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APPENDIX A6.1.4.6 THROMBOXANE B $(TXB)_2$ HEALTH EFFECTS OF SMOKING CESSATION

Short Term Health Effects

Thromboxane B $(TXB)_2$

Internal Report
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Version: 1

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1 BACKGROUND

Thromboxanes (TX) belong to a family of lipids termed eicosanoids that are synthesized from arachidonic acid (AA) by the action of cyclooxygenase (COX) enzymes. Eicosanoids have autocrine or paracrine actions by functioning as vasoconstrictors and potent hypertensive agents, and facilitate platelet aggregation. Thromboxanes were named after their role in thrombus (or clot) formation (thrombosis). Thromboxane A_2 (TXA_2) is generated from prostaglandin H_2 (PGH_2, the precursor for all 2-series prostaglandins and thromboxanes) by thromboxane-A synthase (human thromboxane A synthase is a 60 kDa protein with 533 amino acids and a heme prosthetic group). The enzyme, anchored to the endoplasmic reticulum, is found in platelets, monocytes, and several other cell types. It has prothrombotic properties that include stimulating the activation of new platelets and platelet aggregation. TXA_2 is very unstable in aqueous solution and is hydrolyzed within 30 seconds to the biologically inactive thromboxane B_2 (TXB_2). TXB_2 is released in large quantities from aggregating platelets and is metabolized in the circulation to 11-dehydro TXB_2 (Figure 1). Due to the short half life of TXA_2, 11-dehydro TXB_2, one of the main plasma metabolites of TXB_2, is commonly used as a marker for in vivo TXA_2 synthesis and platelet activation.

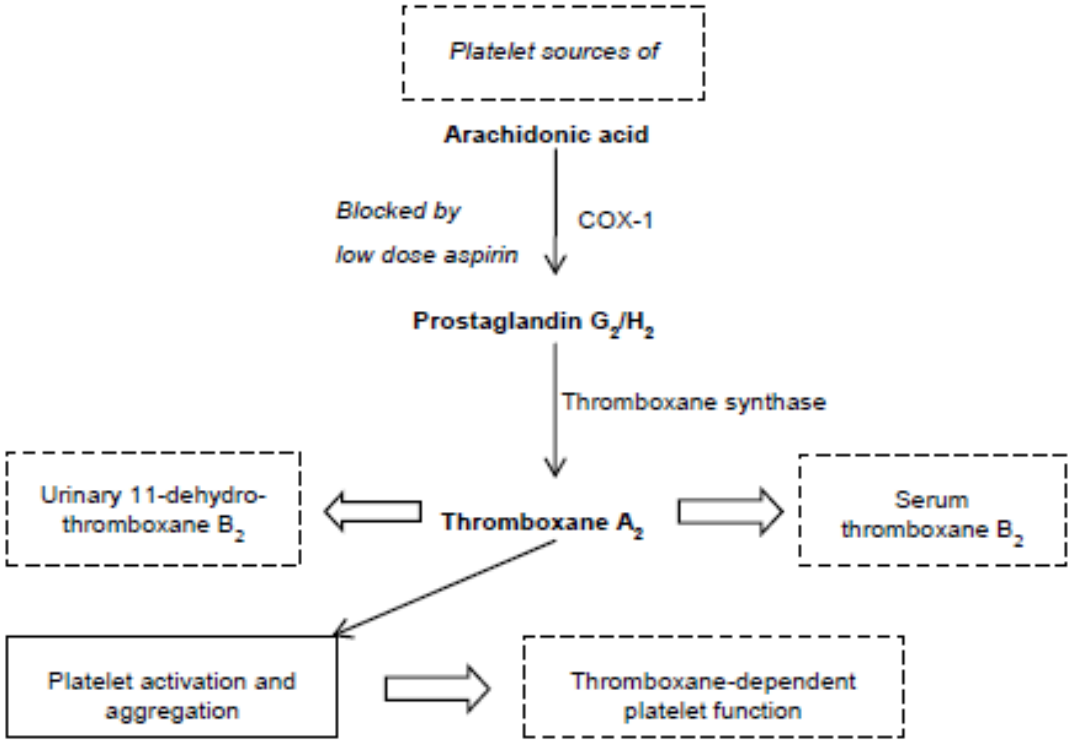


Figure 1. Pathway of thromboxane synthesis (From [1]).

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Although TXA_2 is predominantly derived from platelet COX 1, it can also be produced by other cell types, including macrophage COX 2 [2, 3].

2 METHODS

Three searches of the PubMed literature data base were conducted on August 20th 2015 for English language articles published within the time frame of 2008 to the present day.

Search 1. To identify literature that linked smoking or nicotine replacement therapy to TXB_2 using the search string: (Thromboxane OR 11-dehydrothromboxane B2) AND (smokers OR smoking OR nicotine replacement OR cessation) AND ("2008"[Date - Publication]: "2015"[Date - Publication]) AND English[Language]

Search 2. To identify literature reporting an association between TXB_2 and cardiovascular disease using the search string: (Thromboxane OR 11-dehydrothromboxane)B2 AND ((cardiovascular disease) AND (association)) AND ("2008"[Date - Publication]: "2015"[Date - Publication]))) AND English[Language])

Search 3. To idendify literature reporting an association between TXB_2 and respiratory disease using the search string: (Thromboxane OR 11-dehydrothromboxane B2) AND ((respiratory disease) AND (association)) AND ("2008"[Date - Publication]: "2015"[Date - Publication]))) AND English[Language])

Among the identified studies a set of specific criteria was applied to determine which papers should be selected for inclusion within the report.

