Medicines Adverse Reactions Committee

Meeting date	9/03/2023	Agenda item	3.2.3
Title	**Risk of thromboembolism from vaping- caution with combined oral contraceptives**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Ethinylestradiol and Levonorgestrel	Femme-Tab	AFT Pharmaceuticals
	Microgynon 20/30/50	Bayer New Zealand
	Lo-Oralcon, Oralcon	Viatris Limited
	Levlen	Bayer New Zealand
	Loette	Pfizer New Zealand
	Lynley 150/30ED	Max Health Limited
	Monofeme	Pfizer New Zealand
Ethinylestradiol and Norethisterone	Norimin	Pfizer New Zealand
	Brevinor, Brevinor-1	Pfizer New Zealand
Ethinylestradiol and Desogestrel	Mercilon	Organon Limited
Ethinylestradiol and Drospirenone	Yaz	Bayer New Zealand
	Yasmin	Bayer New Zealand
Ethinylestradiol and Cyproterone acetate	Ginet	REX Medical
	Diane-35	Bayer New Zealand

PHARMAC funding	Microgynon 20 ED, Femme-Tab ED, Brevinor, Norimin, Ginet, and Mercilon are funded
Previous MARC meetings	MARC reports can be found here: https://www.medsafe.govt.nz/committees/MARC/Reports.asp Direct acting oral anticoagulants and risk of recurrent thrombotic events (5 December 2019) Oral contraceptives containing drospirenone or dienogest and risk of VTE (10 September 2015) Drospirenone/ethinylestradiol: risk of venous thromboembolism compared to other combined oral contraceptives (10 September 2009 and 23 September 2010) Desogestrel and venous thromboembolism (20 June 2002) Safety issues with hormonal replacement therapy/oral contraceptives (27 March 2002) Diane-35/Estelle-35 and venous thromboembolism (11 December 2001) HRT and cardiovascular and cerebrovascular disease (11 December 2001) Progestogen-only oral contraceptives and VTE (5 September 2001)

	The safety of oral contraceptives (14 June 2001)
Prescriber Update	• Reminder: Counsel patients about symptoms and signs of venous thromboembolism when prescribing combined oral contraceptives (March 2022) • Using New Zealand data to review the risk of venous thromboembolism with combined oral contraceptives (June 2018) • Hormonal contraceptives and blood clots (August 2014) • Combined oral contraceptives and VTE- putting the risk into perspective (March 2011) • Letter to healthcare professionals about VTE with cyproterone-containing OCs (March 2002) • Oral contraceptives and venous thromboembolism (February 1999) • The risk of venous thromboembolism with third generation oral contraceptives (July 1998)
Classification	Prescription medicine
Advice sought	**The Committee is asked to advise:** • Whether the evidence suggests there is a risk of thromboembolism in people who use electronic cigarettes • Whether there is an increased risk of VTE in women who vape and take a combined oral contraceptive • Whether this topic needs further communication other than MARC's remarks

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1 PURPOSE

In December 2023, Medsafe was alerted to a [redacted]

Venous and arterial thromboembolism are known adverse events linked to combined hormonal oral contraceptives, of which smoking is considered to be a factor that further increases this risk. It is unknown whether vaping/use of electronic cigarettes also carries a risk of thromboembolism either alone or in combination with oral contraceptive use. Given the widespread use of combined oral contraceptives and the number of individuals who vape, the potential risk of harm should be investigated.

The purpose of this paper is to review the current information relating to vaping and risk of thromboembolism, particularly in women that take combined oral contraceptives.

2 BACKGROUND

2.1 Venous thromboembolism: a brief overview of pathophysiology and risk factors

Venous thromboembolism (VTE) results from a clot formation in the venous circulation. VTE is a disease process that can present as deep vein thrombosis (DVT) and/or pulmonary embolism (PE). VTE can be fatal. VTE is not a static disease and is often perceived as a dynamic condition with rapidly changing features based on clinical, radiological, functional, and laboratory findings. In the United States it is estimated that 200,000 new cases of VTE occur annually, including 94,000 with PE. Based on these numbers the incident rate of VTE is estimated to be 23 per 100,000 patients per year-cases [1]. VTE among healthy women of reproductive age is rare, and has an incidence of 5-10 events per 10,000 women-years [2].

2.1.1 Haemostasis and thrombosis pathophysiology

Haemostasis is the process that maintains the integrity of the circulatory system after vascular damage. Vessel-wall injury and the extravasation of blood from the circulation rapidly initiates events in the vessel wall and in the blood to seal the breach. Circulating platelets are recruited to the site of injury where they become a major component of the development of a thrombus. Several activators and inhibitors are involved in maintaining haemostasis as pictured in Figure 1 [3].

Under normal conditions regulatory mechanisms contain thrombus formation. When pathologic processes overwhelm the regulatory mechanisms of haemostasis, excessive quantities of thrombin form, initiating thrombosis [4].

Figure 1. Haemostasis and thrombosis pathway. Source: Pharmacotherapy Handbook 11e (accessed 6 February 2023)

Development of VTE appears to be the result of multiple simultaneously operating factors. A major theory in the pathogenesis of VTE is referred to as Virchow trial which proposes that VTE occurs as a result of [1]:

- Alterations in blood flow
- Vascular endothelial injury
- Alterations in the constituents of the blood

2.1.2 Risk factors for venous thromboembolism

The risk factors of VTE can be divided into two groups: hereditary and acquired, and often multiple are present in a given patient. Risk factors for VTE are listed in Table 1.

Table 1: Hereditary and acquired risk factors for the development of VTE [1, 5].

[redacted]

The incidence of VTE was described in a population-based observational study conducted in Massachusetts, United States. During the data collection period, there were 587 people who experienced an episode of VTE that was diagnosed by a healthcare professional. 329 of the 587 people had three or more of the following risk factors at diagnosis: >48 hours of immobility in the preceding month, hospital admission, surgery, malignancy, or infection within the past three months, or current hospitalisation [6].

Comments:
Hereditary risk factors can be identified through thrombophilia screening. This test is available in New Zealand for those that meet select criteria. Testing is currently not indicated in asymptomatic patients considering use of oestrogen-based contraception or hormone replacement therapy. This is consistent with current international guidelines.

2.2 Use of combined hormonal oral contraceptives and venous thromboembolism

Current use of a combined hormonal oral contraceptive (COC) is associated with an increased risk of VTE compared to no use and some formulations are associated with a greater risk of VTE than others. This increased risk is dependent on the type and dose of progestin. Levonorgestrel or norethisterone are associated with a lower risk of VTE compared with desogestrel, drospirenone or cyproterone acetate. COCs with higher doses of oestrogen (eg ethinylestradiol 50mcg) are also associated with an increased risk for VTE [7].

The exact mechanism for oestrogen-induced thrombosis remains unclear. Human and animal studies have identified pathways/factors altered with oestrogen treatment that are likely to affect the risk of thrombosis. These include increases in levels of Von Willebrand Factor, Factors II, VII, VIII, X, platelet activation and aggregation, and pro-inflammatory cytokine exposure [8].

Data from observational studies suggest that current use of COCs is associated with a three (3) to three and a half (3.5)-fold increase in VTE risk compared with non-use of COC. It is important to note that despite the increased risk, the number of VTE events in women using COCs remains small [7].

The European Medicines Agency (EMA) estimate the absolute risk of VTE during COC use to be between 5-12 per 10,000 women per year of use . The EMA risk for developing VTE with different COCs is presented in Table 2 [7] .

Table 2. EMA estimated risk of developing VTE in a year according to type of combined hormonal contraception used.

[redacted]

COCs are contraindicated if a woman has multiple risk factors that put her at high risk of VTE. If a woman has more than one risk factor it is possible that the increase in risk is greater than the sum of the individual factors.

In these cases the total risk of VTE should be considered and a benefit-risk based decision be made [9]. Smoking is listed as a risk factor for VTE in all COC data sheets available in New Zealand.

Comments:

Overall, the risk of VTE is higher in users of COC compared to non-users. The risk of VTE from COC use is lower than the risk in pregnant women and in the postpartum period.

VTE in the context of COC use is a rare but well-known adverse event, for which smoking is listed as a risk factor. Information about the risk of VTE is included in all the New Zealand data sheets for COCs and Medsafe have published several Prescriber Update articles about this safety concern.

2.3 Smoking as a risk factor for thromboembolism

Tobacco cigarette smoking (TCS) is directly related to vessel-wall damage and may contribute to cardiovascular disease (CVD) through several pathways (Figure 2). Tobacco smoke exposure has been linked to impaired endothelium-dependent vasodilation in macrovascular and microvascular beds, decreases in nitric oxide (NO) availability and increases in inflammatory markers (C-reactive protein, interleukin-6, tumour necrosis factor) in male and female smokers [10].

Figure 2: Proposed cardiovascular effects of smoking. Source: Conklin et al. DOI: 10.1152/ajpheart.00591.2018 (accessed 8 February 2023).

TCS and thrombosis have been studied in several clinical and experimental studies. Findings from these studies were summarised in a review article by Ambrose et al [10].

