School of Medicine
University of Dundee

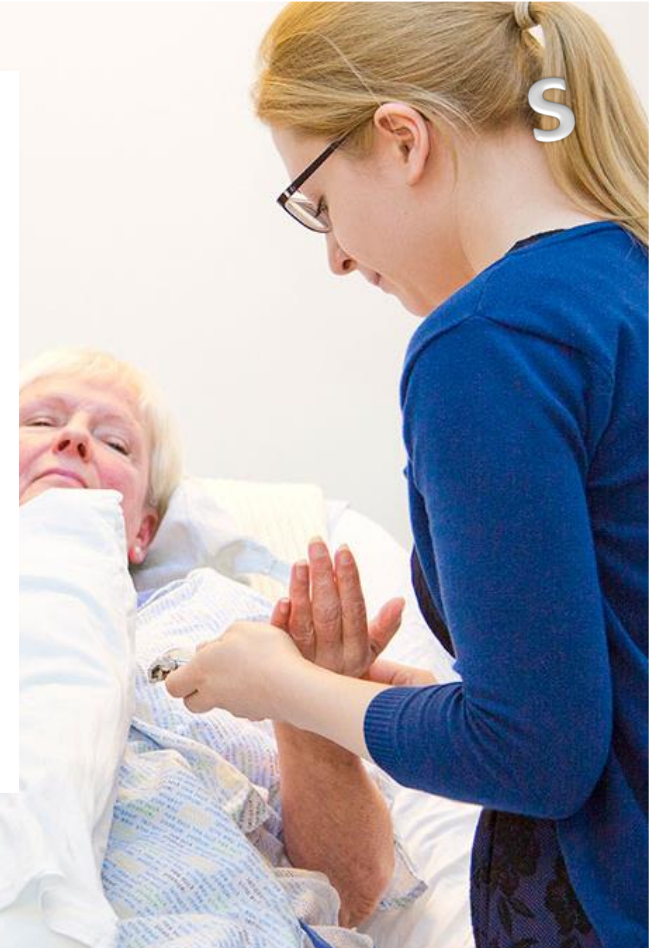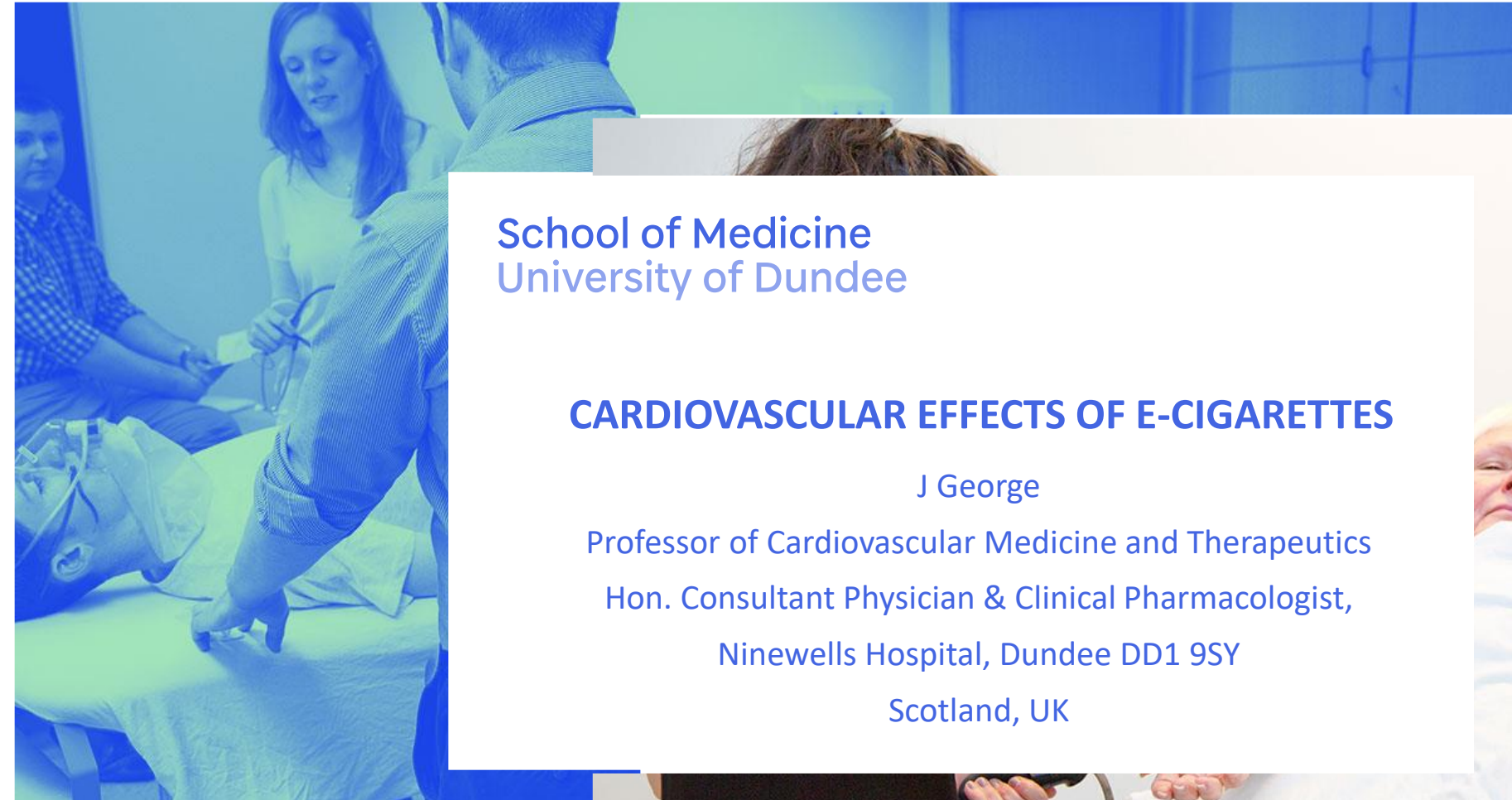## CARDIOVASCULAR EFFECTS OF E-CIGARETTES

J George

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Scotland, UK

VAPING CONFLICTS OF INTEREST

I AM INTERESTED IN IMPROVING CARDIOVASCULAR HEALTH

I HAVE NOT RECEIVED FUNDING FROM INDUSTRY FOR ANY OF MY WORK ON VAPING OR SMOKING

I HAVE NO AFFILIATIONS WITH THE VAPING OR TOBACCO INDUSTRY

I AM NOT SPEAKING ON BEHALF OF ANY ORGANISATION

General DOI

Astra Zeneca, Novartis, Daiichi Sankyo -Advisory Boards

Novartis, Daiichi Sankyo, Pfizer, Astra Zeneca- Grant, Meeting & Travel Funding

Novartis, AstraZeneca, Esperion, Sanofi- Principal Investigator

PhaserBio- Founding Clinical Advisor

Longwood, Roche, PwC- Consulting

Background

- UK fastest growing market in Europe
- Adult Prevalence 11 %- 5.6m adults
- 53% ex-smokers (peak 65% in 2021)
- 51% smokers switch because of belief "less harmful"

- More than half of ex-smokers who successfully quit in the last five years say they used a vape in their last quit attempt, which amounts to 2.7 million ex-smokers, of whom around two thirds are still vaping while around a third have quit vaping as well

- Effective in helping smokers quit (Hajek et al, Beard et al)
- Dual use most common pattern worldwide

*

Public Health Concerns

- Young people uptake exponentially increasing
- FDA largest coordinated enforcement action in history
- US National Youth Tobacco Survey: 78% increase in high school students (2017-18)
- Significantly more likely to go on to smoke TC
- 34% of adolescents in the UK have tried an e-cig
- New generation of nicotine addicts? Different device, same drug…..
- BUT..

