Perioperative Myocardial Infarction

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1. Introduction

Cardiac complications are a major cause of perioperative morbidity and mortality in patients undergoing non-cardiac surgery. Worldwide, more than 300 million adults undergo non-cardiac surgeries each year.[1] Amongst them, as many as 10 million surgeries have major adverse cardiovascular events(MACE) that lead to worst clinical outcomes.[2] Major adverse cardiac events include all-cause mortality or re-hospitalization for a cardiovascular-related illness. Cardiovascular related illnesses include heart failure, reinfarction (nonfatal), ocurrence of angina pectoris and percutaneous coronary intervention(PCI) or coronary artery bypass grafting(CABG).[3] Perioperative myocardial infarction(PMI) has recently been identified as an important, yet often undetected complication after noncardiac surgery associated with high 30-day mortality.[4] In contrast to myocardial infarction, PMI most commonly does not exhibit chest pain, angina pectoris, or dyspnea, and is therefore missed in routine clinical practice in most institutions.[5]

2. Incidence of PMI

Five large studies have evaluated the incidence of PMI after non cardiac surgery.[6-10] Puelacher et al examined PMI among 2018 consecutive patients at increased risk for cardiovascular complications (≥65 years of age or ≥45 years of age with a history of coronary artery disease, peripheral artery disease, or stroke) who underwent 2546 noncardiac surgeries. hsTnT (high sensitivity Troponin T) was systematically assessed both pre- and postoperatively. The incidence of PMI was found to be 16% in Puelacher cohort.[10] Additional information regarding incidence of perioperative MI comes from over 8000 patients in randomized POISE trial of perioperative beta blocker therapy in patients at increased cardiovascular risk undergoing noncardiac surgery. The incidence of MI in POISE trial was 5% at 30 days (4.2 and 5.7 in the beta blocker and placebo groups, respectively).[11] In VISION cohort of 21,842 patients, with high-sensitivity troponin T measurements, 3904 patients (17.9 percent) were adjudicated as having suffered MINS (myocardial injury after non cardiac surgery) , and among these patients,

21.7 percent fulfilled the universal definition of MI.[12] In CARP(Coronary artery Revascularization Prophylaxis) trial, PMI was seen in 27 percent of 377 patients with coronary artery disease scheduled to undergo (high-risk) vascular surgery.[13]

3. Timing of PMI

The results of the POISE trial have demonstrated that majority of PMI(74.1%) occur within 48 hours of non cardiac surgery.[11] In another prospective observational study by Ollila et al, the majority of PMIs (16 of 27, 59.3%) were diagnosed on the first or second postoperative day.[14]

4. Diagnosis of PMI

The third universal definition released in 2012 by the European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association, and World Health Federation(ESC/ACCF/AHA/WHF) defined PMI as the detection of rise or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit and with at least one of the following[15]:

1) Symptoms of ischemia

2) New or presumed new significant ST-segment-T wave changes or new left bundle branch block (LBBB).

3) Development of pathological Q waves in the ECG.

4) Presence of new loss of viable myocardium or new regional wall motion abnormality on cardiac imaging.

5) Identification of an intracoronary thrombus by angiography or autopsy.

5. Outcome

The frequency of cardiovascular complications range between 40-60% during the first week following non cardiac surgery.[16] From surgery to first month, the percentage of cardiac complication ranges between 15-30%.[16] Thereafter reduces to 7-10% till 90 days post surgery.[16] The 30-day mortality rate was 11.6% among patients who had a perioperative MI and 2.2% among those who did not in POISE trial.[11] In the VISION study, the overall 30-day mortality rate was 1.9 percent.[12] Overall, 56 of 2018 patients (2.8%; 95% CI, 2.1–3.6) died within 30 days; 23 (41%; 95% CI, 29–54) died of

cardiovascular causes and 33 (59%; 95% CI, 46–71) died of noncardiovascular causes.[10] One year after surgery, 224 of 2018 (11.2%; 95% CI, 9.8–12.7) patients died; 71(32%; 95% CI, 26–38) died of cardiovascular causes and 153 (68%; 95% CI, 62–74) died of noncardiovascular causes.[10]

6. Early detection and prevention of PMI

Given the silent nature of PMI, many cases remain undiagnosed. However detailed history, assessment of the functional status and identification of the surgical risk involved greatly helps in guiding further need for non invasive stress testing and medical or surgical intervention for optimization of cardiac disease (figure 1). The Revised Cardiac Risk Index (RCRI) and the National Surgical Quality Improvement Program (NSQIP) risk index are two widely used risk indices available that includes various patient related and surgery related factors and predicts the chances for occurrence of PMI(table 1).[17-20] The assessment of functional capacity of patient and surgical risk plays a key role in determining the further management of cardiac patient for non cardiac surgery(table 2 and 3).[21]