- Platelet dysfunction: Platelets isolated from smokers exhibited an increased stimulated and spontaneous aggregation. This may be a result of reduced levels of platelet-derived NO and decreased platelet sensitivity to NO, leading to increased platelet activation and adhesion.
- Altered antithrombotic and prothrombotic factors: Current smokers had higher fibrinogen levels that correlate with the number of cigarettes smoked while ex-smokers had similar fibrinogen levels to non-

smokers. Additionally, smokers were found to have alterations of tissue factor (TF) and TF pathway inhibitor-1 and therefore have a consequent increase in thrombotic potential.

- Alterations in fibrinolysis: studies using human umbilical vein endothelial cells (HUVEC) exposed to serum from chronic smokers noted significant decreases in both basal and substance-P-stimulated tissue plasminogen activator (t-PA). Similarly, decreased plasma t-PA antigen and activity were observed in smokers in samples isolated from brachial and coronary arteries following pharmacologic stimulation.

Several epidemiological studies and systematic reviews have identified smoking as a risk factor for provoked VTE. A summary of the studies and key findings can be found in Table 3.

Table 3: Summary of studies investigating smoking as a risk factor for VTE

Authors, date	Study name	Description and key findings
Enga et al. 2012 [11]	Cigarette smoking and the risk of VTE: The Tromsø Study	Single-centre, prospective, population-based cohort study investigating the association between TCS and VTE in Tromsø, Norway. Information on smoking habits was assessed by self-administered questionnaires in 24,576 subjects. A total of 389 VTE events were registered during a median follow up time of 12.5 years (incident rate of 1.61 per 1000 person years). Heavy smokers (>20 pack-years) had a hazard ratio of 1.46 (95% CI 1.04-2.05) for total VTE and hazard ratio of 1.75 (95% CI 1.14-2.69) for provoked VTE compared with non-smokers. Heavy smoking was apparently a risk factor for provoked VTE in analyses with VTE events as the only outcome.
Goldhaber et al. 1997 [12]	A prospective study of risk factors for pulmonary embolism in women: The Nurses' Health Study	Prospective biennial-based questionnaire study investigating the risk factors for PE in 112,822 women aged 30-55 years and followed up over a 16-year period (1,619,770 person-years of follow up). There were 280 cases of PE of which 125 cases noted a primary diagnosis of PE. Obesity, cigarette smoking, and hypertension were independent predictors of PE. Heavy cigarette smokers had an increased risk of primary PE. The relative risk (RR) of primary PE was 1.9 (95% CI, 0.9-3.7) for women currently smoking 25-34 cigarettes per day and 3.3 (95% CI, 1.7-6.5) for those smoking 35+ cigarettes daily as compared with never smokers.
Hansson et al. 1999 [13]	Smoking and abdominal obesity risk factors for VTE among middle-aged men: 'The Study of Men born in 1913'	Prospective cohort study to investigate the long-term risk factors for DVT and PE among middle-aged men. 855 men participated in a screening examination at the age of 50, and 792 men were re-examined at the age of 54. All men were followed up with periodic examinations until the age of 80. Waist circumference (P=.004) and smoking (P=.02) predicted a venous thromboembolic event in multivariate survival analysis. For men who smoked 15g of tobacco (15 cigarettes) per day or more, the adjusted relative risk of VTE was 2.82 (95% confidence interval, 1.30-6.13; P=.009) compared with non-smokers.
Cheng et al. 2013 [14]	Current and former smoking and risk for VTE: a systematic	Literature search of MEDLINE and EMBASE from January 1966 - June 2013. 32 observational studies were identified involving 3,966,184 participants and 35,151 VTE events.

	review and meta-analysis	Compared with never-smokers, the overall combined RR for developing VTE is 1.17 (95% CI 1.09-1.25) for ever-smokers, 1.23 (95% CI 1.14-1.33) for current smokers, and 1.10 (95% CI 1.03-1.17) for former smokers. The risk of VTE increased by 10.2% for every additional ten cigarettes smoked per day or by 6.1% for every additional ten pack-years. Smoking was associated with an absolute risk increase of 24.3 (95% CI 15.4-26.7) cases per 100,000 person-years.

A large population-based case-control study in the Netherlands was conducted to evaluate TCS as a risk factor for VTE, in conjunction with COC use or factor V Leiden mutation [15]. Participants with a first episode of VTE were recruited from six anticoagulation clinics and additional control subjects recruited using a random digit dialling method.

There were 3,989 patients (who experienced either DVT, PE, or both) and 4,900 control subjects included in the study, all participants were asked to complete a standardised questionnaire.

Results: The RR of DVT by smoking status in different subgroups is presented on Table 4. Current and former smoking were both associated with a moderately increased risk of VTE compared with never-smoking. The odds ratio (OR) for current smoking is 1.43 (95% CI 1.28-1.60) and 1.23 (95% CI 1.09-1.38) for former smoking.

The authors also reviewed the risk of VTE in women aged 18-39 who used a COC and smoked. Women who used COCs and did not smoke had a 3.9-fold increased risk of VTE, those that used COCs and smoked had an 8.8-fold increased risk of VTE compared with never-smokers that did not take a COC (Table 5). Additionally, a high number of pack-years (>20 pack-years) in young smokers was associated with a significantly increased risk of VTE, OR 4.30 (95% CI 2.59-7.14). , The joint effect of Factor V Leiden and current smoking led to a 5.0-fold increased risk compared with never smokers without the mutation.

In order to investigate the mechanism for the association between smoking and VTE, authors adjusted for fibrinogen levels, hypothesizing that the risk of VTE was mediated via elevated fibrinogen levels. The adjustment resulted in slightly decreased risk estimates suggesting that fibrinogen levels are not an important mediator on the effect of smoking on the risk of thrombosis. Overall, authors found smoking to be a moderate risk factor for VTE, and that the risk of VTE in women that smoke is increased with COC use and Factor V Leiden mutation.

Table 4. Relative risk of venous thrombosis by smoking status.

Table 5. Combined effect of smoking status with oral contraceptive use on the risk of VTE in women aged 18-39

Adjusted for age, BMI, and pregnancy.

2.4 Use of electronic cigarettes (vapes) in New Zealand

Vaping refers to the use of an electronic device that heats a liquid turning it into an aerosol (vapour) which the user inhales. Vaping liquids typically contain nicotine, propylene glycol, vegetable glycerine, and various other flavourings [16].

Vaping products are regulated through the Smokefree Environments and Regulated Products Amendment Act (the Act) 2020, which came into force on 11 November 2020. The Act prohibits the sale of vaping products to anyone under the age of 18, places restrictions on where an individual can vape, and sets the requirements for vaping product safety standards that must be met before a product is sold [16].

The use of vapes/electronic cigarettes (ECs) in New Zealand is increasing, particularly amongst the younger population. The ASH Year 10 Snapshot New Zealand surveys 20,000-30,000 students every year on their smoking and vaping behaviour and attitudes. Results from the 2021 survey found that daily smoking has decreased but daily vaping has increased significantly (3.1% in 2019 to 9.6% in 2021) [17].

The New Zealand Health Survey conducted by The Ministry of Health provides information about the health and wellbeing of New Zealanders. Results from the 2021/2022 survey show that vaping/EC use in adults (aged 15-years and older) has increased yearly since 2015/2016 (Table 6). Of the 4,434 adult respondents, 27% admitted to trying vaping/EC, and 8.3% reported daily use [18].

Based on the Health Survey results, daily TCS usage is reported to decrease each year. Since 2015/2016 daily TCS usage has decreased from 14.5% in 2011/2012 to 8% in the latest survey (2021/2022). It is possible that many TCS users have switched to vaping, although this may not be the case in the younger population

Table 6. Vaping/EC use in Adults- Results from the New Zealand Health Survey 2021/2022.

Comments:

Although there is a decreasing trend in TCS use in New Zealand, EC use is increasing in adults and children. Several factors may have contributed to the increase in use including ease of accessibility compared to traditional cigarettes. Prior to the commencement of the Act, companies were able to advertise ECs and they were available to those under the age of 18.

It is unclear whether vaping, like traditional TCS, is linked to an increased risk for VTE. Given the numerous vaping products available and variable chemical formulations, it may be difficult to isolate the main compound that causes harm (if any).

Vaping is considered to be safer than TCS, however there is a risk of harm as documented by cases of vaping linked lung injury. Ongoing longitudinal studies are needed to investigate the long-term safety related to EC use.

3 SCIENTIFIC INFORMATION

There is limited information relating to vaping and VTE, particularly in the context of women who use COCs. Most of the literature available focuses on the risk of CVD linked to ECs. Some of these studies have been included in the literature section, particularly if authors investigated markers of thrombosis.

The long-term safety of ECs remains unclear and is an area where research is ongoing. A longitudinal analysis and a cross-sectional study reported no significant association between exclusive EC use and CVD [19, 20]. However, additional longitudinal studies are essential to further assess this association.

A literature search was conducted to identify articles relating to the risk of VTE in women who take a COC and vaped. This yielded 4 results of which 2 studies were relevant to this paper and are discussed in section 3.1. A second literature search was conducted to identify articles relating to the risk of VTE linked with EC exposure, 11 articles from the search are summarised in section 3.2 and 3.3.

A glossary is provided in section 7.1.

