

Review

The prognostic value of troponin release after adult cardiac surgery – a meta-analysis

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Summary

To assess the accuracy of increased troponin (Tn) concentrations for the prediction of mid-term (≥ 12 months) mortality after coronary artery bypass graft (CABG) and valve surgery, we performed a systematic review identifying all studies reporting on the association between postoperative troponin release and mortality after cardiac surgery. Studies were identified through 30 April 2008 by electronic searches of the MEDLINE, EMBASE and BIOSIS databases. Two reviewers independently selected studies, assessed methodological quality and extracted the data. We primarily considered mid-term (≥ 12 months) and secondarily short-term (≤ 30 days) all-cause mortality. A bivariate random-effects model was used to study determinants and to pool measures of prognostic accuracy of Tn. Seventeen studies fulfilled the inclusion criteria with a total of 237 mid-term deaths in 5189 patients and 296 short-term deaths in 9703 patients. The diagnostic odds ratio of increased Tn concentrations was 5.46 (95% confidence interval (CI) 2.0–14.6) for mid-term mortality and 6.57 (95% CI 4.3–10.1) for short-term mortality after adult cardiac surgery. Alternatively expressed, for troponin elevation, the sensitivity was 0.45 (0.26–0.67) and the specificity 0.87 (0.73–0.90) to predict mid-term mortality. The sensitivity was 0.59 (0.48–0.69) and the specificity 0.82 (0.72–0.89) for short-term mortality. Between-study variability was high. In conclusion, this meta-analysis provides evidence for an association between postoperative Tn release with mid- and short-term all-cause mortality after adult cardiac surgery. However, differences in populations, timing of Tn testing, Tn subunit and Tn assays make definitive conclusions about effect size and cut-off values difficult.

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1. Introduction

The increasing interest in provider profiling and optimisation of health-care resources in cardiac surgery has been accompanied by the development of numerous risk-stratification models [1], which consider pre- and intra-operative risk predictors exclusively. Postoperatively, however, the estimation of prognosis cannot be based solely on risk-stratification tools developed for preoperative risk stratification and provider profiling. Perioperative events have a recognised association with morbidity [2–6] and mortality [7,8] but would, therefore, end up being disregarded.

To extend the prognosis to the postoperative condition, several studies addressed the impact of troponin release on outcome after adult cardiac surgery.

We conducted a systematic review to clarify the prognostic value of postoperatively increased troponin levels

for the prediction of mid-term (≥ 12 months) and short-term (≤ 30 days) all-cause mortality in adults undergoing coronary artery bypass graft (CABG) and valve surgery.

2. Methods

2.1. Study identification

Studies reporting on the association between troponin release and all-cause mortality in adult undergoing CABG and valve surgery were identified through 30 April 2008 by electronic searches of the MEDLINE, EMBASE and BIOSIS databases. All electronic searches were performed without language restriction and were completed by manual searches of the reference list of each article. A search strategy (Appendix 1) based on the terms troponin and cardiac surgical procedures, and validated combinations of prognostic [9,10] and diagnostic terms [11,12] was used.

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All congress abstracts and interventional studies with troponin levels as the endpoint and lacking information about all-cause mortality and cardiac morbidity were excluded, as were reports lacking specific information about patients' number, inclusion/exclusion criteria, event definition, follow-up duration or patient demographics. To avoid considering repeatedly published data, we excluded articles presenting preliminary results if a later article was available.

Study selection was performed independently by two readers (GLB and MG). Inconsistencies were resolved by consensus.

2.2. Descriptive data

Descriptive data of the studies including the study sample size, planned follow-up duration and completeness of follow-up, surgical procedures, median age, gender proportion, elective versus urgent/emergency proportion, acute coronary syndrome (ACS) proportion and definition, troponin cut-off level and timing of blood sample collection were registered. For descriptive purposes, we recorded multivariate adjusted odds ratio (OR) or hazard ratio (HR) estimates, if available, together with the adjustment variables used to derive the troponin effect.

2.3. Outcome data

Data were primarily extracted for mid-term (≥ 12 months) all-cause mortality. Studies reporting on all-cause mortality for short-term (≤ 30 days) or in-hospital periods only were considered secondarily. In addition, the occurrence of major non-fatal adverse cardiac events (MACE) for mid- and short-term was assessed. The latter consisted of myocardial infarction, congestive heart failure and low output syndrome as defined in the respective studies. The number of events was extracted according to troponin levels above and below the given cut-off level to calculate true and false positive and negative rates, respectively, as needed for statistic analysis. Missing information was sought by written correspondence with the authors. One paper [13] reported the study results per unit troponin increase (per $10\text{-}\mu\text{g l}^{-1}$ increase in TnI concentration). In this case, we used the 75th-percentile troponin level ($8.49\ \mu\text{g l}^{-1}$) reported in the paper [13] as the cut-off value.

Mid- and short-term all-cause mortality were statistically analysed. Due to widely diverging definitions of MACE, results for MACE were summarised in a descriptive manner only.

2.4. Study quality assessment

The quality of the methodology of the included studies was evaluated according to the QUADAS-checklist [14]. The questions of the checklist were modified to fit the prognostic setting of our review. Therefore, the terms index test, target condition and reference standard appearing in the QUADAS-checklist were replaced with troponin concentration measurement, mortality, and follow-up/outcome assessment in the modified checklist, respectively. The details of the modified checklist are reported in Appendix 2.

2.5. Statistical analysis

Frequencies are described as number and/or percent and agreement between the readers for inclusion of the retrieved studies as κ -value.

