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Perioperative ST-elevation myocardial infarction: with time of the essence, is there a case for guidelines?

Fiona M. Ratcliffe[1,*], Rajesh Kharbanda[2] and Pierre Foëx[1]

[1]Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford, UK and [2]Department of Cardiology, John Radcliffe Hospital, Oxford, UK

*Corresponding author. E-mail: fiona.ratcliffe2@ouh.nhs.uk

With the announcement by the Royal College of Anaesthetists of the National Audit Programme 7 (NAP7) on perioperative cardiac arrest, it is opportune to examine the management of early perioperative ST-elevation myocardial infarction (STEMI), a life-threatening, adverse event. With pharmacological and technical developments in coronary reperfusion over recent decades, together with substantial evidence on the impact of early reperfusion on survival, primary percutaneous coronary intervention (pPCI) has evolved as first-line treatment for STEMI. There are UK guidelines for the management of STEMI [National Institute for Health and Care Excellence (NICE); updated November 2018][1] and also guidelines on myocardial revascularisation from the European Society of Cardiology and European Association Cardiothoracic Surgery 2018.[2] Yet there is no consensus on the management of STEMI in the perioperative setting.

Perioperative STEMI

Perioperative myocardial infarction (PMI) is an uncommon and life-threatening event. The incidence of PMI depends on

the definition and the cohort of patients, but in a large study of 9 million hospitalisations of patients older than 45 yr undergoing noncardiac surgery, the incidence was 0.9%[3] and up to 11% or more in high-risk groups.[4] Incidence peaks within the first 3 postoperative days,[4,5] and up to one-third are STEMI, mortality from which is up to 30% at 30 days.[4–7] At 1 yr, mortality for PMI and for myocardial injury (troponin elevation alone) was 22% in a recent study.[6] In STEMI, the cause is acute thrombotic occlusion of an epicardial coronary artery, where expedited recanalisation of the occluded artery can salvage the critically ischaemic myocardium, improving left ventricular function and survival.[8] Consideration needs to be given to urgent coronary reperfusion based on experience in non-surgical settings.

Initial management of STEMI in the non-operative setting

The standard practice management of STEMI is by pPCI and stent deployment.[9] This follows sequential advances in reperfusion therapy using both pharmacological and mechanical approaches, with mortality rates for acute myocardial infarction (AMI) decreasing over the past few decades from 15%[9] to 3–4%,[10–14] the greatest impact being in patients with STEMI. Early reperfusion trials used fibrinolysis, but this is now reserved for situations where rapid transfer to cardiac intervention units cannot be achieved and would not be considered after recent surgery with bleeding risk. Crucially, the benefits of pPCI are time-sensitive, with most myocardial cell death occurring within 20 min of occlusion and complete within 6 h.[15] Consistent with this, if pPCI treatment is delivered within 90 min, in-hospital mortality is about 3% and increases to 7.4–12.2% for delays >150 min.[15–17] The Feedback Intervention and Treatment Times for STEMI with 12 675 patients showed a linear relationship between in-hospital mortality and time from first call for help to pPCI or contact-to-balloon time (CtBt). In-hospital mortality was 3.9% for CtBt <90 min *vs* 12.2% for CtBt >90 min.[18] Failure to achieve rapid reperfusion has a longer-term impact on major adverse cardiac events (MACE) at 1 yr of 10.4% when pPCI was performed <240 min from first call, to 18% for >240 min.[19] Similarly, mortality at 7 yr, doubles to 27% for delayed pPCI over 3 h.[17] Thus NICE guidelines recommend pPCI should be achieved within 120 minutes of call for help.

Management of perioperative STEMI

For PMI, a large retrospective analysis of nearly 1 million hospitalisations for noncardiac surgery showed a reduction in hospital mortality rate following PMI over the 8 year period from 2005 to 2013. Within this study, a propensity-matched cohort showed a reduction in mortality from 18.1% to 8.9% by applying an invasive strategy, predominantly PCI but also in some cases coronary artery bypass grafting (CABG) surgery.[3] This would suggest that the clear benefits of pPCI in the non-perioperative period could be transferable to the perioperative setting. With perioperative STEMI occurring in-hospital, one might expect similar, or even greater, advantages from rapid intervention and reperfusion. Nevertheless, there is a reticence to perform pPCI perioperatively because of the perceived bleeding risks with peri-procedural antithrombotic, anticoagulant, and follow-on dual antiplatelet therapy (DAPT), together with the lack of a prospectively designed (operating theatre) policy for rapid management of perioperative STEMI. However, in order to design guidelines it is necessary to appreciate the developments, both mechanical and pharmacological, which underpin successful coronary reperfusion.

