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Is periprocedural CK-MB a better indicator of prognosis after emergency and elective percutaneous coronary intervention compared with post-procedural cardiac troponins?

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Abstract

A best evidence topic in interventional cardiac surgery was written according to a structured protocol. The question we addressed related to the elevation of markers of cardiac damage associated with percutaneous coronary intervention (PCI). We explored and compared the clinical and prognostic relevance of the elevation of creatinine kinase-myocardial band (CK-MB) and cardiac troponin (cTn) levels during the periprocedural period and the post-procedural period, respectively, following an emergency or elective PCI. We found in excess of 390 papers after a systematic literature search, of which 10 represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. From the best evidence available it appears that the monitoring of cardiac biomarkers following a PCI can provide important clinical information about the health of the myocardium, as well as prognostic information on short to mid-term outcomes of mortality up to 3 years. The narrow evidence base advocates the use of periprocedural CK-MB monitoring, recommending that an elevation in CK-MB is a significant predictor of adverse events. Troponins remain a precise and reliable marker of cardiac damage; however, current evidence argues that cTn holds little prognostic relevance until the degree of elevation is almost five times the upper limit of normal (ULN). Thus, the best evidence recommends the use of periprocedural CK-MB routinely during PCI to provide clinical and prognostic information about the degree of myocardial injury and risk of post-procedural morbidity and mortality.

Keywords: Creatinine kinase myocardial band • Troponin • Percutaneous coronary intervention

INTRODUCTION

A best evidence topic was constructed according to a structured protocol as described in the *ICVTS* [1].

THREE-PART QUESTION

What is the [clinical significance and prognostic relevance] of [peri-procedural CK-MB and post-procedural troponin levels] in patients [undergoing elective and emergency PCI]?

CLINICAL SCENARIO

You are at a national interventional cardiology conference attending a very interesting session about the monitoring of biochemical markers during and following PCI. The speaker, a prominent interventionalist and academic in his field states matter-of-factly that 'the monitoring of peri-procedural CK-MB levels is of vital importance as it is a strong predictor of post-procedural adverse events'. An eminent delegate from the floor stands up and contends that 'there is no substantial evidence base to support this claim - and that in fact the monitoring of cardiac troponin levels post-procedurally is much more important as it is a far more sensitive and is an accurate predictor of myocardial damage'. Enthralled by the debate, but unclear about the best evidence surrounding the monitoring of biochemical markers during and following PCI, you resolve to check the literature yourself.

SEARCH STRATEGY

Searched between 2000 and 2013 using PubMed. {[(('creatinine'[MeSH Terms] OR 'creatinine'[All Fields]) AND kinase-myocardial [All Fields] AND ('Band'[Journal] OR 'band'[All Fields])] AND (('troponin'[MeSH Terms] OR 'troponin'[All Fields]) AND levels [All Fields])} AND {'percutaneous coronary intervention'[MeSH Terms] OR ('percutaneous'[All Fields] AND 'coronary'[All Fields]

