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

Dr. Calin Pater, on behalf of Philip Morris International’s Biomedical Research & Development Team

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

4. 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
5. Physicians perceive that diabetes is the most important risk factor for coronary heart disease, followed by hypertension and raised low-density lipoprotein cholesterol.⁵
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.

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)
Smoking cessation and mortality reduction
Systematic review of 20 studies

36% relative risk reduction
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.”
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.”
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.”

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Event rate, % (95% CI)</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quitters (95% CI)</td>
<td>Nonquitters (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>14 (7-27)</td>
<td>31 (23-40)</td>
<td>0.40 (0.18-0.90)</td>
</tr>
<tr>
<td>Amputation-free survival</td>
<td>81 (10-32)</td>
<td>60 (31-50)</td>
<td>0.43 (0.22-0.86)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>8 (3-20)</td>
<td>16 (8-31)</td>
<td>0.72 (0.22-2.31)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (1-14)</td>
<td>5 (2-15)</td>
<td>0.44 (0.10-3.98)</td>
</tr>
<tr>
<td>Major amputation</td>
<td>7 (2-15)</td>
<td>22 (12-37)</td>
<td>0.38 (0.11-1.31)</td>
</tr>
<tr>
<td>MALE</td>
<td>33 (21-49)</td>
<td>31 (19-45)</td>
<td>1.40 (0.80-2.70)</td>
</tr>
</tbody>
</table>

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

*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.
Marked reduction in arrhythmic death and overall mortality after an MI

Smoking cessation: the best antiarrhythmic therapy!

[Graph showing survival rates for smokers and quitters with p = 0.04]
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
“Smoking cessation in these age groups is still beneficial in reducing the excess risk”.

<table>
<thead>
<tr>
<th>Population</th>
<th>Smoking status</th>
<th>Cardiovascular deaths</th>
<th>Acute coronary events</th>
<th>Stroke events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Men</td>
<td>Never smokers</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Former smokers</td>
<td>1.33 1.20 to 1.48</td>
<td>1.18 1.00 to 1.38</td>
<td>1.08 0.97 to 1.21</td>
</tr>
<tr>
<td></td>
<td>Current smokers</td>
<td>1.95 1.69 to 2.25</td>
<td>1.80 1.51 to 2.15</td>
<td>1.44 1.23 to 1.68</td>
</tr>
<tr>
<td>Women</td>
<td>Never smokers</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Former smokers</td>
<td>1.40 1.25 to 1.57</td>
<td>1.24 1.07 to 1.41</td>
<td>1.20 1.06 to 1.36</td>
</tr>
<tr>
<td></td>
<td>Current smokers</td>
<td>2.22 1.86 to 2.65</td>
<td>2.26 1.98 to 2.59</td>
<td>1.78 1.46 to 2.17</td>
</tr>
<tr>
<td>Age 60–69</td>
<td>Never smokers</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Former smokers</td>
<td>1.57 1.43 to 1.72</td>
<td>1.25 1.10 to 1.43</td>
<td>1.22 1.10 to 1.35</td>
</tr>
<tr>
<td></td>
<td>Current smokers</td>
<td>2.45 2.22 to 2.69</td>
<td>2.02 1.78 to 2.28</td>
<td>1.68 1.46 to 1.94</td>
</tr>
<tr>
<td>Age 70+</td>
<td>Never smokers</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Former smokers</td>
<td>1.21 1.08 to 1.36</td>
<td>1.12 0.95 to 1.32</td>
<td>1.10 0.95 to 1.28</td>
</tr>
<tr>
<td></td>
<td>Current smokers</td>
<td>1.70 1.42 to 2.04</td>
<td>1.88 1.41 to 2.52</td>
<td>1.49 1.22 to 1.82</td>
</tr>
</tbody>
</table>
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.\(^1\)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>It is recommended to stop all smoking of tobacco or herbal products, as this is strongly and independently causal of CVD.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>It is recommended to avoid passive smoking.</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

\(^{1}\) European Society of Cardiology Guideline recommendations.
### The five A’s for smoking cessation strategy for routine practice - 2016

