ORIGINAL ARTICLE

Different cardiac biomarkers to detect peri-procedural myocardial infarction in contemporary coronary stent trials: impact on outcome reporting

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ABSTRACT

Objective To assess the differential implications of cardiac biomarker type on peri-procedural myocardial infarction (PMI) reporting.
Setting The Resolute 'All-Comers' stent trial.
Interventions Blood samples for creatine kinase (CK), CK-myoband (CK-MB) mass or cardiac troponin (cTn) (optional) were collected before and at 6, 12 and 18 h after the assigned percutaneous coronary intervention or at discharge. PMIs were adjudicated using either the 2007 universal definition of MI (type-4a) or the extended historical definition of MI.
Patients 2121/2292 patients (92.5%) had an analysable dataset for either biomarker. 890/2121 patients (42%) presented with an acute coronary syndrome (ACS). 267/890 patients (30%) were within 24 h of an ST-segment elevation MI.
Main outcome measures Type-4a MI was diagnosed in 208/2121 patients (9.8%) when cTn was used (CK-MB mass if cTn not available), and in 93/2121 of patients (4.4%) when CK-MB mass was used (cTn if CK-MB mass not available). With the extended historical CK-based definition of MI, PMI was diagnosed in 65/2121 patients (3.1%). Adjudication of type-4a MI in patients with an ACS was problematic with <10% of the potential type-4a MI being confirmed as an event, as compared with approximately 95% in stable patients undergoing elective PCI. Type-4a MI was not associated with the subsequent hazard for cardiac mortality (p=0.6).
Conclusions The percentage of adjudicated PMI events is driven by the MI-definition criteria and biomarker type. Type-4a MI may not be a reliable component of the primary composite end point in coronary stent investigations which recruit patients with ACS.
Trial registration number http://www.ClinicalTrials.gov; Unique identifier: NCT00617084.

INTRODUCTION

In coronary stent investigations the reported incidence of peri-procedural myocardial infarction (PMI) may vary according to the metrics (ie, the definition of MI used for adjudication and the preferred cardiac biomarker) and the clinical presentation of the patient at the time of the index percutaneous coronary intervention (PCI).[1-4] The clinical and therapeutic implications of PMI remain the subject of continuing debate.[1-3]

Contemporary all-comers coronary stent trials reflect routine PCI practice.[5-9] These studies provide a unique opportunity to compare clinical outcomes among patients presenting with and without acute coronary syndromes (ACS). In the Resolute 'All-Comers' (Resolute-AC) trial we implemented two different sets of criteria to define PMI, and sampled three different cardiac biomarkers to detect myocardial injury—namely, creatine kinase (CK), CK-MB isoenzyme (mass) and cardiac-specific troponin (cTn).[5 6]

The purpose of this prespecified subanalysis of the Resolute-AC trial is to improve the understanding of the differential implications of cardiac biomarker type on PMI reporting and the associated death of patients.

METHODS
Study design

The design, detailed methods and end point definitions of the Resolute-AC trial (ClinicalTrials.gov number: NCT00617084) have been detailed in a previous publication.[5] In brief the Resolute-AC is a prospective, multicentre, drug-eluting stent (DES)-versus-DES trial. Between 30 April 2008 and 28 October 2008 17 institutions enrolled a total of 2292 patients with symptomatic coronary artery disease on an all-comers basis, including patients with stable angina, silent angina and ACS. The main outcome measure for this analysis was cardiac death at 2 years.

All outcome measures in Resolute-AC, including MI, were adjudicated by three members of an independent clinical end points committee (CEC) blinded to treatment assignment before locking the database. The institutional review boards of all participating institutions reviewed and approved the protocol of the Resolute-AC trial. All enrolled patients gave written informed consent.

Definitions of MI

MI was defined according to the 2007 universal definition, using as the preferred biomarker either cTn (CK-MB mass when cTn was not available) or CK-MB (cTn when CK-MB mass was not available; Academic Research Consortium (ARC) recommendation), and the extended, historical (WHO) CK-based definition.[10-12]

For the 2007 universal definition of MI, the joint European Society of Cardiology, American College

of Cardiology, American Heart Association and World Heart Foundation task force recently classified cardiac biomarker levels above ×3 the 99th centile of the upper reference limit (URL), as indicative of PMI following PCI. Furthermore, the replacement of CK-MB mass with cTn was recommended for the diagnosis of a PMI in all cases. Although the 2007 universal definition of MI was endorsed by the ARC, after long and intense discussions the ARC recommended that CK-MB mass should remain the preferred biomarker for the diagnosis of PMI.[10][11]

