Accepted author's manuscript. Published in final edited form as: Circulation 2021; 144(19): 1539-1542.
Publisher DOI: 10.1161/CIRCULATIONAHA.121.056959

CIRCULATIONAHA/2021/056959 Invited editorial for *Circulation*

Title: Heating tobacco sticks instead of combusting conventional cigarettes and future heart attacks: Still smoke, and risk

Authors: Reto Auer, MD, MAS[1,2]; Pascal Diethelm, PhD[3]; Aurélie Berthet, PhD [2]

[1] Institute of Primary Health Care (BIHAM), University of Bern, Switzerland

[2] Centre for Primary Care and Public Health (Unisanté), University of Lausanne, Switzerland

[3] OxySuisse, Geneva, Switzerland

Word count: 1497 (1500 words max), References: 14 (15 max), 1 Figure (1 max).

About five years ago, tobacco companies launched and heavily marketed a generation of products that heat tobacco and produce an "aerosol" users inhale. These battery powered devices account for a substantial share of the tobacco market in some countries. The tobacco companies argue that heated tobacco products (HTP) do not produce harmful "smoke" and laboratory analyses do indicate that HTP users inhale a lower concentration of toxic substances than smokers of conventional combustible tobacco cigarettes (CC).[1-4] But some toxic substances produced by HTP are unsafe in any quantity and we don't know if HTP will harm smokers who use them heavily and consistently for years.

The tobacco companies argue that HTP produce "aerosol" and not "smoke" because they have redefined "smoke" as the product of "complete combusion" but the toxicants in CC smoke are mainly produced by *incomplete* combustion (thermogenic degradation, pyrolysis). In *complete* combustion, tobacco and oxygen react to produce heat, carbon dioxide and water; the latter two are notoriously innocuous for health. In HTP, an electronic battery produces heat that directly or indirectly releases nicotine from tobacco: pyrolytic processes and thermogenic degradation occur in most HTP, especially those that heat tobacco to >250°C.[5]

In both CC and HTP, pyrolization, temperature, and the contents of tobacco products combine to produce harmful and potentially harmful constituents (HPHCs) like polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, and carbon monoxide (CO). Despite the tobacco companies' new definition of smoke, pyrolysis, rather than "combustion," is the source of many carcinogenic emissions and we can expect to see health hazards associated with exposure.[4, 5]

To make the “smoke without fire” phenomenon of pyrolysis clearer, it is helpful to think about bread toasters. If we set our toaster to between 200-250°C, the surface of the bread closest to the heating wires will first brown nicely and smell delicious but, if forgotten, will char (thermogenically degrade and pyrolyze) and fill the house with stinking smoke that no one would call “bread vapor.” Though our nose can easily distinguish between “toasted” and “burned,” even tasty toasted bread may be unhealthy. When smokers switch to HTP, they may enjoy the distinctive toasted flavor of tobacco which, like toasted bread, may not be as safe as it is delicious. We thus suggest labeling HTP “tobacco toasting systems” (TTS), to more clearly evoke the thermodynamic processes at play and remind consumers that toasting is a short step away from burning.

The TTS label will also help users distinguish nicotine vaping products (NVP or e-cigarettes) from toasting systems. NVP contain no solid tobacco; instead, they vaporize tobacco-free e-liquids containing propylene glycol, vegetal glycerin, aromas, and nicotine. The aerosol does not typically contain CO or other HPHC found in tobacco cigarettes but, like conventional cigarettes and HTP, NVP release metals, volatile organic compounds, and carbonyls including formaldehyde and acetaldehyde.[6] NVP may be associated with health hazards, but studies suggest they pose less risk for users than HTP.[7-10]

Both thermogenic degradation and pyrolysis are present in CCs and HTP and their emissions contain remarkably similar substances (Table 1).[1-3] Based on laboratory analyses, we expect the health effects of long-term HTP to resemble those of low-intensity CC smoking. If HTP use is comparable to light smoking (1-4 cigarettes per day), heavy and constant HTP use should substantially increase cardiovascular disease (CVD) risk,[11] but we need randomized controlled trials (RCT) to affirm these conclusions with certainty. HTP manufacturers ran a few smallscale RCT that compared CC smoking to HTP use or smoking cessation. Their results align with the laboratory analyses; HTP use is comparable to light smoking.[12, 13] These RCT were not powered to test the effects of HTP on CVD outcomes.

