

Cardiovascular assessment for non-cardiac surgery: European guidelines

The European Society of Cardiology and European Society of Anaesthesiology 'Guidelines on non-cardiac surgery: cardiovascular assessment and management' (Kristensen et al, 2014) are an extremely relevant aid for all hospital medics. This article provides a markedly abridged version to accompany, but not replace them.

The incidence of cardiac complications after non-cardiac surgery depends on surgery type and circumstance, and patient-related risk factors.

Type of surgery

Surgical interventions can be classified as being associated with low, intermediate and high cardiac risk (<1%, 1–5%, and >5% 30-day risk of cardiac death and myocardial infarction respectively)(*Table 1*).

Vascular surgery is 'high-risk', especially infra-inguinal revascularization, whose risk is greater than that of aortic procedures – perhaps as a result of patients' advanced age and high incidence of diabetes, renal dysfunction and ischaemic heart disease.

Laparoscopic, endoscopic or endovascular techniques generally confer lower cardiac risk than 'open' alternatives, but older, sicker and 'urgent' patients feature more frequently in the open cohorts leading to possible bias. Importantly debilitated patients and those with cardiac disease may tolerate pneumoperitoneum or the Trendelenburg position less well.

Patient-related risk factors

Preoperative cardiac evaluation must be tailored to the patient and surgical urgency. After comprehensive history-taking and examination, including assessment of functional capacity and risk indices (below), most 'low cardiac risk' patients can undergo low- and intermediate-risk surgery without delay – risk is not significantly reduced by pharmacological intervention. Cardiac imaging should be performed only where the results would influence management.

Functional capacity

Functional capacity is assessed objectively through exercise testing, but estimated from the 'metabolic equivalents' (METs) of normal activities (one MET = basal metabolic rate at rest; four METs = climbing two flights of stairs; ten METs = strenuous sports) (Fletcher et al, 2001). Inability to run a short distance or climb two flights of stairs (<4 METs) indicates poor functional capacity and raised perioperative cardiac risk. Risk is low

ABSTRACT

In 2014, a joint task force involving the European Society of Cardiology and European Society of Anaesthesiology assembled 'Guidelines on non-cardiac surgery: cardiovascular assessment and management'. The guidelines, subsequently published in the *European Heart Journal*, are intended for physicians and collaborators involved in the perioperative care of patients undergoing non-cardiac surgery, in whom heart disease is a potential source of complications. While the guidelines are an extremely relevant and useful aid for most, if not all, medics within the hospital environment, the sheer size of the document (49 pages) renders it a feat to read and digest. Given the importance of the document for optimizing patient care, this article condenses the guidelines down to help highlight the important details.

when functional capacity is high, even in the presence of stable ischaemic heart disease or other risk factors.

Risk indices

Lee's revised cardiac risk index (Lee et al, 1999) includes six variables:

1. Type of surgery
2. Presence of ischaemic heart disease
3. Heart failure
4. Cerebrovascular disease
5. Renal failure (creatinine level >170 mmol/litre)
6. Insulin-dependent diabetes.

The American College of Surgeons National Surgical Quality Improvement Program database (Gupta et al, 2011) uses five predictors of myocardial infarction or cardiac arrest:

1. Age
2. American Society of Anesthesiologists (ASA) class
3. Type of surgery
4. Functional status
5. Elevated creatinine level (>130 mmol/litre).

Biomarkers

These can suggest myocardial injury (cardiac troponins T and I) or left ventricular dysfunction (B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP)).

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Table 1. Surgical risk estimate according to type of surgery or intervention

Low risk: <1%	<ul style="list-style-type: none"> ■ Superficial surgery ■ Breast ■ Dental ■ Endocrine: thyroid ■ Ophthalmic ■ Reconstructive ■ Carotid asymptomatic (carotid artery endarterectomy or carotid artery stenting) ■ Gynaecological: minor ■ Orthopaedic: minor ■ Urological: minor
Intermediate risk: 1–5%	<ul style="list-style-type: none"> ■ Intra-peritoneal: splenectomy, hiatal hernia repair, cholecystectomy ■ Carotid symptomatic (carotid artery endarterectomy or carotid artery stenting) ■ Peripheral arterial angioplasty ■ Endovascular aneurysm repair ■ Head and neck surgery ■ Neurological ■ Orthopaedic: major ■ Urological: major ■ Gynaecological: major ■ Renal transplant ■ Intra-thoracic: non-major
High risk: >5%	<ul style="list-style-type: none"> ■ Aortic and major vascular surgery ■ Open lower limb revascularization or amputation or thrombectomy ■ Duodeno-pancreatic surgery ■ Liver resection, bile duct surgery ■ Oesophagectomy ■ Repair of bowel perforation ■ Adrenal resection ■ Total cystectomy ■ Pneumonectomy ■ Pulmonary or liver transplant

Adapted from Glance et al (2012)

While small perioperative increases in troponin levels reflect poorer cardiac prognosis, with limited data routine biomarker assessment in non-cardiac surgery is not advised, but may be considered in high-risk patients.