Could it be a harms reduction measure for those who currently smoke tobacco cigarettes?

What are potential toxic effects of E-cigarettes ?

- More efficient in terms of nicotine delivery compared to tobacco cigs
- 7000+ toxicants in TC

BUT contain (low concentrations approx. 1-5% of eq TC)

- Anabasine : reduced adrenomedullary catecholamine production
- Myosamine: DNA toxic, genotoxic (pyridyloxybutylation)
- ß-Nicotyrine: Cyp 2A6 inactivator
- Nicotine itself may accelerate plaque growth (VEGF,TGF,FGF)
- Increases catecholamine release (heart rate, BP, platelets,

by binding Nicotinic Ach receptors)

- Propylene glycol to propylene oxide (Class 2B)

-but most heat not burn

Toxic compound type	Toxic compound	Concentration range cigarette	Concentration range e-cigarette
Carbonyls	Formaldehyde	7–10 μg/puff[2,32,180]	0.12–82 μg/puff[181–184]
	Acetaldehyde	50–140 μg/puff[2,32,180]	0.2–53 μg/puff[181–184]
	Acrolein	6–14 μg/puff[2,32,180]	0.12–3.3 μg/puff[181–184,187]
	Propionaldehyde	0.4–5.9 μg/puff[2,32,180]	0.057–1.79 μg/puff[181,182]
	Crotonaldehyde	1–2 μg/puff[2,32,180]	ND–0.04 μg/puff[188]
N-Nitrosamines	N′-Nitrosonornicotine (NNN)	0.5–370 ng/puff[2,32,180]	ND–0.029 ng/puff[22,183,190]
	N′-Nitrosoanabasine (NAB)	ND–15 ng/puff[2,32,180]	ND–0.01 ng/puff[22,190]
	4-(Methylnitrosamino)-1-(3-pyridyl)- 1-butanone (NNK)	1.2–77 ng/puff[2,32,180]	ND–0.019 ng/puff[22,183,190]
	N′-nitrosoanatabine (NAT)	0.8–16 ng/puff[2,32,180]	ND–0.085 ng/puff[22,190]
VOCs	Toluene	0.8–6.9 μg/puff[2,32,180]	ND–1.53 μg/puff[192]
	Benzene	0.6–4.5 μg/puff[2,32,180]	ND–0.41 μg/puff[192]
Inorganic compounds	Nickel	ND–60 ng/puff[2,32,180]	0.1–6.4 ng/puff[194]
	Cobalt	0.013–0.02 ng/puff[2,32,180]	0.05–0.58 ng/puff[196]
	Chromium	0.4–7 ng/puff[2,32,180]	0.05–9 ng/puff[194]

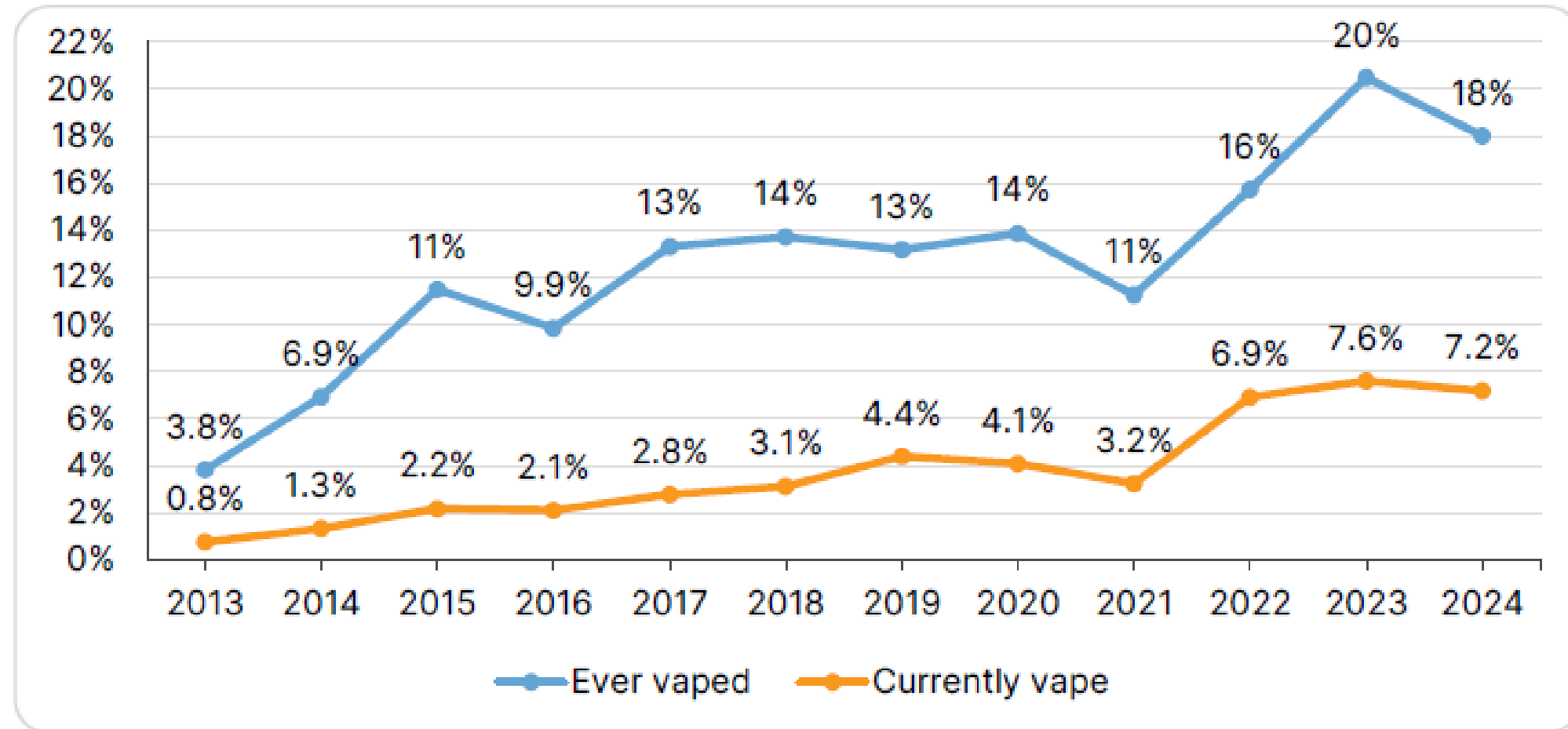Munzel et al. Nov 2020 EHJ 41(41):4057-70