<table>
<thead>
<tr>
<th><strong>A-ASK:</strong></th>
<th>Systematically inquire about smoking status at every opportunity.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A-ADVISE:</strong></td>
<td>Unequivocally urge all smokers to quit.</td>
</tr>
<tr>
<td><strong>A-ASSESS:</strong></td>
<td>Determine the person’s degree of addiction and readiness to quit.</td>
</tr>
<tr>
<td><strong>A-ASSIST:</strong></td>
<td>Agree on a smoking cessation strategy, including setting a quit date, behavioural counselling, and pharmacological support.</td>
</tr>
<tr>
<td><strong>A-ARRANGE:</strong></td>
<td>Arrange a schedule of follow-up.</td>
</tr>
</tbody>
</table>
Six-month abstinence rates for NRT

Continuous abstinence rates on pharmacologic therapy

Gonzalez at al. 2007
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


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
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
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
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

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>E-Cigarettes  (N=438)</th>
<th>Nicotine Replacement  (N=446)</th>
<th>Primary Analysis: Relative Risk (95% CI)†</th>
<th>Sensitivity Analysis: Adjusted Relative Risk (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: abstinence at 52 wk — no. (%)</td>
<td>79 (18.0)</td>
<td>44 (9.9)</td>
<td>1.83 (1.30–2.58)</td>
<td>1.75 (1.24–2.46)‡</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinence between wk 26 and wk 52 — no. (%)</td>
<td>93 (21.2)</td>
<td>53 (11.9)</td>
<td>1.79 (1.32–2.44)</td>
<td>1.82 (1.34–2.47)§</td>
</tr>
<tr>
<td>Abstinence at 4 wk after target quit date — no. (%)</td>
<td>192 (43.8)</td>
<td>134 (30.0)</td>
<td>1.45 (1.22–1.74)</td>
<td>1.43 (1.20–1.71)¶</td>
</tr>
<tr>
<td>Abstinence at 26 wk after target quit date — no. (%)</td>
<td>155 (35.4)</td>
<td>112 (25.1)</td>
<td>1.40 (1.14–1.72)</td>
<td>1.36 (1.15–1.67)‡</td>
</tr>
</tbody>
</table>
| 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.
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.”

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
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
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.
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 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.
Vaping in England: an evidence update February 2019
A report commissioned by Public Health England
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.
Emerging smoke-free regulatory trends

“...new product innovations could make a lot of sense and help people transfer off cigarettes.”
- Scott Gottlieb, Commissioner Food & Drug Administration

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

“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
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
Current smoker not ready to quit now

Treatments
- Motivational interviewing (risks, rewards, roadblocks)
- Prescribe and/or offer free medication samples of stop smoking medications and encourage to reduce quantity smoked
- Discuss the use of non-combustible tobacco product if not interested in using stop smoking medications
- Advise patient to adopt smoke-free home and car policy

Follow-up
Reassess* with patients within 1 month

If ready to quit, refer/connect to stop smoking treatments
If not ready to quit, repeat provision of treatment

* 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.
Tobacco Harm Reduction
Creating a New Category: Reduced-Risk Products

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

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.

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.
Combustion
Elimination of combustion is key

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


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 without combustion
- Preserve elements of the taste, sensory experience, nicotine delivery profile, and ritual characteristics of cigarettes
Scientific assessment approach
PMI’s scientific assessment approach

Assessment Framework

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

Disease Risk

Time

From Epidemiology

Point of Intervention

Smoking

Switching to THS

Cessation


Exposure reduction
Reduced formation of HPHCs by disease categories

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

<table>
<thead>
<tr>
<th>% of Reference Cigarette</th>
<th>Carcinogens in IARC Group 1</th>
<th>Carcinogens (FDA)</th>
<th>Cardiovascular Toxicants (FDA)</th>
<th>Respiratory Toxicants (FDA)</th>
<th>Reproductive and Developmental Toxicants (FDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>97%</td>
<td></td>
<td>93%</td>
<td>92%</td>
<td>92%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Table:

| No. of toxicants | 12 | 29 | 8 | 18 | 7 |

Review

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

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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.

THS does not negatively impact indoor air quality
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.
From risk assessment framework to *in vitro* study design

**In vitro** model: adhesion of monocyctic cells to HCAECs

- 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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**Figure 1:** Effects of THS2.2 sbPBS 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%).