The following inclusion criteria was applied:

Studies investigating the association of cigarette smoking, smoking cessation or nicotine replacement therapy (NRT) on TXB_2

Studies investigating the association of TXB_2 with cardiovascular disease or respiratory disease

The following exclusion criteria were applied:

1. Studies that used the measurement of TXB_2 simply for control purposes (e.g., results were adjusted for differences in TXB_2 between populations, but TXB_2 itself was not an endpoint)
2. Studies involving dietary, pharmacological or exercise interventions in which TXB_2 was an endpoint, but lacking a clear link between TXB_2 and either a disease of relevance or smoking
3. Studies in patients with a disease not covered by the search categories (e.g., cancer, HIV infection, periodontitis) where there was no clear link between TXB_2 and either a disease of relevance or smoking

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4. Studies of passive or parental smoking
5. Studies showing a link between TXB_2 and either a disease of relevance or smoking, but in a defined, narrow population (e.g., pregnant women, individuals with a particular haplotype, individuals with a specific disease) or tissue (e.g., retina, gums)
6. Studies reporting results from *in vivo* animal experiments
7. Studies with no caomparison between smoking and non-smoking/switching/cessation
8. TXB_2 not measured

The literature searches identified nine smoking-related studies that met the inclusion criteria. These are described below.

Table 1. Search results and distribution across the exclusion criteria

	Search 1	Search 2	Search 3
Number of articles retrieved	59	49	15
Articles rejected due to:			
E1. TXB_2 used only as control/biomarker of exposure	4	7	
E2. TXB_2 lacked link to disease or smoking	8	1	
E3. Disease not covered by search categories	15	23	7
E4. Studies of passive or parental smoking			
E5. Studies in a narrow population (e.g. pregnant women)	3	2	3
E6. *In vitro* studies or studies using *in vivo* animal models	8	4	2 0
E7. Studies in which TXB_2 was measured for toxicological or forensic purposes			
E8. Studies with no comparison to smoking and cessation/switching	12	11	3
Articles selected for review	9	1	0

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3 BIOMARKER-DISEASE LINK

3.1 Cardiovascular disease

Platelet adhesion is an essential function in response to vascular injury and is generally viewed as the first step during which single platelets bind through specific membrane receptors to cellular and extracellular matrix constituents of the vessel wall and tissues. This response initiates thrombus formation that arrests hemorrhage and permits wound healing. Pathological conditions that cause vascular alterations and blood flow disturbances may turn this beneficial process into a disease mechanism that results in arterial occlusion, most frequently in atherosclerotic vessels of the heart and brain. Besides their relevant role in hemostasis and thrombosis, platelet adhesive properties are central to a variety of pathophysiological processes that extend from inflammation to immune-mediated host defense and pathogenic mechanisms as well as cancer metastasis [4]. TX and its metabolites are key inflammatory mediators involved in the pathogenesis of CVD. Platelet activation and enhanced coagulation are causally related to cardiovascular events [5] and might be associated with risk factors for CVD such as smoking, hypertension, and hypercholesterolemia.

The importance of platelet activation in CVD was indirectly confirmed by the benefits of antiplatelet agents [6]. A typical example is acetylsalicylic acid (ASA) that irreversibly inhibits the constitutively expressed platelet COX1 by acetylation thus preventing the formation of prostaglandin H2 and TXA_2 resulting in reduced risk of serious cardiovascular events by up to 20% in a broad range of high-risk patients. However, acetylation of platelet COX1 is not functionally effective until the maximal capacity to generate TXA_2 is reduced by at least 95–99%.

An epidemiologic study of 15,603 aspirin-treated patients with either clinically established cardiovascular disease or multiple risk factors enrolled in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial identified modifiable factors or interventions that could lower urinary 11-dehydro TXB_2 concentrations to reduce cardiovascular risks [7] (Table 2). High (top quartile) baseline urinary concentrations of 11-dehydro TXB_2 were associated with an increased risk of stroke, myocardial infarction, or cardiovascular death compared with low (bottom quartile) concentrations. Increasing age, female sex, history of peripheral artery disease, current smoking, and use of oral hypoglycemic or angiotensin-converting enzyme inhibitors were independently associated with higher urinary concentrations of 11-dehydro TXB_2, whereas aspirin doses ≥150 mg/day, history of nonsteroidal anti-inflammatory drug treatment, history of hypercholesterolemia, and statin treatment were associated with lower concentrations of 11-dehydro TXB_2. The authors concluded that the urinary concentration of 11-dehydro TXB_2 in aspirin-treated patients is a valid and modifiable determinant of stroke, myocardial infarction, or cardiovascular death in patients at risk for atherothrombotic events.

Markers of platelet activation are elevated in coronary artery diseases. A study of patients with unstable angina (n=28), stable angina (n=36) and age-/sex-matched patients without coronary artery disease (n=30) showed that TXB_2 levels were significantly higher in

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patients with unstable angina than in patients with stable angina, suggesting that markers of platelet activation could be used as markers for unstable coronary artery disease [8].

