



### Review Article

## Perioperative ischaemia and management of patients with coronary stents: current practice.

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#### Abstract

Perioperative ischaemia is a common cause of cardiac morbidity and cardiac death during perioperative period in patient with coronary artery disease or with other risk factors. The incidence of perioperative ischaemia is about 20 to 70% in patient with coronary artery disease or coronary artery disease risk factors. Post operative cardiac events (the combined incidence of nonfatal myocardial infarction, unstable angina, heart failure and sudden cardiac death) vary between 5.5 to 53% and postoperative myocardial infarction varies between 1.4 to 43%. Prolonged ST- segment depression along with hypercoagulability caused by surgical stress, platelet activation, increased fibrinogen activity and decreased fibrinolytic activities may lead to coronary thrombosis, ischaemia, nonfatal infarction or sudden cardiac death. Patients with coronary stents especially before complete endothelialization of the stents are of high risk category for these complications. Anesthesiologist being a perioperative physician should understand safety issues of these patients to prevent from ischaemia, coronary thrombosis and subsequent infarction or sudden cardiac death. Risk identification, optimization, monitoring, diagnosis of the problem, prevention and management are very crucial during perioperative period to enhance the quality service and patient safety.

**Key words:** Coronary, Myocardial ischaemia, Perioperative, Stents.

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Perioperative cardiac morbidity is the leading cause of death after surgery and anesthesia. The incidence of perioperative ischaemia in coronary artery disease (CAD) patient and CAD risk patients ranges upto 60%.<sup>1</sup> It varies about 20% during preoperative period, 25% during intraoperative period and 41% postoperatively. Post operative myocardial infarction (MI) is usually common till third postoperative days. The reported incidence of postoperative cardiac events (the combined incidence of nonfatal myocardial infarction, unstable angina, congestive heart failure, cardiac death) varies between 5.5 and 53% and that of postoperative myocardial infarction between 1.4 and 38%.<sup>2</sup> Perioperative ischaemia confers nine fold increase in ischemic events defined as cardiac death, nonfatal MI or unstable angina.<sup>2</sup> Over 50,000 patients each year sustain perioperative MI in United States of America (USA).

Unrecognized Perioperative ischaemia and myocardial infarctions are common and up to 50% of perioperative myocardial infarctions may go unrecognized if physicians rely only on clinical signs and symptoms.<sup>3</sup> Large number

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of perioperative ischaemia and myocardial infarctions are not recognized because during this period patients receive analgesics, most of the high risk patients either sedated or ventilated when they may not be able to communicate, surgical patients having potential signs of MI like (hypotension, tachycardia) and symptoms like (shortness of breath, nausea) may have a host of more common potential explanations (e.g., atelectasis, pneumonia, hypovolemia, bleeding, medication side effects etc).

The possible factors of the perioperative ischaemia (Figure 1) may be pain, anaemia, hypovolemia, hypothermia and inflammatory response all they will activate the sympathetic nervous system and cortisol release, with the adverse effects on cardiovascular function and coagulation. The result will be an increase in myocardial oxygen consumption in presence of decreased delivery along with hypercoagulability may lead to myocardial infarction.

