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REVIEW

Clinical update

Implementation of standardized assessment and reporting of myocardial infarction in contemporary randomized controlled trials: a systematic review

Sergio Leonardi[1,2], Paul W. Armstrong[3], Phillip J. Schulte[1], E. Magnus Ohman[1], and L. Kristin Newby[1]*

[1]Duke University Medical Center, The Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715-7969, USA; [2]Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; and [3]The Canadian VIGOUR Centre, University of Alberta, Edmonton, Alberta, Canada

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Myocardial infarction (MI) is a key endpoint in randomized controlled trials (RCTs), but heterogeneous definitions limit comparisons across RCTs or meta-analyses. The 2000 European Society of Cardiology/American College of Cardiology MI redefinition and the 2007 universal MI definition consensus documents made recommendations to address this issue. In cardiovascular randomized trials, we evaluated the impact of implementation of three key recommendations from these reports—troponin use to define MI; separate reporting of spontaneous and procedure-related MI; and infarct size reporting. We searched ClinicalTrials.gov and MEDLINE databases for cardiovascular RCTs with more than 500 patients in which enrolment began between September 2000 and July 2012 and that listed MI in the primary endpoint. We searched English-language publications with primary results or design papers. Of 3222 studies screened, 96 (3.0%) met our criteria. We extracted enrolment start date, number of patients and MI events, follow-up duration, and coronary revascularization rate. Data extraction quality was assessed by duplicated extractions. Of 96 RCTs, 80 had a primary results publication, comprising 608 091 patients and 43 621 endpoint MIs. Myocardial infarction represented 45.3% (95% confidence interval, 40.2–50.4) of events in the primary composite endpoint. Troponin defined MI in 57% (53/93) of trials with an MI definition available. Of these RCTs, three used troponin only if creatine kinase-MB was unavailable, six used troponin to define peri-procedural MI, seven specified the 99th percentile as the MI decision limit, and three reported spontaneous and procedure-related MI separately. None reported biomarker-based infarct size, but five reported MI as multiples of the assay upper limit of normal. Although MI is a major component of cardiovascular RCT primary endpoints, standardized MI reporting and implementation of consensus document recommendations for MI definition are limited. Developing appropriate strategies for uniform implementation is required.

Keywords Myocardial infarction • Clinical trials • Systematic reviews

Introduction

Myocardial infarction (MI) is a widely accepted non-fatal cardiovascular endpoint employed to assess efficacy and/or safety of new treatments in clinical trials. However, failure to use a standard MI definition has emerged as a major challenge. In September 2000, recognizing the superior sensitivity and prognostic utility of troponin compared with creatine kinase (CK)-MB, an expert consensus document from the European Society of Cardiology (ESC) and American College of Cardiology (ACC) provided guidance to the scientific and clinical communities on redefining MI and proposed troponin as the diagnostic 'gold standard'.[1] To improve consistency across randomized controlled trials (RCTs), this document specified that MI endpoints in RCTs be classified as *spontaneous* vs. *related to coronary revascularization procedures* and that the quantity of myonecrosis be determined. A 2007 and, most recently, a 2012 update reasserted troponin as the preferred biomarker for myonecrosis and also recommended that clinicians and investigators categorize MI type according to a five-category classification scheme, including whether the MI was spontaneous

* Corresponding author. Tel: +1 919 668 8805, Fax: +1 919 668 7056, E-mail: kristin.newby@duke.edu

or revascularization-related.[2,3] Prior to the release of the 2012 Universal Definition of MI document, we undertook the current study to evaluate the extent to which the 2000 and 2007 consensus recommendations had been implemented in contemporary cardiovascular RCTs.

Methods

We performed a systematic review of cardiovascular RCTs with more than 500 patients in which MI was part of the primary endpoint. The 500-patient threshold was selected to identify RCTs with enough MI endpoints to adequately assess all recommended components of MI reporting and that would be most likely to affect clinical practice. For the same reason, we limited our search to published trials. Our systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[4]

Search strategy

We separately searched two databases: ClinicalTrials.gov, the official source of the US National Institutes of Health (NIH) for clinical trial registration, and the National Library of Medicine's MEDLINE database. Although RCTs could be registered on ClinicalTrials.gov for the entire period explored (1 September 2000 through 4 July 2012), the NIH mandated registration of all RCTs only after 27 September 2007.[5] Because some trials that started before September 2007 may not have been captured, we used MEDLINE to complement the ClinicalTrials.gov search. Finally, we reviewed online materials using the Google search engine. We restricted our search to RCTs in cardiovascular disease, but did not restrict the type of intervention to which patients were randomized. From this pool of RCTs, those with an enrolment start date before September 2000 were excluded from further analysis. *Figure 1* outlines the results of our database searches, culminating in a final set of 96 RCTs for our study; 80 had primary results published and 16 had only a design paper. Additional details of our search methodology are explained in Supplementary material online, Appendix 1.