3.1 Literature search 1: Risk of VTE in women that take a COC and vape

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to January 13, 2023>, adapted for Scopus, Embase, Cochrane, Scholar, European PMC
Search Strategy:

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1 "electronic cigarette*".mp.
2 Electronic Nicotine Delivery Systems/
3 e-cigarette*.mp.
4 vaping.mp. or Vaping/
5 (vape or vapes).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6 electrically heated cigarette*.mp.
7 electrically heated smoking system*.mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 exp Contraceptives, Oral, Combined/
10 (contracept* adj3 oral*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
11 (contracept* and (pill* or tablet*)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12 *Contraceptive Agents, Female/
13 9 or 10 or 11 or 12
14 8 and 13

15	limit 14 to (english language and yr="2013 -Current")

3.1.1 Riley et al, 2016. Hormonal contraception among electronic cigarette users and cardiovascular risk: a systematic review [21]

Aim: To conduct a systematic review to evaluate data regarding cardiovascular (CV) risks (such as myocardial infarction (MI), stroke, venous thromboembolism, peripheral arterial disease or changes to CV markers) among electronic cigarette users who are exposed to hormonal contraceptives (HCs). The authors had four research questions listed below:

1. Are female EC users who use HCs at heightened risk for adverse CV outcomes compared with female EC uses who do not use HCs?
2. Among the general population (men and women), are EC users at increased risk of adverse CV outcomes (clinical events of changes to intermediary markers) compared with people who do not use ECs (regardless of HC use status)?
3. Among women exposed to nicotine from any source other than cigarettes including smokeless tobacco products and nicotine-replacement therapy, are those who use HC at increased risk of adverse CV outcomes (clinical events or changes to intermediary markers) compared with women who do not use HC?
4. Among women exposed to inhaled propylene glycol or glycerol (additional common components of ECs), are those who use HC at increased risk of adverse CV outcomes (clinical events or changes to intermediary markers) compared with women who do not use HC?

Methods: Authors conducted a systematic review according to the PRISMA guidelines and searched PubMed and Cochrane Library database from database inception through to June 2015.

Results: The following articles were found for each research question; a summary table of the results has been attached as Annex 2.

1. There were no articles found relating to research question 1
2. Thirteen (13) articles met inclusion criteria for this review. One article reported on the clinical outcomes of interest (myocardial infarction), 11 articles measured heart rate (HR) and blood pressure (BP) after EC exposure. In 5 of these articles, investigators followed participants for at least 1 week. In the remaining 7 articles, investigators only report acute outcomes (changes over <5 hours of exposure).
   One article reported on a cross-sectional survey in which EC users reported on perceived changes to health after switching from traditional cigarettes to EC. Twelve (12) of the articles included data on both men and women and one study occurred in women only.
   a. There were 5 articles reporting on CV outcomes among EC users followed longitudinally with a follow up period of 7 days to 1 year (Annex 2 Table 1). There was one fair quality graded double-blind randomised control trial, two poor quality graded case series, one randomised cross over study, and one prospective cohort study. The studies conducted by Caponnetto et al, van Staden et al, Oncken et al, did not find statistically significantly changes in HR or BP after EC use. Nides et al noted a significantly significant ($p<0.004$) increase in HR from a baseline mean HR of 68bpm to 73.3bpm 10 minutes after EC exposure, however the quality of this paper was graded as poor. , A poorly graded prospective cohort study by Manazoli et al identified one acute myocardial infarction reported in a group of dual EC and traditional cigarette users. The age, sex, and level of nicotine intake was not reported for the person that experienced the event.
   b. There were 8 studies reporting acute results after short periods of EC use, none reported on clinical CV outcomes of interest (Annex 2 Table 2). Farsalinos et al (2014a), Vansickel et al (2010), Czogala et al, Szoltysek-Boldys et al did not find any statistically significant changes in HR following EC use. Yan et al, Vansickel et al (2012 and 2013), and Fasalinos et al (2014b) identified changes in HR and self-reported changes to pre-existing diseases in their study participants. The grading of these articles ranged from poor to fair quality.

3. There was one (1) article that met inclusion criteria (Table 3 of annexe 2). This was a nonrandomised trial where investigators exposed 46 female smokers and non-smokers on a HC to a transdermal nicotine patch and a placebo patch for 2.5 hours with a 48 hour wash out period. Participants were divided into four groups: smoking COC users, smoking non-COC users, non-smoking COC users, and non-smoking non-COC users. HR and BP were measured after patch administration. For all groups of women, nicotine administration statistically significantly increased resting heart rate by a mean of 5.1 beats per minute.
4. There were 81 articles identified, of which none met the inclusion criteria for this review.

Discussion: The authors found no direct evidence relating to health effects of ECs among users of HCs. Among studies of EC users in the general population, serious adverse CV events were rare. Only one serious CV event (a case of myocardial infarction) was reported among a group of dual EC and cigarette users who reported switching to ECs only during a 12-month period of observation. No instances of stroke, VTE, or peripheral artery disease were reported.
Eleven (11) articles measured changes to HR after EC use of these, 7 found no significant increase to HR after EC use compared with baseline, 4 studies reported significant changes however, mean HR remained within the normal range after EC exposure.
One study found that acute exposure to both COC and nicotine patch was associated with increases in HR but this increase in HR was within the normal range. There were no studies of propylene glycol or glycerine exposure among HC users. The authors of the paper conclude that EC use was associated with a smaller risk of adverse CV events than conventional cigarettes but that users should exercise caution because of the possibility of adverse health effects.

Comments:
Unfortunately, there was a lack of direct evidence for the primary research question and therefore it is difficult to draw any conclusions about the risk of CV harm in women who take COCs and vape. Most of the studies looked at changes to the intermediary markers CVD (HR and BP). The relationship between the changes in these markers and the risk of developing clinical CVD is unclear.

Of the studies included in the review, only 2 studies (Caponnetto, van Staden) followed EC users for over a 2-week period, and only 1 study directly reported clinical CV events (Manzoli). There were significant limitations and confounding in many of the studies due to a lack of standardised EC dosing across the study sample, lack of comparison groups, small sample sizes, investigators did not validate their exposure outcomes, and generally only fair to poor-quality studies were available. Additionally, as the incidence in smokers is around 2 per 1,000 person years it is unlikely that these studies would find any cases of VTE.

Some of the studies included in the review that did not find statistically significant changes in were directly sponsored by EC companies or EC user advocate groups or did not report their sources of funding (van Staden, Farsalinos 2014a, Szoltysek-Boldys).

Overall, correlating the results of the studies included in this review to the clinical impact of long-term EC use on CVD health is difficult. Therefore, additional research such as prospective cohort studies are required to assess the long-term safety of ECs in relation to CVD. Further research studies could include participants with risk factors that are strongly associated with clinical CV outcomes and be adequately powered to detect changes in these markers.

3.1.2 Theophilopoulos et al, 2021. Provider documentation of electronic nicotine delivery system use among patients prescribed contraception in an academic health centre in the South-eastern United States [22]

Aim: To investigate documentation of electronic nicotine delivery system (ENDS) screening and counselling in the electronic health records (EHR) of women prescribed a HC at an academic health centre in the United States.

Methods: Authors conducted a retrospective EHR review and content analysis of 500 randomly selected female patients (aged 12 and older) who had been prescribed HC and had ENDS documented in their records prior to July 2020. Inclusion criteria consisted of: females aged 12-years and older, history of HC prescription, and ENDS documentation in their health notes matching one of the following keywords 'e-cig, ecig, e cig, vape, vaping, juul, jool'. Records from multiple specialities and clinical settings were reviewed including inpatient and outpatient OB-GYN, paediatrics, family medicine, internal medicine, and surgical subspecialties. Two reviewers independently reviewed all patient records from June to September 2020.

Results: Of the 500 patient records, 28 were excluded as they did not have ENDS documentation. Of the remaining records, 245 (51.9%) of patients reported regular ENDS use. The remaining 227 (48.1%) of patients were non-ENDS users whose health record had an ENDS keyword (eg patient information sheet provided to remind patients to refrain from ENDS use prior to surgery).

- The sample of ENDS users were predominantly white, non-Hispanic, and approximately half were documented as 'never smokers' in the smoking EHR field
- Among ENDS users, there were 82 contraception-related encounters. Table 7 provides a summary of the nature of ENDS documentation (healthcare setting, type of advice provided) in those encounters relating to contraception.
- In 17 of the 82 encounters, the healthcare provider counselled against ENDS use. Within this group three OB-GYNs refused to prescribe HCs for patients using ENDS. In 6 of the 82 encounters patients were given hand-out forms advising to refrain from ENDS use when taking contraception.
- There was one case record of a patient with a documented PE in an emergency department who was prescribed HCs and used ENDS.
- Among the ENDS non-users there were 43 contraception related encounters, and 3 recorded the provision of patient information advising against ENDS use

Table 7. Electronic nicotine systems documentation in encounters relating to contraception.

