Clinical endpoint definitions following percutaneous coronary intervention and their relationship to late mortality: An assessment by attributable risk

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Background: Clinical endpoints are essential in the conduct of clinical research, but their appropriate definitions remain the subject of debate. This analysis explores the relative and absolute risk associated with various definitions for myocardial infarction, bleeding, and revascularization within the context of percutaneous coronary intervention (PCI).

Methods: The REPLACE-2 database of patients undergoing PCI was used. Various definitions of myocardial infarction, bleeding and revascularization were modeled by logistic regression assessing their relationship with 12-months 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% C.I. 3.4-23.0%). The most stringent definition was associated with an attributable risk of 4.6% (95% C.I. 0.6-8.6%). Restrictive definitions of bleeding such as TIMI major bleeding are associated with a high odds ratio of risk (O.R 6.1: 95% C.I.: 2.1-17.7, p=0.001), but low attributable fraction (3.5%, 95% C.I.: 0.9-6.8%).

Conclusions: Stringent endpoint definitions may under-represent the clinical significance of adverse outcomes following PCI. Considering both the proportional and absolute risk associated with definitions may be a more useful method for evaluating clinical trial endpoints. This analysis supports the current definitions of ischemic events but suggests, more liberal definitions of bleeding events may also be relevant to late mortality.
Introduction

The importance of endpoints in clinical trials cannot be understated. Clinical outcomes measured in these terms determine the acceptance and clinical availability of novel pharmacotherapies and procedural techniques. Yet, definitions for clinical events are often chosen arbitrarily, and clinical events are combined into composite primary endpoints 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 endpoints to include bleeding events have also been challenged.(1-7)

Previous analyses have related peri-procedural myonecrosis to late mortality by separating patients into groups defined by various levels of CK-MB elevation and assessing the rate of death in each group.(3-5, 8, 9) A statistically significant increase in mortality has then been interpreted as clinically significant post-procedural MI. However, this approach is dependent on the size of the study. While 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 more modest elevations in cardiac markers, thus declaring only the largest infarctions clinically significant.

An alternative approach is to assess the proportion of patients experiencing late mortality in whom the clinical event is observed: otherwise known as “attributable risk.” This implies that prevention of the clinical event or endpoint will prevent a proportion of late mortality. Hence we explored the relationship between various definitions of peri-procedural MI, revascularization and bleeding events and 12-month mortality within a randomized trial of adjunctive pharmacotherapy for PCI.

Methods

Population

The Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial database was chosen for this analysis, as several key aspects offered the opportunity to address the study questions. First, it remains one of the largest clinical trial datasets in PCI. Second, post-procedural CK-MB data were collected routinely in all patients, while detailed bleeding data were also actively collected, as bleeding was a component of the primary endpoint. Third, 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 include patients undergoing catheter-based reperfusion for ST-segment elevation MI, patients with significant bleeding diatheses, chronic renal failure with serum creatinine >4.0mg/dL or requiring dialysis, and contraindication to clopidogrel or glycoprotein IIb/IIIa inhibition. Eighty-six percent 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. Since 12-month mortality did not differ between the two treatment arms, the entire study population was analyzed collectively.
Endpoint definitions

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

With respect to MI, the original definition of peri-procedural MI used a threshold of CK-MB 3 times the upper limit of normal within 48 hours of PCI or 5 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 hours was defined as CK-MB >2 times the upper limit of normal or the development of new Q waves. In addition, cut-points for peri-procedural MI of CK-MB > 1 times, 2 times, 5 times and 10 times the upper limit of normal within 48 hours were also explored, with MIs after 48 hours as defined above, being included with each new threshold definition. Post-procedural CK-MB elevations among patients presenting with baseline CK-MB elevation (CKMB>1 times ULN) were not considered as MI for each of the definitions (146 elevated post-procedural results discounted). (Figure 1a)

