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Special Issue

Contrast induced nephropathy in vascular surgery

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Abstract

Contrast induced nephropathy (CIN) is traditionally associated with outpatient imaging studies. More recently, patients afflicted with vascular pathologies are increasingly undergoing endovascular treatments that require the use of iodinated contrast media (CM) agents, thus placing them as risk of developing CIN. As perioperative physicians, anaesthetists should be aware of the risk factors and measures that might minimize acute kidney injury caused by CM. This review evaluates recent data regarding preventive measures against CIN and where possible, places the evidence in the context of the patient receiving endovascular surgical treatment. Measures including the use of peri-procedural hydration, N-acetylcysteine, statins, remote ischaemic preconditioning, renal vasodilators and renal replacement therapy and the use of alternatives to iodinated contrast agents are discussed. It should be noted that most of the available data regarding CIN are from non-surgical patients.

Key words: acute kidney injury; contrast media; endovascular procedures

Editor's key points

- A systematic review estimated the overall frequency of CIN in vascular surgery patients exposed to angiography to be 9.2%.
- Patients who develop CIN suffer an increased burden of in hospital and longer term morbidity.
- Maintaining adequate hydration remains a cornerstone of preventing CIN but evidence to support a particular hydration strategy is lacking.
- There is no evidence to support the routine use of NAC in prophylactic protocols for surgical patients at risk of CIN.

Despite efforts to prevent it, contrast induced nephropathy (CIN) remains a significant cause of iatrogenic acute kidney injury (AKI). With the increasing use of endovascular procedures requiring iodine containing contrast media (CM) in older patients and those with significant co-morbidities, the prevention of AKI is assuming greater importance. This narrative review will serve as an update to one previously published in this journal[1] and will concentrate on areas where there have been noteworthy changes, with a focus on patients undergoing vascular surgery where such data are available. Readers are referred to the previous review for more in depth discussion on the risk factors (Table 1),[2–4] the pathophysiology of CIN and renal handling of CM, the details of which remain largely unchanged, and will be mentioned only in brief here.

Definitions

The widely accepted definition for contrast induced nephropathy is a deterioration of renal function, indicated by either an increase in serum creatinine concentration of 25% from baseline, or an absolute increase of 26–44 μmol litre^{-1} (0.3–0.5 mg dl^{-1}) within 48–72 h of i.v. contrast administration.[5] In order to standardize the definition of acute kidney injury from different aetiologies, two groups, the Acute Dialysis Quality Initiative (ADQI) and Acute Kidney Injury Network (AKIN) have separately proposed a system of defining and staging AKI, regardless of the likely cause. These include the RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) and the AKIN systems respectively, the latter being a modification of the former, which should theoretically improve sensitivity and specificity.[6]

Table 1 Risk factors for CIN

Pre-existing renal impairment[2–4]
Diabetes mellitus
Peri-procedural intravascular depletion
Congestive heart failure
Volume and type of contrast administered
Concomitant use of other nephrotoxic drugs

According to the AKIN criteria, stage 1 AKI may be diagnosed if one of the following occurs within 48 h:

- An absolute serum creatinine increase >26.4 μmol litre^{-1} (≥0.3 mg dl^{-1}).
- An increase in serum creatinine ≥50% (≥1.5-fold) above baseline.
- Urine output reduced to ≤0.5 ml kg^{-1} h^{-1} for at least 6 h.

These are not specific to suspected contrast-induced AKI and differ from the previously used definitions of CIN. These criteria may be seen more frequently in future studies of CIN, which will aid the comparison of different studies.

