

NAME OF PROJECT: Identification of platelet activation markers predictive of cardiovascular events

Subcommittee: Platelet physiology in collaboration with the Vascular Biology SSC

- **Person responsible:**

Chair: Marie Lordkipanidzé;

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- **Design:** systematic review and meta-analysis

- **Aim/Objective/Rationale (Needs assessment / Reason)**

The aim of the project is to evaluate the strength of evidence in published literature for the use of different platelet activation markers in the prediction of the occurrence of cardiovascular events. To achieve this aim, the objective of the project is to conduct a comprehensive systematic review of the literature, by means of multiple database query, reporting data on this topic in acute coronary syndrome patients.

Platelets are known to play a fundamental role in acute coronary syndromes. After atherosclerotic plaque rupture, platelets can form occlusive thrombi leading to acute ischemic events. Moreover, an increased platelet activation is often associated with the presence of cardiovascular risk factors including, for example, diabetes mellitus, hypertension, hypercholesterolaemia and smoking. Antiplatelet therapy is, therefore, the key pharmacological treatment in secondary cardiovascular prevention. However, morbidity and mortality in cardiovascular patients remain significant despite the administration of the dual antiplatelet therapy. Despite undisputable benefits of current antiplatelet strategies, a considerable number of patients continue to experience adverse thrombotic events.

It could therefore be assumed that the assessment of platelet activation markers may be a useful tool for an improved characterization of the thrombotic risk in a variety of clinical conditions including acute coronary syndromes.

- **Background**

The improvement of the thrombotic risk stratification especially of coronary artery disease (CAD) patients is a major challenge. The currently used risk scores are designed to predict mortality and/or the incidence of adverse cardiovascular events. They generally include clinical and laboratory parameters such as sex, age, prior infarction, TIMI flow, left ventricular ejection, leukocyte count, creatinine clearance, and diabetes mellitus.

Unfortunately, to date, no risk score takes into consideration the platelet activation status, although increased platelet activation has been associated with various pathological conditions such as myocardial infarction, stroke, peripheral vascular disease and other inflammatory diseases.

Platelet activation can be assessed *ex vivo* by functional tests, such as the classic whole blood- or platelet-rich-plasma-aggregometry and/or point-of-care tests such as VerifyNow or PFA-100, and by flow cytometry through the analysis of the expression of surface platelet activation proteins.

More easily, the evaluation of **soluble activation markers** (through their plasma concentration measurement) could be a promising candidate in order to be included in a risk score. Soluble markers include proteins stored within dense, alpha and lysosomal granules, which can be secreted upon platelet activation, as well as products of receptor shedding (e.g. sGPIb (glycocalicin), sGPV, sGPVI, sP-selectin, sCD40L).

- **Method**

In order to verify the existence of a **soluble platelet activation marker** predictive of cardiovascular events, the project will be organized as follows:

1° step:

Comprehensive review and meta-analysis of the literature reporting the assessment, in CAD patients, and the predictive value for cardiovascular events of the following 14 soluble platelet activation biomarkers:

- CD40L
- GPVI
- Glicocalicin GPIb
- Serotonin
- TSP1
- PF4
- β TG
- SCUBE 1
- MMP2
- MMP9
- 11 deidro TX B2
- 2,3 dInor TX
- GPV
- P selectin

We will perform the literature search using PubMed, Embase and Web of Science databases. Specific keywords will be defined in order to limit the query to our specific topic and appropriate filters (such as original articles, English language, homo sapiens) will be applied.

2° step:

If the systematic review of the literature highlights a lack of studies that investigate/support the predictive value of these markers, an additional analysis will be performed in order to verify whether any of the selected markers is able to discriminate the pathological condition and/or its clinical presentation (acute vs stable cardiovascular disease) from the healthy status.

- **Expected timeline:**

- o Project stage/set up: submitted
- o Launch: ISTH Melbourne meeting, 2019
- o Duration: 1 year
- o Finalization/analysis: 2020
- o Reporting: ISTH Milan meeting, 2020

- **Expected outcomes (ie. publications):**

- o Publication type (SSC Communication, Guidance document or original article):

Systematic review and meta-analysis / call for action

References:

- Ferroni P et al. Biomarkers of platelet activation in acute coronary syndromes. *Thromb Haemost* 2012;108:1109-1123
- Mathur A, Robinson MS, Cotton J, Martin JF, Erusalimsky JD. Platelet reactivity in acute coronary syndromes: evidence for differences in platelet behaviour between unstable angina and myocardial infarction. *Thromb. Haemost.* 2001;85(6):989–94.
- Bucceri S, D'Arrigo P, Franchina G, Capodanno D. Risk Stratification in Patients with Coronary Artery Disease: a Practical Walkthrough in the Landscape of Prognostic Risk Models. *Interventional Cardiology Review* 2018;13(3):112–20
- Kannan M, Ahmad F, Saxena R. Platelet activation markers in evaluation of thrombotic risk factors in various clinical settings. *Blood Rev* 2019 [Epub ahead of print]