SYSTEMATIC REVIEW

Effects of Heated Tobacco Products compared to Conventional Cigarettes on Cardiovascular System: Protocol for a Systematic Review

Effets cardio-vasculaires du tabac chauffé comparé aux cigarettes conventionnelles: protocole de recherche d'une revue systématique de la littérature

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Abstract

Introduction: Heated tobacco products (HTPs) are increasingly marketed as a potentially less harmful alternative to conventional cigarettes. However, their cardiovascular effects compared to traditional smoking remain controversial. This protocol outlines the methodology for a systematic review aiming to assess the cardiovascular impact of HTPs in comparison to conventional cigarette smoking.

Methods: This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines and is registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42024594334). We will search electronic databases, via PubMed, Embase, Cochrane Library, and others, from inception to March 2025. The search strategy will use medical subject heading (MeSH) terms such as "heated tobacco products" AND "cardiovascular health" AND "conventional cigarettes." Eligible studies will include randomized controlled trials and observational studies reporting on cardiovascular outcomes in adult HTP users compared to conventional smokers. Studies will be screened independently by two reviewers for inclusion, and data will be extracted using standardized forms. Quality assessment will utilize Cochrane Risk of Bias tools (MINORS and CONSORT), and evidence strength will be graded with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework. Data synthesis will include meta-analysis and meta-regression performed using SPSS version 2023.

Conclusions: This systematic review will provide a comprehensive synthesis of evidence on the cardiovascular effects of HTPs compared to conventional smoking. The findings aim to inform clinical guidelines, regulatory policies, and future research directions in tobacco harm reduction.

PROSPERO registration: [CRD42024594334]

Key words: adult, smoker, heated tobacco products, cigarettes, cardiovascular complications, heart failure, strokes, blood pressure

Résumé

Introduction: Les produits du tabac chauffé (HTP) sont de plus en plus commercialisés comme une alternative moins nocive aux cigarettes conventionnelles. Leurs effets cardiovasculaires restent controversés. Ce protocole décrit la méthodologie d'une revue systématique visant à évaluer l'impact cardiovasculaire des HTP par rapport au tabagisme conventionnel.

Méthodes: Ce protocole suit les directives PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) et est enregistré auprès du Registre prospectif international des revues systématiques (PROSPERO: CRD42024594334). Nous effectuerons des recherches dans des bases de données électroniques, notamment PubMed, Embase, Web of Science, Cochrane Library et autres, depuis leur création jusqu'en mars 2025. La stratégie de recherche utilisera des termes de rubrique médicale (MeSH) tels que « produits du tabac chauffé » ET « santé cardiovasculaire » ET « cigarettes conventionnelles ». Les études éligibles comprendront des essais contrôlés randomisés et des études observationnelles rapportant sur les résultats cardiovasculaires chez les utilisateurs adultes de HTP par rapport aux fumeurs conventionnels. Les études seront examinées.Les données seront extraites. L'évaluation de la qualité utilisera les outils Cochrane Risk of Bias (MINORS et CONSORT). La force des preuves sera évaluée avec le cadre de notation des recommandations,d'évaluation,de développement et d'évaluations (GRADE). La synthèse des données sera réalisée à l'aide de SPSS version 2023.

Conclusions: Cette revue systématique fournira une synthèse complète des preuves sur les effets cardiovasculaires des HTP par rapport au tabagisme conventionnel. Les résultats visent à éclairer les lignes directrices cliniques, les politiques réglementaires et les futures orientations de recherche.

Enregistrement PROSPERO: [CRD42024594334].

Mots clé: adulte, fumeur, tabac chauffé, cigarettes, complications cardiovasculaires, insuffisance cardiaque, accidents vasculaires cérébraux, pression artérielle

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Introduction

Heated tobacco products (HTPs) have emerged in recent years as a presumed less harmful alternative to conventional cigarettes (1). These products heat tobacco at a lower temperature than combustion, generating an aerosol containing nicotine and other chemical compounds without combustion. However, the cardiovascular impacts of these products remain insufficiently studied.

Tobacco heating technology is based on a unique electronic heating method to produce aerosols from tobacco stakes. Tobacco heating systems operate at lower temperatures (240–350 ◦C) than traditional cigarettes (>600 ◦C), which reduced use temperature, and allows the aerosol to be produced without burning tobacco (2,3).

