Minerva Cardioangiologica
EDIZIONI MINERVA MEDICA



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*Minerva Cardioangiologica* 2020 Jun 02
DOI: 10.23736/S0026-4725.20.05181-6

Article type: Original Article



Article first published online: June 2, 2020
Manuscript accepted: April 10, 2020
Manuscript revised: April 8, 2020
Manuscript received: January 25, 2020

# A randomized trial comparing the acute coronary, systemic, and environmental effects of electronic vaping cigarettes versus heat-not-burn cigarettes in smokers of combustible cigarettes undergoing invasive coronary assessment: Rationale and design of the SUR-VAPES 3 trial

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**Running title**: The SUR-VAPES 3 trial

**Word count**: 4531

**Funding**: This study is supported by Sapienza University of Rome (protocol ID: RG11916B8621D7FF)

**Conflicts of interest**: None

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**ABSTRACT**

**Background**: Traditional combustible cigarette (TCC) smoking remains a major cause of preventable cardiovascular morbidity and mortality. Modified risk products (MRP) such as electronic vaping cigarettes (EVC) and heat-not-burn cigarettes (HNBC) may be safer than TCC but may still have detrimental oxidative, platelet and vascular effects of particular importance to people with symptomatic coronary artery disease (CAD).

**Methods:** We aim to compare the acute coronary, systemic and environmental effects of two leading MRP in 20 TCC smokers admitted for invasive coronary assessment of CAD and willing to quit or after prior failed quitting attempts. After confirmation at angiography of an intermediate coronary stenosis, coronary flow reserve (CFR) will be appraised. Patients will then be randomized 1:1 to use a single EVC or a single HNBC in the catheterization laboratory, followed by repeat CFR measurement. The primary endpoint will be the change in CFR before and after product use. Quantitative coronary angiography, fractional flow reserve (FFR), and instantaneous wave-free ratio (iFR) will also be measured.

**Expected results**: We expect to accrue results able to: 1) test whether MRP have in general a detrimental impact on coronary vascular function in TCC smokers; 2) test whether EVC have a different impact than HNBC on coronary function; 3) provide ancillary pathophysiologic and translational insights on the acute risk and safety profile of MRP in TCC smokers with established cardiovascular disease, including complex correlations between coronary, cardiac, systemic and environmental effects. In addition, by directly informing participants of their individual results, they will be further empowered to quit TCC.

**Conclusion**: The Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR-VAPES) 3 trial will provide important insights into the pathophysiologic

cardiovascular impact of EVC and HNBC, also suitable to inform patients and individualize their smoking cessation strategy.

**KEY-WORDS**

Coronary artery disease; Electronic vaping cigarette; Heat-not-burn; IQOS; JUUL; Smoking

**INTRODUCTION**

Traditional combustible cigarette (TCC) smoking remains one of the leading causes of preventable morbidity and mortality from cardiovascular, respiratory and other diseases, including, for instance, ST-elevation myocardial infarction and post-infarction heart failure, with cessation and abstinence representing the best solution for smokers.(1-3) Despite the availability in many countries of evidence-based pharmaceutical-based treatment options (e.g. bupropion, varenicline or nicotine replacement therapy), and a variety of forms of effective behavioural support, many smokers have difficulties quitting.(4)

Modified risk products (MRP), such as electronic vaping cigarettes (EVC) and heat-not-burn cigarettes (HNBC), represent a useful adjunct to foster cessation and abstinence by delivering nicotine in a more palatable fashion and in higher doses than nicotine replacement therapy, while avoiding the toxic effects of tobacco combustion.(5-6) Typically, EVC are based on an electric heating device delivering aerosols from liquids usually entailing a mixture of glycerol and propylene glycol, flavors, and optionally, but most commonly, variable concentrations of nicotine.(7) Unlike TCC, no combustion occurs in EVC, which are thus considered a less harmful alternative to TCC.(8)

Over the years, several randomized trials have showed that EVC are moderately effective for smoking cessation in TCC smokers.(7,9-10) However, despite such results, the degree of risk of harm associated with EVC is still questioned, and definitive information regarding both acute as well as long term efficacy and safety, including a clear assessment on the amount of ultrafine particles, known to trigger cardiovascular and respiratory inflammatory processes, are unavailable.(5-6) This holds even truer given recent reports of electronic cigarette vaping associated lung injury (EVALI), typically caused by tampering of liquids for EVC.(11)