Incidence of CIN in patients with vascular disease

In the Manual on Contrast Media by the American College of Radiology,[7] the authors made a distinction in terminology between the diagnoses of post-contrast acute kidney injury and contrast induced nephropathy. In the latter CM is considered to be the cause of the renal injury. Be that as it may, very few studies have adequate controls to separate between the two entities and quoted incidences are likely to include a combination of both.[8] Furthermore, the reported incidences of CIN after cardiology and radiology procedures vary widely, owing to variation in the definitions used in earlier studies and the inclusion of patients with different numbers of known risk factors.[9] The aetiology of AKI in patients undergoing endovascular aneurysm repair (EVAR) in the perioperative period is multifactorial, with the kidneys being potentially subjected to a variety of haemodynamic, mechanical and pharmacological insults. Hence it is difficult to attribute AKI after EVAR solely to the adverse effects of CM and data are relatively scarce. An earlier study in patients undergoing EVAR showed that 24% of patients with baseline renal insufficiency had a creatinine increase postoperatively, with this being permanent in around two thirds of patients.[10] More recent data may be found in a multivariate analysis of the American College of Surgeons National Surgical Quality Improvement Program, where 13191 patients were identified as having undergone AAA repairs, 9877 of who had EVAR.[11] The investigators divided these patients as having moderate baseline renal impairment if their eGFR was between 30–60 ml min^{-1}, and severe impairment if their eGFR was <30 ml min^{-1}. Patients with moderate baseline renal impairment had an AKI rate of 1% and a dialysis rate of 1.1%. This compares with an AKI rate of 4.1 and 6.3% respectively in those with severely impaired baseline renal function. However, the definition of AKI used was a creatinine increase of 2 mg dl^{-1} (176 μmol litre^{-1}), a standard that is much higher than that used for the definition of CIN (0.5 mg dl^{-1} /44 μmol litre^{-1}). Interestingly, the odds of developing renal impairment were higher in the open repair group (OR=3, 95% CI 2.2–4.0). This was borne out in another systematic review of open vs EVAR in patients more than 80 yr old, where the relative risk for renal failure was close to three in the open procedure group.[12] Other studies investigating various preventative measures for AKI have shown incidences of CIN between 3–8% of vulnerable patients undergoing angiography in the vascular surgical setting.[13–15] In a systematic review by Zaraca and colleagues[16] the overall frequency of CIN from six eligible studies was 9.2% (79 out of 862 patients).

Clinical consequences of CIN

The sequelae of CIN are variable and difficult to quantify, as there is not a well-demarcated pathophysiological pathway to account for the morbidity and mortality in patients who develop CIN. For the most part, AKI associated with CIN is asymptomatic and transient; like other mild forms of AKI, it requires only observation and supportive management, and rarely requires renal replacement. However, observational studies consistently point to a greater chance of death in those who develop CIN, compared with those who do not, with the odds lasting beyond one yr after detection. Furthermore, data gleaned from randomized trials of therapeutic interventional measures also indicate an added morbidity attributable to the occurrence of CIN.[17] Earlier data indicated an in-hospital mortality rate of up to 30% and a two yr mortality rate of 80%.[2 18] In a prospective cohort analysis, the development of CIN after contrast-enhancing CT scan was shown to be associated with a similar risk of death in one yr as coronary artery disease, heart failure or advanced age.[19] In a prospective study of 9877 subjects with a median follow up of 42 months, the rate of CIN was 11% in those with chronic kidney disease (CKD) and 2% in those without CKD, calculated after adjusting for known confounders of death and excluding patients who had died in hospital (24), had surgery (2999), were on dialysis (250) and had incomplete laboratory data (2233). CIN was associated with long-term mortality for the entire cohort (HR=2.26, CI=1.62 to 2.29, P<0.0001). Subgroup analysis showed that patients with CKD also had a higher long-term mortality if they developed CIN (HR 2.62, CI=1.91 to3.57, P<0.0001) but CIN had no effect on mortality in patients without CKD (HR=1.23, CI 0.47=2.62, P=0.6).[20]

Pharmacology of iodinated contrast media (CM)

Commercially available CM are based on either one (monomers) or two (dimers) tri-iodinated benzene rings. They are further classified according to their ionization and osmolarity. CM vary in their chemical and physical properties but the imaging efficacy is solely based on their ability to attenuate x-rays, which is dependent on the number of iodine molecules present.[21] The ionic form affects the electrical potential of the cell membranes, which accounts for an increased toxicity.[22]