Non-invasive testing

Myocardial ischaemia, left ventricular dysfunction and heart valve abnormalities are major determinants of risk. Preoperative non-invasive testing (e.g. resting or stress echocardiography, cardiopulmonary exercise testing, myocardial perfusion imaging, cardiovascular magnetic resonance imaging, computed tomography angiography) may be informative. Risk stratification

and investigation should be similar to that for patients in the non-surgical setting, and should be undertaken if coronary artery revascularization would also be considered, or to help inform patient choice or change perioperative management (e.g. type of surgery or anaesthetic technique).

Risk-reduction strategies

Pharmacological

The risk:benefit profile of medicating to decrease perioperative cardiac risk should be considered, and contraindications respected.

Beta-blockers

Cardiac beta-receptor antagonists (beta-blockers) decrease myocardial oxygen consumption by reducing heart rate and myocardial contractility. Data from trials of beta-blockers use to reduce perioperative cardiac complications are conflicting – perhaps because of differences in patients, surgery, and beta-blocker type, timing of onset, duration and dose titration. However, the consensus is that beta-blockers may be commenced preoperatively in patients known to have ischaemic heart disease. Beta1-selective antagonists without intrinsic sympathomimetic activity are preferred, with atenolol and bisoprolol over metoprolol. Treatment should ideally be initiated 30 days (and >2 days) preoperatively, with the dose up-titrated to a resting heart rate of 60–70 bpm and systolic blood pressure >100 mmHg.

Statins

Statins prevent atheromatous plaque progression, induce their regression and stabilize them. Data concerning the impact of perioperative statins on all-cause and cardiovascular mortality, and myocardial infarction, are conflicting, but patients with peripheral artery disease should receive statins, and these should be continued after vascular surgery or endovascular intervention. Statin-naive patients with peripheral artery disease should receive them starting >2 weeks before intervention, and continuing for >1 month post-surgery. Statin withdrawal >4 days following aortic surgery is associated with a three-fold risk of postoperative myocardial ischaemia. In non-vascular surgery, no evidence supports preoperative statin treatment if the patient has no other indications.

Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers

The use of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers until the day of surgery is associated with an increased risk of hypotension under anaesthesia, particularly following induction and if simultaneously taking beta-blockers. Vasopressor response may also be impaired. These drugs should thus be stopped 24 hours preoperatively when prescribed for hypertension and restarted at the earliest opportunity postoperatively. In patients with heart failure and systolic left ventricular

dysfunction, angiotensin-converting enzyme inhibitors should be continued perioperatively, and commencement considered for those not already taking them.

Calcium-channel blockers

Routine use of dihydropyridines and non-dihydropyridines is not recommended, and short-acting dihydropyridines (especially nifedipine capsules) should be avoided.

Alpha-2 receptor agonists and nitrates

Routine perioperative intravenous nitroglycerine use conveys no benefit in non-cardiac surgery, and may increase haemodynamic risk. Alpha-2 receptor agonists increase the risk of hypotension or non-fatal cardiac arrest.

Diuretics

Diuretics should be continued until the day of surgery, and resumed as soon as possible afterwards – assuming appropriate dose adjustment and volume status allows. Serum electrolytes should be monitored and corrected appropriately.

Perioperative management in patients taking antiplatelet agents

Aspirin

As continuation of aspirin increases bleeding complication risk by 50% (but not severity), it may need to be discontinued for >7 days before certain ophthalmological, neurosurgical or spinal operations. In subjects at risk of ischaemic heart disease, aspirin non-adherence or withdrawal tripled the risk of a major adverse cardiovascular event.

Low-dose aspirin use in non-cardiac surgery should therefore be individualized, balancing perioperative bleeding and thrombotic risk against cardiovascular benefit.