A bivariate random-effects meta-regression model [15] was used to obtain summary estimates of sensitivity and specificity. The bivariate model preserves the two-dimensional nature of the data through the joint analysis of the pairs of the logarithm transformed (logit) sensitivity $\{\log[\text{sens}/(1 - \text{sens})]\}$ and specificity $\{\log[\text{spec}/(1 - \text{spec})]\}$ of each study in the mixed-model framework. By using the random-effects approach, the model assumes between-study heterogeneity as a consequence of chance variability, differences in study populations and study design of the included studies and allows for it. This bivariate model, thus, calculates a random-effect estimate of the mean sensitivity and specificity together with their 95% confidence intervals (CIs). After back-transformation of the estimates (antilogit) to the probability scale, pooled estimates are plotted within the ROC space and, together with the correlation between the sensitivity and specificity, a 95% confidence area around the summary estimate of sensitivity and specificity can be produced. The 95% confidence area can be viewed as a two-dimensional confidence interval. The main axis of the 95% confidence area reflects the correlation between sensitivity and specificity (threshold effect). In addition to the 95% confidence area, the bivariate models allows for the calculation of a 95% prediction area, which can be viewed as the two-dimensional standard deviation of the individual studies. The area of 95% prediction area that reaches beyond the 95% confidence area reflects significant between-study variation.

Covariates can be introduced into the bivariate model to explain between-study variation of sensitivity and specificity. In this study, we predefined the type of surgery (studies of CABG only vs CABG and/or valvular surgery) as the only explanatory covariate in our model. Moreover, we performed sensitivity analyses restricting meta-analyses to studies that reported a total of at least 10 deaths.

A standard correction of 0.5 was applied to those cells of the 2×2 contingency tables without events. The bivariate model was fitted in SAS version 9.1 for Windows (SAS Institute, Cary, NC, USA).

3. Results

3.1. Description of studies

Seventeen of the 1215 citations identified fulfilled the inclusion criteria (Fig. 1). The chance-corrected κ -value for agreement on study inclusion was 0.7 (crude agreement was 1205/1215 or 0.99).

Two studies reported on mid-term (≥ 12 months) results [16,17], eight on short-term (≤ 30 days) results [18–25] and seven on both [13,26–31], with a total of 237 mid-term deaths by any cause in 5119 patients and 296 short-term deaths by any cause in 9703 patients. Six of the mid-term studies [17,26–28,30,31] described the completeness of their follow-up that ranged from 84% to 100%. Table 1 reports the details of the studies included.

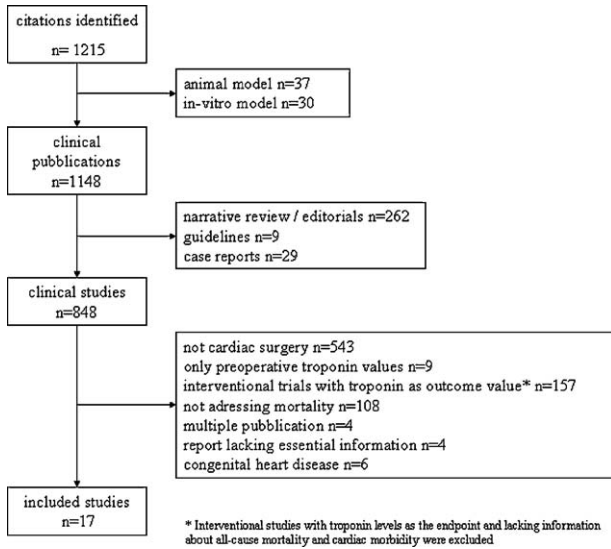


Fig. 1. Selection process of the identified citations.

Two studies [16,20] only showed adjusted associations of troponin with all-cause mortality and crude data could not be obtained. Therefore, these studies could not be used for statistical pooling and were only reported descriptively (Table 2). The adjusted results of both these studies and of the remaining studies presenting adjusted estimates [13,17,22,28] are summarised as published in the respective papers (Table 2). The positive and negative predictive values for all-cause mortality in the single studies are described in Tables 3 and 4, as a meta-analytic method to obtain summary estimates for those values is not available.

3.2. Accuracy of troponin release for the prognosis of all-cause mortality

3.2.1. Summary estimates

The summary estimates of the association (dOR [95% confidence intervals]) of troponin above versus below the cut-off in an individual study and the occurrence of death after adult cardiac surgery was 5.46 (95% CI: 2.0–14.6) for mid-term all-cause mortality and 6.57 (95% CI: 4.3–10.1) for short-term all-cause mortality (Figs. 2 and 3).

Alternatively expressed, troponin elevation had an average sensitivity of 0.45 (0.26–0.67) and a specificity of 0.87 (0.73–0.90) for the prediction of mid-term all-cause

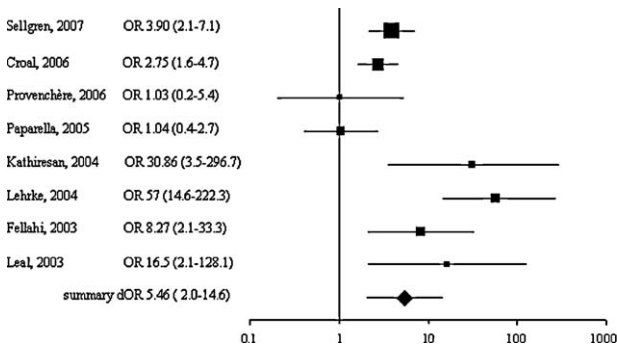


Fig. 2. OR and summary dOR for the association between troponin release and mid-term mortality after cardiac surgery.

