Editorial

Peri-operative myocardial infarction: time for therapeutic trials

The majority of non-cardiac surgery is undertaken to extend or improve the quality of a patient’s life. It is on this background that we are slowly starting to grasp the extent and subsequent impact of a peri-operative myocardial infarction. An analysis of the PeriOperative ISchemic Evaluation (POISE) trial data suggests that peri-operative myocardial infarction is the most common cardiovascular complication following non-cardiac surgery, with an incidence of 5% in patients 45 years or older with cardiovascular risk factors [1]. Patients who suffer a peri-operative myocardial infarction have a 30-day mortality between 11.6% [1] and 21.6% [2]. Considering that over 200 million non-cardiac surgeries are performed annually worldwide, this equates to 10 million peri-operative myocardial infarctions and more than 1.1 million deaths. Together with the fact that peri-operative myocardial infarctions are commonly undiagnosed and undertreated, this represents a significant public health burden, far greater than previously appreciated.

Various efforts have been undertaken to address this problem. These range from epidemiological studies that aim to document accurately the incidence of peri-operative cardiovascular complications and associated clinical risk predictors [3], to the initiation of preventative strategies to decrease peri-operative cardiovascular complications [4–6]. In contrast there has been very little, if any, investigation into the manage-
ment of peri-operative myocardial infarction.

We systematically searched PubMed up to May 2011 for studies reporting therapeutic interventions for peri-operative myocardial infarction, using the terms 'peri(-)operative myocardial infarction' and 'treatment', and extracted all studies that reported treatment modalities in patients suffering peri-operative myocardial infarction following non-cardiac surgery. After screening 2768 abstracts, 33 studies were extracted for more detailed evaluation, of which 20 (eight case series [7–14] and 12 case reports [15–26]) were identified. Astoundingly, considering the estimated annual incidence of peri-operative myocardial infarctions, this entire cohort consists of only 89 patients. In addition, we could not find a single randomised controlled trial of therapeutic interventions for peri-operative myocardial infarction, despite randomised controlled trials for myocardial infarction dating back to the 1980s [27]. This is a damning reflection on the current state of peri-operative cardiovascular medicine.

Further, we believe that the published therapeutic options identified in our search are essentially useless in informing the treatment of peri-operative myocardial infarction. Firstly, the majority of the data are retrospective, and appear to be heavily influenced by both publication and patient selection bias. Patients identified in the search were significantly more likely than those in high-quality observational studies [1] to present with cardiac symptoms or associated haemodynamic instability (chi-squared = 16.29, p = 0.0001 and chi-squared = 154.41, p < 0.0001, respectively), with 14% of the patients we identified suffering asymptomatic myocardial infarction compared with 60% in the observational studies. As peri-operative myocardial infarction is predominantly asymptomatic [1], a fundamental problem with a reliance on retrospective studies is a disproportionate representation of symptomatic patients. It is only with systematic troponin analysis of surgical patients at risk that the true clinical picture of peri-operative myocardial infarction can be seen.

Secondly, we believe that the publications identified are biased towards patients who have had positive outcomes. This is certainly true of the reported short-term mortality of the retrieved cases which was 0% for haemodynamically stable patients, compared with a 30-day mortality of 12.5% in asymptomatic patients in the POISE study [1]. It is, however, impossible to assess whether this is the case for the reported 32.2% mortality for unstable patients in the retrieved cases, as we know of no prospective reports of the outcomes of these patients.

The applicability of the therapeutic recommendations in any of these publications, therefore, has to be questioned [7–26]. Case series and case reports lack two vital components necessary for making an informed decision. Firstly, the denominator (or number of other unreported patients who also sustained a peri-operative myocardial infarction) is unknown. This information is essential in determining whether a therapy is potentially universally effective, or possibly only appropriate for a selected patient cohort. Secondly, these case series lack a matched patient comparison group. It is for these reasons that these retrieved publications do not allow us to make any inferences about the utility of the described therapeutic intervention and the subsequent outcome following peri-operative myocardial infarction [28].