The historical (WHO) definition of MI was used to adjudicate PMI in previous (Medtronic) stent trials in elective patients with simple lesions. The historical definition was adapted ('extended') to better accommodate 'all-comers' populations by considering patients presenting with ACS.[12][13] A hierarchical approach was used for the adjudication of PMI based upon cardiac biomarker availability when an analysable cardiac biomarker dataset was missing (CK-MB mass when CK was not available, cTn when CK and CK-MB mass were not available) (online supplementary table 1). In order to be adjudicated as a trial end point, PMI had to be new, and therefore distinguishable (ie, new clinical signs or symptoms, angiographic flow-limiting complications) from the index clinical event. Dependent on the clinical situation at the time of the index procedure, PMI could be adjudicated considering either (new) symptoms suggestive of ischaemia/infarction (>20 min), ECG changes, appropriate cardiac biomarker data or pathological evidence of MI, or a mixture of these factors.

Ascertainment of peri-procedural myocardial infarction
Blood samples for cardiac biomarkers—CK and CK-MB mass—were issued according to protocol (cTn was optional) within 6 h before the index-PCI procedure, and at 6, 12 and 18 h after the assigned study procedure or at hospital discharge, whichever came first. Additional samples up to 48 h after the index-PCI procedure were also considered in this analysis. An analysable cardiac biomarker set consisted of a baseline value, and at least one other measurement of the same biomarker in the 48 h period after the index-PCI procedure.

Cardiac biomarkers were analysed at local site laboratories, yielding a mixture of biomarker tests and upper limits of normal (supplementary table 2, supplementary appendix). The limitations of the analytical performance of commercial assays for biomarkers were considered. A coefficient of variation at the MI decision limit (99th centile of a healthy reference population) was expected at <10% for CK-MB mass and cTn assays used during this trial.[14–17]

Current analysis
For the purpose of this analysis the Resolute-AC study population was assessed as a cohort. All patients with a reference biomarker available before the index-PCI (baseline), and one or more corresponding samples in the same biomarker family (CPK, CK-MB, cTn) within 48 h after the index-PCI, were suitable for analysis. Seven (7.1) per cent of patients (163/2290) were excluded from the analysis, because either no baseline (n=81, 3.5%) or no samples within 48 h after the index-PCI (n=82, 3.5%) were taken. Six patients had no baseline and no post-PCI biomarker of the same family. Two patients in the study underwent coronary bypass graft surgery within 48 h of the index-PCI procedure and were excluded from this analysis.

A comparison of the rates of PMI using the 2007 universal definition, measuring either cTn (joint task force recommendation) or CK-MB mass (ARC recommendation) as the preferred biomarker, with the extended historical definition, in the adjudication of PMI was undertaken. Subgroup analyses were

performed for patients with (n=890, 42.0%) or without ACS (n=1231, 58.0%). Patients in this analysis were categorised as having ACS at the time of the index-PCI procedure if they had either a biomarker above the URL before the index-PCI procedure and/or clinical signs and/or symptoms (>20 min) consistent with continuing myocardial ischaemia as declared by the investigator. The analysis was repeated in the cohort of patients who had both an analysable cTn and CK-MB dataset (935, n=44.1%).

We assessed the 2-year cardiac mortality in patients with or without PMI according to either the 2007 universal definition of MI using either cTn or CK-MB as preferred biomarker (as outlined earlier) or the extended historical definition of MI.

Statistics
All statistical analyses were exploratory. The counts of PMI are summarised and tabulated according to frequency. Differences in outcomes between patients with and without PMI are compared by Fisher's exact test or χ^2 testing. For univariate analyses, cumulative event rates of cardiac mortality for the different types of PMI at up to 2 years were estimated with Kaplan–Meier analyses and Cox proportional HRs with 95% CIs. Multivariable analyses evaluating the association between PMI and mortality were performed by Cox proportional hazards regression. Multivariable models considered the following baseline covariates: age, sex and diabetes mellitus. Statistical analyses were performed with the use of SAS software, version 9.2 by a dedicated independent statistician. A two-sided p value <0.05 was considered to indicate statistical significance.

RESULTS
Two thousand one hundred and twenty-one of 2290 (92.5%) patients from the Resolute-AC were suitable for analysis. Baseline demographics and clinical characteristics are listed in supplementary table 3. Over one-fifth of patients (n=452, 21.3%) presented with an acute MI within 24 h of symptom onset, including 267 patients (59.1%) with an ST elevation MI. The mean SYNTAX Score was 14.7±9.2.

