The treatment of perioperative myocardial infarctions following noncardiac surgery

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Abstract
Background: Perioperative myocardial infarction (PMI) is a common complication following noncardiac surgery, with a 30-day mortality of 10-20%. Effective therapeutic interventions are of public health importance.
Method: This is a systematic review, aimed to determine the evidence for therapies following PMI.
Results: A PubMed Central search up to May 2011 identified 20 case series and reports (89 patients). We extracted data on the type and timing of treatment and short-term mortality. Short-term mortality differed significantly between haemodynamically stable and unstable patients (0% and 32.2% respectively, p-value = 0.015). Significantly more haemodynamically unstable patients received acute coronary interventions (75.8% vs. 23.1%, p-value = 0.0006). Acute coronary intervention in haemodynamically unstable patients was not associated with improved short-term survival (p-value = 0.53). The high proportion of symptomatic and haemodynamically unstable patients suggests publication bias ($\chi^2 = 16.29$, p-value = 0.0001, respectively).
Conclusion: This systematic review highlights the paucity of evidence for PMI management, and the need for future prospective trials.

Introduction
Recent studies suggest that perioperative myocardial infarction (PMI) is a common complication of noncardiac surgery, with an incidence of 5% in patients who are 45 years or older, with cardiovascular risk factors. This carries a significant health burden. Therefore, efforts to accurately document the incidence of perioperative cardiovascular complications and associated clinical risk predictors, as well as to study preventative strategies to decrease perioperative cardiovascular complications, are appropriate.

We are of the opinion that there have been few, if any, studies examining therapeutic interventions for patients who have had a PMI. This is despite a reported 30-day mortality of between 11.6% and 21.6%. Medical (nonsurgical) trials of patients with myocardial infarction (MI) have highlighted the importance of both the timing and the choice of therapeutic intervention in patients with MI. Thus, through appropriate perioperative therapeutic interventions, the potential may exist for an enormous impact on both the short- and long-term survival of patients following a PMI.

The aim of this systematic review is to determine the evidence for therapeutic interventions following PMI.

Method
We conducted a systematic review of the treatment received, and associated outcomes following PMI in noncardiac surgical patients.

Study end-points
The intention was to extract data on the following:
- The treatment of PMI (medical therapy, invasive coronary intervention, or coronary artery surgical intervention)
- The timing of the intervention (acute, as part of resuscitation associated with the PMI, or delayed, following successful acute therapy for the PMI)
- The short-term (30-day or in-hospital) mortality associated with PMI in relation to the received intervention.

Study identification and selection
On 5 May 2011, a PubMed search was conducted for the period 1966-2011. The terms used in the search strategy were “perioperative myocardial infarction” and “treatment.”
The abstracted data were screened and excluded non-eligible studies. All studies that reported treatment modalities used in patients suffering PMI after noncardiac surgery were included. Non-human studies, cardiac surgical studies, paediatric studies, reviews, comments, and letters to the editor, were excluded. Studies listing PMI or raised troponin levels as outcomes, but not detailing treatment, were also excluded, as were studies that reported on treatment of MI in the nonsurgical (medical) population, or outside of the perioperative period. Within eligible studies, individual patients were excluded from the analysis if they did not experience a PMI, e.g. postoperative angina or preoperative MI.

**Data extraction**

Data on the treatment modality administered to patients with PMI, the timing of the intervention (acute or delayed), haemodynamic stability of the patients following PMI, and the short-term (30-day or in-hospital) mortality, were extracted. Where possible, demographic data, including age, gender, known cardiovascular risk factors, and preoperative cardiovascular medications, were extracted. Citations were independently screened, data abstracted, and methodological quality assessed, using a standardised data extraction sheet. Any disagreements were resolved. In cases where data required clarification, or were not presented in the publication, an attempt was made to contact the original authors.

The extracted data only allowed comparison of conservative and invasive coronary therapies and associated outcomes using χ²-square testing. Publication bias regarding outcomes was assessed by comparing observed vs. expected frequencies using χ²-square testing. All statistical analyses were conducted using GraphPad® software online calculators.

**Results**

The PubMed search identified 2 766 studies between 1966-2011, and an additional two potentially eligible studies were identified from one of the reviewer's own records. Initial abstract screening eliminated 2 735 studies. The remaining 33 studies were extracted for more detailed evaluation, following which a further 13 studies were deemed unsuitable for inclusion. Twenty publications fulfilled our criteria for analysis (see Figure 1).

