# Novel biomarkers for risk stratification in NSTE-ACS: Is there place for Cathepsin S?

**Brief title: Novel biomarkers for risk stratification in NSTE-ACS**

**Cover title: Is there place for Cathepsin S?**

Charalambos Antoniades, MD, PhD[a†], Murray D. Polkinghorne, MBChB, MPhil[a]

[a]Acute Vascular Imaging Centre, Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, OX3 9BQ, UK

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**Corresponding Author:**

Professor Charalambos Antoniades

Acute Multidisciplinary Imaging & Interventional Centre

Level 2 John Radcliffe Hospital

Headington Oxford OX39DU

United Kingdom

[†]Email: charalambos.antoniades@cardiov.ox.ac.uk;

Tel (direct line): +441865228340

**Twitter:** @Charis_Oxford

Precision medicine offers enormous opportunities for improvement of clinical outcomes in cardiovascular medicine, and this is particularly relevant for patients with non-ST elevated acute coronary syndromes (NSTE-ACS) (1). However, the design and deployment of such diagnostic and therapeutic strategies, requires deep understanding of the pathophysiology of NSTE-ACS. Indeed, vascular inflammation is considered to be a fundamental mechanism behind atherosclerotic plaque rupture(2,3), a concept confirmed by the recent clinical trials(4,5) demonstrating reduction of cardiovascular risk by targeting specific inflammatory pathways(6,7). To optimise such therapeutic interventions, there is the unmet need to a) discover the most important druggable therapeutic targets and b) develop new ways to guide the application of high-precision treatments to the right patient, at the most appropriate time, to be effective. Although imaging of disease activity offers unique opportunities to detect the vulnerable plaque and the vulnerable patient(8), strategies that combine imaging biomarkers with clinical risk factors and potentially plasma and/or genetic biomarkers, have the potential to revolutionise precision medicine in acute cardiovascular medicine (9-12).

In search of such therapeutic targets in acute coronary syndromes, cathepsin S (CTSS) has emerged(13). CTSS is one of an 11-member family of cysteine proteases, found to be abundant in atherosclerotic plaques, where it seems to participate in cholesterol metabolism and apoptosis in smooth muscle cells and macrophages(14). Beyond its use as a target for novel therapeutics (13), CTSS has also emerged as a rational blood biomarker of prognostic value. Indeed, clinical studies have demonstrated a positive association between circulating CTSS and the risk of cardiovascular death (15).

Although clinical risk stratification scores, like the Global Registry of Acute Coronary Events (GRACE) risk score, perform well in predicting all-cause mortality and/or myocardial infarction(1) it is unclear whether their performance can improve further by adding plasma biomarkers like cathepsin S.

In this week's issue of *JACC,* Stamatelopoulos et al(16) explore the incremental value of circulating CTSS, for the prognosis of patients with NSTE-ACS over and above the GRACE risk score. The study enrolled 1112 patients with NSTE-ACS, in which serum CTSS levels were used to risk-stratify them for the primary endpoint of all-cause mortality and a secondary endpoint of cardiovascular death over an 8-years follow-up period (17). Patients in the highest CTSS quartiles displayed an increased prevalence of type 2 diabetes mellitus (T2DM) and left ventricular ejection fraction (LVEF), with progressively increasing hsCRP, high-sensitivity troponin-T (hsTnT) and GRACE risk scores across all quartiles. Multivariable analyses revealed that patients in the highest quartile of CTSS had 2.58 times higher risk for cardiovascular death, and 1.89 times higher risk for all-cause mortality, compared to those in the lower quartiles. Importantly, this prognostic value of CTSS remained significant even after adjustment for the GRACE score, LVEF and hsTnT.

This assessment is of clear clinical value, however there are a few areas where additional insight would have been welcome. As a single-centre, retrospective study the findings may suffer from selection bias and external validation in completely independent, and ideally prospective cohorts, is essential to ensure generalisability of the findings. Furthermore, serial CTSS measurements might have allowed us to better appreciate the temporal relationship between CTSS levels and post NSTE-ACS outcomes. Nevertheless, these findings provide impetus for the continued assessment of CTSS as a clinically-relevant biomarker in other conditions in addition to NSTE-ACS (18), like dilated cardiomyopathy(19), atrial fibrillation (20) and others.

