

Causes and prevention of postoperative myocardial injury

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Abstract

Over the past few years non-cardiac surgery has been recognised as a serious circulatory stress test which may trigger cardiovascular events such as myocardial infarction, in particular in patients at high risk. Detection of these postoperative cardiovascular events is difficult as clinical symptoms often go unnoticed. To improve detection, guidelines advise to perform routine postoperative assessment of cardiac troponin. Troponin elevation – or postoperative myocardial injury – can be caused by myocardial infarction. However, also non-coronary causes, such as cardiac arrhythmias, sepsis and pulmonary embolism, may play a role in a considerable number of patients with postoperative myocardial injury. It is crucial to acquire more knowledge about the underlying mechanisms of postoperative myocardial injury because effective prevention and treatment options are lacking. Preoperative administration of beta-blockers, aspirin, statins, clonidine, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, and preoperative revascularisation have all been investigated as preventive options. Of these, only statins should be considered as the initiation or reload of statins may reduce the risk of postoperative myocardial injury. There is also not enough evidence for intraoperative measures such blood pressure optimisation or intensified medical therapy once patients have developed postoperative myocardial injury. Given the impact, better preoperative identification of patients at risk of postoperative myocardial injury, for example using preoperatively measured biomarkers, would be helpful to improve cardiac optimisation.

Keywords

Postoperative period, troponin, myocardial ischaemia, aetiology, prevention and control

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Introduction

Non-cardiac surgery poses a serious circulatory stress test and may trigger cardiovascular events such as myocardial infarction, in particular in patients at high risk.^{1–4} However, ischaemic electrocardiographic signs may be subtle and angina is often masked by strong analgesics, which leads to under-recognition of myocardial injury.^{2–4} To improve detection, routine postoperative assessment of cardiac troponin was recommended by the 2014 European Society of Cardiology (ESC)/European Society of Anaesthesiology (ESA) guidelines.⁵ This notion was based on troponin's strong predictive value for postoperative mortality in a large variety of patients undergoing non-cardiac surgery.^{4,6–14}

Worldwide implementation of routine postoperative troponin monitoring, however, has proved difficult due

to a number of factors. First, clear management strategies for patients with troponin elevation – or postoperative myocardial injury (PMI) – do not exist. Another

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relevant factor is that PMI does not always imply myocardial infarction.^{15–18} Indeed, only 14–40% of the patients with PMI fulfil the criteria of a myocardial infarction according to the third universal definition, and obstructive coronary artery disease (CAD) is absent in almost 30% of patients with PMI.^{11,17,19–21} This highlights the potential relevance of non-coronary triggers of PMI and the challenges regarding adequate patient management. More knowledge about the underlying causes of PMI is needed to improve the management and ultimately the outcome of patients with PMI. In this paper we will elaborate on the aetiology of PMI and discuss its potential prevention and management strategies.

Detection of PMI

The 2014 ESC/ESA guidelines recommend to consider routine monitoring of troponin in the first days after major non-cardiac surgery to detect PMI in high-risk patients (i.e. patients with impaired exercise intolerance or with a revised cardiac risk index (a clinical risk index used to assess the risk of major postoperative cardiac events) value >1 for vascular surgery and >2 for non-vascular surgery).⁵ According to the guidelines both troponin T and troponin I can be used for routine monitoring, as is common in clinical practice.⁵ As far as we know, no direct comparison has been made between both troponin assays in the postoperative setting. A prospective multicentre study in patients presenting to the emergency room with acute chest pain showed that both troponin T and I have high diagnostic and prognostic accuracy.²² However, the time since the onset of symptoms did affect the accuracy of the tests: troponin I seemed to be superior in early presenters, whereas troponin T seemed to be superior in late presenters.²² As troponin is used as a screening tool in patients without symptoms in the postoperative monitoring setting, there is no evidence suggesting that one of the assays should be preferred above the other. Furthermore, the introduction of highly sensitive troponin assays increased the sensitivity in the early diagnosis of myocardial infarction in the non-operative setting.²³ Recent data suggest that using highly sensitive troponin assays may also improve the diagnosis of perioperative myocardial infarction.²⁴ However, comparison with preoperative troponin levels seemed to contribute even more to the improvement of perioperative myocardial infarction diagnosis.