Availability of biomarkers of myocardial necrosis before and within 48 h after the index-PCI
Figure 1A depicts the number of patients with available cardiac biomarker of myocardial injury (BMI) sample values at baseline and one or more sample values within 48 h ('analysable cardiac biomarker dataset', n=2121). The Venn diagrams illustrate the availability of one BMI (CK or CK-MB mass or cTn), two BMI (CK and CK-MB mass or CK and cTn or CK-MB mass and cTn) or all three BMI (CK and CK-MB mass and cTn). Although cTn sampling was an optional investigation in the Resolute-AC trial, an analysable dataset for cTn was available in 55.3% (1173/2121) patients. In addition 44.1% (935/2121) patients had an analysable dataset for both cTn and CK-MB.

Figure 1B depicts all analysable cardiac biomarker sample values datasets (n=2121) in all patients in the analysis, stable patients and patients presenting with ACS with at least one cardiac biomarker sample value above the designated threshold for defining a PMI. Notably, 19.0% (178/935) (figure 1A) of patients with an analysable biomarker dataset available for both cTn and CK-MB mass had a peak cTn >3 times 99th centile URL, but a peak CK-MB ≤3 times 99th centile URL. Figure 1C is limited to patients with an ACS at the time of the index-PCI (n=890). Figure 1D is limited to stable patients having an elective PCI (n=1231).

Figure 1 (A) Patients with an analysable cardiac biomarker sets with both a pre- (baseline) and one or more post-PCI biomarker sample value(s) of the same family. (B—D) Patients, either with or without ongoing MI, with a baseline cardiac biomarker sample value (either for cTn, CK-MB mass, CK) and an increase in the corresponding 6—48 h post-PCI biomarker sample value above the predefined threshold to qualify as a suspect PMI, before final PMI-event adjudication by the clinical end points committee (figure 2B). For patients presenting with an acute coronary syndrome a 20% increase in cardiac biomarker sample value was taken into account (see also figure 1, flowchart). Patients with suspected ongoing MI (figure 2C) at the time of the index-PCI and stable patients undergoing elective PCI (figure 2D) are represented separately. CK-MB, creatine kinase-myoband; CPK, creatine kinase; cTn, cardiac troponin; PMI, peri-procedural myocardial infarction; URL, upper reference limit upper reference limit.
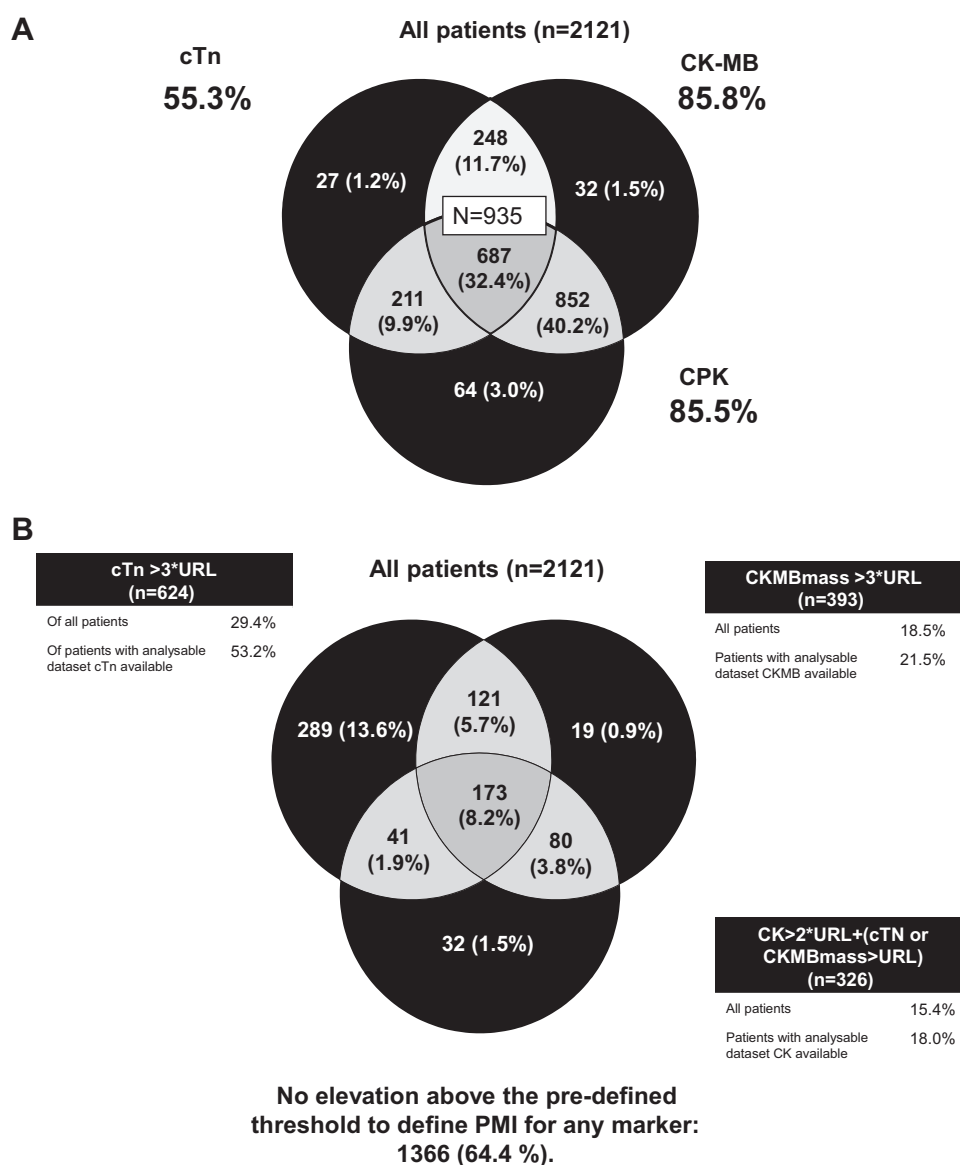
Diagnosis of PMI based on selection of cardiac biomarkers
Elevated biomarkers of myocardial necrosis before and within 48 h after the index-PCI
The number of stable patients undergoing elective PCI with cardiac biomarker elevations above the designated threshold required to define PMI was four times higher when measuring cTn than when measuring CK (161 vs 46 patients), and double when measuring CK-MB mass rather than CK (68 vs 46 patients). Conversely, the number of patients with an ACS at the time of the index-PCI with cardiac biomarker elevations above the designated threshold required to define PMI was only 1.5 times higher when measuring cTn compared with CK (47 vs 19 patients) (table 1).

