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Clinical end point definitions after percutaneous coronary intervention and their relationship to late mortality: an assessment by attributable risk

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Objectives: To explore the relative and absolute risks associated with various definitions for myocardial infarction, bleeding and revascularisation within the context of percutaneous coronary intervention (PCI). **Methods:** The REPLACE-2 (randomised evaluation of PCI linking Angiomax to reduced clinical events) database of patients undergoing PCI was used. Various definitions of myocardial infarction, bleeding and revascularisation were modelled by logistic regression assessing their relationship with 12-month mortality. Estimates from these models were used to calculate the "attributable fraction" for late mortality associated with each definition.

Results: The most liberal definition of myocardial infarction was associated with an attributable risk of 13.7% (95% CI 3.4% to 23.0%). The most stringent definition was associated with an attributable risk of 4.6% (95% CI 0.6% to 8.6%). Restrictive definitions of bleeding such as TIMI (thrombolysis in myocardial infarction) major bleeding are associated with a high odds ratio of risk (6.1, 95% CI 2.1 to 17.7, $p = 0.001$) but low attributable fraction (3.5%, 95% CI 0.9% to 6.8%).

Conclusions: Stringent end point definitions may under-represent the clinical significance of adverse outcomes after PCI. Considering both the proportional and absolute risk associated with definitions may be a more useful method for evaluating clinical trial end points. This analysis supports the current definitions of ischaemic events but suggests that more liberal definitions of bleeding events may also be relevant to late mortality.

The importance of end points in clinical trials cannot be understated. Clinical outcomes measured in these terms determine the acceptance and clinical availability of novel drugs and procedural techniques. Yet definitions for clinical events are often chosen arbitrarily, and clinical events are combined into composite primary end points to attain statistical power rather than based on a clinical rationale. Among clinical trials of adjunctive pharmacotherapy for percutaneous coronary intervention (PCI), the clinical significance of myocardial infarction (MI) defined by post-procedural myonecrosis continues to be debated, and recent attempts to broaden the composite primary end points to include bleeding events have also been challenged.¹⁻⁷

Previous analyses have related periprocedural myonecrosis to late mortality by separating patients into groups defined by various levels of creatine kinase (CK) MB fraction rise and assessing the rate of death in each group.^{3-5 8 9} A significant increase in mortality has then been interpreted as clinically significant postprocedural MI. This approach, however, is dependent on the size of the study. Although the mortality risk of MI is clearly related to the degree of myonecrosis, relatively small studies may lack the power to observe an impact from a more modest rise in cardiac markers, thus declaring only the largest infarctions clinically significant.

An alternative approach is to assess the proportion of patients who die late of an observed clinical event—this is otherwise known as "attributable risk". This implies that prevention of the clinical event or end point will prevent a proportion of late mortality. Hence, we explored the relationship between various definitions of periprocedural MI, revascularisation and bleeding events and 12-month mortality within a randomised trial of adjunctive pharmacotherapy for PCI.

METHODS

Population

The REPLACE-2 (randomised evaluation of PCI linking Angiomax to reduced clinical events) trial database was chosen for this analysis, as several key aspects offered the opportunity to address the study questions. Firstly, it remains one of the largest clinical trial datasets in PCI. Secondly, postprocedural CK-MB data were collected routinely for all patients; detailed bleeding data were also actively collected, as bleeding was a component of the primary end point. Thirdly, 12-month follow up was undertaken. The details of this study are described elsewhere.^{10 11} In summary, this trial examined the relative efficacy of bivalirudin and provisional glycoprotein IIb/IIIa inhibition versus heparin and planned glycoprotein IIb/IIIa inhibition among a broad selection of patients undergoing PCI. Important exclusions from this study were patients undergoing catheter-based reperfusion for ST segment elevation MI and patients with significant bleeding diatheses, chronic renal failure with serum creatinine $> 354 \mu\text{mol/l}$ or requiring dialysis and contraindications to clopidogrel or glycoprotein IIb/IIIa inhibition. Eighty six per cent of patients received at least one coronary stent. Drug-eluting stents were not available at the time of the study. Approval of this study was obtained at each site from their respective ethics committees. As 12-month mortality did not differ between the two treatment arms, the entire study population was analysed collectively.