The 2014 ESC/ESA guidelines do not define a threshold that should be used in the postoperative setting. Hospitals should therefore use the clinical threshold applied in their clinic, which is usually defined as a value exceeding the 99th percentile of a normal reference population as recommended in the third universal definition of myocardial infarction.²⁰

Aetiology

PMI is believed to be primarily the result of type I or type II myocardial ischaemia.^{1,3,17,25} Type I ischaemia is caused by acute coronary thrombosis due to rupture of a vulnerable plaque and can be triggered by perioperative factors such as inflammation, hypercoagulability and blood pressure fluctuations during surgery.^{3,19,26} In type II myocardial ischaemia, factors such as hyper or hypotension, tachycardia and anaemia result in a (more generalised) oxygen supply–demand mismatch (Figure 1, left panel).^{3,19,26}

Until recently, it was assumed that PMI mainly occurs in patients with CAD. However, this assumption was contradicted by a prospective cohort study in 955 non-cardiac surgery patients who underwent preoperative coronary computed tomographic angiography (CCTA), which showed that 20 of 71 postoperative myocardial infarctions (28%) occurred in patients without obstructive CAD.²¹ Similar results were found in a pilot study in elderly patients without a history of ischaemic heart disease undergoing non-cardiac surgery, in which only half of the patients with PMI had obstructive CAD on postoperative CCTA.²⁷ One should note that CCTA is inferior to fractional flow reserve in regard to the determination of the significance of a coronary stenosis, yet such invasive measurements are often not feasible in the postoperative phase. CCTA therefore appears to be a good alternative. Furthermore, it should be noted that the absence of obstructive CAD does not exclude plaque rupture as the cause of PMI, because type I myocardial ischaemia can also occur in mild obstructive lesions.²⁸ A normal CCTA also does not exclude microvascular damage as the cause of PMI. Microvascular damage, for example, can occur in patients with hypertension in whom the chronic hypertensive condition has caused structural and functional coronary microvascular abnormalities such as ventricular hypertrophy and endothelial dysfunction.²⁹ However, the fact that obstructive CAD on CCTA was absent in 30–50% of patients with PMI in those two studies suggests that non-coronary causes, such as cardiac arrhythmias, sepsis and pulmonary embolism, also play a role in a significant proportion of patients with PMI (Figure 1, right panel).^{11,26,30,31} This notion was underlined by Noordzij and colleagues, who reported that non-cardiac complications such as respiratory insufficiency, sepsis and bleeding were associated with a postoperative troponin increase of over 100% compared to preoperative baseline measurements in patients at risk of CAD.³²

A potentially relevant factor in the recognition of the underlying pathology of PMI (and consecutive treatment) may lay in peak troponin concentrations. It has been hypothesised that major postoperative troponin elevations reflect ischaemic cardiac damage and

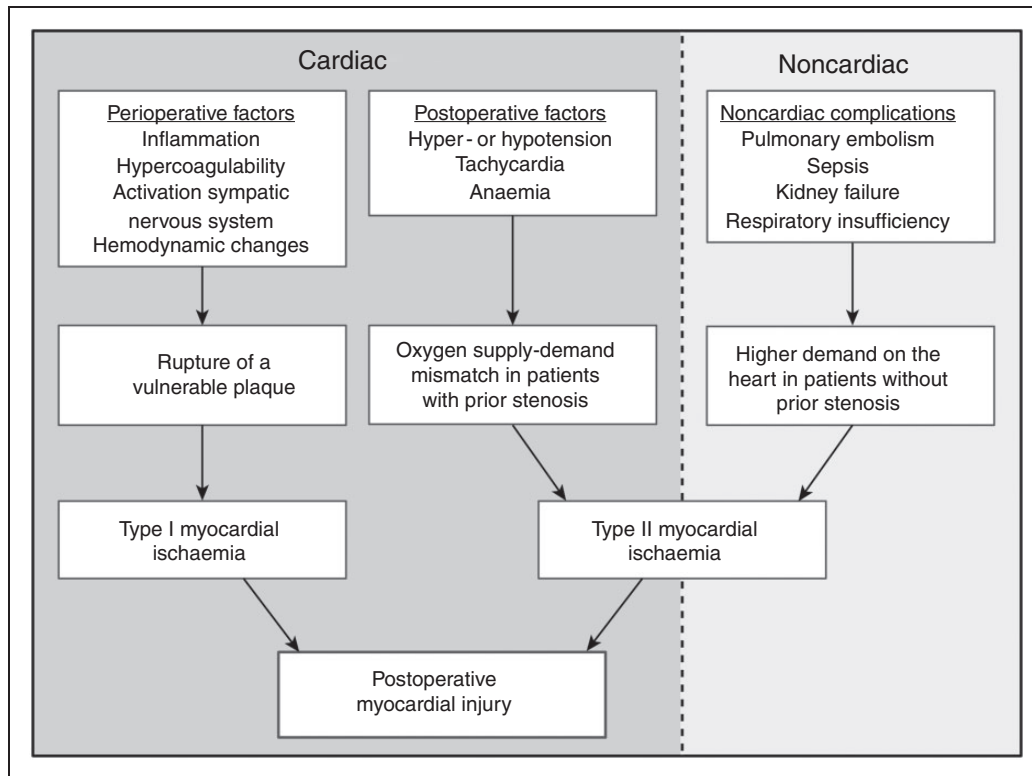


Figure 1. Different pathways leading to postoperative myocardial injury (PMI) including cardiac causes (left panel) and non-cardiac causes (right panel).

