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Assessing the Impact of Switching to the Tobacco Heating System on Cardiovascular Events: Translating Basic Science into Clinical Benefit

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The 6th International Conference on Prehypertension, Hypertension, Metabolic Disorders and Cardiovascular Disease
Vilnius, 3 March 2019

Cardiovascular disease (CVD) burden due to smoking

- Smoking is a well-established risk factor for CVD incidence (morbidity) and mortality.[1]
- Smoking causes ischemic heart disease, cerebrovascular disease, peripheral artery disease, and aortic aneurysm.[2]
- 40% of heart disease is attributable to smoking (population-attributable risk), compared with approximately 24% for cholesterol and 31% for diastolic blood pressure.[3]
- Tobacco smoking is the single most important preventable cause of premature mortality, and quitting smoking is the most cost-effective strategy to prevent CVD.[4]
- Physicians perceive that diabetes is the most important risk factor for coronary heart disease, followed by hypertension and raised low-density lipoprotein cholesterol.[5]

1. Burns DM. Epidemiology of smoking-induced cardiovascular disease. Prog. Cardiovasc. Dis. 46(1), 11–29 (2003).9
2. Ambrose JA et al. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol. 2004;43(10):1731-7.
3. Isles et al. Relation between coronary risk and coronary mortality in women of the Renfrew and Paisley survey: comparison with men, the Lancet, Vol 339: March 21, 1992
4. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a systematic analysis from the Global Burden of Disease Study 2015, Lancet 2017; 389: 1885–906
5. 3Hobbs FD, Erhardt L. Acceptance of guideline recommendations and perceived implementation of coronary heart disease prevention among primary care physicians in five European countries: the Reassessing European Attitudes about Cardiovascular Treatment (REACT) survey. Fam Pract. 2002 Dec;19(6):596-604.

Consumer awareness about risk of smoking

While most people are aware that tobacco use increases the risk of cancer, there are gaps in knowledge of the CVD risks of tobacco use — in many countries, these knowledge gaps are substantial:[1]

- In some countries, the percentage of adults who do not believe that smoking causes heart attacks reaches more than 60%.
- >70% of Chinese smokers, 50% of Indian smokers, and 40% of Dutch smokers are unaware that smoking causes stroke.
- In the U.K., the U.S., and Australia, nearly half of smokers are unaware that secondhand smoke causes heart attacks in non-smokers.

1. Asma S, Mackay J, Song SY, Zhao L, Morton J, Palipudi KM et al. The GATS atlas. Global Adult Tobacco Survey. Atlanta, GA: CDC Foundation; 2015

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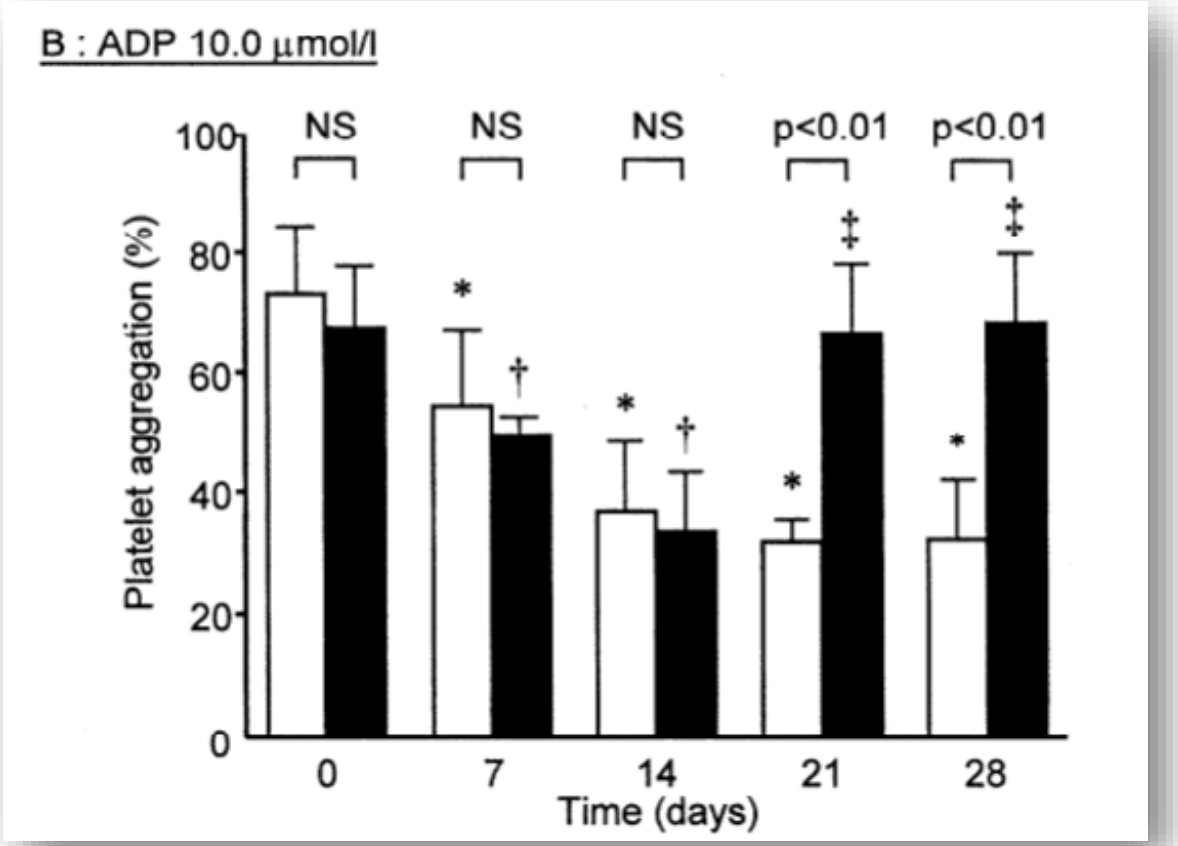
The benefits of smoking cessation

Two-week smoking cessation improves platelet dysfunction

ADP-induced platelet aggregability

Subjects who quit smoking **(open bars)**
Subjects who resumed smoking **(solid bars)**

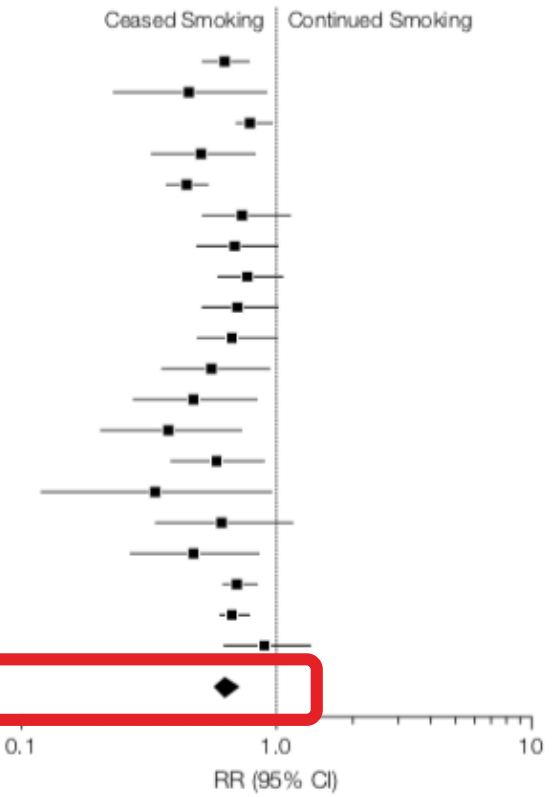


Morita H, Ikeda H, Haramaki N, Eguchi H, Imaizumi T. *J Am Coll Cardiol* 2005;45(4):589-94

Smoking cessation and mortality reduction
Systematic review of 20 studies

36% relative risk reduction

Study	Ceased Smoking: Patients, No.	Ceased Smoking: Deaths, No.	Continued Smoking: Patients, No.	Continued Smoking: Deaths, No.	Weight, %	RR (95% CI)
Aberg et al,[41] 1983	542	110	443	142	8.3	0.63 (0.51-0.79)
Baughman et al,[51] 1982	45	9	32	14	1.8	0.46 (0.23-0.92)
Bednarzewski et al,[36] 1984	455	136	555	205	9.3	0.81 (0.68-0.97)
Burr et al,[38] 1992	665	27	521	41	3.5	0.52 (0.32-0.83)
Daly et al,[43] 1983	217	80	157	129	9.0	0.45 (0.37-0.54)
Greenwood et al,[19] 1995	396	64	136	29	4.5	0.76 (0.51-1.12)
Gupta et al,[37] 1993	173	56	52	24	4.9	0.70 (0.49-1.01)
Hallstrom et al,[46] 1986	91	34	219	104	6.1	0.79 (0.58-1.06)
Hasdai et al,[42] 1997	435	41	734	97	5.2	0.71 (0.50-1.01)
Hedback et al,[52] 1993	83	31	74	40	5.2	0.69 (0.49-0.98)
Herlitz et al,[50] 1995	115	20	102	31	3.2	0.57 (0.35-0.94)
Johansson et al,[7] 1985	81	14	75	27	2.6	0.48 (0.27-0.84)
Perkins and Dick,[47] 1985	52	9	67	30	2.1	0.39 (0.20-0.74)
Salonen,[45] 1980	221	26	302	60	4.0	0.59 (0.39-0.91)
Sato et al,[8] 1992	59	5	28	7	0.9	0.34 (0.12-0.97)
Sparrow and Dawber,[48] 1978	56	10	139	40	2.3	0.62 (0.33-1.15)
Tofler et al,[49] 1993	173	14	220	37	2.5	0.48 (0.27-0.86)
Van Domburg et al,[39] 2000	238	109	318	202	9.8	0.72 (0.61-0.85)
Vlietstra et al,[40] 1986	1490	223	2675	588	10.4	0.68 (0.59-0.78)
Voors et al,[44] 1996	72	26	95	37	4.4	0.93 (0.62-1.38)
Overall	**5659**	**1044**	**6944**	**1884**	**100.0**	**0.64 (0.58-0.71)**



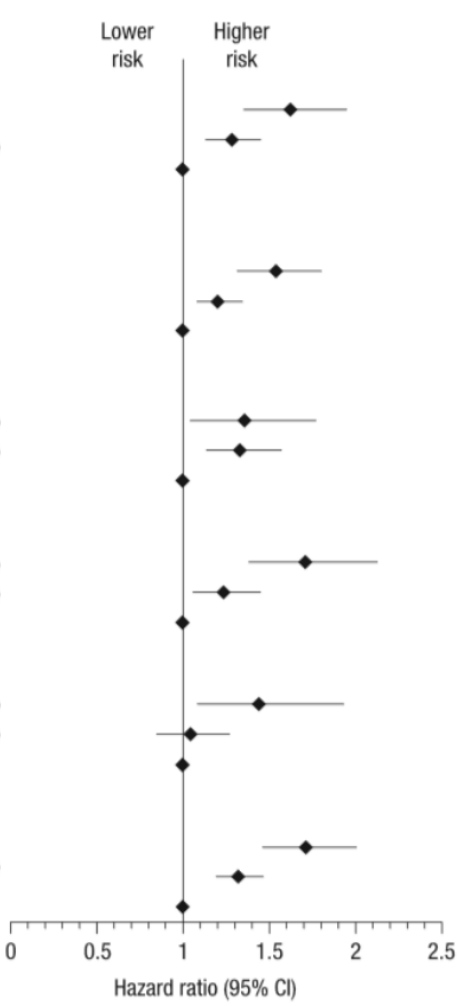
Critchley JA, Capewell S. *JAMA* 2003;290(1):86-97

Impact of smoking status on stable coronary artery disease (CAD)

"Current smokers with stable CAD have a greater risk of future CV events vs quitters."

Time to first event occuring at any point during the full follow-up (split by baseline smoking status)

Outcome by patient group	HR (95% CI)	Individual *P*-values	Overall *P*-values
CV-related death, nonfatal MI			
Current smoker	1.62 (1.35,1.94)	<0.0001	
Former smoker	1.28 (1.13, 1.45)	0.0001	
Never smoked	1.00 (-)		<0.0001
CV-related death, nonfatal MI, or stroke			
Current smoker	1.54 (1.31, 1.8)	<0.0001	
Former smoker	1.2 (1.08, 1.34)	0.0011	
Never smoked	1.00 (-)		<0.0001
CV-related death			
Current smoker	1.36 (1.04, 1.77)	0.0232	
Former smoker	1.33 (1.13, 1.57)	0.0007	
Never smoked	1.00 (-)		0.0021
MI			
Current smoker	1.71 (1.38, 2.12)	<0.0001	
Former smoker	1.24 (1.06, 1.45)	0.0082	
Never smoked	1.00 (-)		<0.0001
Stroke			
Current smoker	1.44 (1.08, 1.93)	0.0127	
Former smoker	1.04 (0.85, 1.27)	0.6981	
Never smoked	1.00 (-)		0.0335
All-cause death			
Current smoker	1.71 (1.46, 2)	<0.0001	
Former smoker	1.32 (1.19, 1.46)	<0.0001	
Never smoked	1.00 (-)		<0.0001