Abbreviations: CK, creatine kinase; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; REPLACE-2, randomised evaluation of PCI linking Angiomax to reduced clinical events; TIMI, thrombolysis in myocardial infarction

End point definitions

The primary end point of the original study was all-cause mortality, MI, urgent revascularisation at 30 days and in-hospital protocol-defined major bleeding. To explore the utility of different ischaemic and bleeding end point definitions, more liberal and more stringent definitions for both ischaemic and bleeding events were also entered into the analysis for comparison.

With respect to MI, the original definition of periprocedural MI was based on a threshold of CK-MB three times the upper limit of normal within 48 h of PCI or five times the upper limit of normal after coronary artery bypass grafting, or the development of new Q waves on ECG. If CK-MB data were unavailable, CK values were used. MI after 48 h was defined as CK-MB > 2 times the upper limit of normal or the development of new Q waves. In addition, cut points for periprocedural MI of CK-MB > 1 times, >2 times, >5 times and >10 times the upper limit of normal within 48 h were also explored, with MIs after 48 h as defined above being included with each new threshold definition. Postprocedural CK-MB rises among patients presenting with baseline CK-MB rise (CK-MB > 1 times the upper limit of normal) were not considered to indicate MI for each of the definitions (146 raised postprocedural results discounted) (fig 1A).

The definition of major haemorrhage in the protocol was broad and included TIMI (thrombolysis in myocardial infarction) major and minor bleeding, as well as any transfusion of red cells ≥ 2 units.¹² Bleeding events not meeting the protocol definition for major bleeding were considered protocol-defined minor haemorrhage. Figure 1B schematically presents the interrelationship between protocol-defined bleeding events and TIMI bleeding events. The impact of blood transfusions on haemoglobin concentrations was adjusted for by the Landefeld index.¹³ To examine the relationship between the various threshold definitions of bleeding and the absolute risk of death within 12 months, bleeding events were considered dichotomously to be protocol-defined major haemorrhage, protocol-defined major and minor haemorrhage, TIMI major bleeding or TIMI major and minor bleeding events. Among patients with more than one bleeding event, only the most severe event was considered.

Urgent revascularisation, either percutaneous or by coronary artery bypass grafting, undertaken within 30 days was regarded as part of the primary end point. In this analysis, the mode of revascularisation was explored separately. The impact of extending this definition to any revascularisation within 30 days was also explored.

Statistical analysis

To investigate the inverse relationship between the relative risk and the absolute proportion of patients at risk of 12-month death associated with each possible end point definition of ischaemia and bleeding after PCI, the odds ratios (ORs) of excess risk and attributable risk were calculated.¹⁴ The population attributable risk attempts to apportion the deaths by 12 months associated with end point experienced within 30 days, as defined. A liberal end point definition associated with a substantial proportion of the deaths by 12 months has a high attributable risk, implying that prevention of such an event will mitigate that proportion of late mortality. Conversely, a stringent end point definition is associated with a high relative risk of late mortality, but affects few patients (fig 2).

Logistic regression models examining the relationship between each definition of MI, bleeding and revascularisation end point and mortality within 12 months were generated and used to provide estimates of the OR for excess risk. Each model adjusted for the baseline characteristics associated with increased mortality by 12 months. These were age > 75 years, a history of diabetes mellitus, history of congestive cardiac failure, anaemia (haemoglobin < 100 g/l), impaired renal function (creatinine clearance < 60 ml/min), body mass index > 28 kg/m² and smoking. Factors known to have a continuous association with mortality (age, haemoglobin, and renal function) were dichotomised at commonly used levels to assist in the clinical interpretation of attributable risk. Within each model, the adjusted population attributable fraction of each definition was then calculated as $(\text{deaths}_T - \text{deaths}_{NE})/\text{deaths}_T$, where deaths_T is the total deaths predicted and deaths_{NE} is the deaths occurring among people not experiencing the clinical event.

