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Management of upper gastrointestinal haemorrhage complicating dual anti-platelet therapy

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Summary

Upper gastrointestinal haemorrhage is a serious complication of aspirin and clopidogrel (dual) anti-platelet therapy with a high morbidity and mortality. Using an illustrative case this article examines the prognostic significance of gastrointestinal haemorrhage and the risk of stopping

anti-platelet therapy. The management of this clinical challenge is reviewed, in the absence of a clinical guideline, with particular reference to the judicious tailoring of anti-platelet therapy, the role of therapeutic endoscopy and the utility of blood transfusion.

The combination of clopidogrel and aspirin, compared with aspirin alone, improves outcome (reinfarction, stroke and death) in patients with non-ST segment elevation myocardial infarction¹ and in patients with ST elevation myocardial infarction receiving thrombolysis.^{2,3} Combined (dual) anti-platelet therapy is also indicated to reduce the incidence of stent thrombosis following percutaneous coronary intervention.⁴ Drug-eluting stents have reduced the incidence of in-stent restenosis but endothelialize slowly and necessitate prolonged dual anti-platelet therapy.⁵ Recent reports of late stent thrombosis have led to calls for even longer, potentially lifelong, courses of combined anti-platelet therapy in patients with these stents.⁶ Upper gastrointestinal haemorrhage is a serious complication of dual anti-platelet therapy with a high morbidity and mortality. This complication will present more frequently to emergency departments

with increasing use of coronary stents and more prolonged courses of combined anti-platelet therapy. This article will outline how to assess the balance of risk between continued haemorrhage and stent thrombosis and, in the absence of established clinical guidelines, will discuss management using an illustrative case.

Case study

A 75-year-old lady presents to hospital with melaena stool. She had been admitted 2 weeks before with an acute coronary syndrome and had two stents placed in her left anterior descending coronary artery. She is currently taking aspirin and clopidogrel. On examination she is undistressed, blood pressure and pulse are 100/70 mmHg and 100 bpm and her admission haemoglobin is 9.2 g/l.

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The challenge is to support the patient during the episode of gastrointestinal haemorrhage with judicious tailoring of anti-platelet therapy, therapeutic endoscopy and blood transfusion if necessary, while minimizing risk of stent thrombosis. Before discussing these therapeutic options in detail, the first part of this article will examine the relationships between anti-platelet therapy and gastrointestinal bleeding, anaemia and myocardial oxygen delivery and the prognostic impact of bleeding in patients with acute coronary syndromes.

Gastrointestinal injury and anti-platelet therapy

The increasing use of dual anti-platelet therapy puts more patients at risk from gastrointestinal injury and bleeding. The risk of significant bleeding may be as high as 1.3% within 30 days of initiating aspirin and clopidogrel.⁷ Aspirin leads to suppression of mucosal prostaglandin synthesis and this facilitates the formation of mucosal erosions. In the United Kingdom Transient Ischaemic Attack study, long term aspirin (over a 4-year period) produced complications ranging from dyspeptic symptoms (31%) to life threatening episodes of bleeding or perforation (3%).⁸ Whether clopidogrel causes mucosal injury or facilitates bleeding from pre-existing mucosal lesions is uncertain. One retrospective analysis reported a frequency of gastrointestinal haemorrhage or 13% in patients with prior peptic ulcer disease treated with clopidogrel.⁹

In randomized controlled trials, among patients with acute coronary syndromes, the addition of clopidogrel to aspirin appears to increase the relative risk of all haemorrhagic events by 50%.¹⁰ However, it must be remembered that the patients in these trials also received other anti-thrombotic medication including glycoprotein IIb/IIIa inhibitors and heparin; moreover, the definition of major bleeding varied between trials making comparison less than straightforward. Nevertheless, the data suggest that the addition of clopidogrel to aspirin increases the absolute risk of major bleeding by around 1%.¹⁰