In addition, the level of TXA_2 is markedly enhanced in atherosclerosis patients. In a study of 42 patients with atherosclerosis who were undergoing surgical revascularization, the urinary levels of 11-dehydro TXB_2 were elevated in patients with atherosclerosis compared with normal subjects [9]. By contrast, the levels of 11-dehydro TXB_2 were reduced in patients taking aspirin [9].

The evidence accumulated here indicate that urinary 11-dehydro TXB_2 levels are increased in patients with or at high risk of CVD, and that interventions with ASA can lower urinary levels. Therefore, 11-dehydro TXB_2 may contribute to the pathophysiology of CVD by promoting platelet activation and aggregation.

3.2 Respiratory disease

Although there were some articles retrieved linking atherothrombosis to COPD, for example [10], or TXB_2 to asthma, e.g. [11] there were no articles that linked TXB_2 to respiratory disease related to cigarette smoke.

4 SMOKING-BIOMARKER LINK

Cigarette smoking is an established risk factor for CVD that induces inflammatory responses and enhances plaque formation in arterial vessels. The cardiovascular effects of smoking are multifactorial, and include the induction of endothelial dysfunction, which promotes vascular interactions with leukocytes, and platelet activation. Platelet activation and enhanced coagulation are causally related to cardiovascular events, and smoking increases platelet aggregation. Thus, smoking might increase the risk of CVD via endothelial dysfunction. Cigarette smoking is consistently associated with elevated 11-dehydro TXB_2 secretion from activated platelets.

Multiple cross-sectional studies have demonstrated that 11-dehydro TXB_2 levels are 29–40% higher in smokers than in non-smokers [12-15]. The 11-dehydro TXB_2 levels were 60% higher in people who smoked ≥20 cigarettes per day with a 10 mg ISO ‘tar’ content [16]. In one study, nicotine equivalents (milligrams per 24 h) were the strongest predictor of 11-dehydro TXB_2 levels in adult smokers compared with non-smokers [13], although gender and the number of cigarettes smoked per day were important factors in another study [17]. 11-Dehydro TXB_2 levels were higher in adult smokers than in non-smokers but were inversely correlated with smoking duration and carboxyhemoglobin, a marker of carbon monoxide exposure [17]. The authors concluded that the inverse association of 11-dehydro TXB_2 levels with smoking duration was influenced by the age of the subjects.

A cross-sectional study of healthy monozygotic twins (n=44, 26 males and 18 females) discordant for smoking status (smoker and non-smoker pairs) showed that urinary 11-dehydro TXB_2 levels were significantly increased in smokers than in non-smoker twins [18].

In patients taking aspirin, tobacco smoking is also associated with higher thromboxane levels and although aspirin therapy reduces thromboxane levels in smokers, it is not reduced to the same level as non-smoking controls on aspirin therapy [15, 19]. Unlike

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COX-1, COX-2 is significantly augmented by inflammatory stimuli, including cigarette smoking, and therefore may account for the positive association between $UTXB_2$ and smoking. Additional evidence that increase TxA_2 generation among smokers is mediated via COX-2 was demonstrated in a study which revealed a reduction in TxA_2 generation with the COX-2 specific inhibitor, rofecoxib, among smokers but not non-smokers [20].

In a study using a newly developed analytical technique to measure metabolites of ω-6 and ω-3 polyunsaturated fatty acids (PUFAs) such as arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (which are the precursors of various bioactive lipid mediators including prostaglandins, thromboxanes, leukotrienes, hydroxyeicosatetraenoic acid, isoprostanes, lipoxins, and resolvins) it was found that there was no difference in urinary 11-dehydro TXB_2 (or 2,3-dinor-8-iso-PGF2α) between smokers and non-smokers (although the authors state that this could be attributed to the dissimilar levels of these compounds among various individuals) [21].

It was also shown, in another study (looking at the effects of aspirin), that there was an association between smoking and TXA2 levels in the absence of platelet COX 1 activity and that smokers were found to have urinary levels of 11-dhTXB2 268 pg/mg creatine (n=9), ex-smokers 179.5 pg/mg creatine (n=18) and non-smokers 164 pg/mg creatine (n=54), showing a clear increase of urinary thromboxane in smoking subjects [22].

Similar differences in urinary TXB2 between smokers and non-smokers were also seen in a study where smokers (who had smoked cigarettes daily for at least 5 years) and nonsmokers (age-matched men who had never smoked) had urinary levels of 11-dihydroxy-TXB2 of 3.1 nmol/nmolcreatine and 0.2 nmol/nmol creatinine, respectively [23].

When smokers (n=20) with a 9-13 year history of tobacco use were compared to non-smokers (n=20) it was found that 24 hour urinary thromboxane levels were significantly higher in smokers (1.67 µg/g creatinine) than in non-smokers (1.21 µg/g creatinine [24].

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Table 2. Overview of studies on Thromboxane B2.

