# Cardiac procedural myocardial injury, infarction and mortality in patients undergoing elective PCI: a pooled analysis of patient-level data

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**ABSTRACT**

**Aims:** The prognostic importance of cardiac procedural myocardial injury and infarction (MI) in chronic coronary syndrome (CCS) patients undergoing elective percutaneous coronary intervention (PCI) is still debated. **Methods and Results.** We analysed individual data of 9081 patients undergoing elective PCI with normal pre-PCI baseline cardiac troponin (cTn) levels. Multivariate models evaluated the association between post-PCI elevations in cTn and 1-year mortality, while an interval analysis evaluated the impact of the size of the myocardial injury on mortality. Our analysis was performed in the overall population and also according to the type of cTn used (52.0% had high-sensitivity cTn [hs-cTn]). Procedural myocardial injury, as defined by the Fourth Universal Definition of MI (post-PCI cTn elevation ≥1x 99$^{th}$ percentile upper reference limit [URL]), occurred in 52.8 % of patients, and was not associated with 1-year mortality (adjOR, 1.35, 95 % CI [0.84 – 1.17], p=0.21). The association between post-PCI cTn elevation and 1-year mortality was significant starting ≥3x 99$^{th}$ percentile URL. Major myocardial injury defined by post-PCI ≥5x 99$^{th}$ percentile URL occurred in 18.2 % of patients, and was associated with two-fold increase in the adjusted odds of 1-year mortality (2.29, 95% CI [1.32 – 3.97], p=0.004. In the subset of patients for whom periprocedural evidence of ischaemia were collected (n=2316), type 4a MI defined by the Fourth UDMI occurred in 12.7% of patients and was strongly associated with 1-year mortality (adjOR 3.21, 95% CI [1.42 – 7.27], p=0.005). Our results are also displayed according to the type of troponin used (hs-cTN or conventional troponin).

**Conclusion.** Our analysis has demonstrated that in CCS patients with normal baseline cTn levels, the post-PCI cTn elevation of ≥5x 99$^{th}$ percentile URL used to define type 4a MI, is associated with 1 year-mortality, and could be used to detect “Major” procedural myocardial injury in the absence of procedural complications or evidence of new myocardial ischaemia.

## INTRODUCTION

Elective percutaneous coronary intervention (PCI) is considered a safe treatment for chronic coronary syndrome (CCS), with a very low rate of major procedural complications [1–3]. Technical advances in PCI and new pharmacological therapies in coronary angiography procedures have resulted in a drastic reduction in PCI-related complications such as acute stent thrombosis, stroke or vascular access bleeding. As a result, elective PCI can currently be performed in ambulatory systems of care with outpatients being treated and discharged on the same day. Although the rate of serious complications is low, post-PCI increases in cardiac biomarkers are frequent, especially in the era of high-sensitivity cardiac troponin [hs-cTn]. However, the prognostic importance of post-PCI cTn elevations in CCS patients undergoing elective PCI in terms of recurrent cardiovascular events and long-term mortality remains debated[4–6].

According to the definition and cardiac biomarker used, recent data have reported significant variability in the incidence of type 4a myocardial infarction (MI) (ranging from 3 to 10%), and procedural myocardial injury (ranging from 25% to 70%)[7–11], with some studies supporting an independent association with recurrent cardiovascular events and long-term mortality[6,7] and some not demonstrating a relationship with adverse outcomes. [5,12] Similarly, minor troponin elevations may or may not be reflected in the loss of viable myocardium, and the association between the loss of small amounts of viable myocardium and further cardiovascular events remains unclear[13–15]. In 2018, an expert consensus group gathering the European Society of Cardiology, the American Heart Association [AHA], the American College of Cardiology [ACC] and the World Heart Foundation published the Fourth Universal Definition of MI (UDMI), and defined procedural myocardial injury as a post-PCI increase of cTn >1x 99$^{th}$ percentile upper reference limit (URL) in patients with normal pre-PCI baseline cTn (<1x 99th percentile URL) [10] The Academic Research Consortium 2 (ARC-2) consensus document advocates a much higher threshold of cTn increase (≥70x 99$^{th}$ percentile URL) to identify significant procedural myocardial injury. Similarly, the Society for Cardiovascular Angiography and Interventions (SCAI) defined “clinically relevant MI” as stand-alone troponin elevations ≥70x the upper limit of normal[14,16]. The clinical validation of these definitions is challenging given the low rate of mortality in CCS patients undergoing elective PCI. Thus, using a pooled patient-level data analysis from large registries of CCS patients with normal pre-PCI baseline cTn levels

undergoing elective PCI and the recent SASSICAIA randomised trial [17], we aimed to provide answers to the following important and unresolved questions for CCS patients undergoing elective PCI: (1) What is the optimal threshold of post-PCI cTn elevation for defining prognostically important procedural myocardial injury, in terms of its association with post-PCI all-cause 1-year mortality?; (2) What is the relationship between the size of post-PCI cTn elevation and prognosis?; (3) Do the results of the analyses differ according to whether conventional cTn or hs-cTn is used?; and (4) Which patient, lesion, and procedure factors independently predict the risk of experiencing procedural myocardial injury and type 4a MI post-PCI?

