Anticipating and managing bleeding complications in patients with coronary stents who are receiving dual antiplatelet treatment

Neeraj Bhala, Jaspal S Taggar, Praveen Rajasekhar, Amitava Banerjee

Coronary artery stents are used to treat the full spectrum of coronary heart diseases, from stable angina through to ST elevation myocardial infarctions, and stent insertions are common medical procedures, with more than 80 000 and 1.3 million performed in the United Kingdom and United States each year, respectively. Both bare metal stents and drug eluting stents, which release anti-proliferative drugs and reduce restenosis, are commonly used. Although drug eluting stents have been associated with lower rates of medium term vascular complications, such as revascularisation, there have been concerns about other rarer later vascular outcomes. Of particular concern is the apparent small absolute risk of in-stent thrombosis with drug eluting stents.

To prevent these vascular complications, treatment with antithrombotic drugs is associated with bleeding at vascular access sites and atherosclerosis share many risk factors. As well as bleeding mediated by platelet inhibition can affect other organs, such as intracranial vessels or, most commonly, the upper gastrointestinal tract. Management of bleeding complications in patients with coronary artery stents is especially challenging because of the need to consider vascular and bleeding risks.

Our narrative review of the risks and benefits of coronary stents and concomitant antiplatelet treatment is based on randomised controlled trials, meta-analyses, systematic reviews, and international guidelines. We focus on how to inform bleeding complications is relatively strong and we gave priority to large well designed randomised controlled trials, systematic reviews, and meta-analyses. Evidence for the management of upper gastrointestinal bleeding after coronary stenting is relatively sparse, however, so other methodological designs were also cited where appropriate.

What are coronary stents?
Coronary artery disease can be treated medically using smoking cessation, blood pressure lowering, cholesterol lowering, and antiplatelet drugs, but in many cases it also requires interventional procedures for reperfusion. Interventions for coronary artery disease include percutaneous coronary intervention and coronary artery bypass grafting. Percutaneous coronary intervention is less invasive than surgery and includes percutaneous transluminal coronary angioplasty, with or without insertion of coronary artery stents. Stents are expandable devices that are inserted within narrowed...
segments of coronary arteries after angioplasty and consist of a tubular wire mesh that forms a “scaffold.”

Coronary stents fall into two broad categories—first generation bare metal stents and later drug eluting stents. The main complication after stent insertion is restenosis of the stented artery, which may require revascularisation procedures. Restenosis is caused by proliferation of cells in the intima, a smooth muscle wall in the coronary vessel (neo-intimal hyperplasia), which together with clots (thromboses) can occlude the stented artery. To help reduce restenosis, drug eluting stents that release anti-proliferative agents—such as sirolimus, tacrolimus, paclitaxel, and zotarolimus—were developed and introduced at the beginning of the 21st century. Rates of revascularisation at one year for drug eluting stents within individual trials were less than 5% compared with 10-25% for bare metal stents.2 3

What is the evidence of benefit for coronary stents?
According to UK national audit data, by 2008, 92% of percutaneous coronary intervention procedures involved stents, with more than 60% of these using drug eluting stents.4 Guidelines vary by country, but in the UK, drug eluting stents are recommended for the treatment of coronary artery disease if the artery to be treated is less than 3 mm wide or the lesion is longer than 15 mm, and if the drug eluting stent is no more than £300 ($480) more expensive than the bare metal stent.5 Although stents are sometime used to treat symptoms, a meta-analysis of randomised trials suggested no difference between percutaneous coronary intervention and conservative medical treatment in terms of death, myocardial infarction, or subsequent revascularisation rates in patients with angina symptoms only.6 In coronary artery disease traditionally treated with bypass surgery (multi-vessel disease or left main stem disease), meta-analyses have confirmed that percutaneous coronary intervention seems to be equivalent in terms of mortality or major adverse vascular events, although the risk of later target vessel revascularisation is higher.6 7

Although restenosis is lower with drug eluting stents than with bare metal stents, they have been associated with late in-stent thrombosis.8 In a meta-analysis of randomised controlled trials, the incidence of definite or probable in-stent thrombosis one to four years after implantation was 0.9% in the sirolimus and paclitaxel eluting stent groups versus 0.4-0.6% in the bare metal stent group, highlighting the relatively low absolute rates of this complication.9 Although in-stent thrombosis has a slightly higher absolute rate (~1.5% per annum) in prospective observational studies,10 meta-analyses of randomised controlled trials have shown that drug eluting stents are not associated with excess mortality after four to five years of follow-up.11 It is still unclear which types of stents (and which specific antiproliferative drugs) offer the best long term management in different populations, so both types of stent are still widely used. Clinicians should use the appropriate national and international guidelines when considering the use of coronary stents.