[redacted]

Discussion: ENDS use is under-documented in encounters relating to contraception, and the rate of counselling against ENDS use is even lower. Among the 245 regular ENDS users, only 24% had documentation of ENDS use in encounters related to contraception prescriptions. This may be related to structural fields in the EHR as they do not specify the type of tobacco product used. The authors noted that although ENDS

documentation related to contraception is low, just under half of the records with ENDS keywords were in patients who have never used ENDS. This may reflect a trend towards increased screening among providers.

Comments:
Among the 82 records where ENDS use was documented and the visit related to contraception use, there were 17 records where the healthcare provider counselled against ENDS use and 3 cases where HC were not prescribed. This may reflect that providers do not believe there's a significant risk associated with ENDS and HCs. Unfortunately, this study did not investigate the healthcare providers reasonings for counselling against use or the decision not to prescribe the HC, which is likely influenced by several other patient factors. Healthcare provider beliefs relating to EC use and counselling could be another area of research.

There was one health record which documented a PE and the patient reported ENDS use, no further details of this case were provided.

This study was conducted in a single academic healthcare system which limits the generalisability of the results. The study also focused on ENDS use documentation rather than healthcare professionals' advice and beliefs on the risks associated with EC use.

3.2 Literature search 2: Risk of VTE in people that vape/use ECs

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to January 17, 2023>>, adapted for Scopus, Embase, Cochrane, Scholar, European PMC

Search Strategy:

1	"electronic cigarette*".mp.
2	Electronic Nicotine Delivery Systems/
3	e-cigarette*.mp.
4	vaping.mp. or Vaping/
5	(vape or vapes).mp.
6	electrically heated cigarette*.mp.
7	electrically heated smoking system*.mp.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	exp Thromboembolism/ or thromboembolism.mp.
10	Pulmonary Embolism/ or blood clot*.mp.
11	exp Thrombosis/
12	Venous thromboembolism.mp. or Venous Thromboembolism/
13	arterial thromboembolism.mp.
14	thrombosis.mp.
15	9 or 10 or 11 or 12 or 13 or 14
16	8 and 15
17	limit 16 to yr="2013 -Current"

3.2.1 Carnevale et al, 2016. Acute impact of tobacco vs electronic cigarette smoking on oxidative stress and vascular function [23]

Aim: To investigate the differences between traditional TCS and EC smoking on oxidative stress and endothelial dysfunction in a cohort of healthy subjects without CVD, and to identify the potential molecular mechanisms underlying the effects of smoking on oxidative stress and vascular function.

Method: Investigators conducted a crossover, single-blind study between September 2014 and March 2015 in 40 healthy subjects (20 smokers and 20 non-smokers, matched for age and sex).

Measurements included brachial flow mediation dilation (FMD), soluble NOX2-derived peptide (sNOX2-dp), 8-iso-prostaglandin F2α (8-isoPGF2α), nitric oxide (NO) bioavailability, and vitamin E levels. The study was divided into two phases with blood samples and FMD measured just before and within 30 minutes of smoking.

1. All subjects (smokers did not smoke for at least 12 hours) smoked one tobacco cigarette with a nicotine content of 0.6mg under supervision of an investigator
2. One-week after the first phase, all subjects inhaled nine puffs of a tobacco flavoured EC (approximately equivalent to 0.6mg of nicotine) under supervision of an investigator

Investigators compared baseline features with unpaired Student *t* tests and the Fisher exact tests, additional hypothesis-generating analysis included paired Student *t* tests, correlation analysis, and linear regression analysis between relative changes in the outcomes of interest. Statistical significance was set at the two-tailed 0.05 level and computations performed using Stata version 13.

Results: Baseline characteristics were similar between smokers and non-smokers (Table 8). There were 3 people included in the study who reported taking a COC. Smokers had higher levels of baseline oxidative stress (sNOX2-dp, 8-isoPGF2α, and NO bioavailability all P <0.001) compared to non-smokers.
After TCS and EC exposure there were significant changes in the levels of sNOX2-dp, 8-isoPGF2α, NO bioavailability and vitamin E levels (all P <0.001) for both smokers and non-smokers (Table 9). Changes in FMD values were decreased in all groups after TCS and EC use however, these changes were not statistically significant.

Additionally, the prespecified inferential analysis based on generalised estimating equations confirmed that all markers of oxidative stress and FMD were significantly and detrimentally affected by smoking. ECs were associated with less detrimental impact than traditional tobacco cigarettes on levels of sNOX2-dp, 8-isoPGF2α, and NO bioavailability (Table 10).

Table 8. Baseline characteristics of study participants

Figure 9. Overall study results

Table 10. Primary inferential analysis of results

Discussion: This study explored the effect of tobacco cigarettes and ECs on oxidative stress and endothelial dysfunction. In smokers and non-smokers without CVD, both forms of cigarettes were associated with an increase in oxidative stress and endothelial dysfunction, as well as a reduction in vitamin E levels. The effects of ECs were less pronounced than those caused by traditional tobacco cigarettes.

This study extends upon previous evidence showing that tobacco smoking acutely and extensively reduces endothelial function and increases serum markers of inflammation of oxidative stress. EC use was also linked to a rapid and acute increase in the circulating markers of oxidative stress, and the activity of NOX2. This raises some concerns regarding the vascular safety of ECs. Further investigation is warranted to investigate the

mechanisms behind the changes in biomarkers and additionally into the various additives and flavours in EC liquids to determine if these added ingredients elicit harmful effects.

Comments:

This study looked at the acute effects on biomarkers of oxidative stress and vascular function following EC use in smokers and non-smokers. The results found statistically significant changes in sNOX2-dp, 8-isoPGF2α, NO bioavailability, and changes in vitamin E serum levels and brachial FMD (not statistically significant) after EC exposure.

NOX2 activation is associated with the development of endothelial dysfunction and progression towards atherosclerosis and CVD. The study results suggests endothelial dysfunction may occur and that there is a risk of vascular harm associated with EC use.

This study only investigates the acute effects of TCS and EC use in a small number of participants. Blood samples and FMD were taken 30 minutes after smoking. The study did not look at the effects of long-term chronic use of ECs on biomarkers. Further clinical large prospective studies are required.

Investigators did not measure nicotine or cotinine levels to validate exposure levels and could not determine if increased levels of nicotine were associated with more significant changes in biomarker levels. Additionally, the authors did not accurately record the occurrence rate of noxious events that occurred in patients during the study period. Some participants who were originally non-smokers reported experiencing respiratory symptoms, but this information was not captured in the results or discussion.

3.2.2 Ramirez et al, 2020. The JUUL e-cigarette elevates the risk of thrombosis and potentiates platelet activation [24]

Aim: To characterise the impact of JUUL exposure on thrombogenesis and platelet function by using a mouse whole-body exposure system and protocol that mimics real-life exposure scenarios of daily EC users.

Method: Investigators used a passive e-vape vapour inhalation system where C57BL/6J (10–12-week-old male mice) were exposed to 70 puffs per day of JUUL EC vape (5% nicotine menthol flavoured pods) for a period of 2 weeks. The effects of JUUL e-vape exposed mice relative to unexposed (clean-air) mice were analysed. Measurements/analysis was conducted on urinary cotinine levels, blood flow in the left carotid artery (in vivo thrombosis model), tail bleeding time, peripheral blood cell and platelet level counts Platelet activity was measured *in vitro* using activated platelet rich plasma, ADP- and thrombin-induced platelet aggregation models. All experiments were completed three times, using blood pooled from 5-8 mice each time. Data was analysed using the GraphPad PRISM statistical software version 7.0. Differences in the mean bleeding and occlusion times were evaluated using the Mann-Whitney *U* test. Significance was accepted a $P < 0.05$.

Results: In order to validate the passive e-vape inhalation system, urinary cotinine levels were measured. As expected, JUUL-exposed mice had significantly higher levels of cotinine compared with control mice ($P < 0.001$).

JUUL-exposed mice had significantly shortened tail bleeding and occlusion time compared to mice exposed to clean air, with a median bleeding time of 35 vs 295 seconds ($P < 0.001$) and occlusion time of 14 vs 200 seconds ($P < 0.01$) (Figure 4). Notably there was no difference in the platelet or other blood cell count between JUUL and clean air-exposed mice.

The *in vitro* test for ADP- and thrombin-induced platelet aggregation found that exposure to JUUL ECs resulted in higher ADP- and thrombin- induced platelet aggregation ($P < 0.01$ and < 0.0001 respectively) compared to clean air control platelets. Similarly, ADP- and thrombin- induced platelet secretion was enhanced in JUUL-exposed mice ($P < 0.01$ and 0.0001 respectively).

Platelets from JUUL-exposed mice had significantly higher ADP- and thrombin- triggered P-selectin activity (Figure 5a), increased integrin GPIIb/IIIa expression (Figure 5b), and agonist mediated phosphatidylserine (PS) expression (Figure 5c) which are critical elements for efficient activation of the coagulation cascade and clot formation.

Figure 4: JUUL exposure shortens the bleeding time in the tail bleeding time assay (A) (P <0.001), and the time to occlusion in the ferric chloride in vivo thrombosis model (B) (P <0.01). Source: Ramirez et al. DOI: 10.1177/1074248420941681 (accessed 25 January 2023).