## METHODS

### Study design and population

Principal investigators of articles investigating the impact of post-PCI cTn elevation on all-cause 1-year mortality were contacted and asked to share their patient-level characteristics and outcomes. We requested the following inclusion criteria to be present in the database: (1) CCS patients admitted for elective PCI for stable obstructive coronary lesions; (2) Baseline pre-PCI cTn <1x 99th percentile URL (normal baseline cTn patients); (3) At least one measurement of post-PCI cTn ≤ 48 hours after the index procedure; and (4) Principal investigators accepting to share all case-specific data. The requested individual patient data included baseline demographics, clinical characteristics, treatments, and baseline and post-PCI cTn levels. De-identified data were transferred in electronic format to the coordinating centre (Duke-NUS Medical School, Singapore), and analysed by the ACTION Study Group at the Pitié-Salpêtrière University Hospital, Paris, France. We contacted 48 investigators who have published or presented work on this topic and obtained 12 positive responses from those willing to share their data. The final list of studies and clinical trials used in the analysis are shown in **Supplemental Table 1A**[5,6,18–23]. For each study, extensive consistency and completeness checks were carried out, followed by preliminary analyses to ensure agreement with the main published results. In addition, the values used for the 99$^{th}$ percentile URL were quality assured. Discrepancies were resolved by direct contact with the principal investigators.

**Baseline and data collection**

We collected all patient baseline characteristics and procedural aspects including medications in each database. Evidence of procedural complications and/or new myocardial ischaemia meeting the criteria for type 4a MI in the Fourth UDMI were collected when available. The following high-risk features for PCI (both patients or procedure-related) were also collected: glomerular filtration rate <60mL/min, diabetes mellitus, multiple stenting/stent (2 or more stents), stent length, left main stem stenting, ACC/AHA lesion classification, lesion location (ostium), bifurcation and chronic total occlusion.

**Study Objectives**

The study objectives were the following:

(1) To determine the incidences of procedural myocardial injury and type 4a MI in CCS patients undergoing elective PCI; (2) To identify the optimal threshold of post-PCI cTn elevation for defining prognostically important procedural myocardial injury in terms of a significant association with 1-year all-cause mortality after adjustment for potential confounders; (3) To perform an interval analysis of post-PCI cTn elevations in order to evaluate the independent impact of different sizes of procedural myocardial injury on 1-year all-cause mortality; (4) To determine whether the interval analyses vary according to whether hs-cTn or conventional cTn is used; (5) To evaluate the association between type 4a MI and 1-year all-cause mortality in CCS patients undergoing elective PCI; and (6) To evaluate the patient, lesion and PCI procedure factors which independently predict of 1-year all-cause mortality in CCS patients undergoing elective PCI.

**Cardiac biomarkers**

All types of cTn assays were considered, as long as they were used with consistency at baseline and post-PCI. The URL of the test was defined as the 99$^{th}$ percentile value obtained in a healthy population with cardiovascular risk <10% and provided by the manufacturer for each study. Special effort was made to ensure that all included studies had baseline values of cTn <1x 99$^{th}$ percentile URL using published values rather than values used in the manuscripts *per se*. When it was unclear if the proper 99$^{th}$ percentile value

had been employed, the principal investigator was consulted. When multiple measurements were performed ≤ 48 h after the PCI, peak values were considered for the analysis **(Supplemental Table 1B**). Demographics of patients excluded because of missing troponin data are displayed in **Supplemental Table 1C.**

**Definitions of procedural myocardial injury and type 4a MI**

In the overall population, procedural myocardial injury was defined as stated in the Fourth UDMI (post-PCI cTn elevation >1x 99$^{th}$ percentile URL) [9,10] in CCS patients with normal baseline pre-PCI cTn values. We also evaluated the rate of "Major" procedural myocardial injury defined by a post-PCI increase in cTn values ≥5-fold the 99$^{th}$ percentile URL regardless of the presence of procedural complication. In the ARC-2 consensus document, significant procedural myocardial injury was defined as post-PCI cTn elevation ≥70x 99$^{th}$ percentile URL[24]. The SCAI defined "clinically relevant MI" as stand-alone post-PCI cTn elevation ≥70x 99$^{th}$ percentile upper limit of normal (ULN) in patients with normal baseline cTn and post-PCI cTn elevation ≥35x 99$^{th}$ percentile ULN plus new pathologic Q-waves in ≥2 contiguous leads (or new persistent left bundle branch block)[12].

In the subset of patients for whom evidence of ischemia were collected, type 4a MI was defined as stated in the Fourth UDMI as post-PCI increases in cTn values ≥5-fold the 99$^{th}$ percentile URL associated with one of the following criteria: (1) signs of acute myocardial ischaemia (new ischaemic ECG changes or new pathological Q wave); (2) imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology; and (3) angiographic findings consistent with a procedural flow-limiting complications such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal coronary embolization. Procedural myocardial injury and major procedural injury were defined by a post-PCI increases in cTn values >1x 99$^{th}$ percentile and 1 ≥5-fold the 99$^{th}$ percentile URL, respectively, without new evidence of ischemia.