Reperfusion options

Mechanical devices

Original stents were bare metal stents (BMS), and required DAPT for 4–6 weeks for prevention of stent thrombosis on the exposed stent surface.[20] However, endothelialisation leads to stent stenosis from neointimal proliferation of smooth muscle cells,[21] necessitating antiproliferative drugs to be added to a polymer on the BMS (sirolimus, paclitaxel, or zotarolimus), forming the first-generation drug-eluting stents (DES). But the delay in endothelialisation of the DES necessitates DAPT for 1 yr to prevent stent thrombosis. Second-generation DES with improved design, eluting antiproliferative drug (e.g. everolimus, biolimus) over 1 month, require DAPT for a shorter duration, although in most studies patients received at least 12 months DAPT. Further developments in DES have occurred,[22] including the Biofreedom stent,[23] which elutes umirolimus over 1 month and so requires DAPT for a minimum of 1 month with aspirin thereafter. These are suitable for elderly patients with more bleeding risk and often in need of non-deferrable surgery.

Percutaneous transluminal coronary angioplasty without stenting

Before stent development, simple balloon angioplasty was used to open up the coronary occlusion. However, percutaneous transluminal coronary angioplasty (PTCA) is associated with acute re-occlusion in about 8.3% of cases (possibly higher in STEMI).[24,25] Patients who undergo elective PTCA are benefited by DAPT, are less prone to sub-acute thrombosis (24 h–30 days), and aspirin alone is protective.[25] Thus balloon angioplasty alone without stenting could be considered in patients at very high risk of bleeding and where there is major concern about the use of antithrombotic drugs and subsequent DAPT if the technical result is satisfactory and the risk of vessel re-occlusion can be managed.

PTCA and deferred stenting

After observational experience with pPCI for STEMI, in about 10% of cases restoration of coronary flow beyond the epicardial vessel is suboptimal with slow flow or no flow in the microcirculation because of chronic *in situ* disease or embolised thrombus. The dense acute thrombotic clot and ruptured plaque provides a challenge for reperfusion and stent deployment. Several trials have studied immediate PCI *vs* PTCA with intravenous antithrombotic drugs, and with or without heparin followed by deferred PCI. The available evidence suggests in that in high-risk STEMI, deferred PCI reduces periprocedural composite events (acute occlusion, no or slow reflow, distal embolisation) and possibly improves longer-term left ventricular function. Of relevance to the perioperative setting, this strategy presents a temporising option for very high-risk surgical bleeding cases, using PTCA and reversible intravenous antithrombotic drugs until the bleeding risk of surgery is deemed low such that PCI could be performed with follow-on DAPT.[26]

Newer technical options

Recently, drug-coated balloons (DCB) coated with antiproliferative drug, usually paclitaxel, can be used to dilate and deposit antiproliferative drug onto the intraluminal wall during angioplasty. These DCB have been used for AMI and are the topic of a recent review.[27,28] Experience with this technique is limited, and risk of premature cessation of one or both components of DAPT for emergency surgery is unknown. Indeed, all options for coronary reperfusion require administration of DAPT.

Pharmacological

Antiplatelet therapy and importance of DAPT with stents

Stent thrombosis is a serious complication, the incidence of which is <2.0% with DES for elective PCI,[29,30] and is 2.5 times greater when performed for pPCI. The mortality rate from stent thrombosis is high, up to 45%.[14,31,32] Pharmacological prevention of stent thrombosis must include a $P2Y_{12}$–adenosine diphosphate (ADP) receptor blocker, usually clopidogrel or ticagrelor,[33] as part of the antiplatelet regimen, as it is the activation of platelet fibrinogen receptors that is associated with stent thrombosis.[25] Blockade of the $P2Y_{12}$ receptors in large trials reduces the incidence of stent thrombosis.[34,35] Clopidogrel, an irreversible platelet $P2Y_{12}$ receptor inhibitor, is effective but as a prodrug has the disadvantage of requiring hepatic activation by cytochrome enzymes, which render it susceptible to genetic polymorphisms present in 30% of the population, thereby attenuating its effectiveness. Prasugrel is a potent, irreversible $P2Y_{12}$ receptor antagonist but not susceptible to genetic polymorphisms; as for clopidogrel, it requires 10 days for return of full platelet function after cessation. Ticagrelor is an oral, reversible non-thienopyridine $P2Y_{12}$ platelet receptor antagonist. Reliable platelet inhibition occurs within 30 min but requires 3 days for return of platelet function after cessation because of its long half-life.[36] Ticagrelor may be a more suitable choice in perioperative STEMI, as the return of spontaneous platelet function is quicker. Aspirin, a cyclooxygenase (COX)-1 inhibitor, has been shown in the Second International Study of Infarct Survival (ISIS-2) trial to improve survival after AMI.[37] The combination of aspirin and a $P2Y_{12}$–ADP receptor blocker forms the cornerstone of DAPT.