Data abstraction

We abstracted study name; enrolment start date; publication year; numbers of patients, MI events, and components in the primary endpoint composite; reference within the publication to the 2000 ESC/ACC consensus document and the 2007 Universal Definition of MI; use of a clinical events classification committee; follow-up duration; and text of the endpoint MI definition used. Accuracy of the MI definition abstracted from the design paper and/or primary manuscript was assessed by contacting trial investigators and obtaining the endpoint MI definition for their respective trials. To ensure the quality of the data extraction process, a 30% random sample of included RCTs was re-reviewed, and the data were collected in a second abstraction sheet. In addition, a random 30% of records from each database was re-reviewed after initial screening was finalized as a quality check on RCT selection. No errors in data abstraction were identified by these quality control measures.

Metrics of guideline recommendations adherence

We determined the proportion of RCTs in which the ESC/ACC 2000 document and the 2007 Universal Definition of MI were referenced by manually reviewing the reference list of the design paper, primary results manuscript, or both. We also determined the proportion of RCTs referencing other consensus documents endorsed by the ESC, ACC, or American Heart Association (AHA). Then, we examined each trial for the use of the following key recommendations in the 2000 ESC/ACC consensus document for MI redefinition and in the 2007 Universal Definition of MI:

Recommendation 1: Use of troponin for MI diagnosis and MI decision limit provided. We evaluated this recommendation in RCTs for which the MI definition (including biomarkers employed) used in the trial was published. In five trials, the biomarker employed was unavailable in the design paper or primary manuscript but was obtained by contacting the investigators.[6–10] We also explored adherence to this recommendation according to coronary revascularization group and tertiles of duration of time between the publication of the ESC/ACC 2000 MI redefinition document and the start of enrolment. To explore the level of adherence to Recommendation 1 as a function of coronary revascularization rate, we created three RCT categories:

- Interventional RCTs: RCTs in which percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) was required by protocol either as part of the randomized intervention or as an inclusion criterion. Only protocol violators did not undergo coronary revascularization, and the rate of revascularization was assumed to be near 100%.
- Acute coronary syndrome (ACS) RCTs: RCTs in which a coronary revascularization could be performed as part of treatment for the index ACS event but was not required.
- Other RCTs: RCTs in which coronary revascularization was possible but not expected (e.g. secondary prevention trials enrolling patients with risk factors but no prior MI or patients with chronic stable coronary artery disease).

Recommendation 2: Separate reporting of spontaneous MI and procedure-related (PCI or CABG) MI.

Recommendation 3: Report of infarct size using area under the troponin or CK-MB curve or peak biomarker values (ESC/ACC 2000 recommendation) or as a multiple of the upper limit of normal (ULN) of the applied cardiac biomarker (2007 Universal Definition of MI recommendation).

Finally, for the subgroup of trials that started after the publication of the 2007 Universal Definition of MI, we also assessed adherence to the five-type classification scheme proposed.

Survey

To assess underpinnings of gaps in implementing consensus document recommendations, we surveyed principal investigators of all 96 RCTs via an online questionnaire. Because some investigators ($n = 17$) led more than 1 RCT, 66 individual investigators were surveyed. The full text of question and answer options is provided in Supplementary material online, Appendix 2. To encourage full participation, we sent e-mail reminders and scheduled telephone calls or in-person visits as needed. Responses were received from 61 of 66 investigators (92.4%), corresponding to responses for 91 of 96 RCTs. Every investigator who responded answered all survey questions completely.

Statistical analysis

The contribution of MI to the primary composite endpoint was examined using a random effects meta-analysis to estimate the mean proportion. This approach assigns weights to trials accounting for both (i) sampling error due to finite sample size within trials and (ii) random variability due to heterogeneous populations among trials. Results are presented using mean point estimates [95% confidence

