Association of urinary 11-dehydro-thromboxane B2 levels in smoking, smoking cessation and Tobacco Heating System use

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Introduction and Objective
Thromboxane is a known mediator in the pathogenesis of cardiovascular diseases and smoking has been associated with its increased levels. Smoking increases thromboxane B2 release by platelets in healthy individuals as well as the excretion of its two major urinary metabolites: 2,3-dinor-Thromboxane B2 and 11-dehydro-thromboxane B2.

Philip Morris International, is currently developing a Tobacco Heating System (THS) that may have the potential to reduce the risk of smoking related diseases. A biomarker of inflammation might be suitable candidates as intermediate clinical risk endpoint.

The aim of our study is to review the available published and in-house data on: 1) the urinary 11-dehydro-thromboxane B2 levels in smokers vs. non-smokers, 2) the influence of smoking cessation on urinary 11-dehydro-thromboxane B2 levels, and 3) the effect switching to THS use on urinary 11-dehydro-thromboxane B2 levels.

Materials and Methods

PUBMED and SCOPUS searches plus a reference list review were performed for studies that evaluated the relationship between smoking or smoking cessation and 11-dehydro-thromboxane B2. Also, data from our in-house clinical studies that had assessed 11-dehydro-thromboxane B2 were also included.

Study Selection

Inclusion Criteria
- Case control or cohort studies
- Adult human populations
- Measurements of 11-dehydro-thromboxane B2 levels by exposure with the following measures available: mean and SD or SE
- Published after 1970

Exclusion Criteria
- Review articles, case reports, articles, editorials
- Reports with incomplete or previously published data

Statistical Analysis

To quantify the effects of smoking and smoking cessation on 11-dehydro-thromboxane B2:
- Pooled mean differences between smokers and non-smokers and 95% confidence intervals were calculated using the fixed-effects model in Review Manager version 5.0 (Cochrane Collaboration, Oxford, UK).
- The degree of heterogeneity between the study results was tested by the I². Funnel plots were used to evaluate publication bias (Macaskill 2001).

Results

11-TXB2, levels pg/mg creatinine – Fixed Effects

<table>
<thead>
<tr>
<th>Study Participants</th>
<th>Smokers</th>
<th>Non-Smokers</th>
<th>Mean</th>
<th>Total</th>
<th>SD</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Confidence Intervals (95%)</th>
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11-TXB2, levels pg/mg creatinine – Random Effects

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Smoking Cessation & TXB2 levels
- There were 3 published studies assessing the influence on smoking cessation on urinary 11-dehydro-thromboxane B2 excretion. All three report decreased levels after cessation
- 11-dehydro-thromboxane B2 levels decreased as early as 3 days after cessation
- The study characteristics are shown in the table below

Summary and Conclusions
In this analysis we found:
- Smokers had statistically significantly higher levels of 11-dehydro-thromboxane B2.
- There were not enough studies to perform meta-analyses on the effects of smoking cessation and THS use, but all publications showed reduced levels of 11-dehydro-thromboxane B2 in THS users as compared to CC smokers.
- Our study shows that 11-dehydro-thromboxane B2 as clinical risk marker of inflammation is significantly increased by cigarette smoking.
- The data support that smoking cessation affects levels of 11-dehydro-thromboxane B2.
- Additionally, the studies assessing THS use showed reductions of 11-dehydro-thromboxane B2 excretion in those who used THS compared to conventional cigarette smokers.
- According to these findings 11-dehydro-thromboxane B2 would be a reliable clinical risk endpoint in the assessment of candidate MRTPs.

References

THS Use & 11-dehydro-thromboxane B2
- Two studies reported 11-dehydro-thromboxane B2 levels in smokers and those who switched to THS were published, one study was on file.
- All studies reported were carried out by PMI
- A decrease in 11-dehydro-thromboxane B2 levels was observed after five days, 1 month and 1 year of switching from smoking conventional cigarette to THS use.
- No meta-analysis was performed due to different length of follow up.
- The study characteristics are found in the table below.