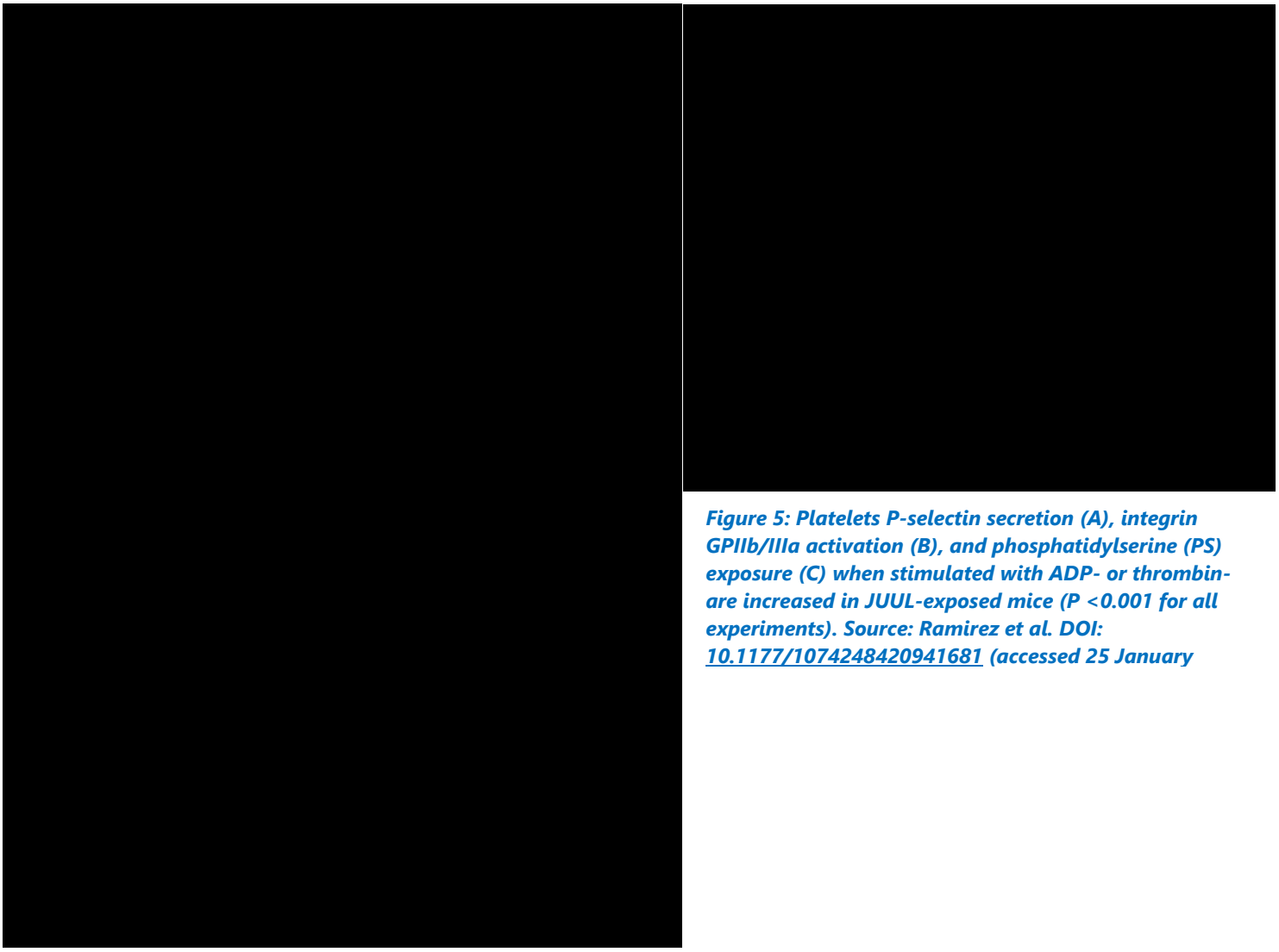


Figure 5: Platelets P-selectin secretion (A), integrin GPIIb/IIIa activation (B), and phosphatidylserine (PS) exposure (C) when stimulated with ADP- or thrombin- are increased in JUUL-exposed mice (P <0.001 for all experiments). Source: Ramirez et al. DOI: 10.1177/1074248420941681 (accessed 25 January

Discussion: The study investigators note that JUUL is a popular model of ECs commonly used in the United States. The manufacturer of JUUL has marketed the product as an EC with a higher safety profile compared to tobacco cigarettes. In this study, investigators sought to identify the haemostasis and thrombotic effects of the JUUL EC on a whole-body mouse model over a 2-week period, using a protocol that mimics real-life exposure.

The mouse model data from this study demonstrated that exposure to JUUL ECs does increase the risk of thrombosis, which is reflected by the prolonged occlusion time when compared to clean air controls. In addition, JUUL exposure altered physiological haemostasis as evidenced by the shortened tail bleeding time. This effect has also been observed in short-term exposure studies conducted with traditional tobacco cigarettes. JUUL exposure had immediate impacts on the platelets of EC exposed mice. The authors found enhanced platelet function, including aggregation, secretion, integrin GPIIb/IIIA activation and increased PS exposure compared to controls. Furthermore, this study found that JUUL's capacity to enhance platelet aggregation was significantly higher than that of other ECs. The underlying mechanisms of these effects are unknown and could be derived from the various different devices and/or concentrations of nicotine.

The long-term effects of EC use in humans is unknown and further research is required in this area. This study provides initial evidence that EC exposure may pose a negative CV (particularly thrombotic) health impact on users.

Comments:

This preclinical study was one of the studies referenced in the [redacted]. There is currently limited information in human studies investigating EC exposure on thrombogenesis. This study provides initial evidence that EC use influences platelet function and possibly thrombosis. Statistically significant increases of P-selectin, GPIIb/IIIa, and PS expression were identified in JUUL exposed mice. These markers all have a significant role in thrombus formation and elevation of these levels could increase the risk for thrombosis.

Further studies are required to evaluate whether these changes in biomarkers occur in human users of ECs, and if any clinically relevant outcomes and safety concerns arise from EC use.

3.2.3 Mohammadi et al, 2022. Chronic e-cigarette use impairs endothelial function on the physiological and cellular levels [25]

Aim: To investigate the association of chronic EC use and vascular impairment on the physiological and cellular levels. A clinical observational study in conjunction with cell culture experiments to determine the effects of EC use on the NO pathway and endothelial permeability.

Method: Participants were recruited from 3 institutions in the United States. A total of 120 healthy volunteers were recruited and matched by age and sex. Endothelial function was measured in chronic EC users, chronic cigarette smokers, and non-users. The authors measured the effects of participants' sera, or EC aerosol condensate, on nitric oxide (NO) and H_2O_2 release and cell permeability in culture endothelial cells. Biomarkers of inflammation, cell adhesion, thrombosis and tissue fibrosis were also analysed. Cell culture tests were performed on HUVEC cells.

Results: Authors measured various endpoints which are summarised in the following bullet points and figures.

- Chronic EC and TC users had reduced FMD relative to non-users (5.3+/-2.3% and 6.5+/-2.8% versus 10.7+/-5.2% respectively).
- HUVECs incubated with serum from EC and TC users released less NO compared to non-users. Serum from EC users and TC smokers caused comparable reductions in NO release by unstimulated and stimulated HUVECs (for unstimulated: 0.65±0.24nM and 0.69±0.29nM versus 0.95±0.37nM, respectively; for stimulated: .21±0.08nM and 0.25±0.12nM versus 0.41±0.04nM).
- HUVECs treated with serum from EC users contained less eNOS protein and NOS3 mRNA expression than those treated with serum from TC users. However, these results were not statistically significant to the levels found in non-users.

- Cell culture supernatant from HUVECs exposed to serum from EC users had significantly higher levels of H_2O_2, compared with non-users (P =0.004). No significant differences were seen with lysed HUVECs.
- Chronic EC users have increased circulating levels of endothelial cell adhesion and inflammatory biomarkers (Figure 6). In the serum samples analysed, S100A8, HMGB1, interferon-β, soluble ICAM-1, von Willebrand factor, and myeloperoxidase were unchanged in smokers but substantially higher in EC users. Conversely, some biomarkers which were unchanged in EC users were higher in TC smokers, such as interleukin-1 β, RAGE and PECAM-1. There were no significant differences in the following biomarkers: granulocyte-macrophage-CSF, UL-6, IL08, CRP, thrombopoietin, D-dimer, VACM-1, TNF-α, S100A12, CCL2, VEGF.

Figure 6: Circulating biomarker results. Source: Mohammadi et al. DOI: 10.1161/ATVBAHA.121.317749 (accessed 25 January 2023)

Discussion: Authors of the study found that chronic EC use, and cigarette smoking resulted in comparable impairment of vascular endothelial function, and in altered serum that reduced NO production from endothelial cells. The distinct patterns of circulating CVD risk biomarkers from chronic users of each product indicate that despite the similar physiological effects, EC use and cigarette smoking trigger fundamentally different molecular responses.

The differences indicate that for vascular health, dual product use of tobacco and electronic cigarettes may cause harm. In this study both EC and TC users had a significant reduction in FMD, a marker often used to

predict long-term CVD. Based on the results, there is a risk of CVD associated with EC use in otherwise healthy individuals.