PMI adjudicated by the CEC
For the 2007 universal definition of MI, type-4a MI was adjudicated by the CEC in 208/2121 patients (9.8%) when cTn was used (CK-MB mass if cTn not available), and in 93/2121 of patients (4.4%) when CK-MB mass was used (cTn if CK-MB mass not ava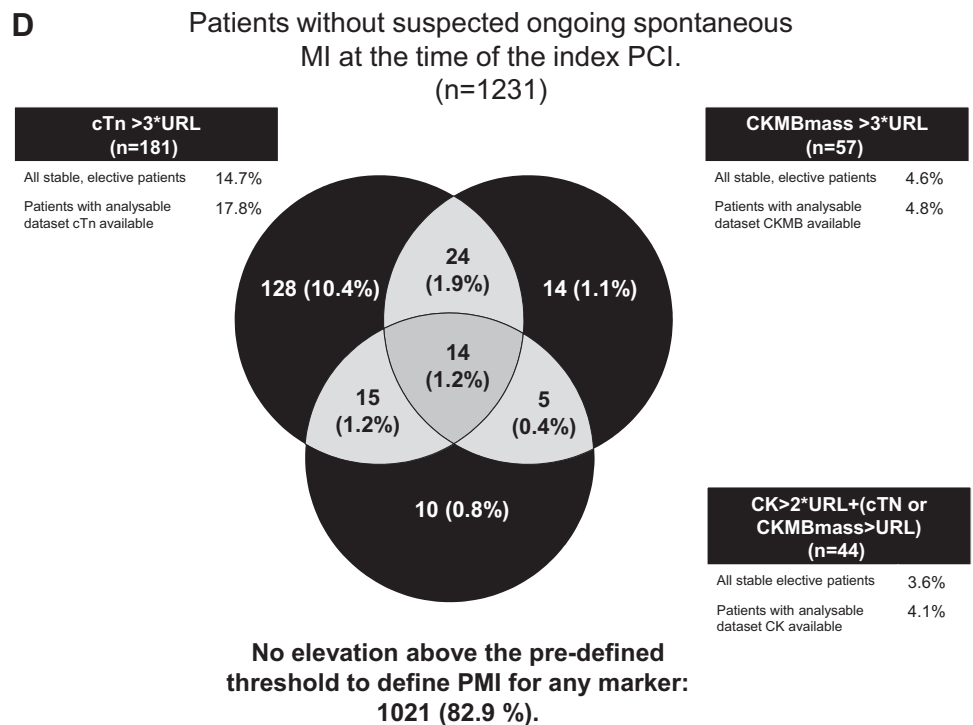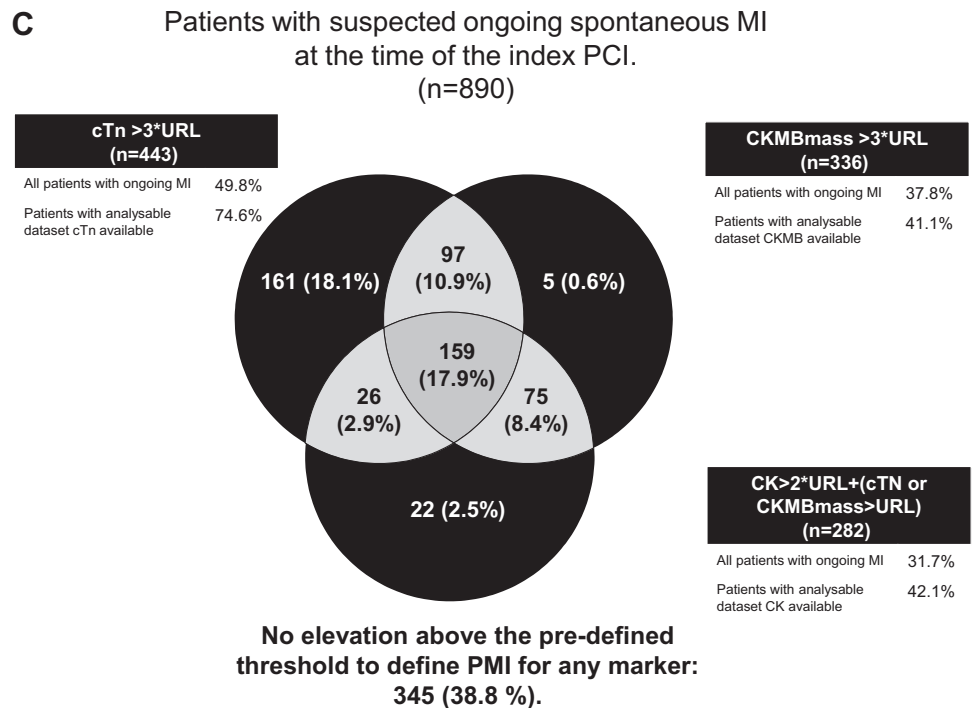ilable, ARC recommendation). With the extended historical CK-based definition of MI, PMI was adjudicated in 65/2121 patients (3.1%).