Author	Country	Study Period	Study Design	Study Population	Study Size; Sex, Age Distrib.	Experimental Group(s) (or Case Definition or At Risk Population)	Control Group(s) (or Controls or Median Follow-up Period)	Selection, Matching Factors
Evidence for an Association between Marker and Disease								
Eikelboom et al. [7]	Multinational	N/A	Randomized, parallel-group, double-blind trial	CHARISMA trial; patients with clinically established cardiovascular disease or multiple risk factors	15,603; M + F; ≥45 years	7802 treated with clopidogrel (75 mg/d)	7801 treated with placebo	Selected for multiple atherothrombotic risk factors, documented coronary disease, documented cerebrovascular disease, or documented symptomatic peripheral arterial disease
Evidence for an Association between Smoking and Marker								
Calapai et al. [12]	Italy	N/A	Short-term, cross-sectional	Healthy Caucasian volunteers	60; M+F; aged 23–43 years	20 smokers and 20 moderate smokers	20 never smokers	Selected for homogenous groups of people based on age, with about a decade of smoking history, number of cigarettes smoked per day, and the tar yield of the cigarettes smoked
Frost-Pineda et al. [13]	USA	N/A	Stratified, cross-sectional, observational, multicenter ambulatory study	Healthy subjects	4662; M+F; aged ≥21 years	3585 adult smokers	1077 non-smokers	Selected for those who smoked ≥1 cigarette/day for ≥12 months
Lowe et al. [12, 16]	UK	N/A	Cross-sectional	Healthy subjects	80; M+F; aged ≥21 years	20 ex-smokers; 20 subjects who regularly smoked ≤10 cigarettes per day; 20 subjects who regularly smoked ≥20 or more cigarettes per day	20 never smokers	Smokers must have smoked their current brand, from a subset of five market-leading brands, for a period exceeding 1 year prior to study commencement.

(table continues)

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Author	Country	Study Period	Study Design	Study Population	Study Size; Sex, Age Distrib.	Experimental Group(s) (or Case Definition or At Risk Population)	Control Group(s) (or Controls or Median Follow-up Period)	Selection, Matching Factors
Liu et al. [17]	USA	N/A	Cross-sectional and observational	Healthy subjects	M+F; aged ≥21 years	4000 smokers	1000 non-smokers	Smoked at least 1 cigarette per day (CPD) for at least the past 12 months, and no use of any other nicotine containing products prior to study visit 1.
Evidence for an Association between Smoking Cessation and Markers								
Saareks et al. [25]	Finland	N/A	Not stated	Healthy subjects	80; M + F; aged 20–45 years	60 healthy smoking volunteers subdivided to 15 smoking cessation;15 smoking cessation plus nicotine chewing gum or 30 smoking cessation plus nicotine patches	20 healthy non-smoking controls	Current smokers with a mean number of cigarettes (0.5–1.2 mg nicotine/cigarette) smoked daily of 19 (range 8–40)
Evidence for an Association between Nicotine Replacement Therapy and Marker								
Roethig et al. [26]	USA	N/A	Randomized, controlled, forced switching, open-label, parallel design	Healthy subjects	M + F; aged 25–65 years	64 electrically heated cigarette smoking system	33 conventional cigarette smoking	Smoked 10–40 manufactured, non-menthol cigarettes with 1–7 mg tar for ≥10 years
Martin LeRoy et al. [27]	Poland	October 2007 and April 2008.	Randomized, open-label, controlled study	Healthy Caucasian smokers	M + F; aged 30–60 years	237 electrically heated cigarette smoking system	79 conventional cigarette smoking	Current smokers of commercially available, non-menthol conventional cigarettes with a 3–10 mg tar yield and a smoking history of ≥10 years

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4.1 Smoking cessation

Smoking cessation has been shown to reduce the risk of cardiovascular diseases [28]. In addition, nicotine replacement therapy (NRT) might help smokers to quit. However, the safety of chronic NRT has not been fully established. An early study revealed a rapid decrease in the excretion of 11-dehydro TXB_2 in 8 women who were quitting smoking [29]. The urinary excretion of TX metabolites decreased rapidly after cessation of cigarette smoking, reaching a low within 3 days.

Literature searches revealed no studies since 2008 describing the effects of smoking cessation on 11-dehydro TXB_2. However, a study conducted in 2001 investigated the effect of smoking cessation or NRT on urinary TX metabolites. The study showed that 11-dehydro TXB_2 levels in non-smokers (20 age-matched controls) were approximately 25% of those in smokers (60 volunteers who had smoked for several years) [25]. 11-Dehydro TXB_2 levels decreased after smoking cessation in all previous smoker groups (including those taking nicotine chewing gum, nicotine patches or no NRT) from starting levels that were approximately double the level in non-smokers. Three days after cessation of smoking, urinary 11-dehydro TXB_2 excretion levels were reduced to approximately 75% of these starting levels, and in 14 days the levels were reduced to approximately 50% of the starting level; that is, to a level similar to that observed in non-smoking controls. In the nicotine chewing gum and in the nicotine patch groups, there were no significant changes in 11-dehydro TXB_2 excretion during the follow-up compared with the initial value. Thus, the authors concluded that nicotine delivered via chewing gum or patches might prevent the decrease in systemic eicosanoid production that occurs after smoking cessation.

Two randomized clinical trials have investigated the effects of switching from conventional cigarettes to modified risk tobacco product candidates on the urinary levels of 11-dehydro TXB_2. In the first study, 316 male and female Polish smokers (10 year history of smoking) were randomized to continue smoking conventional cigarettes (CC; N = 79) or were switched to an electrically heated cigarette smoking system series (EHCSS) K cigarette (N = 237) [27]. Urinary 11-dehydro TXB_2 excretion decreased from baseline to the end of the study (8 weeks) in the EHCSS group (from 14.5 ± 8.5 pg/24 h to 13.3 ± 8.7 pg/24 h), but excretion also decreased in the CC group (from 13.6 ± 5.6 pg/24 h to 13.3 ± 6.8 pg/24 h). 11-Dehyro TXB_2 was not significantly different between the CC group and controls.