The definition of major haemorrhage defined in the protocol was broad, and included the Thrombolysis in Myocardial Infarction (TIMI) 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 hemorrhage. The inter-relationship between protocol-defined bleeding events and TIMI bleeding events are schematically represented in figure 1b. The impact of blood transfusions on haemoglobin levels was adjusted for by the Lanefeld index.(13) To examine the relationship between the various threshold definitions of bleeding and the absolute risk of mortality within 12 months, bleeding events were considered dichotomously as protocol-defined major hemorrhage, protocol-defined major and minor hemorrhage, 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 revascularization, percutaneous or by coronary artery bypass grafting, undertaken within 30 days was considered as part of the primary endpoint. In this analysis, the mode of revascularization has been explored separately. The impact of extending this definition to any revascularization 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 mortality associated with each possible endpoint definition of ischemia and bleeding after PCI, the odds ratio of excess risk and “attributable risk”, respectively, were calculated.(14) The population attributable risk attempts to apportion the deaths by 12 months associated with endpoint experienced within 30 days, as defined. A liberal endpoint 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 endpoint definition is associated with a high relative risk of late mortality, but affects few patients. (Figure 2)

Logistic regression models examining the relationship between each definition of MI, bleeding and revascularization endpoint and mortality within 12 months were generated and used to provide estimates of the odds ratio for excess risk. Each model adjusted for the baseline characteristics associated with increased mortality by 12 months. These included age>75 yrs, a history of diabetes mellitus, history of congestive cardiac failure, anaemia (haemoglobin <10g/dL), impaired renal function...
(creatinine clearance <60ml/min), body mass index >28kg/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 (AF) of each definition was then estimated by calculating:

\[ AF = \frac{Deaths_T - Deaths_{NE}}{Deaths_T} \]

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 (odds ratio and 95% confidence interval) and adjusted absolute contribution (attributable fraction [percentage and 95% confidence intervals]) to late mortality are presented. The impact of MI occurring >48 hours after the index event were also considered separately. Continuous variables are expressed as a mean \( \pm \) standard deviation (SD) or median and inter-quartile ranges for variables with non-gaussian distributions. All discrete variables are expressed as counts and percentages of the study population (n). Analyses were conducted using STATA 8.0 (College Station, TX). A probability of <0.05 was considered statistically significant.

Results

Of the 6010 patients randomized, post-procedural CK, CK-MB values or data pertaining to MIs occurring >48 hours following the index intervention were unavailable in 315 patients, leaving 5695 patients (94.8%) eligible for analysis. Of these, 514 patients (9.1%) and 12 events (1.3%) were included based on total CK data alone. The baseline characteristics of patients included in this analysis are described (Table 1). By 12 months, 116 (2.0%) of these patients had died. Baseline characteristics associated with mortality by 12 months used to adjust the logistic regression models along with their odds ratio and their attributable fraction are presented in table 2.
Threshold definitions of MI and 12-month mortality

Confining the definition of MI to events occurring beyond 48 hours after the index PCI (i.e. ignoring all peri-procedural elevations in creatine kinase) demonstrates a significant relative increase in the risk of mortality by 12 months (O.R.: 13.5, 95% C.I. 5.1-36.0, \( p<0.001 \)). However, since these events are infrequent, 29/5695 (0.5%), confining the endpoint of MI to this definition accounts for only 5.4% (95% C.I. 1.3-9.7%) of the deaths seen by 12 months. Increasingly sensitive thresholds of peri-procedural CK-MB are presented in Figure 3a. With increasingly sensitive definitions of MI (lower thresholds of peri-procedural CK-MB elevation) the odds ratio of risk associated with the definition decreases, but the proportion of deaths attributable to the MI increases. Nevertheless, even CK-MB elevations >1 times the upper limit of normal are significantly associated with mortality by 12 months (OR: 2.0, 95% C.I. 1.3-3.1, \( p=0.001 \)). Employing a definition of MI of CK or CK-MB below 3 times the upper limit of normal is associated with only a small incremental increase in the attributable risk (13.2%, 95% C.I. 5.3-20.3%) increasing to 13.7%, 95% C.I. 3.4-23.0%). In contrast, including only large degrees of peri-procedural myonecrosis (>10 times the upper limit of normal) together with events after 48 hours in the definition of MI is associated with a marked relative excess risk of death (O.R.: 7.7, 95% C.I. 3.1-19.2, \( p<0.001 \)), but since these events are few, 47/5695, the attributable fraction is low (4.6%, 95% C.I. 0.6-8.6%).