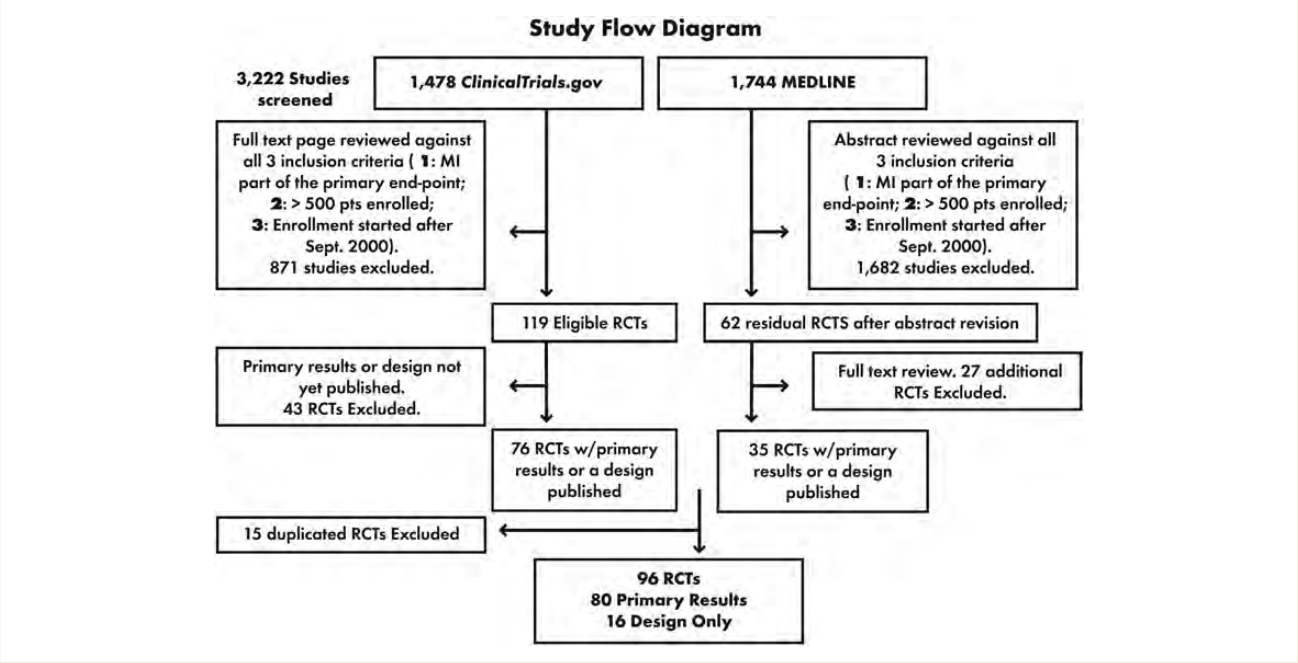

Figure 1 Systematic review and selection of clinical trials.

intervals (CIs)] of the proportion. This proportion was also evaluated considering RCTs by coronary revascularization group and groupings of follow-up duration (timing of endpoint assessment). The same method was used to identify the revascularization proportion in ACS RCTs and Other RCTs. To address the primary hypotheses, for each recommendation, the level of adherence was calculated as the proportion of RCTs fulfilling that recommendation. In addition, for Recommendation 1, we also explored adherence by coronary revascularization group and by time from the publication of the 2000 consensus document to the start of enrolment. In a sensitivity analysis, we examined the use of the three consensus document recommendations in RCTs with more than 100 but 500 or less patients (Supplementary material online, Appendix 3).

Results

Table 1 shows RCTs with a primary results publication available. Of these 80 RCTs, all but 4 (5%)[26,27,30,78] reported the use of a clinical events classification committee blinded to treatment assignment. These MI definitions are detailed in Supplementary material online, *Table S1A–C*, and grouping of trials by coronary revascularization rate is provided in Supplementary material online, *Table S2*. The rate of coronary revascularization was 50.6% (95% CI 40.0–61.1) in ACS RCTs and 4.4% (95% CI 2.1–9.0) in Other RCTs. One published trial reported MI event rates only graphically.[26]

Contribution of myocardial infarction to the primary endpoint

Using 79 RCTs with primary results provided as MI counts, we estimated that MI contributed 45.3% (95% CI 40.2–50.4) of events in the primary composite outcomes of large cardiovascular RCTs. The proportion that MI contributed to the primary composite endpoint decreased with increasing number of endpoint components (Supplementary material online, *Figure S1*) and was highest among Interventional RCTs and trials with a follow-up duration of $\leq$1 month (*Table 2*).

Proportion of RCTs referencing published myocardial infarction definition documents

Among 96 RCTs with a primary results and/or design paper, 7 (7.3%) referenced the ESC/ACC 2000 document for endpoint MI definition and 18 (18.8%) referenced the Universal Definition of MI 2007 publication. In addition, 34 (35.4%) cited another consensus document (27 referenced the Academic Research Consortium definition[89,90]; 7 referenced the ACC Key Standards document,[91] both of which referred to the ESC/ACC 2000 document). Fourteen (14.6%) RCTs published no MI definition.[16,17,22,24,31,39,46,51,58,74,92–95] After contacting investigators, we received and examined 93 of 96 endpoint MI definitions (96.9%). *Table 3* presents an overview of key features of these definitions in the 10 largest RCTs, which accounted for 199 448 patients (32.8% of all patients in RCTs we evaluated). In these trials, both the threshold for spontaneous MI (1× or 2× ULN) and the biomarker used (CK-MB or troponin) varied. Definitions of re-infarction in RCTs that enrolled patients with acute MI also varied (Supplementary material online, Appendix 4 and *Table S3*).

Table 1 Characteristics of 80 cardiovascular published randomized clinical trials ordered by the start date of enrolment