Anaemia and myocardial oxygen delivery

Bleeding and subsequent anaemia reduce oxygen delivery to the myocardium both through reduced haemoglobin and, when blood loss is substantial, through hypoperfusion. Coronary oxygen delivery is the product of haemoglobin concentration and coronary blood flow. The coronary circulation

exhibits tight autoregulation and in the presence of anaemia, if circulating volume is maintained, reduced blood viscosity and coronary vasodilatation result in increased flow to maintain oxygen delivery. Animal studies suggest that normal coronary vascular resistance can decrease 5-fold in these circumstances. This may explain why studies of normovolaemic haemodilution in healthy human volunteers have shown that haemoglobin concentrations of 5 g/l can be tolerated without evidence of myocardial ischaemia.¹¹ In patients with coronary or structural heart disease including left ventricular hypertrophy, the capacity for autoregulation is reduced. The haemoglobin level at which oxygen carriage can be compensated for by reduced viscosity and vasodilatation will, therefore, vary between individual patients depending on the pattern of coronary and myocardial disease. Finally, the physiological consequences of anaemia will be influenced by other factors that alter myocardial oxygen demand, such as pulmonary oedema, tachyarrhythmias, hypertension and the use of inotropes.

The prognostic importance of gastrointestinal bleeding

Any type of bleeding is associated with an adverse prognosis in patients with acute coronary syndromes.^{12,13} For example, there was a close relationship between major bleeding and subsequent myocardial infarction, stroke and death at 30 days in patients enlisted in the OASIS and CURE studies. Approximately 10% of patients experiencing bleeding sufficient to merit transfusion with two or more units of blood will die within 30 days (the comparable figure for patients who do not sustain a bleed is 2.5%). The excess mortality appears to be directly related to the degree of blood loss and is even evident in minor bleeds, which were associated with 2.07 (1.15–3.72) fold increased risk of death compared to no bleeding after adjustment for baseline characteristics.¹³

The treatment of significant bleeding frequently includes the interruption of anti-thrombotic therapy and blood transfusion. These interventions may be necessary but pose a very substantial risk of recurrent ischaemia and stent thrombosis. There are theoretical reasons why stored blood may be harmful in patients with myocardial ischaemia. Nitric oxide levels are low in stored red cells and transfused blood may act as a nitric oxide sink resulting in harmful vasoconstriction.¹⁴ Studies examining blood transfusion in patients with

Table 1 Rockall scoring system for risk of rebleeding and death after admission to hospital with acute gastrointestinal bleeding

Score	0	1	2	3
Age (yr)	<60	60–79	>80	
Shock	No shock Systolic BP > 100 mmHg, HR < 100 bpm	Tachycardia HR > 100 bpm Systolic BP > 100 mmHg	Hypotension Systolic BP < 100 mmHg, HR > 100 bpm	
Comorbidity	Nil major		Cardiac failure, ischaemic heart disease	Renal failure, liver failure, disseminated malignancy
Endoscopic findings				
Diagnosis	No lesion, Mallory Weiss tear with no SRH	All other diagnoses	Malignancy of upper GI tract	
Major SRH	None or dark spot		Blood in upper GI tract, adherent clot, visible or spurting vessel	

SRH, Stigmata of recent haemorrhage.

coronary heart disease have yielded conflicting results, but several studies point to harmful effects.^{12,15,16}

There have been no specific data published from acute coronary syndrome trials on the prognostic impact of gastrointestinal haemorrhage. A survey of over 4000 patients presenting to UK hospitals with acute upper gastrointestinal haemorrhage identified independent variables predictive of mortality.¹⁷ These included age, presence of shock, comorbidity and information obtained from endoscopy including the underlying diagnosis and whether there was direct evidence of active or recent bleeding (stigmata of recent haemorrhage). The investigators devised a scoring system (The Rockall score) based on five variables (Table 1) that predicted mortality and re-bleeding.¹⁷ Patients with cardiac or renal failure had among the highest rates of mortality. Patients with varices or peptic ulceration had an adverse outcome, particularly if active bleeding, a visible vessel or adherent clot were present. By contrast, patients with erosions or oesophagitis followed a relatively benign course. The findings at diagnostic endoscopy are, therefore, very valuable in risk stratification (Figure 1). The risk factors for repeat or continued bleeding are similar to those for mortality and re-bleeding is in itself a potent predictor of mortality in all groups. The relationship between Rockall score, re-bleeding and mortality reported in the UK survey is shown in Figure 2. The study does not provide specific information on the additional risks faced by patients with an acute coronary syndrome nor the influence of individual anti-thrombotic medications, although anti-coagulation with warfarin was associated with increased mortality.