The percentage of the adjudicated PMI over the suspected events based on cardiac biomarker elevations ('event-to-trigger percentages') was predominantly driven by the clinical presentation at the time of the index-PCI, with this percentage being nearly 10-fold higher for stable patients undergoing elective PCI than for patients presenting with an ACS. Adjudication of type-4a MI in patients with a suspected ongoing MI was problematic with <10% of the potential type-4a MI being confirmed as an event by the CEC, as opposed to approximately 95% in stable patients undergoing elective PCI.

PMI in patients with an analysable dataset for both CK-MB mass and cTn
The trends outlined above are similar for the patient subpopulation with analysable cardiac biomarker datasets for both CK-MB and cTn (supplementary table 4). In the subset of patients, in whom an analysable dataset for both cTn and CK-MB mass was available (n=935), myocardial injury—as defined by a cardiac biomarker sample value >99th centile URL—was

Figure 1 Continued

C Patients with suspected ongoing spontaneous MI
at the time of the index PCI.
(n=890)

cTn >3*URL (n=443)

All patients with ongoing MI	49.8%
Patients with analysable dataset cTn available	74.6%

CKMBmass >3*URL (n=336)

All patients with ongoing MI	37.8%
Patients with analysable dataset CKMB available	41.1%

CK>2*URL+(cTN or CKMBmass>URL) (n=282)

All patients with ongoing MI	31.7%
Patients with analysable dataset CK available	42.1%

161 (18.1%) 97 (10.9%) 5 (0.6%) 159 (17.9%) 26 (2.9%) 75 (8.4%) 22 (2.5%)

No elevation above the pre-defined threshold to define PMI for any marker: 345 (38.8 %).

D Patients without suspected ongoing spontaneous
MI at the time of the index PCI.
(n=1231)

cTn >3*URL (n=181)

All stable, elective patients	14.7%
Patients with analysable dataset cTn available	17.8%

CKMBmass >3*URL (n=57)

All stable, elective patients	4.6%
Patients with analysable dataset CKMB available	4.8%

CK>2*URL+(cTN or CKMBmass>URL) (n=44)

All stable elective patients	3.6%
Patients with analysable dataset CK available	4.1%

128 (10.4%) 24 (1.9%) 14 (1.1%) 14 (1.2%) 15 (1.2%) 5 (0.4%) 10 (0.8%)

No elevation above the pre-defined threshold to define PMI for any marker: 1021 (82.9 %).

detected in 54.0% (505/935) measuring cTn and in 49.7% (465/935) measuring CK-MB mass. Type-4a MI was diagnosed in 11.0% (103/935) patients and 5.2% (49/935) patients, respectively.