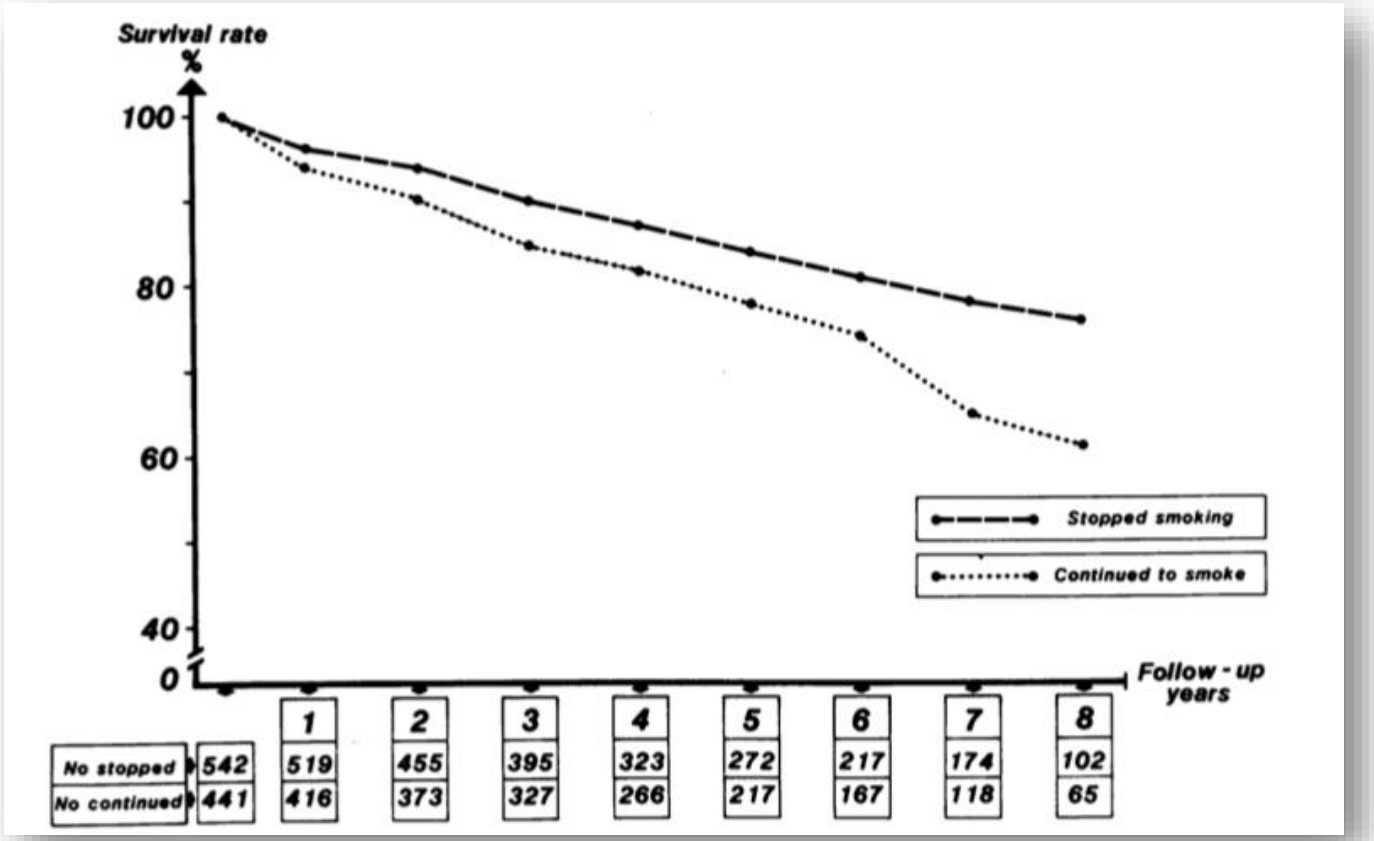


Models have been adjusted for SBP, DBP and LVEF. To maximise the data included, patients with missing LVEF have been included as a missing category, like it has been done for other abstracts. However for patients with missing vessel disease information have been excluded.

J.C. Tardif et al. ESC Congress 2016

Survival curves after myocardial infarction (MI) in relation to smoking status at three months

"Patients who stopped smoking had a **considerably** higher survival rate and lower cumulative frequency of reinfarction."



Aberg A, Bergstrand R, Johansson S, et al. *Br Heart J* 1983;49(5):416-22

Long-term outcome after successful percutaneous coronary intervention (PCI)

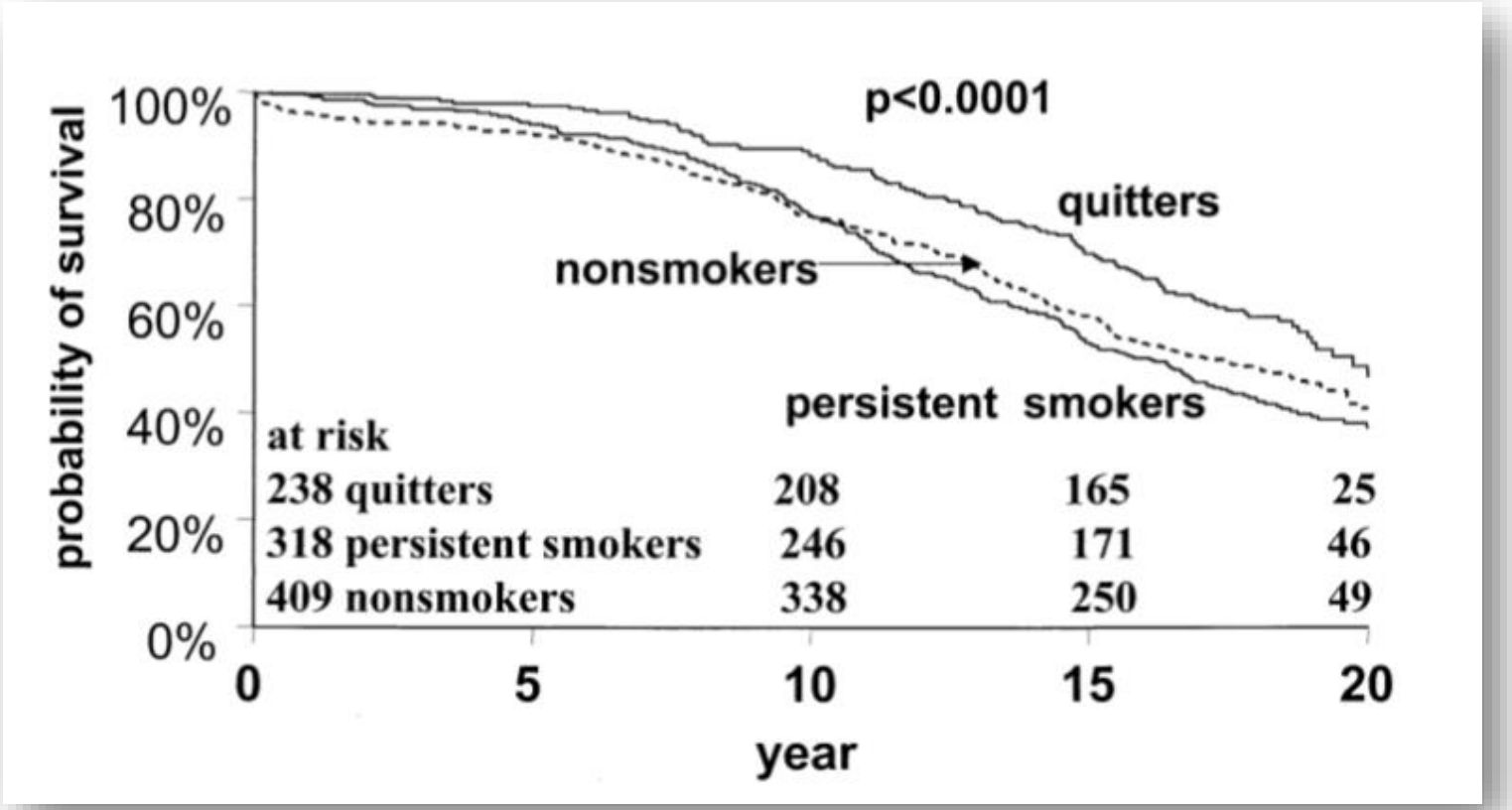
"Patients who continued to smoke after successful PCI are at greater risk for Q-wave infarction and death than non-smokers. The cessation of smoking either before or after percutaneous revascularization is beneficial."

Event	Nonsmokers (N = 2009)	Former Smokers (N = 2259)	Quitters (N = 435)	Persistent Smokers (N = 734)
Death from all causes				
No. of events	296	343	41	97
Unadjusted relative risk	1.0	1.08 (0.92–1.26)	0.56 (0.40–0.77)	0.74 (0.59–0.94)
Adjusted relative risk	1.0	1.34 (1.14–1.57)	1.21 (0.87–1.70)	1.76 (1.37–2.26)
Q-wave myocardial infarction				
No. of events	25	38	9	22
Unadjusted relative risk	1.0	1.41 (0.85–2.33)	1.49 (0.70–3.20)	2.08 (1.17–3.69)
Adjusted relative risk	1.0	1.28 (0.77–2.16)	1.44 (0.64–3.11)	2.08 (1.16–3.72)
Severe angina				
No. of events	846	886	159	307
Unadjusted relative risk	1.0	0.94 (0.86–1.04)	0.80 (0.68–0.95)	0.89 (0.78–1.02)
Adjusted relative risk	1.0	0.99 (0.90–1.09)	0.91 (0.76–1.08)	0.98 (0.86–1.12)
Repeated percutaneous procedure				
No. of events	544	572	108	167
Unadjusted relative risk	1.0	0.96 (0.85–1.08)	0.86 (0.70–1.06)	0.73 (0.61–0.87)
Adjusted relative risk	1.0	0.93 (0.83–1.05)	0.80 (0.64–0.98)	0.67 (0.56–0.81)
Coronary bypass surgery				
No. of events	324	353	62	109
Unadjusted relative risk	1.0	1.0 (0.86–1.17)	0.80 (0.61–1.05)	0.80 (0.64–0.99)
Adjusted relative risk	1.0	0.95 (0.81–1.11)	0.72 (0.54–0.95)	0.68 (0.54–0.86)

Hasdai D, et al. *N Engl J Med 1997*;336(11):755-61

Survival curves after coronary artery bypass graft (CABG)

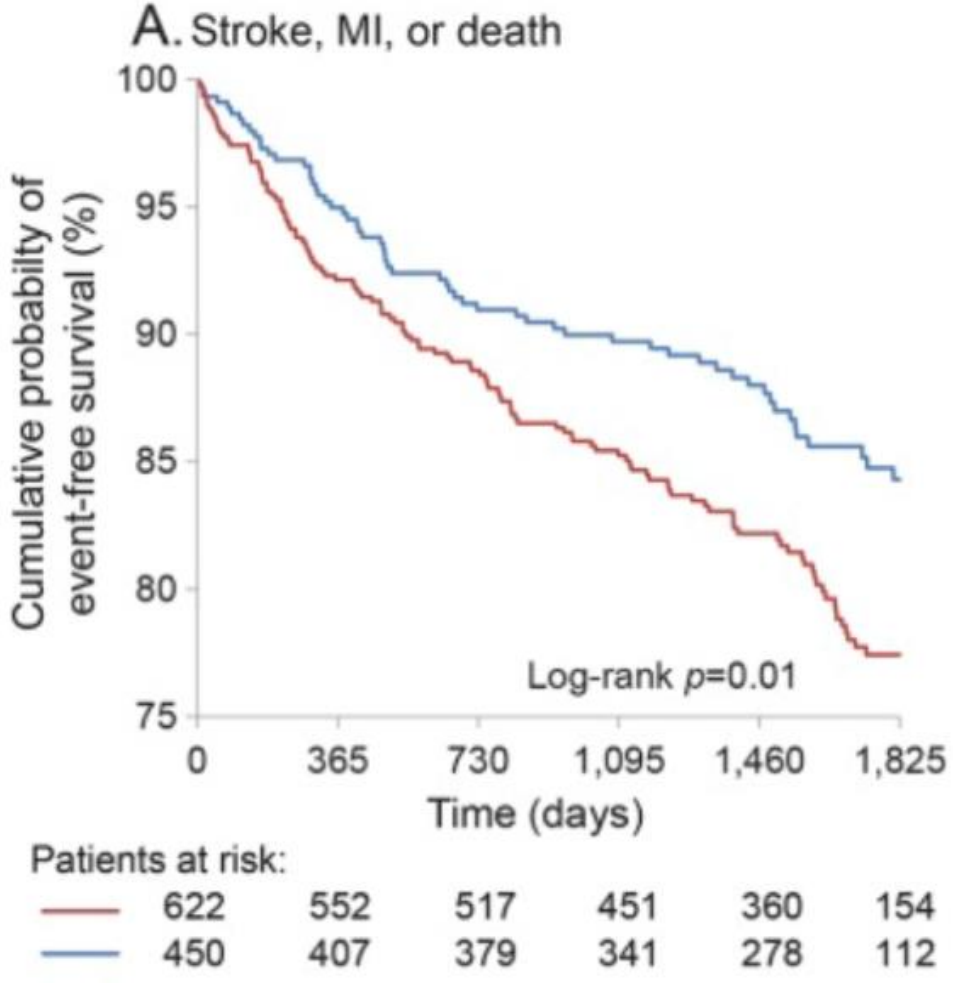
"…the risk of death from any cause was 68% greater in patients who persisted in smoking after CABG than it was in those who quit."



van Domburg RT, Meeter K, van Berkel DF, Veldkamp RF, van Herwerden LA, Bogers AJ. *J Am Coll Cardiol* 2000;36(3):878-83

Smoking cessation and outcomes after stroke or transient ischemic attack (TIA)

Relative risk reduction of CV death, MI, or stroke in quitters was 34% compared to continued smoking.



K. A. Epstein et al. for the IRIS Trial Investigators, Smoking cessation and outcome after ischemic stroke or TIA, NEUROLOGY 2017; 89 (16)

Smoking cessation and outcomes in stable peripheral arterial disease (PAD)

"Patients who quit smoking have lower mortality and improved amputation-free survival compared with patients who continue smoking."