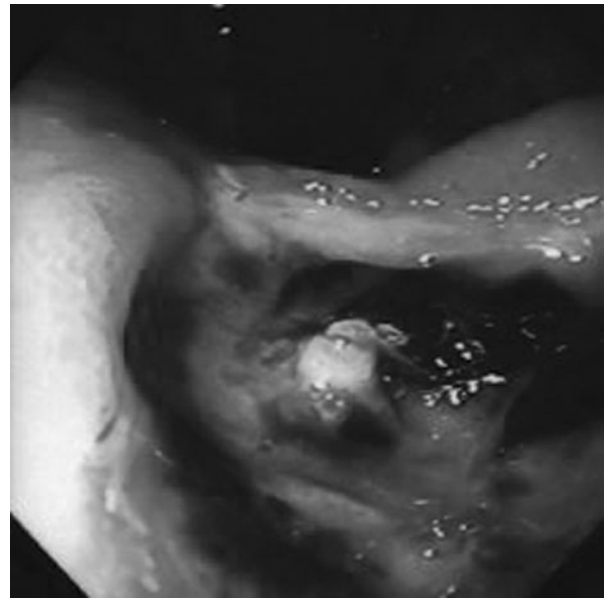


Figure 1. Endoscopic appearance of a large posterior duodenal ulcer with a non-bleeding visible vessel. Without endoscopic treatment there is a 50% risk of re-bleeding.

Management of gastrointestinal haemorrhage in acute coronary syndrome patients

Acute coronary syndrome patients with low-risk gastrointestinal lesions should probably have minimal interruption of anti-platelet therapy and can often be managed conservatively with respect to blood transfusion.

The patient described at the beginning of this article has a predicted 30 day mortality of

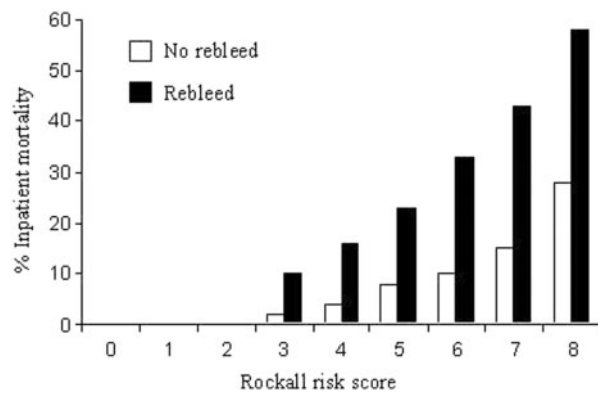


Figure 2. Mortality from upper GI bleeding according to Rockall risk score and presence of rebleeding. Modified from Rockall *et al.*¹⁷

at least 10%, notwithstanding the presence of additional variables such as renal or cardiac failure. The risk can be further qualified by diagnostic endoscopy. If she has ongoing melaena stool her risk of death doubles. In what follows, consideration is given to tailoring anti-thrombotic medication, to the role of therapeutic endoscopy in this patient and to the evidence for blood transfusion in patients with acute coronary syndromes.

Anti-thrombotic medication

The presence of risk markers for stent thrombosis, the location of the stent, and the amount of viable myocardium subtended by the stented vessel all influence the potential risk of interrupting anti-platelet treatment. Stent occlusion in a proximal vessel subtending viable myocardium may well be fatal whereas occlusion of a stent in a marginal branch subtending infarcted territory may pass unnoticed.