What are the recommendations for concomitant antiplatelet drugs?
A wide range of antithrombotic drugs are used during the acute management of coronary intervention, such as heparin, glycoprotein IIb/IIIa inhibitors, and direct thrombin inhibitors. In the acute and longer term management of myocardial infarction and unstable angina, aspirin taken with other antiplatelet agents, such as clopidogrel, reduces the rate of major vascular events in patients with overt occlusive vascular disease.11 12 Moreover, in patients with coronary artery stents, aspirin and clopidogrel dual antiplatelet treatment is prescribed to reduce the risks of in-stent thrombosis and restenosis. These dual antiplatelet regimens are prescribed for varying lengths of time depending on the type and sometimes the site of the coronary lesion. Because the risk of late in-stent thrombosis with the use of drug eluting stents is of particular concern,1 dual antiplatelet treatments are generally recommended for longer with these stents. Although it is unclear how long dual antiplatelet treatment should last,13 some guidelines recommend that patients with drug eluting stents should receive at least 12 months of dual treatment with aspirin and clopidogrel.14 15 Recommendations may be revised if newer antiplatelet agents, such as prasugrel and ticagrelor, replace clopidogrel as a second antiplatelet agent.15 16 Table 1 lists some of the antithrombotic drugs available.16

### Table 1 | Commonly used antithrombotic agents

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Target</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td>Clotting factors II, VII, IX, X</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Heparins</td>
<td>Clotting factor Xa, others</td>
<td>Unfractionated heparin, low molecular weight heparin</td>
</tr>
<tr>
<td>Factor Xa inhibitors</td>
<td>Clotting factor Xa</td>
<td>Fondaparinux, indaparinux, apixaban</td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td>Clotting factor II</td>
<td>Bivalirudin, argatroban, dabigatran</td>
</tr>
<tr>
<td>Fibrinolytics</td>
<td>Plasminogen activators</td>
<td>Plasminogen, alteplase, reteplase, tenecteplase</td>
</tr>
<tr>
<td>Other thrombolytics</td>
<td>Plasminogen</td>
<td>Streptokinase</td>
</tr>
</tbody>
</table>

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Table 2 | Commonly used agents for reversal of bleeding and their mechanism of action

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood products</td>
<td></td>
</tr>
<tr>
<td>Packed red cells</td>
<td>Replacement of red blood cells</td>
</tr>
<tr>
<td>Platelets</td>
<td>Supplies platelets</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>Supplies clotting factors</td>
</tr>
<tr>
<td>Prothrombin complex concentrate</td>
<td>Supplies factors II, VII, IX, X</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Supplies factor VII, von Willebrand factor, and fibrinogen</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>Desamino-D-arginine vasopressin</td>
<td>Releases von Willebrand factor</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Rejuvenates factors II, VII, IX, X</td>
</tr>
<tr>
<td>Protamine</td>
<td>Reverses heparin</td>
</tr>
<tr>
<td>Recombinant factor VIIa</td>
<td>Activates coagulation cascade</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>Antifibrinolytic</td>
</tr>
</tbody>
</table>

Data from three recent large randomised trials showed a 5% risk of major bleeding within 30 days of stent placement, with an associated threefold relative increase of overall mortality at one year.22 Models have been developed to help stratify the risk of bleeding complications in patients with intracoronary stents but have all used a composite outcome that includes all types of bleeding. Examples include registry models that predict major bleeding events in inpatients presenting with non-ST segment elevation myocardial infarction.23 More recently, meta-analyses of large scale randomised trials have developed a scoring system that predicts the 30 day risk of bleeding in patients presenting with acute coronary syndromes.24 In these studies, factors that confer greater risk of bleeding include increasing age, renal impairment, anaemia, and certain antithrombotic agents.