Table IV. Unadjusted and adjusted 5-year outcomes among patients who quit smoking

	Event rate, % (95% CI)			
Outcome	*Quitters*	*Nonquitters*	*Unadjusted HR (95% CI)*	*Adjusted HR (95% CI)*[a]
Mortality	14 (7-27)	31 (23-40)	0.40 (0.18-0.90)	0.33 (0.13-0.80)
Amputation-free survival	81 (10-32)	60 (31-50)	0.43 (0.22-0.86)	0.40 (0.19-0.83)
Myocardial infarction	8 (3-20)	16 (8-31)	0.72 (0.22-2.31)	0.68 (0.20-2.30)
Stroke	2 (1-14)	5 (2-15)	0.44 (0.10-3.98)	0.58 (0.10-5.60)
Major amputation	7 (2-15)	22 (12-37)	0.38 (0.11-1.31)	0.43 (0.12-1.57)
MALE	33 (21-49)	31 (19-45)	1.40 (0.80-2.70)	1.40 (0.69-2.82)

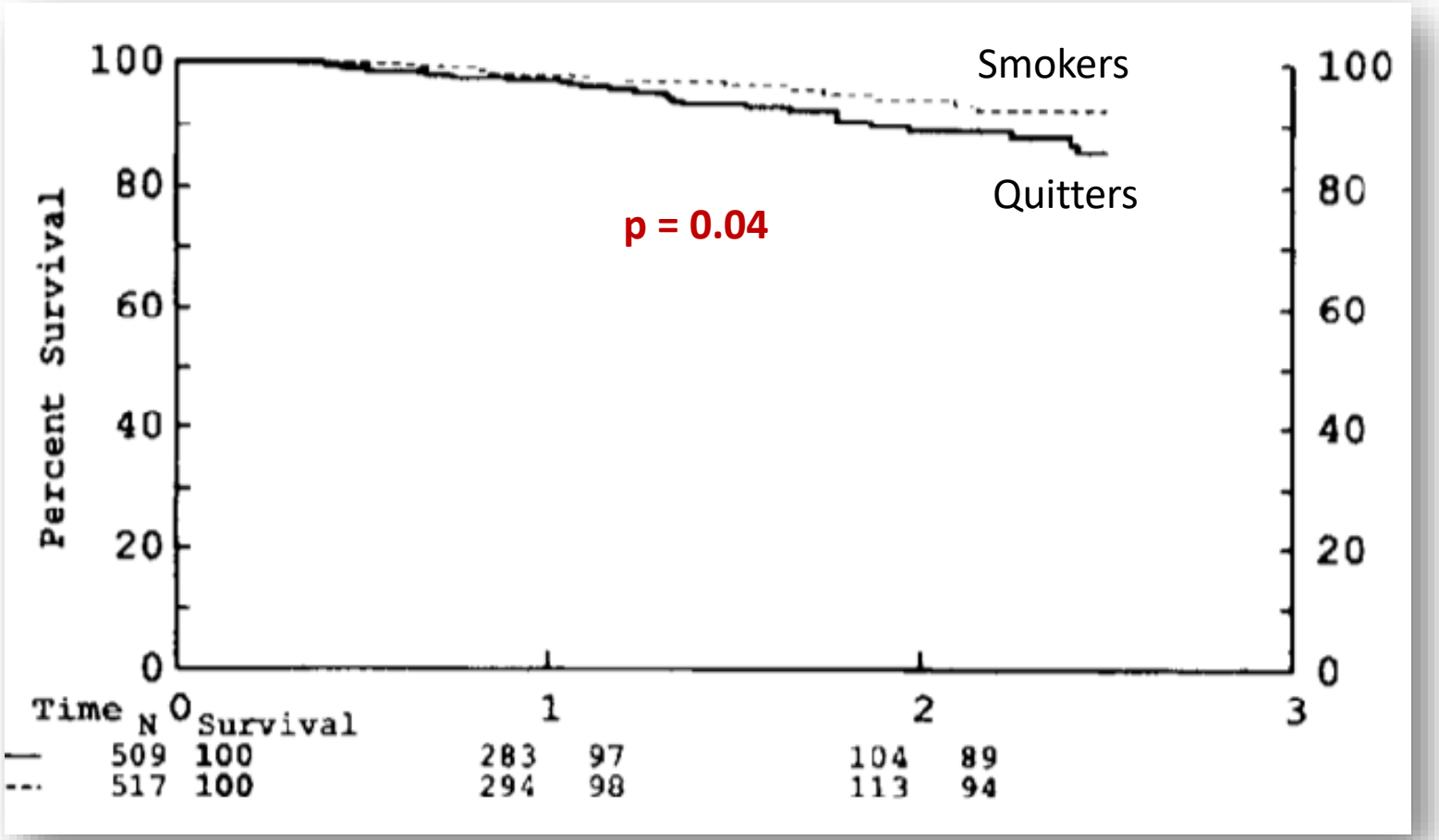
CI, Confidence interval; *HR*, hazard ratio; *MALE*, major adverse limb event.

[a]Includes adjustment for age, diabetes, coronary artery disease, prior myocardial infarction, glomerular filtration rate, prescription of statin medications, prescription of angiotensin-converting enzyme inhibitors, and prescription of β-blocker medications.

E. J. Armstrong et al. ASSOCIATION OF SMOKING CESSATION WITH DECREASED MORTALITY AND IMPROVED AMPUTATION-FREE SURVIVAL AMONG PATIENTS WITH PERIPHERAL ARTERIAL DISEASEJournal of the American College of Cardiology Volume 63, Issue 12 Supplement, April 2014

Marked reduction in arrhythmic death and overall mortality after an MI

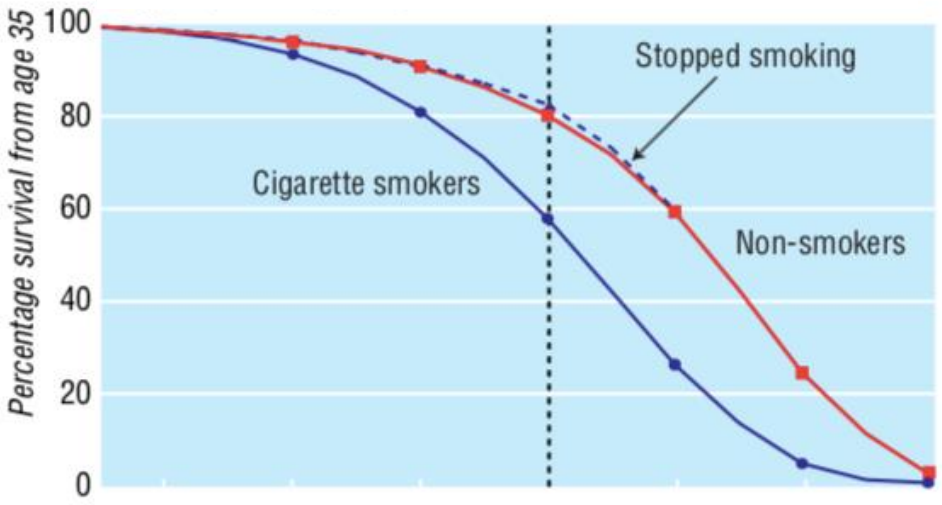
Smoking cessation: the best antiarrhythmic therapy!



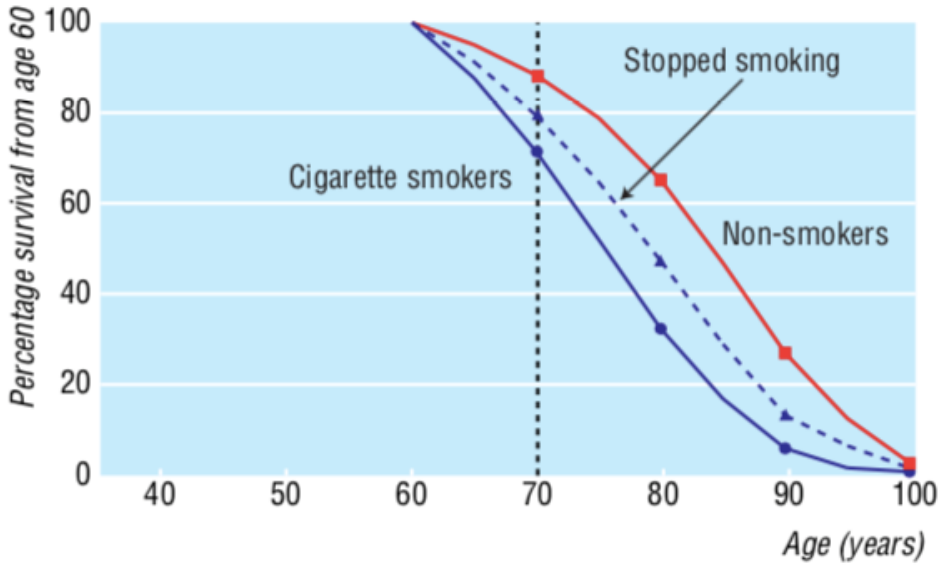
Peters RW, Brooks MM, Todd L, Liebson PR, Wilhelmsen L. *J Am Coll Cardiol* 1995;26(5):1287-92

The earlier patients quit smoking, the greater the benefit!

Stopping smoking at age 25-34



Stopping smoking at age 55-64



Doll R, Peto R, Boreham J, Sutherland I. *BMJ* 2004;328(7455):1519

Never too late to quit!

"Smoking cessation in these age groups is still beneficial in reducing the excess risk".

		Cardiovascular deaths		Acute coronary events		Stroke events	
Population	Smoking status	HR	95% CI	HR	95% CI	HR	95% CI
Men	Never smokers	1.00		1.00		1.00	
	Former smokers	1.33	1.20 to 1.48	1.18	1.00 to 1.38	1.08	0.97 to 1.21
	Current smokers	1.95	1.69 to 2.25	1.80	1.51 to 2.15	1.44	1.23 to 1.68
Women	Never smokers	1.00		1.00		1.00	
	Former smokers	1.40	1.25 to 1.57	1.24	1.07 to 1.41	1.20	1.06 to 1.36
	Current smokers	2.22	1.86 to 2.65	2.26	1.98 to 2.59	1.78	1.46 to 2.17
Age 60–69	Never smokers	1.00		1.00		1.00	
	Former smokers	1.57	1.43 to 1.72	1.25	1.10 to 1.43	1.22	1.10 to 1.35
	Current smokers	2.45	2.22 to 2.69	2.02	1.78 to 2.28	1.68	1.46 to 1.94
Age 70+	Never smokers	1.00		1.00		1.00	
	Former smokers	1.21	1.08 to 1.36	1.12	0.95 to 1.32	1.10	0.95 to 1.28
	Current smokers	1.70	1.42 to 2.04	1.88	1.41 to 2.52	1.49	1.22 to 1.82

Mons et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium, BMJ (online) 350(apr20 2):h1551 · April 2015

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Smoking cessation interventions

European Society of Cardiology Guideline recommendations

The combination of motivational support with pharmacotherapy is considered the most effective approach to help CVD patients, and non-diseased smokers, to quit smoking. [1]

Pharmacotherapies for smoking cessation recommended by clinical guidelines are nicotine replacement therapy (NRT), bupropion, and varenicline. [1]

Recommendations	Class	Level
It is recommended to identify smokers and provide repeated advice on stopping with offers to help, by the use of follow up support, nicotine replacement therapies, varenicline, and bupropion individually or in combination.	I	A
It is recommended to stop all smoking of tobacco or herbal products, as this is strongly and independently causal of CVD.	I	B
It is recommended to avoid passive smoking.	I	B

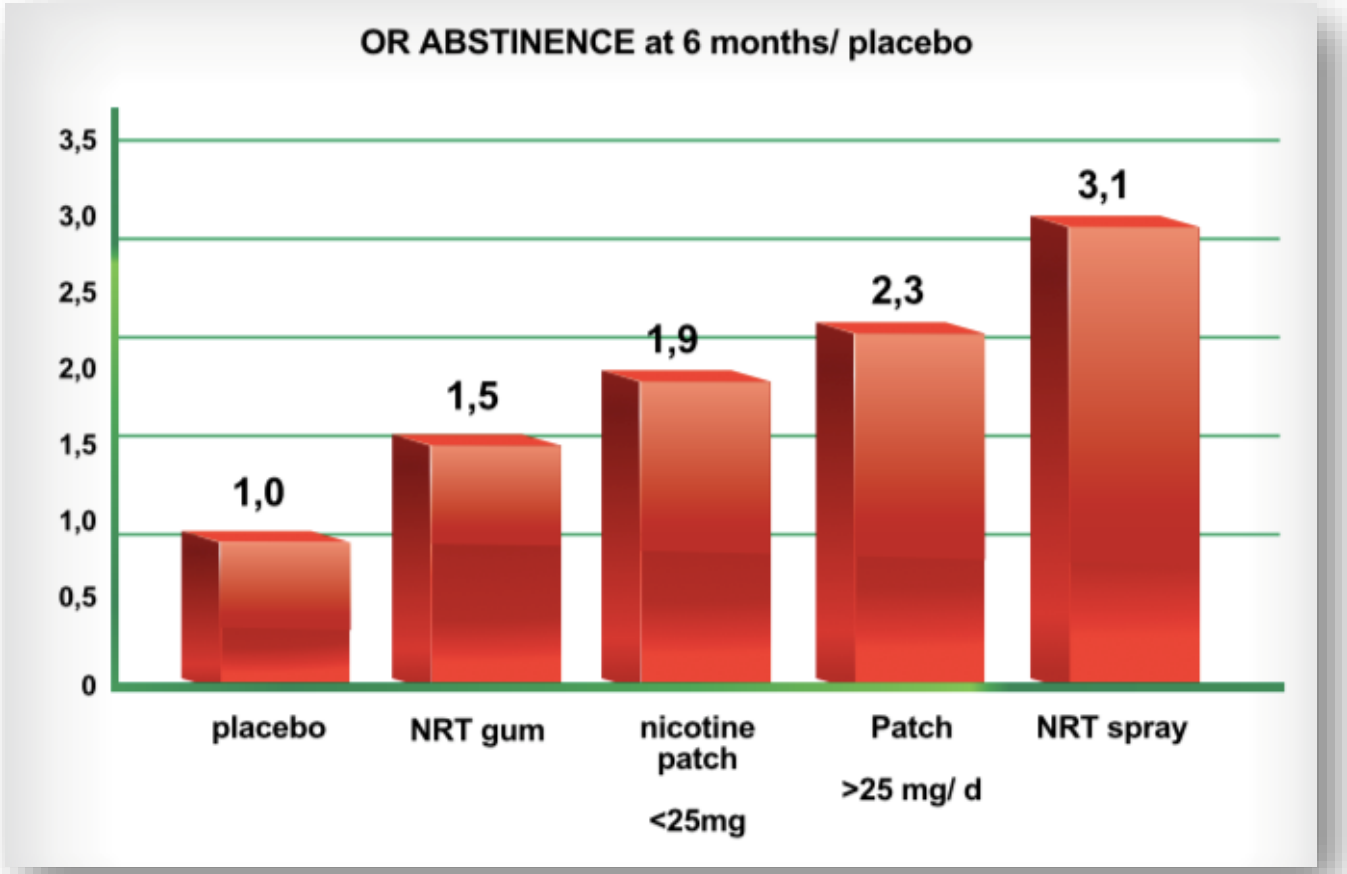
Piepoli MF et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2016;37:2315–81. doi:10.1093/eurheartj/ehw106

The five A's for smoking cessation strategy for routine practice - 2016

A–ASK:	Systematically inquire about smoking status at every opportunity.
A–ADVISE:	Unequivocally urge all smokers to quit.
A–ASSESS:	Determine the person's degree of addiction and readiness to quit.
A–ASSIST:	Agree on a smoking cessation strategy, including setting a quit date, behavioural counselling, and pharmacological support.
A–ARRANGE:	Arrange a schedule of follow-up.