Without RCT data on CVD outcomes, we must rely on observational data to assess the effects of HTP. This data is likely to arrive first from South Korea, Japan and other countries where HTP use is most common. South Korea was the site of the first large-scale study to explore associations between tobacco heating systems, CVD events, and mortality, by Choi et al. In this study, featured in this issue of *Circulation*, Choi et al used the Korean National Health Insurance Services database to generate a cohort of over five million men whose health was screened and evaluated at two points in time (2014-2015 and 2018); their clinical outcomes were followed up

for 1-2 years. Choi et al used data from two health examinations to compute exposure to CC smoking, recent (<5 years) and long-term (>5 years) smoking cessation, with and without exposure to daily non-combustible nicotine or tobacco products (NNTPs). Their dataset was exceptionally complete for a range of relevant covariates and they used it to estimate confounders of the association between exposure to CC, HTP and CVD outcomes. The dataset did not distinguish between HTP and EVP users but the authors estimated, based on market share, that almost all participants had used HTP.

Choi et al first compared ongoing CC-only smokers with CC and NNTP users in probabilistic models. In models that adjusted for a range of confounders, they found that quitting CC with or without NNTPs was *associated* with less CVD than ongoing CC-only smoking, but risk reduction was similar across groups. Since association is not evidence of causation even in prospective cohort studies, they fitted alternate statistical models. They applied propensity score methods based on a range of covariates to match smokers who quit CC and used NNTP and smokers who quit CC and did not use NNTP. These propensity score analyses are Choi et al's key findings. They show that men who quit CC and used NNTP had a higher rate of CVD than those who quit CC and did not use NNTP. Propensity score analyses attempt to estimate observed CVD risk if smokers quit with or without NNTP. A causal interpretation of these results is that CVD risk is higher if smokers quit CC with NNTP than if they quit CC without NNTP.

Choi et al's analyses do provide means to loosely estimate absolute risk reduction from quitting CC with or without HTP. Based on reported CVD incidence in the propensity score analyses, in a hypothetical cohort of 10,000 CC smokers who quit >5 years ago and were followed over 1-2 years, 24 participants who did not use NNTP would develop CVD. This number would nearly double (42) among quitters who used NNTP daily. Since Choi et al did not compute propensity scores to compare ongoing CC users to CC quitters, we cannot confidently compare risk reduction from quitting CC with or without NNTP to risk of ongoing CC smoking. If we conservatively estimate that 62/10,000 older ongoing CC smokers in the cohort would develop CVD, switching from CC to NNTP would cut CVD risk by 20 (62-42/10,000) and quitting CC without NNTP by 38 (62-24/10,000). This suggests an relative risk reduction of switching from CC to NNTP compared to ongoing CC of 32%, and 61% when quitting CC without NNTP.

Our ability to draw causal inferences from these analyses is inherently limited. First, concluding NNTP use alone increased CVD among CC quitters would require we assume that the set of covariates in the propensity score matching model make it possible to confidently predict NNTP exposure in CC quitters. But even a wide range of covariates cannot reveal *why* CC smokers

could successfully quit CC with or without NNTP. We thus need data from a large-scale RCT to better test the *effects* of smoking cessation with or without HTP on CVD. Though Choi et al's attempt to estimate the effect of CC cessation with HTP on CVD is limited, it is still the best effort to date. Second, we need more than 1-2 years of follow-up to accurately determine the differential effect of exposure on CVD outcomes. Third, Choi et al's analyses were limited to men.

Choi et al's findings have policy implications: lower HPHC exposure (as measured in laboratory analyses) does not seem to proportionately reduce HTP health risks. Switching from CC to HTP may achieve some risk reduction with respect to CVD, but that risk remains nevertheless at a high level. A level regulators may find unacceptable compared to established or other potential risk reduction strategies. Regulators should also prevent tobacco companies from engaging in deceptive advertising. For example, consumers remember and feel safer using HTP when ads esuggest IQOS is "90% healthier"[14] More accurate labeling could help consumers better understand the health risks associated with THS "tobacco toasting systems" (TTS).

Health authorities should make clear to HTP producers that claims about harm reduction should not conflate reduced exposure with reduced risk of serious health effects like CVD. These same authorities should demand data from rigorously conducted RCTs that test the effects of HTP on meaningful clinical outcomes like CVD. Until evidence from a large-scale pivotal RCT provides evidence to the contrary, we expect HTP use contribute to CVD and other smoking-related illnesses and recommend it be considered the equivalent of low-grade smoking.[11]

Sources of funding:

RA and AB received research support from the Swiss National Scientific Foundation (grant number *IICT 33IC30_173552), Swiss Cancer Research (grant number *KFS4744-02-2019) and the Swiss Tobacco Prevention Funds (grant number *TPF19.017477).

AB received funding from the Canton of Vaud and Federal Office of Public Health, Switzerland.