The second study investigated the effects of switching from CC to EHCSS on the urinary levels of 11-dehydro TXB_2 over 12 months in 97 healthy adult smokers [26]. In the EHCSS group, 80% of subjects showed a significant decrease in urinary 11-dehydro TXB_2 levels from 1826 ng/24 h at baseline to 1450 ng/24 h compared with the CC group, in which the 11-dehydro TXB_2 levels remained unchanged (1856 ng/24 h at baseline and 1895 ng/24 h postbaseline).

Unfortunately, the findings of these three trials are slightly contradictory. The first showed that cessation of smoking decreased 11-dehydro TXB2 levels but that NRT might counteract the effects of smoking cessation. The second study showed 11-dehydro TXB2 levels decreased after switching to an EHCSS, and to a lesser extent when continuing CC.

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Meanwhile, the third study showed that urinary 11-dehydro TXB2 levels only decreased in subjects who switched to an EHCSS. Therefore, these findings suggest that 11-dehydro TXB2 might have limited use as a biomarker in studies examining the effects of smoking cessation except in heavy smokers.

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Table 3. Evidence for association between TXB2, smoking and smoking cessation.

Author	Subgroup	N	Marker				Effect				Adjustment Factors
			Marker (Medium)	Time of Assessment	Mean Level [unit]	Precision	Comparison	Effect Measured [unit]	Effect Size	Precision	
Association between Smoking and Marker											
Calapai et al. [12]	Smokers Moderate smokers Never-smokers	20 20 20	11-dehydro TXB_2 (urine)	Baseline	1.67 1.36 1.21 (µg/g creatinine)	0.6551 0.4439 0.3709 (SD)	24 h urine	Mean of differences, between groups (µg/g creatinine)	<0.01[a] NS[a] -	N/A N/A	None
Frost-Pineda et al. [13]	Adult smokers non-smokers	3585 1077	11-dehydro TXB_2 (urine)	Baseline	1336 1032 (ng/24 h)	1037 794 (SD)	24 h urine	Mean of differences, between groups (ng/24hr)	<0.0001[b] -	N/A N/A	None

(table continues)

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Author	Subgroup	N	Marker				Effect				Adjustment Factors
			Marker (Medium)	Time of Assessment	Mean Level [unit]	Precision	Comparison	Effect Measured [unit]	Effect Size	Precision	
Lowe et al. [16]	≥20 cigarettes/day ≤10 cigarettes/day Ex-smokers Never-smokers	20 20 20 20	11-dehydro TXB_2 (urine)	Baseline	1.654 1.563 1.519 1.0504 (µg/mg creatinine)	0.644 0.651 0.746 0.2978 (SD)	24 h urine	Mean of differences, between groups (µg/mg creatinine)	0.001[a] 0.001[a] 0.001[a] -	N/A N/A N/A N/A	None
Liu et al. [17]	smokers non-smokers	3585 1077	11-dehydro TXB_2 (urine)	Baseline	1394 1093 (ng/24 hr)	(1351–1436) (1027–1159) (95% CI)	24 h urine	Mean of differences, between groups (ng/24 h)	<0.0001[b]	N/A N/A	Age, sex, race, and BMI

(table continues)

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Author	Subgroup	N	Marker				Effect				Adjustment Factors
			Marker (Medium)	Time of Assessment	Mean Level [unit]	Precision	Comparison	Effect Measured [unit]	Effect Size	Precision	
Evidence for an Association between Smoking Cessation and Marker											
Saareks et al. [25]	Smoking cessation Smoking cessation plus nicotine chewing gum Smoking cessation plus nicotine patches non-smokers	15 15 30 20	11-dehydro TXB_2 (urine)	Last smoking day and 3, 7, and 14 days after cessation of smoking	115.8 107.5 120.0 54.1 (pg/µmol creatinine)	13.2 14.4 16.0 6.6 (SEM)	24 h urine	Mean difference between groups (pg/µmol creatinine)	P<0.05 and <0.01 between study groups and last smoking day	N/A	None

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Studies measured 24-hour urinary 11-dehydro TXB_2 levels by commercially available immunoassay kits [7, 12, 16, 18, 26, 30] or radioimmunoassay [29]. Urinary data were presented as an absolute value and, in most cases, with corrections for creatinine excretion. One study used liquid chromatography–mass spectrometry/mass spectrometry (LC–MS/MS) to measure 11-dehydro TXB_2 levels [27].

5 CONCLUSION

Urinary 11-dehydro TXB_2 may be a useful biomarker in studies examining the association between smoking and CVD events (but not those related to respiratory disease) although inter-individual variability might limit its reliability in smaller trials. The measurement of 11-dehydro TXB_2 as a biomarker was subject to considerable inter-subject variability that may limit its reliability in clinical trials of reduced risk tobacco products. If this biomarker is not able to reliably discriminate heavy smokers from moderate smokers, it is unlikely to distinguish between conventional tobacco use and reduced risk tobacco use. Finally, smoking cessation and NRT had inconsistent effects on urinary 11-dehydro TXB_2 in the studies to date. Therefore, urinary 11-dehydro TXB_2 appears to be unreliable as a biomarker for assessing the effects of smoking cessation until further studies provide clear evidence for the direction of changes in urinary 11-dehydro TXB_2 following smoking cessation or switching. Historic evidence shows that TXB_2 is increased in smokers compared to non-smokers and given the ease of measuremt of this biomarker it might be worthwhile for the monitoring of oxidative stress-related platelet activation.