6.1Current recommendations of biomarkers

Recently the increase in level of biomarkers have been used to predict the short and long term mortality in cardiac patients undergoing non cardiac surgery.[22] In a meta-analysis by McFall et al, myocardial infarction was taken as the primary outcome. They found myocardial infarction in 235 of 2179 patients within 30 days of non cardiac surgery. Their study also demonstrated elevated preoperative plasma level of natriuretic peptide (i.e., a B-type natriuretic peptide [BNP] level of ≥92 ng per liter or an N-terminal pro-BNP [NT-proBNP] level of ≥300 ng per liter) as the strongest independent preoperative predictor of the primary outcome.[23] Their study showed that, as compared with a preoperative clinical model alone, preoperative measurement of natriuretic peptide levels improved risk estimation among both patients who had the primary outcome and those who did not.

In 2017 report of VISION study, an absolute change of 5 ng/L across any two perioperative measurements of high sensitivity cardiac Troponin T (hs-cTnT) was

independently associated with an increase in 30-day mortality.[12] Maile et al, in their study also showed that higher levels of preoperative cardiac troponin I(greater than 0.34ng/dl) were associated with higher 30-day mortality, and longer time to surgery appeared to reduce this risk for individuals with mild preoperative troponin elevation.[24] Puelacher et al measured hs-cTnT in 2018 consecutive patients at increased risk for cardiovascular complications(≥65 years of age or ≥45 years of age with a history of coronary artery disease, peripheral artery disease, or stroke) in both pre- and postoperative phase.[10] They found comparable mortality amongst patients with PMI not fulfilling additional criteria (ischemic symptoms, new ECG changes, or imaging evidence of loss of viable myocardium) versus those that did. Canadian Cardiovascular guidelines strongly recommend measuring BNP prior to surgery in all patients who are >65 years and >45 years with significant cardiovascular disease or RCRI≥1.[25]

6.2 Role of coronary revacularization

The need of coronary angiography and subsequent revascularization is restricted to intermediate-to-high risk surgery. The beneficial effects of myocardial revascularization over optimal medical management to prevent perioperative major adverse cardiac events are limited to symptomatic patients and those with an extensive documented ischaemia. Consequently, in both European and American guidelines, indications for invasive coronary angiography and revascularization are scarce (Table 4).[21,26] In addition, Canadian guidelines recommended against preoperative prophylactic coronary revascularisation for patients with stable coronary artery disease.[25] The type of coronary revascularization, surgical coronary artery bypass or percutaneous coronary intervention, depends on the extent and complexity of the coronary artery disease and on the urgency of non cardiac surgery, which influences the duration of antiplatelet therapy.

In a meta analysis which recruited patients from CARP and DECREASE-V trial, pre-operative coronary revascularisation was associated with **significantly increased 30-day mortality and late composite outcomes of death and nonfatal myocardial infarction.[27] Preoperative CABG was found to be associated with worse early**

outcome following vascular surgery, although long term outcomes were improved.[27]

7. Anaesthetic management

Induction of anaesthesia in a cardiac patient should be smooth and all measures should be taken to prevent pressor response to laryngoscopy and intubation. The effect of anaesthetic agents and neuraxial anaesthesia on hemodynamics must be taken into account for a global anaesthestic management. Despite a large body of literature, no specific evidence has been found for reduction of cardiac risk in neuraxial anaesthesia over general anaesthesia. In a recent prospective observational study, 86 preoperative non- cardiac surgery patients were separated randomly into the general or spinal anesthesia groups. 12 lead electrocardiograms and hs-cTns on the operation day and post operation 1, 2 and 3 days were obtained. No difference was found in the hs-cTns levels in both the groups.[28] Intense monitoring of blood pressure and maintaining mean arterial pressure above 70 mmHg has been shown to decrease the perioperative MI. Threshold for putting invasive aterial line is minimum in patients at high risk of MACE.

7.1 Surgical Apgar Score

The surgical Apgar score is an important tool in determining the postoperative morbidity and mortality from intraoperative events. The score is calculated at the end of surgery from the estimated blood loss, lowest mean arterial pressure and lowest heart rate entered in the anaesthesia record during surgery. The score is the sum of the points from each category (maximal score 10 points). A score <7 is associated with an increase in postoperative morbidity and mortality(table 5).[29] Keeping close monitoring in ICU or HDU is essential for such patients along with biomarker screening postoperatively.

8. Postoperative period

The risk of perioperative MI peaks within the first 3 postoperative days, a period of time when patients begin to mobilize fluids administered in the operating room, and a time when the thrombotic risk may be most pronounced. Surgery is accompanied by a

catecholamine surge that is exacerbated by postoperative pain. Subsequent increases in heart rate and BP can lead to a diffuse myocardial oxygen supply/demand mismatch in the postoperative patient. Ablation of stress response, adverse haemodynamics, and hypercoagulable responses is most critical for good postoperative outcome.