Table 1: The best evidence papers

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Jang *et al.* (2012), Catheter Cardiovasc Intervent, UK [2] Meta-analysis (level 1a)	10 studies were identified that included 48 022 patients who underwent PCI between 1999 and 2011	Overall RR % of mortality with a CK-MB elevation >1 times the ULN	1.74% (95% CI 1.42–2.13, $P < 0.001$)	This meta-analysis showed that even a small increase in CK-MB levels during PCI is associated with significantly higher risk of late mortality Monitoring cardiac enzymes during PCI may help predict long-term clinical outcome
		RR% of mortality with a CK-MB elevation of 1 to <3 times the ULN	1.48% (95% CI 1.25–1.77, $P < 0.001$)	
		RR% of mortality with a CK-MB elevation of 3 to <5 times the ULN	1.71% (95% CI 1.23–2.37, $P = 0.001$)	
		RR% of mortality with a CK-MB elevation of ≥5 times the ULN	2.83% (1.98–4.04), $P > 0.001$)	
Zimarino *et al.* (2012), Atherosclerosis, UK [3] Systematic review (level 1b)	14 major studies were identified which included 74 253 patients who had PCI between 2000 and 2011. (A major study defined as $n > 50$). Three meta-analyses with the largest sample sizes are included here used as outcomes measures	Nienhuis *et al.* [4]	cTn elevation after PCI is associated with increased risk of death and death/MI	This systematic review reports that isolated cTnT/I rise after PCI over the currently proposed threshold of three times the URL—in the absence of any increase in CK-MB—appears to be over-sensitive to diagnose MI, and cannot be considered an independent predictor of late adverse outcome
		Testa *et al.* [5]	cTn elevation >3 × URL are associated with an increased risk of death	
		Feldman *et al.* [6]	cTnT and cTnI elevation are associated with an increased all-cause mortality and death/MI	
Cavallini *et al.* (2005), Eur Heart J, Italy [7] Multicentre prospective cohort study (level 2a)	Study included 3494 consecutive patients undergoing PCI from February 2000 to October 2000 in a total of 16 Italian tertiary centres	Detection of CK-MB elevation (%) and association with increased 2-year mortality as OR	CK-MB elevation detected in 16% of patient population OR: 1.9 (95% CI 1.3–2.8, $P < 0.001$)	This cohort study found that post-procedural elevations of CK-MB, but not cTn increase the risk of 2-year mortality
		Degree of CK-MB elevation as an independent predictor of risk of death as (adjusted) OR	Adjusted OR per unit: 1.04 (95% CI 1.01–1.07, $P = 0.009$)	
		Detection of cTn and association with increased 2-year mortality as OR	cTn elevation detected in 44.2% of patient population OR: 1.2 (95% CI 0.9–1.7 $P = 0.2$)	
Nageh *et al.* (2013), BMJ Heart, UK [8] Prospective cohort study (level 2c)	Study included 316 consecutive patients who underwent PCI between 1999 and 2000	OR of association between post-procedural cTn increase and death at 18 months	3.28 (95% CI 1.7–6.4, $P = 0.01$)	This study found that a post-procedural increase in cTn was independently and significantly predictive of an increased risk of adverse events at 18 months
		Post-PCI PPV for adverse events at 18 months	0.47 (OR: 18.9, 95% CI 9.7–37, $P < 0.0001$)	
		Post-PCI NPV for adverse events at 18 months	0.96 (OR: 18.9, 95% CI 9.7–37, $P < 0.0001$)	
Kini *et al.* (2004), Am J Cardiol, USA [9] Prospective cohort study (level 2b)	Study included 2873 patients who underwent PCI between 1999 and 2001	Kaplan–Meier estimates of death (%) for postprocedural elevation of CK-MB and cTn		This study found that periprocedural CK-MB elevation of >5 times the normal value is an independent predictor of mid-term mortality and a valuable marker for PCI prognosis in low-to-medium risk patients, whereas cTn—though frequently elevated—does not predict mortality
		Group 1: normal CK-MB (<16 U/l) or cTn (<2 ng/ml)	CK-MB: 2.1% ($P = 0.002$) cTn: 2.2% ($P = 0.58$)	
		Group 2: 1–3 times the normal values of CK-MB and cTn	CK-MB: 2.7% ($P = 0.002$) cTn: 2.3% ($P = 0.58$)	
		Group 3: >3–5 times the normal values of CK-MB and cTn	CK-MB: 1.7% ($P = 0.002$) cTn: 2.9% ($P = 0.58$)	
		Group 4: >5 times the normal values of CK-MB and cTn	CK-MB: 10.3% ($P = 0.002$) cTn: 2.1% ($P = 0.58$)	