Dual antiplatelet therapy

Coronary stenting requires post-procedural dual antiplatelet therapy to avoid stent thrombosis. Whenever possible, surgery should proceed without discontinuation of aspirin, with elective surgery postponed (and dual antiplatelet therapy continued) for a minimum of 4 weeks and ideally <3 months after bare metal stent implantation, 6 months for second- and third-generation drug-eluting stents, and for 12 months for first-generation drug-eluting stents. In patients undergoing myocardial revascularization for high-risk acute coronary syndromes, dual antiplatelet therapy is recommended for 1 year irrespective of stent type. If surgery can not be delayed, it should be undertaken in hospitals where 24/7 cardiac catheterization availability allows immediate treatment of stent occlusion. Dual antiplatelet therapy management must be discussed between surgeon and cardiologist, weighing the risk of surgical bleeding against life-threatening stent thrombosis (on or off dual antiplatelet therapy respectively). Excessive or life-threatening perioperative bleeding in a patient receiving antiplatelet therapy should be treated with platelet transfusion.

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Perioperative management in patients on anticoagulants

Here, the risk:benefit ratio must be calculated on an individual basis.

Vitamin K antagonists

In low-risk patients with an international normalized ratio ≤ 1.5 , surgery can usually proceed safely with minimal bleeding risk. In those with high thromboembolic risk (e.g. mechanical prosthetic heart valves, recent venous thromboembolism or thrombophilia), stopping vitamin K antagonists is dangerous and these patients will need bridging therapy with unfractionated heparin or therapeutic-dose low molecular weight heparin. Both agents have advantages and disadvantages, and haematologists should help guide choice and timings of starting, stopping and then re-starting bridging therapy. Depending on the type of surgery, and whether adequate haemostasis has been achieved, vitamin K antagonists should be restarted postoperatively, normally by administering 150% of the preoperative maintenance dose for two consecutive days. The maintenance dose should be administered thereafter, and unfractionated heparin or low molecular weight heparin continued until the international normalized ratio returns to preoperative therapeutic levels.

Non-vitamin K antagonist oral anticoagulants

Non-vitamin K antagonist oral anticoagulants have short biological half-lives and a well-defined ‘on’ and ‘off’ action providing renal function is normal. ‘Bridging’ to surgery is thus generally unnecessary, and postoperative resumption of treatment should be delayed for 1–2 days (in some cases 3–5 days) until post-surgical bleeding risk is diminished. An exception is the patient with high thromboembolic risk whose surgical intervention is delayed for several days. In patients considered to have a ‘normal’ bleeding risk, non-vitamin K antagonist oral anticoagulants should be stopped for a period of 2–3 times their respective half-lives before surgery, and for a period of 4–5 times the half-lives before procedures with a high bleeding risk.

Reversal of anticoagulant therapy

Vitamin K antagonists: If anticoagulation is required before urgent surgery in patients on vitamin K antagonists, low-dose (2.5–5 mg) intravenous or oral vitamin K will lower the international normalized ratio in 6–12 hours. Additional administration of fresh frozen plasma or prothrombin complex concentrate will have an immediate effect. Anticoagulant effects of unfractionated heparin or low molecular weight heparin are usually reversed 4–8 hours respectively after stopping treatment. Protamine sulphate

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immediately reverses the action of unfractionated heparin, whereas the anti-Xa activity of low molecular weight heparin will not be completely neutralized (maximum 50%).

Non-vitamin K antagonist oral anticoagulants: Bleeding should be managed with symptomatic and supportive measure and haematological advice sought early. Specific non-vitamin K antagonist oral anticoagulant antidotes are novel (idarucizumab [Praxbind]), and may thus be difficult to get hold of. Prothrombin complex concentrate, recombinant factor VIIa and haemodialysis may offer benefit.

Revascularization

In patients with known or suspected ischaemic heart disease who are scheduled for major non-cardiac surgery, indications for coronary angiography or preoperative revascularization are similar to those in the non-surgical setting. If surgery can be safely delayed, symptoms of myocardial ischaemia should be fully investigated and treated beforehand. Asymptomatic (silent) myocardial ischaemia should not be sought before non-cardiac surgery – coronary angiography and/or revascularization before non-cardiac surgery confers no benefit beyond optimal medical management.