Both the relative impact of each definition (OR and 95% confidence interval (CI)) and the adjusted absolute contribution (attributable fraction (percentage and 95% CI)) to late

Figure 1 Schematic representation of the relationship between the various (A) ischaemic definitions and (B) bleeding definitions used in the analysis. CK, creatine kinase; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction; ULN, upper limit of normal.

Figure 2 Schematic representation of the inverse relationship between attributable risk and relative (odds ratio) of 12 month mortality risk associated with liberal and stringent clinical event definitions. More liberal definitions result in a greater number of events being recorded. More stringent definitions are associated with greater relative risk of late mortality but affect fewer people.

mortality are presented. The impact of MI occurring > 48 h after the index event was also considered separately. Continuous variables are expressed as mean (SD) or median and interquartile range for variables with non-Gaussian distributions. All discrete variables are expressed as counts and percentages of the study population. Data were analysed with STATA V.8.0 (College Station, Texas, USA). A probability of < 0.05 was considered significant.

RESULTS

Of the 6010 patients randomly assigned, postprocedural CK and CK-MB concentrations or data pertaining to MIs occurring > 48 h after the index intervention were unavailable for 315 patients, leaving 5695 patients (94.8%) eligible for analysis. Of these, 514 patients (9.0%) and 12 events (1.3%) were included based on total CK data alone. Table 1 describes the baseline characteristics of patients included in this analysis. By 12 months, 116 (2.0%) of these patients had died. Table 2 presents baseline characteristics associated with death by 12 months used to adjust the logistic regression models along with their OR and their attributable fraction.

Threshold definitions of MI and 12 month mortality

Confining the definition of MI to events occurring beyond 48 h after the index PCI (that is, ignoring all periprocedural rises in CK) led to a significant relative increase in the risk of death by 12 months (OR 13.5, 95% CI 5.1 to 36.0, $p < 0.001$). As these events were infrequent (29 of 5695; 0.5%), however, confining the end point of MI to this definition accounted for only 5.4% (95% CI 1.3% to 9.7%) of the deaths seen by 12 months. Figure 3A presents increasingly sensitive thresholds of periprocedural CK-MB. With increasingly sensitive definitions of MI (lower thresholds of periprocedural CK-MB rise) the OR of risk associated with the definition decreased, but the proportion of deaths attributable to MI increased. Nevertheless, even CK-MB rises > 1 times the upper limit of normal were significantly associated with mortality by 12 months (OR 2.0, 95% CI 1.3 to 3.1, $p = 0.001$). Applying a definition of MI of CK or CK-MB < 3 times the upper limit of normal was associated with only a small incremental increase in the attributable risk (13.2%, 95% CI 5.3% to 20.3%) increasing to 13.7% (95% CI 3.4% to 23.0%). In contrast, including only large degrees of periprocedural myonecrosis (> 10 times the upper limit of normal) with events after 48 h in the definition of MI was associated with a marked relative

Table 1 Patient characteristics according to whether they were alive or had died by 12 months

Characteristic	Dead by 12 months (n = 116)	Alive by 12 months (n = 5579)	p Value
Age (years)	72 (62–77)	63 (54–71)	<0.001
Women	36.2%	25.4%	<0.001
Diabetes	26.8	39.6%	0.002
Hypertension	74.1%	66.7%	0.090
Smoker within 1 year	26.4%	26.5%	0.967
Body mass index (kg/m ²)	27.5 (24.2–31.2)	28.7 (25.7–32.5)	0.005
Prior myocardial infarction	37.5%	34.7%	0.115
Prior CABG	29.3%	18.3%	0.002
Prior PCI	37.9%	34.7%	0.479
Congestive cardiac failure	28.7%	6.6%	<0.001
Cerebrovascular accident	1.8%	2.4%	0.668
Creatinine clearance <60 ml/min	39.6%	15.0%	<0.001
Acute coronary syndrome indication	16.5%	22.7%	0.117
Baseline haemoglobin <100 g/l	6.9%	1.0%	0.001
Worst ACC/AHA lesion B2 or C	57.3%	54.8%	0.604
Multivessel intervention	15.8%	19.1%	0.340

Body mass index is presented as mean (interquartile range).

