Impact of Periprocedural Myocardial Biomarker Elevation on Mortality following Percutaneous Coronary Intervention: A Pooled Patient-Level Analysis of Contemporary Stent Trials

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BACKGROUND

The treatment of coronary stenosis with the use of second-generation drug-eluting stents has been associated with a decrease in the rate of major adverse coronary events. Despite this overall trend towards lower number of events in current practice, the clinical and prognostic significance of peri-procedural biomarker elevation after percutaneous coronary intervention (PCI) has generated widespread debate. The classification of threshold biomarker elevations with or without ancillary criteria as significant myocardial injury or myocardial infarction has potential consequences for the patient, for the physician where used as a metric for quality of care and for the development and appropriate assessment of new therapies in clinical trials. Periprocedural events may, when they reflect substantial loss of myocardium, have a significant association with hard clinical outcomes. Several studies showed a strong association of post-PCI creatinine kinase myoband (CK-MB) elevation with subsequent cardiovascular events; unfortunately CK-MB is no longer an assay in routine use at most institutions. The Universal Definition of myocardial infarction taskforce embraced cardiac Troponin (cTn) as the biomarker of choice because is a more sensitive and specific biomarker for the early detection of myocardial necrosis and thus facilitates early diagnosis and triage in patients presenting acutely with chest pain. By default, it has thus become the only biomarker generally available in the periprocedural setting. This increased sensitivity may permit the detection of subtle differences, among devices, in clinical trials. However, attempts to unravel the prognostic significance of troponin elevation related to coronary intervention, alone or in association with other criteria such as proposed by the UDMI Taskforce, have produced conflicting results.

The objective of this study was to explore the association between biomarker elevation, with CK MB or cTn following PCI and mortality in patients undergoing PCI for stable angina with normal baseline values.

METHODS

Patient-level data from 5 contemporary coronary stent trials and one large registry (LEADERS study, TWENTE trial, DUTCH PEERS study, RESOLUTE AC study, PROTECT study and EVENT registry) were pooled. **Table 1**, all cause mortality of stable angina patients, with normal baseline biomarkers, was compared between patients with and without different cut-off values of cTn and CK MB (≥1× to <3, ≥3× to <5, ≥5× to <10, ≥10× to <20, ≥20× to <35x, ≥35× to <70 and ≥70×).

All studies were conducted following the Guidelines of Good Clinical Research Practice and were approved at the various ethics committees in the participating centers.

Statistical analysis

The individual patient based data was collected from the above-mentioned clinical studies. The pooling of the different data sets was performed by Cardialysis, (Rotterdam, the Netherlands) which is an independent academic research organization. The continuous variables are presented as means (plus standard deviation) and categorical variables are summarized as frequencies. Kaplan-Meier curves were created to compare groups as follows: Group A (CKMB <5 and cTn <35); Group B (CKMB < 5 and cTN ≥ 35); Group C (CKMB ≥ 5 and cTN < 35) and; group D (CKMB ≥ 5 and cTN ≥ 35). Following univariate analysis for the selection of significant variables, a multivariable analysis using Cox Regression was performed to investigate the independent predictors of death. Biomarkers were forced into the model as categorical covariates (model A: CKMB ratio ≥5 and cTn ratio ≥35; model B: CKMB ratio ≥10 and cTn ratio ≥70). The analysis was performed using SAS version 9.3 (SAS Institute Inc, Cary, NC) and a p<0.05 was considered significant.

RESULTS

A total of 13452 patients were included in this pooled analysis. Most (72.7%) were male and mean age was 64.2 years; 31.3% of them were diabetics. The left anterior descending coronary artery was the most frequent (48.5%) target vessel and the majority of lesions were of moderate or severe complexity (type B1: 30.0%; type B2: 30.6% and type C: 28.7%). Most patients had one vessel disease (78%). Nearly all (96.5%) patients were treated with drug-eluting stents. A mean of 1.7 stents per patient were implanted with a mean stented length of 31.3 mm.