The MRP market expanded substantially in 2014 when new HNBC were introduced by tobacco companies. These devices heat a disposable tobacco stick with a thin metallic blade, such that tobacco leaves are maintained at a temperature of ~350°C, much lower than the temperature achieved in TCC (~800°C), thus avoiding combustion, fire, ash, smoke, and pyrolysis.(12) Despite these claims from manufacturers, limited independent research on HNBC has been conducted to date, and no prospective studies have focused on either EVC or HNBC in TCC smokers with established cardiovascular disease.(4-5) This appears of key relevance given the differential effects that TCC, EVC and HNBC may have on individuals in keeping with their specific baseline features and clinical history.(13)

Research independent of the tobacco industry suggests that both EVC and HNBC may exert detrimental effects on oxidative stress, platelet aggregation, and vascular function (**Figure 1**).(5-6,12-16) In particular, our group has pioneered the comprehensive assessment of oxidative, platelet and vascular function of EVC in apparently healthy subjects, showing already in 2016 that EVC have a less detrimental impact on oxidative stress, redox reserve, platelet aggregation, and flow-mediated dilation, in comparison to TCC (**Figure 2**).(15) More recently, we have expanded these findings in the randomized Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR-VAPES) 2 trial, which aimed at validating prior findings from our own group and others, while comparing EVC versus HNBC.(16) In this trial, we showed that EVC and HNBC have both detrimental effects on oxidative stress, redox reserve, platelet aggregation, and endothelial function, as well as blood pressure and heart rate, with some key differences between these products. Namely, HNBC appeared less impactful than EVC on oxidative stress and blood pressure. Similar findings have been reported by other researchers in several studies focusing on apparently healthy individuals, confirming that, while being substantially less harmful than TCC, both EVC and HNBC may adversely impact on cardiac, vascular, and pulmonary

function, with evident pro-inflammatory and oxidative mechanism likely underlying these effects.(17-18)Yet, to date, no prospective study has focused on coronary effects of either EVC or HNBC, nor used invasive measurements of vascular function (universally considered as the gold standard to appraise coronary function), or included smokers with established coronary artery disease (CAD) or other types of cardiovascular disease, willing to quit smoking.(5)

## METHODS

### Design

The SUR-VAPES 3 study will be a randomized trial focusing on the acute coronary, systemic, and environmental effects of EVC versus HNBC in chronic smokers of TCC with who, because of symptomatic cardiovascular disease or objective evidence of myocardial ischemia, have been admitted to hospital for invasive coronary assessment. The protocol will be submitted for ethical approval, and will be registered online in clinicaltrials.gov.

### Aims and hypotheses

The study will have four aims:

1) To appraise invasively the acute effects of two MRP on coronary function (measured invasively with coronary flow reserve [CFR] and other means as well) and anatomy, oxidative stress, redox reserve, platelet function, inflammation, heart rate (HR), blood pressure (BP), pulse wave velocity (PWV), and environmental pollution when used in the catheterization laboratory by patients with angiographic evidence of atherosclerotic CAD, with CFR being the primary endpoint of the study. We hypothesize that MRP such as EVC and HNBC will have collectively detrimental coronary, systemic and environmental effects.(16)

2) To compare the acute effects of EVC versus HNBC on coronary function and anatomy, oxidative stress, redox reserve, platelet function, inflammation, HR, BP, PWV and environmental pollution, maintaining CFR as the primary endpoint, hypothesizing that EC and HNBC exert different coronary, systemic, and environmental effects,(16)

3) To appraise for hypothesis-generating purposes the association, correlation and clustering between coronary function and anatomy, oxidative stress, redox reserve, platelet function, inflammation, HR, BP, PWV and environmental pollution.

4) To directly inform participants of the study results, in order to further empower them in their effort to quit smoking and choose the most effective and safe MRP.