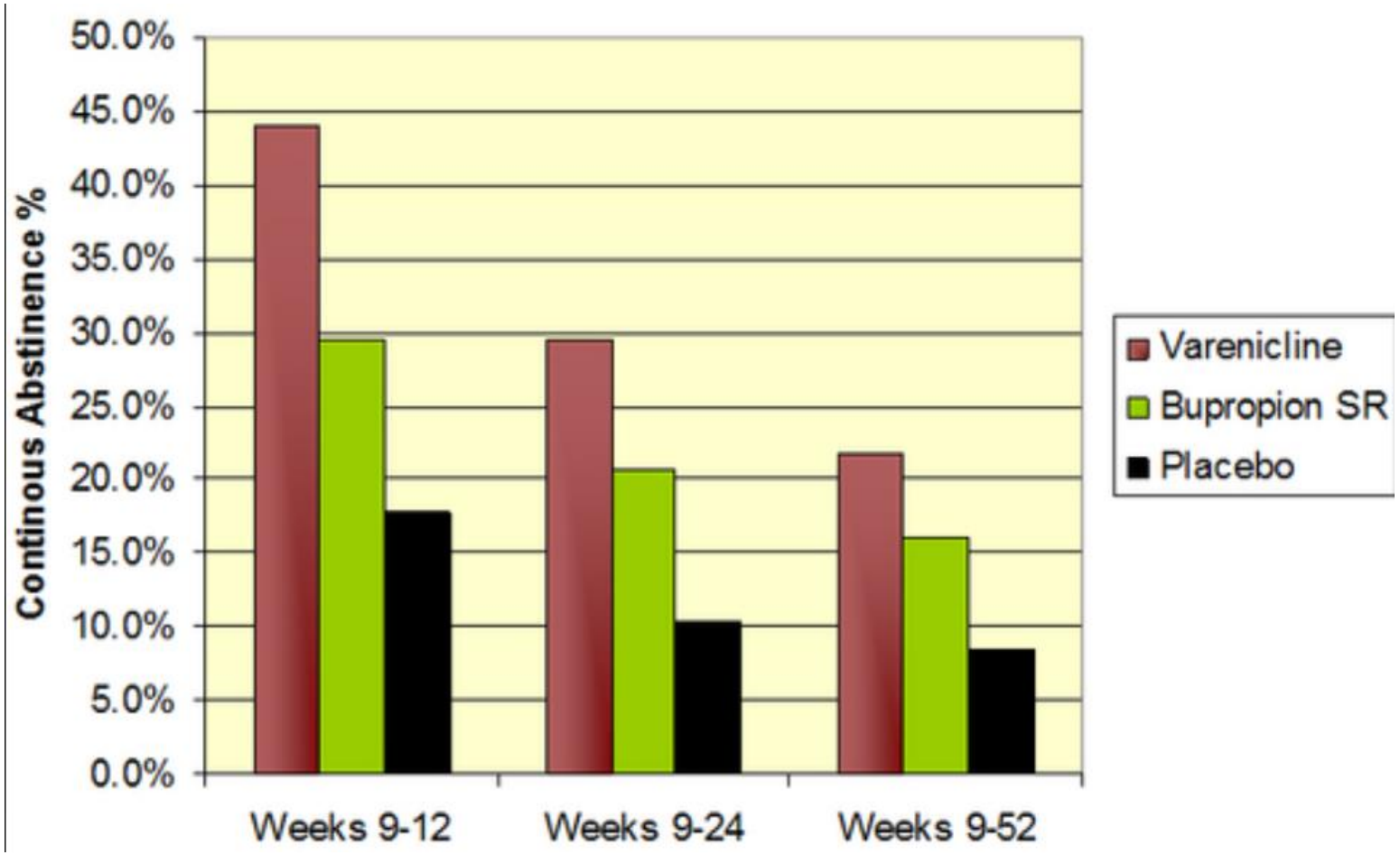
Piepoli MF et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2016;37:2315–81. doi:10.1093/eurheartj/ehw106

Six-month abstinence rates for NRT



ENSP European smoking cessation guidelines 2012 http://ensp.org/wp-content/uploads/2016/12/ENSP-ESCG_FINAL.pdf

Continuous abstinence rates on pharmacologic therapy



Gonzalez at al. 2007

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Limitations of smoking cessation interventions in clinical practice

Implementation of guideline recommendations in clinical practice

- The time spent by primary care physicians discussing risk factors and lifestyle changes or treatment is only 16.5 minutes per patient on average.[1]
- Lack of time is the main barrier to greater implementation of guideline recommendations.[1]
- In a smoking cessation audit carried out in 2016 by the British Thoracic Society among nearly 15,000 inpatients in the U.K. showed that:
  - More than one in four patients were not asked if they smoke, and
  - Nearly three out of four smokers were not asked if they would like to quit smoking
  - Of these patients, just 20% were referred to a hospital smoking cessation service

1. Hobbs FD, Erhardt L. Acceptance of guideline recommendations and perceived implementation of coronary heart disease prevention among primary care physicians in five European countries: the Reassessing European Attitudes about Cardiovascular Treatment (REACT) survey. Fam Pract. 2002 Dec;19(6):596-604.
2. British Thoracic Society 2016, British Thoracic Society Smoking Cessation Audit Report, Smoking cessation policy and practice in NHS hospitals National Audit Period: 1 April – 31 May 2016 https://www.brit-thoracic.org.uk/document-library/audit-and-quality-improvement/audit-reports/bts-smoking-cessation-audit-report-2016/ Accessed on Jan 10th 2019

Smoking cessation in CAD: persistent smokers 48.6%

- Cross-sectional study
- 7,998 patients <80 years post-CABG, PCI, acute coronary syndrome
- Interview and exam six months later

Results:

➢16.0% of patients were smoking cigarettes at time of the event

➢48.6% of those smoking at the time of the event were persistent smokers six months later

Kotseva K, Wood D, De Bacquer D, et al. *Eur J Prev Cardiol* 2016;23(6):636-48

Smoking cessation after stroke: persistent smokers 57%

- Prospective cohort of 405 stroke patients
- Educated about risk reduction during their initial recovery period
- Participants contacted at three months for a follow-up interview

Results:

➢112 were current smokers at the time of stroke

➢At three months, 57% of the baseline smokers were still smoking

Sauerbeck et al.,Smoking cessation after stroke: education and its effect on behavior. J Neurosci Nurs. 2005 Dec;37(6):316-9, 325.

Smoking cessation in PAD: persistent smokers 72%

- 1,272 patients with PAD and new or worsening claudication
- Interviews collected smoking status and cessation interventions at baseline, three, six, and 12 months

Results:

➢At 12 months, 72% of all smokers continued to smoke

Patel et al. Underutilization of Evidence-Based Smoking Cessation Support Strategies Despite High Smoking Addiction Burden in Peripheral Artery Disease Specialty Care: Insights from the International PORTRAIT Registry
Journal of the American Heart Association. 2018;7:e010076

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Electronic cigarettes

Electronic cigarettes as smoking cessation intervention

- Because of their similarity to cigarettes, e-cigarettes have the potential to target both the behavioral and physiologic components of cigarette smoking, including nicotine addiction and hand-to-mouth behavior.[1]
- A 2015 meta-analysis of randomized clinical trials involving 7,551 participants determined that e-cigarettes are effective tools for smoking cessation and reduction in the general population.[2]
- Nicotine-filled e-cigarettes were more effective for cessation than those without nicotine (pooled risk ratio 2.29, 95%CI 1.05-4.97).[2]

1. Franck C et al, *Am J Cardiol* 2018;121:1105–11
2. Rahman MA, Hann N, Wilson A, Mnatzaganian G, Worrall-Carter L. *PLoS ONE* 2015;10:E0122544

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy

Peter Hajek, Ph.D., Anna Phillips-Waller, B.Sc., Dunja Przulj, Ph.D., Francesca Pesola, Ph.D., Katie Myers Smith, D.Psych., Natalie Bisal, M.Sc., Jinshuo Li, M.Phil., Steve Parrott, M.Sc., Peter Sasieni, Ph.D., Lynne Dawkins, Ph.D., Louise Ross, Maciej Goniewicz, Ph.D., Pharm.D., Qi Wu, M.Sc., and Hayden J. McRobbie, Ph.D.

ABSTRACT

BACKGROUND

E-cigarettes are commonly used in attempts to stop smoking, but evidence is limited regarding their effectiveness as compared with that of nicotine products approved as smoking-cessation treatments.

P. Hajek et al. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy, NEJM 30 Jan 2019, DOI: 10.1056/NEJMoa1808779

The NEW ENGLAND JOURNAL of MEDICINE

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Table 2. Abstinence Rates at Different Time Points and Smoking Reduction at 52 Weeks.*

Outcome	E-Cigarettes (N=438)	Nicotine Replacement (N=446)	Primary Analysis: Relative Risk (95% CI)†	Sensitivity Analysis: Adjusted Relative Risk (95% CI)
Primary outcome: abstinence at 52 wk — no. (%)	79 (18.0)	44 (9.9)	1.83 (1.30–2.58)	1.75 (1.24–2.46)‡
Secondary outcomes				
Abstinence between wk 26 and wk 52 — no. (%)	93 (21.2)	53 (11.9)	1.79 (1.32–2.44)	1.82 (1.34–2.47)§
Abstinence at 4 wk after target quit date — no. (%)	192 (43.8)	134 (30.0)	1.45 (1.22–1.74)	1.43 (1.20–1.71)¶
Abstinence at 26 wk after target quit date — no. (%)	155 (35.4)	112 (25.1)	1.40 (1.14–1.72)	1.36 (1.15–1.67)‡
Carbon monoxide–validated reduction in smoking of ≥50% in participants without abstinence between wk 26 and wk 52 — no./total no. (%)	44/345 (12.8)	29/393 (7.4)	1.75 (1.12–2.72)	1.73 (1.11–2.69)‖

E-cigarettes are commonly used in attempts to stop smoking, but evidence is limited regarding their effectiveness as compared with that of nicotine products approved as smoking-cessation treatments.

P. Hajek et al. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy, NEJM 30 Jan 2019, DOI: 10.1056/NEJMoa1808779

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Risk-proportionate requirements for regulatory environment

The role of nicotine

"It is primarily the toxins and carcinogens in tobacco smoke – not the nicotine – that cause illness and death."

-NICE Public Health Guidance: Tobacco: Harm Reduction Approaches to Smoking (2013)

Nicotine, though addictive and not risk-free, is not the primary cause of smoking-related diseases

"Nicotine is the core of the problem but also the centerpiece of the solution."

Mitch Zeller, director of US FDA's Center for Tobacco Products; Presentation at Food and Drug law Institute Conference (Washington 26 October 2017)

"Nicotine is the very same compound FDA has approved for over 30 years as a safe and effective medication. People are dying from the tobacco-related diseases from the smoke particles, not the nicotine… Can we start to take a different look at this?"

Mitch Zeller, Director of US FDA's Center for Tobacco Products; Presentation at Legacy Foundation

Public Health England · FDA · Royal College of Physicians · NICE National Institute for Health and Care Excellence

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National Institute for Health and Care Excellence Guidelines on e-cigarettes

For people who smoke and who are using, or are interested in using, a nicotine-containing e-cigarette on general sale to quit smoking, explain that:

- Although these products are not licensed medicines, they are regulated by the Tobacco and Related Products Regulations 2016
- Many people have found them helpful to quit smoking cigarettes
- People using e-cigarettes should stop smoking tobacco completely, because any smoking is harmful
- The evidence suggests that e-cigarettes are substantially less harmful to health than smoking but are not risk-free
- The evidence in this area is still developing, including evidence on the long-term health impact

https://www.nice.org.uk/guidance/ng92/chapter/Recommendations#advice-on-ecigarettes

U.K. House of Commons Science and Technology Committee Report 2018

- E-cigarettes present an opportunity to significantly accelerate already declining smoking rates.
- E-cigarettes should not be treated in the same way as conventional cigarettes.
- The U.K. government should continue to review the evidence on the health effects of e-cigarettes annually and extend that review to heat-not-burn products.
- The committee required that there should be a shift to a more risk-proportionate regulatory environment, where regulations, advertising rules, and tax duties reflect the evidence of the relative harms of the various e-cigarettes, heat-not-burn products, and other tobacco products available.

House of Commons Science and Technology Committee E-cigarettes, Seventh Report of Session 2017–19 Report, Ordered by the House of Commons to be printed 16 July 2018
https://www.parliament.uk/business/committees/committees-a-z/commons-select/science-and-technology-committee/news-parliament-2017/e-cigarettes-report-publication-17-19/

Public Health England

Protecting and improving the nation's health

Underpinning evidence for the estimate that e-cigarette use is around 95% safer than smoking: authors' note

The estimate that e-cigarette use is around 95% safer than smoking is based on the facts that:

- the constituents of cigarette smoke that harm health – including carcinogens – are either absent in e-cigarette vapour or, if present, they are mostly at levels much below 5% of smoking doses (mostly below 1% and far below safety limits for occupational exposure)
- the main chemicals present in e-cigarettes only have not been associated with any serious risk

Our review[i] aimed to assess whether studies that have recently been widely reported as raising new alarming concerns on the risks of e-cigarettes changed the conclusions of the previous independent review (Britton and Bogdanovica, 2014) and other reassuring reviews.

We concluded that these new studies do not in fact demonstrate substantial new risks and that the previous estimate by an international expert panel (Nutt et al, 2014) endorsed in an expert review (West et al, 2014) that e-cigarette use is around 95% safer than smoking, remains valid as the current best estimate based on the peer-reviewed literature.