Bleeding events

TIMI major bleeding is the most stringent and therefore, least liberal definition of haemorrhage. Consequently, this definition is associated with a substantial relative risk of mortality within 12-months (Figure 3b) Employing a dichotomous endpoint of bleeding that includes both TIMI major and TIMI minor bleeding is associated with statistically significant relative excess mortality over the follow-up period, with a marginal increase in attributable risk of mortality by 12 months. Protocol-defined major bleeding is 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) is also significantly associated with an excess mortality (O.R 1.6, 95% C.I. 1.0-2.3, \( p=0.033 \)). It is also associated with a marked increase in the attributable fraction (11.0%, 95% C.I. 0.6-23.0%).

Revascularization events

Urgent repeat percutaneous coronary intervention, coronary artery bypass grafting and an endpoint including the combination of these are associated with a substantial excess in the risk of late mortality. Furthermore, despite the infrequency of these events, urgent revascularization is associated with an attributable risk of 6.2% with respect to late mortality. Extending the definition to any revascularization does not substantially change these results (Table 3).

Combined composite endpoint

Selecting the composite endpoint that includes MI (CK-MB >3 times upper limit of normal), protocol defined minor haemorrhage, and urgent revascularization is associated with an attributable fraction of 25.8% (95% C.I.: 13.4-36.4%). After adjusting for other baseline clinical variables associated mortality at 12 months results in an attributable fraction of 27.0%, implying that approximately a quarter of
the events observed by 12 months may be prevented if no patients experienced any of the events included in the composite endpoint.

Discussion

Endpoint 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. However, following coronary revascularization catastrophic events such as mortality are now uncommon and trials powered to address these events are logistically demanding. The use of composite endpoints incorporating non-fatal events, in order to increase event rates and increase power, are now commonplace. However, the clinical significance of these endpoint definitions remains debated. One of the central questions in this debate is how well these endpoint definitions perform as surrogate markers of mortality. This analysis explores the inverse relationship between the proportion of patients considered at risk of late mortality with the relative excess in death associated with various bleeding and ischemic definitions. Describing this relationship may enable a more balanced approach to selecting composite endpoints used in clinical trials, by weighting both relative and absolute relationship of a specific clinical event definition with late mortality.

The risks associated with myonecrosis and bleeding are proportional to their magnitude and hence continuous in nature. In contrast clinical endpoints used as efficacy criteria in clinical trials often require a dichotomous definition (i.e. 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 post-procedural CK-MB elevation and the endpoint 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 represent 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. I.e. 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 endpoint 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 endpoint is reduced or eliminated.

Exploring the definitions of ischemic and bleeding events by various severities or degrees is analogous to performing a relative operating characteristic analysis. In this analysis, using the most liberal threshold of post-procedural myonecrosis as the definition for MI has the greatest “sensitivity” for late mortality, but lower “specificity” (more patients will be identified as having post-procedural MI, without experiencing late mortality). At the other extreme, confining the diagnosis to very high degrees of post-procedural myonecrosis will result in high specificity for late mortality, but with low sensitivity. Methodology for choosing an optimal definition, to our knowledge, has not been developed. However, with regard to post-procedural myonecrosis, this analysis does suggest a threshold level of >3 times upper limit of normal may be optimal tradeoff 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 peri-procedural myocardial infarction commonly used in randomized clinical trials and advocated by quality of care initiatives such as the American College of Cardiology Clinical Data Standards. (15) Furthermore this threshold level is similar to the CK-MB definition for spontaneous myocardial infarction of >2 times the upper limit of normal. (15)

Selecting among post-procedural bleeding endpoint definitions is more problematic, since 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 lesser degrees of bleeding requires further clarification since their identification and classification may be more subjective. Improved objective definitions of bleeding events of lesser magnitude are required to refine these estimates of relative and attributable risk.

While this analysis demonstrates a relationship between post-procedural myocardial necrosis, unplanned repeat revascularization and bleeding events with mortality observed within 12 months, it is not proof that these events are truly critical in the causal pathway. These events may simply reflect the risk of future mortality 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 odds ratios in evaluating the relationship between a non-fatal clinical endpoint and future mortality. Nevertheless, ample clinical evidence supports the causal relationship between ischemic, bleeding and revascularization 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 anti-thrombotic therapy in PCI conducted to date. Confirmation from other studies and registries will be valuable in establishing estimates with greater precision.