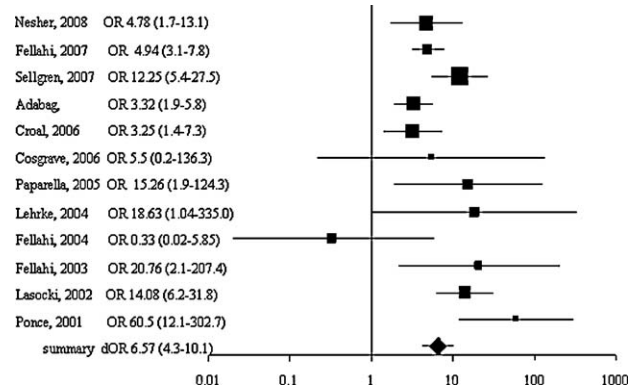


Fig. 3. OR and summary dOR for the association between troponin release and short-term mortality after cardiac surgery.

mortality. For the prediction of short-term all-cause mortality, elevated troponin reached an average sensitivity of 0.59 (0.48–0.69) and a specificity of 0.82 (0.72–0.89).

The bivariate 95% confidence area in the ROC plane around the pooled mean values [32] of sensitivity and specificity are depicted in Fig. 4a and b.

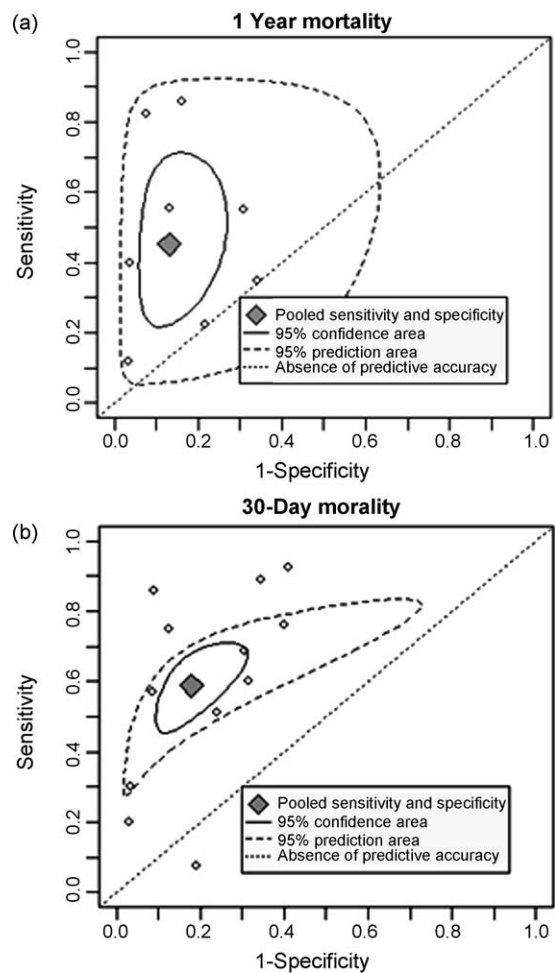


Fig. 4. (a) Summary estimate and 95% confidence area of the sensitivity and specificity of troponin release for mid-term mortality. The 95% prediction area is a measure for between-study variability. (b) Summary estimate and 95% confidence area of the sensitivity and specificity of troponin release for short-term mortality. The 95% prediction area is a measure for between-study variability.

Table 1
Characteristics of the included studies.

Study	Design	Sample size	Events (%)	Endpoint	Follow-up	CABG (%)	Elective surgery (%)	Male (%)	Age (years)	Tn unit	Cut-off ($\mu\text{g l}^{-1}$)	Increased Tn levels	Sample collection time
Nesher et al. (2008) ¹	Prospective cohort of consecutive patients	1515	21 (0.01)	All-cause mortality	Inhospital	100	62	82	65	TnT ^a	0.8	40.6%	Peak value
Sellgren et al. (2007)	Retrospective cohort of consecutive patients	2751	119 (9.7)	All-cause mortality	30 days/ 24 months	72.0	100	74	66	TnT ^b	2.0	3.7%	96 h
Riedel et al. (2006)	Prospective cohort of consecutive patients	70	20 (8.7)	MACE	36 months	100.0	100	92.8	60.2	TnI ^c	15.0	32.8%	Peak value
Croal et al. (2006)	Prospective cohort of consecutive patients	1356	65 (4.8)	All-cause mortality	30 days/ 12 months	76.7	100	75.0	66.2	TnI ^d	Continuous values	2 and 24 h	
Provenchère et al. (2006)	Prospective cohort of consecutive patients	92	9 (9.8)	All-cause mortality	Inhospital/ 12 months	46.7	100	66.3	66.0	TnI ^e	13.0	2.2%	24 h
Paparella et al. (2005)	Cohort of consecutive patients	230	20 (8.7)	All-cause mortality	Inhospital/ 24 months	100.0	NS	78.7	65.1	TnI ^f	13.0	36.5%	Peak value
Kathiresan et al. (2004)	Prospective cohort of consecutive patients	136	7 (5.2)	All-cause mortality	12 months	100.0	NS	77.0	67.0	TnT ^g	1.58	20.0%	18–24 h
Lehrke et al. (2004)	Prospective cohort of consecutive patients	204	11 (5.4)	All-cause mortality	Inhospital/ 24 months	64.7	100	64.7	63.3	TnT ^a	0.46	6.9%	48 h
Fellahi et al. (2003)	Prospective cohort of consecutive patients	202	9 (4.4)	All-cause mortality	Inhospital/ 24 months	100.0	100	90.6	64.0	TnI ^h	13.0	2.5%	24 h
Leal et al. (2003)	Cohort of random patients	88	5 (5.6)	All-cause mortality	Inhospital/ 12 months	100.0	NS	73.9	NS	TnI ⁱ	2.5	2.3%	24 h
Berendes et al. (2003)	Prospective cohort of consecutive patients	60	10 (16.7)	All-cause mortality	24 months	100.0	100	80.0	64.0	TnI ^j	Not applicable	12 h	
Fellahi et al. (2007) ²	Prospective cohort of consecutive patients	431	121 (28.1)	All-cause mortality and MACE	Inhospital	0.0	100	64	73	TnI ^h	9.3 ³ , 11.8 ⁴	41.3%	24 h
Adabag et al. (2007)	Cohort of consecutive patients	1186	51 (4.3)	30-day mortality	30 days	58.7	92.7	99.0	66.0	TnI ^h	Continuous values	24 h	
Cosgrave et al. (2006)	Prospective cohort of consecutive patients	100	2 (2)	30-day mortality	30 days	100.0	100	83.0	62.0	TnT ^k	1	5.0%	24 h
Fellahi et al. (2004)	Randomized controlled study without difference in the groups	359	6 (1.6)	All-cause mortality	Inhospital	60.7	100	72.4	67.0	TnI ^h	13	20.6%	24 h
Lasocki et al. (2002)	Prospective cohort of consecutive patients	502	28 (5.6)	All-cause mortality	Inhospital	37.0	93	86.8	63.0	TnI ^l	13.0	11.0%	20 h
Eigel et al. (2001)	Prospective cohort of consecutive patients	540	21 (3.9)	All-cause mortality, MACE	Inhospital	100.0	100	69.0	68.7	TnI ^m	0.495	NS	End of CPB
Ponce et al. (2001)	Cohort of consecutive patients	147	14 (9.5)	All-cause mortality	Inhospital	0.0	100	54.4	59.1	TnI ⁿ	38.85	16.0%	14 h