Mc Neill et al. E-cigarettes : an evidence upadte
Public health England 2015

Public Health England

Protecting and improving the nation's health

Vaping in England: an evidence update February 2019

A report commissioned by Public Health England

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/781748/Vaping_in_England_an_evidence_update_February_2019.pdf

Public Health England

Protecting and improving the nation's health

Implications

Overall, England continues to take small progressive steps towards ensuring vaping remains an accessible and appealing alternative to smoking.

Smokers should be advised to stop smoking as soon as possible and explore all available options for support, including EC.

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/781748/Vaping_in_England_an_evidence_update_February_2019.pdf

Emerging smoke-free regulatory trends

FDA

*"…**new product innovations** could make a lot of sense and **help people transfer off cigarettes**"*

- Scott Gottlieb, Commissioner Food & Drug Administration

Public Health England

*"help people to quit smoking by **permitting innovative technologies that minimise the risk of harm**" / "maximise the availability of safer alternatives to smoking"*

Ministry of Health

*"**heat-not-burn**, snus, moist snuff, dissolvable and inhaled nicotine **may be significantly safer than cigarettes**."*

- Nicky Wagner, Associate Health Minister

A growing number of countries are recognizing the benefit of novel smoke-free products

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. ■, NO. ■, 2018

PUBLISHED BY ELSEVIER

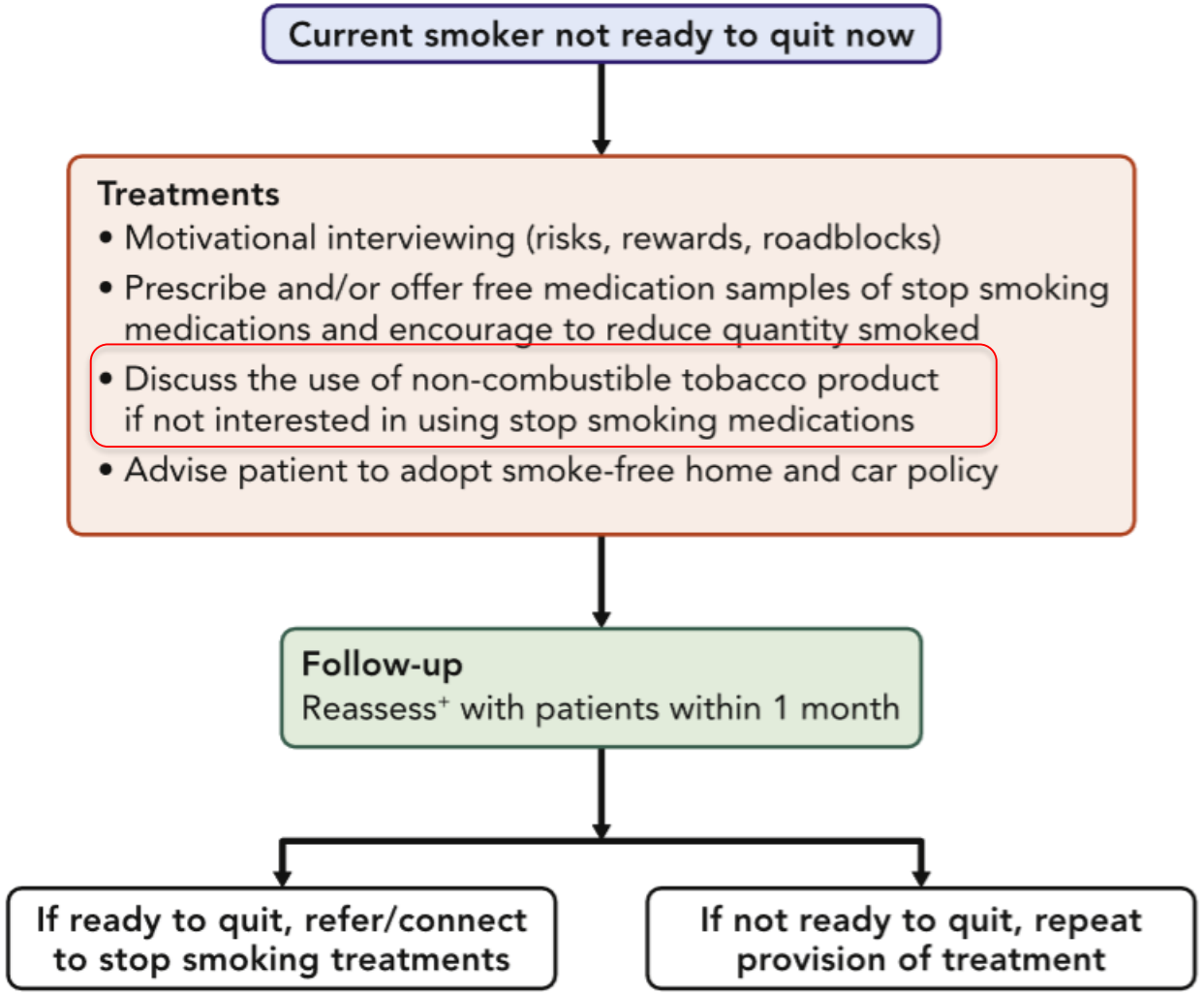
EXPERT CONSENSUS DECISION PATHWAY

2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment

A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents

Rajat S. Barua et al. 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents, Journal of the American College of Cardiology Volume 72, Issue 25, December 2018

FIGURE 3 Algorithm for Patients Not Ready to Quit



+ Reassess by connecting with the patient within ~ 1 month through the following: face-to-face contact during an office visit, sending MyChart query, e-mail or text message, or calling the patient on the phone.

Rajat S. Barua et al. 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents, Journal of the American College of Cardiology Volume 72, Issue 25, December 2018

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Tobacco Harm Reduction

Creating a New Category: Reduced-Risk Products

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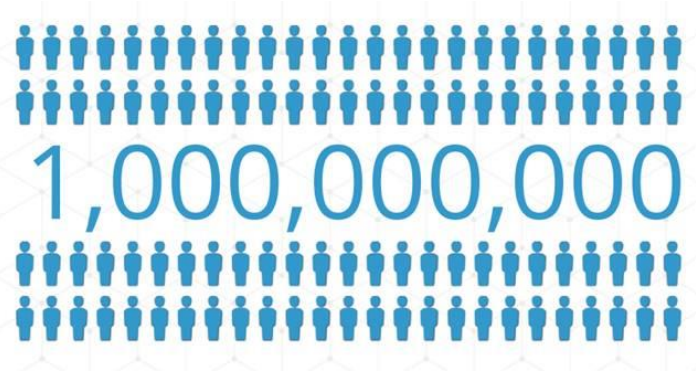
Reduced-Risk Products ("RRPs") is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking.

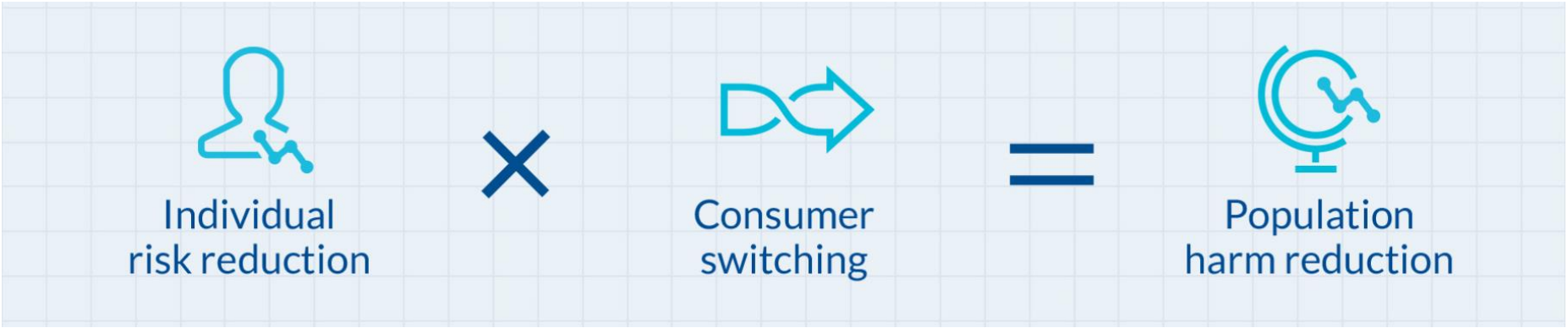
We have a range of RRPs in various stages of development, scientific assessment, and commercialization.

Because our RRPs do not burn tobacco, they produce far lower quantities of harmful and potentially harmful compounds than found in cigarette smoke.

What Is the objective of Tobacco Harm Reduction?

- Smoking is addictive and causes a number of serious diseases
- Worldwide, it is estimated that more than **1 billion people** will continue to smoke in the foreseeable future*
- Offering smoke-free alternatives to adult smokers is a sensible, complementary addition to existing tobacco control strategies





Successful harm reduction requires that current adult smokers be offered a range of Reduced-Risk Products they can fully switch to, should they decide not to quit.

* http://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index4.html
Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013)
Note: Reduced Risk Products ("RRPs") is the term PMI uses to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switched to these products versus continued smoking.

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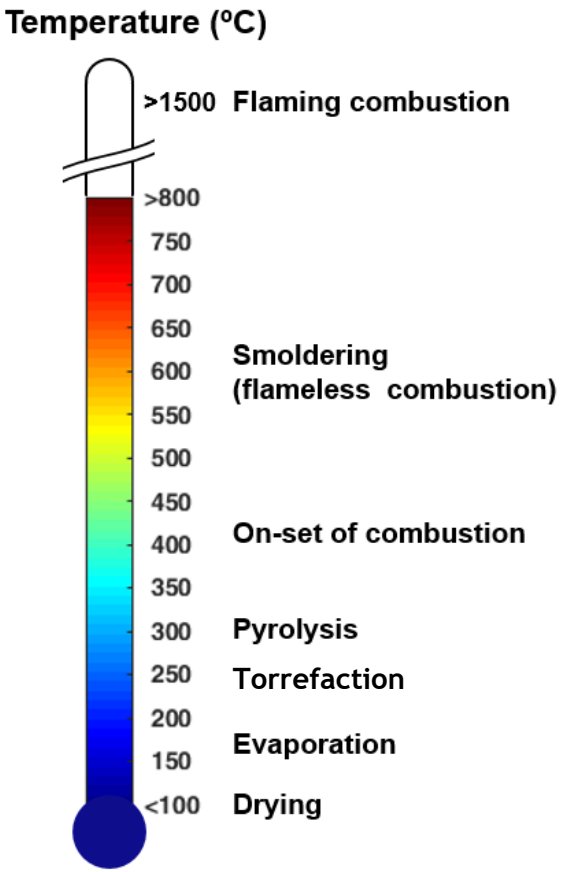
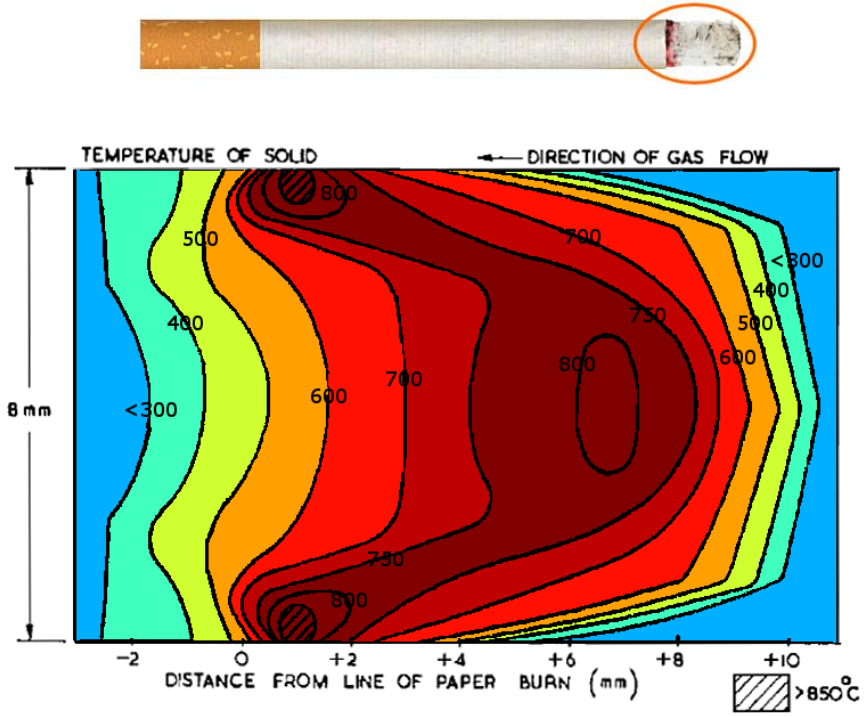
Combustion

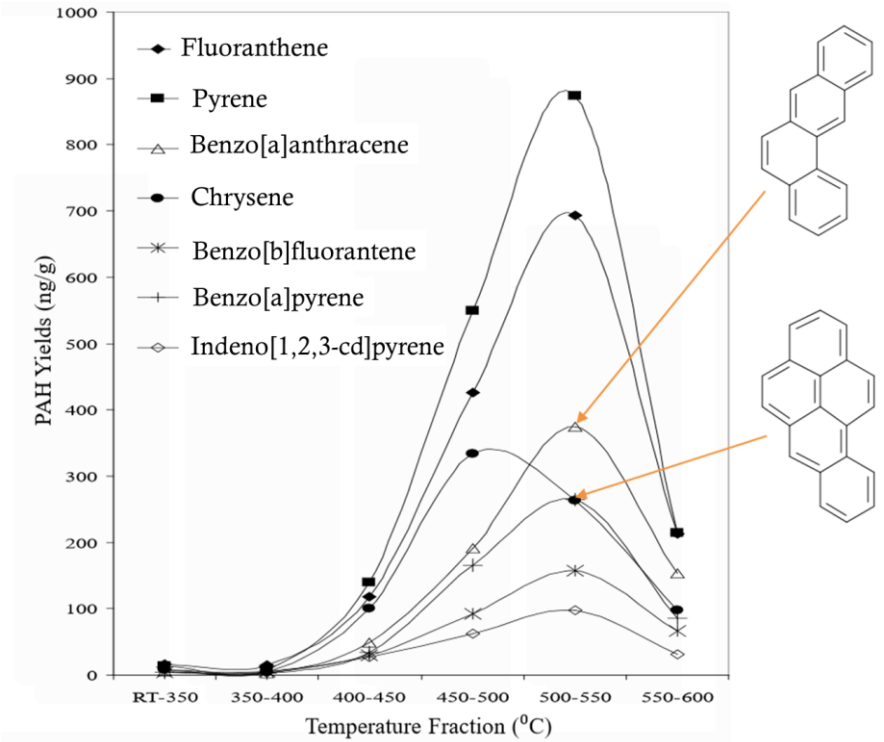
Elimination of combustion is key

Scientific studies have shown that as the temperature of tobacco increases, the levels of harmful chemicals formed increase





Source: Baker R. R., 1975, Temperature variation within a cigarette combustion coal during the smoking cycle, High Temp. Sci., 7, 236-247. Coloration by PMI.