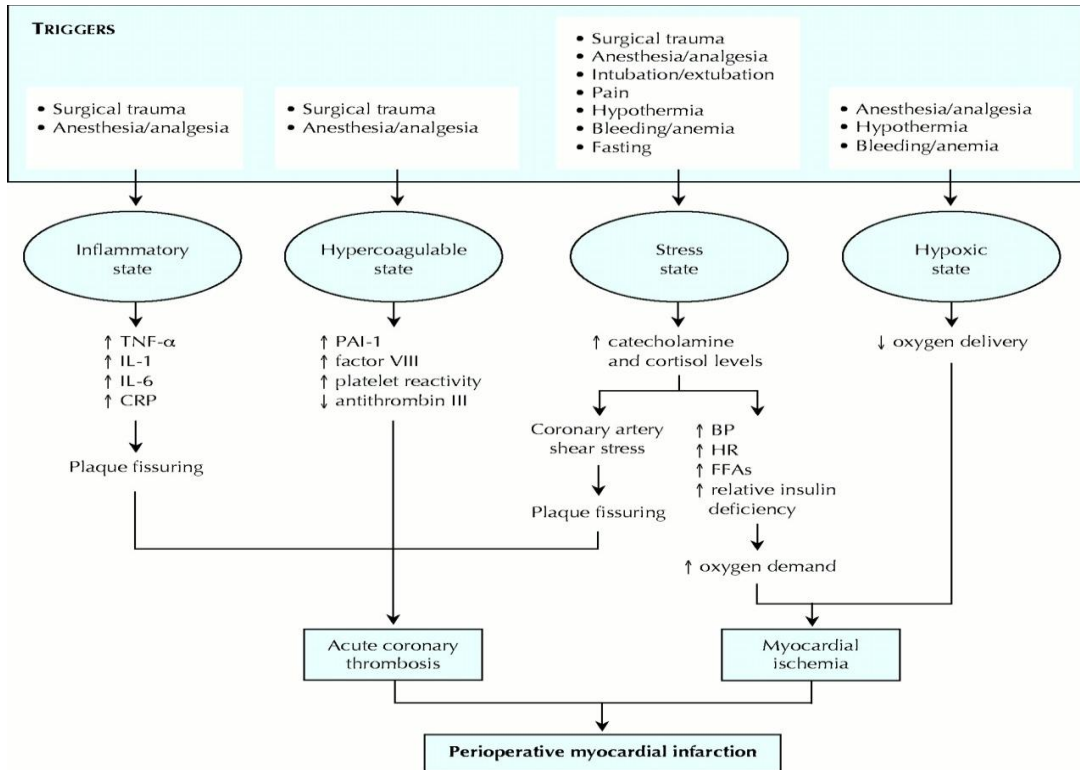


Figure 1: Potential triggers of states associated with perioperative elevations in troponin levels, arterial thrombosis and fatal myocardial infarction. (Devereaux P et al. CMAJ 2005;173:627-634)

**Monitoring modalities**

Electrocardiography (ECG): Surface ECG is the most commonly used modality, less costly, non invasive. Computerized ST – segment analysis helps to detect the ischaemia because > 80% ischaemia episodes present as ST- depression. Ischaemia may lead to infarction, especially when the ischaemia is sustained over time (>2 hours) but it is unreliable in left ventricular hypertrophy (LVH), strain patterns, ventricular pacing and in some arrhythmias. During intraoperative period V5 could detect 75% of ischaemia, lead II and V5 could 80% and lead II, V5 and V4 could detect up to 96 to 98% ischaemia.<sup>4</sup>