Table 4. Strength of association of TXB2 with disease.

Sufficient evidence of a causal relationship	Limited mechanistic evidence for a potential role of platelets in CVD. Most evidence is observational, especially the increased levels of 11-dehydro TXB_2 in patients with CVD.
Sufficient evidence of a relationship	There is indirect evidence for a role of 11-dehydro TXB_2 in CVD because inhibition of COX1 with ASA decreases TXA_2 and 11-dehydro TXB_2 levels, which is correlated with reduced risk of CVD. 11-Dehydro TXB_2 levels were higher in patients who developed stroke, myocardial infarction, or cardiovascular death compared with individuals without CVD.

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Search 1 *(Thromboxane OR 11-dehydrothromboxane B_2) AND (smokers OR smoking OR nicotine replacement OR cessation) AND ("2008"[Date - Publication]: "2015"[Date - Publication]) AND English[Language]*

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Search 2 *(Thromboxane OR 11-dehydrothromboxane B_2) AND ((cardiovascular disease) AND (association)) AND ("2008"[Date - Publication]: "2015"[Date - Publication]))) AND English[Language])*

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6.4 Appendix 4 References retrieved using search 3

Search 3 *(Thromboxane OR 11-dehydrothromboxane B_2) AND ((respiratory disease) AND (association)) AND ("2008"[Date - Publication]: "2015"[Date - Publication])) AND English[Language])*

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Sep;25(8):491-7. doi: 10.1055/s-0028-1085068. Epub 2008 Aug 22. PubMed PMID: 18726836.

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6.5 Appendix 5 Articles excluded from Search 1

Exclusion criteria E1 TXB_2 used only as control/biomarker of exposure

Larsen SB, Grove EL, Neergaard-Petersen S, Würtz M, Hvas AM, Kristensen SD. Determinants of reduced antiplatelet effect of aspirin in patients with stable coronary artery disease. PLoS One. 2015 May 18;10(5):e0126767. doi: 10.1371/journal.pone.0126767. eCollection 2015. PubMed PMID: 25993271; PubMed Central PMCID: PMC4436265

Carroll RC, Craft RM, Snider CC, Aligeti VR, Wortham DC. A comparison of VerifyNowR with PlateletMappingR--detected aspirin resistance and correlation with urinary thromboxane. Anesth Analg. 2013 Feb;116(2):282-6. doi: 10.1213/ANE.0b013e318277de06. Epub 2013 Jan 9. PubMed PMID: 23302970.

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Exclusion criteria E2 TXB_2 lacked link to disease or smoking

Fuentes E, Palomo I. Mechanism of antiplatelet action of hypolipidemic, antidiabetic and antihypertensive drugs by PPAR activation: PPAR agonists: new antiplatelet agents. Vascul Pharmacol. 2014 Sep;62(3):162-6. doi: 10.1016/j.vph.2014.05.008. Epub 2014 May 27. Review. PubMed PMID: 24874279.

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Exclusion criteria E3 Disease not covered by search categories

Gonçalves LH, Silva MV, Duarte RC, Dusse LM, Fernandes AP, Bosco AA, Gomes KB, Carvalho Md. Acetylsalicylic acid therapy: influence of metformin use and other variables on urinary 11-dehydrothromboxane B2 levels. Clin Chim Acta. 2014 Feb 15;429:76-8. doi: 10.1016/j.cca.2013.11.028. Epub 2013 Dec 4. PubMed PMID: 24316050.

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Nelson EA. Venous leg ulcers. BMJ Clin Evid. 2011 Dec 21;2011. pii: 1902. PubMed PMID: 22189344; PubMed Central PMCID: PMC3275133.

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Seok JI, Joo IS, Yoon JH, Choi YJ, Lee PH, Huh K, Bang OY. Can aspirin resistance be clinically predicted in stroke patients? Clin Neurol Neurosurg. 2008 Feb;110(2):110-6. Epub 2007 Oct 26. PubMed PMID: 17964711.

Exclusion criteria E4 Studies of passive or parental smoking

None

Exclusion criteria E5 Studies in a narrow population (e.g. pregnant women)

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Exclusion criteria E6 *In vitro* studies or studies using *in vivo* animal models

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Huang RY, Li MY, Ng CS, Wan IY, Kong AW, Du J, Long X, Underwood MJ, Mok TS, Chen GG. Thromboxane A2 receptor α promotes tumor growth through an autoregulatory feedback pathway. J Mol Cell Biol. 2013 Dec;5(6):380-90. doi: 10.1093/jmcb/mjt038. Epub 2013 Oct 9. PubMed PMID: 24115277.

An J, Li JQ, Wang T, Li XO, Guo LL, Wan C, Liao ZL, Dong JJ, Xu D, Wen FQ. Blocking of thromboxane A_2 receptor attenuates airway mucus hyperproduction induced by cigarette smoke. Eur J Pharmacol. 2013 Mar 5;703(1-3):11-7. doi: 10.1016/j.ejphar.2013.01.042. Epub 2013 Feb 8. PubMed PMID: 23399768.