Limitations

First, prevention of mortality is not the only reason for innovation in medicine. Some events captured in composite primary endpoints may be important targets for assessing efficacy because of substantial morbidity. This is particularly true of repeat revascularization and severe bleeding events. However, formal quantitative assessment of morbidity requires the collection of quality of life data, an undertaking that is very resource intensive and frequently omitted in clinical trials. Second, an inter-dependence of clinical events needs to be recognized, since patients experiencing ischemic 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 modeling, the odds ratio and attributable risk estimates represent the independent contribution of these events to late mortality. Third, 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, validity of estimates of relative risk and attributable fraction are dependent 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 ant-thrombotic therapies.
Conclusions

Current definitions of MI used in trials of PCI account for approximately 13% of fatal events observed by 12 months. The combination of MI, bleeding and revascularization accounts for approximately a quarter of the deaths observed by 12 months. These data support the current thresholds for defining ischemic 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 endpoints selected for combination in composite primary endpoints used in future studies.
Acknowledgement

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Table and figure legends

Figure 1: Schematic representation of the relationship between the various (a) ischemic definitions and (b) bleeding definitions used in the analysis.

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.

Figure 3: Odds ratios (line) and attributable risk (shaded area) for 12-month mortality associated with various definitions of (a) myocardial infarction, and (b) protocol defined bleeding.

Table 1: Patient characteristics

Table 2: Odds Ratio and Attributable Risk for baseline clinical factors associated with mortality by 12 months

Table 3: Relative and Attributable Risk for Revascularization Endpoints and Mortality by 12 months
### Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Death by 12 months</th>
<th>Alive by 12 months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=116)</td>
<td>(n=5579)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (yrs) (median, IQR)</strong></td>
<td>72 (62-77)</td>
<td>63 (54-71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female (%)</td>
<td>36.2</td>
<td>25.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>26.8</td>
<td>39.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>74.1</td>
<td>66.7</td>
<td>0.090</td>
</tr>
<tr>
<td>Smoker within 1 year(%)</td>
<td>26.4</td>
<td>26.5</td>
<td>0.967</td>
</tr>
<tr>
<td><strong>BMI (kg/m(^2)) (mean ± SD)</strong></td>
<td>27.5(24.2-31.2)</td>
<td>28.7(25.7-32.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>37.5</td>
<td>34.7</td>
<td>0.115</td>
</tr>
<tr>
<td>Prior CAGB (%)</td>
<td>29.3</td>
<td>18.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Prior PCI (%)</td>
<td>37.9</td>
<td>34.7</td>
<td>0.479</td>
</tr>
<tr>
<td>Congestive Cardiac Failure (%)</td>
<td>28.7</td>
<td>6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular Accident (%)</td>
<td>1.8</td>
<td>2.4</td>
<td>0.668</td>
</tr>
<tr>
<td>Creatinine Clearance &lt; 60ml/min (%)</td>
<td>39.6</td>
<td>15.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute coronary syndrome indication (%)</td>
<td>16.5</td>
<td>22.7</td>
<td>0.117</td>
</tr>
<tr>
<td>Baseline haemoglobin &lt;10g/dL (%)</td>
<td>6.9</td>
<td>1.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Worst ACC/AHA Lesion B2 or C (%)</td>
<td>57.3</td>
<td>54.8</td>
<td>0.604</td>
</tr>
<tr>
<td>Multi-vessel intervention (%)</td>
<td>15.8</td>
<td>19.1</td>
<td>0.340</td>
</tr>
</tbody>
</table>
Table 2: Odds Ratio and Attributable Risk for baseline clinical factors associated with mortality by 12 months