Continued

Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Nallamothu *et al.* (2003), Am J Cardiol, USA [10] Retrospective cohort study (level 3a)	Study identified 2796 consecutive patients who underwent PCI at a tertiary-care referral centre between 1997 and 2001. Only 1157 patients were included in the analysis	HR of post-PCI cTn levels 1–3 times normal 3–5 times normal 5–8 times normal ≥8 times normal	 1.1 (95% CI 0.6–2.2, *P* = 0.74) 0.9 (95% CI 0.3–3.0, *P* = 0.85) 1.2 (95% CI 0.4–4.0, *P* = 0.78) 2.4 (95% CI 1.2–5.0, *P* = 0.018)	This study found that not only was cTn frequently elevated in patients after PCI, but that levels ≥8 times the normal value decreased long-term survival. It was concluded that patients with large elevations of cTn should be treated in a similar fashion to those with high periprocedural CK-MB levels
Natarajan *et al.* (2004), Am J Cardiol, USA [11] Prospective cohort study (level 3a)	Study included 1128 patients who underwent PCI between 1997 and 1999	1-year mortality (% of patient population) (*n* = 1128) cTnI negative (*n* = 9390) cTnI 1–4 times ULN (*n* = 86) cTnI ≥5 ULN (*n* = 103)	1.2% 1.0% 1.1% 2.9%	This study found that elevated cTn with concomitant CK elevations (i.e. isolated troponin elevations) posed no additional risk of 1-year mortality. It was also found that these cTnI elevations, though five times the ULN were not prognostically significant predictors of 1-year mortality
Loeb *et al.* (2010), Clin Cardiol, USA [12] Prospective cohort study (level 3a)	Study included 907 patients who underwent PCI between 1998 and 2006	Significant independent predicators of reduced long-term survival Significant univariate predictors of survival	Maximal post-PCI cTn (*P* = 0.0272) TrMX of 3.62 ng/ml or above (*P* = 0.0451)	This study found that the majority of low-risk patients could be expected to display cTn elevations within 24 h of PCI being carried out. It was also concluded that there was an adverse effect on long-term survival in patients with the largest post-PCI cTn elevations
Adgey *et al.* (1999), Clin Cardiol, USA [13] Review article (level 4a)	Study included eight studies with a total sample size of 7764 patients who underwent PCI	Kong *et al.*, [14] 1-year mortality in patients with detected CK-MB elevation	6.6% (*P* = 0.02) vs 2.6% in control patients	This study found that long-term monitoring of patients with non-Q-wave MI may be appropriate, as supported by the incremental risk of death associated with a periprocedural CK-MB elevation
Grines *et al.* (2011), J Am Coll Cardiol, USA [15] Editorial review (level 5a)	Seven relevant papers were reviewed, these papers all examined patients who underwent PCI	Currently recommended threshold of cTn level in the diagnosis of MI Lim *et al.* [16] study analysis defined 'optimal' threshold of cTn level in the diagnosis of MI	0.15 ng/ml constitutes a Type 4a periprocedural MI 2.7 ng/ml constitutes a Type 4a periprocedural MI	This study found that CK-MB elevations were much more reliable in determining the occurrence of MI post-PCI; it was also found that cTn level elevations were—as the current guidelines stand—of limited value in the diagnosis of MI after PCI as well as prognostically

AND 'intervention'[All Fields]) OR 'percutaneous coronary intervention'[All Fields]}.

SEARCH OUTCOME

In total, 396 papers were found using the reported search. Of these, 10 papers were selected to provide the best evidence to answer the question. These are presented in Table 1.

RESULTS

Jang *et al.'s* [2] recent meta-analysis (10 studies, $n = 48\,022$) presented data to support a direct correlation between the degree of elevation of periprocedural CK-MB levels, long-term mortality and reduced long-term survival. The overall risk ratio (RR%) of mortality with a CK-MB elevation >1 times the ULN was 1.74% (95% confidence interval [CI] 1.42–2.13, $P < 0.001$). The meta-analysis also demonstrated an exposure–response relationship between RR of mortality and increasing CK-MB values: 1.48 (95% CI 1.25–1.77, $P < 0.001$) with CK-MB elevation 1–<3 × ULN and 1.71 (95% CI 1.23–2.37, $P = 0.001$) with CK-MB elevation 3–5 × ULN.