Study name	Start date	PubYear	Patients	MI, *n*	MI, %	Follow-up duration
REPLACE 1[11]	November 2000	2004	1056	50	75.8	48 h
PROVE IT TIMI 22[12]	November 2000	2004	4162	292	28.8	2 years[a]
MATCH[13]	December 2000	2004	7599	121	9.8	18 months
ESTEEM[14]	January 2001	2003	1883	83	32.7	6 months
ISAR SWEET[15]	January 2001	2004	701	32	54.2	1 year
SIRIUS[16]	February 2001	2003	1058	32	20.5	9 months
PROactive[6]	May 2001	2005	5238	223	20.5	34.5 months[a]
ADVANCE[17]	June 2001	2007	11 140	91	5.1	4.3 years[a]
ICTUS[18]	July 2001	2005	1200	149	56.7	1 year
SYNERGY[19]	August 2001	2004	10 027	1207	85.1	30 days
FIRE[20]	October 2001	2003	651	124	88.6	30 days
REPLACE 2[21]	October 2001	2003	6010	392	68.3	30 days
OnTARGET[22]	November 2001	2008	25 620	1291	30.6	56 months[b]
PRIMO CABG[23]	January 2002	2004	3099	252	85.4	30 days
JIKEI HEART[24]	January 2002	2007	3081	36	14.9	3.1 years[b]
CHOIR[25]	March 2002	2006	1432	38	17.1	16 months[b]
ALMICAD[26]	April 2002	2007	1233	NA[c]	NA[c]	24 months
Lee *et al.*[27]	April 2002	2005	689	13	81.3	30 days
RACS[28]	April 2002	2007	1004	20	64.5	180 days
ExTRACT TIMI 25[29]	October 2002	2006	20 479	767	34.2	30 days
HEART 2D[30]	October 2002	2009	1115	136	35.5	32 months[a]
CHARISMA[31]	October 2002	2006	15 603	301	27.2	28 months[b]
Nussmeier *et al.*[32]	January 2003	2005	1671	2	2.0	40 days
CLARITY TIMI 28[33]	February 2003	2005	3491	108	16.9	Index H
ARTS II[34]	February 2003	2007	607	38	44.2	30 days, 1 year
PASSION[35]	March 2003	2006	619	11	16.7	1 year
OASIS 5[36]	March 2003	2006	20 078	527	45.7	9 days
Windecker *et al.*[37]	April 2003	2005	1012	32	37.2	9 months
ARISE[38]	June 2003	2008	6144	243	22.9	24 months[a]
ACTIVE W[39]	June 2003	2006	6706	59	14.8	1.28 years[b]
PROXIMAL[40]	July 2003	2007	594	7	12.3	30 days
ACUITY[41]	August 2003	2006	13 819	704	45.6	30 days
OASIS 6[42]	August 2003	2006	12 092	317	25.1	30 days
EASY[43]	October 2003	2006	1005	107	51.2	30 days
TYPHOON[44]	October 2003	2006	2019	9	11.7	1 year
PRIMO CABG II[45]	July 2004	2011	4254	549	82.7	30 days
SORT OUT II[46]	August 2004	2008	2098	98	43.4	18 months
MULTI STRATEGY[47]	October 2004	2008	744	15	48.4	30 days
MERLIN TIMI 36[48]	October 2004	2007	6560	477	32.9	30 days
TRITON TIMI 38[49]	November 2004	2007	13 608	1095	76.9	15 months
EARLY ACS[50]	November 2004	2009	9492	690	76.0	96 h
BEAUTIFUL[51]	December 2004	2008	10 917	425	25.4	19 months[b]
DOORS[52]	January 2005	2012	900	62	66.0	30 days
SYNTAX[53]	March 2005	2009	1800	71	26.9	1 year
HORIZONS-AMI[54]	March 2005	2008	3602	65	16.9	30 days
PRECOMBAT[55]	March 2005	2011	600	8	13.3	1 year
I CARE[56]	April 2005	2008	1434	24	49.0	18 months[d]
COSTAR II[57]	May 2005	2008	1700	50	33.3	8 months
ISAR LEFT MAIN[58]	July 2005	2009	607	29	32.6	1 year
AIM HIGH[10]	September 2005	2011	3414	172	30.9	3 years[a]

Continued

Table I *Continued*

Study name	Start date	PubYear	Patients	MI, *n*	MI, %	Follow-up duration
ISAR REACT 3[59]	November 2005	2008	4570	238	61.2	30 days
CRESCENDO[60]	December 2005	2010	18 695	282	38.2	13.8[a]
CHAMPION-PCI[61]	April 2006	2009	8877	534	94.3	48 h
CURRENT[62]	June 2006	2010	25 086	514	47.6	30 days
RIVAL[63]	June 2006	2011	7021	125	46.8	30 days
ISAR REACT 4[64]	July 2006	2011	1721	117	61.9	30 days
SPIRIT IV[65]	August 2006	2010	3687	82	45.1	1 year
CH. PLATFORM[66]	September 2006	2009	5022	368	93.2	48 h
PLATO[67]	October 2006	2009	18 093	1097	58.4	12 months
MEND CABG II[68]	November 2006	2008	3023	243	89.0	30 days
LEADERS[69]	November 2006	2008	1707	88	52.4	9 months
ZEST[70]	November 2006	2010	2645	164	56.9	1 year
CORONARY[71]	November 2006	2012	4752	328	68.6	30 days
PRODIGY[72]	December 2006	2012	2013	80	40.4	24 months
COMPARE[73]	February 2007	2010	1800	43	71.7	1 year
REAL LATE[74]	July 2007	2010	2701	17	53.1	2 years
ECLAT STEMI[75]	July 2007	2012	786	74	77.9	30 days
ISAR TEST 4[76]	September 2007	2009	2603	99	27.6	1 year
TRA 2°P TIMI 50[77]	September 2007	2012	26 449	1237	56.1	30 months[b]
MI FREEE[78]	November 2007	2011	5855	423	40.1	13.1 months
ISAR CABG[79]	November 2007	2011	610	30	27.3	1 year
TRACER[80]	December 2007	2011	12 944	1319	61.8	502 days[b]
ISAR TEST 5[81]	February 2008	2011	3002	77	19.7	1 year
RESOLUTE AC[82]	May 2008	2010	2292	93	50.0	1 year
AIDA STEMI[83]	July 2008	2012	2065	34	25.0	90 days
ISAR REACT 3A[84]	August 2008	2010	2505	209	92.5	30 days
ATLAS ACS[85]	November 2008	2012	15 526	613	61.2	13 months
PLATINUM[86]	January 2009	2011	1530	21	28.8	1 year
APPRAISE 2[87]	March 2009	2011	7392	376	65.7	241 days
Litt *et al.*[88]	July 2009	2012	1370	15	100.0	30 days