**Statistical Analysis**

Baseline characteristics were reported as proportions for categorical variables and medians with interquartile ranges for continuous variables. Groups were A multivariate logistic regression was performed to evaluate the association between each unit of ratio used as a threshold and 1-year mortality including the following baseline clinical and angiographic characteristics – age, diabetes, active or prior smoking, hypertension, eGFR < 60 ml/min, prior MI, prior coronary artery bypass graft surgery, multivessel stenting, number of stents, - associated with 1-year mortality and procedural myocardial injury or type 4a MI (univariate p<0.2). This analysis of thresholds was then stratified by type of cTn (hs-cTn or conventional cTn). In the second set of analysis, a similar multivariate logistic regression models were used to perform the interval analysis estimating the association between pre-defined size categories of procedural myocardial injury (≥1 to 5x URL; ≥5 to 35x URL; ≥35 to 70x URL; ≥ 70x URL) and 1-year all-cause mortality as compared to the reference category of patients without post-PCI cTn elevation (<1x URL). Survival curves were performed with the Kaplan-Meier method to display the risk of mortality according to these size categories and compared with the log-rank test. Following the statistical princeps of biomarker evaluation[25,26] the receiver operating characteristic (ROC) curve analysis was evaluated to assess the performance (sensitivity, specificity) of post-PCI cTn in predicting mortality. Finally, we performed a multivariate stepwise logistic regression using two models in order to determine the factors associated with procedural myocardial injury and type 4a MI. In the first model, we included baseline clinical and angiographic variables with less than 10% of missingness associated with procedural myocardial injury and type 4a MI (univariate p-value <0.2). In the second model, we included all available baseline characteristics, included angiographic complexity (lesion type ACC/AHA, ostial lesion or not, bifurcation or not), irrespective of the proportion of missing data. The statistical tests were performed using GraphPad Prism version 6.00 for Windows (GraphPad Software, San Diego California). Logistic regression was performed with the R foundation for statistical computing Vienna, Austria. All tests were two-sided with a statistical threshold for significance of 0.05.

## RESULTS

### Patient, lesion and PCI procedure characteristics

The consort diagram is presented in **Figure 1.** Among 34 667 patients with individual data, 25 593 patients underwent an elective PCI procedure, 9 912 were excluded because they had a mildly elevated cTn, 3 010 because of missing post-PCI cTn values and 2817 because of missing one-year status. The characteristics and outcomes of patients excluded are displayed in the appendix (**Supplemental Table 1D and Supplemental Figure 1)**. Finally, 9081 patients with a normal baseline cTn value, and a cTn measured within 48 hours of PCI and a 1-year follow-up were analysed. The biomarkers used in the overall population were high sensitivity cTn in 52.0 % of the patients and conventional cTn in 47.0 %. cTnT was the most frequent biomarker used (59.3%) as compared with cTnI (40.7%). Among the 9 081 patients with complete follow up, 135 (1.49%) patients died within the first year of PCI. Baseline clinical and angiographic characteristics of our cohort according to the type of troponin are displayed in **Table 1 and 2.**.

**Incidence of procedural myocardial injury**

Overall, the incidence of procedural myocardial injury as defined by the Fourth UDMI was 52.8 %. This incidence varied with the type of cTn assay used, ranging from 23.8% in centers using conventional cTn assay to 79.8% in centers using the hs-cTn assay. When using the 5x 99$^{th}$ percentile URL threshold, major procedural myocardial injury occurred in 18.2 % of patients in our overall population (10.1% when evaluated by conventional cTn and 25.8 % when evaluated by hs-cTn). The incidence of procedural myocardial injury as defined by ARC-2 was substantially lower and occurred in 1.05 % of the patients with normal pre-PCI baseline cTn levels (1.08 % when evaluated by conventional cTn and 1.02 % when evaluated by hs-cTn).

**Association between procedural myocardial injury on 1-year all-cause mortality**

Associations between adjusted OR for 1-year mortality and X-fold increase in the post-PCI cTn values in the population with baseline cTn levels are displayed in **figure 2**. The association with 1-year mortality became significant beyond a 3-fold elevation above the URL with a continuous increase in mortality until a 25-fold elevation with a significant and constant widening of the confidence interval as the number of events detected decreased accordingly. Procedural myocardial injury defined by the Fourth UDMI was not associated with 1-year mortality (adjOR, 1.35 95 % CI [0.84 – 1.17], p=0.21). Major procedural myocardial

injury defined as a post-PCI elevation in cTn ≥5x 99th percentile URL was significantly associated with 1-year mortality with an adjOR of 2.29, 95% CI [1.32 – 3.97], p=0.004. Importantly, the association of major procedural myocardial injury with 1-year mortality was similar when analyzed separately for center using conventional cTn (adjOR of 2.05, 95% CI [1.07 – 3.90], p=0.02) or hs-cTn (adjOR of 2.31, 95% CI [1.27 – 4.20], p<0.01). On the other hand, the less frequent procedural myocardial injury as defined by ARC-2 was strongly associated with 1-year mortality (adjOR 4.15, 95% CI [1.62 - 10.64], p<0.01). The determination of threshold performance measured by the ROC analysis are displayed in **Supplemental Table 2** and the multivariate analysis of risk factors associated with 1-year mortality is presented in **Table 3A**.

**Size categories of procedural myocardial injury and association with 1-year all-cause mortality**

In the interval analysis, we evaluated the prognostic impact of different size categories of procedural myocardial injury according to the post-PCI cTn threshold stratified by type of cTn used (hs-cTn or conventional cTn) after adjustment for cofounders. The results of the unadjusted and adjusted OR for the association with 1-year mortality analysis are provided in **Table 4,** and the results of the Kaplan-Meier curves showing the survival of the population is displayed in **Figure 3.** We found that when using conventional cTn, only large procedural myocardial injury (≥ 70x 99th percentile URL compared with < URL) was associated with increased risk of 1-year mortality (adjOR 5.97 95% CI (1.65 – 21.59), p=0.002. When using hs-cTn, a lower elevation of post-PCI cTn (≥ 5 to 35x 99th percentile URL) which occurred in 22.78% of the patients was associated with 1-year mortality (adjOR 3.99, 95% CI [1.12 - 14.25], p=0.016). The analysis survival stratified by type of troponin and size categories of procedural myocardial injury is displayed in **Supplemental Figure 2**.