Biomarkers results

A total of 11613 and 10639 patients respectively had CK MB and cTn measurements. Both biomarkers were measured in 8859 patients. The frequencies of biomarker elevations by different ratios are presented in Table 3. The overall percentage of patients with elevated biomarkers following PCI was 23.9% for CK MB and 68.4% for cTn. Thresholds that have been proposed, based on the SCAI or UDMI definitions with or without additional criteria, are CKMB/cTn ≥5 or ≥10 or cTn ≥5, ≥35 and ≥70. The frequencies of those elevations vary considerably.

Biomarkers elevation and mortality

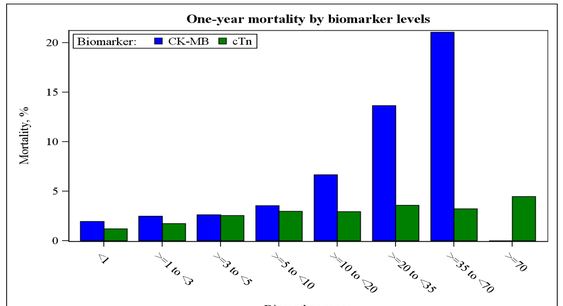
A total of 259 (1.9%) patients died within the first year following index PCI; the unadjusted mortality rates using different thresholds of either CKMB or cTn are presented in **Figure 1**. In addition, unadjusted mortality rates using most common thresholds (CKMB ≥5 or ≥10 or cTn ≥35 and ≥70) in combination are shown in **table 2**. Kaplan-Meier curves were created to compare mortality rates between different groups: Group A (CKMB <5 and cTn <35) had a mortality rate of 1.9% and was used as reference for the comparisons. Group B (CKMB < 5 and cTN ≥ 35) had 1.8%, plog rank 0.9682; Group C (CKMB ≥ 5 and cTN < 35) had 4.0% plog rank 0.1134; group D (CKMB ≥ 5 and cTN ≥ 35) had 6.5% plog rank <0.0001. Similarly, for the higher biomarker thresholds categories we used as reference Group A (CKMB <10 and cTn <70), it had a mortality rate of 1.9%. Group B (CKMB < 10 and cTN ≥ 70) had 2.0%, plog rank 0.9165; Group C (CKMB ≥ 5 and cTN < 35) had 9.1% plog rank 0.0008; group D (CKMB ≥ 5 and cTN ≥ 35) had 10.4% plog rank <0.0001**. Figure 2**.

Several clinical variables were tested for their univariate association with mortality. The following had a significant association: age, prior MI, lesion complexity, prior CABG, diabetes mellitus, gender number of implanted stent and hyperlipidemia.

Two different Cox multivariate analyses were performed, in which the lower and higher thresholds of cTn and CKMB ratios post procedure were forced into the model (model A and B) respectively. In model A (CKMB ratio ≥5 and cTn ratio ≥35 were forced in), age, prior MI, lesion complexity, CK-MB ratio ≥5 and diabetes mellitus were independent predictors of increased mortality, while hyperlipidemia showed to be associated with reduced mortality. cTn ratio (≥35) was not independently associated with mortality. In model B (Model A. CKMB ratio ≥10 and cTn ratio ≥70 were forced in), age, prior MI, lesion complexity and CK-MB ratio ≥10 were independent predictors of mortality, while hyperlipidemia appeared to reduced mortality. cTn ratio (≥70) was not independently associated with mortality.

Table 1. Study	Stent type	N	Age (yrs)	Female (%)	DM (%)	Non ACS(n)
LEADERS trial	BES and SES	1707	64.5	24.7	24.3	639
TWENTE trial	EES and ZES	1391	64.2	27.5	21.6	670
DUTCH PEERS trial	EES and ZES	1811	64.5	27.0	17.5	747
RESOLUTE AC trial	EES and ZES	2292	64.3	23.1	23.4	1130
PROTECT trial	ZES and SES	8709	62.2	23.5	27.5	3998
EVENT registry	BMS and DES	6347	64.7	32.5	35.4	6268

Fig 1



One-year mortality rates assiociated with specified ranges of peak cTn and peak CK-MB normalized to the individual clinical center upper limit of normal.