ACC, American College of Cardiology; AHA, American Heart Association; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Table 2 Odds ratio and attributable risk for baseline clinical factors associated with death by 12 months

Risk factor	Odds ratio	95% CI	Attributable risk (%)	95% CI
Age >75 years	1.5	0.9 to 2.6	9.7	-3.1 to 20.9
History of heart failure	4.1	2.6 to 6.5	21.0	11.5 to 29.4
Renal impairment*	2.5	1.5 to 4.1	22.6	9.3 to 33.9
Smoking history	1.4	0.9 to 2.2	7.2	-4.0 to 17.9
History of diabetes	1.6	1.1 to 2.5	14.5	0.9 to 26.2
Anaemia†	4.4	1.9 to 10.0	5.5	0.7 to 9.5

*Creatinine clearance <60 ml/min; †haemoglobin <10 g/l.

excess risk of death (OR 7.7, 95% CI 3.1 to 19.2, $p < 0.001$) but, as these events were few (47 of 5695), the attributable fraction was low (4.6%, 95% CI 0.6% to 8.6%).

Bleeding events

TIMI major bleeding was the most stringent and therefore least liberal definition of haemorrhage. Consequently, this definition was associated with a substantial relative risk of death within 12 months (fig 3B). Applying a dichotomous

end point of bleeding that includes both TIMI major and TIMI minor bleeding was associated with significant relative excess mortality over the follow-up period, with a marginal increase in attributable risk of death by 12 months. Protocol-defined major bleeding was also associated with a significant relative excess mortality, with an increase in the attributable fraction. Broadening the definition to a very liberal bleeding definition (any bleeding down to and including protocol-defined minor bleeding) was also significantly associated with an excess mortality (OR 1.6, 95% CI 1.0 to 2.3, $p = 0.033$). It was also associated with a pronounced increase in the attributable fraction (11.0%, 95% CI 0.6% to 23.0%).

Revascularisation events

Urgent repeat PCI, coronary artery bypass grafting and an end point of these combined were associated with a substantial excess in the risk of late mortality. Furthermore, despite the infrequency of these events, urgent revascularisation was associated with an attributable risk of 6.2% with respect to late mortality. Extending the definition to any revascularisation did not substantially change these results (table 3).

Composite end point

Selecting the composite end point of MI (CK-MB > 3 times upper limit of normal), protocol-defined minor haemorrhage and urgent revascularisation was associated with an attributable fraction of 25.8% (95% CI 13.4% to 36.4%). After adjustment for other baseline clinical variables, associated mortality at 12 months resulted in an attributable fraction of 27.0%, implying that about a quarter of the events observed by 12 months may be prevented if no patients experienced any of the events in the composite end point.

DISCUSSION

End point definitions used in clinical trials represent a trade-off between competing interests. From a clinical perspective, events chosen should have clear relevance to patients and clinicians. After coronary revascularisation, however, catastrophic events such as death are now uncommon and trials powered to address these events are logistically demanding. The use of composite end points incorporating non-fatal events, to increase event rates and increase power, is now commonplace. The clinical significance of these end point definitions, however, continues to be debated. One of the central questions in this debate is how well these end point definitions perform as surrogate markers of death. This analysis explores the inverse relationship between the proportion of patients considered at risk of late death and the relative excess mortality associated with various bleeding and ischaemic definitions. Describing this relationship may enable a more balanced approach to selecting composite end points used in clinical trials, by weighting both the relative and the absolute relationship of a specific clinical event definition to late mortality.

Figure 3 Odds ratios (dotted line) and attributable risk (shaded area) for 12 month mortality associated with various definitions of (A) myocardial infarction and (B) protocol-defined bleeding. TIMI, thrombolysis in myocardial infarction; ULN, upper limit of normal.