Because data on cause specific bleeding complications in patients with coronary stents are sparse, some of the evidence needs to be extrapolated from the wider population—for example, from large scale randomised trials of antithrombotic drugs.25 Although treatments to reverse the effects of thrombosis (table 2) are available, they can be used only in specific settings, and the emergency focus is on resuscitation and treatment of the underlying cause.26

Bleeding from vascular access sites

Vascular access for percutaneous coronary interventions can be via the transfemoral, transradial, or transbrachial sites, although the last site is rarely used now because of the risk of upper limb ischaemia.21 22 A recent large randomised trial assessing radial and femoral approaches found both to be safe and effective for percutaneous coronary intervention. However, at 30 days, 42 of 3507 patients in the radial group had large haematomas compared with 106 of 3514 in the femoral group (hazard ratio 0.40, 95% confidence interval 0.28 to 0.57; P<0.0001), so the radial approach, the default route in most European countries, may be preferable.23

The incidence of vascular access complications after percutaneous coronary intervention is reported to be 2-6%, with the highest risk in the first month; risk factors include increasing age, female sex, renal impairment, and certain antithrombotic agents.18 19 Access site complications include haematoma, pseudoaneurysm, arteriovenous fistula formation, lower limb ischaemia, femoral artery infection, and retroperitoneal bleeding.24 25 Mild bruises and small haematomas are common; these usually resolve with time without the need for specific investigation or treatment. However, a large or enlarging lump at the site of arterial access suggests an enlarging haematoma or the formation of a pseudoaneurysm, which requires investigation with vascular ultrasound imaging. If a large haematoma or pseudoaneurysm is found, it should be managed by the interventionist and may require surgical repair.

Retroperitoneal bleeding may occur after puncture of the femoral artery above the inguinal ligament, although this is rare (<1% of all percutaneous coronary interventions). Blood in the retroperitoneum may cause severe abdominal pain or back pain, with no obvious haematoma formation in the groin, and if not immediately recognised the patient may develop persistent hypotension. Treatment of a large retroperitoneal bleed is often conservative, with fluid replacement and careful monitoring of vital parameters, although it may need surgical evacuation and repair.25

Intracranial bleeding

Intracranial haemorrhage is one of the most severe complications associated with antiplatelet treatment and is associated with high mortality and morbidity. The risk of spontaneous intracranial haemorrhage is less well defined for patients with coronary artery stents, although it seems to be more likely with use of antithrombotic drugs. Evidence from meta-analyses of randomised trials suggests those taking aspirin alone or dual antiplatelet treatment have an increased relative risk of intracranial haemorrhage,26 27 with a large randomised trial suggesting a low absolute rate (~0.3% a year) in patients receiving dual antiplatelet treatment.28

Because of the small subgroups available, evidence for the risk factors of intracranial haemorrhage specific to patients receiving multiple antithrombotics or coronary artery stents is limited. However, factors associated with spontaneous intracranial bleeds in the general population include hypertension, excess alcohol consumption, male sex, advanced age, and smoking.29

Although intracranial haemorrhage is uncommon, doctors should maintain a high index of suspicion in patients with coronary stents and promptly refer any patient with sudden onset of focal neurological signs for prompt radiological and physician review. The management of patients with intracranial haemorrhage is beyond the scope of this article but it broadly involves patient resuscitation, correction of coagulopathy, and specialist neurosurgical intervention. Antithrombotic agents are often withdrawn in the acute setting, although liaison with cardiology colleagues is required in later management. A previous BMJ article provides a comprehensive review on the management of spontaneous intracerebral haemorrhage.30

Upper gastrointestinal bleeding

The risk of gastrointestinal bleeding is increased in people taking dual antiplatelet drugs, although other comorbidities probably play a role. Bleeding can occur at any site in the gastrointestinal tract, but it is most common in the upper gastrointestinal tract. Acute upper gastrointestinal bleeding is the most common gastrointestinal emergency or bleeding complication requiring hospital admission in the UK, with an estimated annual incidence...
Patients usually present after vomiting fresh or altered blood (haematemesis) or passing dark tarry stools (melena or digested blood), classically with epigastric pain. However, patients with coronary artery stents can present atypically as a result of severe volume loss, with anginal chest pain or postural dizziness.