CABG: coronary artery bypass graft; NS: not stated; MACE: major adverse cardiac events; CPB: cardiopulmonary bypass.

^a Elecsys 2010, Roche Diagnostics.

^b Kit not stated.

^c Opus kit, Dade-Behring.

^d ADVIA, Bayer Diagnostics.

^e RXL HM, Dade-Behring.

^f Not fully stated, Dade Behring.

^g Elecsys 1010, Roche Diagnostics.

^h AxSYM, Abbot Laboratories.

ⁱ Access, Sanofi-Pasteur.

^j Dimention RxL, Dade-Behring.

^k Cardiac T Diagnostics Reader, Roche Diagnostics.

^l Stratus II, Dade-Behring.

^m Stratus CS, Dade-Behring.

ⁿ Stratus, Dade-Behring.

¹ Only CABG patients included (all-cause mortality data was available for these patients only).

² Non-CABG patients included.

³ Cut-off value for valve surgery.

⁴ Cut-off value for combined surgery.

Table 2
Multivariate association of troponin increase with stated endpoints of the included studies.

Study	Events	Tn	Endpoint	Multivariate adjusted association	Adjustment variables
Croal et al. (2006)	n = 65	I	12-month mortality	OR 1.1 (1.03–1.2) per 10 µg l ⁻¹	Age, gender, BMI, smoking status, hypertension, diabetes, hypercholesterolaemia, inotrope requirement, EuroSCORE, cross-clamp time, previous myocardial infarction, NYHA functional class, left main stem stenosis >50%, EF <50%, preoperative creatinine, estimated GFR, complex surgery, postoperative ventricular dysrhythmia, postoperative septicemia
Kathiresan et al. (2004)	n = 7	T	12-month mortality	OR 5.4 (4.5–232.5)	Age, gender, presenting syndrome, cardiovascular risk factors, medication, CAD's extent, EF, repeat CABG, type of cardioplegia, surgical procedures
Lehrke et al. (2004)	n = 11	T	24-month mortality	OR 4.9 (1.02–23.9)	Gender, type of surgery, preoperative TnT levels, cross clamp-time, cardiovascular risk factors
Berendes et al. (2004)	n = 10	I	24-month mortality	HR 1.0 (0.83–1.2)	Preoperative BNP, duration of intraoperative myocardial ischaemia, Cleveland score, preoperative left ventricular ejection fraction, postoperative wall motion abnormalities
Nesher et al. (2008)	n = 255	T	Inhospital mortality and MACE	OR 2.7 (2.08–3.5)	Age >70 years, gender, EF <40%, CPB time, NYHA functional class, preoperative cerebrovascular accident
Lasocki et al. (2002)	n = 28	I	Inhospital mortality	OR 6.7 (2.3–19.3)	Age, gender, diabetes, altered LV function, emergent surgery, NYHA functional class, surgery type, CPB time, chest drainage volume, postoperative arterious pO ₂
Eigel et al. (2001)	n = 21	I	Inhospital mortality and MACE	OR 17 (5.5–54)	Age, gender, diabetes EF <40%, Cleveland clinic preoperative severity score, ross clamp time, CPB time, preoperative creatine level, number of grafts

BMI: body mass index; NYHA: New York Heart Association; EF: ejection fraction; GFR glomerular filtration rate; LV: left ventricular; CPB: cardiopulmonary bypass.

3.2.2. Between-study variability and sensitivity analysis

For sensitivity, the 95% prediction interval ranged from 0.09 to 0.88 and from 0.31 to 0.82 for mid- and short-term all-cause mortality, respectively. For specificity, the 95% prediction interval ranged from 0.44 to 0.98 and from 0.38 to 0.97 for mid- and short-term all-cause mortality, respectively. Therefore,

Table 3
Positive and negative predictive values of the single studies for mid-term all-cause mortality.

Study	Positive predictive value	Negative predictive value
Sellgren et al. (2007)	0.15	0.96
Croal et al. (2006)	0.10	0.96
Provenchere et al. (2006)	0.10	0.90
Paparella et al. (2005)	0.10	0.90
Kathiresan et al. (2004)	0.22	0.99
Lehrke et al. (2004)	0.50	0.98
Fellahi et al. (2003)	0.19	0.97
Leal et al. (2003)	0.33	0.97

Table 4
Positive and negative predictive values of the single studies for short-term all-cause mortality.