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Mullins KB, Thomason JM, Lunsford KV, Pinchuk LM, Langston VC, Wills RW, McLaughlin RM, Mackin AJ. Effects of carprofen, meloxicam and deracoxib on platelet function in dogs. Vet Anaesth Analg. 2012 Mar;39(2):206-17. doi: 10.1111/j.1467-2995.2011.00684.x. Epub 2012 Jan 17. PubMed PMID: 22248445.

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Milara J, Ortiz JL, Juan G, Guijarro R, Almudever P, Martorell M, Morcillo EJ, Cortijo J. Cigarette smoke exposure up-regulates endothelin receptor B in human pulmonary artery endothelial cells: molecular and functional consequences. Br J Pharmacol. 2010 Dec;161(7):1599-615. doi: 10.1111/j.1476-5381.2010.00979.x. PubMed PMID: 20698855; PubMed Central PMCID: PMC3010570.

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Atherosclerosis. 2008 Feb;196(2):608-16. Epub 2007 Aug 13. PubMed PMID: 17706224.

Exclusion criteria E7 Studies in which sICAM was measured for toxicological or forensic purposes

None

Exclusion criteria E8 Studies with no comparison to smoking and cessation/switching

Larsen SB, Grove EL, Pareek M, Kristensen SD, Hvas AM. Calprotectin and platelet aggregation in patients with stable coronary artery disease. PLoS One. 2015 May 13;10(5):e0125992. doi: 10.1371/journal.pone.0125992. eCollection 2015. PubMed PMID: 25970343; PubMed Central PMCID: PMC4430524.

Vazzana N, Ganci A, Cefalù AB, Lattanzio S, Noto D, Santoro N, Saggini R, Puccetti L, Averna M, Davì G. Enhanced lipid peroxidation and platelet activation as potential contributors to increased cardiovascular risk in the low-HDL phenotype. J Am Heart Assoc. 2013 Apr 4;2(2):e000063. doi: 10.1161/JAHA.113.000063. PubMed PMID: 23557750; PubMed Central PMCID: PMC3647282.

Sadeghi M, Emami A, Ziyaei N, Yaran M, Golabchi A, Sadeghi A. Aspirin resistance and ischemic heart disease on Iranian experience. Adv Biomed Res. 2012;1:33. doi: 10.4103/2277-9175.99345. Epub 2012 Aug 3. PubMed PMID: 23210092; PubMed Central PMCID: PMC3507033.

Salama MM, Morad AR, Saleh MA, Sabri NA, Zaki MM, ElSafady LA. Resistance to low-dose aspirin therapy among patients with acute coronary syndrome in relation to associated risk factors. J Clin Pharm Ther. 2012 Dec;37(6):630-6. doi: 10.1111/j.1365-2710.2009.01083.x. Epub 2009 Aug 12. PubMed PMID: 23121257.

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Warner JH, Liang Q, Sarkar M, Mendes PE, Roethig HJ. Adaptive regression modeling of biomarkers of potential harm in a population of U.S. adult cigarette smokers and nonsmokers. BMC Med Res Methodol. 2010 Mar 16;10:19. doi: 10.1186/1471-2288-10-19. PubMed PMID: 20233412; PubMed Central PMCID: PMC2846953.

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Vila L, Martinez-Perez A, Camacho M, Buil A, Alcolea S, Pujol-Moix N, Soler VM, Antón R, Souto JC, Fontcuberta J, Soria JM. Heritability of thromboxane A2 and prostaglandin E2 biosynthetic machinery in a Spanish population. Arterioscler Thromb Vasc Biol. 2010 Jan;30(1):128-34. doi: 10.1161/ATVBAHA.109.193219. Epub 2009 Oct 22. PubMed PMID: 19850905; PubMed Central PMCID: PMC2831176.

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6.6 Appendix 6 Articles excluded from Search 2

Exclusion criteria E1 TXB_2 used only as control/biomarker of exposure

Karolczak K, Pietruszynski R, Drzewoski J, Kasznicki J, Watala C. Aspirin dose increase from 75 to 150 mg suppresses red blood cell contribution to suboptimal platelet response to aspirin in patients with CAD. Cardiovasc Drugs Ther. 2013 Dec;27(6):549-58. doi: 10.1007/s10557-013-6480-y. PubMed PMID: 23963688.

Olson MT, Kickler TS, Lawson JA, McLean RC, Jani J, FitzGerald GA, Rade JJ. Effect of assay specificity on the association of urine 11-dehydro thromboxane B2 determination with cardiovascular risk. J Thromb Haemost. 2012 Dec;10(12):2462-9. doi: 10.1111/jth.12026. PubMed PMID: 23072449; PubMed Central PMCID: PMC3718475.

Chakroun T, Addad F, Yacoub S, Abderrezak F, Gerotziafas GT, Abdelkafi S, Hassine M, Gamra H, Hatmi M, Elalamy I. The cyclooxygenase-1 C50T polymorphism is not associated with aspirin responsiveness status in stable coronary artery disease in Tunisian patients. Genet Test Mol Biomarkers. 2011 Jul-Aug;15(7-8):513-6. doi: 10.1089/gtmb.2010.0225. Epub 2011 Mar 24. PubMed PMID: 21434767.

Seidel H, Rahman MM, Scharf RE. Monitoring of antiplatelet therapy. Current limitations, challenges, and perspectives. Hamostaseologie. 2011 Feb;31(1):41-51. doi: 10.5482/ha-1146. Review. PubMed PMID: 21311822.