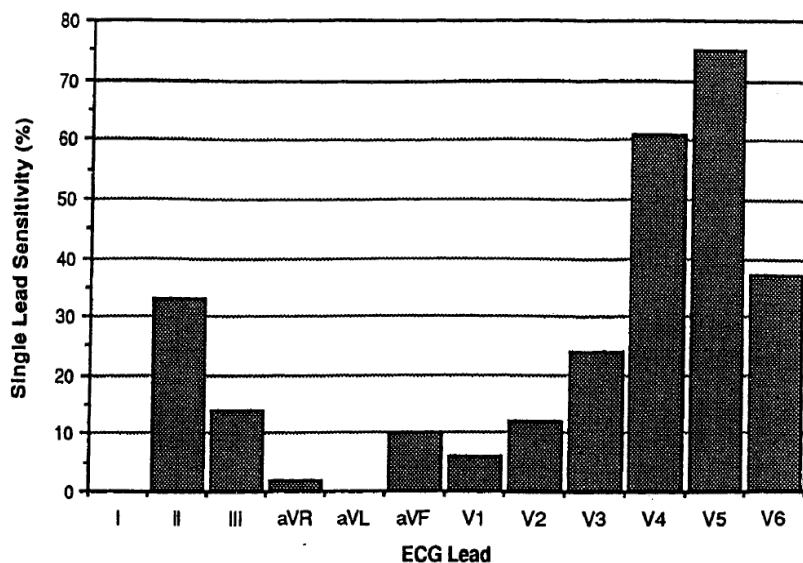


Figure 2: The sensitivity of individual ECG leads to detect myocardial ischaemia is variable; V5 has the greatest sensitivity. MJ London, M Hollenberg, MG Wong et al: Intra-operative myocardial ischaemia: Localization by 12-lead ECG. *Anesthesiology* 69:232-241,1998.

Trans-esophageal Echocardiography (TEE): Evidences suggest segmental wall motion abnormality occurs earlier than the ECG changes at the onset of the ischaemia. The echocardiographic changes during ischaemia are thinning of ventricular wall during systole and thereafter wall motion abnormality. It requires well trained person, cost involvement and may be difficult in a wake patient during regional anaesthesia technique and postoperative period.

Pulmonary Artery Catheter (PAC): Ischaemia detection is possible with this technique but is distant third choice after ECG or TEE because continuous inflation of balloon tipped catheter is not possible and requires frequent inflation of catheter. Changes in wedge/pulmonary artery (PA) waveforms or absolute increase in mean PA wedge pressure more than 10 mmHg are suggestive of ischaemia.

Cardiokimography (CKG): A capacitive plate is placed over the chest wall that senses the movement of the heart throughout the cardiac cycle by interaction of radiofrequency (10 to 20 MHz) electromagnetic field generated by a sensing coil with the thorax. It can qualitatively detect the abnormal motion of the anterior wall. Abnormal motion of anterolateral, posterolateral and inferolateral wall can not be detected. It is nonsensitive technique and not feasible to apply in thoracic and upper abdominal procedures.

### Diagnosis

There is no accepted gold standard for the diagnosis of myocardial ischaemia. Generally, the diagnosis can be based on hemodynamic (pulmonary artery capillary wedge and/or left atrial pressure wave), electrocardiographic (ECG), functional (echocardiogram), metabolic (coronary lactate production), biochemical (release of creatine kinase-MB isoenzyme and/or troponin) or regional perfusion (scintigram) parameters.<sup>5</sup>

The cardiac troponins T and I, which are highly specific and sensitive for myocardial injury (figure 3), which shows best enzymatic detection of the MI by cardiac troponin T and I which may last up to two weeks after two to three hours of infarction, while CPK-MB may persist only upto 72 hr and is less specific.<sup>6</sup> The European Society of Cardiology and the American College of Cardiology have proposed following two criteria satisfy the diagnosis of an acute, evolving or recent myocardial infarction: (i) a typical increase and gradual decrease in troponin concentrations or more rapid increase and decrease in creatine kinase-MB concentration in combination with at least one of the following: (a) typical ischaemic symptoms, (b) development of pathological Q-waves in the ECG, (c) ECG changes indicative of myocardial ischaemia (ST-segment elevation or depression), and (d) coronary artery intervention; and (ii) pathological findings of an acute myocardial infarction.