From the 20 publications finally selected, 89 patients with PMI were identified, as included in eight case series and 12 case reports. The type of surgery, patient demographics, co-morbidities and preoperative medication are tabulated in Table I.

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**Figure 1**: Flowchart of systematic review process
### Table I: Characteristics of the included studies

| References          | Type of surgery                              | PMI\(^a\) (n) | Age     | Sex | Co-morbidities          | Preoperative medications                      |
|---------------------|----------------------------------------------|----------------|---------|-----|-------------------------|-----------------------------------------------|
| Medina-Polo et al\(^{22}\) | Simultaneous pancreas-kidney transplantation | 1              | 66      | Not reported | DM,\(^1\) HT\(^1\) | Not reported                                  |
| Lee et al\(^{18}\)  | Neurosurgery (lumbar fusion)                 | 6              | 62      | Male | DM, HT                  | Not reported                                  |
|                     |                                              | 70             | Male    | HT, CVA\(^1\) | Not reported                        |
|                     |                                              | 67             | Female  | HT  | Not reported             |                                               |
|                     |                                              | 66             | Male    | HT  | Not reported             |                                               |
|                     |                                              | 62             | Female  | HT  | Not reported             |                                               |
|                     |                                              | 64             | Male    | DM, HT | Not reported            |                                               |
| Chang et al\(^{13}\) | Vascular                                     | 2              | Not reported | Not reported | Not reported | Not reported                                  |
| Chang et al\(^{15}\) | Head and neck                                | 7              | 66      | Male | Not reported             | Not reported                                  |
|                     |                                              | 73             | Male    | Not reported | Not reported                        |
|                     |                                              | 69             | Male    | Not reported | Not reported                        |
|                     |                                              | 81             | Female  | Not reported | Not reported                        |
|                     |                                              | 67             | Female  | Not reported | Not reported                        |
|                     |                                              | 85             | Female  | Not reported | Not reported                        |
|                     |                                              | 64             | Male    | Not reported | Not reported                        |
| Berger et al\(^8\)  | Abdominal (14), orthopaedic (11), vascular (11), urology (5), neurological (3), other (4) | 41             | 70 (± 7.7) | Male (65\%) | HT (73\%), CAD (48\%), DM (29\%) | CCB\(^e\) (29\%), aspirin (27\%) |
| Malek et al\(^{20}\) | Urology                                       | 1              | Not reported | Not reported | Not reported | Not reported                                  |
| Mangano et al\(^{11}\) | Thoracic (1), vascular (7), neurological (1), orthopaedic (1) | 10             | 69 ± 9  | Male | CAD (all) | Not reported                                  |
| Gewertz et al\(^{14}\) | Vascular                                     | 2              | Not reported | Not reported | Not reported | Not reported                                  |
| Ito et al\(^{18}\)  | Vascular                                     | 1              | 66      | Male  | HT, IGT, no CAD         | Intravenous heparin (stopped 12 hours prior to surgery) |
| Uchida et al\(^{17}\) | Neurosurgery                                 | 1              | 80      | Female | PVD                   | Not reported                                  |
| Mottard et al\(^{13}\) | Orthopaedic                                  | 1              | 72      | Male  | PVD                   | Statin, warfarin (changed to LMWH\(^f\)) |
| Schmitto et al\(^{25}\) | Obstetric                                     | 1              | 22     | Female | None                  | Not reported                                  |
| Ishiwhita et al\(^{17}\) | Neurosurgery                                 | 1              | 68      | Female | None                  | Not reported                                  |
| Fippel et al\(^{13}\) | Orthopaedic                                   | 1              | 21     | Male  | None                  | None                                          |
| Takahashi et al\(^{18}\) | Vascular                                     | 1              | 67     | Male  | Aortic valve replacement | Warfarin until 3 days preoperatively |
| Corda et al\(^{12}\)  | Vascular                                     | 1              | 84     | Female | HT, RAS, PVD         | CCB                                           |
| Lim et al\(^{17}\)   | General surgery                               | 1              | 70     | Male  | None                  | Not reported                                  |
| Winship et al\(^{28}\) | Bilateral adrenalectomy                       | 1              | 64     | Male  | Conn's syndrome, HT, CAD, previous CABG\(^h\) | Spironolactone, captopril, amlodipine, terazosin, steroids |
| Ishiyama, Tsujitou\(^{15}\) | Vascular                                     | 1              | 73     | Male  | HT, CAD, renal dysfunction | Dialysis                                      |
| Roth et al\(^{14}\)   | Orthopaedic                                   | 1              | 47     | Male  | DM, HT                 | Propranolol, chloropropamide, enalapril       |