Table 2 Biomarker group	No death within 1 Y post-procedure	Death within 1 Y post-procedure	Percentage %
Panel A			
A: CKMB < 5 and cTn < 35	8004	150	**1.9**
B: CKMB < 5 and cTn ≥ 35	383	7	**1.8**
C: CKMB ≥ 5 and cTn < 35	99	4	**4.0**
D: CKMB ≥ 5 and cTn ≥ 35	199	13	**6.5**
Panel B			
A: CKMB < 10 and cTn < 70	8362	158	**1.9**
B: CKMB< 10 and cTn ≥ 70	202	4	**2.0**
C: CKMB ≥ 10 and cTn < 70	44	4	**9.1**
D: CKMB ≥ 10 and cTn ≥ 70	77	8	**10.4**

Fig 2

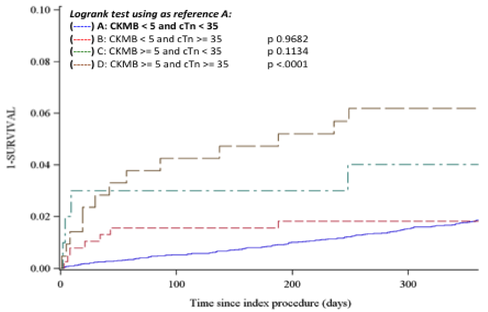
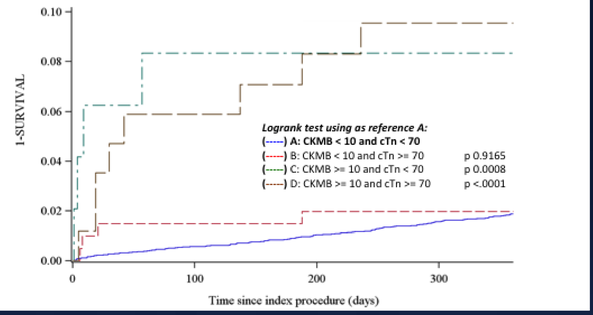


Fig 2



DISCUSSION

Our results show that, with second generation DES, CKMB and cTn elevations were not a frequent occurrence after elective PCI in stable patients; We also found that elevations of CKMB ≥5 and ≥10 x ULN were associated independently with increased 1-year mortality. However, cTn elevations were not associated with increased mortality. Although any single threshold value of CKMB is an arbitrary choice that represents a trade- off between sensitivity and specificity in predicting subsequent mortality, such thresholds are nonetheless important because they are frequently used as end points for clinical trials of both cardiovascular drugs and devices. However, cTn has become the cardiac biomarker of choice in the acute setting and has largely replaced CK MB in all settings, such as peri-procedural, in most clinical sites around the world. CKMB is often no longer available as a routine clinical chemistry test in many institutions. As a result, cTn has or will become the default biomarker to assess periprocedural myocardial injury except when core lab collection and testing of assays is implemented, a measure which is often costly and impractical. In the present report, elevations of cardiac troponin post-PCI were not associated with mortality.

LIMITATIONS

1. Despite the large number of patients included, the number of deaths was small;
2. It may be that troponin elevations impact nonfatal clinical complications which may be important;
3. EKG and angiographic data is not available to correlate them with biomarker findings

CONCLUSION

Following elective PCI in stable patients treated with second generation DES, CKMB and cTn elevations remain common. There was an increased mortality rate with even small elevations of CKMB after PCI, only elevations ≥5 x ULN were associated with increased 1-year mortality in our categorical analyses. On the other hand, cTn elevation was not independently associated with mortality

CONFLICT OF INTEREST

Hector. M. Garcia-Garcia declare no conflict of interest