Associated 2-year cardiac mortality

During the 2-year follow-up 54 patients in Resolute-AC died owing to cardiac causes, 51 of them are in the 2121 cohort. PMI versus no PMI adjudicated by the extended historical definition of MI was associated with 2-year crude cardiac mortality (HR=3.5; 95% CI 1.4 to 8.9; p=0.007), but not type-4a when

cTn was used (HR=1.2; 95% CI 0.5 to 2.9; p=0.65) or when CK-MB (HR=1.4; 95% CI 0.4 to 4.4; p=0.61) was used to adjudicate MI (table 2, figure 2). After adjustment for baseline covariates, PMI by the extended historical definition of MI, analysed as dichotomous variable, remained a significant correlate of 2-year mortality (HR=3.7, 95% CI 1.4 to 9.2, p=0.0065).

DISCUSSION

The Resolute-AC study design provided a unique opportunity to study the implications of the use of different biomarkers for the detection of myocardial injury in patients undergoing PCI, and

Table 1 Peri-procedural myocardial infarction (PMI) adjudication upon cardiac biomarkers guided either by the 2007 universal (troponin based)-myocardial infarction (MI) definition or the WHO (creatine kinase (CK)-based)-MI definition in counts and percentages (all patients; N=2121)

	2007 Universal-MI definition		WHO-MI definition extended for AC trials
	Primary marker cTn, (CK-MB mass if cTn unavailable)*	(ARC recommendation) Primary marker CK-MB mass, (cTn if CK-MB mass unavailable)*	Primary CK (with confirming cTn or CK-MB), (CK-MB mass if CK unavailable, cTn if CK and CK-MB mass unavailable)*
Stable angina (N=1231)			
Adjudicated PMI/trigger† to PMI	161/190 (84.7)	68/75 (90.7)	46/52 (88.5)
Investigator reported	73/84 (86.9)	35/35 (100.0)	30/31 (96.8)
ACS (N=890)			
Adjudicated PMI/trigger† to PMI	47/519 (9.1)	25/366 (6.8)	19/354 (5.4)
Investigator reported	12/20 (60.0)	7/12 (58.3)	6/10 (60.0)

*In 1533/2121 (72%), 1975/2121 (93%) and 1983/2121 (93.4%) cases the preferred biomarker, respectively cardiac specific troponin (cTn), creatine kinase (CK) and CK-myoband (MB), was available for analysis.

†Trigger is defined as a suspected PMI based upon cardiac biomarker sample value elevation and/or clinical signs or symptoms consistent with myocardial ischaemia.

ACS, acute coronary syndrome; ARC, Academic Research Consortium.

the adjudication of unreported PMI among patients presenting with or without an ACS at the time of the index procedure. The main conclusions of this analysis are:

1. PMI constituted the majority of all MIs in the Resolute-AC PCI trial. However, the PMI event count varied considerably according to the choice of cardiac biomarker and/or the criteria used for adjudication. Comparing the 2007 universal definition of MI and the extended historical (WHO) CK-based definition of MI, using cTn resulted in a tripling of the rate of PMI. Applying the 2007 universal definition of MI with cTn resulted in a doubling of the rate of PMI compared with CK-MB mass.
2. The PMI 'event-to-trigger' percentage was dependent on the clinical presentation at the time of the index-PCI procedure, rising from <9% in patients presenting with ACS at the time of the index-PCI procedure, to >80% in patients undergoing elective PCI for stable symptomatic coronary artery disease regardless of which biomarker one uses.
3. The frequency of undetected MI with the 2007 universal definition of MI was approximately five times higher than the extended historical (WHO) CK-based definition of MI, mainly reflecting the greater sensitivity of cTn to detect myocardial injury (with subsequent investigator under-reporting).
4. More than 50% of adjudicated PMI events in patients undergoing elective PCI for stable symptomatic coronary artery disease were unreported and only detected through analysis of serial cardiac biomarker sample values.
5. In Resolute-AC, type-4a MI with the actual proposed biomarker thresholds and regardless of the biomarker used, was not associated with subsequent cardiac mortality at 2 years.

This analysis represents the largest prospective comparison of the three most commonly used serum biomarkers for detection of PMI. These findings are likely to be representative of

contemporary PCI practice, as patient-, lesion- and procedure-related risk factors are all previously established predictors of PMI,[3] and the baseline and angiographic characteristics of Resolute-AC have been reported to be consistent with other recently reported 'real-world' coronary stent investigations.[5–8 18] The stable patient subset undergoing elective PCI to treat stable coronary lesions matched those recruited in historical stent trials.