In the serum taken from EC users there were significant increases in the levels of circulating ICAM-1, S100A8, von Willebrand factor and myeloperoxidase. These substances are associated with inflammation, endothelial leakiness, cell permeability, thrombosis, endothelial dysfunction, and oxidative stress. Additionally, HUVECs exposed to EC user serum produced significantly more H_2O_2, a reactive oxygen species associated with endothelial dysfunction. Combined, these findings suggest that EC users have an increased level of markers associated with endothelial oxidative stress, leading to endothelial dysfunction and an increased risk of future CV events.

In conclusion, chronic EC use impaired FMD comparatively to chronic cigarette smoking and led to changes in blood serum levels that decreased NO production from cultured endothelial cells without conclusive changes in eNOS gene and protein expression. Serum taken from EC users and smokers had higher levels of endothelial cell adhesion, pro-inflammatory, and thrombotic mediators. The study findings highlight that EC use is not without CV risk and may cause adverse events that may overlap with those of smoking.

3.2.4 Benowitz et al, 2020. Twenty-four-hour cardiovascular effects of electronic cigarettes compared with cigarette smoking in dual users [26]

Aim: To compare the effects of TCS and ECs on HR, BP, and urine catecholamine excretion in dual users. Secondary aims were to compare the effects of TCS and ECs on biomarkers relating to potential mechanisms of CVD including oxidative stress, platelet activation, and inflammation.

Method: 36 healthy dual CS and EC users (average age of 35-years) participated in a crossover study. Participants that had used an EC in the 15-days prior to study enrolment and smoked at least 5 cigarettes over the past 30 days were included. The study was conducted between December 2015 and February 2018. Participants were not asked to modify their smoking or EC use behaviour before screening. After screening, participants completed two 1-week study blocks: 1 cigarette only and 1 EC only block. The first 4 days of each block consisted of at-home TCS, or EC use which served as a washout and stabilisation period. Participants were admitted to a clinical research ward on day 5 of each block. On day 6 and 7 there was no limit to the amount of TCS/EC used by participants. An enforced nicotine abstinence period of 2 days occurred between the two blocks. Participants were also able to use different types of ECs including variable-voltage tanks, pods, fixed-power tanks.

Measurements were taken on day 6 and 7 of each block and during the abstinence period. Measures included plasma nicotine and cotinine serum levels, ambulatory HR, systolic and diastolic BP, urine epinephrine, norepinephrine and dopamine concentrations. Oxidative stress was assessed using urine 8-isoPGF2α levels, platelet activation via urine 11-dehydro-thromboxane B2 (11-dhTxB2) levels and inflammation was assessed using plasma interleukin-6 and -8 levels.

The primary comparison between the study arms was performed using nonlinear mixed models. A priori, sample size calculation determined that a sample size of 36 would give >80% power to detect corrected differences between TCS and EC arms. All analyses were conducted with SAS version 9.4 or R version 3.5, with 2-tailed P values< 0.05 considered significant.

Results: On average, participants smoked 15.6 cigarettes and vaped 1.95g during day 6 and 7. Overall, plasma nicotine levels were significantly higher during cigarette smoking, although in 25% of participants, nicotine levels during EC use exceeded levels during smoking. Mean plasma cotinine concentrations while smoking and using ECs were 246ng/mL (229-264) and 182ng/mL (158-207) respectively.

Mean HR and BP was higher with TCS than EC use and higher with EC than with no use during the abstinence period.

Urine epinephrine, norepinephrine, and dopamine excretion was not significantly different across the different interventions. Changes in urine 8-isoPGF2α and 11-dhTxB2 were not significant, although for the latter there was a trend for higher levels with TCS and EC use compared with no product use (Figure 7). Plasma IL-6 and IL-8 were similar while smoking and vaping and both levels were significantly higher compared with no product use (Figure 8).

Figure 7: Within-participant relative 24-hour urine biomarker concentrations. Source: Benowitz et al. DOI: 10.1161/JAHA.120.017317 (accessed 25 January 2023)

Figure 8: Within-participant relative plasma biomarker concentrations. Source: Benowitz et al. DOI: 10.1161/JAHA.120.017317 (accessed 25 January 2023)

Discussion: This study was performed to investigate and compare the 24-hour CV effects of EC use compared with TCS and no product use in participants that regularly use both EC and traditional cigarettes. The authors observed that in general, nicotine exposure corresponded with a higher HR in people who smoked tobacco cigarettes than those who use an EC. Within the study, participants were able to choose their own vaping device, and as expected variable voltage ECs (which deliver higher doses of nicotine) were associated with higher HR. Given the increase in HR and BP during the intervention blocks, an increase in urine catecholamines levels was expected but this did not occur. The reason for this negative outcome is unclear.

Given the timing of the measurements and short abstinence period, authors did not see a significant change in urine levels of 8-isoPGF2α and 11-dhTxB2. Reduction in urine levels of these biomarkers are noted to occur 3-7 days after smoking cessation. The study did identify a trend with higher average levels of the two biomarkers with TCS compared with EC use, however this difference was not statistically significant. Overall, the 24-hour patterns of haemodynamic effects of TCS and ECs in dual users is similar. TCS and EC use had similar effects on biomarkers of inflammation raising concern about the CV safety of EC use.

Comments:

This study found that TCS and EC use had similar effects on biomarkers of inflammation and CV measures such as HR and BP.

Limitations of the study include small sample size, short duration of experimental conditions particularly the product abstinence stage. The true extent of changes in biomarkers may not be captured in a 2 day period. Patients were also allowed to choose their own TC brand and vaping device. This resulted in variability in product exposure as different products will have different levels of ingredients/excipients, which could also attribute to CV harm. In order to reflect real-life exposure, participants were able to choose when/how much to smoke. However, given that the study was partly conducted in a research centre, external validity is reduced as social and environmental factors that influence for TCS/EC use are not typically present in a research centre.

The results in this study may be helpful for regulatory purposes but epidemiological studies of long-term EC users, including those with pre-existing CV disease, are needed to fully understand the impact of EC use on CV health.

3.2.5 Nocella et al, 2018. Impact of tobacco versus electronic cigarette smoking on platelet function [27]

Aim: To conduct a crossover single blind study to investigate platelet function in a cohort of healthy subjects after EC versus cigarette smoking.

Method: Between September 2014 and March 2015, 40 healthy participants (20 smokers and 20 non-smokers, matched for age and sex) were recruited into the study trial.
The study was divided into two phases. In the first phase, all participants smoked one tobacco cigarette with a mean nicotine content of 0.6mg. One week later, in phase two, the same subjects vaped 9 puffs from tobacco-flavoured EC (equivalent to 0.6mg nicotine content).
Blood samples were taken before and 5 minutes after smoking/vaping in each study phase to obtain platelet rich plasma and measure biomarkers of platelet activation including levels of soluble(s) sCD40L, sP-selectin, platelet aggregation %. Nicotine exposure was measured using cotinine serum levels. Analysis was conducted using Students unpaired and paired *t* test, chi-square test and carried out with SPSS v18.0. statistical significance was set at the 2-tailed 0.05 level.

Results: At baseline, characteristics (age, height, weight, BP) were similar between smokers and non-smokers however, smokers had higher baseline levels of sCD40L and sP-selectin markers than non-smokers.
Results are presented in Table 11. After TCS and EC exposure, significant changes in the levels of both sCD40L, sP-selectin, and platelet aggregation were noted in both smokers and non-smokers (all $P < 0.01$). No

significant difference was observed between smokers and non-smokers in these markers with the exception of platelet aggregation, which was higher in non-smokers after TCS than in smokers.

A significant difference for product type (EC vs TC) was found in smokers with respect to platelet activation (P =0.031). No significant difference was observed for sCD40L and sP-selectin (P =0.101 and 0.052 respectively).

In non-smokers there was a significant difference in platelet aggregation, sCD40L and sP-selectin (P <0.001, =0.007, =0.007 respectively)

Table 11: Overall results table.

Discussion: In this study, the use of both TCS and ECs in smokers and non-smokers without CVD, led to an increase in platelet activation. The effects of ECs were less pronounced that TCS in non-smokers, and the effects of ECs in smokers showed a less detrimental impact than TCS but only for platelet aggregation. This study supports previous *in vitro* studies that have identified changes in platelet activity following TCS and EC exposure. The data suggest that both TCS and ECs have a detrimental effect on the process of thrombosis. Even if ECs have a less impact, people who vape should be informed on the potential risk of harm.

Comments:
Similarly to other papers included in this report, this study only reports acute responses to EC use. There is a lack of information relating the components of both TCS and ECs used in the study and such excipients could influence platelet response in a different manner. Further large prospective cohort studies are needed to assess the long-term safety of ECs.

3.2.6 Kerr et al, 2018. Acute effects of electronic and tobacco cigarettes on vascular and respiratory function in healthy volunteers: a cross-over study [28]

Aim: To assess the acute effects of nicotine containing ECs versus TCS on vascular and respiratory function and circulating microparticles, particularly platelet microparticles (PMPs) and endothelial microparticles (EMPs).