Factors associated with a greater risk of such bleeding in patients taking antplatelet drugs have been investigated as part of observational studies and post hoc analyses of randomised trials. Risk factors include a history of peptic ulcer disease; increasing age; male sex; concomitant use of anticoagulants, steroids, or non-steroidal anti-inflammatory drugs; Helicobacter pylori infection; baseline anaemia; diabetes; and smoking.\textsuperscript{1,2} Although the strongest and most consistent predictor is a history of upper gastrointestinal bleeding,\textsuperscript{3,4} the risk of complications is greater with an increasing number of risk factors.\textsuperscript{5} A large case-control study to evaluate upper gastrointestinal bleeding in patients using single and dual antplatelet drugs in the Danish population found an odds ratio for bleeding of 1.8 in people taking low dose aspirin alone, 1.1 in those taking clopidogrel alone, and 7.4 in those taking both.\textsuperscript{6} Increased dose and duration of dual antplatelet treatment are also likely to affect the risk of upper gastrointestinal bleeding.\textsuperscript{7-9} Although estimates from randomised trials in patients with coronary stents are rare, estimates of risk can be extrapolated from other studies. For example, in a randomised trial of clopidogrel plus aspirin in patients with acute coronary syndromes without ST segment elevation, gastrointestinal bleeding occurred in 1.3% of those on dual antplatelet treatment at one month,\textsuperscript{10} with a reported 3% annual risk in patients taking low (≤100 mg) long term doses of aspirin.\textsuperscript{11} Subsequent observational analyses of patients having percutaneous coronary intervention in this trial suggest that this aspirin dose offers the best long term risk-benefit balance.\textsuperscript{11}

Can clopidogrel and proton pump inhibitors be used together to reduce the risk of bleeding?

The recent joint North American cardiology and gastroenterology consensus guidelines recommend that patients taking dual antplatelet drugs who are at high risk of upper gastrointestinal bleeding (as outlined above) should be co-prescribed proton pump inhibitors, because of their considerable gastroprotective effect.\textsuperscript{12} Although retrospective studies had raised concerns that such treatment might reduce the cardiovascular efficacy of clopidogrel, this observation could be prone to biases.\textsuperscript{12} A randomised controlled trial of 3627 patients taking aspirin and clopidogrel randomised to omeprazole or placebo found no difference in the rate of adverse vascular outcomes between groups.\textsuperscript{13} Pharmacodynamic studies in other randomised trials support these findings,\textsuperscript{13,14} suggesting that proton pump inhibitors have little, if any, effect on the cardiovascular efficacy of clopidogrel. Hence, gastroprotectant therapy should not be withheld for prevention of bleeding in high risk groups or for treatment of acute bleeding.\textsuperscript{15}

How is acute upper gastrointestinal bleeding managed?

Guidelines, such as those published by the British Society of Gastroenterology,\textsuperscript{16} highlight the need for a team approach, with an experienced endoscopy team and a surgical team in close proximity. Circulatory resuscitation is vital, initially with crystalloid or colloid fluids, and consideration of blood products according to haemodynamic status.\textsuperscript{17} Baseline blood tests should include a full blood count, coagulation studies, biochemistry, and blood group for crossmatch. After resuscitation, haemodynamic status must be monitored carefully and may require involvement of specialist intensivists before moving to endoscopy (for diagnosis and potential treatment). Evidence from randomised trials supports the acute administration of gastroprotectants, such as intravenous proton pump inhibitors, in patients with confirmed peptic ulcer bleeding.\textsuperscript{18}

Risk stratification scores can be used to assess the patient’s risk of a re-bleed or death.\textsuperscript{19} Figure 1 shows an algorithm for the suggested management of a patient with coronary artery stents presenting with a large upper gastrointestinal bleed. This should also include prompt discussion with an interventional cardiologist after initial assessment.