**Subjects**

We will recruit 20 adult patients who define themselves as current smokers of TCC (at least 10 TCC per day for at least the past 10 years), explicitly willing to quit smoking TCC or having failed previous attempts at quitting smoking, admitted for the work-up of CAD and undergoing invasive coronary angiography (**Figure 3**). Emergent cases (i.e. resuscitated cardiac arrest, shock, ST-elevation myocardial infarction, or symptomatic arrhythmias), patients with insulin-dependent diabetes or chronic renal failure (estimated glomerular filtration rate <60 mL/min/1.73 $m^2$), and those with unprotected left main disease or proximal left anterior descending disease will be excluded. After intracoronary administration of 300-600 μg nitrates, and demonstration at coronary angiography of a coronary stenosis of intermediate severity (40-69% diameter stenosis by visual estimation) suitable for functional assessment, patients will be offered inclusion in the study.(19)

**Procedures**

After providing written informed consent, the femoral vein will be percutaneously accessed with an 8 French catheter, a 6 French Multipurpose diagnostic catheter will be placed in the coronary

sinus, and the 6 French coronary diagnostic catheter will be exchanged for an appropriate coronary guiding catheter (**Figure 4**). In case of challenging anatomy, 5 minutes after attempting to selectively engage the coronary sinus, the catheter will be placed in the right atrium close to the sinus ostium to avoid further delay. Blood samples will be obtained from the ascending aorta, the coronary sinus (or right atrium), and the femoral vein.(20) All patients will undergo invasive measurement of CFR under maximal hyperemia, as well as fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR), all validated indices of the functional severity of an angiographically ambiguous coronary lesion and suitable for measurement with the same diagnostic microcatheter (ComboWire, Philips, Amsterdam, The Netherlands) delivered through an atraumatic 0.014" floppy guidewire (BMW, Abbott Vascular, Santa Clara, CA, USA).(21-22)

Subsequently, patients will be randomized 1:1 to vape a leading EVC (Juul, Golden tobacco flavor, 9 mg/ml nicotine concentration, Juul Labs, San Francisco, CA, USA) or a leading HNBC (IQOS, Amber label, Altria, Henrico County, VA, USA), each for a total of 9 puffs in 5-10 minutes, in keeping with the regimens used in the SUR-VAPES 1 and 2 trials.(15-16,23) Afterwards, coronary angiography will be repeated, as CFR, FFR and iFR measurents. Finally, blood will be drawn again from the ascending aorta, the coronary sinus, and the femoral vein within 1 minute after CFR, FFR and iFR measurement. HR, BP and ECG will be recorded repeatedly (at 1 minute interval) throughout, and PWV will be measured before and after smoking using the unnaccessed upper limb. Anticoagulation will be achieved with repeated intravenous boluses of unfractionated heparin, aiming at maintaining activated clotted time between 250 and 350 seconds.

Considering the results of CFR, FFR, and iFR, percutaneous coronary intervention (PCI) will then be performed at the attending physician's discretion and in keeping with established practice guidelines. In case of PCI, all invasive measurements as well as blood draws and PWV appraisal will be repeated after achieving a satisfactory final angiographic and clinical result, thus providing a

third set of measurements. In case of multiple ambiguous lesions, invasive functional measurements for this study purposes will be performed on a single lesion only, leaving though room at the physician's discretion to use the ComboWire for other lesions as well. In case of the concomitant presence of an ambiguous lesion and an angiographically significant lesion, the choice to perform PCI beforehand, and then proceed with the study protocol for the ambiguous lesion, will be at physician's discretion.

During the procedures, patients will be video-recorded to explicitly appraise and quantify puffing patterns, including duration and depth of puffs, as well as inhalation and exhalation patterns (e.g. nasal vs oral). In addition, environmental pollution in the catheterization laboratory will be measured with a portable, laser-operated aerosol mass analyzer (DustTrak II Environmental Monitor, model 8530, TSI, 0.1-10 µm particle size, TSI, Shoreview, MN, USA), 50 cm distant from the participant.(24) Measurements will be performed continuously beginning 1 minute before smoking and ending 31 minutes later. All participants will be directly informed of their individual results, as soon as they are available, and at study end with a detailed written report to further empower them to quit TCC. Patients will be followed up to 30 days after enrolment, to collect details on adverse effects (including death, myocardial infarction, repeat revascularization, stroke, bleeding, or vascular complication) and smoking and other produce use behaviors.