\(^a\) = perioperative myocardial infarction, \(^b\) = diabetes mellitus, \(^c\) = hypertension, \(^d\) = cerebrovascular accident, \(^e\) = calcium channel blocker, \(^f\) = coronary artery disease, \(^g\) = myocardial infarction, \(^h\) = congestive cardiac failure, \(^i\) = impaired glucose tolerance, \(^j\) = peripheral vascular disease, \(^k\) = low-molecular-weight heparins, \(^l\) = renal artery stenosis, \(^m\) = coronary artery bypass graft
Demographic data, co-morbidities and preoperative medical therapy were not reported for a number of the patients. Of the 89 patients, the most commonly performed surgeries were vascular in 29.2% (n = 26), orthopaedic in 16.8% (n = 15), abdominal in 15.7% (n = 14), and neurosurgical in 13.4% (n = 12). Other surgeries included head and neck (n = 7), urological (n = 6), “other” (n = 5), transplant (n = 1), general surgery (n = 1), obstetric (n = 1) and thoracic (n = 1).

The presentation of the PMI, haemodynamic stability, time to intervention, type of therapy (medical and haemodynamic support), coronary revascularisation, and patient outcomes, are tabulated in Table II.

The presentation of the PMI, the presence of haemodynamic instability, the short-term mortality of the patients in the included studies, and the expected 30-day mortalities from a previous meta-analysis and randomised controlled trial, are tabulated in Table III. A single study is not included in this table as we had insufficient data to classify outcomes, hence the two patients from this study were excluded, leaving 87 patients for analysis. Of these 87 patients, PMI presented as asymptomatic or unspecified in 12 patients (13.8%), while 75 patients were symptomatic. Of these 75 patients, 13 (14.9%) were haemodynamically stable, with no mortality in this group. The remaining 62 patients (69.7%) were haemodynamically unstable, and had a short-term mortality of 32.2%. Short-term mortality differed significantly between haemodynamically stable and unstable patients (0% and 32.2% respectively, p-value = 0.015).

There were four patients in this series, two with preoperative myocardial infarction, one with intraoperative myocardial infarction, and one with postoperative myocardial infarction. Three of the four patients demised. The fourth patient was left severely disabled. We could not determine which of the patients demised.

Patient management differed significantly according to haemodynamic presentation (see Table IV). Haemodynamically unstable patients received significantly more acute coronary interventions than haemodynamically stable patients [47/62 (75.8%) vs. 3/13 (23.1%) respectively, p-value = 0.0006]. However, within the haemodynamically unstable patient group, the short-term mortality rates did not differ between those who received acute coronary intervention vs. those who did not, namely [14/47 (29.8%) and 6/15(40%), respectively (p-value = 0.53). The case series of Chang et al was excluded from this analysis as we could not determine which of the patients with PMI had died, thus the analysis included 87 of the 89 identified patients for this review.

We found evidence of potential publication bias. The proportion of asymptomatic patients presented in this review is significantly less than the expected 35% (p2 = 16.29, p-value = 0 < 0001). The proportion of haemodynamically unstable patients is also significantly more than the expected 18% (p2 = 154.41, p-value < 0.0001).

**Discussion**

We found no completed randomised controlled trials of therapeutic interventions for PMI, despite the fact that in nonsurgical patients, randomised controlled trials for MI date back nearly 30 years. This would be understandable if PMI treatment was considered to be similar to that of a nonsurgical MI, and hence therapies would be expected to have similar efficacies between medical and surgical patients. However, significant differences clearly exist between these two patient cohorts. In particular, the postoperative patient is exposed to an environment associated with haemodynamic instability, procoagulation, sympathetic stress, and potential bleeding and hypoxia. The pathophysiology of the PMI may also be slightly different to the nonsurgical MI. These factors may explain why the majority of PMIs present with ST segment depression, rather than ST segment elevation that is characteristic of medical patients. Finally, while anticoagulants are used extensively in managing nonsurgical MI, in the perioperative patient, this raises concerns of significant bleeding. Therefore, it is likely that the management of PMI requires specific therapeutic investigation and therapies.