Source: McGrath, T.E., Wooten, J.B., Chan W.G. and Hajaligol, M.R., 2007, Formation of polycyclic Aromatic Hydrocarbons from Tobacco: the "Link" between Low Temperature Residual Solid and PAH Formation, Food and Chemical Toxicology, 45,6,1039-1050

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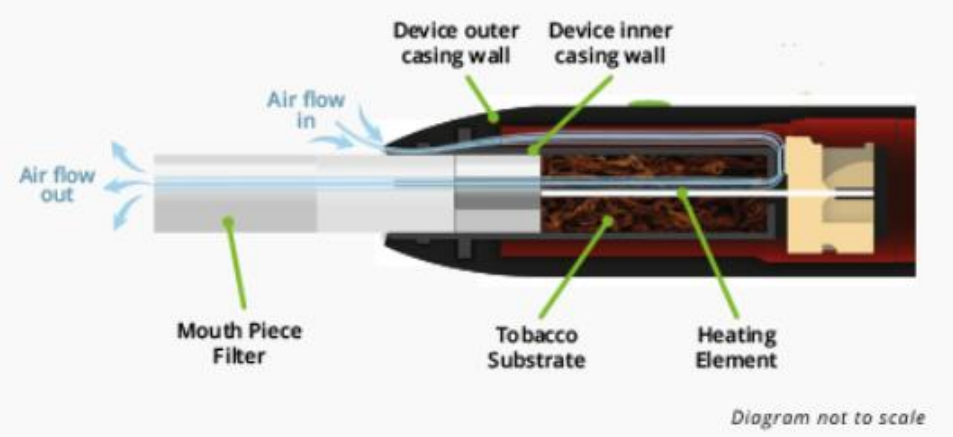
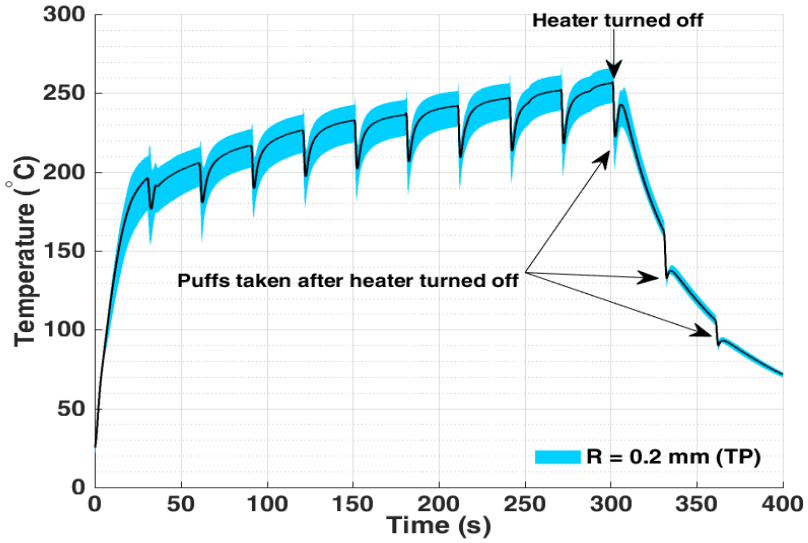
The Tobacco Heating System 2.2

Why heat tobacco rather than burn it?

The Tobacco Heating System (THS) (currently commercialized as *IQOS* in >40 countries) is designed and has been demonstrated to:

- Heat tobacco <u>without</u> combustion
- Preserve elements of the taste, sensory experience, nicotine delivery profile, and ritual characteristics of cigarettes





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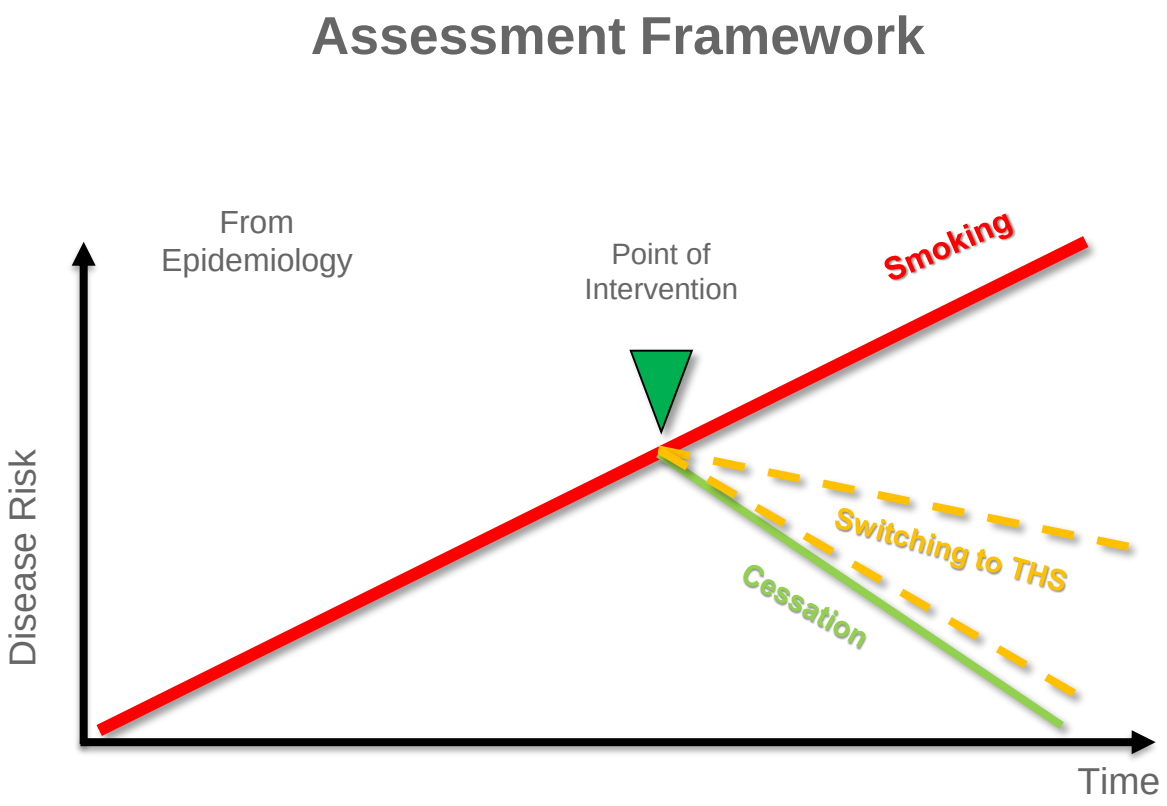
Scientific assessment approach

PMI's scientific assessment approach



- Post-Market Studies and Surveillance
- Consumer Perception and Behavior Assessment
- Clinical Trials
- Systems Toxicology Assessment
- Standard Toxicology Assessment
- Aerosol Chemistry and Physics
- Product Design and Control Principles

Smith, M.R., et al., Evaluation of the Tobacco Heating System 2.2. Part 1: Description of the system and the scientific assessment program. *Regulatory Toxicology and Pharmacology* (2016). http://dx.doi.org/10.1016/j.yrtph.2016.07.006
IOM (Institute of Medicine). Scientific standards for studies on modified risk tobacco products. Washington, DC: The National Academies Press. 2012.

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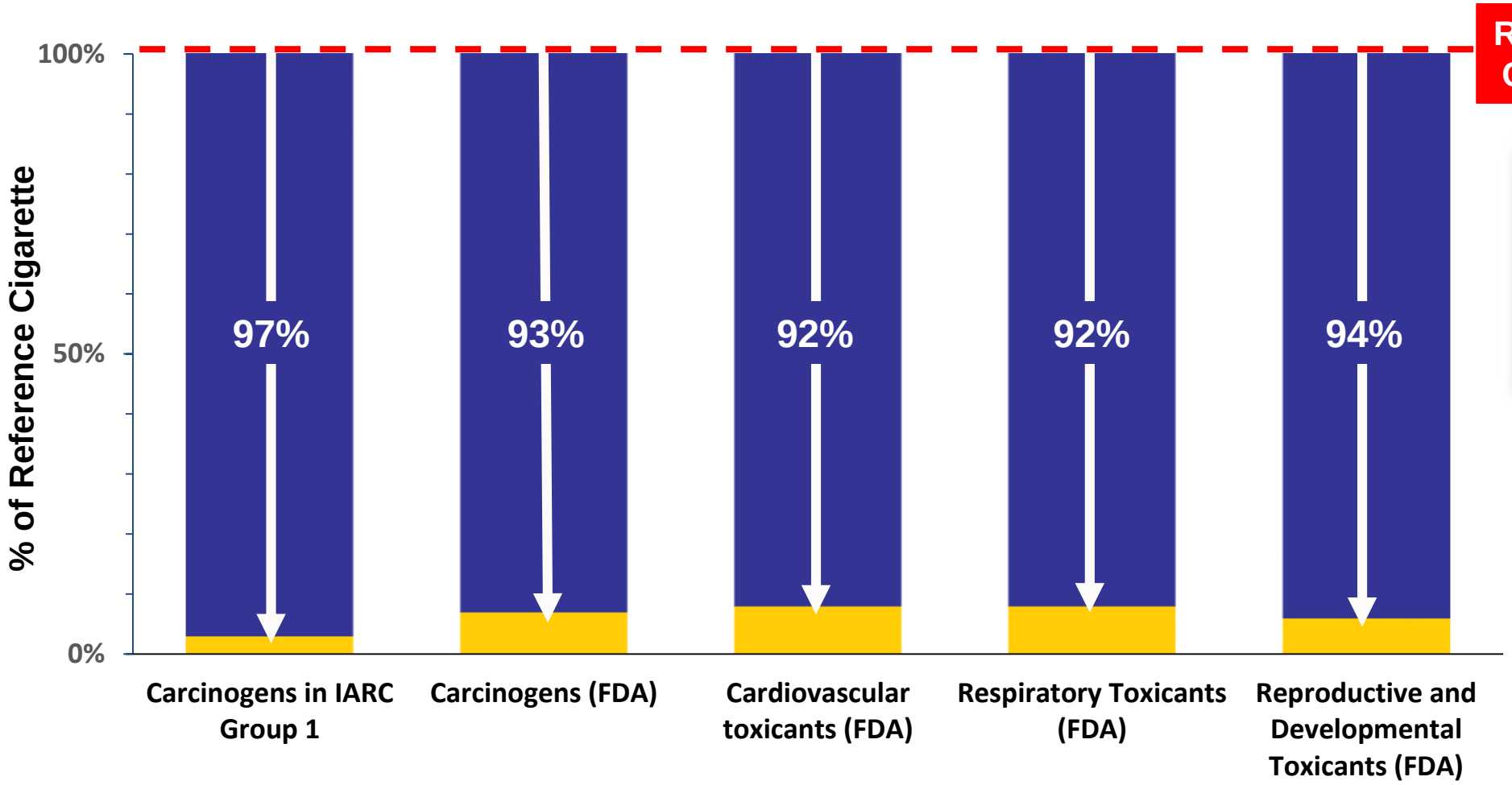
Exposure reduction

Reduced formation of HPHCs by disease categories



No. of toxicants	12	29	8	18	7

THS 2.2 produces an aerosol that contains **on average 90-95% lower levels of harmful and potentially harmful constituents (HPHC) than a reference cigarette**[1]

CV toxicants: acrolein, benz(a)anthracene, benzene, butyraldehyde, hydrogen cyanide, lead, phenol, propionaldehyde

1 Schaller J-Pat al. Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. Regul Toxicol Pharmacol. 2016; Suppl 2. Available from: http://www.sciencedirect.com/science/article/pii/S0273230016302902 (Accessed on 03 May 2017):S27-47.
Note: Intense Health Canada's Smoking Regime; Comparison on a per-stick basis; Excludes Nicotine

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THS does not negatively impact indoor air quality

Chemosphere 206 (2018) 568–578

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

Review

A review of the impacts of tobacco heating system on indoor air quality versus conventional pollution sources

Violeta Kaunelienė*, Marija Meišutovič-Akhtarieva, Dainius Martuzevičius

Department of Environmental Technology, Kaunas University of Technology, Radvilenu pl. 19, Kaunas, LT50254, Lithuania

HIGHLIGHTS

- THS generated pollution was compared against general indoor air quality.
- The usage of THS indicated as a low emitting indoor air pollution source.
- Exposure to significantly higher pollution levels occurs in public environments.
- Conventionally measured pollutants are not able to represent IAQ due to THS use.