According to ACC/AHA guidelines, postoperative troponin assays may be useful in very high-risk patients[26], the 2017 Canadian guidelines recommend to obtain daily troponin measurements for 48–72 h after non-cardiac surgery in patients with baseline risk of more than 5% for cardiac death or nonfatal myocardial infarction.[25] Canadian guidelines also recommend measurement of preoperative brain natriuretic peptide levels(BNP) to enhance preoperative risk assessment in patients>65 years or patients> 45 years with significant cardiovascular disease or have Revised Cardiac Risk Index≥1. According to European Society of Cardiology/European Society of Anesthesiology, measurement of cardiac biomarkers troponin and/or BNP measured in the preoperative and/or postoperative period if patient has Lee Score≥2 for vascular surgery and ≥3 for non vascular surgery. Also if the surgical Apgar Score is ≤7 at the end of surgery.[25] If an increase of troponin is observed, clinical examination, electrocardiogram and a cardiologist visit are probably useful alongwith immediate correction of precipitating factors of troponin increase (hypovolaemia, hypoxemia, excessive activation of the sympathetic nervous system).

9. Perioperative management of cardiac medications

i) β blockers- Results of the POISE trial showed that, while perioperative continuation of beta blockers is recommended in patients currently receiving that medication, starting a beta blocker preoperatively without having time for individual titration exposes the patients to serious cardiovascular adverse events, as hypotension, bradycardia and stroke, and increases overall mortality.[30] Moreover, all beta blockers are not pharmacologically equivalent. Oral atenolol or bisoprolol should be preferred to metoprolol during the preoperative period because of its greater β1 cardio selectivity.[31]

ii) α 2 agonists- many previous trials suggest that low dose clonidine produces less hypotension than beta-blockers.[30,32] The POISE-2 study, in which 10,010 patients were randomly assigned to receive clonidine or a placebo, showed

that clonidine had no effect on the rates of myocardial infarction, stroke, or death.[33]

However in comparison to clonidine, β blockers showed better heart rate control and only limited hypotension.[30,32] Some authors have suggested that the harm associated with beta-blocker use in the POISE study resulted from an excessive dose.[34] Other authors have suggested that it is more appropriate to initiate beta-blockade weeks, instead of hours, before surgery.[35]

iii) Renin Angiotensin Inhibitors- Withdrawal of RAS drugs on the day of surgery is recommended as profound refractory hypotension can occur if continued. The recent guidelines of the Canadian Cardiovascular Society strongly recommend withholding RAS inhibitors starting 24 h before non-cardiac surgery in chronically treated patients, whatever the reason for the drug prescription.[34] However non resumption of RAS inhibitors at postoperative day 2 was strongly associated with increased 30-day mortality in a large cohort of patients.[36]

iv) Statins- continuation of statins in perioperative period have been known to decrease mortality by 50% and improve long term outcomes.[37] The preoperative introduction of statins to prevent major adverse cardiac events should be done at least one week prior to surgery.

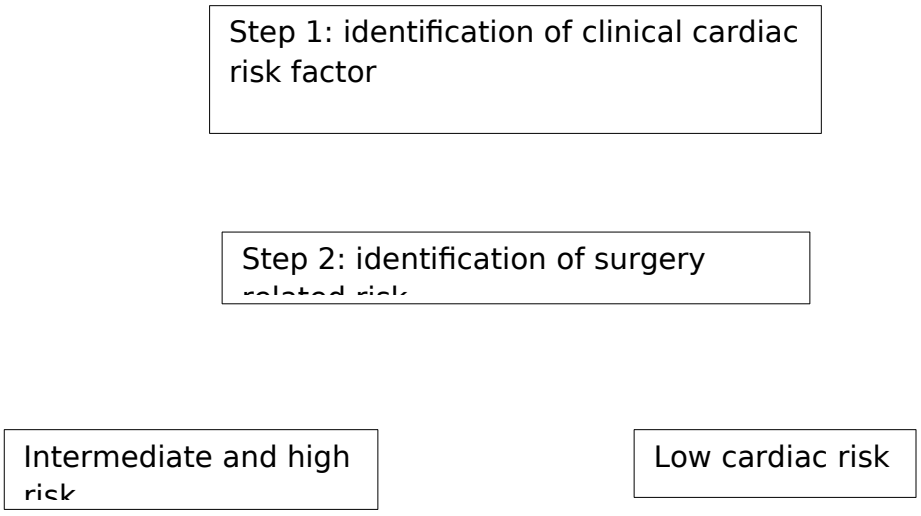
v) Antiplatelet drugs- balancing bleeding and thrombotic risks is a major problem in patients on antiplatelet drugs during perioperative period. Following PCI, it is reasonable to delay surgery till the re-endothelialization period, which would be 14 days after ballooning, 30 days after bare metal stent placement, and at least 3 months (preferentially 6 months) after DES placement.[38] Aspirin can be continued, except for intracranial procedures when aspirin cessation may be considered for 3–4 days prior to surgery.[31]