PubYear is the year of publication; MI, *n* is the absolute number of myocardial infarction within the primary endpoint; MI, % is the proportion of myocardial infarction endpoint events within the primary composite.
[a]Mean follow-up duration.
[b]Median follow-up duration.
[c]The ALMICAD trial did report the actual number of MI events.
[d]The I CARE trial was terminated early at 18 months for efficacy.

Recommendation 1: use of troponin for myocardial infarction diagnosis and myocardial infarction decision limit provided

Among 93 RCTs with an MI definition provided, troponin was used to define the MI endpoint in 53 (57%). This proportion was 66.7% ($n = 34$) among 51 RCTs that referenced any consensus document for MI definition. Three of 93 RCTs used troponin to define endpoint MI only if CK-MB was unavailable,[36,62,88] 6 used troponin to define procedural MI, and 7 specified the 99th percentile as the MI decision limit. All other RCTs ($n = 40$) used CK-MB or total CK to define endpoint MI. The use of troponin to define endpoint MI by revascularization group and by time between ESC/ACC 2000 publication and the start of RCTs enrolment is shown in *Figure 2A* and *B*, respectively. Among trial types, adherence to Recommendation 1 was lowest among Interventional RCTs, and by time from publication to enrolment start, the highest use of troponin occurred among RCTs that began >74 months after the publication of the ESC/ACC 2000 document.

Recommendation 2: separate reporting of spontaneous myocardial infarction and myocardial infarction related to surgical or percutaneous coronary revascularization procedures

Three trials (3.7%) reported spontaneous and procedural MI separately.[18,77,80] The ICTUS trial, which adhered to the 2000 ESC/ACC MI redefinition, compared an early invasive strategy with a

selective invasive strategy in patients with non-ST-segment elevation MI.[18] Overall, 149 MIs occurred; 32.9% were spontaneous and 67.1% were procedure-related. The TRACER[80] and TRA 2°P TIMI 50[77] trials reported MI using the five-type classification scheme proposed by the 2007 Universal Definition of MI.

Table 2 Myocardial infarction contribution to the primary endpoint by revascularization group and by follow-up duration

Category	Group	*n*	MI % (95% CI)
Revascularization rate	Interventional	46	53.2 (45.7–60.5)
	ACS	16	46.8 (37.1–56.8)
	Other	17	24.3 (18.1–31.8)
Follow-up duration	≤1 month	31	64.3 (55.5–72.1)
	Between 1 month and 1 year	25	35.6 (29.0–42.9)
	>1 year	23	32.2 (24.8–40.6)

Proportion of MIs in the primary composite endpoint was calculated using random effects estimates with 95% CIs.
CI, confidence interval; MI, myocardial infarction.

Recommendation 3: report of comparison of size of myocardial infarction between treatment and control groups in addition to the presence/absence of myocardial infarction

No trials reported a comparison of infarct size between treatment and control groups, using area under the biomarker curve. Five trials compared MI rates between treatment and control groups, using size thresholds (e.g. 3×–5× ULN, 5×–10× ULN, or >10× ULN), but did not provide actual peak levels.[11,20,21,40,68]

Similar results for the use of the three recommendations explored were observed in sensitivity analyses of RCTs with more than 100 but 500 or less patients (Supplementary material online, *Table S4*).

2007 Universal Definition of Myocardial Infarction adherence

Of the 96 trials included, 25 (26.0%) started enrolment after the publication of the 2007 Universal Definition of MI. Of these, 11 (44.0%) referenced this definition in the design or primary results paper. Troponin defined endpoint MI in 19 (76.0%). Nine (36.0%) used the five-type classification scheme to define endpoint MI, but seven of these nine adapted this classification, typically for PCI-related (type 4a) MI definition, by using CK-MB instead of troponin.

Table 3 Key features of the myocardial infarction definition in the 10 largest randomized clinical trials

Trial	Spontaneous MI		PCI-related MI		CABG-related MI	
	Preferred biomarker	Fold elevation above ULN	Preferred biomarker	Fold elevation above ULN	Preferred biomarker	Fold elevation above ULN
TRA 2°P TIMI 50[77a]	cTn	1	CK-MB	3	CK-MB/cTn	5
ONTARGET[22b]	NA	NA	NA	NA	NA	NA
CURRENT[62]	CK-MB/cTn	2	CK-MB	3	CK-MB	5 (w/ Qw) or 10 (w/o Qw)
ExTRACT TIMI 25[29]	CK-MB/cTn	1	CK-MB	3	CK-MB	5 (w/ Qw) or 10 (w/o Qw)
OASIS 5[36]	CK-MB	2	CK-MB	3	CK-MB	5 or Qw
CRESCENDO[60]	CK-MB/cTn/CK	2/1/2	CK-MB	3	CK-MB	5 (w/ Qw) or 10 (w/o Qw)
PLATO[67]	CK-MB/cTn	1	CK-MB	3	CK-MB	5 (w/ Qw) or 10 (w/o Qw)
CHARISMA[31c]	CK-MB/cTn	2/1	–	–	–	–
ATLAS[85d]	CK-MB/cTn	1	CK-MB	3	CK-MB	5 (w/ com) or 10 (w/o com)
ACUITY[96]	CK-MB/cTn	1	CK-MB	3	CK-MB	5 (w/ Qw) or 10 (w/o Qw)