Figure 1. Smoking status among current adult e-cigarette users, Great Britain (2013–2024)
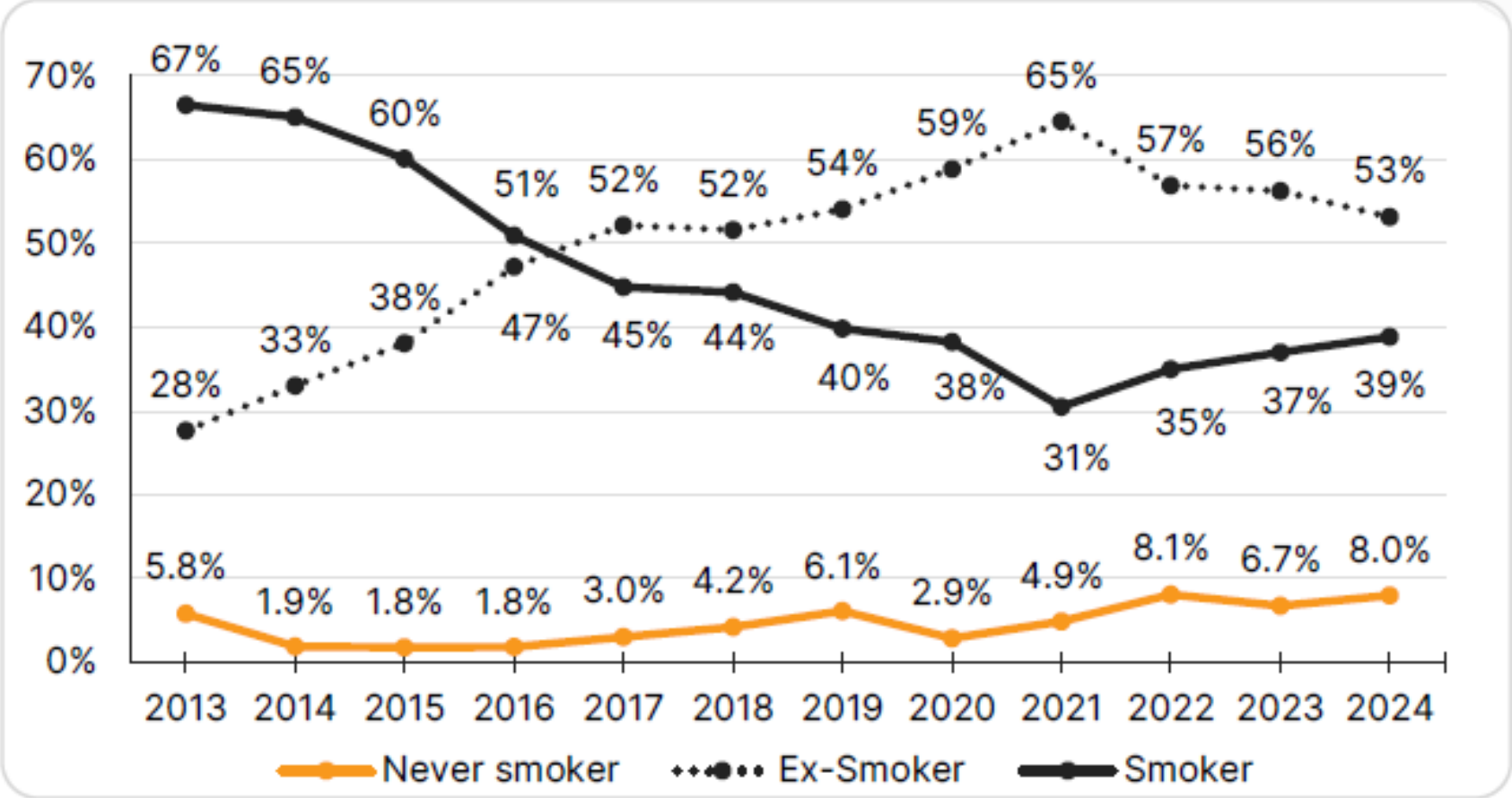
ASH Smokefree GB Adult Surveys 2013-2024. *Unweighted base: Adult current vapers (2013=325, 2014=498, 2015=614, 2016=667, 2017=669, 2018=738, 2019=854, 2020=787, 2021=826, 2022=1,089, 2023=1,079, 2024=1,408)*

Figure 1. Use of e-cigarettes by GB youth (11-17), 2013-2024

ASH Smokefree GB Youth Surveys, 2013-2024. *Unweighted base: All 11–17-year-olds (2013=1,895, 2014=1,817, 2015=1,834, 2016=1,735, 2017=2,151, 2018=1,807, 2019=1,982, 2020=2,029, 2021=2,109, 2022=2,111, 2023=2,028, 2024=2,574).*

The problem with Observational studies in Vaping…

HHS Public Access
Author manuscript
Am J Prev Med. Author manuscript; available in PMC 2019 October 01.

Published in final edited form as:
Am J Prev Med. 2018 October ; 55(4): 455–461. doi:10.1016/j.amepre.2018.05.004.

Association Between Electronic Cigarette Use and Myocardial Infarction

Talal Alzahrani, MD[1], Ivan Pena, MD[1], Nardos Temesgen, MD[1], and Stanton A. Glantz, PhD[2]

[1]Department of Medicine, George Washington University, Washington, District of Columbia;

[2]Department of Medicine, Cardiovascular Research Institute, Philip R. Lee Institute for Health Policy Studies, Center for Tobacco Control Research and Education, University of California, San Francisco, San Francisco, California

Risk of MI from traditional Cigarettes x 2.72 (2.29-3.24)

but E-Cig X 1.79 (1.20-2.60)

US National Health Interview Surveys- Alzahrani et al. Am J Prev Med. 2018 Oct;55(4):455-461

American Journal of Preventive Medicine

RESEARCH ARTICLE

Re-examining the Association Between E-Cigarette Use and Myocardial Infarction: A Cautionary Tale

Clayton R. Critcher, PhD,[1] Michael Siegel, MD, MPH[2]

- **FLAW 1 :** Vaping observational studies are never fully able to account for prior tobacco smoking
- Researcher justification: We do not need to perform this type of analysis... because we used multivariable analysis which is adjusted for confounding factors including smoking
- **FLAW 2**: These studies assume e-cigarettes and conventional cigarettes pose independent risks but
- Majority of vapers are dual users or ex-vapers*
- There is no reliable evidence that e-cigarette use is associated with ever having had a myocardial infarction among never smokers
- E-cigarette use was associated with lifetime myocardial infarction occurrence only among current or ex- smokers

- *E-cigarette evidence update – patterns and use in adults and young people – UK Health Security Agency*

CV Risk normalization post smoking cessation

Time After Quitting	Cardiovascular Risk Change
20 minutes	Heart rate drops and begins to return to normal.
12 hours	Carbon monoxide levels normalize, increasing oxygen levels.
1-2 years	Risk of coronary heart disease falls 50% with significant reductions starting.
3-6 years	Risk of coronary heart disease reduced by 50% compared to current smokers.
10-15 years	Risk approaches that of never smokers for lighter smokers; heavy smokers may take longer. **(Cancer risk falls for lung, mouth, throat and larynx by 50% at 10 years)**
15-20 years	Risk is almost the same as never smokers for most, with heavy smokers potentially needing more time.

CAVEAT: Survival bias!

