

Leukotrienes and residual inflammatory risk in coronary artery disease

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The current European guidelines on cardiovascular disease (CVD) prevention do not recommend routine assessment of biomarkers for refinement of risk stratification, mainly due to the lack of state-of-the-art assessment of their added value on top of conventional risk factors.¹ Although the function and origin of a candidate biomarker, and whether it is causally related to CVD, have been stated to be irrelevant from the perspective of risk stratification,¹ a recent position paper from the European Society of Cardiology emphasized the value of biomarkers having possible causal involvement, with eicosanoids as one example of such causally related biomarkers in atherosclerosis.²

The LTIMI (Leukotrienes and Thromboxane In Myocardial Infarction) study aimed to assess the predictive value of these lipid mediators from the eicosanoid class in coronary artery disease (CAD). In this issue of the *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Stodólkiewicz et al³ present the results from the LTIMI study for urinary leukotriene E₄ (LTE₄). Notably, the investigators demonstrated increased urinary LTE₄ levels in patients with acute coronary syndromes (ACSs) as compared with those with stable CAD.³ Leukotrienes are inflammatory lipid mediators derived from the 5-lipoxygenase pathway of arachidonic acid metabolism (FIGURE 1) and have emerged as major players in the development of atherosclerosis and ischemic heart disease,⁴ which makes them an attractive candidate for causally related biomarkers of CVD risk.

Due to the absence of measurable circulating levels, other matrices have been used to demonstrate the value of leukotrienes as CVD biomarkers, including saliva⁵ and urine.^{6,7} Urinary LTE₄ was established in studies on asthma as a reliable measure of the whole-body leukotriene production,^{6,7} and was subsequently shown to be increased in, for example, CVD.⁸ A further insight into urinary LTE₄ as a CVD risk marker has also been provided by studies on patients with

obstructive sleep apnea. The studies revealed that both obesity and severity of nocturnal hypoxia were independent predictors of increased urinary LTE₄ levels,⁹ which have been linked to reactions promoting atherosclerosis.¹⁰

Given the above, urinary LTE₄ could potentially complement other inflammatory biomarkers in CVD risk stratification, of which high-sensitivity C-reactive protein (hs-CRP) has been the most extensively studied.^{11,12} Indeed, Stodólkiewicz et al³ showed that both urinary LTE₄ and hs-CRP levels were increased in patients with ACS compared with those with stable CAD in the LTIMI study. However, urinary LTE₄ and hs-CRP levels were not associated with each other, suggesting a possible differential predictive value, depending on which inflammatory biomarker is measured.

The recent CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) trial reinforced the role of inflammation as a causal factor in atherosclerosis.¹¹ Using a hs-CRP level of 2 mg/l or higher as an inclusion criterion, interleukin-1 β (IL-1 β) antibody treatment led to an approximately 15% risk reduction for a combined endpoint including nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death after a median follow-up of 3.7 years. The CANTOS trial consequently raised the notion of a residual inflammatory risk in patients with CAD and the assessment of hs-CRP as an inflammatory biomarker to identify patients potentially more likely to benefit from the addition of an anti-inflammatory treatment to conventional secondary prevention.¹¹

In addition to the IL-1 β antibody canakinumab,¹¹ also other anti-inflammatory treatments are under evaluation in atherosclerosis and CAD.¹³ In this context, it is important that antileukotrienes are currently used in asthma,⁷ and that experimental^{4,14} as well as retrospective pharmacoepidemiological studies¹⁵ support the beneficial effects of targeting the leukotriene pathway in CVD. The question arises of whether increased urinary LTE₄ levels could then be

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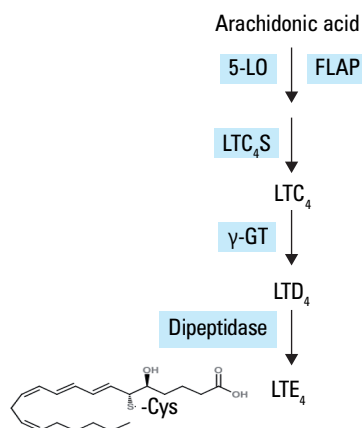
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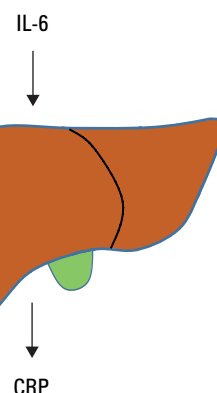
FIGURE 1

Leukotriene (LT) biosynthesis through the 5-lipoxygenase (5-LO) pathway of arachidonic acid metabolism, generating the urinary biomarker LTE_4 . The acute phase reactant C-reactive protein (CRP) is also shown.

Abbreviations: CVD, cardiovascular disease; FLAP, 5-LO-activating protein; γ -GT, γ -glutamyltranspeptidase; IL-6, interleukin 6; LTC_4S , LTC_4 synthase



Urinary biomarker
Possible causal involvement in atherosclerosis
Lacks reference values
– Acute coronary syndrome
– Atherosclerosis
– Obesity
– Obstructive sleep apnea



Circulating biomarker
Most extensively studied CVD biomarker
High-sensitivity measurement techniques
Established cutoff values for CVD risk
Not implemented in clinical guidelines

used as a biomarker to identify patients with CAD with an activated leukotriene pathway as a driver of the atherosclerotic process, similarly to the use of hs-CRP in the CANTOS trial. The results of the LTIMI study presented in this issue of the journal become even more important in the context of urinary LTE_4 as a potential biomarker to select patients for evaluating antileukotrienes as optimizers of CVD prevention. However, the baseline urinary LTE_4 levels were not significantly different between the patient groups stratified according to whether the event occurred during the 1-year follow-up or not.³ Nevertheless, such analysis of the baseline values based on events in the follow-up instead of a prospective design based on urinary LTE_4 levels at baseline may not allow to fully assess the predictive value of urinary LTE_4 . It should also be noted that making the same comparison between the groups with or without events during the follow-up did not reveal a predictive value for baseline hs-CRP in this population either.³ Moreover, the assessment of baseline biomarkers during the acute phase cannot rule out that not only atherosclerosis but also myocardial ischemia may have considerably contributed to the observed inflammatory response. Consequently, urinary LTE_4 levels exhibited substantial variations over time, indicating that larger cohorts with more careful monitoring of the time points of sampling in relation to, for example, the onset of chest pain may be needed to fully assess urinary LTE_4 as a prognostic biomarker of CVD.

In summary, the study by Stodółkiewicz et al¹³ makes an important contribution to clarifying the role of biomarkers in CVD, as well as reinforces the role of inflammation in general, and leukotrienes in particular, in ACS. At the same time,

the study also emphasizes the need for state-of-the-art large biomarker trials to fill the gaps in knowledge when it comes to identifying the optimal inflammatory biomarkers for CVD risk stratification and to guide therapeutic decision making in patients with CAD.

NOTE The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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