The diagnosis of acute, evolving or recent MI requires, in the absence of pathological confirmation, a typical rise and/or fall of biomarkers of myocardial necrosis in conjunction with clinical evidence of myocardial ischaemia.[10] A PMI is defined by a typical new cardiac biomarker elevation above a predefined threshold occurring during the immediate peri-procedural period (<48 h), and an established causality to the index study procedure. This causality may or may not be declared by the investigator (eg, coronary artery dissections, distal plaque embolisation). With ACS the PMI must be identified as a new event, clearly distinct from the index clinical event in the same predefined peri-procedural period of 48 h. In the Resolute-AC trial, most suspected PMIs were reported by the investigators at clinical sites. Yet not all cardiac biomarker elevations above the predefined threshold ('triggers') will identify new events.

The adjudication of PMI in an 'All-Comers' trial resembling everyday PCI practice may be characterised by a signal-to-noise problem. For this analysis we disentangled two specific clinical situations—patients with or without an ACS at the time of the index-PCI. The adjudication of type-4a MI, implementing the 2007 universal definition of MI, in patients with acute presentations (ie, ACS) at the time of the index-PCI is problematic, and exacerbated when measuring a sensitive biomarker such as cTn.[19] Unless there is a clear indication that the cardiac biomarker sample values were falling after the index event and then rising again (above the predefined thresholds) after the index-PCI procedure, there would be insufficient biomarker data

Table 2 Two-year cardiac mortality according to the occurrence of procedure-related MI (different definitions) or not
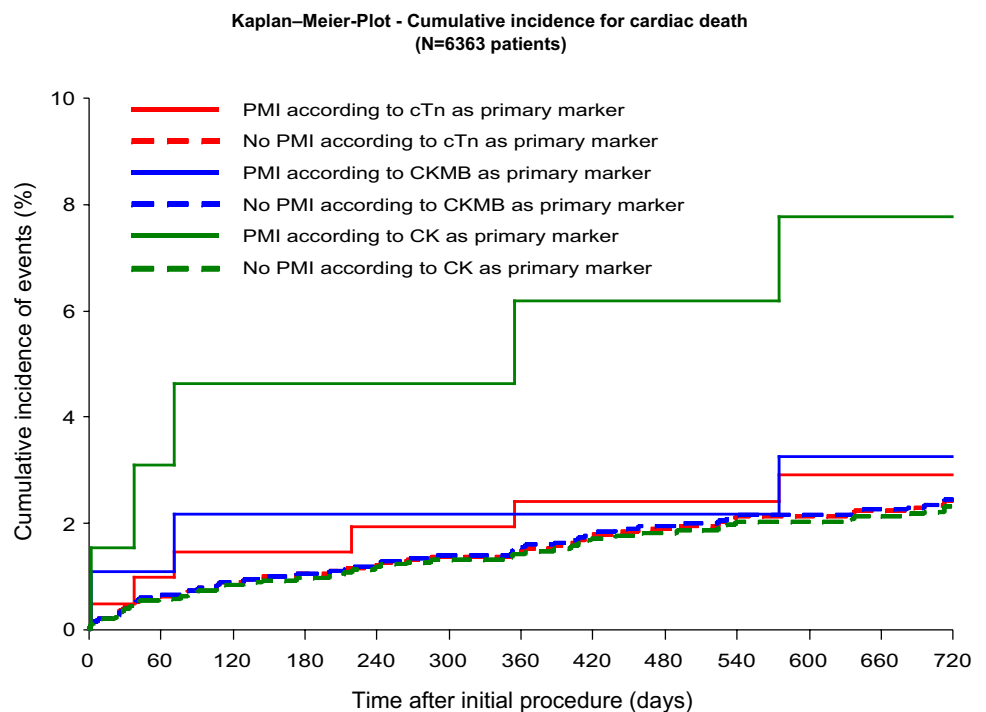
Primary biomarker	KM estimate, PMI* (%)	KM estimate, no PMI* (%)	Log rank, p value	HR and 95% CI†
cTn	2.90	2.43	0.649	1.2 (0.5 to 2.9)
CK-MB	3.25	2.44	0.606	1.4 (0.4 to 4.4)
CK	7.74	2.31	0.007	3.5 (1.4 to 8.9)

*Percentage failure based on Kaplan—Meier (KM) estimates.

†Cox Model, assuming proportional Hazards.

CK-MB, creatine kinase-myoband; cTn, cardiac troponin; KM, Kaplan—Meier; PMI peri-procedural myocardial infarction.

Figure 2 Cumulative cardiac mortality according to PMI up to 2-years. Shown are the Kaplan—Meier curves for cardiac mortality after the occurrence of PMI according to either the extended historical definition of MI (green) and the 2007 universal definition of MI measuring cTn (CK-MB if cTn is not available) (red) or CK-MB (cTn if CK-MB is not available, Academic Research Consortium recommendation) (blue). CK-MB, creatine kinase-myoband; cTn, cardiac troponin; PMI, peri-procedural myocardial infarction.