**Incidence of Type 4a MI and association with 1-year all-cause mortality**

The number of patients having baseline normal cTn levels in whom evidence of procedural complication and/or new myocardial ischaemia was collected, was limited (n=2316). The incidence of type 4a MI was 12.7% (n=294) as determined by a post-PCI cTn elevation ≥5x 99th percentile URL, and an additional criteria of procedural complication and/or evidence of myocardial ischaemia (**Figure 4**). Of these 294 patients with type 4a MI, 250 (85.0%) had at least new ischemic ECG changes or Q waves, 177 (60.0%)

patients had angiographic evidence of coronary obstruction and 12 (4.1%) had imaging evidence of loss of myocardium. Type 4a MI was independently associated with 1-year mortality in the multivariate analysis performed in this patient subset (adjOR 3.21, 95% CI [1.42 – 7.27], p=0.005) **(Table 3B).** Interestingly, we found that 70% of patients with a large procedural myocardial injury (defined as post-PCI cTn >35x URL) were in fact a large type 4aMI with at least one reported angiographic complication or new ischaemic ECG changes.

**Independent predictors of procedural myocardial injury and type 4a MI**

Risk factors for developing procedural myocardial injury (as defined by Fourth UDMI) and prognostically important procedural myocardial injury (as defined above) were identified in patients with normal cTn levels and are shown in **Table 4.** Impaired kidney function, left main stem disease or left anterior descending artery PCI as well as stent length and male sex were shown to be independent predictors of procedural myocardial injury. Interestingly, prior MI, patients treated for hypertension and women were less likely to develop such complications. Predictors of type 4a MI could only be evaluated in the subgroup of patients with evidence of new myocardial ischaemia, and these were similar to the risk factors for procedural myocardial injury.

## DISCUSSION

The prognostic significance of procedural myocardial injury, as defined by the Fourth UDMI is unclear, with some studies showing an association between post-PCI cTn elevations (>1x 99$^{th}$ percentile URL) and MACE or long-term mortality[4,6,7], whereas others do not[5,11]. Some of this discordance may be due to many studies ignoring the need to only include patients with normal pre-PCI baseline cTn levels, others using inappropriately high values for the 99$^{th}$ percentile URL[27], and some discrepancies arising from using either conventional cTn or hs-cTn assays. The present study was designed to provide evidence regarding the optimal threshold of post-PCI cTn elevation for predicting 1-year all-cause mortality in CCS patients undergoing elective PCI, and assess the association between the size of procedural myocardial injury and 1-year mortality. Both analyses were performed overall and separately then using either conventional cTn or hs-cTn assays.

The results of this pooled analysis of patients with individual data can be summarized as follows: (1) The Fourth UDMI definition of procedural myocardial injury (>1x 99$^{th}$ percentile URL) is very sensitive but not specific, as half of CCS patients met the diagnostic criteria after PCI, an incidence that is increased to almost 80% with hs-cTn, and not associated with 1-year all-cause mortality in our study; (2) Elevation of post-PCI cTn levels beyond 3-fold the baseline level is independently associated with 1-year all-cause mortality with a continual increase in specificity, although this was also associated with a marked decrease in sensitivity and the proportion of the events detected; (3) Major myocardial injury defined with the same post-PCI cTn threshold elevation as for type 4a MI (≥5x 99$^{th}$ percentile URL), but without the additional evidence of new myocardial ischaemia, occurred in 18.2% of patients, and was independently associated with a 2-fold increase in 1-year all-cause mortality, regardless of the type of troponin used (conventional cTn or hs-cTn); (4) Both larger and smaller extents of procedural myocardial injury were associated with an increased risk of mortality, although the former had a more pronounced prognostic impact as they were often underdiagnosed type 4a MIs; (5) Type 4a MI, which is vastly under-reported in clinical studies as it combines biomarkers and ECG, clinical or angiographic criteria, occurred in 12.7% of patients in our study and was a strongly associated with 1-year all-cause mortality; (6) The utilisation of a hs-cTn assay, increases by 3-fold the incidence of procedural myocardial injury with definitions based on a lower threshold using conventional cTn (UDMI), whereas it remained unchanged with definitions using a higher threshold (ARC-2/SCAI) and our analysis suggests to use different thresholds of post-PCI cTn values according to the type of assay used (35-fold increase for conventional cTn and a 5-fold increase for hs-cTn) instead of theses definitions; and (7) Finally, we identified independent predictors of both procedural myocardial injury and type 4a MI, as well as 1-year all-cause mortality, which can be considered to be risk factors in contemporary elective PCI.

The definition of procedural myocardial injury has been an ongoing subject of controversy in terms of its clinical relevance for the detection of PCI-related complications and their management, but also for trials evaluating revascularisation strategies in CCS patients [28]. CK-MB assays are no longer available in many centers and cTn assays, especially high sensitivity assays, have progressively become the preferred cardiac biomarker given their superior sensitivity for the detection of procedural myocardial injury due to

their higher range and discrimination properties. However, evidence linking post-PCI cTn elevations to patient prognosis using the Fourth UDMI is still lacking.

Our findings demonstrate that the 1x 99$^{th}$ percentile URL threshold selected for defining procedural myocardial injury by the Fourth UDMI is too sensitive and is not associated with 1-year all-cause mortality after adjustment for confounding factors. On the contrary, a much higher threshold such as the one defined by the ARC-2 or SCAI initiative (≥70-fold)[24] increased the specificity and selection of patients with the greatest extent of myocardium loss and risk of death, but this was associated with a significant reduction in sensitivity, thereby missing the vast majority of events in the population with normal baseline troponin.