In 2012, Zimarino *et al.* [3], presented a systematic review (14 studies, $n = 74\,253$) which advised that isolated cTn level elevation after PCI over and above the currently defined threshold of three times the URL—with no increase in CK-MB—was too sensitive to diagnose myocardial infarction (MI) and that it could not be considered an independent predictor of post-procedural adverse outcomes [4–6]. Cavallini *et al.* [7] in a 2005 multicentre prospective cohort study ($n = 3494$) showed that post-procedural elevations of CK-MB, but not cTnI, increased the risk of 2-year mortality. CK-MB level elevation was detected in 16% of the patient population and was associated with an increase in the risk of 2-year mortality; OR 1.9 (95% CI 1.3–2.8, $P < 0.001$). The degree of CK-MB elevation was found to be an independent predictor of mortality, expressed as an (adjusted) OR. Adjusted OR per unit: 1.04 (95% CI 1.01–1.07, $P = 0.009$). cTnI elevation was detected in 44.2% of the patient population and was not shown to be associated with a significant increase in the risk of 2-year mortality; OR: 1.2 (95% CI 0.9–1.7, $P = 0.2$). However, Nageh *et al.* [8] in a 2013 prospective cohort study ($n = 316$) found that a post-procedural increase in cTnI was independently and significantly predictive of an increased risk of adverse events at 18 months; OR between post-procedural cTnI increase and death at 18 months: 3.28 (95% CI 1.7–6.4, $P = 0.01$).

Kini *et al.* [9], in a 2004 prospective cohort study ($n = 2873$) in patients who underwent PCI, found that periprocedural CK-MB elevation more than five times the normal value is an independent predictor of mid-term mortality and a valuable marker for post-PCI prognosis in low-to-medium risk patients, whereas troponin (although frequently elevated) does not predict mortality. The analysis was based on Kaplan–Meier curves demonstrating patient survival. Patients were first stratified into four groups depending on the degree of periprocedural CK-MB elevation. Kaplan–Meier estimates of death (%) for post-procedural elevation of CK-MB and cTnI in Group 1 (normal CK-MB <16 U/l or troponin I <2 ng/ml) were CK-MB: 2.1% ($P = 0.002$) cTnI: 2.2% ($P = 0.58$). Similarly, in Group 2 (1–3 times the normal values of CK-MB and cTnI), the values were CK-MB: 2.7% ($P = 0.002$) cTnI: 2.3% ($P = 0.58$). In Group 3 (>3–5 times the normal values of CK-MB and cTnI), the values were CK-MB: 1.7% ($P = 0.002$) cTnI: 2.9% ($P = 0.58$). Finally, in Group 4 (>5 times the normal values of CK-MB and cTnI), the values were CKMB: 10.3% ($P = 0.002$) cTnI: 2.1% ($P = 0.58$).

Nallamothu *et al.* [10], in a 2003 retrospective cohort study ($n = 2796$), posited that cTnI levels were frequently elevated in patients after PCI and that cTnI levels eight or more times the normal value indicated a decreased long-term survival. It was also concluded that patients with large elevations in cTnI levels should be treated in a similar fashion to those with high periprocedural CK-MB levels. The hazard ratio (HR) of post-PCI cTnI levels eight or more times normal was 2.4 (95% CI 1.2–5.0, $P = 0.018$), and was significantly associated with decreased long-term survival. On the contrary, Natarajan *et al.* [11], in a 2004 prospective cohort study ($n = 1128$), found that elevated troponin levels without concomitant creatinine kinase elevations posed no additional risk of 1-year mortality.

Loeb *et al.* [12], in a 2010 prospective cohort study ($n = 907$), showed that the majority of low-risk patients displayed cTnI elevations within 24 h of a clinically uneventful PCI being carried out. But it was also highlighted that there was a reduction on long-term survival in patients with the largest post-PCI cTnI elevations. The group showed that maximal post-PCI cTnI was a significant independent predictor of reduced long-term survival ($P = 0.0272$). They also noted that a maximal cTnI (TrMX) of 3.62 ng/ml was a significant univariate predictor of survival. These findings were in keeping with previous work completed by Adgey *et al.* [13, 14].

Grines *et al.* [15], in a 2011 editorial review (of seven key papers), stated that CK-MB elevations were much more reliable in determining the occurrence of MI post-PCI. They also discerned that cTnI elevations were of limited value in the diagnosis of MI and prognostically following a clinically uneventful PCI. The review examined the current recommendations surrounding the agreed cTnI threshold level in the diagnosis of MI; 0.15 ng/ml (constituting a Type 4a periprocedural MI). The results were contested by Lim *et al.* [16] in 2011, which recommended that the optimal threshold of cTnI in the diagnosis of MI should be 2.7 ng/ml.