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In vitro models of disease

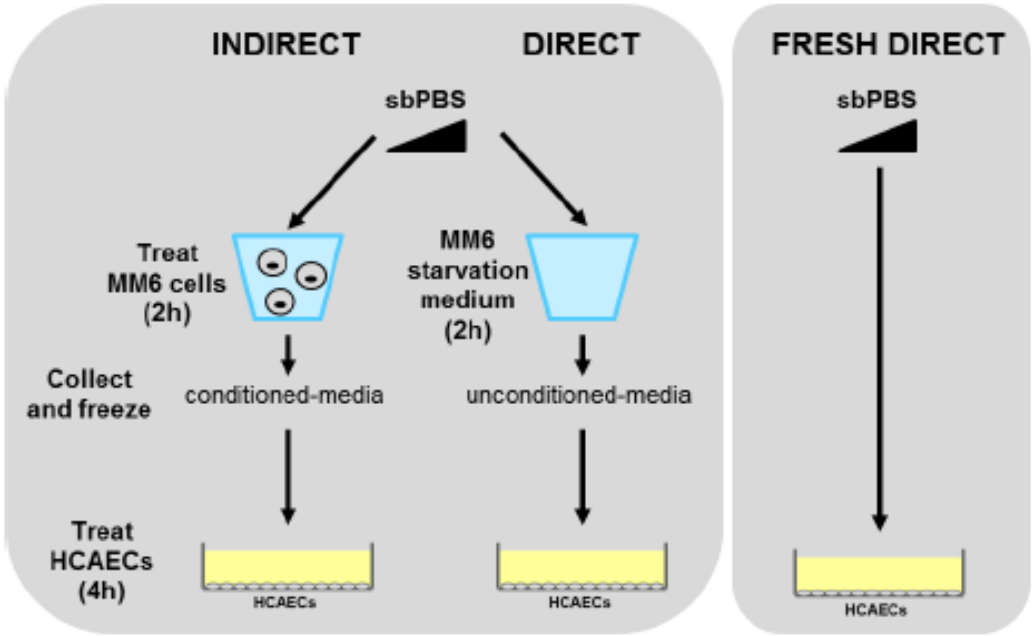
From risk assessment framework to *in vitro* study design

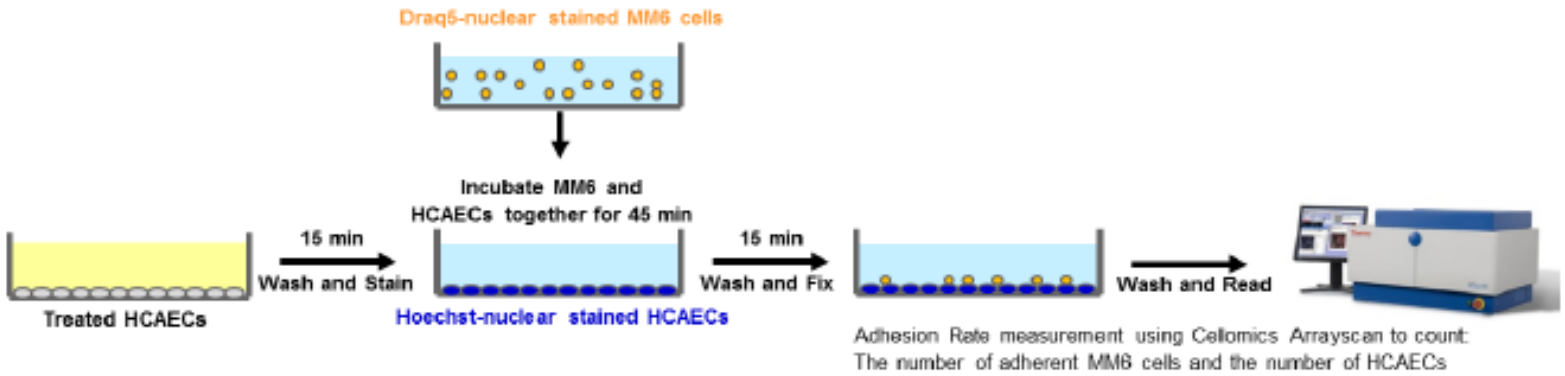
In vitro model: adhesion of monocytic cells to human coronary arterial endothelial cells (HCAEC)

1. **Cell exposure to 3R4F or THS 2.2 (aqueous smoke / aerosol extract)**

2. **Treatment of HCAECs**

3. **Adhesion assay**
   - Untreated MM6 cells and 4h-treated HCAECs were nuclear-stained for 15 minutes and then incubated together for 45 minutes
   - After cell fixing and washing, remaining adherent MM6 cells and HCAECs were counted
   - The adhesion rate was calculated





Poussin et al. Systems toxicology-based assessment of the candidate modified risk tobacco product THS2.2 for the adhesion of monocytic cells to human coronary arterial endothelial cells. *Toxicology 2016*; 73–86.

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From risk assessment framework to *in vitro* study design

In vitro model: adhesion of monocytic cells to HCAECs

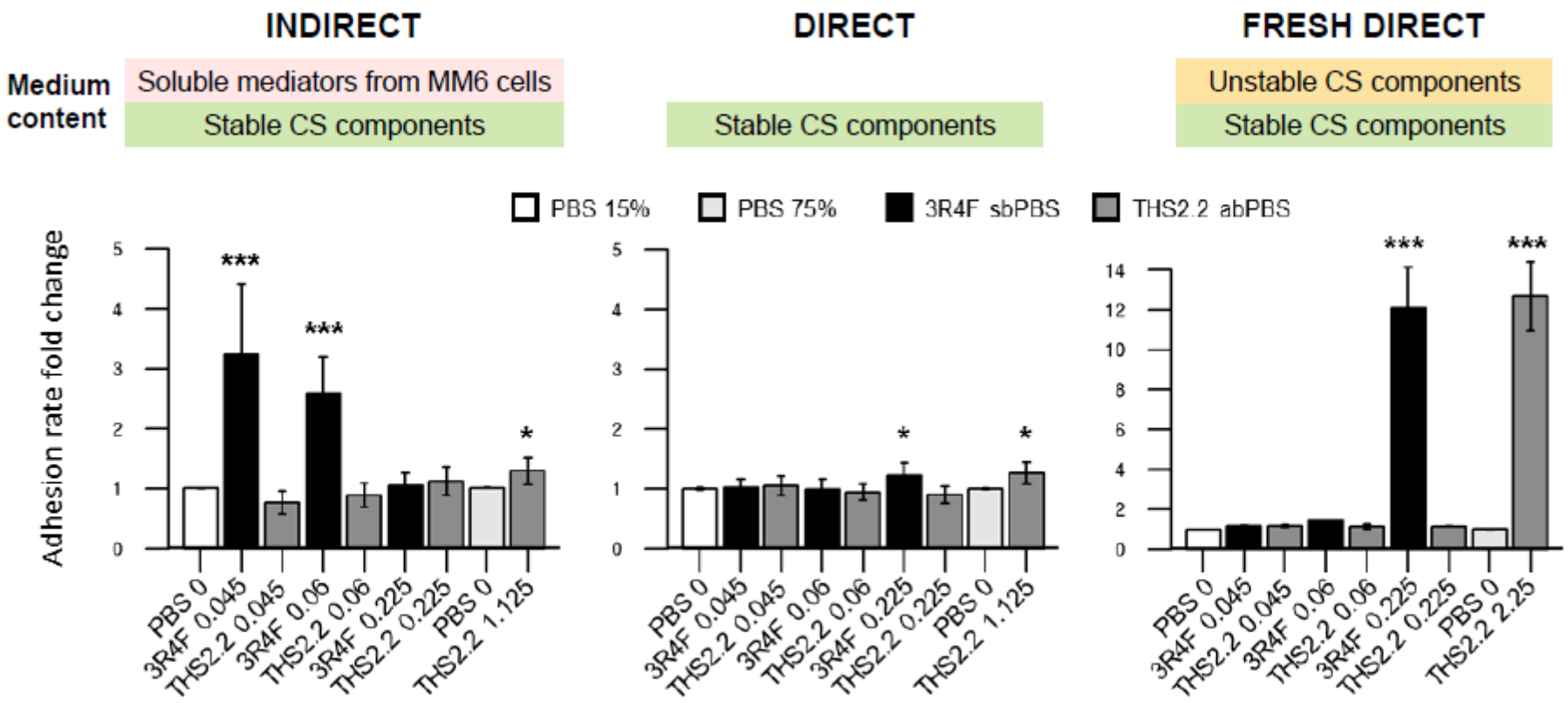

*Figure 1: Effects of THS2.2 abPBS and 3R4F sbPBS on the adhesion of MM6 cells to HCAECs following indirect, direct, and fresh direct treatments of HCAECs. Bar charts represent fold changes of the adhesion rate relative to respective vehicle controls. The adhesion rate reflects the number of adherent MM6 cells relative to the total number of HCAECs counted in the same well multiplied by 100. Data are presented as the mean ± SEM; N=2–3 independent experiments (n=3–6 replicates). *p≤0.05, ***p≤0.001 vs. 0 puffs/ml (PBS 15% or 75%).*

- 3R4F aqueous cigarette smoke extract promoted adhesion of MM6 cells to HCAECs in indirect and fresh direct exposure conditions
- At the same concentrations, no significant adhesion of MM6 cells to HCAECs was promoted by THS
- The concentrations of THS 2.2 required to be increased by ~10 and 20 times to observe similar effects at functional and molecular levels to the ones observed with 3R4F

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Poussin et al. Systems toxicology-based assessment of the candidate modified risk tobacco product THS2.2 for the adhesion of monocytic cells to human coronary arterial endothelial cells. *Toxicology 2016*; 73–86.

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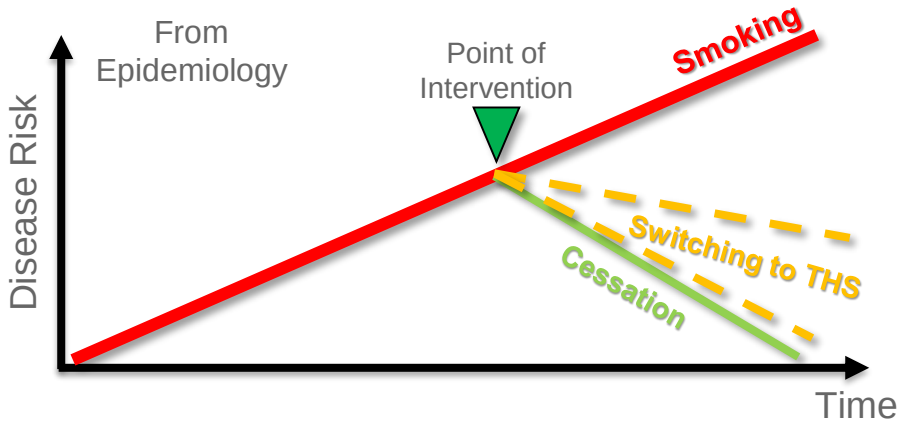
Animal models of disease

From risk assessment framework to *in vivo* study design

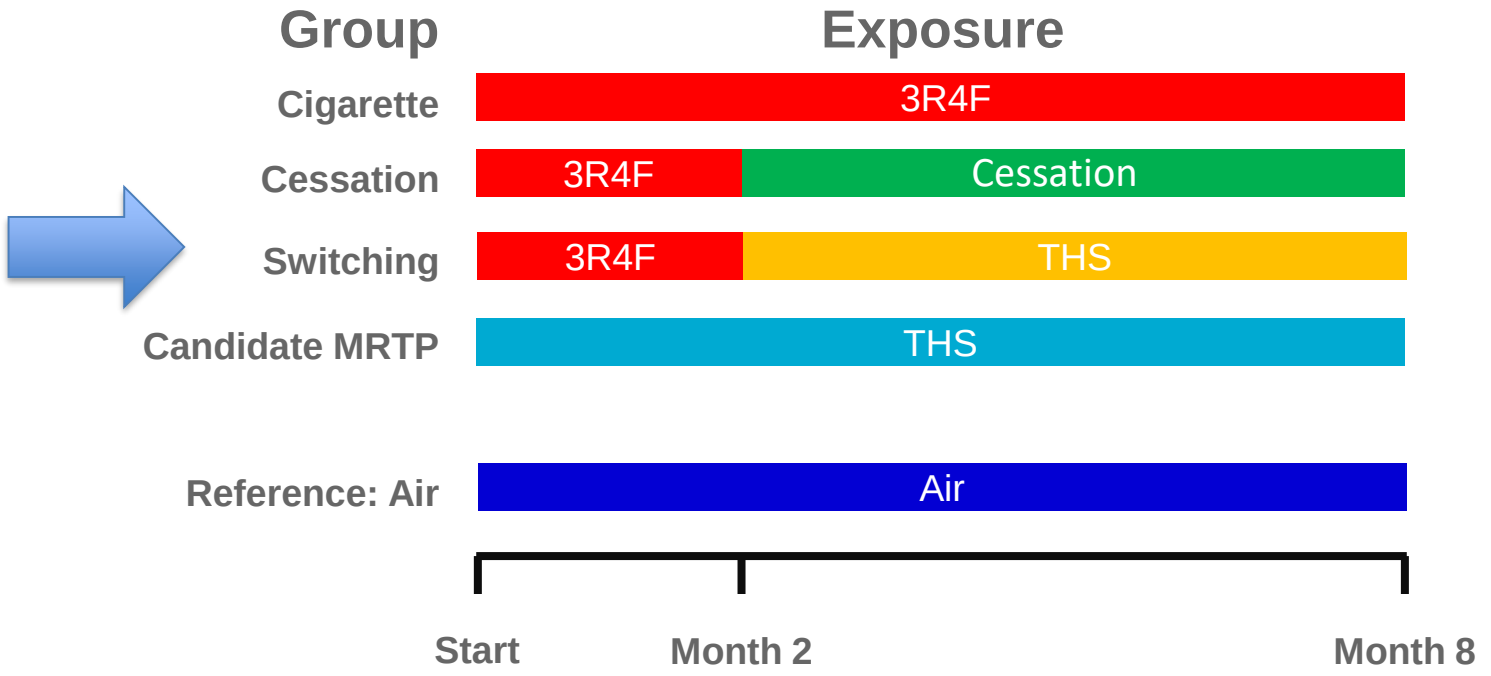
ApoE$^{-/-}$ mouse model: *in vivo* study to investigate atherosclerotic plaque of the aortic arch

- Eight-month duration (approximately 40% of lifetime)
- Comprehensive analysis of molecular changes and mechanistic impact
- Exposure dose corresponds to ~30 cigarettes per day in human comparison