Major myocardial injury, defined by a post-PCI cTn elevations ≥5x 99$^{th}$ percentile URL, regardless of the presence of angiographic complications and/or evidence of new myocardial ischaemia (ECG, angiographic, imaging) was associated with a significant two-fold increase in the risk of all-cause mortality. This was the case whether hs-cTn or conventional cTn was used. Crucially, the prognostic importance of the post-PCI cTn threshold elevation of ≥5x 99$^{th}$ percentile URL was supported by the interval analysis that demonstrated that even intermediate sized procedural myocardial injury (≥5x and <35x 99$^{th}$ percentile URL) was associated with a 3.3x increase in 1-year all-cause mortality. However, for conventional cTn, a larger amount of procedural myocardial injury (≥35x 99$^{th}$ percentile URL) was needed to show an independent association with an increase in 1-year all-cause mortality. The differences in thresholds between conventional cTn and hs-cTn likely relates to the differing risk profiles of the patient cohorts, with the group of patients with normal baseline hs-cTn likely to be of lower risk compared to the patient group with normal baseline conventional cTn due to the better prognostic performance of hs-cTn over conventional cTn at the lower values.

The present study also demonstrated that the additional angiographic or clinical criteria used to define type 4a MI in the Fourth UDMI, are unfortunately underreported in PCI registries, and that a threshold based solely on the post-PCI biomarker elevation appears to be an alternative to type 4a MI in cases of absence of adjudication or collection of evidence of new myocardial ischaemia on the ECG or the angiography. Of note, angiographic evidence of myocardial ischaemia was present in 90% of patients of our cohort with large peri-procedural myocardial infarctions (≥35x 99$^{th}$ percentile URL).

Our study also demonstrates that this 5x threshold is meaningful when used in combination with a hs-cTn assay, which may serve as a warning flag to consider periprocedural angiographic defects not captured during the procedure. In addition, this threshold may be used to differentiate patients at low risk from higher risk patients and enable to implement more intensive secondary prevention therapy or to guide early discharge in the context of ambulatory care. Of note, the incidence of type 4a MI observed in our subgroup analysis (12.7%) was on the higher side when compared to previous studies including the SACCICAIA trial (3%), the cohort of Zeitouni et al[6] (7%), the study by Yang et al (10.3%), and further large studies are needed to confirm the incidence of type 4a MI in CCS patients undergoing PCI, especially with high sensitivity assays[11].

It remains unclear whether mortality and hard clinical events following a procedural myocardial infarction are a consequence of risk factors related to the complexity of the procedure and/or the patient's vulnerability or a result from the extent of cardiac injury. Our results show higher adjusted ORs for one-year mortality with a higher post-PCI cTn threshold, confirming that large extents of procedural myocardial injury have a stronger prognostic impact when compared to smaller extents of procedural myocardial injury. In 90 % of patients with large procedural myocardial injury may, a loss of branch or distal embolization was reported by the investigators – displaying an actual myocardial infarction rather than a biomarker reflecting an injury. Importantly, our analysis demonstrates for that smaller extents of procedural myocardial injury (post-PCI cTn elevations above the 5-fold threshold and below the 35-fold threshold) are also prognostically significant as they are associated with a 2.5-fold increased risk of mortality when detected with hs-cTn. However, for conventional cTn, only a larger extent of cTn elevation (>35-fold threshold) was prognostically significant. Therefore, as expected, in CCS patients with normal baseline cTn levels, the threshold of post-PCI elevation that predicts clinical outcomes varies according to the type of cTn.

Although unmeasured risk factors such as atheroma burden, plaque composition and blood vulnerability were not measured in our study, we found that both procedural- and patient-related high-risk features were risk factors for procedural cardiac injury and 1-year mortality. Recent ESC guidelines have proposed the use of more potent $P2Y_{12}$ inhibitors such as ticagrelor or prasugrel in patients perceived to

be at high ischaemic risk or requiring complex elective PCI procedures[29]. The randomised control SASSICAIA trial comparing a pre-PCI loading dose of prasugrel to clopidogrel was prematurely stopped due to enrolment issues and found a non-significant 10% relative decrease in the rate of procedural events with prasugrel compared to clopidogrel (NCT0254861). Further studies on preventive strategies in patients with high risk features are needed, and the ongoing randomised ALPHEUS trial (Assessment of Loading with the $P2Y_{12}$ inhibitor Ticagrelor or clopidogrel to Halt ischemic Events in patients Undergoing elective coronary Stenting, NCT02617290) should provide more data in this regard[30].

Our analysis is not without its limitations. First, a large portion of patients were excluded from the database, because of missing PCI troponin measurements, potentially adding a degree of ascertainment bias although their baseline characteristics were similar (**Supplemental Tables 1C and D**). Missing data also involved characteristics associated with periprocedural MI, such as use of atherectomy, lesions calcifications or left ventricular ejection fraction. Secondly, the mortality rate was low, but our large population carries enough power to identify the threshold associated with a two to four-folds increased risk of mortality at 1 year after adjustment for confounders. Thirdly, while we chose a homogenous set of low-risk patients admitted for elective PCI, there was some variability in the characteristics collected especially in the criteria of type 4a MI which were only reported in a minority of studies[6,20,21] and the SASSICAIA trial – leading to a potential variability in the proportion of type 4a MI. Finally, CK-MB levels were not collected and serial measurement of cTn was not systematically performed, but this also reflects the current standard practice in elective PCI.