What is the role of blood transfusion?

The purpose of blood transfusion is to correct global or regional oxygenation and to improve haemostasis. The role of blood transfusion in patients with exsanguinating haemorrhage is self evident, but its role in patients with less severe haemorrhage is unclear.\textsuperscript{20} The most recent British Society of Gastroenterology audit of blood use in upper gastrointestinal bleeding, which defined the appropriate threshold for transfusion as a serum haemoglobin of less than 100 g/L, found that 5-15% (depending on clinical setting) of transfusions were unnecessary.\textsuperscript{21} The current Scottish Intercollegiate Guidelines Network guideline for management of upper gastrointestinal bleeding recommends transfusion after the loss of 30% of the circulating volume, and provides guidance on how this can be estimated.\textsuperscript{22}

Systematic reviews of studies of blood transfusion in upper gastrointestinal bleeding have reported variable outcomes, including a higher re-bleeding rate and increased incidence of coagulopathy in patients receiving blood transfusions.\textsuperscript{23} Observational studies in populations

TIPS FOR NON-SPECIALISTS

- In a patient with bleeding after insertion of a coronary stent first deal with the basics of cardiorespiratory support, adequate intravenous access, and appropriate fluid management.
- Then institute appropriate diagnostic and therapeutic strategies to locate and treat the cause of bleeding (for example, upper gastrointestinal endoscopy for an upper gastrointestinal bleed, interventional cardiology for a post-procedural bleed).
- Although patients with exsanguinating bleeding complications may need blood products, they should be used with caution in those who are clinically stable. Other medical treatments can be used depending on the aetiology of bleeding (such as gastroprotectants for upper gastrointestinal ulcers).
- Deal with the patient’s immediate bleeding problem. This may include reappraosing drug treatment, but bear in mind that these patients are usually at high risk for vascular events. Discussion with specialists (such as an interventional cardiologist) may help prevent later vascular complications (such as stent thrombosis).
- Close liaison between the admitting physician, cardiologists, gastroenterologists, radiologists, intensivists, and others as appropriate is essential to ensure optimal management.
How soon should upper gastrointestinal endoscopy take place?

The British Society of Gastroenterology recommends that all patients with suspected upper gastrointestinal bleeding should undergo upper gastrointestinal endoscopy within 24 hours of presentation, but that those at risk of haemodynamic compromise warrant prompt endoscopy out of hours.\textsuperscript{w25} Small retrospective studies have shown endoscopy to be safe after acute coronary syndromes, although its timing should be considered on a case by case basis.\textsuperscript{w26 w27}

Should antiplatelet agents be withheld in a major bleed?

After the acute episode of upper gastrointestinal bleeding has resolved, consider measures to reduce the risk of recurrent events, such as stopping concomitant non-steroidal anti-inflammatory drugs and eradicating \textit{H pylori}. Although it may be intuitive to withhold dual antiplatelet treatment in this context, the patients’ vascular risk must be evaluated and reduced appropriately. For example, although aspirin is stopped acutely in an upper gastrointestinal bleed, a small randomised trial found that continuation of aspirin with a proton pump inhibitor five days after endoscopic haemostasis reduced death at eight weeks, mainly through a reduction in vascular thrombotic events.\textsuperscript{w28} Withholding antiplatelet drugs in patients with coronary stents affects the risk of stent thrombosis, so discussion with interventional cardiologists is vital in these patients. A systematic review suggested that continuation of one antiplatelet drug (potentially with gastroprotectant cover) may be beneficial after adequate haemostasis in patients with coronary artery stents, especially if bleeding occurs more than a month after coronary intervention.\textsuperscript{w29} Careful consideration must be given to balancing the risk of stent thrombosis (after antiplatelet withdrawal) and that of bleeding (with antiplatelet continuation). Although the evidence on which to base a decision in a high risk patient with continued bleeding is limited, we would suggest withholding aspirin and using clopidogrel in some settings, because of clopidogrel’s relatively safer gastrointestinal profile (fig 1).