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds ratio</th>
<th>95% C.I.</th>
<th>Attributable risk (%)</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;75yrs</td>
<td>1.5</td>
<td>0.9-2.6</td>
<td>9.7</td>
<td>-3.1-20.9</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>4.1</td>
<td>2.6-6.5</td>
<td>21.0</td>
<td>11.5-29.4</td>
</tr>
<tr>
<td>Renal Impairment&lt;sup&gt;ψ&lt;/sup&gt;</td>
<td>2.5</td>
<td>1.5-4.1</td>
<td>22.6</td>
<td>9.3-33.9</td>
</tr>
<tr>
<td>Smoking history</td>
<td>1.4</td>
<td>0.9-2.2</td>
<td>7.2</td>
<td>-4.0-17.9</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>1.6</td>
<td>1.1-2.5</td>
<td>14.5</td>
<td>0.9-26.2</td>
</tr>
<tr>
<td>Anaemia&lt;sup&gt;φ&lt;/sup&gt;</td>
<td>4.4</td>
<td>1.9-10.0</td>
<td>5.5</td>
<td>0.7-9.5</td>
</tr>
</tbody>
</table>

<sup>ψ</sup>Creatinine clearance<60ml/min. <sup>φ</sup>Haemoglobin <10mg/dL
Table 3: Odds Ratio and Attributable Risk for Revascularization Endpoints and Mortality by 12 months

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% C.I.</th>
<th>P value</th>
<th>Attributable Risk (%)</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgent PCI</td>
<td>8.4</td>
<td>3.3-21.3</td>
<td>&lt;0.001</td>
<td>4.6</td>
<td>0.7-8.3%</td>
</tr>
<tr>
<td>Urgent CABG</td>
<td>7.0</td>
<td>1.6-31.3</td>
<td>0.011</td>
<td>1.5</td>
<td>-0.8-3.8%</td>
</tr>
<tr>
<td>Urgent Revascularization</td>
<td>8.4</td>
<td>3.7-18.7</td>
<td>&lt;0.001</td>
<td>6.2</td>
<td>1.7-10.5%</td>
</tr>
<tr>
<td>Any PCI</td>
<td>3.2</td>
<td>1.3-7.7</td>
<td>0.010</td>
<td>3.6</td>
<td>-0.5-7.5%</td>
</tr>
<tr>
<td>Any CABG</td>
<td>4.8</td>
<td>1.4-16.1</td>
<td>0.011</td>
<td>2.1</td>
<td>-0.8-5.0%</td>
</tr>
<tr>
<td>Any Revascularization</td>
<td>3.8</td>
<td>1.8-7.8</td>
<td>&lt;0.001</td>
<td>5.8</td>
<td>0.7-10.6%</td>
</tr>
</tbody>
</table>
References


<table>
<thead>
<tr>
<th>CKMB elevation</th>
<th>CK&gt;1 ULN (n=940)</th>
<th>CK&gt;2 ULN (n=532)</th>
<th>CK&gt;3 ULN (n=388)</th>
<th>CK&gt;5 ULN (n=190)</th>
<th>CK&gt;10 ULN (n=47)</th>
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<table>
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<tr>
<th>Mls occurring &gt;48hrs (n=29)</th>
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</table>

| Mls defining by CK MB elevation occurring ≤48hrs |

<table>
<thead>
<tr>
<th>Transfusion ≥2 Units</th>
</tr>
</thead>
</table>

| Intra-cerebral Haemorrhage (n=3) |

| TIMI Major |
| TIMI Major/Minor |
| Protocol Major |
| Protocol Major/Minor |

TIMI Major: n=(35)  TIMI Major/Minor: n=(157)  Protocol Major: n=(173)  Protocol Major/Minor: n=(1,321)
Liberal definition: Affects a large proportion of the population with low overall relative risk of late mortality

Stringent definition: Affects a small proportion of the population with high overall relative risk of late mortality

Relative Risk of late mortality associated with event

Absolute Proportion of patients experiencing the event

Spectrum of possible clinical event definitions

Event Definitions with high sensitivity

Event Definitions with high specificity
A: Myocardial infarction definitions and late mortality

![Graph showing percent attributable fraction and odds ratio for different levels of enzyme elevation.]

B: Bleeding definitions and late mortality

![Graph showing percent attributable fraction and odds ratio for different bleeding definitions.]

- Percent Attributable Fraction
- Odds Ratio

For A: 
- >1xULN: 2.0%
- >2xULN: 2.8%
- >3xULN: 3.5%
- >5xULN: 5.3%
- >10xULN: 7.6%

For B: 
- Protocol major/minor bleed: 1.6%
- Protocol major bleed: 2.2%
- TIMI major/minor bleed: 4.0%
- TIMI major bleed: 6.1%