## CONCLUSIONS

Procedural myocardial injury defined by the Fourth UDMI occurs in nearly 50% (using conventional cTn assays) and in nearly 80% (using hs-cTn assays) of CCS patients undergoing elective PCI with normal baseline cTn values, and was not associated with an increase in 1-year all-cause mortality. Our participant-level pooled analysis has shown that “major” procedural myocardial injury defined as a post-PCI elevation in cTn (either hs-cTn or conventional cTn) ≥5x $99^{th}$ percentile elevation was independently associated with a higher risk of 1-year all-cause mortality. This threshold was supported for hs-cTn, where the interval

analysis demonstrated that a post-PCI elevation in cTn (≥5 and <35x 99$^{th}$ percentile URL) was independently associated with an increased risk of 1-year all-cause mortality. However, conventional cTn was less discriminatory, as only a higher post-PCI cTn elevation (≥70x 99$^{th}$ percentile URL) was significantly associated with 1-year all-cause mortality. Both major procedural myocardial injury and type 4a MI are independent predictors of 1-year mortality after PCI and have the potential to serve as quality metrics in clinical practice and endpoints in clinical trials evaluating preventive pharmacological treatment or procedural strategies.

## Disclosures

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**FIGURES and TABLES**

**Figure 1**: Consort diagram

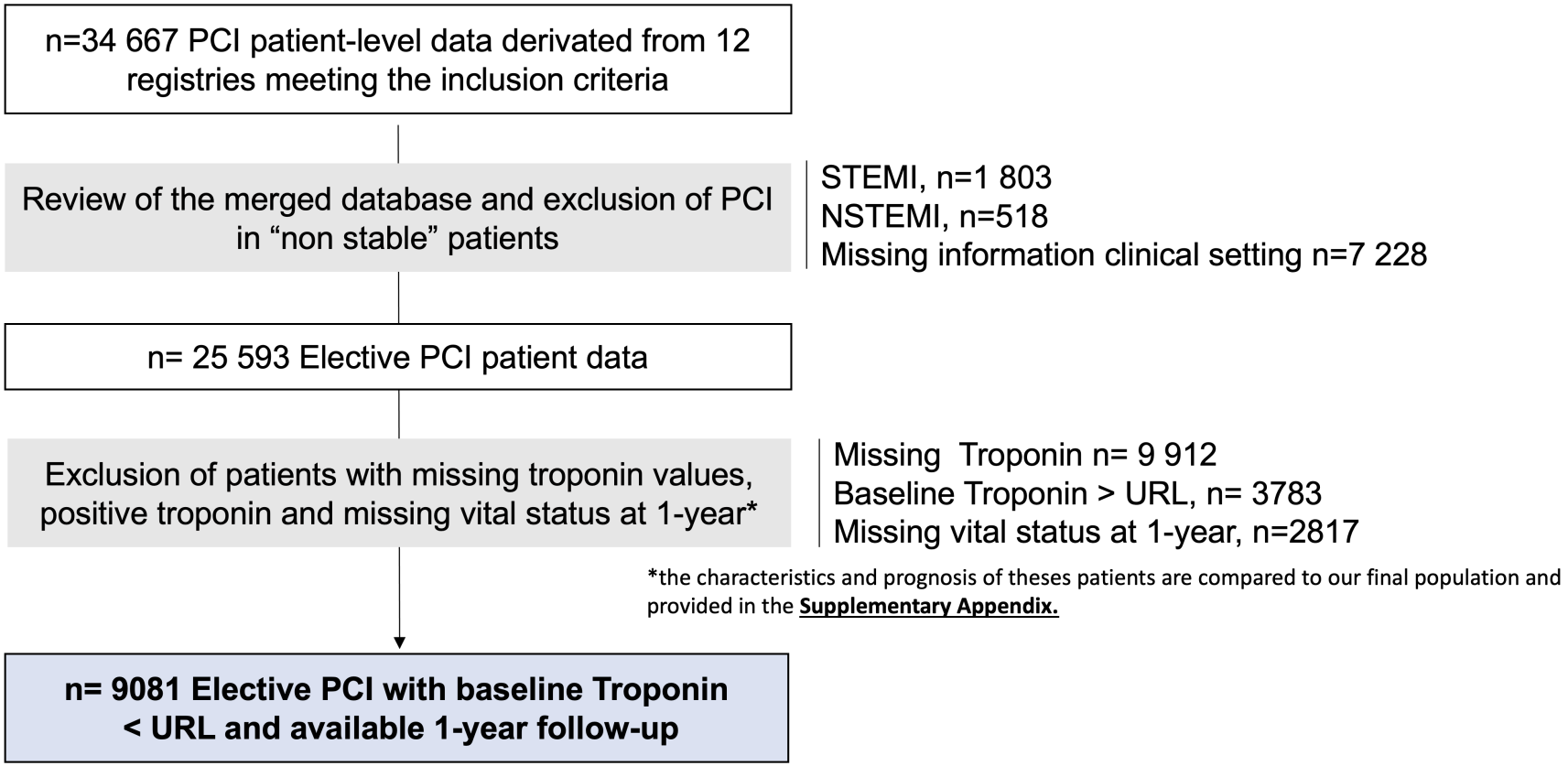


**Figure 2 (Central figure).** Adjusted odds ratio (OR) of mortality at 1 year according to post-PCI cTn level / URL ratio in patients with normal pre-PCI baseline cTn levels. The solid blue line represents the adjusted odds ratio and the dotted lines represent the lower and upper 95% confidence intervals.