Cessation of aspirin prescribed for primary or secondary prevention was associated with a 1.8-fold relative risk of arterial thrombosis in a meta-analysis of studies involving over 50 000 patients with coronary artery disease.¹⁸ The average time from aspirin cessation to thrombotic event in this out-patient population was 10 days. The risk is greater for patients who have had an acute coronary syndrome. In patients who have had coronary stenting the hazard of withholding anti-platelet therapy is even higher; indeed, premature discontinuation of anti-platelet therapy is the most important predictor of early stent thrombosis. A prospective observational analysis of 2229 consecutive patients receiving drug eluting stents reported stent thrombosis in 1.3% of cases within 9 months.¹⁹ The group of patients whose aspirin and clopidogrel were

stopped within the first 30 days of stent implantation had a subacute stent thrombosis incidence of 29%.¹⁹ Studies have confirmed the importance of renal failure, diabetes, anatomically more complex bifurcation lesions, cardiac failure and length of stent as independent predictors of stent thrombosis.²⁰ Although these factors are associated with up to 10-fold increased risk, their impact is dwarfed by the effect of stopping anti-platelet therapy.

Measures of platelet function such as aggregation and bleeding time remain altered for up to 5 days after stopping clopidogrel or aspirin in healthy volunteers.^{21,22} The period for which therapeutic anti-thrombotic effect remains is unknown and may be shorter in patients who are actively bleeding. We recommend withholding both aspirin and clopidogrel for 24 h after a significant upper gastrointestinal haemorrhage. An assessment can be made of the risk of sustained bleeding during this period and will depend heavily on the findings at diagnostic endoscopy. Ultimately, the decision to restart anti-platelet therapy must balance the perceived risk and likely consequence of stent thrombosis against the possibility of continuing or recurrent haemorrhage. It is obviously important to establish the details of any coronary procedures the patient has undergone before making this judgement.

Clopidogrel is more effective than aspirin as monotherapy for the prevention of coronary thrombosis;²³ it is also associated with increased bleeding during surgery.²⁴ There is evidence of a rebound thrombotic effect following cessation of clopidogrel in the context of dual anti-platelet therapy.²⁵ Aspirin is more likely to have a causative role in upper gastrointestinal injury and withholding aspirin may facilitate mucosal healing. For all these reasons and in the absence of trial evidence that might support a clinical guideline, we usually recommend the resumption of clopidogrel within one or two days, and aspirin within 1–2 weeks (depending on the degree of gastrointestinal injury), after a significant GI bleed.

Upper GI endoscopy

In this patient, visualizing the bleeding lesion will inform decision making; endoscopy may also lead to therapeutic intervention that can improve outcome. Although trials have not consistently demonstrated an impact on mortality there is a strong consensus among gastroenterologists that early endoscopy reduces the risk of re-bleeding, the need for surgical intervention and blood transfusion requirements.²⁶ Current guidelines for endoscopy in any patient presenting with upper gastrointestinal

haemorrhage emphasize the importance of prior resuscitation.²⁶ The major risk from this procedure is cardiorespiratory depression associated with sedation. Assuming no evidence of ongoing myocardial ischaemia nor any significant desaturation related to congestive cardiac failure we would arrange endoscopy for this patient within 24h of admission. A recent UK review of patient outcomes and death following emergency endoscopy highlighted the need to perform these procedures on high-dependency units with access to invasive monitoring and anaesthetic.²⁷

Blood transfusion

There is abundant evidence that pre-existing anaemia is associated with adverse outcomes in patients with acute myocardial infarction undergoing percutaneous coronary intervention.²⁸ This is not to say that correction of anaemia will improve prognosis; indeed, it may be hazardous. The CRUSADE National Quality Improvement Initiative involves a broad sampling of clinical practices across the USA for patients presenting with non-ST segment myocardial infarction. A striking finding was the large variation in the transfusion rates with an average of 10.3% (0–28%) in the non-CABG population. Patients who received transfusion were more sick at baseline but transfusion appeared to confer an adverse outcome even after adjustment for other identifiable clinical factors.¹⁵ In a prospective randomized trial comparing a liberal transfusion strategy (target haemoglobin between 10.0 and 12.0 g/dl) with a restrictive strategy (target haemoglobin between 7.0 and 9.0 g/dl) among patients with a wide range of illnesses, a higher threshold for transfusion was associated with lower in-hospital mortality.¹⁶ Subgroup analysis revealed conflicting messages: significantly increased rates of myocardial infarction and pulmonary oedema in the liberally transfused group but a non-significant trend towards adverse outcome in the subgroup of patients with pre-existing coronary disease who received a restrictive transfusion policy. In contrast, another study has reported that blood transfusion improved prognosis in elderly patients presenting with acute myocardial infarction and anaemia.²⁹ These apparently disparate findings may be explained by differences in physiological adaptation and the strain already present on cardiac reserve in response to pre-existing anaemia. Thus, in patients with chronic anaemia, transfusion needs may differ from those in patients who become anaemic as a result of bleeding in the context of an acute coronary syndrome.