We believe that the studies identified in this systematic review should not guide therapeutic management of PMI patients, as it is predominantly retrospective, and appears to be heavily influenced by both publication and patient selection bias. Therefore, the bias in these data would seriously affect the reported outcomes associated with any of the interventions reported. Secondly, the majority of patients identified in this systematic review presented with symptomatic PMI, either through patient cardiac symptoms, or associated haemodynamic instability. Therefore, this review does not reflect the majority of patients with a PMI. The PeriOperative IShemic Evaluation (POISE) trial, with high quality observational data with respect to PMI, showed that > 60% of patients with a PMI are asymptomatic. In the POISE trial, only 19% of the patients with a PMI developed congestive cardiac failure.

In our systematic review, > 80% of patients with a PMI had haemodynamic instability (see Table III). This suggests that data reported in the literature is biased towards critically ill PMI patients. It is likely that identified publications are also biased towards patients who had positive outcomes. We...
### Table II: Presentation, diagnosis and management of perioperative myocardial infarctions

| References          | PMI presentation | Time of first intervention | Medical therapy | Haemodynamic therapy | CR and timing | Outcome          |
|---------------------|------------------|-----------------------------|-----------------|----------------------|---------------|------------------|
| **Case series**     |                  | Time | Diagnosis | Haemodynamics | Time | Diagnosis | Haemodynamics | Medical therapy | Haemodynamic therapy | CR and timing | Outcome |
| Medina-Polo et al.  | Perioperative    | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Survived |
| Lee et al.          | Perioperative    | Day 3 | Abdominal pain | Stable | Delayed | Conservative | Not reported | No | Survived |
|                     |                  | Day 1 | Typical symptoms | Stable |             | Conservative | Not reported | No | Survived |
|                     |                  | Day 0 | Typical symptoms | Stable |             | Conservative | Not reported | No | Survived |
|                     |                  | Day 1 | Typical symptoms | Stable |             | Conservative | Not reported | PTCA after failed conservative therapy | Survived |
|                     |                  | Day 0 | Typical symptoms | Stable |             | Conservative | Not reported | No | Survived |
|                     |                  | Day 7 | Dyspnoea, cyanosis, diaphoresis | Stable | Delayed | Conservative | Not reported | CABG after failed conservative therapy | Survived |
| Chang et al.        | Intraoperatively (1), postoperatively (1) | Abrupt onset of shock | Unstable | Emergent | Not reported | IABP or percutaneous pacing | Emergency PCI in both | Death or severe disability |
|                     |                  | Day 1 | ECG, troponins | Unstable | Undetermined | Aspirin | CABG day 2 | Discharged |
|                     |                  | Day 3 | ECG, troponins | Unstable | Undetermined | Aspirin | CABG day 7 | Discharged |
|                     |                  | Day 1 | ECG, troponins | Unstable | Undetermined | Aspirin, digoxin, diuretics, antihypertensives | None | Discharged |
|                     |                  | Day 3 | ECG, troponins | Stable | Undetermined | Aspirin, digoxin, diuretics | None | Discharged |
|                     |                  | Days 3 and 15 | ECG, troponins | Stable | Undetermined | Aspirin, digoxin, heparin, antihypertensives | None | Died day 99 |
|                     |                  | Day 8 | ECG, troponins | Unstable | Undetermined | Aspirin, heparin, diuretics, antihypertensives | PCI | Died day 74 |
| Berger et al.       |                  | 1.6 (± 1.9) | Typical symptoms | ECG | Shock (21/48) | 11.1 h (± 17.4) for angiography | Not reported | 21/48 IABP, 16/48 pacing | PTCA 41, CABG 2 | 31/48 survived |
| Malek et al.        | Perioperatively  | Not reported | Not reported | Not reported | Not reported | Conservative | Not reported | No | Not reported |
| Mangano et al.      |                  | Day 3 | ECG, CKMB | Not reported | Not reported | Not reported | Not reported | No | Died day 8 |
|                     |                  | Day 15 | ECG, CKMB | Not reported | Not reported | Not reported | Not reported | No | Died day 16 |
|                     |                  | Day 2 | ECG, CKMB | Not reported | Not reported | Not reported | Not reported | No | Died day 43 |
|                     |                  | Day 29 | ECG, CKMB | Not reported | Not reported | Not reported | Not reported | No | Noncardiac death day 69 |
|                     |                  | Day 2 | ECG, CKMB | Not reported | Not reported | Not reported | Not reported | No | Died day 73 |
### Table II: Presentation, diagnosis and management of perioperative myocardial infarctions