**Measurements**

On top of ECG, HR, and BP, PWV will be evaluated with the validated iHeart device. Quantitative coronary angiography will be performed according to established methods to compute minimum lumen diameter, reference vessel diameter, and lesion length, and will be compounded by measurement of Thrombolysis in Myocardial Infarction Frame Count (TFC).(19) CFR, FFR and iFR

will be measured achieving maximal hyperemia with intracoronary adenosine (60 µg).(21-22) Oxidative burden and redox reserve will be appraised measuring levels of soluble Nox2-derived peptide, nitric oxide bioavailability, isoprostanes, H2O2, serum H2O2 breakdown activity, and vitamin E.(15-16) Platelet function will be appraised measuring levels of CD40L and P-selectin, and measuring platelet aggregation.(14,16) Inflammation will be appraised measuring interleukin-1, neutrophil myeloperoxidase content, and NFkB activation in CD45+ cells.(20) High-sensitivity troponin will be measured as well. Finally, plasma cotinine will be measured with a commercial assay. Notably, all blood-, serum- or plasma-derived samples will be measured after obtaining them from the three access sites: the ascending aorta, the coronary sinus, and the femoral vein. Video recordings will be analyzed after the procedures and puff duration, intensity, and pattern will be appraised, together with inhalation and exhalation style. Environmental pollution will be measured focusing on different types of particulate matter (PM), ie PM10, PM5, PM2.5 and PM1, measured close (0.5 meter) to the participant, according to established methods.(25)

**Primary endpoint**

The primary endpoint will be the change in CFR before versus after EVC vs HNBC use.

**Analysis**

The randomization list will be computer-generated, using 5 blocks of 4 units. Allocation concealment will be ensured by using sealed opaque envelopes. Continuous variables will be described as mean and standard deviation, and categorical variables as count (%).The main inferential analysis will be based on a multilevel mixed effects linear model, with an identity

covariance matrix, forcing in the model as needed each end point value, timing of sampling, product type, and their interaction as fixed effects, with participant and order as random effects, similar to the model already used for the prior SUR-VAPES trials.(15-16) Other analyses will include linear regression, logistic regression, and ordinal regression, for hypothesis-generating purposes. Moreover, unsupervised learning with hierarchical and k-means clustering will also be performed as previously shown.(22) Assuming a baseline CFR of 2.70, a CFR after product use of 1.50, and a standard deviation of 0.77,(4), 16 patients (8 per group) would be adequate to achieve 2-tailed 0.05 alpha and 0.2 beta (Stata script: 'power twomeans 2.7 1.5, sd(0.77)'), which will be increased to 20 subjects (10 per group) to accommodate for potential protocol deviations. Statistical significance will be at the 2-tailed 0.05 level. Computations will be performed with Stata 13.

**RESULTS**

This trial will be the first to compare the coronary, systemic and environmental effects of EVC versus HNBC when used by patients who have a history of being chronic tobacco smokers undergoing invasive coronary assessment for established CAD. Accordingly, they will complement and either confirm or disprove prior evidence from non-invasive assessment of apparently healthy smokers or volunteers, focusing on invasive assessment and smoking subjects with actual cardiovascular disease. Most importantly, findings of the present study will be crucial to inform on future long-term comparative trials of EVC versus HNBC in smoking patients, in order to pinpoint exactly which subjects and which products represent the best combination to maximize chances of cessation and abstinence, while minimizing untoward coronary, systemic, and environmental effects. Finally, by directly informing participants of their individual results, the study will further empower them to quit TCC, thus ensuring a scientifically and ethically sound research endeavor.

**DISCUSSION**

Our proposed randomized trial has many innovative features. First, being a randomized trial, this controlled prospective study will provide the most internally valid scientific testing of our chosen hypothesis. In a scientific arena dominated mostly by observational and retrospective studies, thus at high risk of selection, performance, adjudication and attrition bias, our project promises to provide objective and independent comparative evidence.(24) In particular, despite the small sample, the size of the study will be adequate to test adequately differences in the primary endpoint when comparing invasive effects of MRP.