Many of the risk factors for upper gastrointestinal bleeding are shared with those for vascular thrombotic events—for example, analyses of a large randomised trial (using multiple anti thrombotics) found that in-stent thrombosis at one year after stent insertion was more likely in patients with a history of gastrointestinal bleeding (5.8\%) than in those without (2.4\%).\textsuperscript{w30} The reasons for this association include the presence of shared risk factors, reduced coronary perfusion as a result of haemodynamic compromise, and cessation of antiplatelets at the time of bleeding and at discharge. Other independent predictors for in-stent thrombosis include inadequate stent expansion at insertion, bifurcation lesions, renal failure, diabetes, and impaired left ventricular ejection fraction.\textsuperscript{w30} However, the most important risk factor for in-stent thrombosis is the cessation of dual antiplatelet treatment: the risk increases with greater time off treatment, particularly more than five days, and if treatment is stopped within the first month of the procedure.\textsuperscript{w31 w32 w33}

Suggested algorithm for assessing and treating patients with coronary artery stents on dual antiplatelet treatments presenting with upper gastrointestinal bleeding. *Assessment may be influenced by the effect of drugs (such as \textit{$beta$} blockers) on blood pressure or pulse. NSAIDs=non-steroidal anti-inflammatory drugs

with coronary stents suggests that blood transfusion carries a risk for ischaemic outcomes that is independent of bleeding itself.\textsuperscript{w33} The reasons for this are unclear, but the effect of blood transfusion on coagulation could play a role. Although transfusion and blood products will continue to be used in this setting, especially for patients with haemodynamic compromise, their optimal role is uncertain.\textsuperscript{w34}
Current and future scenarios

This review has focused on the emergency management of bleeding, but multidisciplinary discussions would also be relevant in other scenarios, such as emergency surgery. Bleeding complications can also be anticipated and managed for elective procedures, such as non-cardiac surgery after placement of a coronary stent. Anaesthetic and surgical liaison with a cardiologist, ideally well in advance of the procedure, could help ensure appropriate management. In the future, the management of bleeding complications in patients with coronary stents will be even more complex. For example, the effects of commonly used long term treatments that can exacerbate bleeding, such as non-steroidal anti-inflammatory drugs, must be carefully considered. Another increasingly common clinical scenario is that of the patient with a coronary artery stent who needs long term oral anticoagulation for indications such as atrial fibrillation. Current consensus guidelines advocate the use of triple therapy (dual antiplatelet drugs and oral anticoagulants), which, although potentially beneficial for the prevention of vascular outcomes, is even more likely to increase the risk of bleeding. The risk benefit balance of concomitant warfarin in patients with atrial fibrillation, venous thromboembolism, and metallic heart valves (mitral and aortic) must be considered on a case by case basis. Although further randomised evidence is needed, consideration needs to be given to stratification and treatment to reduce the risk of bleeding complications when assessing these patients.

The complexity of deciding the appropriate treatment in patients with coronary stents is already challenging. More potent antiplatelets (such as prasugrel and ticagrelor), newer anticoagulants (such as bivalirudin, dabigatran, fondaparinux, and idraparinux), and newer types of coronary stents are being developed for widespread use, and they will require even more careful evaluation of their associated benefits and hazards. Ongoing research is needed to provide further reliable evidence for the appropriate use of stents, associated medical treatments, and complications. Patients admitted with bleeding complications will continue to need multidisciplinary management for the prevention and treatment of haemorrhagic and vascular sequelae.

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Spherocytosis should be classified as trait, mild, moderate, or severe (table). Depending on the severity of the condition, folate treatment and splenectomy (with lifelong postoperative folate treatment), penicillin prophylaxis), with or without cholecystectomy, may be needed. Transfusions may also be needed in aplastic crises.


Muscle weakness and mild difficulty in walking were reported in 46% of cases. The blood results show a haemolytic anaemia. The lymphocytosis with reactive lymphocytes seen on the blood results of the study. A risk score to predict bleeding in patients with acute coronary syndromes. A risk score to predict bleeding in patients with acute coronary syndromes. A review of the management of peripheral vascular complications under conventional and complex percutaneous coronary interventional procedures. A risk score to predict bleeding in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. Lancet 2011;377:1409-20.