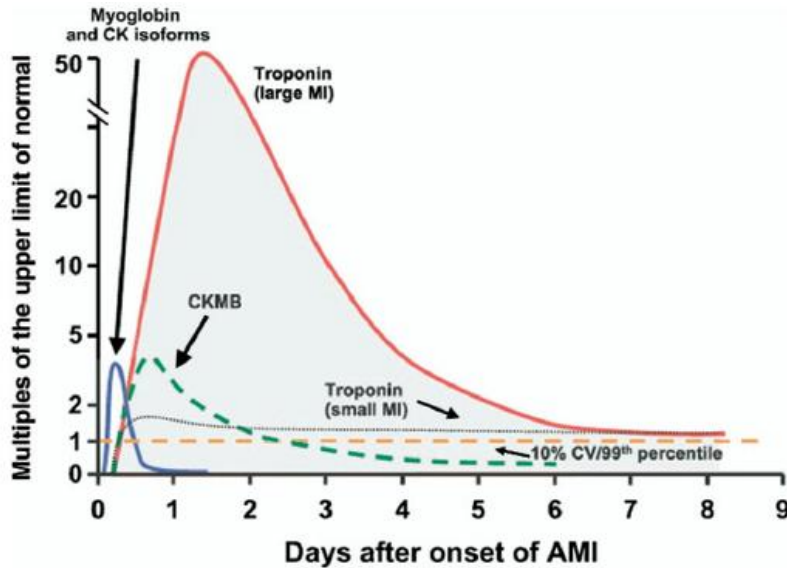


Figure 3: Biochemical markers release, peak and duration of elevation. J Am Coll Cardiol 2011;57(19):e215-367.

Characteristics of perioperative ischaemia and infarction: Most ischemic episodes start at the end of surgery and during emergence from anaesthesia. The vast majority (more than 90%) of postoperative episodes of myocardial ischaemia are silent. Postoperative ST-segment changes are almost exclusively episodes of ST-segment depression rather than elevation.<sup>7</sup> Long-duration (single duration >20 to 30 min or cumulative duration >1 to 2 h) ST-segment change, rather than merely the presence of postoperative ST-segment depression, seems to be the important factor associated with adverse cardiac outcome.<sup>8</sup>

Most of the post operative myocardial infarctions (60 to 100%) are of the non-Q-wave type. The vast majority of perioperative myocardial infarctions are preceded by episodes of ST-segment depression and prolonged ischaemia.

Angiographically thrombus and plaque ruptures resulting embolism to distal part of the coronaries are uncommon, which suggests prolonged ischaemia and ST-depression being underlying reason.

### Interventions for prevention

**$\beta$ -Adrenoceptor antagonists:** Perioperative  $\beta$ -blocker therapy can provide a 60 to 65% reduction in the likelihood of non-fatal myocardial infarction and cardiac death. They reduce heart rate, pressure and contractility and reduce oxygen consumption. In patients with suspected or documented coronary artery disease, it may reduce the incidence and severity of perioperative myocardial ischaemia and infarction.<sup>5</sup>

**$\alpha_2$ -Adrenoceptor agonists:** They attenuate perioperative haemodynamic instability, inhibit central sympathetic discharge, reduce peripheral norepinephrine release and dilate poststenotic coronary vessels.

**Aspirin:** It eliminates the diurnal variation in plaque rupture, reduce the inflammatory mediators, and reduce platelet aggregation.

**Statins:** They have the property of coronary plaque stabilization by their anti-inflammatory action.

Coronary stent thrombosis is one of the leading causes of perioperative ischaemia, infarction and death of the patient who undergo noncardiac surgery in early period after stenting when there is no complete endothelialisation of the coronary stents. In Nepal only around 1000 patients undergo PCI and stenting of coronary vessels each year.<sup>9</sup> Of the more than 2 million patients undergoing PCI annually world wide, more than 90% will receive one or more intracoronary stents.<sup>10</sup> Approximately 5% of patients in this group will undergo noncardiac surgery within the first year after stenting, and an increasing number will continue to present for surgery thereafter.<sup>11</sup> Because success of the stents requires long-term antiplatelet therapy, management of patients with

these devices poses a dilemma to the anesthesiologist. The dilemma is stent thrombosis on discontinuation of the antiplatelet therapy and bleeding during surgery on continuation of the antiplatelet therapy.