10. **Management of cardiac patient with PMI**

Once initial diagnosis of PMI is established by elevated cardiac troponin levels and ECG changes, all patients with PMI should be started with aspirin and statins as they have been known to be associated with reduced 30 day mortality.[9] Cardiologist need to be involved at the earliest so that if any intervention needs to be planned it can be done. In addition to aspirin and statins, continuous electrocardiographic monitoring (potentially in a monitored setting) for at least 24 hours is advised, particularly if the diagnosis is made within the first 24 hours of surgery. Hemodynamic stabilization which includes ensuring adequate mean arterial pressure (70mmHg) without tachycardia, ensuring adequate gas exchange (avoiding hypoxia and hypercarbia) with adequate pain relief and temperature control. Further management depends on the type of event, ST elevation MI(STEMI) or non ST elevation MI(NSTEMI) (figure 2). In case of ST-segment elevation acute myocardial infarction, an acute coronary occlusion is likely to occur and rapid coronary reperfusion is the only reasonable treatment.[39] The institution of other antiplatelet drugs should be done after discussing undue surgical/cardiac risk that leads to worsening of myocardial injury. In most patients, fibrinolytic therapy is not an option given the recent surgical procedure. Urgent primary percutaneous coronary intervention after careful discussion of the benefits and risks with all healthcare providers is usually done. For patients who receive no reperfusion therapy, one year of aspirin plus a $P2Y_{12}$ receptor blocker (dual antiplatelet therapy) is recommended. Acute coronary syndrome without ST-segment elevation (NSTEMI) is rarely in relation with a plaque rupture and a type 1 myocardial infarction mechanism. Rather, their primary cause is a type 2 mechanism, due to an imbalance between the intakes and the needs of the myocardium. The mismatch may be caused by hypoxia, hypertension, hypotension, hypothermia, sepsis, anaemia and/or arrhythmias. Correcting all these disturbances at the earliest so that the myocardial damage does not extend is the goal of managing these high risk patients. There is no need of anti thrombotic therapy, usually the treatment of cause is the key for resolution of PMI. However some cases may require coronary angiography when patients presents with hemodynamic instability of cardiac cause, persistent angina or ventricular arrhythmias.[40]

Conclusion

Reported cardiovascular complications occurring in non cardiac surgeries represent just the tip of iceberg. With the outcome of results of recent large population trials, the sequential measurement of biomarkers have proven to have a beneficial role in predicting mortality following non cardiac surgery.[12,41,42] cTns has emerged as a useful tool that may help the clinician in the diagnosis of perioperative myocardial ischaemic injury. However some questions are still raised. Should the detection of ischaemia be restricted to moderate- to high-risk patients undergoing high-risk surgical procedures, or should it be applied to a broader number of patients? What should be optimal timing (frequency, extent) for blood sampling for cTns determination? Large randomized clinical trials would be needed to confirm clinical benefit of medical interventions based on routine hsTnT and BNP screening postoperatively. Till definitive protocols are not available, it is important that we rely on intensive risk stratification strategies and aggressive medical management before anaesthetizing a cardiac patient for non cardiac surgery and ensuring homeostasis especially with respect to blood pressure and heart rate control. A holistic approach involving anaesthesiologist, cardiologist and surgeon especially in high risk patients and bringing in the heart team concept for overall management of the high risk cardiac patients for non cardiac surgery is worthwhile for good outcome.



