Appropriate criteria for the definition of type 4a MI

Silvain J.[1]*, Hausenloy D.J[2-5]. and Zeitouni M.[1]

[1] Sorbonne Université, ACTION Study Group, INSERM UMRS 1166, Institut de Cardiologie, Hôpital Pitié-Salpêtrière (AP-HP), Paris, France

[2] Cardiovascular & Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore

[3] National Heart Research Institute Singapore, National Heart Centre, Singapore

[4] Yong Loo Lin School of Medicine, National University Singapore, Singapore

[5] The Hatter Cardiovascular Institute, University College London, London, UK

*** Address for Correspondence:**

Johanne Silvain, MD, PhD

Sorbonne Université, ACTION Study Group, Institut de Cardiologie, Hôpital Pitié-Salpêtrière (Assistance Publique-Hôpitaux de Paris)

47-83 bld de l'Hôpital, 75013 Paris, France

Email :johanne.silvain@aphp.fr ; Twitter: @ActionCoeur.

We thank our Swedish colleagues from the Department of Medical Sciences at the Uppsala Clinical Research Center for their comment on our work on periprocedural myocardial infarction and injury. They asked for additional data on the prognosis of patients who had an increase of cardiac troponin (cTn) after an elective percutaneous coronary intervention (PCI) that was lower than 5 x 99th percentile upper reference limit but also had one of the non-cTn criteria for type 4a MI, i.e., clinical or electrocardiographic signs of myocardial ischemia, imaging evidence of loss of viable myocardium or procedural disruption of coronary blood flow. We agree that more data are needed to clarify the prognostic independence and additive value of non-biomarkers related evidence of myocardial ischemia in the setting of elective PCI, as they are underreported. First, we would like to note that the subjective but practical clinical sign of ischemia (prolonged chest pain) present in the 3rd Universal definition of MI was removed from the 4th Universal definition of MI. In our patient level data pooled analysis[2] the number of patients having baseline normal cTn levels in whom evidence of procedural complication and/or new myocardial ischemia was collected, was limited (n=2316), with 352 (15.2%) having either ECG changes, loss of viable myocardium or angiographic evidence of slow flow or dissection, that was associated in 95% of the cases with an increase of post-PCI troponin level ≥ 5 x ULN demonstrating the meaningful correlation between major myocardial injury defined by ≥ 5 x ULN (regardless of ischemic signs) and periprocedural ischemia. Therefore, the presence of non-cTn evidence of ischemia was relatively uncommon, most likely overlooked and/or under-reported, in patients that had a troponin level above the URL and < 5 x URL and this prevents us from making any firm conclusions in this matter. In our previous work on periprocedural myocardial infarction using the 3rd Universal definition of MI[1], we reported an incidence of 7.0% of type 4a myocardial infarction (MI) with the following evidence of prolonged ischemia: angiographic complication (slow flow, coronary dissection)(71%), followed by prolonged chest pain (64%) and electrocardiogram changes

(31%). The individual prognosis values of these criteria were not evaluated; however, their presence increased the association between post-PCI increase of cTn ≥5 x 99th percentile and recurrent cardiovascular events at one year while major myocardial injury (standalone increase of cTn ≥5 x 99th percentile) did not (HR 1.9, 95% CI 1.3—5.5; P< 0.001 and HR 1.7 95% CI 0.9—2.3; 35 P= 0.056, respectively). Finally, we agree that further data are needed to validate the appropriate non-cTn related criteria of the definition of MI. Several prespecified analyses of the ALPHEUS trial[3] are ongoing and should provide more insights into this important topic

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