Pre-administration of the $P2Y_{12}$ receptor blocker ticagrelor before PCI, was shown in the Ambulance for New ST Elevation Myocardial Infarction to Open The Coronary Artery (ATLANTIC) trial for out-of-hospital administration, not to improve pre-PCI coronary reperfusion.[33] This is unsurprising in the setting of STEMI, in which there is already occlusion of the coronary artery but is pertinent to the perioperative setting when pre-administration of antiplatelet drugs would be controversial in the setting of very recent surgery with associated bleeding risk.

The risk of stent thrombosis is highest in the first 24–48 h and remains significant up to 4 weeks and longer for DES.[38] Thus, although there may be evidence to suggest alteration in DAPT is not correlated with MACE after noncardiac surgery in patients with stents, the relative risk of stent thrombosis in the early days after DES is at its highest, and greater than the risks from bleeding events.[38,39] Overall, the literature suggests that after insertion of stents, early administration of DAPT is essential. The question is then: 'Is there evidence that DAPT unacceptably increases bleeding risk from the postoperative surgical site?' There is limited data on DAPT after surgery, and therefore reliance on available data from surgery performed in the presence of DAPT is important.

What is the surgical bleeding risk with DAPT or anticoagulants?

The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial studied patients undergoing CABG on clopidogrel and aspirin *vs* placebo and aspirin, and showed a non-significant difference in life-threatening bleeding events of 5.6% *vs* 4.2%, respectively, but with a trend to reoperation for bleeding events when clopidogrel had been stopped less than 5 days before surgery.[40] Similar studies for CABG surgery have supported the observation that bleeding risk is small, and need for blood transfusion and reoperation for bleeding is infrequent.[41,42]

For aspirin, the PeriOperative ISchaemic Evaluation-2 trial (POISE 2) on patients undergoing noncardiac surgery found that aspirin 100 mg increased the risk of major bleeding to 4.6% compared with 3.8% with placebo but only in high-risk cardiovascular patients, and there was no difference in life-threatening bleeding.[43] A large meta-analysis on more than 30 000 patients with stents undergoing noncardiac surgery while receiving DAPT, clopidogrel, or aspirin monotherapy *vs* control showed a minimal increase in bleeding risk and no increase in risk of re-intervention for bleeding.[44] These studies excluded surgeries such as obstetric and neurosurgical.

A review on premature discontinuation DAPT concluded that there was a significant risk of stent thrombosis within 1 month of stent deployment (up to 30%), but that for minor to moderate surgery, the bleeding risk on DAPT is small.[39] However, if there is a likelihood of further noncardiac surgery of high bleeding risk, then suitable alternative reperfusion options might be considered. A recent systematic review of the perioperative management of DAPT in patients undergoing noncardiac surgery after PCI concluded that 'evidence regarding the perioperative management of antiplatelet management is insufficient to guide practice' because there was no visible trend in major cardiac events or bleeding rates within a given antiplatelet strategy.[45] The recent Occurrence of Bleeding and Thrombosis during Antiplatelet therapy in Noncardiac surgery (OBTAIN) study of 847 subjects reported that withholding antiplatelet therapies in noncardiac surgery did not increase MACE, but both DAPT and aspirin monotherapy were associated with an increased risk of serious bleeding of 4%, a similar event to other studies.[46]

Anticoagulants are used systematically at the time of PCI. Is this a major risk factor for bleeding complications after surgery? In vascular surgery (carotid endarterectomy, surgery of the abdominal aorta and its branches, peripheral vascular surgery), heparin is routinely administered during surgery and with great attention being paid to haemostasis, bleeding is maintained within acceptable limits. Therefore, for STEMI in the perioperative setting, the surgeon may consider that if the operation was felt to be haemostatically secure, and there were no untoward intraoperative bleeding complications, the standard management for STEMI as set out in the NICE guidelines[1] could be recommended. Nevertheless for cases of higher postoperative risk of surgical bleeding, modification of the 'standard' protocol may be necessary.