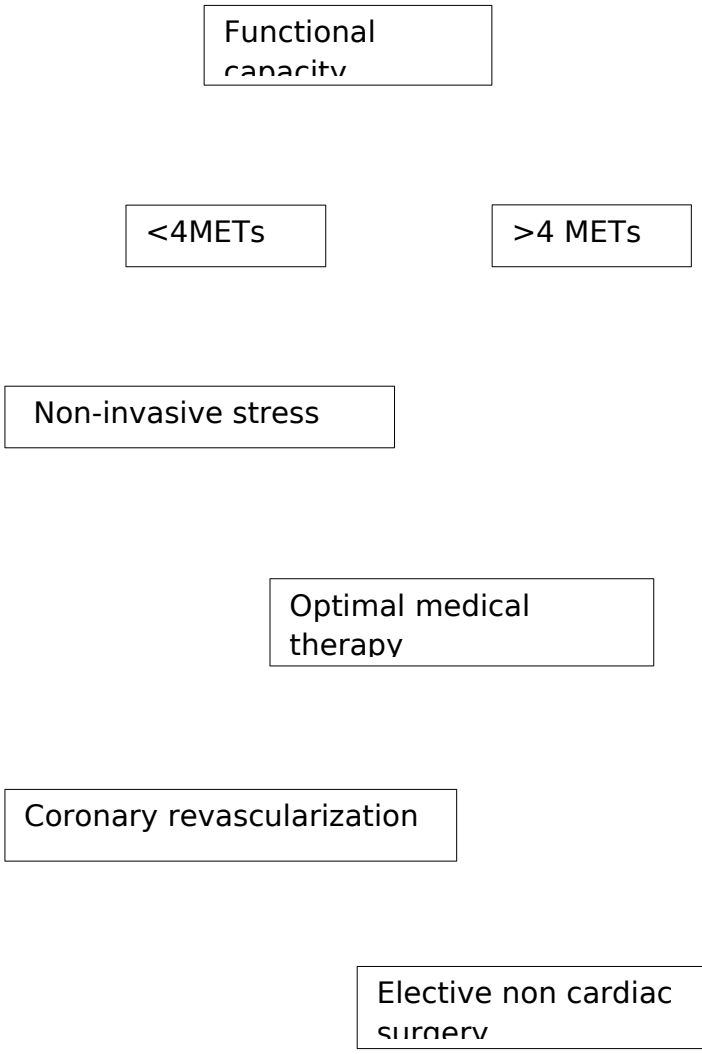
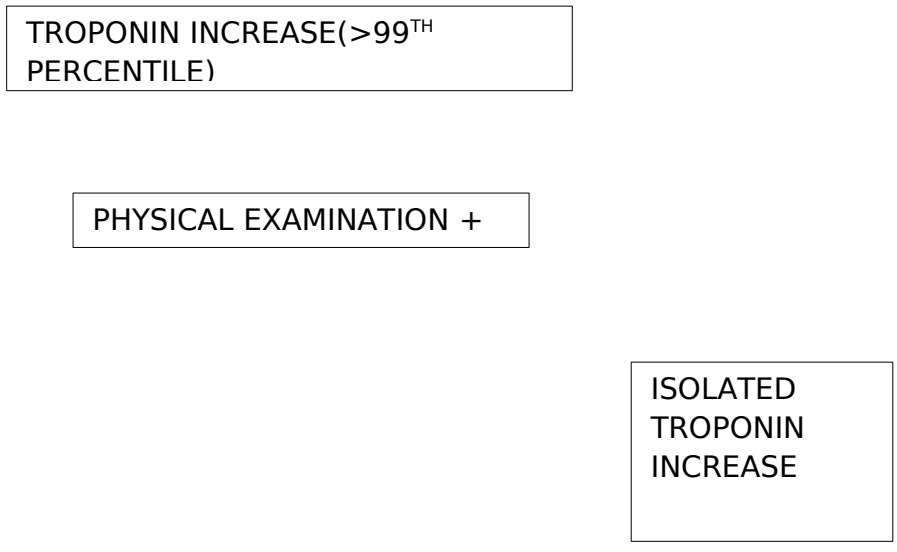


Figure 1 Algorithm for optimal preoperative cardiac risk evaluation and modification.