[a]TRA 2°P TIMI 50 definition of CABG-related MI required additional complications beyond biomarker criterion (new Q-waves or new left-bundle branch block; angiographically documented graft or native coronary artery occlusion; or imaging evidence of new loss or viable myocardium).
[b]No MI definition published for ONTARGET.
[c]The CHARISMA trial did not use a separate MI definition for procedure-related MI.
[d]ATLAS definition of CABG-related MI required additional complications beyond biomarker criterion (new Q-waves or new left-bundle branch block; angiographically documented graft or native coronary artery occlusion; or imaging evidence of new loss or viable myocardium) for CK-MB elevation between 5× and 10× the ULN.
CABG, coronary artery bypass grafting; CK-MB, creatine-kinase-MB; com, additional complications; cTn, cardiac troponin; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; Qw, Q-waves; ULN, upper limit of normal; w/, with; w/o, without.

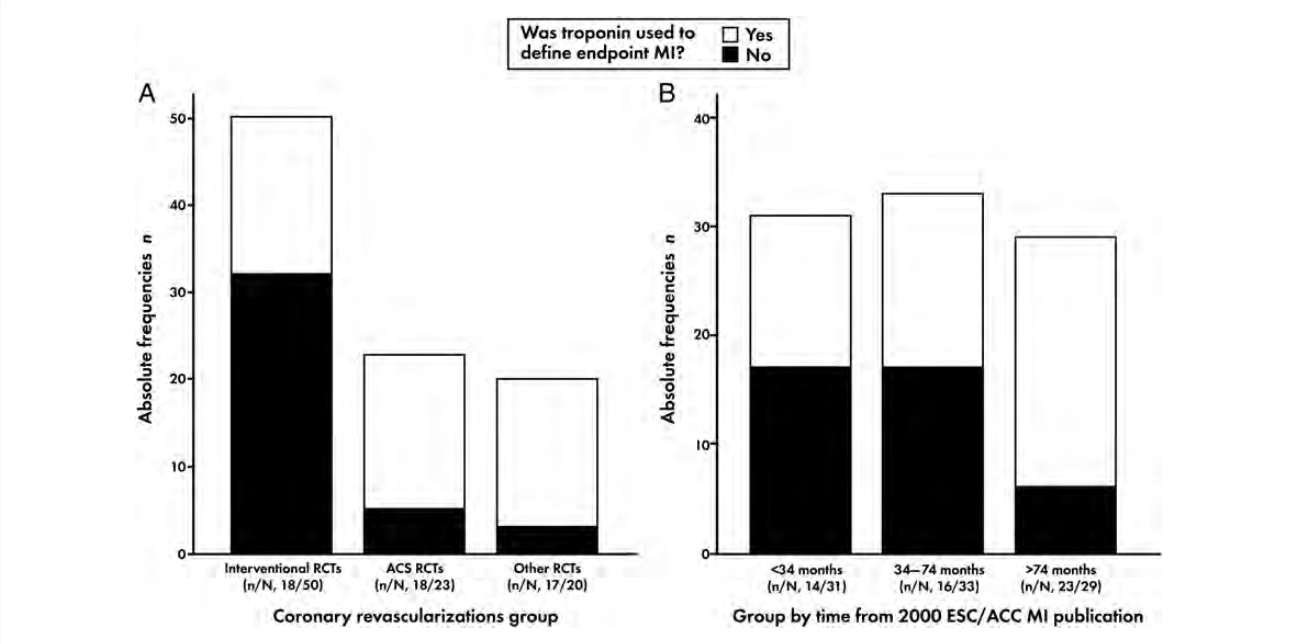

Figure 2 (*A*) Troponin use for endpoint myocardial infarction definition by coronary revascularization group. (*B*) Troponin use for endpoint myocardial infarction definition by time from the publication of 2000 ESC/ACC MI document to the start of trial enrolment.

Survey results

A survey was administered to the investigators between April 2011 and July 2012. Of 61 unique investigators responding to the survey, 54 (88.5%) responded that the use of a standard MI definition in RCTs was important, but 40 of those 54 (74.1%) also indicated that the ESC/ACC/AHA/WHF (World Heart Federation) task force definition created challenges related to assay variability and definition of re-MI and PCI-related MI. Overall, 54 investigators (88.5%) said troponin should be used to define MI in RCTs, but 18 added that they would not use high-sensitivity troponin assays. Of these 54, 38 (70.4%) specified their preference for troponin to define spontaneous but not procedural MI. The most common reasons for not favouring troponin in the procedural setting were as follows: (i) the recommended diagnostic threshold for troponin was too low ($n = 23$, 60.5%); (ii) a belief that there was a lack of clinical relevance of asymptomatic troponin elevations after procedures ($n = 10$, 26.3%); and (iii) these elevations are a marker of atherosclerosis burden but have no independent relationship with mortality ($n = 10$, 26.3%).