complications, whereas minor postoperative troponin elevations typically reflect non-cardiac complications with only mild effects on the myocardium.^{33,34} Minor troponin elevations, however, still strongly predict mortality.^{6,7,12} An example of a non-cardiac complication with cardiac implications is pulmonary embolism, which places a high demand on the myocardium due to hypoxia, hypotension and increased right ventricular pressures.^{35,36} In this, it should be noted that troponin is a strong independent predictor of mortality in patients with pulmonary embolism in the emergency department.^{35,36} We found central or segmental pulmonary embolisms in approximately one third of elderly patients with PMI after non-cardiac surgery compared to 20% in patients without postoperative troponin elevation.²⁷ Hence, not only myocardial infarction, but also other serious yet treatable postoperative complications can be recognised by troponin monitoring. Moreover, excessive emphasis on myocardial ischaemia may lead to failure of recognition of these non-coronary causes of PMI.

Prediction

Clinical risk indices, such as the revised cardiac risk index, are recommended for perioperative risk stratification.⁵ At present, electrocardiography (ECG) and

additional imaging are only indicated in patients undergoing high-risk surgery or in the presence of risk factors.⁵ Echocardiography may, for example, be considered for patients undergoing high-risk surgery, because echocardiogram characteristics including left ventricular dysfunction and heart valve abnormalities are independent predictors of adverse cardiovascular events after non-cardiac surgery.^{5,37} It should be noted that additional imaging tests should only be performed if results are likely to influence perioperative management.

Preoperative cardiac biomarkers also convey strong predictive value for postoperative myocardial infarction and mortality.^{38–40} In a retrospective study among patients undergoing non-emergent non-cardiac surgery, the mortality risk was found to be related to both the magnitude of preoperative troponin elevation and the time between peak troponin levels and surgery.⁴¹ Moreover, preoperative B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are also shown to be independent predictors of PMI and mortality after non-cardiac surgery.^{39,40} Elevated BNP levels are a marker of increased filling pressures and could indicate a potential benefit of preoperative cardiac optimisation. Preoperative troponin and/or NT-proBNP monitoring may therefore lead to changes in patient management, but may also contribute to knowledge about the pathophysiology of PMI.

The difference between pre and postoperative troponin levels, possibly combined with NT-proBNP levels, may help to distinguish between different causes of PMI.

Other interesting biomarkers for the future are markers of inflammation, because inflammatory changes within atherosclerotic plaques play an important role in the progression of atherosclerosis and plaque destabilisation.⁴² The proinflammatory lipoprotein-associated phospholipase A2 (Lp-PLA2) has for example been associated with the risk of cardiovascular events and plaque stability.^{43–45} Lp-PLA2 or other proinflammatory biomarkers might therefore be useful to detect patients with vulnerable plaques in the future.

Prevention

Perioperative medication

The treatment cornerstones of CAD are beta-blockers, aspirin and statins.⁴⁶ These drugs were also the first to be tested in preoperative risk reduction for PMI, yet their efficacy was limited and not without risks. For instance, the modest protective effect of beta-blockers regarding perioperative non-fatal myocardial infarction was hampered by an increased risk of stroke, hypotension and most importantly, mortality (relative risk (RR) 1.3, 95% confidence interval (CI) 1.0–1.6).^{47,48} It should be noted that beta blockade was initiated in high dosages and shortly before surgery, while for example it is recommended to start beta-blockers at least one week before surgery in reducing postoperative atrial fibrillation risk.⁴⁹ The efficacy of aspirin was assessed in the POISE-2 trial, which showed no significant difference in death and non-fatal myocardial infarction between aspirin and placebo treatment (hazard ratio (HR) 0.99, 95% CI 0.86–1.15). The risk of major bleeding, however, was increased in the aspirin group (HR 1.23, 95% CI 1.01–1.49).⁵⁰ The perioperative use of low-dose clonidine – an α_2 -adrenergic agonist that reduces blood pressure by inhibiting sympathetic outflow – was also studied in the POISE-2 trial, and did not prove beneficial for the combined endpoint of death and non-fatal myocardial infarction either (HR 1.08, 95% CI 0.93–1.26).⁵¹