The role of prophylactic revascularization in patients with non-ST elevation acute coronary syndromes requiring non-cardiac surgery is not known. If surgery can be safely delayed, priority should be given to management of non-ST elevation acute coronary syndromes. Otherwise balloon angioplasty alone, or percutaneous coronary intervention using a bare metal stent or new generation drug-eluting stent, may be considered.

Specific diseases

Presence of the following conditions increases perioperative cardiac event risk.

Chronic heart failure with reduced or preserved left ventricular ejection fraction

Patients with chronic heart failure with preserved left ventricular ejection fraction are more likely to be older, female, hypertensive with atrial fibrillation, and less likely to have coronary artery disease. Generally, their prognoses are also better. Similar perioperative management is recommended in chronic heart failure patients with either reduced or preserved left ventricular ejection fraction, including assessment of left ventricular ejection fraction, general clinical status and volume overload. Elevated circulating natriuretic peptide concentrations correlate with morbidity and mortality. Routine preoperative transthoracic echocardiography should not be performed

in all, but considered in patients with known or suspected heart failure and in high-risk surgical populations. Overall functional capacity and cardiopulmonary reserve are best assessed through cardiopulmonary exercise testing – anaerobic thresholds of $<11 \text{ mL O}_2/\text{kg}/\text{min}$ suggest increased perioperative morbidity and mortality (Guazzi et al, 2012).

For patients newly diagnosed with heart failure, non-urgent surgery should be delayed >3 months. Heart failure medications should be continued throughout the perioperative period, especially beta-blockers. In general, all medications should be continued until the day of surgery – in those very susceptible to perioperative hypotension, transient discontinuation on the day before surgery may be considered (see angiotensin-converting enzyme inhibitor and angiotensin-receptor blocker section above). If stopped, all heart failure medications should be restarted as soon as possible postoperatively: administration via nasogastric tube or bioequivalent intravenous doses should be considered.

Arterial hypertension

Patients with pre-existing hypertension more commonly demonstrate profound hypotension at induction of anaesthesia, or intraoperative blood pressure lability. As a decrease in blood pressure $>20 \text{ mmHg}$ for >1 hour is a risk factor for postoperative complications, perioperative blood pressure should be maintained at 70–100% of baseline, avoiding excessive tachycardia.

In patients with preoperative hypertension, signs of organ damage should be sought. In patients with grade 1 or 2 hypertension (systolic blood pressure $<180 \text{ mmHg}$, diastolic blood pressure $<110 \text{ mmHg}$), delaying surgery to optimize therapy offers no benefit. However, in such cases, antihypertensive medications should be continued during the perioperative period.

Valvular heart disease

Any patient with known or suspected valvular heart disease should have echocardiography to determine the need for treatment before surgery.

Aortic stenosis

Severe aortic stenosis (valve area $<1.0 \text{ cm}^2$, maximum jet velocity $>4 \text{ m/sec}$ and/or mean aortic pressure gradient $\geq 40 \text{ mmHg}$) is particular high risk. If symptomatic, valve replacement should be considered before elective surgery. For those at high risk for valvular surgery or where replacement is contraindicated, balloon aortic valvuloplasty or transcatheter aortic valve implantation may be considered. In asymptomatic patients, non-cardiac surgery of low or intermediate risk can be performed safely – invasive haemodynamic monitoring and avoiding rapid changes in volume status and heart rate and rhythm are essential.

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Mitral stenosis

With valve area $>1.5 \text{ cm}^2$ or in asymptomatic patients with significant mitral stenosis (valve area $<1.5 \text{ cm}^2$) and systolic pulmonary artery pressure $<50 \text{ mmHg}$, non-cardiac surgery can be performed with low risk of major adverse cardiovascular event. With significant mitral stenotic signs and symptoms, risk from non-cardiac surgery is significantly higher – percutaneous mitral commissurotomy (or open surgical repair) should be considered preoperatively.

Primary aortic regurgitation and mitral regurgitation

In severe aortic or mitral regurgitation, left ventricular function should be assessed. If preserved, non-cardiac surgery can be performed without additional risk. If impaired ($<30\%$) or symptomatic, non-cardiac surgery should be performed only if necessary. Non-significant aortic regurgitation and mitral regurgitation do not independently increase the cardiovascular risk during non-cardiac surgery.

Patients with prosthetic valve(s)

Those without valvular or ventricular dysfunction can undergo non-cardiac surgery without additional risk. Oral anticoagulants are temporarily replaced by unfractionated heparin or low molecular weight heparin at therapeutic doses.