For each of the 96 trials in our analysis, we asked the principal investigator to specify whether a standardized MI definition was used; we obtained responses for 91 trials. A standard MI definition was reported in 49 trials (53.8%); 22 reported using the universal MI definition.

Discussion

In this large and broad cross-section of contemporary RCTs in cardiovascular disease, we estimated that MI contributes an average of 45.3% of events in primary endpoint composites. Despite the frequency and importance of MI as an endpoint component in RCTs that establish the evidence for the use of therapies in cardiovascular practice, MI definition was heterogeneous and implementation of recent consensus recommendations for defining MI was low. Overall, only 57.0% of RCTs used troponin to define endpoint MI, whereas 43.0% of trials used the less-specific CK-MB or total CK. This trend was especially evident among RCTs studying revascularization, of which only six trials specified troponin to define procedure-related MI. One in seven trials failed to publish any criteria for MI definition. Although the use of troponin was more frequent among RCTs in which enrolment started >74 months after the publication of the 2000 ESC/ACC consensus MI definition document, overall these findings suggest a lack of standardized implementation of one of the most important endpoint definitions in cardiovascular RCTs.

Use of troponin to define endpoint myocardial infarction

Owing to nearly absolute myocardial specificity, the use of troponins I and T was emphasized in the ESC/ACC 2000 redefinition of MI consensus statement[1] and reinforced in the 2007 Universal Definition of MI document.[2] Thus, it is noteworthy that slightly more than half of cardiovascular RCTs we examined used troponin to define endpoint MI. Even among RCTs that referenced a consensus document, only 66.7% used troponin to define endpoint MI and only 7 specified the recommended 99th percentile as the MI decision limit. These findings are in sharp contrast to the rapid uptake of troponins to define MI in clinical practice.[97]

Because failure to implement a standard approach to define MI in RCTs impairs systematic comparison of results across trials, our

findings underscore the need to (i) increase awareness of consensus documents; (ii) overcome impediments to implementation of consensus recommendations in RCTs; and (iii) develop uniform standards for determining and reporting endpoint MI in RCTs and defining the role of troponin.

Spontaneous and procedural myocardial infarction reporting and infarct size

Remarkably, only three of 80 RCTs separately reported spontaneous and procedural MI, whereas five reported MI rates between treatment arms, using threshold biomarker size, and no RCT provided actual peak biomarker levels. Although there is general agreement that procedure-related myocardial necrosis has some prognostic implication, it remains controversial as to how best to weigh its impact relative to spontaneous MI.[96] Indeed, separate reporting was a key consideration driving the five-group classification in the 2007 and 2012 MI definition documents.[2,3] Finally, it may be useful to compare the effect of treatments using a more sensitive, continuous measure of myonecrosis, such as the peak biomarker value, in addition to the presence/absence of MI. Without consistently defining and reporting MI, it will remain challenging to compare studied populations and reported results across trials.

Understanding gaps in the implementation of consensus document recommendations

Implementation of consensus recommendations for MI definition and reporting is likely time-dependent. The use of troponin to define endpoint MI was higher in RCTs that began >74 months after ESC/ACC MI 2000 redefinition, compared with earlier trials. This may reflect increased acceptance over time of troponin as the preferred biomarker to define MI. It may also reflect that establishing endpoint definitions in the design phase of clinical trials often precedes the start of enrolment. However, even at 34–74 months (about 3–6 years after the 2000 redefinition document was published), only 48.5% of trials used troponin to define endpoint MI: this suggests it was unlikely the only factor in our findings.

Troponin was used least often to define MI in Interventional RCTs. Although the association of CK-MB elevation (mainly defined as >3× ULN) with death after coronary revascularization has been demonstrated, whether this relationship exists for troponin and at what level of elevation above the 99th percentile is less certain.[98–100] This has prompted debate about the use of troponin to define procedure-related MI.[101] Our investigator survey revealed a reluctance to use troponin to define procedure-related MI; only 16 of 61 investigators favoured troponin to define procedure-related MI. The most common reason cited (60.5%) was the low recommended diagnostic threshold (i.e. 3× ULN for PCI-related MI). It is reassuring that the most recent version of the Universal Definition of MI has addressed this concern by raising the recommended threshold for peri-PCI MI from 3× ULN to 5× ULN, although the task force recognizes that these thresholds are arbitrary.[3]