VESUVIUS Trial (Vascular Effects of Smoking Usual Cigarettes Versus electronIc cigaretteS)
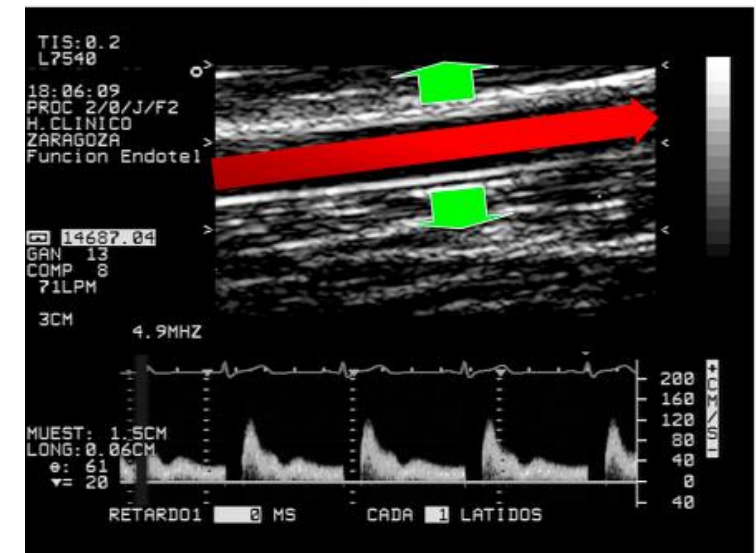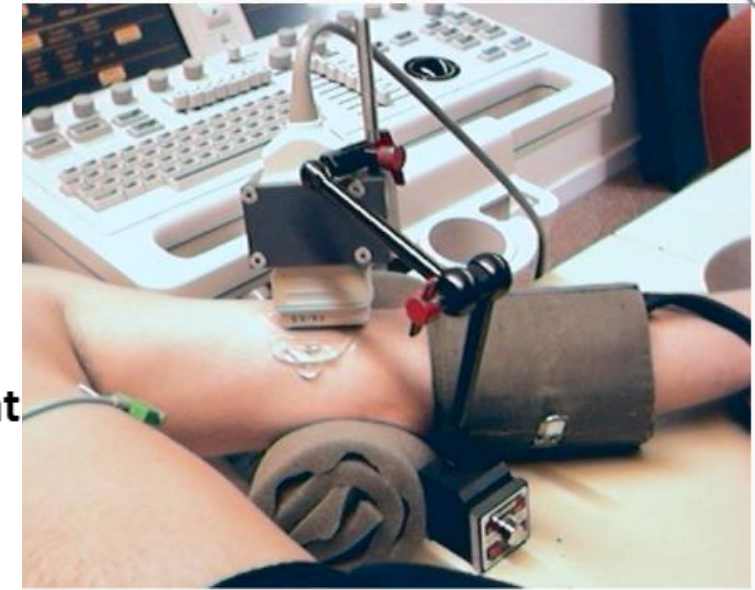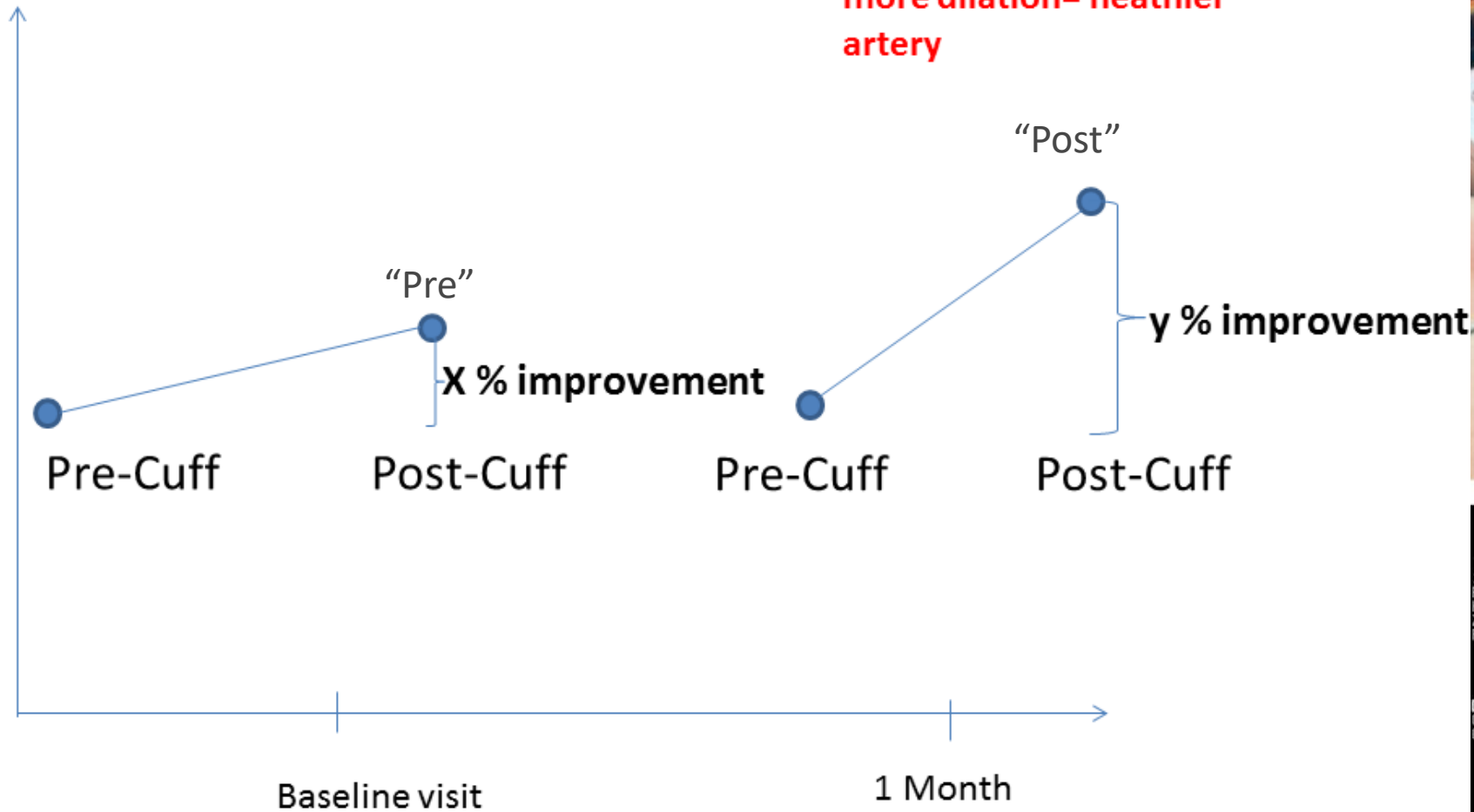
- BHF funded
- Prospective, randomised, open-labelled blinded endpoint trial with a parallel preference cohort
- Largest randomised trial on EC worldwide to-date
- Smokers aged 18 years and over who had smoked at least 15 cigarettes/day for at least 2 years and were free from established CV disease
- Randomised to e-cigarettes with nicotine (16mg), e-cigarettes without nicotine or continue tobacco cigs (parallel preference cohort)
- 1 month switch
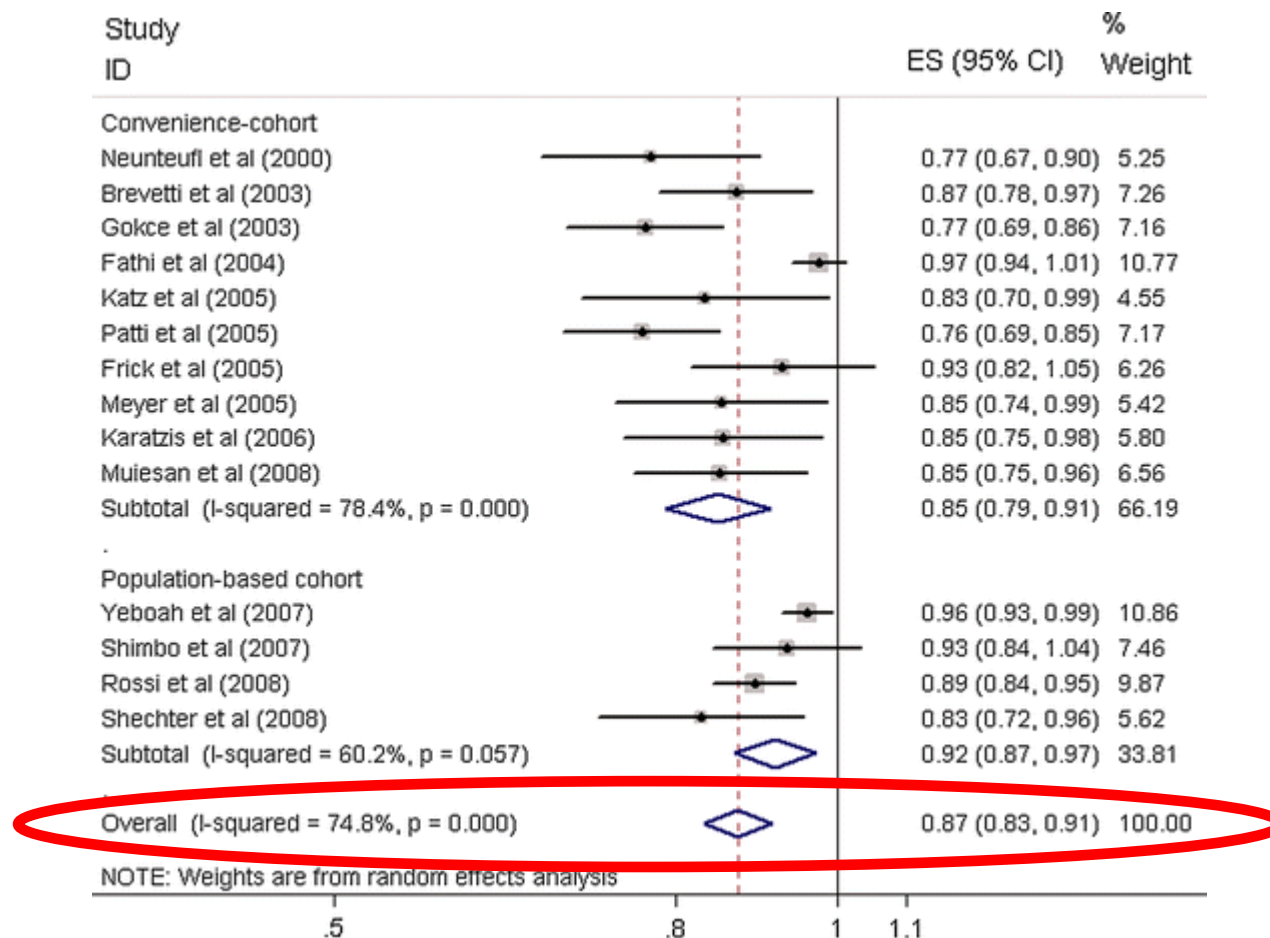- Primary Endpoint: Flow Mediated Dilatation