Poussin et al. Systems toxicology-based assessment of the candidate modified risk tobacco product THS2.2 for the adhesion of monocyctic cells to human coronary arterial endothelial cells. Toxicology 2016; 73–86.
Animal models of disease
From risk assessment framework to *in vivo* study design

**ApoE<sup>−/−</sup> 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**

- From Epidemiology
- Point of Intervention
- Switching to THS
- Cessation

**Group**
- Cigarette: 3R4F
- Cessation: 3R4F Cessation
- Switching: 3R4F THS
- Candidate MRTP: THS
- Reference: Air

**Exposure**

- Start
- Month 2
- Month 8

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

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

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

Plaque surface area (mm²)
Mean ± SEM

Aorta mean occlusion (%)
Mean ± SEM

Plaque volume (mm³)
Mean ± SEM

*: different from sham (p<0.05), #: different from cigarette smoke (p<0.05)
Clinical Exposure Response Study
Study design and disposition – Exposure Response Study

ZRHR-ERS-09-US (Clinical trials.gov: NCT02396381)

- n = 496 Cigarettes
- n = 488 THS 2.2

ZRHR-ERS-09-EXT (Clinical trials.gov: NCT02649556)

- n = 363 (86%) Cigarettes
- n = 309 (81%) THS 2.2

15 sites in U.S.
Primary objective and co-primary endpoints

Smoking cessation

Epidemiologic link to smoking-related disease?
Affected by smoking status
Reversible upon smoking cessation

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.

<table>
<thead>
<tr>
<th>Co-primary endpoints</th>
<th>Representative of patho-mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid metabolism</td>
<td>HDL-C</td>
</tr>
<tr>
<td>Clotting</td>
<td>11-DTX-B2</td>
</tr>
<tr>
<td>Endothelial function</td>
<td>sICAM-1</td>
</tr>
<tr>
<td>CO acute effect</td>
<td>COHb</td>
</tr>
<tr>
<td>Inflammation</td>
<td>WBC</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>PGF$_{2\alpha}$</td>
</tr>
<tr>
<td>Lung function</td>
<td>FEV$_1$</td>
</tr>
<tr>
<td>Genotoxicity</td>
<td>Total NNAL</td>
</tr>
</tbody>
</table>
## Changes in endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Change from CC-use</th>
<th>Observed change LS mean difference / relative reduction</th>
<th>Hailperin-Rüger adjusted CI</th>
<th>1-sided p-value (0.0156)</th>
<th>THS directional change vs. SA (literature)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C</td>
<td>Difference</td>
<td>3.09 mg/dL</td>
<td>1.10, 5.09</td>
<td>&lt;0.001*</td>
<td>✓ significant</td>
</tr>
<tr>
<td>WBC count</td>
<td>Difference</td>
<td>-0.420 Gl/L</td>
<td>-0.717, -0.123</td>
<td>0.001*</td>
<td>✓ significant</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>% Reduction</td>
<td>2.86 %</td>
<td>-0.426, 6.04</td>
<td>0.030</td>
<td>✓</td>
</tr>
<tr>
<td>11-DTX-B2</td>
<td>% Reduction</td>
<td>4.74 %</td>
<td>-7.50, 15.6</td>
<td>0.193</td>
<td>✓</td>
</tr>
<tr>
<td>8-epi-PGF$_{2a}$</td>
<td>% Reduction</td>
<td>6.80 %</td>
<td>-0.216, 13.3</td>
<td>0.018</td>
<td>✓</td>
</tr>
<tr>
<td>COHb</td>
<td>% Reduction</td>
<td>32.2 %</td>
<td>24.5, 39.0</td>
<td>&lt;0.001*</td>
<td>✓ significant</td>
</tr>
<tr>
<td>FEV$_1$ %pred</td>
<td>Difference</td>
<td>1.28 %pred</td>
<td>0.145, 2.42</td>
<td>0.008*</td>
<td>✓ significant</td>
</tr>
<tr>
<td>Total NNAL</td>
<td>% Reduction</td>
<td>43.5 %</td>
<td>33.7, 51.9</td>
<td>&lt;0.001*</td>
<td>✓ significant</td>
</tr>
</tbody>
</table>

* 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
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
Independent verification of PMI’s science – government 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.”
Thank you for your attention