Method: A single-centre, prospective, randomised cross-over study was conducted between June 2016 to December 2016. Twenty healthy male smokers were recruited into the study and assigned to one of two study arms. Baseline characteristics of the participants are presented in Table 12. Participants were exposed to each intervention (TCS and ECs) on separate study days. Study investigations (HR, blood samples, serum soluble

adhesion and selectin molecules, microparticles concentrations, forced expiratory volume and vital capacity) were performed pre- and post-intervention.
Normality of data was assessed using visual inspection of boxplots and the Shapiro-Wilk test. Statistical analysis was set at 0.05 and analysis conducted using SPSS software and GraphPad Prism.

Table 12: Baseline characteristics of study participants.

Results: Table 13 summarises the CV and circulating microparticle changes following the use of both interventions. One minute following the use of TCS and ECs, HR was significantly increased (P <0.001) whereas BP remained unchanged.
Following EC use, reactive hyperaemia index (RHI) (a marker of microvascular reactivity) increased (P =0.006) and the augmentation index (a marker of arterial stiffness) increased (P =0.01). When the augmentation index was standardised to HR of 75bpm, the change was not statistically significant (P >0.05).
The serum concentrations of sP-selectin decreased following EC exposure (P =0.026). However, no significant changes in the concentrations of sP-selectin were seen following TCS exposure (P >0.05). No significant changes in concentrations of PECAM-1, sICAM-1, sVCAM-1, sE-selectin were noted following EC use.
Five minutes following TCS, the total number of circulating microparticles, EMPs and PMPs all significantly increased. The only significant change for microparticles following EC use was an increase in PMPs (P <0.001).
In terms of respiratory function, no statistically significant changes were seen for FEV1, FVC, FEV1/FVC following use of ECs. Peak expiratory flow significantly decreased following EC use (P =0.019).

Table 13: Cardiovascular parameters and circulating biomarkers of vascular function at baseline and following EC and TC use.

[redacted]

Discussion: In this crossover randomised study, authors explored the immediate effects of ECs and TCs on endothelial function, arterial stiffness, CV haemodynamic parameters, pulmonary function and circulating microparticles. Both TCS and ECs were associated with a rise in HR which was expected as nicotine is known to activate the sympathetic nervous system. Patients had an increase in RHI following EC use, which suggests a deterioration in endothelial function. No patterns were observed in relation to changes in the serum levels of soluble adhesion molecules (ICAM-1, P-selectin, VCAM-1).

From a respiratory perspective, no significant changes relating to FEV1, FVC and FEV1/FVC were observed. However, an immediate reduction in PEF was observed following the electronic cigarette use, which was not seen following TCS. This may be suggestive of a defensive physiological response against the irritants in EC liquids.

For the CV risk of ECs to be estimated and fully understood, data from longitudinal observational studies need to emerge and this may take many years. Biomarkers of CVD may have a role in assessing the probability of

whether EC exposure is likely to be associated with CVD. Therefore, biomarker studies may have an important role in developing an understanding of any potential CV risks associated with long-term EC use.

Comments:

This biomarker study suggests that acute exposure to TCS and CS negatively influences vascular and respiratory function. The study has several limitations including small sample size, lack of generalisability (only men were recruited, and only one specific EC device and liquid was used). Participants were asked to self-report/confirm smoking abstinence which may have led to mis-recollection (nicotine/cotinine levels were not measured). Serial blood sampling was not performed so the changes in biomarkers after exposure may not be accurately reflected in the results. At the time of the study, no other similar studies were available to allow for comparative and power calculations to be made. Participants may also have been exposed to different levels of nicotine as they were able to smoke their preferred brand of cigarette during the TCS phase and also exhibited different smoking and vaping techniques. Lastly, participants were asked to smoke outside the research facility before going back inside to undergo testing/sample collection. There may have been delays during this transition time and some participants may not have had their sample collected at the 5-minute mark.

3.2.7 Qasim et al, 2018. Short-term e-cigarette exposure increases the risk of thrombogenesis and enhances platelet function in mice [29]

Aim: To investigate the mechanistic impact of ECs on platelet function and thrombogenesis in mice by using a whole-body/*in vivo* model that resembles real-life cigarette exposure scenarios.

Method: C57BL/6 10J mice were exposed over 2 sessions to a total of 200 EC puffs per day, each exposure period lasting for 5 days to 1 week. Vapour was generated using a 4-chamber passive e-vape inhalation system. The puff duration was 3 seconds, with an interval of 1 minute which mimics real life exposure. A control group was matched for age and sex and were exposed to clean air.
Measurements were taken 1 hour after the last exposure session. Endpoints measured include cotinine plasma concentrations, tail bleeding time, *in vivo* ferric chloride carotid artery injury induced thrombosis model, platelet count, *in vitro* platelet aggregation, flow cytometric analysis, and leukocyte activation. All experiments were performed at least 3 times and analysed via GraphPad PRISM software. Mann-Whitney test, ANOVA test and t tests were used to compare results. Significance accepted as $P < 0.05$.

Results: Platelets from EC exposed mice had enhanced aggregation, dense and α granule secretion, activation of GPIIb-IIIa integrin, phosphatidylserine expression, and resistant to inhibition to prostacyclin relative to clean air-exposed platelets. EC exposed mice exhibited a shorted thrombosis occlusion and bleeding time. The tail bleeding time in EC exposed mice averaged at 52 +/- 18 seconds, whereas clean air exposed mice had a tail bleeding time of 585 +/- 15 seconds.

Discussion: This study used a validated animal exposure module to investigate the impact of short-term EC exposure on platelet function. Based on the study results, authors suggest that EC exposure in mice may result in a prothrombotic phenotype. Short-term EC exposure causes a hyperactive state of platelets that are resistant to inhibition by prostacyclin, potentially elevating the risk for thrombosis. Future studies are required to determine the thrombosis risk of ECs in human subjects.

3.2.8 Richardson et al, 2021. Effects of electronic cigarette flavourants on human platelet aggregation ex vivo [30]

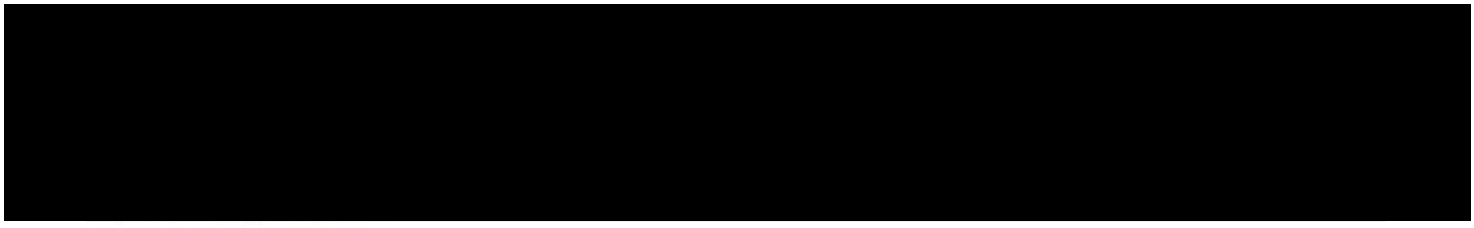
Aim: To quantify the effects of 15 common EC flavourants (benzyl alcohol, citronellol, eugenol, menthol, cinnamaldehyde, vanillin, isoamyl acetate, eucalyptol, limonene, diacetyl, menthone, methyl-butyric acid, 2,5-demethylpyrazine, acetylpyridine, and maltol) on adenosine diphosphate (ADP)-induced human platelet aggregation.

Method: Human platelets were taken from blood samples of self-reported healthy male and female volunteers at the University of Louisville Health Sciences Centre and samples were analysed within a 3-hour period of blood draw. Investigators used the Born method of turbidimetric aggregation to measure platelet aggregation. Platelet rich plasma and platelet poor plasma were pre-incubated with flavourants before stimulation with ADP. Total aggregation was defined as the final aggregation (%) at 5-minutes after ADP. P1 (%) was defined from onset of aggregation until an inflection point, P2(%) was calculated as the difference between total aggregation and P1 (Figure 9). Percentage responses for total aggregation, P1, and P2, were compared with control (ADP only) and for each flavourants, statistical analysis was done using SigmaPlot version 12 software with statistical significance accepted at P <0.05.

Figure 9. Schematic of ADP-induced phase 1 and phase 2 human platelet aggregation ex vivo. Source: Richardson et al. DOI: 10.1016/j.toxrep.2022.04.003 (accessed 12 February 2023).

Results: Eugenol was the only flavourant to have an effect on ADP-induced platelet aggregation (Table 14). Eugenol significantly decreased total aggregation resulting from the inhibition of P2 response. This result was concentration dependent and was significant even at the lowest concentration (10µM).

Table 14: Concentration-dependent effects of eugenol on ADP-induced human platelet total and biphasic aggregation ex vivo.



Discussion: Eugenol, more commonly known as clove oil, has previously been identified as a potent antithrombotic agent of platelet aggregation. Of the 15 flavourants tested in this study, eugenol proved useful as a strong positive control flavourant that directly inhibits ADP-induced platelet aggregation *ex vivo*. Given that previous studies have noted that EC exposure may increase platelet aggregation it is possible that flavourants may not be a contributing factor in platelet aggregation.