Statins may be more promising to prevent PMI. A meta-analysis reported a reduced incidence of mortality (RR 0.5, 95% CI 0.3–0.9) and myocardial infarction (RR 0.5, 95% CI 0.4–0.8) after non-cardiac surgery in statin-naïve patients who were randomly assigned to receive statins compared to placebo.⁵² Due to a limited number of studies and patients at that time, there were insufficient data for clear recommendations. The VISION study, a large cohort study published in 2016, showed similar results; preoperative statin therapy was independently associated with a lower risk of

cardiovascular outcomes at 30 days among patients undergoing non-cardiac surgery (RR 0.8, 95% CI 0.7–0.9).⁵³ The initiation of statins in statin-naïve patients should therefore be considered in high-risk patients, for example those undergoing vascular surgery.⁵

In addition to the initiation of statins, reload therapy with high-dose statin in long-term statin users may also reduce cardiovascular events after surgery because of rapid anti-inflammatory and antithrombotic properties and plaque stabilising effects.⁵⁴ A recent randomised controlled trial (RCT) showed that preoperative rosuvastatin reload therapy (the administration of high-dose rosuvastatin 2 hours before surgery) decreased the incidence of cardiovascular events after non-cardiac emergency surgery compared to placebo in patients with long-term statin therapy and stable CAD (3.6% vs. 8.0%, $P=0.03$).⁵⁵ It would be interesting to see whether this association is also true for patients undergoing non-emergency surgery and what the effect of reload therapy would be on overall mortality.

Angiotensin-converting enzyme (ACE) inhibitors are thought to preserve organ function independently of their blood pressure-lowering effect. However, both a large cohort study and recent meta-analysis found no evidence to support that perioperative ACE inhibitors or angiotensin receptor blockers (ARBs) can prevent cardiovascular events after surgery.^{56,57} Furthermore, withholding ACE inhibitors or ARBs 24 hours before surgery in long-term users decreases intraoperative hypotension and may be associated with a lower risk of the composite outcome of all-cause death, stroke or myocardial injury (RR 0.82, 95% CI, 0.70–0.96).^{58,59} Perioperative ACE inhibitor/ARB cessation could therefore be useful, which should be assessed in future trials. In the meantime, continuation of these drugs during the 24 hours preceding surgery should be carefully considered.⁵

Preoperative revascularisation

Preoperative revascularisation was first investigated in the CARP trial, which showed no significant effect on long-term mortality in patients with stable angina and significant CAD undergoing vascular surgery (RR 1.0, 95% CI 0.7–1.4).⁶⁰ However, patients with significant left main stenosis were excluded in that study. A more recently performed RCT in asymptomatic patients without a history of CAD undergoing carotid endarterectomy investigated the effect of coronary angiography followed by selective revascularisation on the incidence of myocardial infarction. This strategy significantly reduced the incidence of late myocardial infarction (HR 0.1, 95% CI 0.02–0.3).⁶¹ All patients received life-long dual antiplatelet therapy after discharge,

but it should be noted that patients who had undergone preoperative revascularisation received dual antiplatelet therapy perioperatively, whereas all other patients underwent surgery under single antiplatelet therapy. The effect found in this study might therefore be partly explained by the difference in antiplatelet regimes between groups. Concluding, up to now there is not enough evidence to perform (selective) preoperative revascularisation, yet one should note that evidence on new generation stents is absent. It would be interesting to use fractional flow reserve measurements in future studies to determine the influence of flow-limiting lesions on PMI and other outcomes.

Preoperative exercise training

Preoperative exercise training may be of interest in the prevention of PMI because it has been associated with a reduced risk of postoperative complications in both cardiac and non-cardiac settings.^{62–64} However, large RCTs with standardised training programmes are needed to confirm current evidence and to identify which type of exercise training works best for which patients.^{63,64}

Blood transfusion

Decreased postoperative haemoglobin levels are associated with higher complication and mortality rates.^{65–67} However, this does not necessarily imply that more accessible blood transfusions will improve cardiovascular outcomes and mortality rates. Indeed, no difference in 60-day survival, 3-year survival and cause of death was found in a RCT comparing a restricted blood transfusion strategy (maintain haemoglobin ≥ 80 g/L; 5.0 mmol/L) with a liberal strategy (maintain haemoglobin ≥ 100 g/L; 6.3 mmol/L) after hip surgery in elderly patients with high cardiovascular risk.^{68,69} Although blood transfusion may be beneficial for some patients, the benefits of blood transfusion probably do not outweigh the risks in asymptomatic patients. A restricted strategy, i.e. restriction of transfusions to patients with symptoms or with haemoglobin levels below the threshold of 80 g/L, is therefore recommended.⁷⁰

Intraoperative measures

In the intraoperative period the patient is very closely monitored, which creates opportunities for preventive interventions. For example, blood pressure optimisation may be relevant, as the results of recent cohort studies suggest that intraoperative hypotension is associated with PMI.^{71–73} However, it remains uncertain whether this is a causal association. The same goes

for intraoperative arrhythmias.^{3,71} Furthermore, medications targeting blood pressure and heart rate also have their side effects. Goal-directed therapy by cardiac output-guided haemodynamic therapy has been investigated previously, but the frequency of myocardial injury was not affected in a RCT among patients undergoing gastrointestinal surgery.⁷⁴ Concluding, so far there are no evidence-based intraoperative measures to reduce the incidence of PMI.³⁴