Second, our focus on CFR and ancillary measures of the functional severity of a coronary stenosis such as fractional flow reserve and instantaneous wave-free ration, on top of quantitative coronary angiography and TFC is completely unprecedented in users of MRP, and while we may guess that prior findings on the vascular effects of MRP of tobacco exploiting non-invasive measurements will be confirmed in our study, this remains to be proven, but of key scientific and clinical relevance.(19,22) Third, our aim at comparing the two leading prototypical MRP, i.e. Juul, as EVC, and IQOS, as HNBC, is unprecedented, as no other study to date has ever compared in prospective fashion these novel yet widely used devices. This is most important as Juul represents the US leader in EVC, but has been questioned in terms of its effects on public health given its very high nicotine content and market appeal to teenagers, while IQOS is the global leader in HNBC, and its usage has been recently approved in the United States as well (while both are already available for routine use in Italy and Europe at large).(26)

In addition, our focus on chronic smokers of TCC, who actually have established coronary atherosclerosis as demonstrated by invasive coronary angiography, represents a novel approach for a prospective, randomized trial, and our findings have potential to shape and guide future

research on MRP in chronic smokers in the secondary prevention setting of cardiovascular disease.(27-28) Restriction of inclusion to current smokers only will reinforce the need to consider MRP such as EC or HNBC mainly as an alternative to TCC, thus discounting any promoting effort for their use among non-smokers. Furthermore, our integrative approach involving a plethora of secondary and ancillary endpoints will provide a veritable mine of pathophysiologic insights on the coronary, cardiac, vascular, systemic and environmental effects of acute use of MRP. In particular, we will be able to test whether EVC and HNBC have any effect, and if so, any differential one, on several dimensions of cardiovascular and systemic physiology. In addition, by analyzing their correlation and association, we will be able to explore potential clustering features among such effects (e.g. the correlation between pro-inflammatory and oxidative effects).(22) The appraisal of environmental contamination simultaneously with coronary and systemic responses will permit a unique yet precise analysis of the association between product use patterns, biologic responses and environmental pollution. Finally, direct patient information will prove useful to guide individual decision making of patients wishing to switch from TCC to a given MRP.

Moreover, the choice of multisite blood draws, able to generate veritable gradients of measurements from arteries to coronary sinus and femoral vein, in particular represents an almost unheard approach, which, combined with the selective inclusion of patients with right coronary dominance and left coronary lesions ,will inform on intracoronary and intracardiac gradients in oxidative stress, redox reserve, inflammation, and myocardial injury.(20) This approach, while technically demanding, can be safely implemented, and will provide for the first time ever in the literature a glimpse at the coronary-specific and cardiac-specific effects of using MRP such as EVC and HNBC. Finally, this study will be independent from any tobacco company sponsorship, or other biases, and thus key to further motivate public academic institutions such as

Sapienza University of Rome to fund other independent high-quality research projects such as the one hereby proposed.(27-30)

In conclusion, the SUR-VAPES 3 trial will provide important independent insights into the comparative pathophysiologic cardiovascular impact of EVC and HNBC, and has potential to inform patients and individualize their smoking cessation strategy.

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**Figure 1.** Graphical summary of the acute effects of electronic vaping cigarettes (EVC) and heat-not-burn cigarettes (HNBC) . H2O2=hydrogen peroxide; sNOX2-dp=soluble NOX2-derived peptide.

**Figure 2.** Multidimensional cardiovascular toxicity of electronic vaping cigarettes (EVC) FMD=flow mediated dilation; NO=nitric oxide; ROS=reactive oxygen species.

**Figure 3.** Design of the Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR-VAPES) 3 trial. BP=blood pressure; CAD=coronary artery disease; CFR=coronary flow reserve; FFR=fractional flow reserve; HR=heart rate; iFR=istantaneous wave-free ratio; ox-redox=oxidation reduction; PWV=pulse wave velocity; QCA=quantitative coronary angiography; TFC=Thrombolysis In Myocardial Infarction Frame Count;

**Figure 4.** Technical details of the Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR-VAPES) 3 trial. H2O2=hydrogen peroxide; sNOX2-dp=soluble NOX2-derived peptide.