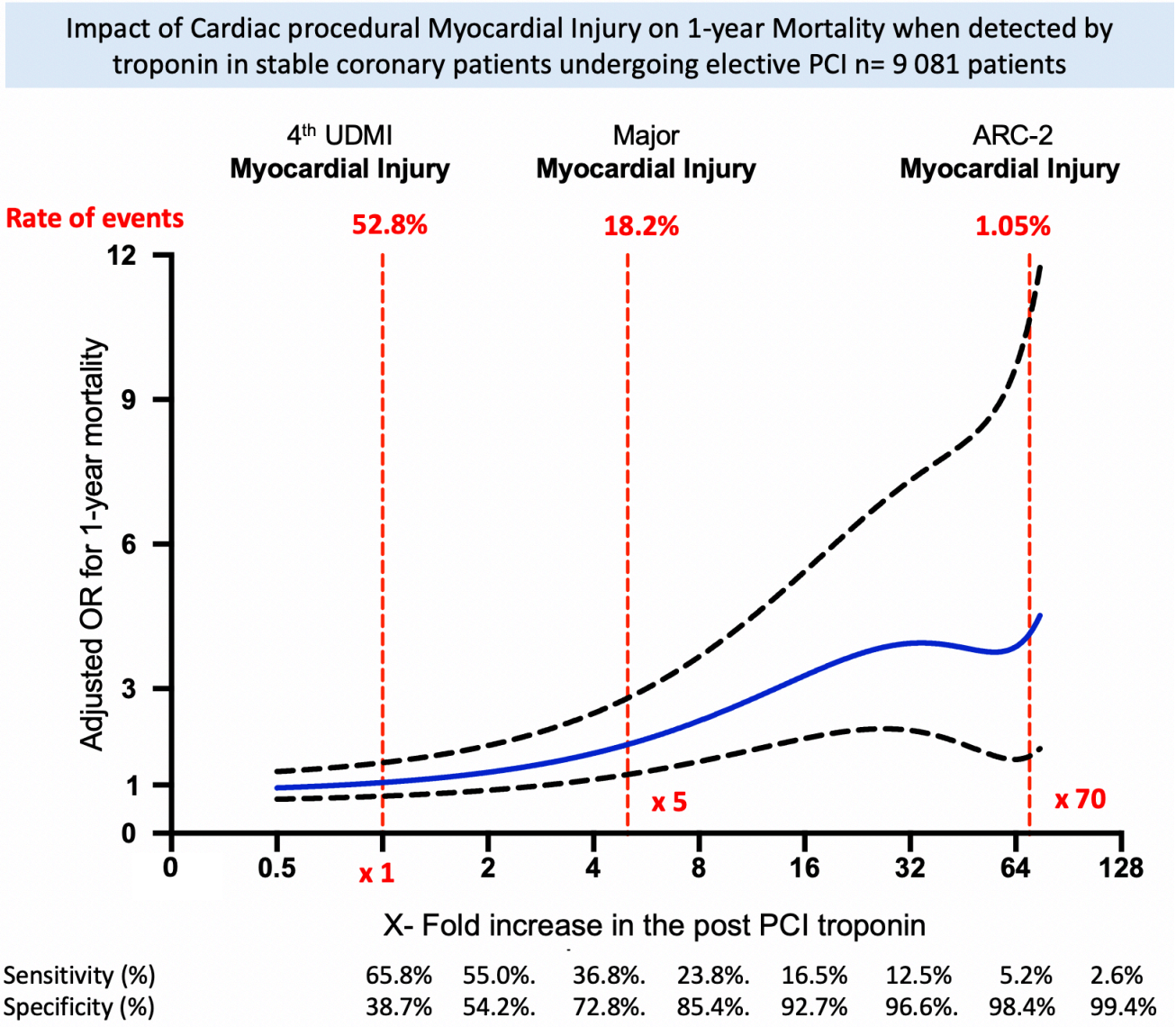
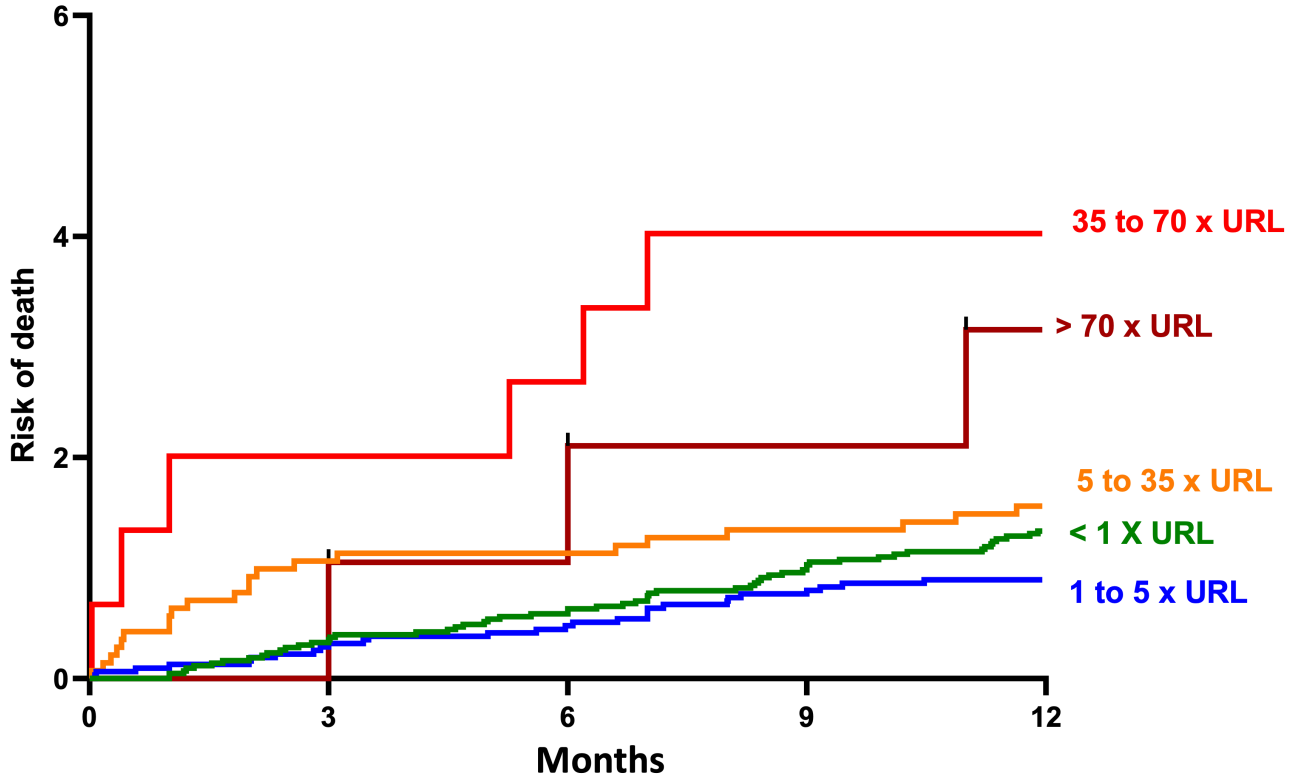
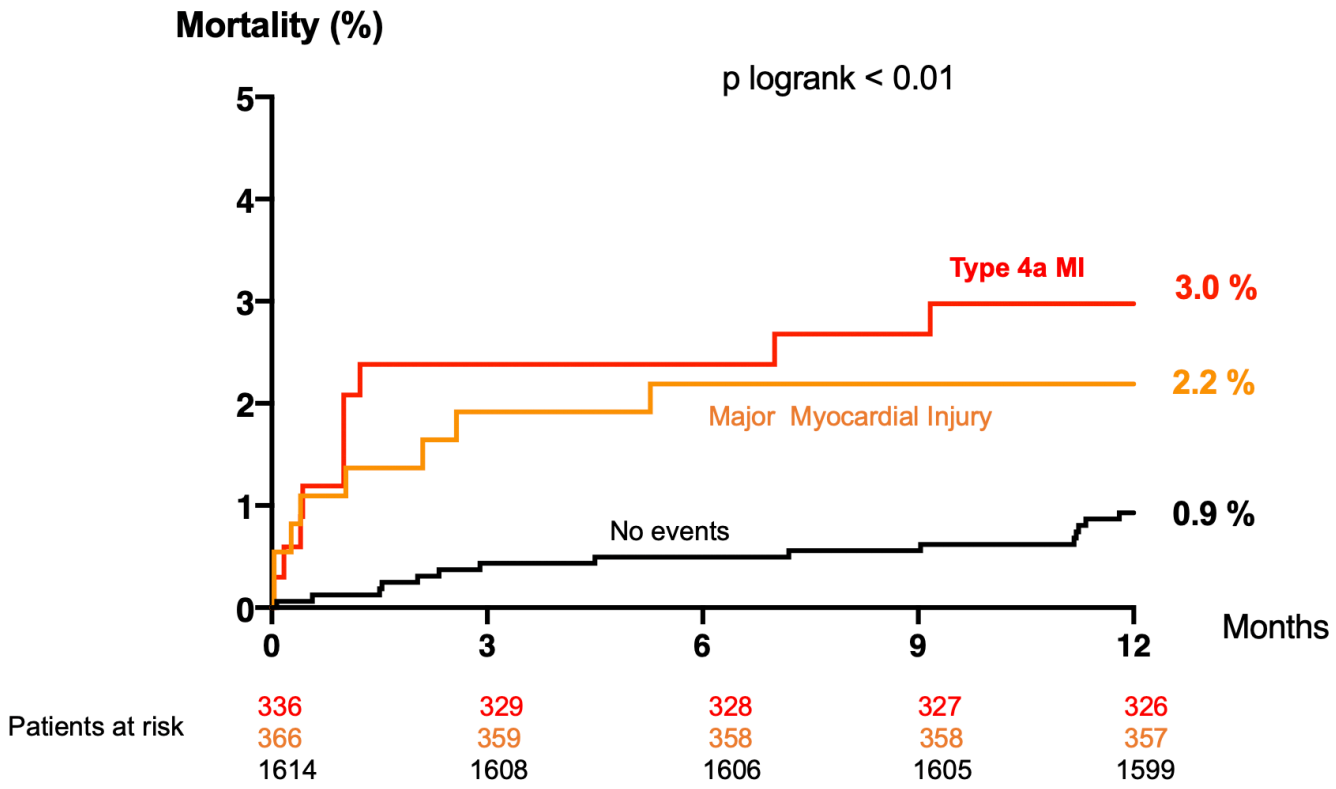


**Figure 3.** One-year mortality in CCS patients with normal baseline cTn and post-PCI cTn elevations divided into 5 categories (unadjusted comparison)




| | | | | | |
|---|---|---|---|---|---|
| < URL | 4279 | 4264 | 4251 | 4234 | 4219 |
| 1 to 5 x URL | 3144 | 3132 | 3125 | 3118 | 3114 |
| 5 to 35 x URL | 1413 | 1398 | 1394 | 1364 | 1391 |
| 35 to 70 x URL | 149 | 146 | 146 | 143 | 143 |
| >70 x URL | 95 | 95 | 94 | 92 | 91 |

**Figure 4.** All-cause mortality at 1 year according to the type of procedural event (type 4a MI according to Fourth UDMI in Red or prognostically important "Major" procedural myocardial injury in Orange) in patients with normal pre-PCI baseline cTn levels for whom evidence of new myocardial ischaemia were collected (n=2316).



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