Arrhythmias

Both chronic arrhythmias and the discovery of a new arrhythmia mandates preoperative cardiological review and appropriate investigation, referring to appropriate guidelines (Yegnasubramanian, 2016).

Renal disease

Impaired renal function is associated with adverse postoperative cardiovascular outcomes, including myocardial infarction, stroke and progression of heart failure. Chronic kidney disease is a risk factor for the development of acute kidney injury following non-cardiac surgery: estimated glomerular filtration rate should be calculated in all patients (a value of $<60 \text{ ml/min/1.73m}^2$ correlates significantly with major adverse cardiovascular event) and proteinuria assessed (as urinary albumin:creatinine ratio).

An increased risk of acute kidney injury is also associated with age >56 years, male sex, presence of cardiac failure, ascites, hypertension or diabetes, or emergency or intraperitoneal surgery. Supportive measures (e.g. maintenance of adequate intravascular volume, use of vasopressors, avoidance of nephrotoxic agents) should be considered in all at-risk patients. Strategies to prevent acute kidney injury caused by iodinated contrast include minimizing administered volume, using less nephrotoxic

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agents, provision of prophylactic renal replacement therapy, and use of pharmacological agents to counteract contrast nephrotoxicity. Pre-procedural hydration with intravenous isotonic fluids is the most effective method of reducing the risk of contrast-induced acute kidney injury, and normal saline or isotonic sodium bicarbonate (1.26%) may be administered. The benefit of prophylaxis using N-acetylcysteine to prevent contrast-induced acute kidney injury remains unproven.

Cerebrovascular disease

Stroke (usually thromboembolic) occurs in 0.1% of non-cardiac surgical patients, but is associated with a 700% increase in perioperative mortality (absolute risk $>20\%$) (Mashour et al, 2011). Perioperative arterial hypotension is a risk factor, as is withdrawal of anticoagulation for atrial fibrillation or of antiplatelet agents (in those with atheromatous disease) during the hypercoagulable perioperative state. Patients with symptoms suggestive of transient ischaemic attack or stroke in the preceding 6 months should receive preoperative neurological consultation.

For those with symptomatic carotid artery disease, revascularization should be performed before other surgery. In asymptomatic patients with severe carotid occlusive disease, carotid revascularization is more for the long-term prevention of stroke than perioperative stroke reduction and may be performed before or after the planned non-cardiac surgery. Aside from revascularization, patients with carotid stenosis benefit from aggressive cardiovascular risk-factor modification, and in the perioperative setting, statins should be continued, aspirin and beta-blockers should not be withdrawn if possible, and blood pressure should be carefully controlled.

Any patient with peripheral artery disease is at increased risk of cerebrovascular accident and perioperative acute myocardial infarct, so should be thoroughly assessed and investigated for ischaemic heart disease. Routine exercise or imaging testing is not warranted in the absence of symptoms or other risk factors.

Pulmonary disease

This increases perioperative risk, especially of postoperative pulmonary complications. Risk is particularly high in patients with smoking-related lung disease, and after abdominal or thoracic surgery. Chronic obstructive pulmonary disease and obesity hypoventilation syndrome are also especially associated with cardiovascular pathology, and such patients (and any with pulmonary artery hypertension) require cardiac risk assessment.

KEY POINTS

- The incidence of cardiac complications after non-cardiac surgery depends on the interaction between the type of surgery and the circumstances under which it occurs, and patient-related risk factors.
- Surgical interventions can be divided into those associated with low-, intermediate- and high-cardiac risk.
- Preoperative cardiac evaluation must be tailored to the patient and surgical urgency.
- Cardiac imaging should be performed only where results would influence management.
- Continuing or ceasing dual antiplatelet therapy in those with coronary stents, must be discussed between surgeon and cardiologist, weighing risk of surgical bleeding against life-threatening stent thrombosis.

Independent of age, gender and smoking history, every 10% decrease in forced expiratory volume in 1 second is associated with a 30% increase in cardiovascular mortality and a 20% increase in non-fatal coronary events (Sin et al, 2005). Chronic obstructive pulmonary disease is a risk factor for ischaemic heart disease, and also leads to cor pulmonale with associated right heart failure. In patients with chronic obstructive pulmonary disease, perioperative cardiovascular risk must be assessed and managed, and pulmonary function optimized. Education regarding preoperative smoking cessation (>2 months before surgery), chest physiotherapy and lung expansion manoeuvres is advocated, as may be muscular endurance training and re-nutrition if required. Beta-blockers and anticholinergic agents should be continued until the day of surgery in all symptomatic patients with chronic obstructive pulmonary disease who also have bronchial hyper-reactivity. In some cases, the use of short-term systemic or inhaled steroids may be considered.