Study	Positive predictive value	Negative predictive value
Nesher et al. (2008)	0.03	0.99
Fellahi et al. (2007)	0.47	0.85
Sellgren et al. (2007)	0.09	0.99
Adabag et al. (2007)	0.09	0.97
Croal et al. (2006)	0.05	0.99
Cosgrave et al. (2006)	0.12	0.98
Paparella et al. (2005)	0.10	0.99
Lehrke et al. (2004)	0.06	1.00
Fellahi et al. (2004)	0.01	0.98
Fellahi et al. (2003)	0.11	0.99
Lasocki et al. (2002)	0.28	0.97
Ponce et al. (2001)	0.50	0.98

the data showed large between-study variability as reflected by the large area of the 95% prediction area beyond the 95% confidence area (Fig. 4a and b).

To address between-study variability, we initially assessed threshold effect, a frequent source of variability between diagnostic studies. Threshold effect was not present in the mid-term results (correlation coefficient between logit (sensitivity) and logit (specificity) 0.07, $p = 0.9$). In contrast, threshold analysis resulted in a significant threshold effect for short-term data (correlation coefficient between logit (sensitivity) and logit (specificity) 0.64, $p = 0.024$).

Subsequently, we determined whether the results from CABG surgery populations versus mixed CABG and/or valvular surgery populations differed. The variable dOR ($p = 0.80$ for mid-term and $p = 0.88$ for short-term all-cause mortality), sensitivity ($p = 0.60$ for mid- and $p = 0.77$ for short-term all-cause mortality) and specificity ($p = 0.80$ for mid-term and $p = 0.90$ for short-term all-cause mortality) were not significantly influenced by the type of cardiac surgery.

Finally, we performed sensitivity analyses by restricting the pooled analyses to studies reporting at least 10 deaths. The dOR in studies with more than 10 deaths was 4.65 (0.98–22.16) and 6.63 (3.83–11.47) for mid- and short-term all-cause mortality, respectively. The mean sensitivity in the studies with more than 10 deaths was 0.43 (0.16–0.75) and 0.58 (0.46–0.69) for mid- and short-term, respectively. The specificity in the same studies was 0.86 (0.63–0.96) and 0.83 (0.68–0.91) for mid- and short-term all-cause mortality, respectively.

3.3. Quality assessment

All of the included studies fulfilled the requirements of a representative spectrum of patients, of outcome verification in the whole cohort, of equal outcome evaluation, regardless of the troponin results and of availability of clinical data. We considered the description of the troponin measurement (index test) sufficient for replication in 15

studies [13,16–22,24,26–28,30]. Sixteen [13,16–26,28–31] of 17 studies clearly described their criteria for selecting patients. Of the 12 studies that did not address in-hospital all-cause mortality, only eight described the follow-up methods (execution of the reference standard) used [13,17,26,28–30]. Only two studies [18,19] stated that outcome was interpreted without knowledge of the troponin results. Six of the 17 studies described the reasons for withdrawal [18,22] or loss of follow-up [26,28,30].

4. Discussion

4.1. Clinical interpretation

The data summarised in this meta-analysis showed a clear association between troponin release after cardiac surgery and mid- and short-term all-cause mortality. The evidence of the prognostic impact of troponin release after adult cardiac surgery is supported by a concentration–response effect reported in a study by Croal et al. [13] for mid-term all-cause mortality and in studies by Adabag et al. [18] and by Neshet et al. [25] for the short-term all-cause mortality.

A similar association between troponin release and outcome has previously been shown primarily in non-surgical populations, for example, in patients presenting with ACSs [33–36], in patients undergoing percutaneous coronary intervention (PCI) for stable angina or ACS [37], and in critically ill patients [38]. In addition, an association between troponin release and outcome was shown for patients undergoing major non-cardiac surgery [39–44].

The strength of association between troponin release and outcome in these conditions was comparable to the association found in patients after cardiac surgery reported here. One study in patients with ACS reported an OR of 3.1 (95% CI: 2.3–4.1) for 30-day [36] mortality and an OR of 1.93 (95% CI: 1.46–2.53) for 1-year mortality. After non-cardiac surgery, the association between elevated troponin and all-cause mortality ranged from 10.2 (2.8–37) at 12 months [40] to 2.15 (1.4–3.4) at 32 months [39]. Thus, the association between loss of myocardial cells (expressed by troponin release) and mortality lies in a similar range independent of the initial cause for myocardial damage.

Troponin is not expected to be in the circulation in patients with no previous heart operation. Accordingly, any measurable troponin release can be associated with adverse outcome. This fact is reflected by cut-off values for adverse outcome near the upper reference limits for the troponin tests used [33–36,38–48]. In contrast, patients undergoing cardiac surgery, atriotomy, surgical manipulation, incomplete cardioprotection, aortic cross-clamping [49], defibrillation and reperfusion damage related to on-pump surgery are expected to experience a certain and inevitable degree of troponin release. As expected, cut-off levels found in studies of patients after cardiac surgery were several times higher than the upper limit of the test kits [22,24–26,29,30]. Thus, troponin concentrations exceeding a certain level (caused by some unavoidable surgery-induced troponin release) indicate more extensive myocardial damage, and this more severe myocardial damage is associated with adverse outcome.

Increased troponin release after on-pump cardiac surgery showed higher specificity than sensitivity, provided the cut-offs applied in the different studies. This suggests a stronger average ability of a positive troponin test for the prediction of all-cause mortality than of a negative troponin test to exclude it. In clinical practice, elevated troponin concentration after on-pump cardiac surgery represents, therefore, a sign indicating patients at risk for higher mid- and short-term all-cause mortality.

