

# Abstract

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## Incomplete inhibition of thromboxane biosynthesis by ASA: determinants and effect on cardiovascular risk

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**BACKGROUND:** Incomplete inhibition of thromboxane generation has been associated independently and significantly with an increased risk of serious cardiovascular (CV) events in one large study of high vascular risk patients treated with acetyl salicylic acid (ASA).

**AIMS:** First, to determine the external validity of the association of elevated urinary 11-dehydro thromboxane B2 concentrations with increased CV risk in an independent population of high vascular risk patients. Second, to determine if there are any modifiable factors or interventions that lower urinary 11-dehydro thromboxane B2 concentrations in ASA-treated patients at high risk of CV events and may thereby reduce CV risk.

**METHODS:** Urinary 11-dehydro thromboxane B2 concentrations were prospectively measured in 3,261 ASA-treated patients at least one month after being randomly assigned placebo or clopidogrel in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. Patients were followed-up for the first occurrence of stroke, myocardial infarction or CV death.

**RESULTS:** Baseline urinary 11-dehydro thromboxane B2 concentrations in the highest quartile were associated with an increased risk of stroke, MI or CV death compared with the lowest quartile (Adjusted Hazard Ratio [HR] 1.66; 95% CI: 1.06 to 2.61, p=0.03). Increasing age, female sex, history of peripheral artery disease, current smoking, and oral hypoglycemic or angiotensin converting enzyme (ACE) inhibitor therapy were independently associated with higher urinary concentrations of 11-dehydro thromboxane B2, while ASA dose  $\geq 150$ mg/d, history of treatment with non-steroidal anti-inflammatory drugs (NSAIDs), history of hypercholesterolemia, and statin treatment were associated with lower concentrations. Randomization to clopidogrel (vs. placebo) did not reduce urinary 11-dehydro thromboxane B2 levels nor did it reduce the hazard of CV events in patients in the highest quartile of urinary 11-dehydro thromboxane B2 levels.

**CONCLUSIONS:** In aspirin treated patients, urinary concentrations of 11-dehydro thromboxane B2 are an externally valid and potentially modifiable determinant of stroke, MI or CV death in patients at risk of atherothrombotic events. The potential for higher doses of ASA and statins to reduce urinary 11-dehydro thromboxane concentrations and CV risk should prompt randomized evaluation of the clinical efficacy of titrating doses according to urinary 11-dehydro thromboxane B2 concentrations, and the clinical efficacy of other treatments that reduce thromboxane production.