Table 3 Odds ratio and attributable risk for revascularisation end points and death by 12 months

End point	Odds ratio	95% CI	p Value	Attributable risk (%)	95% CI
Urgent PCI	8.4	3.3 to 21.3	<0.001	4.6	0.7% to -8.3%
Urgent CABG	7.0	1.6 to 31.3	0.011	1.5	-0.8% to 3.8%
Urgent revascularisation	8.4	3.7 to 18.7	<0.001	6.2	1.7% to 10.5%
Any PCI	3.2	1.3 to 7.7	0.010	3.6	-0.5% to 7.5%
Any CABG	4.8	1.4 to 16.1	0.011	2.1	-0.8% to 5.0%
Any revascularisation	3.8	1.8 to 7.8	<0.001	5.8	0.7% to 10.6%

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

The risks associated with myonecrosis and bleeding are proportional to their magnitude and hence continuous in nature. In contrast, clinical end points used as efficacy criteria in clinical trials often require a dichotomous definition (that is, event or no event). Previous approaches to establishing the impact of non-fatal clinical events have stratified the study cohort by magnitude and assessed the relative risk of death in each group, declaring clinical significance only when the difference appears to be statistically significant.¹⁻⁵ In the case of postprocedural CK-MB rise and the end point of MI, such an approach has limited power to declare an effect with smaller degrees of myonecrosis, particularly when the number of patients in each group is small. Hence, with relatively few events, only the largest degrees of myonecrosis, with the highest relative risks, appear to be significantly associated with mortality. Yet, within these cohorts, deaths among patients with very large degrees of myonecrosis are a small proportion of the overall deaths observed.¹⁻⁴ Confining the definition of MI to such high degrees of myonecrosis is very specific but may not be sensitive—that is, such an approach may lead to missed opportunities for the prevention of late deaths. Assessment from the perspective of attributable risk seeks to identify the proportion of total deaths that appear to be associated with the given end point definition. This approach, in addition to relative risk, has the advantage of evaluating the proportion of late deaths that may be prevented if the non-fatal clinical end point is reduced or eliminated.

Exploring the definitions of ischaemic and bleeding events by various severities or degrees is analogous to analysing relative operating characteristics. In this analysis, using the most liberal threshold of postprocedural myonecrosis as the definition for MI has the greatest “sensitivity” for late mortality but lower “specificity” (more patients will be identified as having postprocedural MI, without experiencing late death). At the other extreme, confining the diagnosis to very high degrees of postprocedural myonecrosis will result in high specificity for late death but with low sensitivity. Methods for choosing an optimal definition, to our knowledge, have not been developed. With regard to postprocedural myonecrosis, however, this analysis does suggest that a threshold of > 3 times the upper limit of normal may be an optimal trade-off between relative risk and attributable risk. Definitions below this level do not appear to impart substantial increases in attributable risk. Therefore, these findings support the definition for periprocedural MI commonly used in randomised clinical trials and advocated by quality-of-care initiatives such as the American College of Cardiology clinical data standards.¹⁵ Furthermore, this threshold is similar to the CK-MB definition for spontaneous MI of > 2 times the upper limit of normal.¹⁵

Selecting among postprocedural bleeding end point definitions is more problematic, as an intuitive compromise between sensitivity and specificity is not immediately evident. Little difference in the absolute and relative risk of

late mortality is evident across the currently used measures of bleeding events. Nevertheless, an excess in the relative risk of bleeding is evident across the various definitions, consistent with a clear excess in late mortality associated with bleeding events observed by others.¹⁶ Interpreting the contribution of smaller degrees of bleeding requires further clarification, as their identification and classification may be more subjective. Improved objective definitions of bleeding events of smaller magnitude are required to refine these estimates of relative and attributable risk.