Should a benefit in prognostic value by the combination of troponin and preoperative risk-stratification tools be confirmed, then troponin measurements might be of particular interest to identify the false negative patients of the preoperative risk-stratification, that is, the patients misclassified by preoperative risk stratification as having a good prognosis.

We analysed the effect of the type of surgery and found no impact of surgery type on the association between troponin concentration and mortality. This may be due to the limited power of the sensitivity analysis resulting from too few studies. It may also be based on the fact that studies enrolling CABG patients only were compared to studies addressing any type of cardiac surgery. However, the latter often included a large proportion of CABG patients, which diluted the potential difference in the predictive value of troponin, as described by Croal et al. [13] in the subgroup of patients undergoing CABG alone. In this meta-analysis, separate evaluation of CABG versus valvular surgery patients was not possible as the data of the subgroup of patients undergoing valvular surgery was generally not presented.

4.2. Methodological consideration

Following the concept of diagnostic research, the bivariate model allows a two-dimensional perception of troponin as a diagnostic test to predict mortality. Thus, we can appreciate that for both mid- and short-term all-cause mortality, elevated troponin levels generally showed a higher specificity (0.73–0.90) than sensitivity (0.26–0.67).

The large number of false-negative results may be related to non-cardiac death. This point is supported by the lower number of false-negative classifications during the first period (in-hospital or 30 days) after cardiac surgery when the ratio of cardiac versus non-cardiac death is expected to be higher. An alternative interpretation is that most studies calibrated their cut-off values in a way that resulted in high specificity and low sensitivity, as their goal was to detect a hard outcome (death by any cause) by a single parameter, rather than excluding its occurrence (as in a screening situation).

The studies included showed large between-study variability. Frequent sources of between-study variability in diagnostic or prognostic accuracy parameters include different threshold values used to determine individual study sensitivities and specificities. Such a threshold effect is reflected by a negative correlation between sensitivity and specificity of the single studies or by a positive correlation between sensitivity and specificity in the summary ROC plane. There was a significant threshold effect in studies addressing short-term but not mid-term all-cause mortality. Alternatively expressed, reports yielding high sensitivities

and low(er) specificities were missing for mid-term but not for short-term all-cause mortality. This may be due to the choice of cut-off values (with more emphasis on specificity and less on sensitivity) and endpoint (all-cause mortality, due to the shift of the cardiac versus non-cardiac cause of death ratio towards non-cardiac death after an extended follow-up).

To address the potential effect of a small number of events, we also restricted our analysis to studies with a total of at least 10 deaths as a potential source of variability without detection of any difference. This may be the consequence of low power of the sensitivity analysis due to the few articles available.

By the assessment of the study quality, we did not identify striking differences between the studies. Follow-up completeness, method to assess outcome and blinding of study collaborators to troponin concentration were rarely described. However, all-cause mortality as primary outcome does not allow for interpretation. Most studies suffered from a limited sample size. Further, all studies failed to provide statements on sample size calculation and its adequacy.

4.3. Limitations

Caution in the appraisal of the pooled results is warranted in the presence of large between-study variability, even when considering calculation from random-effect model. The large between-study variability seems to be based on characteristics other than those mentioned above. First, the included studies differed in study population as reflected by marked differences in mortality, independent of the type of surgery performed. Second, the studies assessed all-cause mortality after a variable follow-up period and with different degrees of completeness. However, potential censoring of observations was not considered in the bivariate model. Third, the assays used and the timing of blood sample collection (0–96 h postoperatively) as well as the measured troponin subunit differed.

A further limitation is that the presented dORs reflect unadjusted association between troponin release and all-cause mortality after cardiac surgery. To what extent increased troponin values implement the prognostic value of established preoperative risk stratification cannot be addressed by the results of this meta-analysis.

We limited the statistical analysis to all-cause mortality. If data on MACE were published in a study reporting on mortality, we summarised the results for MACE only descriptively due to the widely diverse definitions of MACE. The study by Riedel et al. [50] was excluded as it reported on MACE only.

It should be emphasised that we focussed on postoperative troponin readings disregarding the impact preoperative readings.

An additional limiting factor is the reduced number of studies available despite using a sensitive search strategy without language restriction for three electronic databases and a manual search of the reference lists of the included papers (Appendix 1).

Finally, in our hypothesis, we did not pre-specify whether one dimension (sensitivity or specificity of the bivariate

model) was expected to dominate the hypothesised prognostic value expressed by dOR.

5. Conclusions

This systematic review and meta-analysis supports the association between postoperative Tn release and mid- and short-term all-cause mortality after adult cardiac surgery. However, differences in the populations, outcome definitions, timing of the Tn testing, Tn subunit and Tn assays make a definitive conclusion regarding effect size difficult, and regarding cut-off values impossible.