Over the last few decades, it has become clear that singular biomarkers for cardiovascular disease often fail to effectively translate into clinical practice in part owing to an incomplete capturing of disease pathophysiology and poorly implemented performance benchmarks. This has introduced the need for a more holistic approach in biomarker development, that would include networks of biomarkers in the context of multi-omic panels (9). It is likely that the value of biomarkers like CTSS would be critical if used as part of such a multi-omic approach; that may also incorporate clinical risk factors, genetic information and advanced imaging, integrated using prognostic modelling or artificial intelligence approaches. Integration of all these approaches is essential for the introduction of precision medicine in clinical practice (Figure 1) (12).

Overall, this elegant work by Stamatelopoulos et al(16), provides the first clear evidence of the superiority of CTSS in stratifying long-term mortality risk in patients with NSTE-ACS beyond the GRACE risk score. This is in line with our current mechanistic understanding of the relationship between CTSS and atherosclerotic disease and paves the way for further investigations into the validity of CTSS as a prognostic biomarker in acute coronary syndromes, as a stand-alone biomarker as well as part of multi-omic, multifactorial prognostic models that could transform clinical care in the near future.

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**Figure 1: Present and future of risk stratification, leading to precision medicine**. Current clinical practice uses fragmented data for cardiovascular risk stratification, that include clinical information, individual biomarkers as well as imaging, assuming that the experienced clinician will weight and interpret these multi-dimensional data, making decisions about the management of the patient. The future is expected to use artificial intelligence to interpret digital information about the patient, multi-omic screening and advanced image analysis tools, which will be integrated into prognostic models that will guide clinical care. Then we will have achieved implementation of precision medicine in clinical practice. CVD: Cardiovascular disease; T2DM: Type 2 diabetes mellitus; NSTE-ACS: Non ST-elevated Acute coronary syndromes; CKD: Chronic kidney disease; CMR: Cardiac magnetic resonance; LVEF: Left ventricular ejection fraction; hsTnT: High sensitivity troponin T; CCTA: Computed tomography angiography; PET: Positron emission tomography; FAI: Fat attenuation index; AI: artificial intelligence; ML: Machine learning.

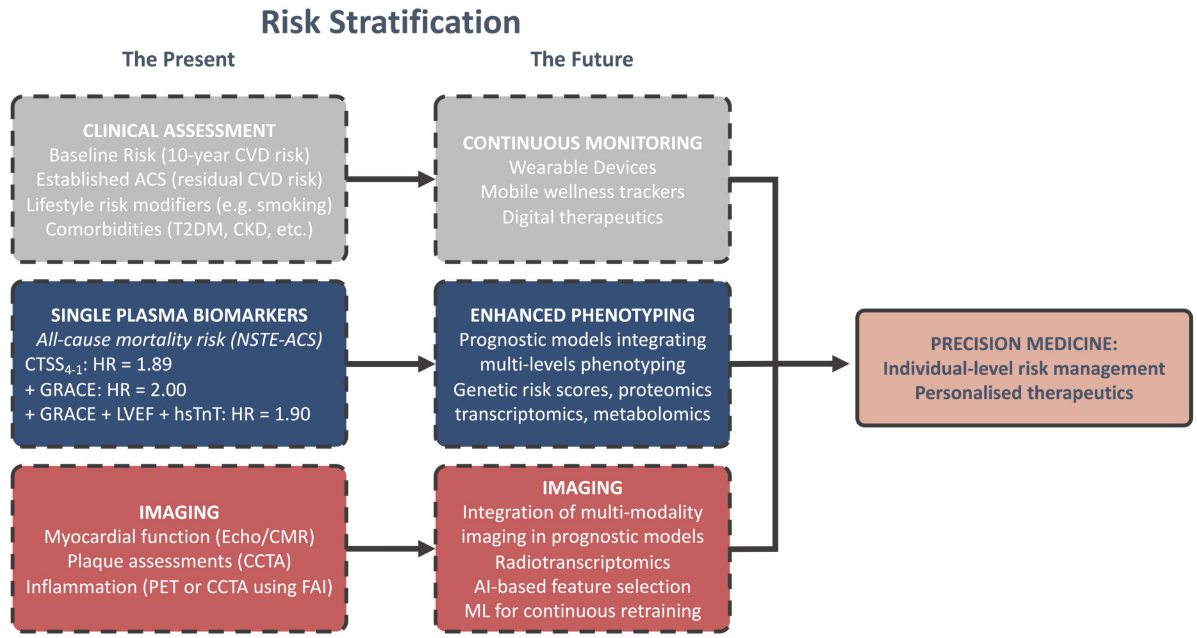


**Figure 1:** The present and future of risk stratification, leading to precision medicine.


**Antoniades Headshot**