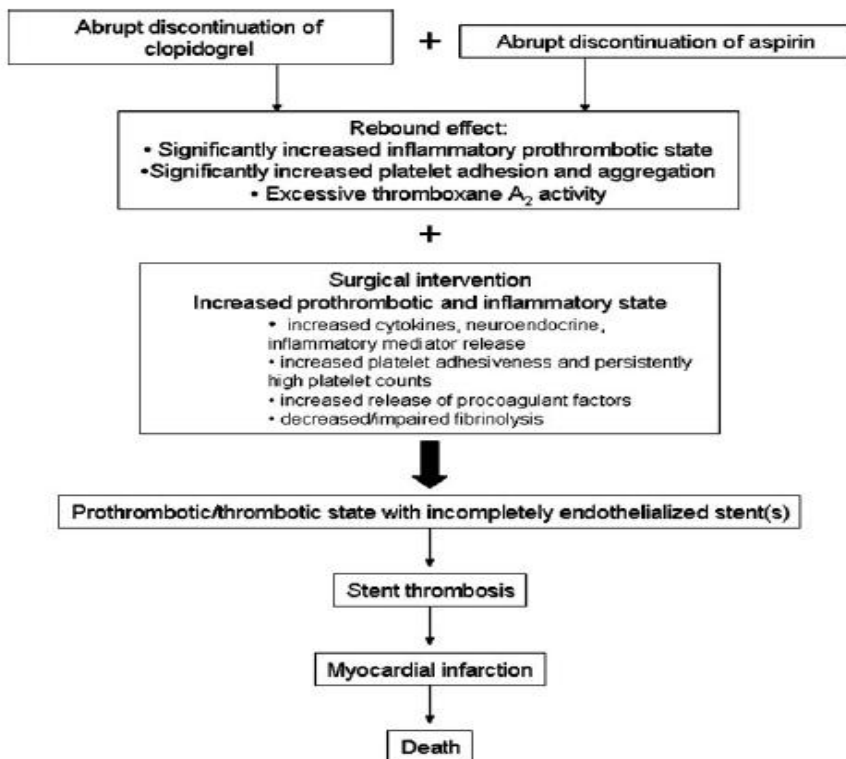


Figure 4: Showing abrupt discontinuation of antiplatelet agent and its consequences.

Abrupt discontinuation of antiplatelets in patients with coronary stent increases the 5 to 10 times cardiac death.<sup>12</sup>

After coronary stenting patients are recommended to continue dual antiplatelet therapy (aspirin and clopidogrel) till endothelialization of the stent (6 weeks for the bare metal stent and 12 months for drug eluted stents), there after usually aspirin is continued life long.<sup>13</sup> These patients while going for non-cardiac surgery carry a significant risk of stent thrombosis and which is more evident in early period before endothelialization. The risk factors are time after stenting, stents on bifurcations, overlapping stents, long stents, type of the stents, diabetes mellitus and renal failure.

AHA/ACC guideline 2007 suggests the following algorithm for the perioperative management of the patients with coronary stents. Figures 5 and 6 show the flowchart for management strategy of this category of the patients. For the patients with bare metal stents, if the surgery is elective, then postpone for 6 weeks and continue aspirin if at all possible. If surgery is in intracranial space, spinal canal or posterior chamber of the eye, stop aspirin and restart as soon as possible postoperatively. If it is before 6 weeks of the stenting then continue dual antiplatelet therapy perform surgery except in intracranial, posterior chamber of the eye and spinal canal surgery or adopt the bridging therapy.

For the patients with drug eluting stent where dual antiplatelet therapy is continued for 12 months and elective surgery is postponed for the 12 months and perform surgery with aspirin if at all possible after this period. However some recently published articles recommend equally safe to perform the elective surgeries after six months of DES implantation.<sup>14</sup> Where aspirin continuation is not recommended, it should be stopped and restarted as soon as it is possible after surgery or apply bridging therapy with the infusion of tirofiban or eptifibatid and withhold it few hours before surgery and restart as early as possible after surgery. Before 12 months of drug eluting stents implanted either continue dual antiplatelet agents or apply bridging therapy. All these noncardiac surgeries should be done where 24 hour intervention of coronary artery is performed or the

cardiologist who can perform the coronary stenting should be available with necessary gadgets, equipments safety backup.