References

- [1] Nilsson J, Algotsson L, Hoglund P, Luhrs C, Brandt J. Comparison of 19 preoperative risk stratification models in open-heart surgery. *Eur Heart J* 2006;27:867–74.
- [2] Martin CB, Shaw AD, Gal J, Aravindan N, Murphy F, Royston D, Riedel BJ. The comparison and validity of troponin I assay systems in diagnosing myocardial ischemic injury after surgical coronary revascularization. *J Cardiothorac Vasc Anesth* 2005;19:288–93.
- [3] Force T, Hibberd P, Weeks G, Kemper AJ, Bloomfield P, Tow D, Josa M, Khuri S, Parisi AF. Perioperative myocardial infarction after coronary artery bypass surgery. Clinical significance and approach to risk stratification. *Circulation* 1990;82:903–12.
- [4] Gray RJ, Matloff JM, Conklin CM, Ganz W, Charuzi Y, Wolfstein R, Swan HJ. Perioperative myocardial infarction: late clinical course after coronary artery bypass surgery. *Circulation* 1982;66:1185–9.
- [5] Higgins TL, Estafanous FG, Loop FD, Beck GJ, Blum JM, Parandani L. Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. A clinical severity score. *JAMA* 1992;267:2344–8.
- [6] Namay DL, Hammermeister KE, Zia MS, DeRouen TA, Dodge HT, Namay K. Effect of perioperative myocardial infarction on late survival in patients undergoing coronary artery bypass surgery. *Circulation* 1982;65:1066–71.
- [7] Gensini GF, Fusi C, Conti AA, Calamai GC, Montesi GF, Galanti G, Noferi D, Carbonetto F, Palmarini MF, Abbate R, Vaccari M. Cardiac troponin I and Q-wave perioperative myocardial infarction after coronary artery bypass surgery. *Crit Care Med* 1998;26:1986–90.
- [8] Quaini E, Colombo T, Russo C, Vitali E, Pellegrini A. Hospital morbidity and mortality after myocardial revascularisation surgery: current changes in risk factors. *Eur J Cardiothorac Surg* 1995;9:275–82.
- [9] Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey. *BMC Med* 2004;2:23.
- [10] Wilczynski NL, Haynes RB. Optimal search strategies for detecting clinically sound prognostic studies in EMBASE: an analytic survey. *J Am Med Inform Assoc* 2005;12:481–5.
- [11] Haynes RB, Wilczynski NL. Optimal search strategies for retrieving scientifically strong studies of diagnosis from Medline: analytical survey. *BMJ* 2004;328:1040.
- [12] Wilczynski NL, Haynes RB. EMBASE search strategies for identifying methodologically sound diagnostic studies for use by clinicians and researchers. *BMC Med* 2005;3:7.
- [13] Croal BL, Hillis GS, Gibson PH, Fazal MT, El-Shafei H, Gibson G, Jeffrey RR, Buchan KG, West D, Cuthbertson BH. Relationship between postoperative cardiac troponin I levels and outcome of cardiac surgery. *Circulation* 2006;114:1468–75.
- [14] Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003;3:25.
- [15] van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med* 2002;21:589–624.
- [16] Berendes E, Schmidt C, Van Aken H, Hartlage MG, Wirtz S, Reinecke H, Rothenburger M, Scheld HH, Schluter B, Brodner G, Walter M. Reversible cardiac sympathectomy by high thoracic epidural anesthesia improves