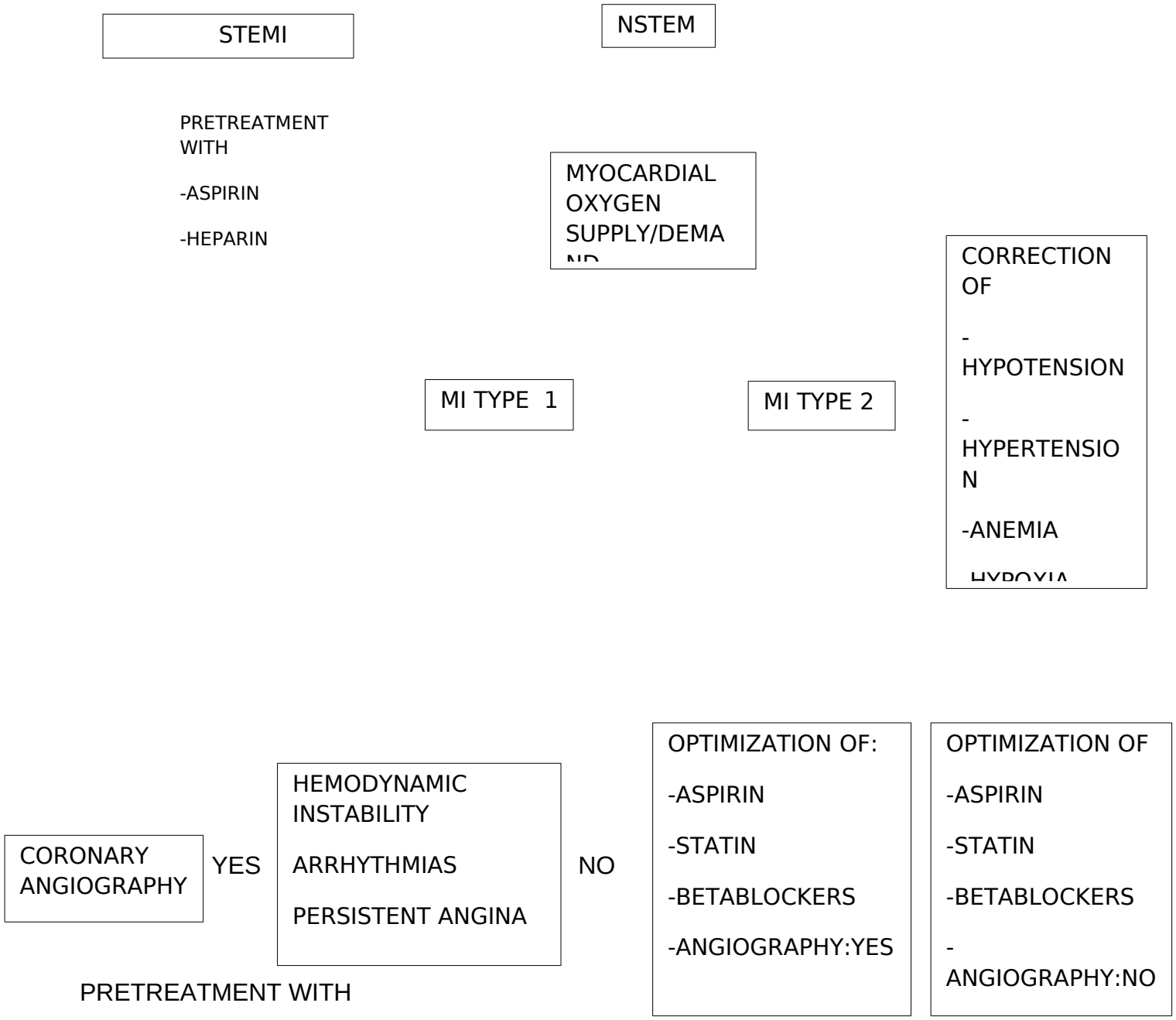


FIGURE 2: Algorithm for postoperative management of PMI

Table 1 Comparison of Revised Cardiac Risk Index(RCRI) and National Surgery Quality Improvement Program(NSQIP)

	RCRI	**NSQIP**
Factors used	History of ischemic	Age

	heart disease History of heart failure History of cerebrovascular accident Insulin dependent Diabetes Mellitus Preop serum creatinine>2mg/dl Undergoing suprainguinal vascular, intraperitoneal, or intrathoracic surgery	Serum creatinine>1.5mg/dl American Society of Anesthesiology(ASA) class Functional status Type of surgery
Interpretation	**Low risk** 0 risk factor:0.5%risk 1 risk factor:1.3%risk **Elevated risk** 2 risk factors: 3.6% risk ≥3 factors: 9.1% risk Risk of MACE	Web based calculator gives a percent risk:www.qxmd.com/calculator_245/gupta-perioperative-cardiac-risk
Derivation and validation study design	Prospective cohort 1989-1994 Single hospital	Historical national database 2007-2008 Multicentre (200 hospitals)
Advantages	Used for more than a decade	Surgery specific
Disadvantages	Not applicable for advanced laparoscopic surgeries Functional capacity not a variable Severe aortic stenosis is not included Definition of myocardial infarction is based on creatine kinase MB(CK-MB): CK-MB>5% of total CK, or >3% of total CK with electrocardiographic changes	Coronary artery disease, aortic stenosis are not variables Myocardial infarctions may have been overdiagnosed due to troponin elevation of unknown significance

MACE = major adverse cardiac events

Table 2 Preoperative evaluation of the surgery related risk

Low risk: <1%	**Intermediate risk:1-5%**	**High risk:>5%**
Superficial surgery	Intraperitoneal: splenectomy, hiatal hernia repair, cholecystectomy	Aortic and major vascular surgery
Breast	Carotid symptomatic (CEA or CAS)	Open lower limb revascularization or amputation or thromboembolectomy
Dental	Peripheral arterial angioplasty	Duodeno-pancreatic surgery
Endocrine: thyroid	Endovascular aneurysm repair	Liver resection, bile duct surgery
Eye	Head and neck surgery	Oesophagectomy
Reconstructive	Neurological or orthopedic:major (hip and spine surgery)	Repair of perforated bowel
Carotid asymptomatic (CEA or CAS)	Urological or gynecological :major	Adrenal resection
Gynecology: minor	Renal transplant	Total cystectomy
Orthopedic:minor(meniscectomy)	Intra-thoracic non – major	Pneumonectomy
Urological :minor(transurethral resection of prostate)		Pulmonary or liver transplant