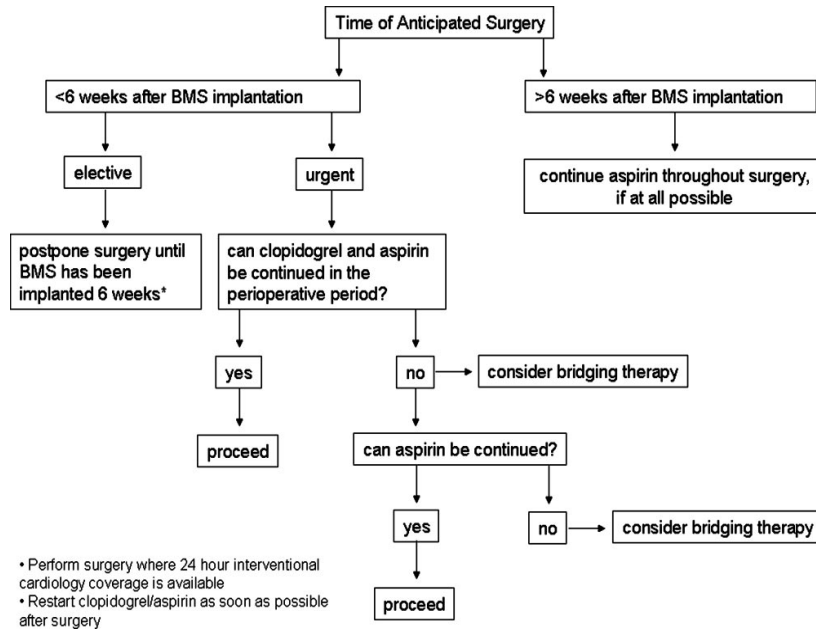


Figure 5: Proposed algorithm for perioperative management of patients with bare-metal stents based on current literature.\*The 2007 ACC/AHA perioperative guidelines state, “it appears reasonable to delay elective noncardiac surgery for 4–6 wk to allow for at least partial endothelialization of the stent, but not for more than 12 wk, when restenosis may occur.”

For the management of drug eluting stents the following flowchart is applicable (AHA/ACC 2007 recommendations):