Management of patients with PMI

While several studies have addressed the preventive measures of PMI, only a few studied treatment strategies. Intensified medical therapy (i.e. platelet inhibitors, beta-blockers, statins and/or ACE inhibitors) was reported to improve 12-month mortality in patients with PMI after vascular surgery in a retrospective cohort study (HR 2.80, 95% CI 1.05–24.2 for not receiving intensified therapy).⁷⁵ This finding, however, was not reproduced in a RCT of 70 patients with PMI after emergency orthopaedic surgery, in which cardiological care (consisting of admission to a coronary care unit with 24 hours telemetry and assessment by a cardiologist) did not improve mortality after one year (17% in both cardiological care and standard care groups).⁷⁶ The relative inefficacy of such intensified cardiac monitoring may be attributable to underlying pathologies that do not respond to improved cardiac monitoring (e.g. sepsis, acute kidney injury or pulmonary embolism) or the inevitability of minor cardiac injury in high-risk patients who are required to undergo surgery. Indeed, a recent observational study showed that cardiac intervention was initiated in only 38% of patients with PMI after major non-cardiac surgery.¹¹ This may also reflect the absence of a standardised treatment protocol. We propose routine follow-up focused on both cardiac and non-cardiac complications, including a history, physical examination and ECG in all patients with PMI. In this, heart rate variability, indicating stress situations, is a very simple but valuable diagnostic tool. ECGs might show abnormalities indicative of myocardial ischaemia including new Q-waves or ST-segment deviations,²⁰ but they might also point towards other conditions such as arrhythmias and pulmonary embolisms.^{26,35} Additional biomarkers and/or cardiopulmonary imaging including echocardiography should be considered to improve management in patients in whom the pathophysiology of PMI is uncertain.

Current guidelines

As mentioned above, the 2014 ESC/ESA guidelines recommend to consider routine troponin monitoring in

Table 1. Summary of main findings.**Underlying mechanisms of PMI**

Type I ischaemia:	Rupture of vulnerable plaque.
Type II ischaemia:	Oxygen supply-demand mismatch in patients with prior stenosis or higher demand on the heart in patients without prior stenosis including pulmonary embolism, sepsis, kidney failure and respiratory insufficiency.

Prediction

Clinical risk indices:	Recommended for risk stratification (for example RCRI).
ECG and other imaging:	Only indicated in (high)-risk patients.
Preoperative biomarkers:	Preoperative biomarkers such as troponin and BNP levels may be used in the future for preoperative cardiac optimisation.

Prevention

Medication:	No evidence that preoperative administration beta-blockers, aspirin, clonidine, ACE-inhibitors or ARBs can reduce PMI. Initiation of statins should be considered in high risk statin naïve patients. Reload statin therapy in statin users may also reduce PMI.
Revascularisation:	Not enough evidence to perform (selective) preoperative revascularisation.
Exercise training:	Not enough evidence and a lack of specific guidelines to recommend preoperative exercise training.
Blood transfusion:	Restricted strategy (haemoglobin < 80g/L or symptoms) is recommended.
Intraoperative measures:	No evidence-based intraoperative measures to reduce PMI so far.

Management of patients with PMI

Intensified medical therapy:	Not enough evidence to prove that intensified medical therapy is effective.
Our follow-up proposal:	Routine follow-up focused on both cardiac and noncardiac complications including history, physical examination and ECG. Additional biomarkers and imaging should be considered when aetiology of PMI is uncertain.

Abbreviations: PMI: postoperative myocardial injury; RCRI: revised cardiac risk index; ECG: electrocardiography; BNP: B-type natriuretic peptide; ACE-inhibitors: Angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers.

high-risk patients.⁵ We believe that routine troponin monitoring is indeed useful to detect not only silent myocardial infarctions, but also other potentially treatable (non-coronary) postoperative complications in elderly patients. To optimise further the effects of routine monitoring, the selection of patients in whom monitoring is applied should be improved potentially by incorporating preoperative biomarkers.

It is not surprising that the 2014 guidelines lack recommendations on effective prevention or treatment options for patients with PMI, because the efficacy of investigated pharmacological and other measures is limited and treatment is not without risks. In order to improve the management of patients with PMI we need to gather more insight into the causes of PMI: you can simply treat patients better when you know what you are treating.

A summary of the current knowledge on underlying mechanisms, prediction, prevention and management options of PMI can be found in Table 1.