Usage of HTPs went viral worldwide. The data shows that HTP is mainly used in combination with other products, mainly by the youngest generation and those who never smoke. The dual use of these products, their high use among younger generations and the interest of non-smokers are worrying, and point to the need for close monitoring of HTP for prevalence and user characteristics (4–6).

Studies conducted by the manufacturer's affiliates have claimed that IQOS produces fewer harmful constituents than combustible cigarettes (7,8). Though other studies have demonstrated that these products still contain and produce toxic constituents, some of which may be present in even greater amounts in IQOS and that users are not necessarily at lower levels of risk (2,9–11). A meeting of the FDA's Tobacco Products Scientific Advisory Committee was held on 24 and 25 January 2018, during which the concept of « Modified Risk Tobacco Products » (MRTP) was introduced and the application of those products was debated. The ensuing discussion by the committee focused on the principle that actual disposable data was not sufficient to support statements suggesting MRTP to be less harmful than traditional tobacco products.

One of the early studies addressing the cardiovascular impacts of HTPs, Glantz and Bareham, highlighted that while these products might reduce exposure to certain toxic substances, they still pose significant cardiovascular risks (12). The authors concluded that HTP use could lead to functional impairments similar to those observed in conventional smokers, urging caution in marketing them as a "safer" alternative.

Cardiovascular diseases (CVDs) are one of the leading causes of mortality among smokers. While some preliminary studies have suggested that HTPs may be associated with reduced risks compared to conventional cigarettes, there is limited robust data on their impact on parameters such as endothelial function, cardiovascular events, and inflammatory biomarkers (13).

Board objective

To compare the cardiovascular impacts of using heated tobacco products (HTPs) to the cardiovascular impacts of using conventional cigarettes in adults.

Specific objectives

1. To compare the risk of nonfatal stroke of using heated tobacco products (HTPs) to the risk of nonfatal stroke of using conventional cigarettes in adults.
2. To compare the risk nonfatal myocardial infarction of using heated tobacco products (HTPs) to the risk nonfatal myocardial infarction of using conventional cigarettes in adults.
3. To compare the risk of revascularization procedures in patients using heated tobacco products (HTPs) to the risk of revascularization procedures in patients using conventional cigarettes
4. To compare the risk cardiovascular death of using heated tobacco products (HTPs) to the risk cardiovascular death of using conventional cigarettes in adults.

Methods

Study Design and Registration

This systematic review will be conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (14). The study protocol has been registered in PROSPERO (CRD42024594334).

Information Sources and Search Strategy

Databases to be searched include PubMed, Web of Science, EMBASE, Scopus, Google Scholar, and the Cochrane Library. Additional manual searches will be conducted in the references of included studies.

Search terms will include the following keywords and terms :

"Adult", "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", "MACE", "myocardial infarction", "stroke", "heart attack", "coronary artery disease"The search strategy will be adapted to each database.

In Pubmed, the research equation used was:

("Cigarette Smoking" [Mesh] OR "Tobacco Smoking" [Mesh] OR "smoking" [tw] OR "Tobacco Use"[Mesh] OR "Tobacco Use"[tw] OR "Tobacco Products"[Mesh] OR "Tobacco Products"[tw] OR "Smokers"[Mesh] OR "Smokers"[tw] OR "cigar*" [tw]) AND ("heated tobacco products"[tw] OR "HTP"[tw] OR "IQOS"[tw] OR "heat-not-burn"[tw] OR "heated tobacco" [tw] OR "carbon-heated tobacco" [tw] OR "tobacco heating product" [tw] OR "tobacco vapor product" [tw] OR "ifuse" [tw] OR "fuse" [tw] OR "pulze" [tw] OR "teeps" [tw] OR "pax" [tw] OR "mok" [tw] OR "lil" [tw] OR "htp" [tw] OR "thp" [tw] OR "ths" [tw] OR