The improved safety profiles of the non-ionic low-osmolar or iso-osmolar CM (osmolality equal to that of blood) have resulted in universal uptake in clinical practice.[23–25] Osmolality was thought to play an important role in the pathogenesis of CIN, but the anticipated benefit of lower incidence of CIN by reducing osmolality has not been borne out in meta-analyses that compared the risks of CIN between high-osmolar and low-osmolar CM; and between low-osmolar and iso-osmolar CM regardless of the routes of administration.[25 26]

There has been a shift in thinking that suggests viscosity may be a particularly important contributing factor in the development of CIN, especially with low-osmolar CM having up to a 50-fold increase in viscosity.[27–29] The complex interaction of

osmolality and viscosity in the development of CIN, may explain the mixed results with iso-osmolar CM in reducing CIN.[30–32] All CM are similar, essentially having low lipophilicity, low protein binding and undergoing renal excretion without significant metabolism.[33] CM are distributed from the intravascular compartment to highly perfused organs, such as the liver and kidney with the exception of the brain parenchyma when there is an intact blood-brain barrier.[34 35] CM elimination half-life is between 90–120 min with normal excretory function, but is delayed in the presence of renal insufficiency.[35]

A number of earlier studies pointed to the association of volume of contrast used with the development of CIN such that it has been incorporated as a component of a proposed risk scoring system.[3] It has to be stressed however that there are no randomized trials designed to evaluate this issue specifically, as it may be considered unethical to expose patients to unnecessary amounts of contrast. As the volume of CM used may reflect the complexity of the pathology or required procedure, it may be argued that observational studies could be biased towards selecting out a subset of patients at higher risk of developing CIN. Some are of the opinion that limiting the volume of CM may in fact negatively impact upon the evaluation of patients undergoing diagnostic procedures and have produced retrospective data refuting the association between CM dose and rate of CIN.[36] Yet others are still producing observational evidence, indicating that exceeding the maximal allowable dose still adversely affects patient outcome.[36] On balance, irrespective of the type of contrast used, judiciously limiting the contrast load should still form an essential part of CIN prophylaxis until more convincing data suggest otherwise.

Preventative measures

Hydration

Although there are no direct trials comparing hydration to placebo, hydration remains the foundation of preventative strategies against the development of CIN. Many of the studies evaluating potential benefits of other strategies have incorporated hydration for both the control and intervention groups. Consensus, however, has not yet been achieved with respect to the optimal volume, composition and regime of fluid administration. A meta-analysis suggested that there is minimal difference in efficacy between oral and i.v. hydration.[37] However, it may be difficult to coordinate oral hydration with fasting time in the immediate preoperative period and some will favour i.v. hydration for high risk patients shortly before surgery.[38] Hydration with 0.9% saline may be superior to hypotonic saline, as is the administration of fluids over a longer period compared with a shorter time.[39]

Based on the premise that alkalinization of the urine may decrease the generation of hydroxyl free radicals that can harm the renal tubules, several studies have been performed to evaluate the use of isotonic bicarbonate rather than isotonic 0.9% saline as the hydration agent. Many of these have similar deficiencies in methodology such as small sample sizes and lack of power. Meta-analyses have also found a moderate to high degree of heterogeneity, publication bias and different treatment effect, thus resulting in different overall effects. On the whole, some of the studies suggest bicarbonate is not inferior to 0.9% saline, while others show some benefits. Nevertheless, not many international organizations have recommended choosing bicarbonate over 0.9% saline, but have suggested hydration with either solution over no hydration. However, physicochemical drug compatibilities are a concern and concomitant drug administration through the i.v. line used for isotonic bicarbonate, should be avoided.

There is a body of evidence around forced diuresis with matching fluid replacement. This was studied in the REMEDIAL II[40] and MYTHOS[41] trials. Where forced diuresis was achieved using diuretics or osmotic agents alone and without adequate fluid replacement, the treatment was ineffective or even detrimental.[42–44] In comparison using an automated fluid delivery system that matches fluid administration to urine output, investigators from both these trials were able to achieve urine output in the range of 300 ml h^{-1} in some of their patients and were able to reduce the event rate of CIN to roughly half that of their comparator arms respectively. The event rate for pulmonary oedema in the REMEDIAL II trial was 2.1% in the hydration group compared with 0.7% in the control group (P=0.62). This compares with rates of 6 and 12% in the treatment and control groups respectively (P=0.15) in the MYTHOS trial.