Kaplan–Meier-Plot - Cumulative incidence for cardiac death
(N=6363 patients)

— PMI according to cTn as primary marker
--- No PMI according to cTn as primary marker
— PMI according to CKMB as primary marker
--- No PMI according to CKMB as primary marker
— PMI according to CK as primary marker
--- No PMI according to CK as primary marker

to adjudicate a PMI.[19 20] The critical challenge for the members of the CEC is to distinguish whether a new MI was induced by the index-PCI procedure (ie, additional component of an already injured myocardial region, new procedural flow-limiting complications), or if the cardiac biomarker release was still the tail end of the continuing initial myocardial insult.[1 19]

In Resolute-AC, while the event-to-(biomarker) trigger ratio was as low as 5% for the 2007 universal definition of MI, these events proved to be numerically important and contributed to half of the unreported PMIs (based on serial cardiac biomarker sample value analyses only) (table 1). It should be emphasised that including clinical information from the investigator, such as evidence of new myocardial ischaemia and coronary artery flow-limiting complications, resulted in a 10 times higher event-to-trigger percentage, and may improve the signal-to-noise ratio (table 1). Conversely, in stable patients undergoing uncomplicated contemporary elective PCI, >50% of PMIs were detected upon review of serial cardiac biomarker sample values alone, with >80% of all suspected type-4a MI adjudicated as an event. On the basis of the traditional concept of PMI described here, considering a high 'trigger' and 'trigger-to-event ratio' in stable patients undergoing elective PCI, the missing biomarker data may affect outcome reporting and should be considered while interpreting trial results.

The extent of myocardial injury following PCI, as detected by release of CK and/or CK-MB mass, has been correlated with late clinical outcomes in several studies.[21–27] Despite these findings, the threshold level of cTn associated with a prognostic significance remains elusive.[1 10] This analysis adds to the evidence that type-4a MIs, as a class in real-world patients with the current set biomarker thresholds, are not of significant prognostic importance after PCI using contemporary management strategies. Cardiac biomarker elevation following PCI should therefore always be interpreted in relation to the clinical presentation at the time of the index procedure.

The lack of association between a CK-MB mass elevation more than three times the diagnostic level based on the 2007 universal definition of MI, and 1-year mortality among patients with moderate to high risk ACS undergoing PCI, was also reported in the ACUITY trial.[23] Conversely, in the EVENT (Evaluation of drug eluting stents and ischaemic events) registry, consisting of almost 5000 patients undergoing elective PCI, the same degree of cardiac enzyme elevation independently predicted 1-year mortality. In addition, the EVENT investigators reported similar hazards for negative clinical outcomes related to cTn, but only when 20 times the upper limit of normal was used as decision limit.[24] Patients in the subanalysis in the EVENT registry were, however, not separated on the detection of a baseline cTn level ≥99th centile of the URL.

In patients with ACS it is undisputed that an increased cTn (baseline) is a marker of patients at increased risk.[27] Furthermore, it appears that almost all the prognostic information is contained in the baseline cardiac enzyme value, and that this may be a reflection of the underlying coronary atherosclerotic burden and/or plaque instability. At what level, if any, additional cTn elevation following PCI contributes to the hazard for 1-year negative outcomes remains unanswered.

This issue(s) and the stark variations in reported rates of PMI call into question the inclusion of PMI as a component of the primary composite end points of contemporary coronary device trials, particularly when recruiting patients presenting with ACS.

Limitations

This study has several limitations. First, in 2008 cTn was not yet widely implemented as cardiac biomarker to detect myocardial injury, thereby according to protocol cTn sampling was optional in Resolute-AC. Despite this limitation, up to 54% of patients had an analysable cTn dataset and the major conclusions of the study were unchanged when a subset of patients with both cTn and CK-MB were sampled (supplementary table 3). While recent advances in assay technology have led to more sensitive and precise cTn assays, the issues raised in this manuscript towards trial conduct and data interpretation remain, and may even be accentuated.[28]

Our results did not include the direct metrics (eg, MRI) of the extent of myocardial injury. The findings of the study do, however, suggest that most MIs were small or moderate. We cannot exclude the possibility of a slight variation in the results if a central core laboratory had undertaken the analyses of the cardiac biomarkers.[29] The 99th centile of the reference medical decision cut-off point for the cTn assays was determined in each local laboratory by internal studies with the specific assay that is used in clinical practice. The previous limitations do, however, cause no concern in interpreting the major conclusions of this analysis.

CONCLUSIONS

As currently defined, type-4a MI following PCI is not a valid outcome measure in contemporary outcome trials. Meaningful thresholds for individual cardiac biomarkers should be identified based on large outcome trials. Adjudication of PMI in patients with an ACS at the time of the index-PCI remains problematic.

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