Intravenous reversible antiplatelet drugs

As the risk of bleeding with conventional DAPT at the time of PCI cannot be discounted, there may be an important role for rapidly reversible antiplatelet agents. These agents include tirofiban, a GPIIb/IIIa platelet receptor blocker that allows return of platelet function after 4–8 h when stopped, and cangrelor, a $P2Y_{12}$ platelet receptor blocker with a half-life of 3–5 min with return of platelet function after 30–60 min when stopped. These agents have been used as bridging therapy for urgent surgery in patients with recent stents on DAPT[47,48] In one study on 67 patients with tirofiban bridging therapy, perioperative stent thrombosis was 4% and major bleeding events were 7.8%.[47] Another study using tirofiban bridging therapy showed no mortality, AMI, stent thrombosis, nor re-exploration for bleeding.[47]

Cangrelor has been used as bridging therapy for surgical patients with stents and DAPT presenting for cardiac surgery with only non-significant increase in minor bleeding.[49]

A large trial involving 30 000 patients compared peri-procedural cangrelor infusion *vs* loading dose clopidogrel and standard anti-thrombin infusion. The cangrelor group *vs* standard therapy showed a reduced composite endpoint of mortality/AMI/revascularisation/stent thrombosis of 3.8% *vs* 4.7%, and particularly stent thrombosis of 0.5% *vs* 0.8%, respectively. Life-threatening bleeding at 48 h was 0.2% with cangrelor.[50] Another study on PCI using peri-procedural cangrelor *vs* placebo with follow-on clopidogrel, showed acute stent thrombosis was 0.2% *vs* 0.6%, other MACE at 48 h of 0.2% *vs* 0.7%, and no increased risk of blood transfusion, but major bleeding risk increased for the cangrelor group of 5.5% *vs* 3.5%, respectively.[51] Thus cangrelor is suitable for use during pPCI, as it is an effective, intravenous, rapidly reversible drug with a small risk of major bleeding, so it could be considered suitable for use in patients with perioperative STEMI at high risk of surgical bleeding.

Anti-thrombotic agents

These agents are used during PCI to help break down the occluding thrombus. Bivalirudin is an intravenous, short-acting, reversible direct anti-thrombin drug. In the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial, bivalirudin monotherapy *vs* bivalirudin and GPIIb/IIIa inhibitor *vs* unfractionated heparin and GPIIb/IIIa inhibitor was compared in patients with acute coronary syndromes undergoing early invasive strategy. The bivalirudin alone group showed similar rates of ischaemia but significantly lower bleeding rates of 3.3% *vs* 8.9% for heparin and GP11b/111a inhibitor.[52]

Other antithrombotic treatments commonly used include unfractionated heparin (70–100 IU kg^{-1} aiming for activated clotting time of 250–300 s). Routine post-procedural heparin anticoagulation is not recommended,[53] but postoperative prophylactic low molecular weight heparin should be considered. The GPIIb/IIIa drugs (tirofiban, eptifibatide, abciximab) are potent intravenous antiplatelet receptor antagonists used during PCI. They are effective and reduce non-fatal myocardial infarction. They are associated with more minor bleeding events but not major bleeding events.[54] They tend to be reserved for dissolution of dense resistant thrombus during PCI.

Management strategies

The verdict is still out on the best management of perioperative STEMI, which will depend on the residual bleeding risk of the noncardiac surgery. Ideally for all cases of perioperative STEMI, a coronary angiogram should be expedited as soon as possible, using the radial artery approach to limit bleeding. The initial diagnostic angiogram is used to establish the cause of the myocardial infarction. The occluded vessel can be identified, and treatment can then be planned depending upon the location of the occlusion, the extent of jeopardised myocardium, and the anatomical features of the culprit plaque. The technical complexity of any planned procedure must be balanced by the potential risk/benefit assessment and surgical site bleeding risk. Consideration should be given to use of balloon angioplasty alone, deferred stent deployment, primary stenting, and the option of rescue CABG surgery.

We propose a guide (Table 1) to management based on bleeding risk as a function of time from surgery to STEMI.

Table 1 Possible approach to management of STEMI based on the bleeding risk as a function of the timing of the STEMI after surgery. STEMI, ST-elevation myocardial infarction; NICE, National Institute for Health and Care Excellence

Bleeding risk	Delay after surgery		
	0–24 h	24–48 h	48–72 h
High	Bespoke protocol 1	Bespoke protocol 2	NICE guideline
Intermediate	Bespoke protocol 2	NICE guideline	NICE guideline
Low	NICE guideline	NICE guideline	NICE guideline

Bespoke protocol 1

No immediate aspirin and clopidogrel.
Short-acting antiplatelet agent (tirofiban, eptifibatide, cangrelor).
Consider balloon angioplasty followed by deferred conventional PCI at the appropriate time if risk of bleeding is very high.
Follow-on aspirin and ticagrelor once definitive stent/procedure undertaken.