FMD

More Nitric Oxide= more dilation= heathier artery

"Post"

"Pre"

X % improvement

y % improvement

Pre-Cuff   Post-Cuff   Pre-Cuff   Post-Cuff

Baseline visit   1 Month

Prediction of future CV events by Flow Mediated Dilatation

Meta-Analysis (Inaba et al) Pooled relative risks for Cardiovascular events:

**1% improvement in FMD = 13% reduction in Cardiovascular events**

Inaba et al. Int J Cardiovascular Imaging Aug 2010; 26 (6):631-640

Baseline Characteristics

	Tobacco Cigarettes	E-cigarettes plus nicotine	E-cigarettes minus nicotine
N (%)	40 (35·0)	37 (32·5)	37 (32·5)
Gender- Male, n (%)	13 (32·5)	14 (37·8)	12 (33·4)
Age, mean (95%CI)	44·2 (40·4, 47·9)	48.0 (44·7, 51·3)	48·4 (43·5, 53·3)
Weekly alcohol intake (units), median (IQR)	0 (0, 11·0)	0 (0,10·0)	4.0 (0, 12·0)
BMI, mean (95%CI)	26·7 (25·0-28·5)	28·1 (25·8-30·4)	27·1 (25·4-28·8)
CO ppm, median (IQR)	12·0 (7·3, 20·8)	12·0 (7·5, 16·0)	11·0 (7·0, 14·0)
CO% COHb, median (IQR)	2·6 (1·8, 4·0)	2·6 (1·9, 3·2)	2·4 (1·8, 2·9)
Age started smoking, median (IQR)	15·0 (13·0,16·5)	14·0 (13·0,16·0)	16·0 (13·0,18·0)
Cigarettes per day, median (IQR)	20 (15,20)	18 (15,20)	18 (15,20)
Years smoked, median (IQR)	29·0 (19·5,36.5)	36·0 (25·0,41·0)	32·0 (22·0,40·0)
Pack year history, median (IQR)	25.4 (15.5,36.5)	33.3 (21.8,44.0)	27 (19·9,36·8)
Did parents smoke n (%)	No	8 (20·0)	6 (16.2)	10 (27·0)
	Yes	32 (80·0)	31 (83·8)	27(73·0)
Other smokers in the home	0	23 (57·5)	24 (64·9)	29 (78·4)
	1	15 (37·5)	13 (35·1)	8 (21·6)
	2	2 (5·0)	0	0

Primary Outcome
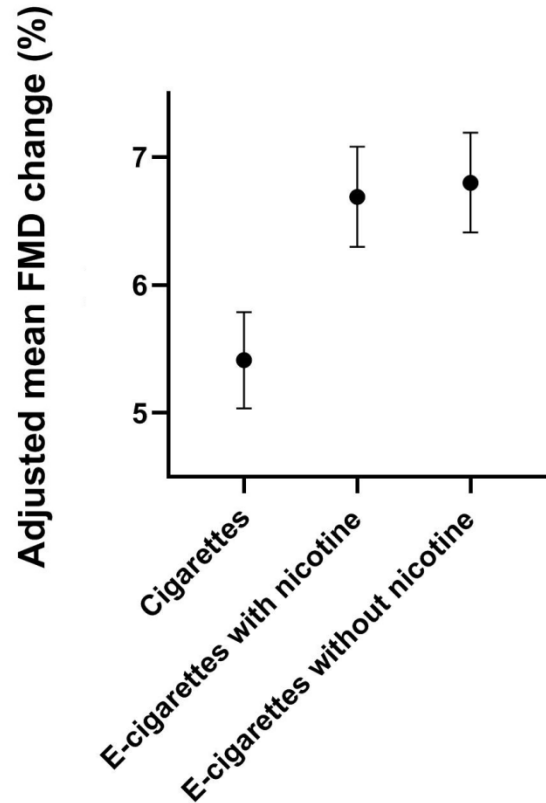
Primary Outcome*	Difference between arms in change Regression Coefficient (95% CI)	P value
Change in FMD (+1 group, 1 = TC, 2 = EC + nicotine, 3 = EC - nicotine)	0·73 (0·41, 1.05)	<0·0001
Secondary Outcomes*	Difference between arms in change Regression Coefficient (95% CI)	p-value
Change in FMD (EC without nicotine vs TC (ref))	1·52 (0·90, 2.15)	<0·0001
Change in FMD (EC with nicotine vs TC (ref))	1·44 (0·78, 2·09)	<0·0001
Change in FMD (All EC vs TC (ref))	1·49 (0·93, 2·04)	<0·0001
Change in FMD (EC without nicotine vs EC with nicotine (ref))	0·09 (-0·52, 0·69)	0·78