Conclusion

Prevention and treatment of PMI has mainly focused on CAD as its main underlying cause, yet recent

evidence suggests that non-coronary causes of PMI may also be involved. Given the current lack of both effective prevention and treatment options, it is critical to acquire more knowledge about the underlying pathophysiological mechanisms of PMI. Furthermore, in order to optimise routine monitoring, better identification of patients who benefit from such a monitoring strategy is necessary.

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LVW, RBG, WAK and DEG contributed to the conception or design of the work. LVW, JARW, LMP, HMN, WAK and DEG contributed to the acquisition or interpretation of the work. LVW, RBG and WAK drafted the manuscript. JARW, LMP, HMN and DEG critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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References

- Devereaux PJ, Goldman L, Cook DJ, et al. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ* 2005; 173: 627–634.
- Devereaux PJ, Xavier D, Pogue J, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med* 2011; 154: 523–528.
- Landesberg G, Beattie WS, Mosseri M, et al. Perioperative myocardial infarction. *Circulation* 2009; 119: 2936–2944.
- Landesberg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol* 2003; 42: 1547–1554.
- Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on Non-cardiac Surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesth. *Eur Hear J* 2014; 35: 2383–2431.
- Devereaux PJ, Chan MT, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012; 307: 2295–2304.
- van Waes JAR, Nathoe HM, de Graaff JC, et al. Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation* 2013; 127: 2264–2271.
- Levy M, Heels-Ansdell D, Hiralal R, et al. Prognostic value of troponin and creatine kinase muscle and brain isoenzyme measurement after noncardiac surgery: a systematic review and meta-analysis. *Anesthesiology* 2011; 114: 796–806.
- Oscarsson A, Eintrei C, Anskar S, et al. Troponin T-values provide long-term prognosis in elderly patients undergoing non-cardiac surgery. *Acta Anaesthesiol Scand* 2004; 48: 1071–1079.
- Oberweis BS, Smilowitz NR, Nukala S, et al. Relation of perioperative elevation of troponin to long-term mortality after orthopedic surgery. *Am J Cardiol* 2015; 115: 1643–1648.
- van Waes JAR, Grobbee RB, Nathoe HM, et al. One-year mortality, causes of death, and cardiac interventions in patients with postoperative myocardial injury. *Anesth Analg* 2016; 123: 29–37.
- Beattie WS, Karkouti K, Tait G, et al. Use of clinically based troponin underestimates the cardiac injury in non-cardiac surgery: a single-centre cohort study in 51,701 consecutive patients. *Can J Anaesth* 2012; 59: 1013–1022.
- Devereaux PJ, Bickard BM, Sigamani A, et al. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2017; 317: 1642.
- Ekeloef S, Alamili M, Devereaux PJ, et al. Troponin elevations after non-cardiac, non-vascular surgery are predictive of major adverse cardiac events and mortality: a systematic review and meta-analysis. *Br J Anaesth* 2016; 117: 559–568.
- Nathoe HM, van Klei WA and Beattie WS. Perioperative troponin elevation: always myocardial injury, but not always myocardial infarction. *Anesth Analg* 2014; 119: 1014–1016.
- Horr S, Reed G and Menon V. Troponin elevation after noncardiac surgery: significance and management. *Cleve Clin J Med* 2015; 82: 595–602.
- Botto F, Alonso-Coello P, Chan MT, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* 2014; 120: 564–578.
- Beckman JA. Postoperative troponin screening a cardiac cassandra? *Circulation* 2013; 127: 2253–2256.
- Devereaux PJ and Sessler DI. Cardiac complications in patients undergoing major noncardiac surgery. *N Engl J Med* 2015; 373: 2258–2269.

20. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012; 60: 1581–1598.
21. Sheth T, Chan M, Butler C, et al. Prognostic capabilities of coronary computed tomographic angiography before non-cardiac surgery: prospective cohort study. *BMJ* 2015; 350: h1907.
22. Gimenez MR, Twerenbold R, Reichlin T, et al. Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction. *Eur Heart J* 2014; 35: 2303–2311.
23. Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J* 2012; 33: 2252–2257.
24. Brown JC, Samaha E, Rao S, et al. High-sensitivity cardiac troponin T improves the diagnosis of perioperative MI. *Anesth Analg* 2017; 125: 1455–1462.
25. Gualandro DM, Campos CA, Calderaro D, et al. Coronary plaque rupture in patients with myocardial infarction after noncardiac surgery: frequent and dangerous. *Atherosclerosis* 2012; 222: 191–195.
26. Grobbee RB, van Klei WA, Grobbee DE, et al. The aetiology of myocardial injury after non-cardiac surgery. *Neth Heart J* 2013; 21: 380–388.
27. Grobbee RB, van Waes JA, Leiner T, et al. Unexpected cardiac CT findings in patients with postoperative myocardial injury. *Anesth Analg* 2018; 126: 1462–1468.
28. Pizzi C, Xhyheri B, Costa GM, et al. Nonobstructive versus obstructive coronary artery disease in acute coronary syndrome: a meta-analysis. *J Am Heart Assoc* 2016; 5: 1–15.
29. Kaski JC and Vitale C. Microvascular angina and systemic hypertension. *E-Journal Cardiol Pract* 2016; 14.
30. van Klei WA, Grobbee DE, Grobbee RB, et al. Detection and management of asymptomatic myocardial injury after noncardiac surgery. *Eur J Prev Cardiol* 2013; 20: 918–921.
31. Sellers D, Srinivas C and Djaiani G. Cardiovascular complications after non-cardiac surgery. *Anaesthesia* 2018; 73: 34–42.
32. Noordzij PG, van Geffen O, Dijkstra IM, et al. High-sensitive cardiac troponin T measurements in prediction of non-cardiac complications after major abdominal surgery. *Br J Anaesth* 2015; 114: 909–918.
33. Landesberg G and Jaffe AS. ‘Paradox’ of troponin elevations after non-cardiac surgery. *Br J Anaesth* 2015; 114: 863–865.
34. Mauermann E, Puelacher C and Buse GL. Myocardial injury after noncardiac surgery: an underappreciated problem and current challenges. *Curr Opin Anaesthesiol* 2016; 29: 403–412.
35. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014; 35: 3033–3080.
36. Matthews JC and McLaughlin V. Acute right ventricular failure in the setting of acute pulmonary embolism or chronic pulmonary hypertension: a detailed review of the pathophysiology, diagnosis, and management. *Curr Cardiol Rev* 2008; 4: 49–59.
37. Rohde LE, Polanczyk CA, Goldman L, et al. Usefulness of transthoracic echocardiography as a tool for risk stratification of patients undergoing major noncardiac surgery. *Am J Cardiol* 2001; 87: 505–509.
38. Nagele P, Brown F, Gage BF, et al. High-sensitivity cardiac troponin T in prediction and diagnosis of myocardial infarction and long-term mortality after noncardiac surgery. *Am Heart J* 2013; 166: 325–332.
39. Ryding A, Kumar S, Worthington AM, et al. Prognostic value of brain natriuretic peptide in noncardiac surgery: a meta-analysis. *Anesthesiology* 2009; 111: 311–319.
40. Rodseth RN, Biccari BM, Le Manach Y, et al. The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery. *J Am Coll Cardiol* 2014; 63: 170–180.
41. Maile MD, Jewell ES and Engoren MC. Timing of pre-operative troponin elevations and postoperative mortality after noncardiac surgery. *Anesth Analg* 2016; 123: 135–140.
42. Libby P. Inflammation in atherosclerosis. *Nature* 2002; 420: 868–874.
43. Maiolino G, Bisogni V, Rossitto G, et al. Lipoprotein-associated phospholipase A2 prognostic role in atherosclerotic complications. *World J Cardiol* 2015; 7: 609–620.
44. Chung H, Kwon HM, Kim J, et al. Lipoprotein-associated phospholipase A2 is related to plaque stability and is a potential biomarker for acute coronary syndrome. *Yonsei Med J* 2014; 55: 1507–1515.
45. Liu YS, Hu XB, Li HZ, et al. Association of lipoprotein-associated phospholipase A(2) with characteristics of vulnerable coronary atherosclerotic plaques. *Yonsei Med J* 2011; 52: 914–922.
46. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC Guidelines on the management of stable coronary artery disease: the Task Force on the Management of Stable Coronary Artery Disease of the European Society of Cardiology. *Eur Heart J* 2013; 34: 2949–3003.
47. Wijesundera DN, Duncan D, Nkonde-Price C, et al. Perioperative beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 64: 2406–2425.
48. Bouri S, Shun-Shin MJ, Cole GD, et al. Meta-analysis of secure randomised controlled trials of beta-blockade to prevent perioperative death in non-cardiac surgery. *Heart* 2014; 100: 456–464.
49. Gorenek B, Pelliccia A, Benjamin EJ, et al. European Heart Rhythm Association (EHRA)/European Association of Cardiovascular Prevention and Rehabilitation (EACPR) position paper on how to prevent atrial fibrillation endorsed by the Heart Rhythm Society (HRS) and Asia Pacific Heart Rhythm Society (APHRS). *Eur J Prev Cardiol* 2017; 24: 4–40.
50. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med* 2014; 370: 1494–1503.