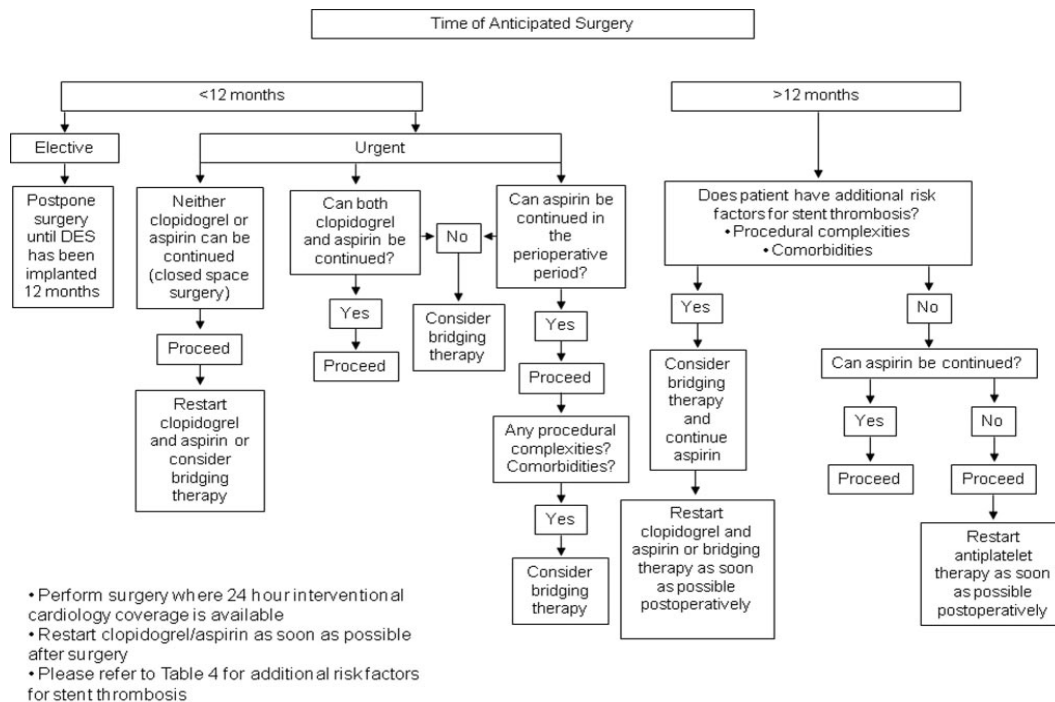


Figure 6: Proposed algorithm for perioperative management of patients with drug-eluting stents based on current literature (AHA/ACC 2007 Recommendations).

### **Bridging therapy**

Replacement of standard oral antiplatelet therapy with a short-acting agent to act as a bridge for the period between discontinuation of clopidogrel and/or aspirin and surgery has been suggested.<sup>15</sup>

“Bridging therapy” with aspirin and heparin: Heparin is commonly used as a substitute to aspirin or thienopyridines, because of its efficacy in the treatment of unstable angina and non–ST-segment elevation myocardial infarction. However, heparin is an antithrombin agent and not an antiplatelet. The use of antithrombotics such as unfractionated heparin (UFH) and low molecular weight heparin (LMWH) has been proposed in perioperative management of drug eluted stents (DES). However, these therapies have not been proven to be effective.<sup>16</sup> Stent thrombosis is a platelet mediated process, it is expected that antithrombotics (UFH and LMWH) are not ideal for “bridging”.

“Bridging therapy” with aspirin and a glycoprotein (GP) IIb/IIIa inhibitor: GP IIb/IIIa is a platelet integrin. Platelet activation transforms the integrin into a state of high affinity to fibrinogen, which is the final common pathway of platelet aggregation and clot formation. GP IIb/IIIa inhibitors act by blocking fibrinogen-mediated cross-linking between platelets, thereby inhibiting platelet aggregation.<sup>17</sup> Abciximab (ReoPro, Eli Lilly and Company, Indianapolis, Indiana) causes a prolonged irreversible antagonism of GP IIb/IIIa leading to platelet aggregation inhibition that lasts for at least 48 h and up to 7 days.<sup>18</sup> Given its prolonged inhibition time, abciximab should not be used perioperatively. The synthetic peptides eptifibatide (Integrilin, Millennium Pharmaceuticals, Boston, Massachusetts) and tirofiban (Aggrastat, Merck and Co., Inc., West Point, Pennsylvania) are competitive reversible binders to GP IIb/IIIa receptors and dissociate rapidly with less affinity than abciximab.<sup>19</sup> Their half-life is quite short, and platelet function is about 60% to 100% restored 2 to 4 h after stopping the infusion, making them potentially suitable for perioperative use.<sup>20</sup>

### **Considerations for regional anesthesia for patients with coronary artery stents**

In patients with coronary artery stents, particularly DES, the use of regional anesthesia (RA) must be carefully considered. RA, particularly neuraxial blockade, attenuates the hypercoagulable perioperative state by blunting the sympathetic response. Systemic absorption of local anesthetics provides antiplatelet effects by blocking Thromboxan A<sub>2</sub> and decreasing platelet aggregation.<sup>21,22</sup>

It is generally interpreted from the 2003 American Society of Regional Anesthesia (ASRA) guidelines that the thienopyridines and dual-antiplatelet therapy are contraindications to neuraxial anesthesia or peripheral nerve blockade in noncompressible regions that cannot be observed for bleeding.<sup>23</sup>

Although the ASRA recommends discontinuing clopidogrel 7 days and ticlopidine 14 days before RA; they also state, “Variances from recommendations may be acceptable based on the judgment of the responsible anesthesiologist”. Following the guidelines confers no guarantee that neuraxial anesthesia will be free from bleeding complications.