Assessment Framework



Note: The descriptions in the chart are for illustrative purposes only



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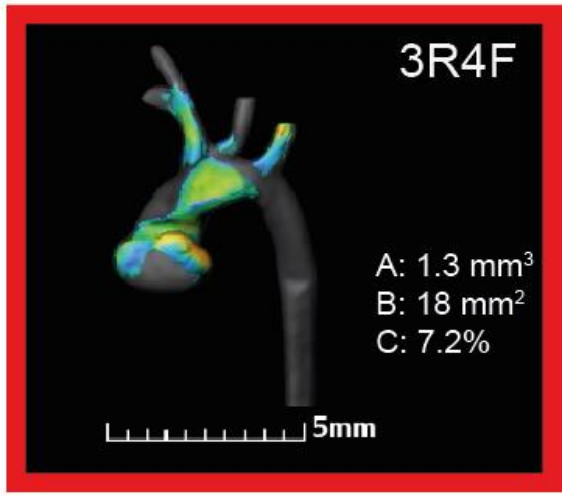
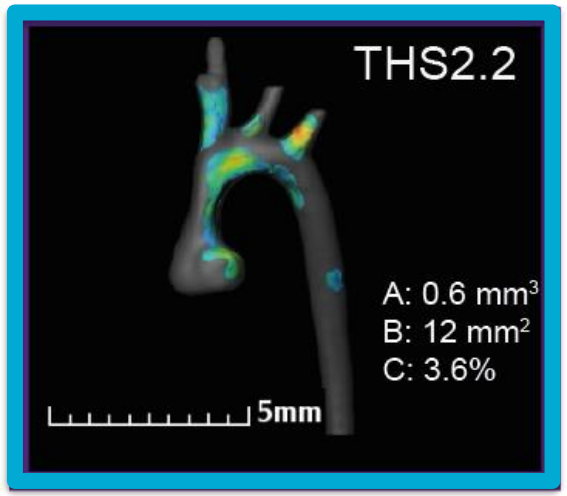
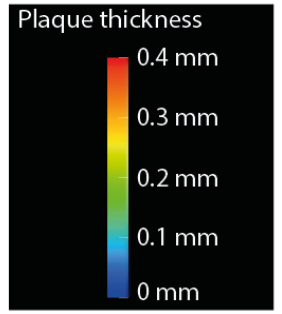
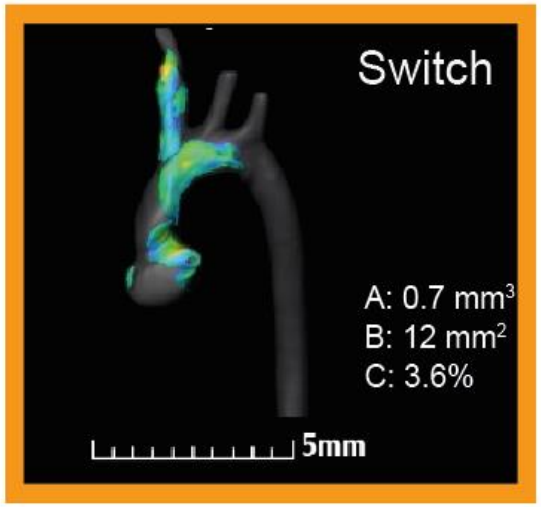
Poussin C at al. Systems toxicology-based assessment of the candidate modified risk tobacco product THS2.2 for the adhesion of monocytic cells to human coronary arterial endothelial cells. Toxicology. 2016; 339:73-86.

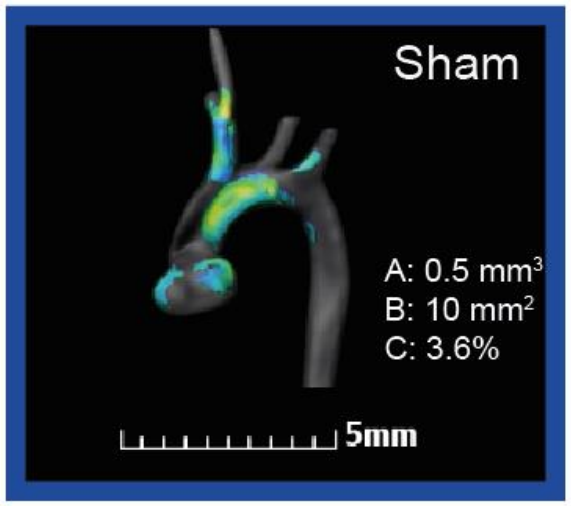
Atherosclerotic plaque in the aortic arch
Data from µCT at Month 7

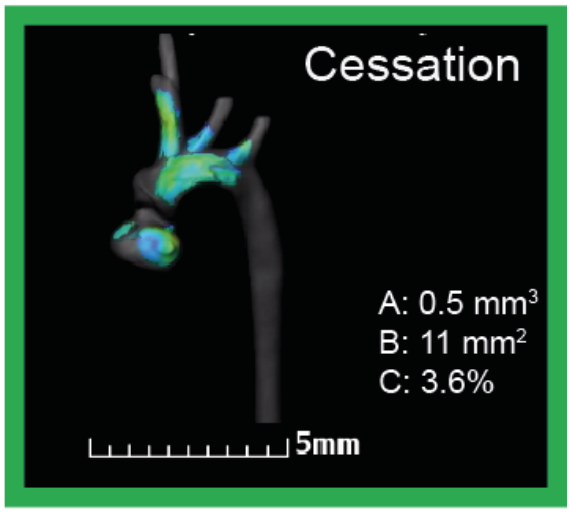












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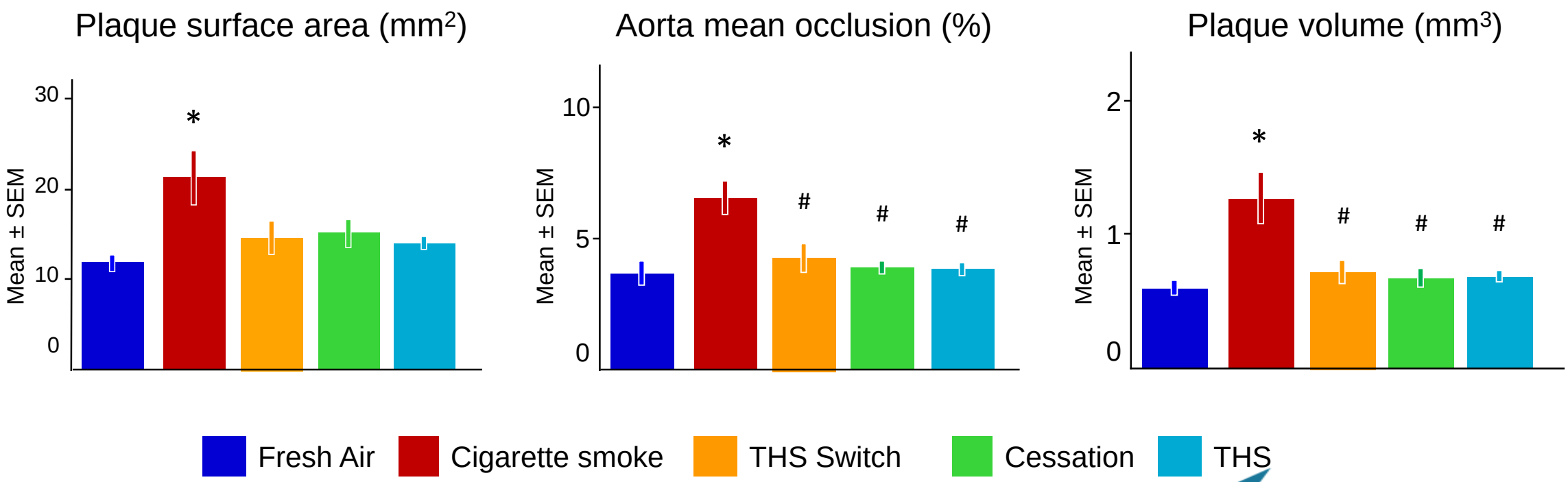
Phillips, B., et al. (2015). "An 8-month systems toxicology inhalation/cessation study in Apoe−/− mice to investigate cardiovascular and respiratory exposure effects of a candidate modified risk tobacco product, THS 2.2, compared with conventional cigarettes." Toxicological Sciences **149(2): 411-432.**

Atherosclerotic plaque in the aortic arch
Data from µCT at Month 7

Disease endpoint for CVD

Atherosclerotic plaque in the aortic arch

Data from µCT at Month 7



*: different from sham (p<0.05), #: different from cigarette smoke (p<0.05)

Phillips, B., et al. (2015). "An 8-month systems toxicology inhalation/cessation study in Apoe−/− mice to investigate cardiovascular and respiratory exposure effects of a candidate modified risk tobacco product, THS 2.2, compared with conventional cigarettes." Toxicological Sciences **149(2): 411-432.**

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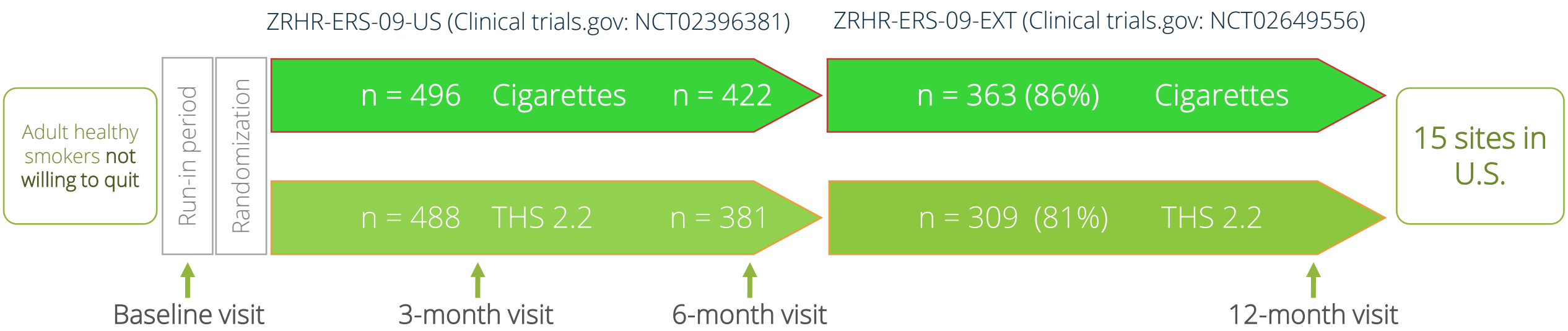
Clinical Exposure Response Study

Study design and disposition – Exposure Response Study



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Primary objective and co-primary endpoints

Smoking cessation

Epidemiologic link to smoking-related disease?

Affected by smoking status

Reversible upon smoking cessation

Co-primary endpoints representative of patho-mechanims	
Lipid metabolism	HDL-C
Clotting	11-DTX-B2
Endothelial function	sICAM-1
CO acute effect	COHb
Inflammation	WBC
Oxidative stress	$PGF_{2\alpha}$
Lung function	FEV_1
Genotoxicity	Total NNAL

Assess the changes across a set of the "eight co-primary endpoints" in smokers who switch from smoking cigarettes to using THS as compared to those continuing to smoke cigarettes for six months

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Changes in endpoints

Endpoint	Change from CC-use	Observed change LS mean difference / relative reduction	Hailperin-Rüger adjusted CI	1-sided *p*-value (0.0156)	THS directional change vs. SA (literature)
HDL-C	Difference	3.09 mg/dL	1.10, 5.09	<0.001*	✓ significant
WBC count	Difference	–0.420 GI/L	–0.717, –0.123	0.001*	✓ significant
sICAM-1	% Reduction	2.86 %	–0.426, 6.04	0.030	✓
11-DTX-B2	% Reduction	4.74 %	–7.50, 15.6	0.193	✓
8-epi-$PGF_{2\alpha}$	% Reduction	6.80 %	–0.216, 13.3	0.018	✓
COHb	% Reduction	32.2 %	24.5, 39.0	<0.001*	✓ significant
FEV_1 %pred	Difference	1.28 %pred	0.145, 2.42	0.008*	✓significant
Total NNAL	% Reduction	43.5 %	33.7, 51.9	<0.001*	✓significant

* denotes significant *p*-value at the 1.5625% level, following test multiplicity adjustment using the Hailperin-Rüger approach

- All CREs shifted in the same direction as the smoking cessation effect observed in the literature
- Five out of eight CREs were statistically significant compared to continued smoking

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Summary - potentially reduced risk products

- The attributable risk of smoking to cardiovascular disease is high, and smoking cessation therapies and interventions have significant limitations
- Cardiovascular effects of potentially reduced risk products have been assessed in extensive pre-clinical and clinical programs (in healthy subjects)
- Full switching is the best option for current adult smokers continuing to use tobacco
- Observations likely to translate into clinical relevant outcomes (i.e., reduction in CV death, MI, and stroke)
- Clinical benefit to be assessed as a next step of PMI's THS assessment program

  → Improve primary and secondary CVD prevention in clinical practice

Increasing number of third-party studies

Aerosol Chemistry

- Committee on Toxicology (COT)
- British American Tobacco
- National Tobacco Quality Supervision and Test Center
- Federal Institute for Risk Assessment (BfR)
- University of Bern
- National Institute of Public Health
- Food & Drug Administration
- Onassis Cardiac Surgery Center
- National Institute for Public Health and the Environment (RIVM)
- Ministry of Food and Drug Safety

Indoor Air quality

- Fondazione IRCCS Istituto Tumori
- Sapienza University
- Medved Research Center of Preventing Toxicology, Food and Chemical Safety

Pre-Clinical

- British American Tobacco
- UCSF
- Roswell Park Comprehensive Cancer Center

Clinical

- Kazan Federal University
- National Scientific Centre "M.D. Strazhesco Institute of Cardiology"
- British American Tobacco

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Independent verification of PMI's science – goverment bodies

Federal Institute for Risk Assessment (BfR) (Germany, 2018) – in line with our results:

"The herein confirmed reductions of relevant toxicants by about 80-99% are substantial"

U.S. Food and Drug Administration (FDA) Briefing Document (U.S., 2018) – in line with our results:

"*The independent testing performed by STL* [FDA's Southeast Tobacco Laboratory] *confirmed the lower levels of selected* [harmful and potentially harmful compounds] *HPHCs in the aerosol from the HeatSticks compared to mainstream cigarette smoke*."

Public Health England (U.K., 2018) – in line with our results:

"*Compared with cigarette smoke, heated tobacco products are likely to expose users and bystanders to lower levels of particulate matter and harmful and potentially harmful compounds. The extent of the reduction found varies between studies*."

National Institute for Public Health and the Environment (RIVM) (Netherlands, 2018) – in line with our results:

"The use of heatsticks with the IQOS is harmful to health, but probably less harmful than smoking tobacco cigarettes."

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Thank you for your attention