CLINICAL BOTTOM LINE

The narrow evidence base advocates the use of periprocedural CK-MB monitoring, recommending that an elevation in CK-MB is a significant predictor of adverse events. Troponins remain a precise and reliable marker of cardiac damage; however, current evidence argues that cTn holds little prognostic relevance until the degree of elevation is extremely high. Thus, the best evidence recommends the use of periprocedural CK-MB routinely during PCI to provide clinical and prognostic information about the degree of myocardial injury and risk of post-procedural morbidity and mortality.

Conflict of interest: none declared .

REFERENCES

[1] Dunning J, Prendergast B, Mackway-Jones K. Towards evidence-based medicine in cardiothoracic surgery: best BETS. Interact CardioVasc Thorac Surg 2003;2:405–9.
[2] Jang JS, Jin HY, Seo JS, Yang TH, Kim DK, Kim DS *et al.* Prognostic value of creatine kinase-myocardial band isoenzyme elevation following

percutaneous coronary intervention: a meta-analysis. Catheter Cardiovasc Intervent 2012;81:959–67.
[3] Zimarino M, Cicchitti V, Genovesi E, Rotondo D, De Caterina R. Isolated troponin increase after percutaneous coronary interventions: does it have prognostic relevance? Atherosclerosis 2012;221:297–302.
[4] Neinhuis MB, Ottervanger JP, Bilo HJ, Dikkeschei BD, Zijlstra F. Prognostic value of troponin after elective percutaneous coronary intervention: a meta-analysis. Catheter Cardiovasc Interv 2008;71:318–24.
[5] Testa L, Van Gaal WJ, Biondi Zoccai GG. Myocardial infarction after percutaneous coronary intervention: a meta-analysis of troponin elevation applying the new universal definition. QJM 2009;102:396–78.
[6] Feldman DN, Minutello RM, Bergman G, Moussa I, Wong SC. Relation of troponin I levels following non-emergent percutaneous coronary intervention to short and long-term outcomes. Am J Cardiol 2009;104:1210–5.
[7] Cavallini C, Savonitto S, Violini R, Arrraiz G, Plebani M, Olivari Z *et al*. Impact of the elevation of biochemical markers of myocardial damage on long-term mortality after percutaneous coronary intervention: results of the CK-MB and PCI study. Eur Heart J 2005;26:1494e8.
[8] Nageh T, Sherwood RA, Harris BM, Thomas MR. Prognostic role of cardiac troponin I after percutaneous coronary intervention in stable coronary disease. Heart 2005;91:1181–5.
[9] Kini AS, Lee P, Marmur JD, Lee P, Agarwal A, Duffy M *et al*. Correlation of postpercutaneous coronary intervention creatine kinase-MB and troponin I elevation in predicting mid-term mortality. Am J Cardiol 2004;93:18–23.
[10] Nallamothu BK, Chetcuti S, Mukherjee D, Grossman P, Kline-Rodgers E, Werns S *et al*. Prognostic implication of troponin I elevation after percutaneous coronary intervention. Am J Cardiol 2003; 91:1272–4.
[11] Natarajan MK, Kreatsoulas C, Velianou JL, Mehta SR, Pericak D, Goodhart DM. Incidence, predictors, and clinical significance of troponin-I elevation without creatine kinase elevation following percutaneous coronary interventions. Am J Cardiol 2004;93:750–3.
[12] Loeb HS, Liu JC. Frequency, risk factors, and effect on long-term survival of increased troponin I following uncomplicated elective percutaneous coronary intervention. Clin Cardiol 2010;33:E40–4.
[13] Adgey AA, Matthew TP, Harbinson MT. Periprocedural creatine kinase-MB elevations: long-term impact and clinical implications. Clin Cardiol 1999; 22:257–65.
[14] Kong TQ Jr, Davidson CJ, Meyers SN, Tauke JT, Parker MA, Bonow RO. Prognostic Implication of creatine kinase elevation following elective coronary artery interventions. J Am Med Assoc 1997;277:461–6.
[15] Grines C, Dixon S. A nail in the coffin of troponin measurements after percutaneous coronary intervention. J Am Coll Cardiol 2011;57: 662–663.
[16] Lim CCS, Van Gaal WJ, Testa L. With the "universal definition," measurement of creatine kinase myocardial band rather than troponin allows more accurate diagnosis of periprocedural necrosis and infarction after coronary intervention. J Am Coll Cardiol 2011;57:653–61.