Aspirin alone does not appear to increase the risk of neuraxial hematoma, and does not appear to interfere with the performance of neuraxial blockade.<sup>23</sup> However, the concurrent use of UFH or LMWH increases the risks of bleeding and neuraxial hematoma in the presence of aspirin monotherapy.

In patients receiving LMWH prophylaxis alone, the current ASRA guidelines recommend delaying neuraxial blockade at least 12 hours after the last LMWH dose. Patients receiving higher doses will require delays of at least 24 hours to assure normal hemostasis at the time of needle placement. However, in patients who have received UFH for >4 days, a platelet count should be obtained to exclude heparin-induced thrombocytopenia. For patients receiving bridging therapy with eptifibatide or tirofiban, 8 hours must elapse before a neuraxial blockade can be performed.

Current ASRA guidelines recommend removal of an epidural catheter 1 h before administration of UFH, and 2 h before LMWH.

### Management of perioperative stent thrombosis

Along with the supportive therapy immediate percutaneous coronary intervention (PCI) is the treatment of choice and that is the reason why such patients should be managed where such facilities are available. Administration of thrombolytic therapy is often prohibitive in the perioperative period and is less effective for the reperfusion.<sup>24</sup>

### Novel developments and future

A number of different stents with pro-healing surfaces (endothelial progenitor cells-CD34 receptor) are becoming available which may allow much more rapid and complete endothelialisation of the stented segment. The Genous-R stent consists of a standard stainless steel stent, which is coated in a matrix containing monoclonal antibodies targeted specifically at the CD34 receptor. This receptor is exclusive to the surface of endothelial progenitor cells, which are preferentially captured onto the stent surface. Once attached to the stent surface, the endothelial progenitor cells mature into endothelial cells, rapidly creating a smooth endothelial surface within the stented segment without the risk of restenosis. The requirement of dual antiplatelet therapy is about 28 days. The biological stents require less than 12 days of dual antiplatelet therapy.<sup>15</sup>

Prasugrel, a more potent thienopyridine but may cause more bleeding. For this reason it is not preferred perioperatively. Ticagrelor (AZD6140) is also a novel oral adenosine diphosphate P2Y<sub>12</sub> receptor antagonist. It is more potent but chance of bleeding is less with action of 6 to 13 hours. It can be stopped just 24 hours before surgery and can be restarted post operatively with less major adverse cardiac events (MACE). Cangrelor is also a novel reversible P2Y<sub>12</sub> receptor antagonist that is administered intravenously. Given its rapid onset, reversibility, and a 3-min half-life, cangrelor would be a potential "bridging therapy" in the perioperative setting. In this case, cangrelor would be stopped minutes before procedure and resumed sooner than other antiplatelets post-operatively. Moreover, even maintaining cangrelor throughout surgery might be considered, given its clinical profile. PRT060128 is an investigational, direct-acting, reversible P2Y<sub>12</sub> receptor antagonist that can be administered orally or intravenously. Various other novel antiplatelet agents, such as the protease-activated receptor-1 antagonist E5555, thrombin receptor antagonists such as SCH-530348, and new thromboxane inhibitors such as the NCX-4016 are all undergoing investigations.<sup>25</sup>

### Conclusion

Prolonged perioperative ischaemia is the main cause of infarction and may go undetected if proper monitoring is not adopted. Acute stent thrombosis due to activation of platelets and hypercoagulability during perioperative period is eminent in patients with coronary stents. Perioperative management of patients with stents is a critical issue. Maintenance of dual antiplatelet therapy remains the mainstay of stent thrombosis (ST) prevention. In cases with high risk for bleeding, maintaining short-term single antiplatelet therapy with aspirin is associated with low risk of stent thrombosis. If aspirin must be discontinued, various management strategies for bridging antiplatelet activity could be considered, although there are few evidence-based data in this regard. Furthermore, intensive peri-operative monitoring and prompt intervention are of paramount importance should ST occur. It will be better if such patients are operated in the hospital where 24 hours percutaneous coronary intervention services are available.

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