51. Devereaux PJ, Sessler DI, Leslie K, et al. Clonidine in patients undergoing noncardiac surgery. *N Engl J Med* 2014; 370: 1504–1513.
52. de Waal BA, Buise MP and van Zundert AAJ. Perioperative statin therapy in patients at high risk for cardiovascular morbidity undergoing surgery: a review. *Br J Anaesth* 2014; 114: 44–52.
53. Berwanger O, Le MY, Suzumura EA, et al. Association between pre-operative statin use and major cardiovascular complications among patients undergoing non-cardiac surgery: the VISION study. *Eur Heart J* 2016; 37: 177–185.
54. Wang L, Peng P, Zhang O, et al. High-dose statin pre-treatment decreases periprocedural myocardial infarction and cardiovascular events in patients undergoing elective percutaneous coronary intervention: a meta-analysis of twenty-four randomized controlled trials. *PLoS One* 2014; 9: 1–21.
55. Xia J, Qu Y, Yin C, et al. Preoperative rosuvastatin protects patients with coronary artery disease undergoing noncardiac surgery. *Cardiology* 2015; 131: 30–37.
56. Zou Z, Hb Y, Yang B, et al. Perioperative angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers for preventing mortality and morbidity in adults. *Cochrane Database Syst Rev*. Epub ahead of print 2016. DOI: 10.1002/14651858.CD009210.pub2. www.cochranelibrary.com.
57. Turan A, You J, Shiba A, et al. Angiotensin converting enzyme inhibitors are not associated with respiratory complications or mortality after noncardiac surgery. *Anesth Analg* 2012; 114: 552–560.
58. Rosenman DJ, McDonald FS, Ebbert JO, et al. Clinical consequences of withholding versus administering renin-angiotensin-aldosterone system antagonists in the preoperative period. *J Hosp Med* 2008; 3: 319–325.
59. Roshanov PS, Rochwerg B, Patel A, et al. Preoperative administration of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. *Anesthesiology* 2017; 126: 1–3.
60. Mcfalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med* 2009; 351: 2795–2804.
61. Illuminati G, Schneider F, Greco C, et al. Long-term results of a randomized controlled trial analyzing the role of systematic pre-operative coronary angiography before elective carotid endarterectomy in patients with asymptomatic coronary artery disease. *Eur J Vasc Endovasc Surg* 2015; 49: 366–374.
62. Marmelo F, Rocha V and Gonçalves D. The impact of prehabilitation on post-surgical complications in patients undergoing non-urgent cardiovascular surgical intervention: systematic review and meta-analysis. *Eur J Prev Cardiol* 2018; 25: 404–417.
63. Pouwels S, Hageman D, Gommans LNM, et al. Preoperative exercise therapy in surgical care: a scoping review. *J Clin Anesth* 2016; 33: 476–490.
64. Tew GA, Ayyash R, Durrand J, et al. Clinical guideline and recommendations on pre-operative exercise training in patients awaiting major non-cardiac surgery. *Anaesthesia* 2018; 73: 750–768.
65. Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; 348: 1055–1060.
66. Chatterjee S, Wetterslev J, Sharma A, et al. Association of blood transfusion with increased mortality in myocardial infarction: a meta-analysis and diversity-adjusted study sequential analysis. *JAMA Intern Med* 2013; 173: 132–139.
67. Valentijn TM, Hoeks SE, Martienus KA, et al. Impact of haemoglobin concentration on cardiovascular outcome after vascular surgery: a retrospective observational cohort study. *Eur J Anaesthesiol* 2013; 30: 664–670.
68. Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med* 2011; 365: 2453–2462.
69. Carson JL, Sieber F, Cook DR, et al. Liberal versus restrictive blood transfusion strategy: 3-year survival and cause of death results from the FOCUS randomised controlled trial. *Lancet* 2015; 385: 1183–1189.
70. Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: a clinical practice guideline from the AABB*. *Ann Intern Med* 2012; 157: 49–58.
71. van Waes JAR, van Klei WA, Wijesundera DN, et al. Association between intraoperative hypotension and myocardial injury after vascular surgery. *Anesthesiology* 2016; 124: 35–44.
72. Hallqvist L, Martensson J, Granath F, et al. Intraoperative hypotension is associated with myocardial damage in noncardiac surgery: an observational study. *Eur J Anaesthesiol* 2016; 33: 450–456.
73. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013; 119: 507–515.
74. Gillies MA, Shah ASV, Mullenheim J, et al. Perioperative myocardial injury in patients receiving cardiac output-guided haemodynamic therapy: a substudy of the OPTIMISE Trial. *Br J Anaesth* 2015; 115: 227–233.
75. Foucrier A, Rodseth R, Aissaoui M, et al. The long-term impact of early cardiovascular therapy intensification for postoperative troponin elevation after major vascular surgery. *Anesth Analg* 2014; 119: 1053–1063.
76. Chong CP, van Gaal WJ, Ryan JE, et al. Does cardiology intervention improve mortality for post-operative troponin elevations after emergency orthopaedic-geriatric surgery? A randomised controlled study. *Injury* 2012; 43: 1193–1198.