Table 3 Preoperative functional myocardial capacity evaluation

Physical ability(Dukes scale)	**METs**	**VO_2(ml/kg/min)**	**Physical activity without symptoms**	**Level of surgical risk**
Excellent	>10	>35	Swimming, tennis, basketball	Low
Very good to good	7-10	25-35	Rise>2 floors fast walking	
Moderate	4-7	14-25	Rise >2 floors housework	
Weak	<4	<14	Walking at home,washing,dressing	Moderate to high
Non measurable	?	?	None	

Table 4: Recommendations regarding coronary angiography

Recommendations	AHA/ACC		EHS/ESA	
	Class	**LOE**	**Class**	**LOE**
Indications for preoperative angiography and revascularization are similar to those in the the nonsurgical setting			I	C
STEMI in the setting of nonurgent noncardiac surgery			I	A
NSTEMI in setting of nonurgent noncardiac surgery			I	B
Patients with proven ischemia and unstabilized chest pain on optimal medical therapy, undergoing nonurgent noncardiac surgery			I	C
Stable cardiac patients undergoing nonurgent carotid endarterectomy			IIb	B
Routine coronary angiography is not recommended	III	C		
Stable patients undergoing low-risk surgery			III	C

NSTEMI=Non ST elevation myocardial infarction

STEMI-ST elevation myocardial infarction

AHA-American Heart Association

ACC-American College of Cardiology

EHS-European Heart Society

ESA-European Society of Anesthesiologists

LOE- Level of Evidence

Table 5 Surgical Apgar Score

	0 point	1 point	2 point	3 point	4 point
Estimated blood loss(ml)	>1000	601-1000	101-600	≤100	
Lowest mean arterial pressure(mmHg)	<40	40-54	55-69	≥70	
Lowest heart rate (bpm)	>85	76-85	66-75	56-65	≤55

REFERNCES

1) Weiser TG, Haynes AB, Molina G, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. Lancet. Apr 27.2015 385(Suppl 2):S11.
2) Smilowitz NR, Berger JS. Perioperative Management to Reduce Cardiovascular Events. Circulation. Mar 15; 2016 133(11):1125–1130

3) Tsai T, Wang CP, Lu WL, Hung WC, Wu CC, Lu LF, et al. The burden of major adverse cardiac events in patients with coronary artery disease. BMC Cardiovascular Disorders 2017 17:1

4) Devereaux PJ, Biccard BM, Sigamani A, Xavier D, Chan MT V., Srinathan SK, Walsh M, Abraham V, Pearse R, Wang CY, Sessler DI, Kurz A, Szczeklik W, Berwanger O, Villar JC, Malaga G, Garg AX, Chow CK, Ackland G, Patel A, Borges FK, Belley-Cote EP, Duceppe E, Spence J, Tandon V, Williams C, Sapsford RJ, Polanczyk CA, Tiboni M, Alonso-Coello P, Faruqui A, Heels-Ansdell D, Lamy A, Whitlock R, LeManach Y, Roshanov PS, McGillion M, Kavsak P, McQueen MJ, Thabane L, Rodseth RN, Buse GAL, Bhandari M, Garutti I, Jacka MJ, Schünemann HJ, Cortes OL, Coriat P, Dvirnik N, Botto F, Pettit S, Jaffe AS, Guyatt GH. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2017;317:1642–1651

5) Ekeloef S, Alamili M, Devereaux PJ, Gögenur I. Troponin elevations afternon-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.
6) 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.
7) van Waes JA, Nathoe HM, de Graaff JC, et al. Myocardial injury after noncardiac surgery and its association with short-term mortality. Circulation 2013; 127:2264.
8) 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.
9) 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.
10) Puelacher C, Lurati Buse G, Seeberger D, et al. Perioperative Myocardial Injury After Noncardiac Surgery: Incidence, Mortality, and Characterization. Circulation 2018; 137:1221
11) POISE Study Group, Devereaux PJ, Yang H, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008; 371:1839-47.
12) Writing Committee for the VISION Study Investigators, Devereaux PJ, Biccard BM, 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.
13) McFalls EO, Ward HB, Moritz TE, et al. Predictors and outcomes of a perioperative myocardial infarction following elective vascular surgery in patients with documented coronary artery disease: results of the CARP trial. Eur Heart J 2008; 29:394.
14) Ollila A,Vikatmaa L, Virolainen J, Vikatmaa P, Leppäniemi A, Albäck A, et al. Perioperative myocardial infarction in non-cardiac surgery patients: a prospective observational study. Scandanavian Journal of surgery 2017, Vol. 106(2) 180–186

15) Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012; 126:2020

[16] Barbera JP,Calderón SM, Sánchez MV. Cardiac Complications of Major Elective Non-Cardiac Surgery: Incidence and Risk Factors. Rev Esp Cardiol. 2006;59(4):329-37

17)Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery.Circulation 1999; 100:1043–1049.