George et al, JACC 2019

Results In Context (vs Healthy volunteers)
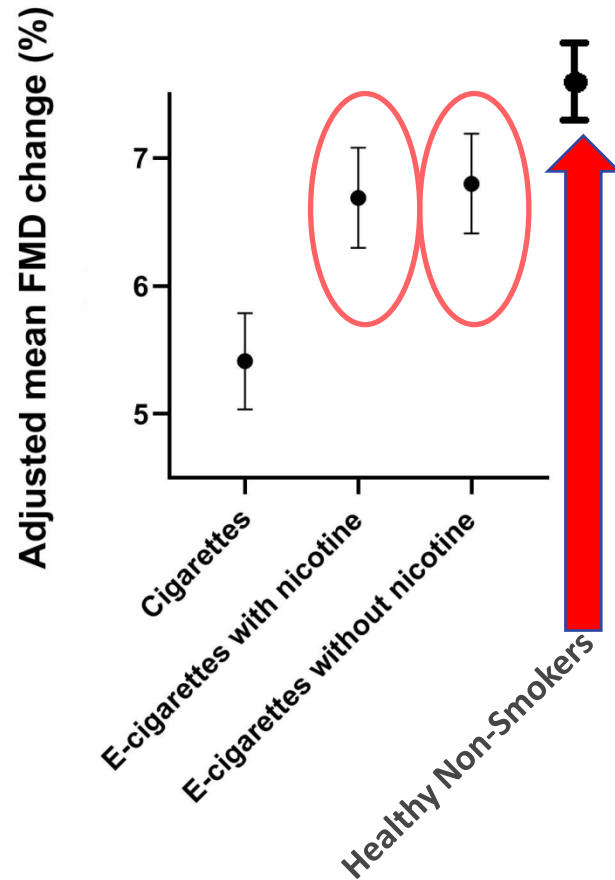
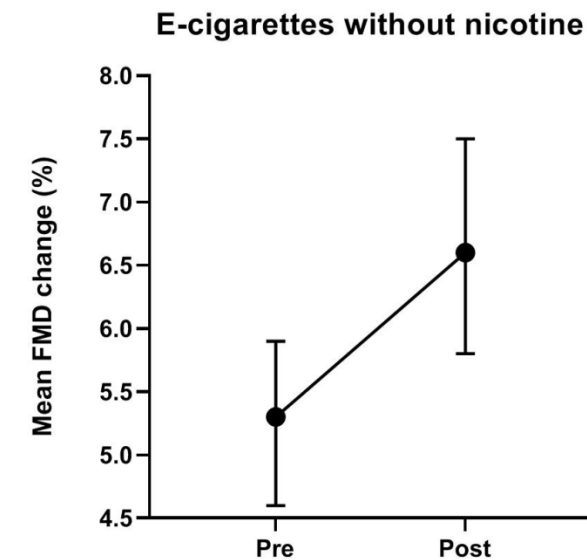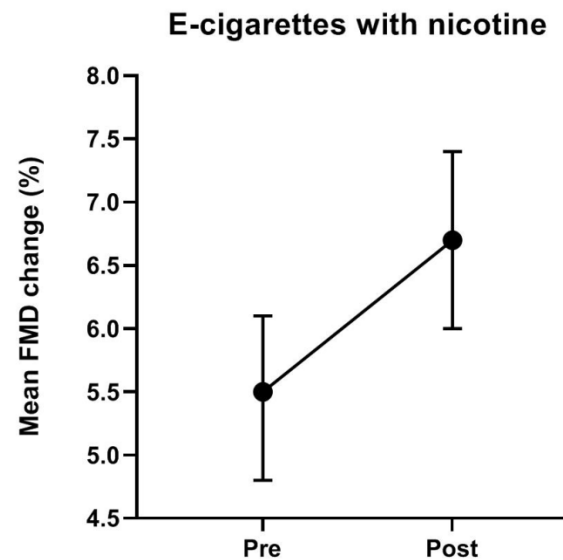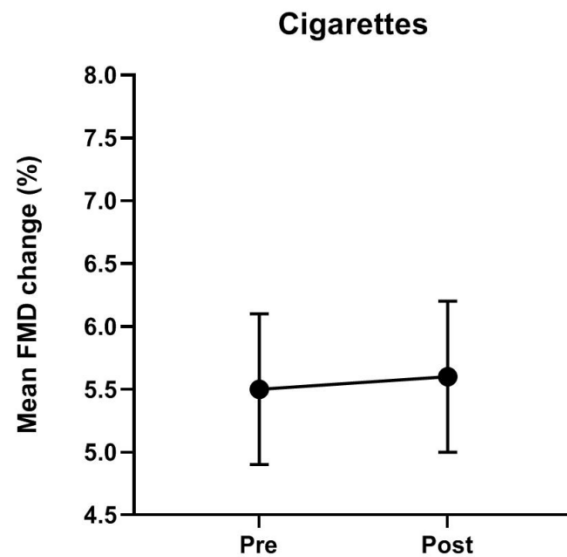**Age- and sex-matched Non-Smoking Healthy Volunteer Data mean FMD 7.7%**

Over 4 week switch, chronic smokers who:

1) Switched between TC and EC + nicotine (5.5% to 6.7%)

2) Switched between TC and EC – nicotine (5.3% to 6.6%)

Primary Outcome (Con't)

Cigarettes

E-cigarettes with nicotine

E-cigarettes without nicotine

George et al, JACC 2019 Dec 24;74(25):3112-3120

Gender differences in Primary Outcome

Primary Outcome*		Difference between arms in change Regression Coefficient (95% CI)	P value
Change in FMD (+1 group, 1 = cigarettes, 2 = e-cig + nicotine, 3 = e-cig no nicotine)	Male	0·213 (-0·248, 0·675)	0·351
	Female	1·049 (0·617, 1·480)	<0·0001
Change in FMD (EC without nicotine vs TC (ref))	Male	0·448 (-0·451, 1·347)	0·315
	Female	2·183 (1·336, 3·030)	<0·0001
Change in FMD (EC with nicotine vs TC (ref))	Male	0·822 (-0·067, 1·710)	0·069
	Female	1·824 (0·942, 2·706)	<0·0001
Change in FMD (EC without nicotine vs EC with nicotine (ref))	Male	-0·374 (-1·239, 0·492)	0·384
	Female	0·359 (-0·449, 1·167)	0·377

Effect of Compliance on Primary Outcome

	Sex	TC Mean (95%CI)	EC with nicotine Mean (95%CI)	EC without nicotine Mean (95%CI)
Low CO (0-5 ppm)	Male	0·28*	1·23 (0·02,2·44)	0·79 (0·38,1·21)
	Female	0·29*	1·58 (0·50,2·66)	2·26 (1·31,3·21)
	Both	0.29 (0.22-0.35)	1·46 (0·71,2·22)	1·74 (1·05,2·43)
Middle CO (6-11 ppm)	Male	0·17 (-0·57,0·91)	0·81 (-5·39,7·00)	-0·23 (-3·13,2·68)
	Female	-0·64 (-1·76,0·47)	0·87 (0·02,1·72)	1·43 (0·71, 2·15)
	Both	-0·32 (-1·01, 0·37)	0·86 (0·22,1·50)	1·05 (0·31, 1·79)
High CO (12-32 ppm)	Male	0·43 (-0·40,1·25)	0·83 (-0·40,2·07)	0.51 (-3·81,4·83)
	Female	0·16 (-0·30,0·62)	1·74 (-0·77,4·25)	1·55 (0·59,2·52)
	Both	0·23 (-0·14, 0·60)	1·20 (0·23,2·16)	1·11 (-0·03,2·24)