The postoperative patient is exposed to a unique environment with risk factors that include haemodynamic instability, a procoagulant milieu and surgical bleeding. The pathophysiology of the peri-operative myocardial infarction is different to the non-surgical myocardial infarction [29], where in addition to plaque rupture and myocardial oxygen supply–demand imbalances, de novo coronary thrombosis may play a key role. These factors may partly explain why the majority of peri-operative myocardial infarctions present with ST segment depression rather than ST segment elevation [1,30]. Finally, surgical bleeding presents a major hurdle for peri-operative cardiovascular medicine and management of myocardial infarction. Significant bleeding in the POISE trial was an independent predictor of myocardial infarction [1] and mortality [4], and this raises significant concerns about the appropriate use of peri-operative anticoagulants, which are at the cornerstone of the medical management of myocardial infarction. These differences between peri-operative and medical (non-surgical) myocardial infarctions make it inappropriate to adopt medical protocols and therapies for postoperative use. It is clear that the management of peri-operative myocardial infarction requires specific therapeutic investigation.

The current evidence regarding peri-operative myocardial infarction is summarised in Table 1 using the Oxford 2011 Levels of Evidence [31]. We appear to be making progress in accurately documenting the prevalence of the problem and the accuracy of diagnostic tests, as well as establishing appropriate prophylactic interventions, but we have no good evidence for the utility of peri-operative myocardial infarction therapy and/or its potential harms.

Two factors suggest that the development of an appropriate, effective therapy for peri-operative myocardial infarction could have an enormous impact on both short- and long-term patient survival. Firstly, interventional therapeutic trials are likely to show greater clinical benefit than preventative strategies [32], and secondly, medical (non-surgical) trials of myocardial infarction patients have highlighted that the success of therapeutic interventions for myocardial infarction are dependent on the type and timing of the intervention and the
dose of pharmacologic interventions [33].

It is for these reasons that we need to embark urgently on prospective randomised controlled trials of therapeutic interventions for peri-operative myocardial infarction. Presently, there is a single placebo-controlled randomised trial for vascular patients with asymptomatic isolated troponin elevation underway [34]. Studies of the management of medical (non-operative) myocardial infarction have identified a set of well-established effective interventions. Our reticence in determining their safety in peri-operative patients denies surgical patients potential benefit, and where established therapies may be inappropriate in the surgical patients, exposes them to unnecessary harm. Currently, there is also no evidence to indicate whether a conservative medical therapeutic approach or an acutely invasive coronary approach is preferable for patients with stable and unstable peri-operative myocardial infarction. Both these approaches need to be prospectively investigated. In addition, therapeutic trials should be undertaken for each of the three presentations of acute peri-operative coronary injury: i) haemodynamically stable peri-operative myocardial infarction; ii) unstable peri-operative myocardial infarction; and iii) isolated troponin elevation [2].

We can no longer continue to ignore a population of 10 million patients who subsequently have a mortality rate of over 10%. This major public health issue needs to be urgently addressed.

Acknowledgements

No external funding and no competing interests declared. BMB is supported by a Medical Research Council of South Africa self-initiated research grant. RNR is supported by a Canadian Institutes of Health Research Scholarship (the Canada-HOPE Scholarship).

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Table 1 Oxford 2011 Levels of Evidence concerning peri-operative myocardial infarction [31]

<table>
<thead>
<tr>
<th>Question</th>
<th>Level of evidence</th>
<th>Reference or examples</th>
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<tbody>
<tr>
<td>How common is the problem?</td>
<td>Step 1: local or current random sample surveys</td>
<td>VISION study currently underway [3]</td>
</tr>
<tr>
<td>Is this diagnostic test accurate? (Diagnosis)</td>
<td>Step 2: individual cross-sectional studies with consistently applied reference standard</td>
<td>VISION study [3]</td>
</tr>
<tr>
<td>What will happen if we do not add a therapy? (Prognosis)</td>
<td>Step 3: inception cohort studies</td>
<td>POISE [1], DECREASE-IV [5]</td>
</tr>
<tr>
<td>Does this intervention help? (Treatment benefits)</td>
<td>Step 4: case series</td>
<td>Outlined in this article</td>
</tr>
<tr>
<td>What are the common (and rare) treatment harms? (Treatment harms)</td>
<td>No evidence</td>
<td>Outlined in this article</td>
</tr>
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**Anaesthesia, 2011, 66, pages 1081-1087**


doi:10.1111/j.1365-2044.2011.06984.x