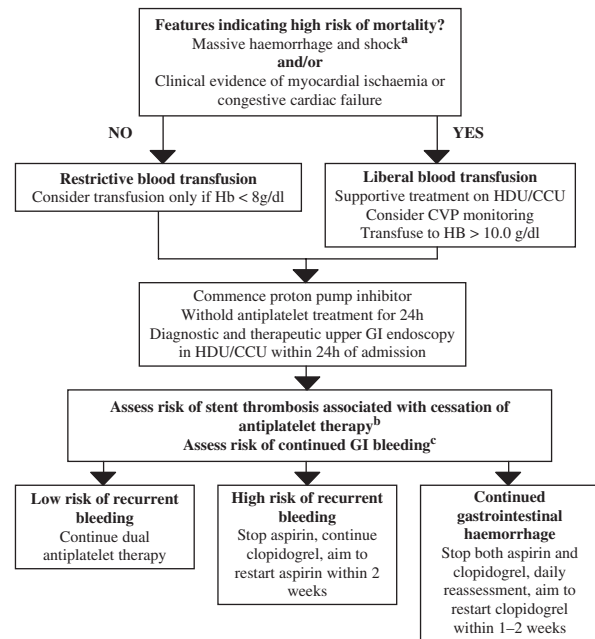


Figure 3. An algorithm for assessing and treating patients on dual antiplatelet therapy presenting with non-variceal upper gastrointestinal haemorrhage. ^aSBP < 100 mmHg, HR > 100 bpm. Clinical assessment may be complicated by the impact of cardiac medication on blood pressure and pulse. ^bFactors associated with a high risk of stent thrombosis: impaired LV systolic function, diabetes mellitus, renal failure, long segment of stent (>20 mm), recent coronary intervention (within 3 months of bare metal stent, within 12 months of drug eluting stent). ^cFactors associated with increased risk of continued bleeding: endoscopic diagnosis (visible vessel and stigmata of recent haemorrhage).

A Cochrane analysis and a more recent review both concluded that further trial work would be required before determining transfusion thresholds in patients with coronary disease.^{30,31} Transfusion requirements have to be individualized for these complex patients. It is unlikely that a single transfusion threshold will be suitable for all. In our opinion, a restrictive transfusion policy would be appropriate for this patient, maintaining the haemoglobin above 8 g/dl. Ongoing evidence of ischaemia or cardiac failure would merit a higher haemoglobin target.

Prevention

Patients presenting with acute coronary syndromes at high risk of developing upper gastrointestinal haemorrhage should be identified on admission and considered for prophylactic proton pump inhibitor therapy. Risk factors include advanced age, a history of upper gastrointestinal disease and regular steroid

or non-steroidal analgesic medication. Although no clinical trials have examined this proposal directly, the combination of aspirin and esomeprazole reduces recurrent bleeding dramatically in patients who have sustained previous gastrointestinal haemorrhage on aspirin alone.³² Thoughtful drug prescription may also help to minimize risk; for example it may be wise to avoid long-acting anti-thrombotic medication in unstable patients. Low-molecular weight heparins may accumulate in renal failure and other drug regimens may offer a better risk/benefit ratio. The OASIS-5 trial, for example, demonstrated that fondaparinux was as effective but caused less bleeding than enoxaparin.³³

Conclusion

This patient presents a complex clinical problem that is best managed by a cardiologist and a clinician with therapeutic endoscopy expertise. An algorithm for assessment and treatment is set out in Figure 3. Her treatment should be based on a careful clinical (and endoscopic) assessment of the competing risks from ongoing haemorrhage and stent thrombosis. Minimizing interruption of anti-platelet therapy and adopting a restrictive blood transfusion policy, with invasive monitoring, will, in our view, offer the best chance of a favourable outcome.

Conflict of interest: None declared.

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