"chtp" [tw]) AND ("Cardiovascular Diseases"[Mesh] OR "Cardiovascular Diseas*"[tw] OR "Heart Diseases"[Mesh] OR "cardiovascular system" [tw] OR "Vascular Stiffness"[Mesh] OR "Vascular Stiffness"[tw] OR "arterial Stiffness"[tw] OR "blood pressure" [Mesh] OR "blood press*" [tw] OR "Oxidative Stress"[Mesh] OR "Oxidative Stress"[tw] OR "Cardiac Events" [tw] OR "flow-induced dilation" [tw] OR "adverse effects"[tw] OR "risk" [tw] OR "parameters" [tw] OR "pulse wave velocity" [tw] OR "systolic function" [tw] OR "diastolic function" [tw] OR "Strain" [tw]) AND ((fft[Filter]) AND (2015:2025[pdat]))

Inclusion and Exclusion Criteria

Population

Inclusion Criteria:

• Adults (>18 years) who use either heated tobacco products (HTPs) or conventional cigarettes.

Exclusion Criteria:

• Adult smokers who use else other forms of tobacco or nicotine delivery systems (e.g., vaping, nicotine patches).
• Adults smokers who use simultaneously heated tobacco products (HTPs) and conventional cigarettes

Studies

Inclusion Criteria:

• Randomized controlled trial (RCTs): Studies that randomly assign participants to either the intervention group (HTPs) or the comparator group (conventional cigarettes).
• Cohort Studies: Observational studies where participants are grouped based on their exposure to HTPs or conventional cigarettes and followed over time to assess cardiovascular outcomes.
• Case-Control Studies: Studies that compare individuals with cardiovascular events (cases) to those without (controls) based on their exposure to HTPs or conventional cigarettes.

Exclusion Criteria:

Studies sponsored by the tobacco industry

Study Selection and Data Extraction

Search results will be imported into a reference management software (EndNote) to remove duplicates. Two independent reviewers will select studies in three steps:
1. Screening titles and abstracts,
2. Reviewing abstracts then full texts of potentially eligible studies,
3. Final inclusion based on predefined criteria.

Extracted data will include:
- Study information (authors, year, location, study type),
- Participant characteristics (sample size, age, sex, comorbidities),
- Type of tobacco product used, duration of exposure,
- Main outcomes: cardiovascular events, biomarkers, and other measured effects.

Quality Assessment and Risk of Bias

The quality of observational studies will be assessed using the MINORS Scale. Randomized controlled trials will be assessed with the CONSORT scale. Two independent reviewers will evaluate each study, resolving disagreements through consensus or a third reviewer.
The tool used includes 14 items that are answered with “yes,” “no,” or “not applicable.” These will then be converted into a dichotomous rating (“yes”=1, “no” and “not applicable”=0). Every citation will receive a score by summing up all 14 items. Poor, fair, and good study quality will correspond to a score of 0-5, 6-9, and 10-14, respectively. The scores will be added to the data collection form prior to the analyses. The results of the risk of bias assessment will be presented in a table.

Data analysis

Qualitative Synthesis

A narrative description of the studies will be presented.

Quantitative Synthesis

Statistical analyses will include fixed-effects or random-effects models depending on the level of heterogeneity (evaluated with the I^2 test) and pooled results expressed as odds ratios (OR) or standardized mean differences (SMD).

Sensitivity Analyses

Studies with high risk of bias will be excluded.

Ethics and dissemination

This study does not involve primary data collection and thus poses no ethical concerns. Results will be submitted to a peer-reviewed journal. Attention will be given to disseminating results in a format accessible to policymakers and the public.

Discussion

Anticipation of Results

This systematic review and meta-analysis aim to evaluate the cardiovascular effects of heated tobacco products (HTPs) compared to conventional cigarettes. 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 cigarette. 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 (15). 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.

Potential Impact of Results

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 conventional cigarettes, 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. Additionally, the findings could highlight gaps in evidence, emphasizing the need for further high-quality randomized trials on this subject.

Implications of Expected Results

By synthesizing the current evidence, this study 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. The review could help clinicians counsel patients more effectively on the risks and benefits of HTP use and contribute to broader discussions on tobacco harm reduction strategies.

Potential Limitations

Several limitations of this systematic review 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. Finally, the reliance on available studies may introduce publication bias, particularly if negative or non-significant results are underreported in the litterature.

Conclusions

This systematic review will shed light on the cardiovascular impacts of heated tobacco products, guiding public health policies and clinical practices. It will address current knowledge gaps on this increasingly relevant topic.

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