on imaging is associated with biochemical injury.

Similarly, **advanced vascular assessments** such as carotid intima-media thickness (CIMT), would provide more information than pulse wave velocity (PWV), and arterial stiffness. All those parameters become essential tools in identifying early vascular damage in high-risk populations (26,27). None of the reviewed studies applied CIMT measuring. It would offer insight into structural changes, atherosclerotic plaque burden and arterial remodeling over time complementing functional abnormalities. It is also very sensitive to lifestyle and metabolic risk factors (smoking, diabetes, obesity and dyslipidemia).

Moreover, echocardiographic strain imaging, as used by Yaman et al., is a powerful tool, but a full cardiac magnetic resonance (CMR) imaging evaluation could provide more sensitive detection of fibrosis, inflammation, and perfusion abnormalities (28–30). Inflammatory and fibrotic myocardial changes are known sequelae of chronic exposure to cardiotoxins, including tobacco (31,32), and could well apply to HTPs.

On the oxidative and inflammatory front, future studies should go beyond measuring CRP or 8-epi-PGF2α and incorporate a **panel of redox biomarkers**, including advanced oxidation protein products (AOPP), myeloperoxidase (MPO), isoprostanes, and nitric oxide metabolites (33–35). Furthermore, immune cell profiling (e.g., circulating Tregs, Th17), endothelial progenitor cell counts, and mitochondrial function assays could illuminate less visible yet critical effects.

Looking Beyond the Acute: The Call for Longitudinal Research

Researchers rightly emphasize that the true cardiovascular impact of HTPs will remain hidden unless **mid- and long-term follow-up studies** are conducted. All five included studies limit themselves to either acute exposure or short-term substitution protocols (maximum 90 days). Yet atherosclerosis, cardiac remodeling, and vascular degeneration are cumulative processes, whose clinical consequences unfold over months or years.

Therefore, it is imperative to initiate **prospective cohort studies** or even **pragmatic randomized trials** with robust cardiovascular endpoints: myocardial infarction, stroke, arrhythmias, sudden cardiac death, and hospitalizations for heart failure. Observational data linking HTP exposure with increased carotid plaque burden, microvascular dysfunction, or ventricular hypertrophy would be valuable additions to the current field (36–38).

HTPs and e-cigarettes should also be **directly compared** in similar protocols. Although they share some characteristics, the differences in aerosol composition, temperature, and delivery mechanism may have significant physiological implications. The lack of comparative data across devices is a critical knowledge gap.

Strengths and Potential Limitations

This review applied rigorous methodology in study selection, bias assessment (RoB 2 and ROBINS-I), and data synthesis. Several limitations, however, should be acknowledged. First, the heterogeneity in study designs, populations, and measured outcomes may limit the comparability of results, potentially affecting the robustness of the meta-analysis. Second, the exclusion of studies sponsored by the tobacco industry, while necessary to avoid bias, may result in the omission of some data, especially given the limited independent research on HTPs. For instance, Lüdicke et al. conducted one of the few long-term substitution trials but their study was funded by the tobacco industry, raising legitimate concerns about result manipulation (18). Finally, the reliance on available studies may introduce publication bias, particularly if negative or non-significant results are underreported in the literature.

Conclusions

This systematic review shows that heated tobacco products (HTPs) exert acute cardiovascular effects that are largely similar to those of conventional cigarettes. Consistent evidence of endothelial dysfunction and myocardial strain raises concern about their presumed safety. Given

the absence of mid- or long-term outcome data, the cardiovascular risk profile of HTPs remains unproven. These results highlight the need for independent longitudinal studies and caution against marketing these products as harmless alternatives to traditional smoking. The expected findings would support the need for strict regulatory oversight of HTPs, potentially aligning them with existing restrictions on conventional cigarettes. Clinicians and policymakers should remain cautious and rely on independent scientific evidence to guide tobacco control strategies.

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