Chen JP, Hou D, Pendyala L, Goudevenos JA, Kounis NG. Drug-eluting stent thrombosis: the Kounis hypersensitivity-associated acute coronary syndrome revisited. JACC Cardiovasc Interv. 2009 Jul;2(7):583-93. doi: 10.1016/j.jcin.2009.04.017. Review. PubMed PMID: 19628178.

Addad F, Chakroun T, Abderazek F, Ben-Farhat M, Hamdi S, Dridi Z, Gamra H, Hassine M, Samama MM, Elalamy I. Response variability to aspirin and one-year prediction of vascular events in patients with stable coronary artery disease. J Thromb Thrombolysis. 2010 Jan;29(1):108-13. doi: 10.1007/s11239-009-0335-1. PubMed PMID: 19381450.

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Exclusion criteria E2 TXB_2 lacked link to disease or smoking

Faraday N, Yanek LR, Vaidya D, Kral B, Qayyum R, Herrera-Galeano JE, Moy TF, Becker DM, Becker LC. Leukocyte count is associated with increased platelet reactivity and diminished response to aspirin in healthy individuals with a family history of coronary artery disease. Thromb Res. 2009 Jul;124(3):311-7. doi: 10.1016/j.thromres.2008.12.031. Epub 2009 Jan 30. PubMed PMID: 19185906; PubMed Central PMCID: PMC2763116.

Exclusion criteria E3 Disease not covered by search categories

Mir A, Frank S, Journeycake J, Wolovitis J, Guleserian K, Heistein L, Lemler M. Aspirin Resistance in Single-Ventricle Physiology: Aspirin Prophylaxis Is Not Adequate to Inhibit Platelets in the Immediate Postoperative Period. Ann Thorac Surg. 2015 Jun;99(6):2158-64. doi: 10.1016/j.athoracsur.2015.02.026. Epub 2015 Apr 25. PubMed PMID: 25921261.

Wang J, Xiong X, Feng B. Aspirin resistance and promoting blood circulation and removing blood stasis: current situation and prospectives. Evid Based Complement Alternat Med. 2014;2014:954863. doi: 10.1155/2014/954863. Epub 2014 Feb 18. Review. PubMed PMID: 24696702; PubMed Central PMCID: PMC3948594.

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Salama MM, Morad AR, Saleh MA, Sabri NA, Zaki MM, ElSafady LA. Resistance to low-dose aspirin therapy among patients with acute coronary syndrome in relation to

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associated risk factors. J Clin Pharm Ther. 2012 Dec;37(6):630-6. doi: 10.1111/j.1365-2710.2009.01083.x. Epub 2009 Aug 12. PubMed PMID: 23121257.

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Exclusion criteria E4 Studies of passive or parental smoking

None

Exclusion criteria E5 Studies in a narrow population (e.g. pregnant women)

Vazzana N, Guagnano MT, Cuccurullo C, Ferrante E, Lattanzio S, Liani R, Romano M, Davì G. Endogenous secretory RAGE in obese women: association with platelet activation and oxidative stress. J Clin Endocrinol Metab. 2012 Sep;97(9):E1726-30. doi: 10.1210/jc.2012-1473. Epub 2012 Jul 3. PubMed PMID: 22761461.

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Exclusion criteria E7 Studies in which sICAM was measured for toxicological or forensic purposes

None

Exclusion criteria E8 Studies with no comparison to smoking and cessation/switching

Medina S, Domínguez-Perles R, Moreno DA, García-Viguera C, Ferreres F, Gil JI, Gil-Izquierdo Á. The intake of broccoli sprouts modulates the inflammatory and vascular prostanoids but not the oxidative stress-related isoprostanes in healthy humans. Food Chem. 2015 Apr 15;173:1187-94. doi: 10.1016/j.foodchem.2014.10.152. Epub 2014 Nov 7. PubMed PMID: 25466142.

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6.7 Appendix 7 Articles excluded from Search 3

Exclusion criteria E1 TXB_2 used only as control/biomarker of exposure

None

Exclusion criteria E2 TXB_2 lacked link to disease or smoking

None

Exclusion criteria E3 Disease not covered by search categories

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Exclusion criteria E4 Studies of passive or parental smoking

None

Exclusion criteria E5 Studies in a narrow population (e.g. pregnant women)

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Exclusion criteria E6 *In vitro* studies or studies using *in vivo* animal models

Zhou W, Abdurahman A, Umar A, Iskander G, Abdusalam E, Berké B, Bégaud B, Moore N. Effects of Cydonia oblonga Miller extracts on blood hemostasis, coagulation and fibrinolysis in mice, and experimental thrombosis in rats. J Ethnopharmacol. 2014 May 28;154(1):163-9. doi: 10.1016/j.jep.2014.03.056. Epub 2014 Apr 4. PubMed PMID: 24704668.

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Exclusion criteria E7 Studies in which sICAM was measured for toxicological or forensic purposes

None

Exclusion criteria E8 Studies with no comparison to smoking and cessation/switching

Naik MU, Stalker TJ, Brass LF, Naik UP. JAM-A protects from thrombosis by suppressing integrin αIIbβ3-dependent outside-in signaling in platelets. Blood. 2012 Apr 5;119(14):3352-60. doi: 10.1182/blood-2011-12-397398. Epub 2012 Jan 23. PubMed PMID: 22271446; PubMed Central PMCID: PMC3321861.

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