Secondary Outcomes

Secondary Outcomes*	Difference between arms in change Regression Coefficient (95% CI)	p-value
Carotid Femoral Pulse Wave Velocity	-0·167 (-0·402, 0·069)	0·164
≤20 pack years (n=27)	-0·471 (-0·834, -0·107)	0·014
>20 pack years (n=70)	+0·031 (-0·271, 0·332)	0·839
Heart Rate	-1·190 (-3·050, 0·670)	0·207
≤20 pack years (n=31)	+2·647 (0·278, 5·016)	0·030
>20 pack years (n=82)	-2·825 (-5·223, -0·426)	0·022
Augmentation Index @ 75bpm	0·112 (-1·833, 2·058)	0·909
Oxidized LDL	-1·113 (-5·458, 3·232)	0·612
High-sensitivity CRP #	0·039 (-0·221, 0·299)	0·769
Tissue Plasminogen Activator#	-0·036 (-0·123, 0·052)	0·425
Platelet Activation Inhibitor 1#	0·007 (-0·131, 0·116)	0·906
Systolic Blood pressure	-2·158 (-4·789, 0·472)	0·107
Diastolic Blood pressure	-1·126 (-2·624, 0·372)	0·139

George et al, JACC 2019

So its less harmful (NOT safe) than smoking in the healthy population....

What about advice after a heart attack?

Is it too late for smokers to switch to EC?

Would switching reduce the risk of a further heart attack?

What about Passive Exposure to Vaping?

What about news reports on EVALI?

Prognosis after switching to electronic cigarettes following percutaneous coronary intervention: a Korean nationwide study

Danbee Kang [1,2], **Ki Hong Choi** [3,*], **Hyunsoo Kim**[1], **Hyejeong Park**[1], **Jihye Heo**[1,2], **Taek Kyu Park**[3], **Joo Myung Lee** [3], **Juhee Cho** [1,2], **Jeong Hoon Yang** [3], **Joo-Yong Hahn**[3], **Seung-Hyuk Choi**[3], **Hyeon-Cheol Gwon**[3], and **Young Bin Song** [3]

[1]Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [2]Department of Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, Seoul, Republic of Korea; and [3]Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 06351, Republic of Korea

Median follow-up post PCI of 2.4 years

 During a median follow-up of 2.4 years, the cumulative incidence of MACE was lower among E-cigarette switchers (10%) or quitters (13.4%) than among continued combustible cigarette users (17%).

Multivariable-adjusted hazard ratios with 95% confidence intervals for MACE were 0.82 (0.69–0.98)(**18% risk reduction**) for switchers to E-cigarettes and 0.87 (0.79–0.96) **(13% risk reduction**) for successful quitters.

 Compared to dual users, **entirely switching to E-cigarettes was associated with a significantly lower MACE risk** (hazard ratio 0.71; 95% confidence interval 0.51–0.99) i.e. **29% risk reduction of a further event**

Effects of switching away from Tobacco (Systematic Review- *in press*)

- 23 studies , 11668 patients

- Duration of follow up 1 month -36 months

- Consistent improvements in ALL measures of vascular function (Pulse Wave Velocity, Augmentation Index, Flow Mediated Dilatation)

- Variable impact of different smoking cessation methods

- Similar effects between Varenicline (Champix®) and E-cigarettes

- Nicotine Replacement Therapy not as effective as Varenicline and E-Cigarettes for smoking cessation and longer-term abstinence

- Magnitude of Imporvement: PWV: Increase by 1 m/s corresponded to an age-, sex-, and risk factor-adjusted risk increase of 14%, 15%, and 15% in total CV events, CV mortality, and all-cause mortality, respectively

- Average of -1.1m/s reduction in PWV in healthy volunteers and -1.25m/s reduction in those with CV co-morbidities suggesting a greater gain from smoking cessation for those with established CV disease over 24 months

George et al, Eur J Prev Med 2025

Vascular effects of Passive Exposure (VAPE)

Investigating novel biomarkers in saliva and urine in 300 women and children passively exposed to smoking, vaping vs healthy volunteers

Dundee-Abertay-St Andrews collaboration
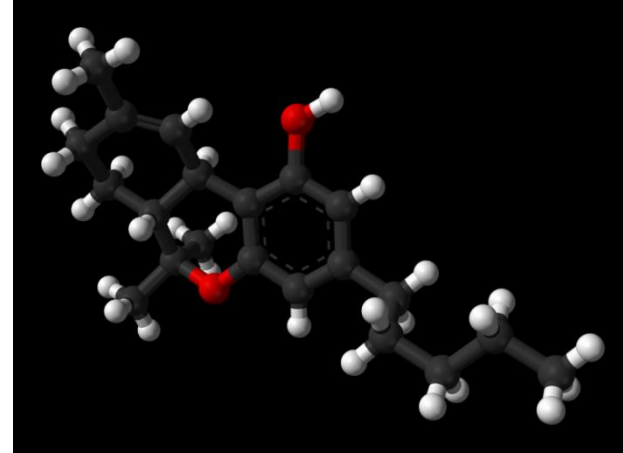
Recruiting now

https://vape-study.abertay.ac.uk/

- Approx. 1500 cases of EVALI reported to CDC (Oct 2019)

- 33 deaths in 24 states in USA

- Majority of cases – EC purchased from unlicensed sources

- **NOT** linked to nicotine containing EC

Tetrahydrocannabinol (THC)

- Lipid in cannabis for plants self-defence/insect predation/ UV light

- psychoactive substance in cannabis/marijuana

- Highly lipid soluble/ disrupts surfactant

- EC "efficient" delivery of high concentration THC directly to lungs

- 1 min CBD smoking= 90 mins of Endo dysfunction

Current Pulmonary issues (2)

Vitamin E acetate

- CDC report 8/11/19, Blount et al NEJM 19/12/19, Hartnett et al NEJM 19/12/19: **Vit E acetate - culprit agent in EVALI**

- – D and – L isomers of Vitamin E (alpha tocopherol)- unlike natural Vit E

- Synthesised from petrochemicals

- Commonly used topical agent- skin lightening, reduced scarring, wound healing

- long chain hydrocarbon with high affinity for surfactant/ disrupter

- Used as a "cutting" / adulterating agent due to cost of pure THC/CBD oil

- Used to defeat "the bubble test"

- Hypersensitivity Chemical Pneumonitis
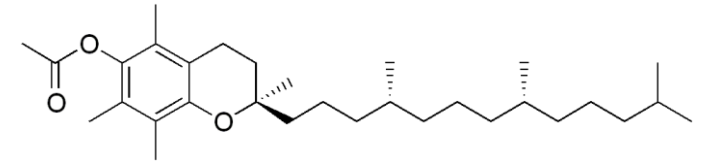
Conclusions - 1

- Early benefit to vascular function from switching from TC to EC

- Within 1 month of switching, 1·5% improvement between TC and EC without nicotine, 1·4% improvement between TC and EC with nicotine and a 1·5% improvement between TC and both EC arms combined

- (NB: Pooled adjusted relative risks of CV events was 13% lower with every 1% improvement in FMD)