In this study, only one agonist (ADP) was used to test aggregation. Use of other agonists (thrombin, collagen, epinephrine) should be considered in future research as they may reveal other pathways of platelet aggregation. Secondly, this study only used parental compounds of flavourants. It is important to consider how flavourants undergo heating and thermal degradation when used in ECs. This could result in toxic degradation products that may influence platelet activation. To address these gaps in knowledge, further studies should be conducted to assess the effects of EC liquid excipients (including flavourants) on platelet aggregation.

3.3 International case reports

There are a small number of case reports within the literature relating to ECs and thromboembolism. These cases also mention electronic cigarette or vaping product use-associated lung injury (EVALI). EVALI is an acute or subacute respiratory illness that can be severe and life threatening. The exact pathogenesis of EVALI is unknown but the key risk factor is use of an EC or similar product. No single constituent has been identified that is common to all cases but potential toxins include tetrahydrocannabinol (THC) and vitamin E acetate [31].

3.3.1 Light et al, 2020. Unprovoked pulmonary embolism despite prophylaxis as a sequela of e-cigarette or vape-associated lung injury [32]

Authors describe a case of EVALI in a 38-year-old female with THC exposure who subsequently developed PE despite appropriate prophylaxis. The patient presented with acute shortness of breath after starting a THC-containing vape cartridge two-months prior to presentation. She had no history of thrombophilia or connective tissue disease and was physically active. EVALI was suspected based on her clinical presentation, radiographic findings, and lack of evidence of alternative eitology. She was treated with prednisone and given compression devices to prevent VTE. She re-presented two days after discharge with worsening dyspnoea and was found to have multiple subsegmental PEs requiring treatment with rivaroxaban.

The authors state that this was a unique case of acute PE in a young, ambulatory women whose only risk factor was inpatient care for EVALI. They propose that EVALI may have led to a hyperinflammatory and hypercoagulable state predisposing her to a subsequent PE.

3.3.2 Harada et al, 2021. A 20-year-old man with e-cigarette or vaping product use-associated lung injury and thrombotic coagulopathy [33]

Authors present a case of EVALI, and coagulopathy associated thrombotic events in a 20-year-old male with a history of recreation drug use. The patient presented with respiratory and gastrointestinal symptoms accompanied by a 22kg weight loss over 6 months. He used nicotine and THC based ECs and vaped multiple times per day for an 18-month period. The case met the CDC criteria for EVALI and in addition thrombi were detected in the pulmonary arteries, right saphenous vein, and right ventricle. A segmental infarct was noted in the inferior pole of the left kidney. The patient was treated with antibiotics, prednisone, and a series of anticoagulants (heparin, enoxaparin, and apixaban on discharge). Workup for genetic thrombophilia's and malignancy were unremarkable.

This case not only illustrates the adverse pulmonary effects of THC-containing ECs (stating that THC products contaminated by vitamin E acetate has been the primarily implicated cause) but also warns of the thrombogenic potential associated with EVALI. This is the second case report of post-EVALI thrombogenesis.

3.3.3 Balinski et al, 2022. Vaping-related clotting phenomena presenting as central retinal vein occlusion [34]

Authors report a case of a 23-year-old male who presented with intermittent left-sided eye pressure and vision loss. On examination, he was found to have decreased visual acuity, retinal haemorrhage, and an impending central retinal vein occlusion (CRVO) in his left eye. Past medical history included sports induced asthma and self-reported Raynaud's phenomenon. Infectious disease, autoimmune labs, and thrombophilia screening tests were normal.

Risk factors for CRVO include advanced age, diabetes, hypertension, and genetic thrombophilia disorders. Social factors including smoking and EC use should be considered as aetiologies of an underlying hypercoagulable state. In this case the patient had no significant past medical or family history but noted a four-year history of vaping. His lab findings were non-specific but diagnostic imaging demonstrated vascular changes suggestive of underlying hypercoagulability. His significant vaping history was considered the likely cause of this hypercoagulable state and resultant CRVO.

4 CARM data

CARM hold a collection of reports associated with vaping products. As of 20 January 2023, there were no cases of DVT or PE.

5 DISCUSSION AND CONCLUSIONS

New Zealand has seen a steady increase in the number of adults and adolescents who have taken up vaping, some have switched from traditional tobacco cigarettes, where others have started due to changes in societal trends and behaviours. The use of ECs and vaping are considered to be safer than TCS but this is not to say there is no risk from ECs. EVALI has accounted for numerous emergency department and hospital admissions in the United States and THC and vitamin E acetate found in ECs have been linked this disorder. There is emerging evidence relating to the risk of thrombosis associated with ECs but little is known about the long-term effects of chronic EC use, particularly in relation to thrombosis and risk of CVD. This emerging evidence was noted in a recent [redacted]

To date there are no studies that have identified a causal relationship between vaping and thrombosis. Longitudinal studies have investigated the risk if CVD and CV events in people that use electronic cigarettes but have not found an increased incidence of CV events. However, there is some literature in mice (Ramirez et al, Qasim et al) and in humans (Mohammadi et al, Benowitz et al, Nocella et al, and Kerr et al) that have noted an increase in physiological markers associated with thrombosis and CVD, such as changes in sP-selectin, brachial FMD, and NO levels, in patients who use traditional tobacco and ECs. There are several limitations to these studies, such as lack of power due to small sample size, that they are often done in an acute setting (results taken <24 hours following exposure) and therefore give no long-term information and that they study different types of ECs (nicotine content, device type). As noted by Riley et al, many studies investigating CV risk with ECs have been of poor quality with major confounders and therefore results of these studies should be interpreted with caution.

When comparing the biomarkers of thrombosis in studies, traditional TCS is associated with more detrimental results suggesting a higher risk of thrombosis compared to EC use. However, these studies do not exclude the risk of thrombosis with ECs. There is also concern that excipients found in vaping liquids could have harmful effects Very limited information is available on the safety of these excipients. Richardson et al looked at common flavourants and their effect on platelet aggregation. Only eugenol (which was included to be a strong control) demonstrated the ability to influence platelet aggregation.

In the context of women taking COCs, there is no literature that directly investigates the incidence of VTE in women who vape. The study by Theophilopoulos et al noted that although the use of ECs is widespread, it may not be well documented by healthcare professionals and therefore explaining harm associated with EC use may be lacking. All the studies in this report highlight the need for ongoing research investigating the long-term risks of EC use.

6 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the evidence suggests there is a risk of thromboembolism in people who use electronic cigarettes
- Whether there is an increased risk of VTE in women who vape and take a combined oral contraceptive
- Whether this topic needs further communication other than MARC's remarks

7 ANNEXES

Annex 1: [redacted]

Annex 2: Riley et al. study results

Annex 3: Reference articles (Carnevale et al, Mohammadi et al, Nocella et al, Riley et al)

7.1 Glossary

Term	Description
Adenosine diphosphate (ADP)	An agonist of platelet activation
Augmentation index	Indirect measure of arterial stiffness
β3 integrin	A subunit of integrins
Brachial flow-mediated dilation (FMD)	A test to measure the widening of an artery when blood flow increases in that artery. Typically used as a validated measure to quantify endothelial function.
CD36, CD55, and CD59	A leukocyte surface protein
CD40 ligand	A platelet receptor for CD40 that triggers an inflammatory and coagulation response
Cotinine	Metabolite of nicotine
Endothelial microparticles (EMPs)	EMPs are released from activated or apoptotic endothelial cells and serve as a marker of endothelial function.
Glycoprotein Ib-V-IX	A cluster of adhesive receptors on platelets. Von Willebrand factor binds to this complex
Glycoprotein VI	A collagen receptor on platelets
Interleukin 6, 8	Pro-inflammatory cytokines
Nicotinamide adenine dinucleotide phosphate oxidase (NOX)-2- peptide	NOX refers to a family of enzymes, NOX2 is expressed in platelets and expression limits platelet activation
Nitric oxide (NO)	NO is released by the endothelium and prevents platelet adhesion to the vessel wall and inhibits further recruitment of platelets to a thrombus.
Phosphatidylserine	A phospholipid component of the cell membrane, expression promotes efficient phagocytosis by macrophages
Platelet microparticles (PMPs)	Released in response to platelet activation and mediate cell communication.
Protease activated receptor 1 (PAR1)	A thrombin receptor on platelets; equivalent to Par4 on mouse platelets; activation initiates cell-signalling pathways
P-selectin	An adhesion molecule on activated platelets and endothelial cells that binds to PSGL-1 on leukocytes
P2Y1 and P2Y2	An ADP receptor on platelets
Signalling lymphocyte activation molecule	An adhesion molecule found on platelets
Reactive hyperaemia index	Non-invasive measure of endothelial function, which is correlated with cardiovascular risk factors including obesity, cholesterol, diabetes, smoking
Tissue factor	Membrane protein that initiates blood coagulation
Tissue factor pathway inhibitor (TFP)	A protein that, when bound to factor Xa blocks the activity of the tissue factor- VIIa complex
Von Willebrand factor	A plasma protein that is the carrier for factor VIII and is critical for the adhesion of platelets to the vessel wall
8-iso-prostaglandin F2a-III	Biomarker of oxidative stress

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