Disclosures:

RA, PD and AB report no conflicts

Acknowledgments:

We thank Kali Tal, PhD for her editorial assistance and Julian Jakob, MD for his critical review of the manuscript.

References:

1. Jankowski M, Brożek GM, Lawson J, Skoczyński S, Majek P and Zejda JE. New ideas, old problems? Heated tobacco products – a systematic review. *International Journal of Occupational Medicine and Environmental Health*. 2019;32:595-634.
2. Kopa PN and Pawliczak R. IQOS – a heat-not-burn (HnB) tobacco product – chemical composition and possible impact on oxidative stress and inflammatory response. A systematic review. *Toxicology Mechanisms and Methods*. 2020;30:81-87.
3. Mallock N, Pieper E, Hutzler C, Henkler-Stephani F and Luch A. Heated Tobacco Products: A Review of Current Knowledge and Initial Assessments. *Frontiers in Public Health*. 2019;7.
4. Auer R, Concha-Lozano N, Jacot-Sadowski I, Cornuz J and Berthet A. Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name. *JAMA Intern Med*. 2017;177:1050-1052.
5. Davis B, Williams M and Talbot P. iQOS: evidence of pyrolysis and release of a toxicant from plastic. *Tob Control*. 2018.
6. Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K and Leischow SJ. Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette. *Addiction*. 2018;113:2099-2106.
7. Shahab L, Goniewicz ML, Blount BC and et al. Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: A cross-sectional study. *Annals of Internal Medicine*. 2017;166:390-400.
8. Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR and Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev*. 2020;10:Cd010216.
9. Dusautoir R, Zarcone G, Verriele M, Garçon G, Fronval I, Beauval N, Allorge D, Riffault V, Locoge N, Lo-Guidice JM and Anthérieu S. Comparison of the chemical composition of aerosols from heated tobacco products, electronic cigarettes and tobacco cigarettes and their toxic impacts on the human bronchial epithelial BEAS-2B cells. *J Hazard Mater*. 2021;401:123417.
10. Critcher CR and Siegel M. Re-examining the Association Between E-Cigarette Use and Myocardial Infarction: A Cautionary Tale. *American Journal of Preventive Medicine*. 2021.
11. Hackshaw A, Morris JK, Boniface S, Tang JL and Milenković D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. *Bmj*. 2018;360:j5855.
12. Ludicke F, Picavet P, Baker G, Haziza C, Poux V, Lama N and Weitkunat R. Effects of Switching to the Tobacco Heating System 2.2 Menthol, Smoking Abstinence, or Continued Cigarette Smoking on Biomarkers of Exposure: A Randomized, Controlled, Open-Label, Multicenter Study in Sequential Confinement and Ambulatory Settings (Part 1). *Nicotine Tob Res*. 2017.
13. Haziza C, de La Bourdonnaye G, Donelli A, Poux V, Skiada D, Weitkunat R, Baker G, Picavet P and Lüdicke F. Reduction in Exposure to Selected Harmful and Potentially Harmful Constituents Approaching Those Observed Upon Smoking Abstinence in Smokers Switching to the Menthol Tobacco Heating System 2.2 for 3 Months (Part 1). *Nicotine Tob Res*. 2020;22:539-548.

14. East KA, Tompkins CNE, McNeill A and Hitchman SC. 'I perceive it to be less harmful, I have no idea if it is or not:' a qualitative exploration of the harm perceptions of IQOS among adult users. *Harm reduction journal*. 2021;18:42.

Table 1: Product content, heating temperature and composition aerosol between nicotine inhaling devices.

	Nicotine inhaler	**Vaporizer (EVP)**	**Heated tobacco product (HTP)**	**Conventional tobacco cigarette (CC)**
Product contents				
- Nicotine	+	+	+	+
- Tobacco leaves	-	-	+	+
- Propylene glycol (PG), glycerol	-	+	+	?
- Aromas	-	+	+	+
- Other additives	-	-	+	+
Temperature	18-25°C	100-240°C	~160°-330°C	640-780°C
Composition aerosol				
- Nicotine	**+**	**+**	**+**	**+**
- Carbon dioxyde (CO_2)	-	-	+	+
- Water (H_2O)	+	+	+	+
- Carbon monoxyde (CO)	-	-	+	+
- Policyclic aromatic hydrocarbons (PAH)	-	-	+	+
- Tobacco-specific nitrosamines (TNSAs)	-	-	+	+
- Organic volatile compounds, carbonyls (VOCs)	**+**	**+**	**+**	**+**

- : non applicable; +: Presence;?: no information available in literature.