18) Gupta PK, Gupta H, Sundaram A, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation 2011; 124:381–387

19)Mandaliya R , Merli G. Do cardiac risk stratification indexes accurately estimate perioperative risk in noncardiac surgery patients? Cleveland Clinic Journal of Medicine. 2018;85(1):35-39

20)Ford MK, Beattie WS, Wijeysundera DN. Systematic review: prediction of perioperative cardiac complications and mortality by the Revised Cardiac Risk Index. Ann Intern Med 2010; 152: 26-35

21)Kristensen SD, Knuuti J, Saraste A, Anker S, Botker HE, Hert SD, 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 Anaesthesiology (ESA). Eur Heart J. 2014;35:2383–431

22)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.

23)McFalls EO, Ward HB, Krupski WC, et al. Prophylactic coronary artery revascularization for elective vascular surgery: study design. Control Clin Trials 1999; 20:297-308.

24)Maile MD, Jewell ES, Engoren MC. Timing of Preoperative Troponin Elevations and Postoperative Mortality After Noncardiac Surgery. Anesth Analg 2016;123:135–40

25) Duceppe E, Parlow J, MacDonald P, Lyons K, McMullen M, Srinathan S, et al. Canadian cardiovascular society guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. Can J Cardiol 2017;33:17–32.

26) Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:2215–45.

[27] Biccard BM, Rodseth RN. A meta-analysis of the prospective randomized trials of coronary revascularisation before non cardiac vascular surgery with attention to the type of coronary revascularisation performed. Anaesthesia 2009;64:1105-13

[28] Mansuroglu C, Turhan T, Ornek E, Yildiz N, Ornek D, et al. Comparison of Spinal or General Anesthesia for Cardiac Complications with Using High Sensitive Cardiac Troponins in Non-cardiac Surgeries. Angiol 2016;4: 170-74.

29)Haynes AB, Regenbogen SE, Weiser TG, Lipsitz SR, Dziekan G, Berry WR, et al. Surgical outcome measurement for a global patient population: validation of the surgical Apgar score in 8 countries. Surgery 2011;149:519–24.

30)Wijeysundera 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.Circulation 2014; 130: 2246-64.

31)Fellahi J-L, Godier A, Benchetrit D, Berthier F, Besch G, Bochaton T, et al. Perioperative management of patients with coronary artery disease undergoing

noncardiac surgery: Summary from the French Society of Anaesthesia and Intensive Care Medicine 2017 convention. Anaesth Crit Care Pain 2018(article in press)

32)Darvish-Kazem S, Alderazi AE, Walsh M, et al. Vascular safety and efficacy of perioperative clonidine treatment in patients undergoing non-cardiac surgery:systematic review and meta-analysis. Can J Cardiol 2009; 25B: 158. Abstract

33)Devereaux PJ, Sessler DI, Leslie K, et al. Clonidine in patients undergoing noncardiac surgery. N Engl J Med 2014; 370: 1504-13

34)Angeli F, Verdecchia P, Karthikeyan G, et al. Beta-blockers and risk of all cause mortality in non-cardiac surgery. Ther Adv Cardiovasc Dis 2010; 4: 109-18.

35)Fleisher LA, Poldermans D. Perioperative beta blockade: where do we go from here? Lancet 2008; 371: 1813-4.

36)Lee SM, Takemoto S, Wallace AW. Association between withholding angiotensin receptor blockers in the early postoperative period and 30-day mortality. A cohort study of the veterans affairs healthcare system. Anesthesiology 2015;123:288–306.

37)Berwanger O, Le Manach Y, Suzumura EA, Biccard B, Srinathan SK, Szczeklik W, et al. Association between preoperative statin use and major cardiovascular complications among patients undergoing noncardiac surgery: the VISION study. Eur Heart J 2016;37:177–85

38)Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/ STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA

Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. Circulation 2016; 134: e123-55

39)Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blo¨mstrom-Lundqvist C, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–619.

40)Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267–315.

41)Rodseth RN, Biccard BM, Chu R, et al. Postoperative B-type natriuretic peptide for prediction of major cardiac events in patients undergoing noncardiac surgery: systematic review and individual patient meta-analysis. Anesthesiology 2013; 119:270.

42)Rodseth RN, Biccard BM, Le Manach Y, et al. The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: a systematic review and individual patient data meta-analysis. J Am Coll Cardiol 2014; 63:170.