- Females demonstrated greater improvement than males

George et al, JACC 2019 Dec 24;74(25):3112-3120

Conclusions -2

- Trend towards lower blood pressure in the EC arms could be important

- Vascular stiffness was also significantly reduced within 1 month of switching in smokers of ≤ 20 pack years

- Those who complied best with allocated therapy - most improvement in endothelial function

- No difference between the two EC arms (with and without nicotine) for this acute study

George et al, JACC 2019 Dec 24;74(25):3112-3120

Conclusions - 3

- Never to late to switch – CAD patients have substantially lower risk of a further CV event when switching to EC

- Tobacco avoidance is key

- It is about harms reduction for tobacco cigarette smokers

- These are unlikely to be completely safe devices and should **not** be tried by non-smokers/ young people

- **Unregulated flavouring and youth uptake are concerning issues globally**

- Evidence from VESUVIUS that they are *less harmful* than tobacco cigarettes from a cardiovascular health perspective

- Key to have nuanced legislation and not throw baby out with the bathwater

Acknowledgements

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Professor Alberto Fiore
Professor Ed Stephens

British Heart Foundation

tctu
TAYSIDE CLINICAL TRIALS UNIT

Immunoassay Biomarker Core Laboratory

DEBU
DUNDEE EPIDEMIOLOGY & BIOSTATISTICS UNIT

Abertay University

University of St Andrews

THANK YOU

j.george@dundee.ac.uk

KEY 3 POINT SUMMARY

- These are not completely safe devices and should **<u>not</u>** be tried by non-smokers/adolescents

- Evidence from VESUVIUS that they are *less harmful* than tobacco cigarettes from a vascular health perspective

- Chronic tobacco smokers, esp. women, benefit from switching to e-cigarettes from a CV perspective

Endothelial Dysfunction

- Earliest detectable change in vascular health
- Correlates with long-term Cardiovascular outcomes

FLOW MEDIATED DILATATION
- Non-invasive
- Cuff occlusion 5 mins
- NO release on reperfusion
- NO mediated (Endothelial-dependent) vasodilation
- Brachial artery diameter measured
- Performed at start (baseline) and at 1 month

PULSE WAVE VELOCITY/ Aix: Arterial Stiffness
BIOMARKERS: Ox LDL, hs-CRP, tPA, PAI-1
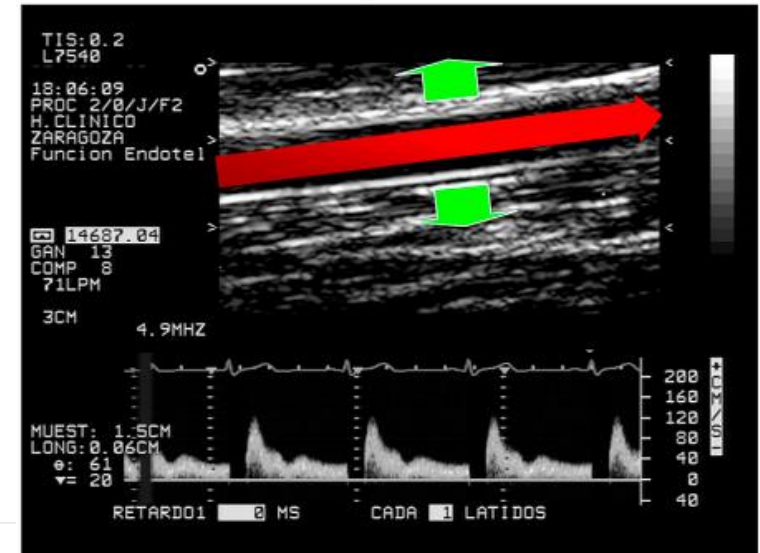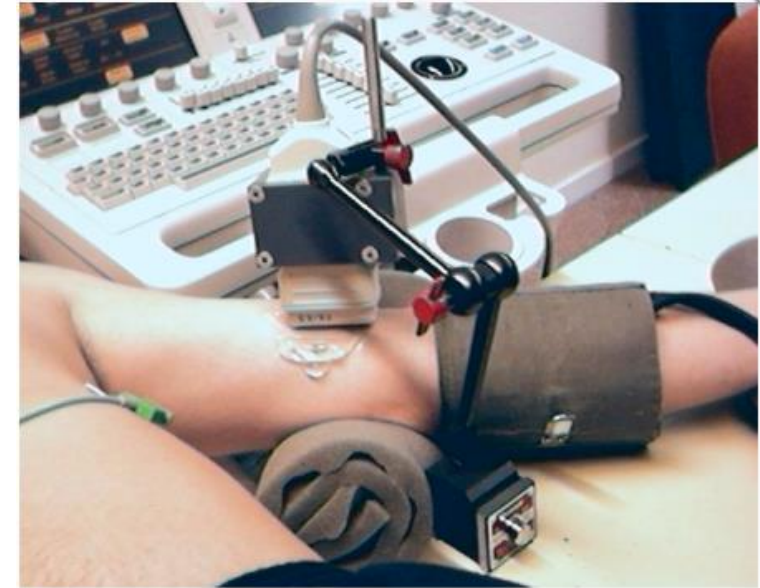
Compliance

Exhaled Carbon Monoxide

CO Levels fall when switching completely from TC to EC (Yan et al. *Regul Toxic Pharmacol* 2015)

Incentive

£40 voucher on completion of both visits

Improved completion rate from 66% to 88%

Statistical analysis

- Primary analysis: per protocol

- FMD : Multiple Linear regression on FMD at 4 weeks (covariates: Baseline FMD & treatment Grp)

- Minimisation variables: experimental group, baseline age (≤40 years; >40 years), sex (male; female) and smoking pack years (≤20 pack years; >20 pack years)

- Propensity score as adjustment covariate also

(binary outcome of randomised vs non-randomised using logistic regression)

Ingredient list of Nicotine Free E-Cig

Component	**Content（%）**
1,2-Propylene glycol	≤79.44 57-55-6
Glycerol	≤20 56-81-5
Cyclotene	≤0.55 765-70-8
8-Methyl-1,8-nonanediol	≤0.01 54725-3-4

Nicotine content

VESUVIUS- 16mg

18 mg most popular concentration for those wishing to quit smoking (Dawkins et al Addiction 2013)

Tobacco flavour most popular flavour

Max EU- 20mg

Max USA-

Impact of nicotine on CV system: activation of sympathetic NS-acute rise (caffeine effect)

Nicotine reduces coronary blood flow via stimulating alpha 1 adrenagenic receptors but increases coronary blood flow by increasing cardiac output;

Acute rises in HR and BP not seen in chronic nicotine exposure

Long term NRT does not increase CV events (Hubbard, Britton et al (Tobacco Control 2005; 14(6):416-21

Propensity Score Variables

Age, mean (95%CI)
Weekly alcohol intake (units), median (IQR)
BMI, mean (95%CI)
Employment Status, n (%)
Systolic BP (mmHg), mean (95%CI)
Diastolic BP (mmHg), mean (95%CI)
Heart Rate (bpm), mean (95%CI)
CO% COHb, median (IQR)
Oxidised LDL mU/L, median (IQR)
Hs-CRP, mg/L, median (IQR)
PAI-1, median (IQR)
t-PA, median (IQR)
Cuff change (%), mean (95% CI)
Average Integral % change, median (IQR)
AIx@75 (%), median (IQR)
Carotid femoral PWV m/s, median (IQR)
Years smoked, median (IQR)
Any previous use of e-cigarette
Other smokers in the home