- regional left ventricular function in patients undergoing coronary artery bypass grafting: a randomized trial. *Arch Surg* 2003;138:1283–90. discussion 1291.
- [17] Kathiresan S, Servoss SJ, Newell JB, Trani D, MacGillivray TE, Lewandrowski K, Lee-Lewandrowski E, Januzzi Jr JL. Cardiac troponin T elevation after coronary artery bypass grafting is associated with increased one-year mortality. *Am J Cardiol* 2004;94:879–81.
- [18] Adabag AS, Rector T, Mithani S, Harmala J, Ward HB, Kelly RF, Nguyen JT, McFalls EO, Bloomfield HE. Prognostic significance of elevated cardiac troponin I after heart surgery. *Ann Thorac Surg* 2007;83:1744–50.
- [19] Cosgrave J, Foley B, Ho E, Bennett K, McGovern E, Tolan M, Young V, Crean P. Troponin T elevation after coronary bypass surgery: clinical relevance and correlation with perioperative variables. *J Cardiovasc Med (Hagerstown)* 2006;7:669–74.
- [20] Eigel P, van Ingen G, Wagenpfeil S. Predictive value of perioperative cardiac troponin I for adverse outcome in coronary artery bypass surgery. *Eur J Cardiothorac Surg* 2001;20:544–9.
- [21] Fellahi JL, Gue X, Philippe E, Riou B, Gerard JL. Isoflurane may not influence postoperative cardiac troponin I release and clinical outcome in adult cardiac surgery. *Eur J Anaesthesiol* 2004;21:688–93.
- [22] Lasocki S, Provenchere S, Benessiano J, Vicaud E, Lecharny JB, Desmots JM, Dehoux M, Philip I. Cardiac troponin I is an independent predictor of in-hospital death after adult cardiac surgery. *Anesthesiology* 2002;97:405–11.
- [23] Ponce G, Romero JL, Hernandez G, Padron A, Cabrera E, Abad C. The non Q wave myocardial infarction in conventional valvular surgery. Diagnosis with cardiac troponin I. *Rev Esp Cardiol* 2001;54:1175–82.
- [24] Fellahi JL, Hedouire F, Le Manach Y, Monier E, Guillou L, Riou B. Determination of the threshold of cardiac troponin I associated with an adverse postoperative outcome after cardiac surgery: a comparative study between coronary artery bypass graft, valve surgery, and combined cardiac surgery. *Crit Care* 2007;11:R106.
- [25] Nesher N, Alghamdi AA, Singh SK, Sever JY, Christakis GT, Goldman BS, Cohen GN, Moussa F, Fremes SE. Troponin after cardiac surgery: a predictor or a phenomenon? *Ann Thorac Surg* 2008;85:1348–54.
- [26] Fellahi JL, Gue X, Richomme X, Monier E, Guillou L, Riou B. Short- and long-term prognostic value of postoperative cardiac troponin I concentration in patients undergoing coronary artery bypass grafting. *Anesthesiology* 2003;99:270–4.
- [27] Leal JC, de Paula Neto A, Avanci LE, Braile MC, de Godoy MF, Braile DM. Risk stratification with troponin I in patients undergoing myocardial revascularization surgery. *Arq Bras Cardiol* 2003;80:279–88.
- [28] Lehrke S, Steen H, Sievers HH, Peters H, Opitz A, Muller-Bardorff M, Wiegand UK, Katus HA, Giannitsis E. Cardiac troponin T for prediction of short- and long-term morbidity and mortality after elective open heart surgery. *Clin Chem* 2004;50:1560–7.
- [29] Paparella D, Cappabianca G, Visicchio G, Galeone A, Marzovillo A, Gallo N, Memmola C, Schinosa Lde L. Cardiac troponin I release after coronary artery bypass grafting operation: effects on operative and midterm survival. *Ann Thorac Surg* 2005;80:1758–64.
- [30] Provenchere S, Berroeta C, Reynaud C, Baron G, Poirier I, Desmots JM, lung B, Dehoux M, Philip I, Benessiano J. Plasma brain natriuretic peptide and cardiac troponin I concentrations after adult cardiac surgery: association with postoperative cardiac dysfunction and 1-year mortality. *Crit Care Med* 2006;34:995–1000.
- [31] Sellgren A, Nilsson F, Jeppsson A. The relationship between ASAT, CKMB, Troponin-T and mortality after cardiac surgery. *Scand Cardiovasc J* 2007;1–5.
- [32] Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;58:982–90.
- [33] Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. *Fragmin during Instability in Coronary Artery Disease*. *N Engl J Med* 2000;343:1139–47.
- [34] Ohman EM, Armstrong PW, Christenson RH, Granger CB, Katus HA, Hamm CW, O'Hanesian MA, Wagner GS, Kleiman NS, Harrell Jr FE, Califf RM, Topol EJ, GUSTO IIA Investigators. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. *N Engl J Med* 1996;335:1333–41.
- [35] Heesch C, Goldmann BU, Terres W, Hamm CW. Cardiovascular risk and therapeutic benefit of coronary interventions for patients with unstable angina according to the troponin T status. *Eur Heart J* 2000;21:1159–66.
- [36] Heidenreich PA, Alloggiamento T, Melsop K, McDonald KM, Go AS, Hlatky MA. The prognostic value of troponin in patients with non-ST elevation acute coronary syndromes: a meta-analysis. *J Am Coll Cardiol* 2001;38:478–85.
- [37] Kizer JR, Muttref MR, Matthai WH, McConnell J, Nardone H, Sonel AF, Keane MG, Wilensky RL. Role of cardiac troponin T in the long-term risk stratification of patients undergoing percutaneous coronary intervention. *Eur Heart J* 2003;24:1314–22.
- [38] Quenot JP, Le Teuff G, Quantin C, Doise JM, Abrahamowicz M, Masson D, Blettery B. Myocardial injury in critically ill patients: relation to increased cardiac troponin I and hospital mortality. *Chest* 2005;128:2758–64.
- [39] Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, Weissman C, Mosseri M. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol* 2003;42:1547–54.
- [40] Filipovic M, Jeger R, Probst C, Girard T, Pfisterer M, Gurke L, Skarvan K, Seeberger MD. Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major noncardiac surgery in patients at risk of coronary artery disease. *J Am Coll Cardiol* 2003;42:1767–76.
- [41] Martinez EA, Nass CM, Jermyn RM, Rosenbaum SH, Akhtar S, Chan DW, Malkus H, Weiss JL, Fleisher LA. Intermittent cardiac troponin-I screening is an effective means of surveillance for a perioperative myocardial infarction. *J Cardiothorac Vasc Anesth* 2005;19:577–82.
- [42] Kim LJ, Martinez EA, Faraday N, Dorman T, Fleisher LA, Perler BA, Williams GM, Chan D, Pronovost PJ. Cardiac troponin I predicts short-term mortality in vascular surgery patients. *Circulation* 2002;106:2366–71.
- [43] Le Manach Y, Perel A, Coriat P, Godet G, Bertrand M, Riou B. Early and delayed myocardial infarction after abdominal aortic surgery. *Anesthesiology* 2005;102:885–91.
- [44] Motamed C, Motamed-Kazerounian G, Merle JC, Dumerat M, Yakhoul L, Vodinh J, Kouyoumoudjian C, Duvaldestin P, Becquemin JP. Cardiac troponin I assessment and late cardiac complications after carotid stenting or endarterectomy. *J Vasc Surg* 2005;41:769–74.
- [45] Khan NA, Hemmelgarn BR, Tonelli M, Thompson CR, Levin A. Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease: a meta-analysis. *Circulation* 2005;112:3088–96.
- [46] Kuwabara Y, Sato Y, Miyamoto T, Taniguchi R, Matsuoka T, Isoda K, Yamane K, Nishi K, Fujiwara H, Takatsu Y. Persistently increased serum concentrations of cardiac troponin in patients with acutely decompensated heart failure are predictive of adverse outcomes. *Circ J* 2007;71:1047–51.
- [47] Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, Angelici L, Barlera S, Parrinello G, Maggioni AP, Tognoni G, Cohn JN. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation* 2007;116:1242–9.
- [48] Perna ER, Macin SM, Canella JP, Augier N, Stival JL, Cialzeta JR, Pitzus AE, Garcia EH, Obregon R, Brizuela M, Barbagelata A. Ongoing myocardial injury in stable severe heart failure: value of cardiac troponin T monitoring for high-risk patient identification. *Circulation* 2004;110:2376–82.
- [49] Takeda S, Nakanishi K, Ikezaki H, Kim C, Sakamoto A, Tanaka K, Ogawa R. Cardiac marker responses to coronary artery bypass graft surgery with cardiopulmonary bypass and aortic cross-clamping. *J Cardiothorac Vasc Anesth* 2002;16:421–5.
- [50] Riedel BJ, Grattan A, Martin CB, Gal J, Shaw AD, Royston D. Long-term outcome of patients with perioperative myocardial infarction as diagnosed by troponin I after routine surgical coronary artery revascularization. *J Cardiothorac Vasc Anesth* 2006;20:781–7.