Bespoke protocol 2

No immediate aspirin and clopidogrel.
Immediate PCI.
Short-acting antiplatelet agent (tirofiban, eptifibatide, cangrelor).
Follow-on aspirin and ticagrelor.
For both bespoke protocols, periprocedural heparinisation as appropriate.

Since many surgeries are currently undertaken while patients receive DAPT, and many receive heparin during their operation, for perioperative STEMI following surgery of minor to moderate bleeding risk, management should be by the standard protocol for acute STEMI according to the 2018 NICE guidelines.[1] After surgery of high bleeding risk, if sufficient time has elapsed from surgery, then standard protocol for the management of acute STEMI could, likewise, be followed. However, for surgery of high bleeding risk and early perioperative STEMI, there is a case for a bespoke protocol (Table 1) with PTCA, intravenous reversible anti-thrombotic agents with or without heparin, and deferred PCI until the risk of bleeding becomes negligible. For the bespoke protocols, pre-administration of oral aspirin with or without clopidogrel or ticagrelor could be omitted, but their administration is absolutely necessary once definitive mechanical reperfusion has been deployed.

Importantly these proposed guidelines are for the management of acute STEMI, for which immediate treatment of the acute coronary artery occlusion has been shown to improve survival (speed is of the essence), supporting a policy for immediate PCI.

For other coronary syndromes the importance of immediate intervention is less clear and speed is less critical and a diagnostic coronary angiogram with the help of guidelines allows useful time on which to make an informed management strategy.

Authors' contributions

Drafting of the initial version of the manuscript: FR.
Subsequent development of manuscript with authors PF and RK: FR.
Contribution to the concepts, issues, and presentation of this manuscript: PF.
Design of bespoke protocols for pPCI: RK.
Provided advice on the narrative: RK.

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Declaration of interests

The authors declare that they have no conflicts of interest.

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Use of the GRADE approach in systematic reviews and guidelines

Anders Granholm[1], Waleed Alhazzani[2,3] and Morten H. Møller[1,4,*]

[1]Department of Intensive Care 4131, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark, [2]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada, [3]Department of Medicine, Division of Critical Care, McMaster University, Hamilton, ON, Canada and [4]Centre for Research in Intensive Care, Copenhagen, Denmark

*Corresponding author. E-mail: mortenhylander@gmail.com

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Environmental impacts of nitrous oxide: no laughing matter! Comment on *Br J Anaesth* 2019; 122: 587-604 by Muret et al., *Br J Anaesth* 2019:123: e481–e482, doi: 10.1016/j.bja.2019.06.013

Response to comments on 'The European Society of Anaesthesiology Task Force review on the place of nitrous oxide in current clinical practice' (*Br J Anaesth* 2019; 122:587–604) by Buhre et al., *Br J Anaesth* 2019:123: e482–e483, doi: 10.1016/j.bja.2019.06.021

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach is a systematic and transparent approach for rating the certainty of evidence in systematic reviews and clinical practice guidelines, and for developing and determining the strength of clinical practice recommendations.[1] While use of GRADE in systematic reviews is currently only mandated by a few (~4%) journals within anaesthesia and intensive care medicine,[2] it is becoming a *de facto* standard for high-quality systematic reviews, and it is an essential component of trustworthy guidelines. GRADE has been adopted by more than 100 organisations worldwide, including the Cochrane Collaboration, the WHO, UpToDate®, the UK National Institute for Health and Clinical Excellence, and many societies within the fields of anaesthesia and critical care.[3] Knowledge about GRADE is therefore necessary not only for researchers and guideline panel members, but also for clinicians who use and rely on systematic reviews and guidelines for their clinical practice. Here, we provide an introduction and overview of the GRADE approach after the publication of a narrative review on nitrous oxide in the *British Journal of Anaesthesia*[4] and subsequent discussion related to its apparent use of GRADE and concerns about the methodological adequacy.[5–7]

Overview of GRADE

An overview of the GRADE approach is presented in Figure 1.[8] The process of developing a systematic review or clinical practice guideline starts with assemblance of a review group or guideline panel, which should ideally include academic and frontline clinicians, methodologists, and, for guidelines, other key stakeholders including patient representatives. The initial phases consist of selection of the topics and settings of interest, formulating population, intervention, comparator, outcomes (PICO) questions,

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