Obesity hypoventilation syndrome (obesity, daytime hypoventilation and sleep-disordered breathing) is associated with ischaemic heart disease, heart failure (and obesity-related cardiomyopathy), pulmonary hypertension and cor pulmonale, and increased perioperative mortality. Patients at high risk of obesity hypoventilation syndrome who are undergoing major surgery should be referred for specialist investigation.

Pulmonary arterial hypertension (mean pulmonary arterial pressure >25 mmHg at rest) can be primary or the consequence of diverse lung vascular or parenchymal diseases, or of cardiac disease (e.g. mitral valve disease or intra-cardiac shunts). It is associated with increased postoperative complications, including right ventricular failure, myocardial ischaemia and postoperative hypoxia. Treatment should be optimized preoperatively, and management should be at a centre with appropriate expertise. Patients receiving pulmonary arterial hypertension-specific therapy must not have drugs withheld for the preoperative fasting state, and may require temporary conversion to intravenous and/or nebulized treatment until they are able to reliably absorb via the enteral route.

Congenital heart disease

Patients with congenital heart disease are at increased risk from non-cardiac surgery, but risk varies with the degree of associated heart failure, pulmonary hypertension, arrhythmias and blood shunting, and the complexity of the underlying condition. Complicated patients should only undergo non-cardiac surgery after thorough evaluation by a multidisciplinary team in a specialized centre.

Disturbed glucose metabolism and perioperative monitoring

Diabetics face greater perioperative mortality or morbidity. Blood glucose concentration fluctuation should be minimized and hypoglycaemia or hyperglycaemia avoided. In the intensive care unit, blood glucose concentrations below 6.1 mmol/litre are not recommended and insulin infusions should be instigated if blood glucose concentrations reach 10.0 mmol/litre.

Conclusions

Both surgical and patient-related factors determine the risk of developing cardiac complications after non-cardiac surgery. The extent of preoperative cardiac evaluation must be guided by a comprehensive history and examination. The risks and benefits of delaying non-cardiac surgery to optimize a patient's pathophysiology must be evaluated case-by-case, with advice from other specialties where necessary. **BJHM**

Conflict of interest: none.

- Fletcher GF, Balady GJ, Amsterdam EA et al (2001) Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation* **104**(14): 1694–1740. <https://doi.org/10.1161/hc3901.095960>
- Glance LG, Lustik SJ, Hannan EL et al (2012) The Surgical Mortality Probability Model: derivation and validation of a simple risk prediction rule for non-cardiac surgery. *Ann Surg* **255**: 696–702. <https://doi.org/10.1097/SLA.0b013e31824b45af>
- Guazzi M, Adams V, Conraads V et al; EACPR; AHA (2012) Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Eur Heart J* **33**(23): 2917–2927. <https://doi.org/10.1093/eurheartj/ehs221>
- Gupta PK, Gupta H, Sundaram A et al (2011) Development and validation of a risk calculator for prediction of cardiac risk after surgery. *Circulation* **124**(4): 381–387. <https://doi.org/10.1161/CIRCULATIONAHA.110.015701>
- Kristensen SD, Knuuti J, Saraste A et al.; Authors/Task Force Members (2014) 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management. *Eur Heart J* **35**(35): 2383–2431. <https://doi.org/10.1093/eurheartj/ehu282>
- Lee TH, Marcantonio ER, Mangione CM et al (1999) Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* **100**(10):1043–1049. <https://doi.org/10.1161/01.CIR.100.10.1043>
- Mashour GA, Shanks AM, Kheterpal S (2011) Perioperative stroke and associated mortality after noncardiac, nonneurologic surgery. *Anesthesiology* **114**(6): 1289–1296. <https://doi.org/10.1097/ALN.0b013e318216e7f4>
- Sin DD, Wu L, Man SFP (2005) The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest* **127**(6): 1952–1959. <https://doi.org/10.1378/chest.127.6.1952>
- Yegnasubramanian S (2016) Prostate cancer epigenetics and its clinical implications. *Asian J Androl* **18**(4): 549–558. <https://doi.org/10.4103/1008-682X.179859>