Although this analysis shows that postprocedural myocardial necrosis, unplanned repeat revascularisation and bleeding events are related to mortality observed within 12 months, this relationship is not proof that these events are truly critical in the causal pathway. These events may simply reflect the risk of future death associated with other unmeasured clinical characteristics. Therefore, one cannot be assured that the prevention of these events will provide the reductions in late mortality predicted by the attributable risk calculation. Of course, this logic also applies equally to the use of relative risk or ORs in evaluating the relationship between a non-fatal clinical end point and future death. Nevertheless, ample clinical evidence supports the causal relationship of ischaemic, bleeding and revascularisation events with late mortality, and it is the magnitude of this relationship that requires further clarification. This analysis provides estimates from the largest study of antithrombotic treatment in PCI conducted to date. Confirmation from other studies and registries will be valuable in establishing estimates with greater precision.

Limitations

Firstly, prevention of death is not the only reason for innovation in medicine. Some events captured in composite primary end points may be important targets for assessing efficacy because of substantial morbidity. This is particularly true of repeat revascularisation and severe bleeding events. Formal quantitative assessment of morbidity requires the collection of quality-of-life data, however—an undertaking that is very resource intensive and often omitted in clinical trials. Secondly, an interdependence of clinical events needs to be recognised, as patients experiencing ischaemic events are more likely to require repeat invasive procedures and therefore are at greater risk of bleeding.¹⁷ Nevertheless, to the extent possible, by adjustment through logistic regression modelling, the OR and attributable risk estimates represent the independent contribution of these events to late mortality. Thirdly, the magnitude of attributable risk is inherently related to the characteristics of the population in question. Assessing these relationships in other clinical trial and registry populations would be of value in refining these estimates. Lastly, the validity of estimates of the relative risk and attributable fraction depends on the accuracy of the data acquired. In contrast to periprocedural MI that often relies solely on CK-MB data, bleeding events are subject to

investigator variations in reporting. Improved methods for acquiring and possibly adjudicating bleeding events are required in this era of potent combination antithrombotic drugs.

Conclusions

Current definitions of MI used in trials of PCI account for about 13% of fatal events observed by 12 months. The combination of MI, bleeding and revascularisation accounts for about a quarter of the deaths observed by 12 months. These data support the current thresholds for defining ischaemic events in clinical trials and quality-of-care audits. More liberal definitions of bleeding may better identify patients at risk. Analysis by attributable risk may aid in the evaluation of end points selected for combination in composite primary end points used in future studies.

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Long term prognosis of heart failure after acute coronary syndromes without ST elevation

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Please visit the Heart website [www.heartjnl.com] for a link to the full text of this article.

Background: Information about long term outcomes of patients with acute coronary syndromes (ACS) who have clinically diagnosed heart failure is scarce.

Methods: In a UK registry, this study evaluated patients with non-ST elevation ACS, recording treatment, and clinical outcomes for six months. In a subgroup, a four year mortality follow up was performed to estimate the impact of the clinical diagnosis of heart failure on survival.

Results: Of 1046 patients, 139 (13%) had a history of clinically diagnosed heart failure. At discharge, ACE inhibitors were prescribed for 58% and 28%, of those with and without a history of heart failure respectively ($p < 0.001$). Rates of angiography, percutaneous intervention, and coronary artery bypass graft were 17.3% and 29.2% ($p = 0.003$), 5.0% and 8.4% ($p = 0.17$), and 5.0% and 7.5% ($p = 0.3$) for these groups respectively. Death or new myocardial infarction at six months occurred in 22% and 10% ($p < 0.001$) and at four years death occurred in 60% and 20% of these groups respectively ($p < 0.001$). In a multivariate analysis prior heart failure carried an odds ratio of 2.0 ($p = 0.001$) for death or myocardial infarction at six months and 2.4 ($p < 0.001$) for death over four years. New heart failure was associated with an increased risk of death at six months (20% compared with 5%, $p < 0.001$).

Conclusion: A clinical history of heart failure carries a substantial risk of death in patients admitted with ACS without ST elevation. Nearly 60% of those with prior heart failure are dead after four years. After adjustment for confounding factors, prior heart failure more than doubles the risk compared with those with no history.

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