In the absence of this fluid delivery device, or a clinical environment where a regimen of high volume forced diuresis can be safely delivered, a practical protocol for elective patients undergoing procedures involving CM, may be the administration of either isotonic 0.9% saline, or sodium bicarbonate, at a rate of 1 ml kg^{-1} h^{-1} for 12 h before and 12 h after the anticipated contrast administration, and for more emergent procedures a regime of 3 ml kg^{-1} h^{-1} for 1 h before and 1 ml kg^{-1} h^{-1} for 6 h after is appropriate. The abbreviated regime may also be indicated for those in whom sustained volume expansion is not feasible.[39] The Prevention of Serious Adverse Events following Angiography (PRESERVE) trial is in the pipeline (NCT01467466). This study aims to enrol 8680 patients, and to evaluate the effectiveness of isotonic sodium bicarbonate compared with isotonic saline and oral N-acetyl cysteine vs oral placebo.

N-acetylcysteine

As far as pharmacological prophylaxis is concerned, N-acetylcysteine (NAC) is probably the most widely studied pharmacological agent for the prevention of CIN. NAC is inexpensive, easy to administer and has a favourable safety profile (although not totally harmless, as anaphylactoid reactions have been reported when used via the i.v. route in other clinical contexts[45]); it also may have free radical scavenging and organ protective effects.[46] However the results regarding its efficacy are equivocal and to date no firm recommendations can be given for its routine use, especially in light of the ACT trial (see Table 2).[13 14 47–69] This is probably attributable to heterogeneity in the design of the studies, ranging from definition of CIN, types of CM used, co-morbidities of patients, dose of NAC, routes of administration and of the co-interventions used, most notably that of hydration protocols. The disparity in study designs is reflected in differences in rates of baseline events and effect sizes reported. To complicate matters, NAC has been shown to decrease serum creatinine, an effect that is likely to be independent of changes in glomerular filtration rate (GFR).[70] Direct comparison studies suggest that the higher dose oral regimen of 1200 mg twice daily, may be more beneficial than 600 mg twice daily.[71 72] More relevant to the perioperative setting, Lawlor and colleagues[15] could find no additional benefit of NAC over hydration alone in patients undergoing vascular procedures in a small (n=78), single centre trial. It is of interest that NAC at high doses was not reno-protective in patients undergoing cardiac bypass and abdominal aortic aneurysm repair.[73 74]

In the largest and most methodologically rigorous trial to date, the Acetylcysteine for Contrast-Induced Nephropathy

Table 2 Summary of evidence for N-Acetylcysteine from clinical trials comparing NAC with control. This table contains randomized trials involving patients undergoing either coronary or peripheral angiography, with a primary outcome that measures the incidence of CIN as defined as a 25% increase in serum creatinine from baseline or a 0.5 mg dl^{-1} (44 μmol $litre^{-1}$) increase in the absolute value, within 48-72 h of i.v. contrast administration. C, coronary angiography; P, peripheral angiography; PO, per oral; RR, relative risk; CI, 95% confidence interval