| References | PMI presentation | Time of first intervention | Medical therapy | Haemodynamic therapy | CRP and timing | Outcome |
|------------|------------------|---------------------------|-----------------|----------------------|----------------|---------|
|            |                  |                           |                 |                      |                |         |
| Case reports |                 |                           |                 |                      |                |         |
| Ito et al16 | Intraoperatively | ECG changes, RWMA's | Unstable       | Immediate            | ISDN, lignocaine for VT1 | No       | Survived |
| Uchida et al27 | Intraoperatively | VFm                      | Unstable       | Immediate            | Nicorandil, nitrates, calcium antagonists, heparin | Cardioversion, catecholamines | No       | Discharged |
| Mottard et al18 | On completion of surgery | ECG changes | Unstable       | Immediate            | Aspirin, clopidogrel, ACE-I (later) | Ephedrine, atropine, adrenaline, IABP | PCI      | Survived |
| Schmitto et al22 | Intraoperatively, on administration of oxytocin | Chest pain, troponins | Unstable       | Immediate haemodynamic support. Later, medical | Metoprolol, midazolam | Ephedrine, colloid | No       | Survived |
| Iwashita et al17 | 2 hours postoperatively | ECG changes, CNS symptoms | Unstable       | Immediate            | Not reported       | Not reported | Emergency PCI | Survived |
| Fippel et al (abstract)13 | Day 1, day 6 | Not reported | Unstable       | Immediate            | Thrombolysis       | IABP      | PTCA 'after resuscitation' | Not reported |
| Takahashi et al20 | 6 hours postoperatively | VF, angiography | Unstable       | Immediate            | Not reported       | Not reported | PTCA | Not reported |
| Corda et al23 | Intraoperatively (post-induction) | RWMA | Stable         | Immediate            | Nitroglycerin, metoprolol, milrinone | No       | No       | Survived |
| Lim et al19 | Day 2 | ECG, echo, cardiac enzymes | Unstable       | Preoperatively       | Not reported       | Dopamine, dobutamine, noradrenaline, IABP, Finally, vasopressin | No       | Survived |
| Winship et al26 | Day 4 | Chest pain and cardiac arrest | Unstable       | Immediate            | Not reported | Not reported | No | Died 24 hours post-MI |
| Ishiyama, Tsujimoto21 | Preoperatively | Chest pain, ECG | Unstable       | Immediate            | Not reported       | Adrenaline, dopamine, dobutamine, lignocaine | No | Died day 29 |
| Roth et al20 | Intraoperatively | ECG changes, echo | Stable         | Immediate            | Nitroglycerin, verapamil, esmolol, morphine | Neosynephrine, lignocaine for VPCs | PTCA within 30 min |

a = perioperative myocardial infarctions, b = coronary revascularisation, c = typical symptoms were defined as chest pain, dyspnea, diaphoresis, and palpitations, d = percutaneous transluminal coronary angioplasty, e = coronary artery bypass grafting, f = intra-aortic balloon pump, g = percutaneous transluminal intervention, h = echo echocardiography, i = creatine kinase MB fraction, j = regional wall motion abnormalities, k = isosorbide dinitrate, l = ventricular tachycardia, m = ventricular fibrillation, o = central nervous system, p = post myocardial infarction, q = ventricular premature contractions
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Table III: Short-term (in-hospital and 30-day) mortality associated with the type of presentation of perioperative myocardial infarctions (PMI)

| Category                        | Presentation n (%) | Observed short-term mortality n (%) | Expected 30-day mortality (%) |
|---------------------------------|--------------------|-------------------------------------|------------------------------|
| Unspecified or asymptomatic PMI | 12 (13.8)          | 3 (25)                              | 11.6-21.6*                   |
| Haemodynamically stable symptomatic PMI | 13 (14.9)      | 0 (0)                               | 11.6-21.6*                   |
| Haemodynamically unstable PMI   | 62 (69.7)          | 20 (32.2)                           | No known reports             |

Table IV: Acute invasive coronary interventions associated with the presentation of a perioperative myocardial infarction

| Presentation       | Medical therapy only | Invasive coronary intervention |
|--------------------|----------------------|-------------------------------|
| Haemodynamically stable | 10                   | 3                             |
| Haemodynamically unstable | 15                  | 47                            |

*p-value = 0.0006
Chang et al\(^\text{10}\) is excluded from this analysis.

Conflict of interest

No external funding and no competing interests are declared.

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