About one-fourth of respondents were concerned about clinical relevance, including that asymptomatic troponin elevation post-procedure is not clinically important or that it is a marker of atherosclerosis burden but has no independent relationship with mortality. Concerns have also been raised that interpreting peri-procedural troponin elevations is challenging and may be less relevant among patients with pre-procedural elevation.[102,103] Increasingly sensitive troponin assays will add more complexity to this debate by increasing the proportion of patients with elevated baseline troponin levels. However, a recent analysis of pooled data from more than 10 000 clinical trial patients with non-ST-segment elevation ACS that assessed troponin trends before and at the time of PCI found that (i) in using pre-procedural troponin trends to identify patients with stable or falling troponin levels, 57% of patients could be assessed for peri-PCI MI, and (ii) if troponin levels were stable or falling before PCI, then a new troponin re-elevation post-PCI was associated with worse outcomes, even after accounting for pre-procedural troponin levels.[104] The importance of assessing cardiac marker trends before PCI in adjudicating peri-PCI MI was also emphasized by the recent 2012 Universal Definition of MI.[2,3] Thus, enhanced use of a standard MI definition that incorporates troponin will likely be most successful by iteratively addressing investigator concerns. Only reassessment of the degree of implementation of the 2012 Universal Definition of MI in several years will confirm whether the changes (which are consistent with our survey findings of reasons for failure of significant implementation to date) were successful in increasing standardized MI definition in clinical trials. We believe our survey not only has provided important insights into investigator concerns about implementing standard MI definitions in clinical trials, but it can also serve as the framework for the future reassessments of implementation.

Concern about the relevance of peri-procedural troponin elevations and MI definition thresholds does not entirely explain the low implementation of the Universal Definition of MI. Even ACS RCTs and Other RCTs incompletely incorporated ESC/ACC consensus recommendations for troponin use to define MI, particularly at the 99th percentile. This may reflect ongoing concerns about precision of some assays at the 99th percentile. Even if assays are very precise at the 99th percentile, it is also unknown whether smaller MIs that may be detected and that generally are associated with lower risk for adverse outcomes would affect the ability to detect overall treatment differences in RCTs. New generation troponin assays with even higher sensitivity will likely add more uncertainty, as recently acknowledged by the Third Universal Definition of MI.[3] It is noteworthy that more than one-quarter of investigators surveyed favoured troponin to define MI, but not the use of high-sensitivity assays due to potential 'noise' or non-clinically relevant MI event detection. Although these concerns could lead to troponin use at a cutoff above the 99th percentile, they would not solely explain overall low rates of incorporation of troponin testing into MI endpoint definitions. To this point, 11.5% of investigators felt troponin should not be used at all to define MI in RCTs.

Future directions

The low use of consensus document recommendations we observed identifies a pressing need to implement standard definition and reporting of MI endpoints in cardiovascular RCTs. We

believe that the reporting criteria developed by the ACC/AHA/ESC/WHF Writing Group for Redefinition of Myocardial Infarction should be required as part of the standardized CONSORT (Consolidated Standards of Reporting Trials) reporting system for clinical trials now adopted by major medical journals.[105] Using this type of standardized reporting system, such as that recently developed for bleeding,[106] would make it easier for both clinicians and clinical trialists to understand findings of RCTs. Moreover, we suggest that the redefinition of MI writing group consider modifications that address concerns and perspectives among investigators that were identified in our survey. Other specific efforts and measures that may facilitate uniform definition and reporting include the following: (i) requirements from regulatory authorities for standard MI definition in RCTs in which MI is a key component of the primary endpoint, including appropriate distinction of MI types; and (ii) requirements by journal editors that actual data for necrosis markers used to determine MI endpoints in RCTs be submitted as a supplementary file with each primary results manuscript so that they are publically available. This would provide an important opportunity for investigators, regulators, and critics to examine varying definitions of MI (e.g. varying troponin thresholds for MI) and how they affect trial results.

To successfully implement standard definition and reporting of MI in RCTs, logistical issues, including pros and cons of local laboratory vs. core laboratory troponin measurement, must be addressed. In particular, if local measurements are used, how best to incorporate and account for the wide variety and lack of standardization of available troponin assays and their varying performance characteristics must be resolved.

Limitations and strengths

We acknowledge some limitations of our systematic review but also would point to its strengths. Whereas one author (S.L.) screened and abstracted all the data, we implemented rigorous quality checks to ensure complete and consistent data abstraction. Also, the inclusion/exclusion criteria and parameters assessed were stringent, reducing the likelihood of bias that could substantially alter the results. These contentions are supported by our sensitivity analysis that examined smaller RCTs, revealing similar findings. Furthermore, we limited our search to primary results and/or design papers. RCTs may report the incidence of spontaneous and procedural MI in a secondary publication.[107] However, because the consensus recommendations were designed for use in primary MI endpoint determination, we felt that a stringent approach to addressing their implementation for primary results presentation was important. More importantly, reporting results according to these key recommendations in secondary publications, which are more difficult to identify and often occur well after the primary results are published, creates unnecessary obstacles to understanding the primary results. Finally, the quality of data management and monitoring, which is usually not publicly or readily available, was not analysed in our systematic review.

Conclusions

Although MI contributes significantly to primary outcome measures in contemporary RCTs, low implementation of the 2000 ESC/ACC MI redefinition and 2007 Universal Definition of MI consensus recommendations was evident. This was particularly true regarding the use of troponin to define MI. Given the importance of MI as a metric in clinical practice, clinical trials, and epidemiological studies, it is necessary to better understand this failure and to create appropriate strategies for uniform implementation of recommendations. Our survey, from a broad cross-section of contemporary RCTs, underscores the need for further investigation to establish the most appropriate and clinically meaningful definition of peri-procedural MI.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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