Study	NAC (N) (dose in mg)	Control (N)	Procedure	PO or i.v.	Incidence NAC vs Control	Comments
Investigators ACT (2011)[14]	1172 (1200)	1136	P,C	PO	12.7 vs 12.7%	RR=1 (0.81-1.25) P=0.97
Amini et al. (2009)[47]	45 (600)	45	C	PO	11.1 vs 14.3% (P=0.656)	
Azmus et al. (2005)[48]	196 (600)	201	C	PO	7.1 vs 8.4% (P=0.62)	
Briguori et al. (2004)[49]	92 (600)	91	P,C	PO	4.1 vs 13.7% (P=0.019)	Fenoldopam in control group
Carbonell et al. (2007)[50]	107 (600)	109	C	i.v.	10.2 vs 10.1%	Normal renal function
Carbonell et al. (2010)[51]	39 (600)	42	C	i.v.	5.1 vs 23.8%	Chronic renal failure OR=0.17; CI=0.03-0.84; (P=.027)
Coyle et al. (2006)[52]	68 (600)	69	C	PO	9.2 vs 1.4% (P=0.043)	
Diaz-Sandoval et al. (2002)[53]	25 (600)	29	C	PO	8 vs 45% (P=0.005)	RR=0.21 CI=0.06 to 0.8
Ferrario et al. (2009)[54]	99 (600)	101	P,C	PO	8.1 vs 5.9% (P=0.6)	
Fung et al. (2004)[55]	46 (400)	45	C	PO	17.4 vs 13.3% (P=0.8)	
Goldenberg et al. (2004)[56]	41 (600)	39	C	PO	10 vs 8% (P=0.52)	
Gomes et al. (2005)[57]	77 (600)	79	C	PO	10.4 vs 10.1% (P=1)	
Gulel et al. (2005)[58]	25 (600)	25	C	PO	12 vs 8%	
Kay et al. (2003)[59]	102 (600)	98	C	PO	4 vs 12%	RR=0.32 CI=0.10-0.96; P=0.03
Kim et al. (2010)[60]	80 (600)	86	C	PO	5 vs 15.1% (P<0.05)	
MacNeill et al. (2003)[61]	21 (600)	22	C	PO	5 vs 32% (P=0.046)	
Miner et al. (2004)[62]	95 (2000)	85	C	PO	9.6 vs 22.2% (P=0.04)	
Ochoa et al. (2004)[63]	36 (1000)	44	C	PO	8 vs 25% (P=0.051)	OR=3.7 CI=0.94-14.4
Oldemeyer et al. (2003)[64]	49 (1500)	47	C	PO	8.2 vs 6.4% (P=0.74)	
Rashid et al. (2004)[13]	46 (1000)	48	P	i.v.	17.6 vs 14.3% (P>0.05)	
Sadat et al. (2011)[65]	21 (600)	19	P	PO	1/21 vs 3/19 (P=0.33)	
Sandhu et al. (2006)[66]	53 (600)	53	P	PO	2.8 vs 0%	
Seyon et al. (2007)[67]	20 (600)	20	C	PO	2.5 vs 7.5%	
Shyu et al. (2002)[68]	60 (400)	61	C	PO	3.3 vs 24.6% (P<0.001)	
Thiele et al. (2010)[69]	126 (1200)	125	C	i.v.	14 vs 20% (P=0.28)	

(ACT) Trial Investigators, have convincingly demonstrated a lack of efficacy for NAC in reducing the incidence of CIN, mortality or need for dialysis at 30 days, a finding that was observed in all subgroups analysed, including those with renal impairment.[14] This was a multicentre trial involving 46 different sites and 2308 patients with at least one risk factor for the development of CIN, randomized to receive either 1200 mg of NAC or placebo. The usual definition of CIN (see above) was used as the primary endpoint and an intention to treat analysis was used. The event rate for both groups was 12.7% (RR=1, CI=0.81 to 1.25, P=0.97). There was also no difference in the combined end point of 30 day mortality or need for dialysis (2.2% in treatment vs 2.3% in the control group, HR 0.97, CI=0.56 to 1.69, P=0.92). These effects were consistent across all subgroup analyses. Hence there is no evidence of overall benefit to support the routine use of NAC in prophylactic protocols for surgical patients at risk of CIN.

Statins

Evidence for possible perioperative benefit from the pleiotropic effects of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), has continued to emerge over the past decade.[75] With respect to CIN, initial retrospective analysis pointed to an association with pre-procedural statin use and a reduction in the incidence of CIN.[76] In a follow-up study of 434 patients undergoing PCI, statin-treated patients had a lower incidence of CIN (3 vs 27%, $p<0.0001$) and a superior post-procedural creatinine clearance (80 (20) vs 65 (16) ml min^{-1}, $p<0.0001$). These benefits were seen across all subgroups except those with a pre-existing creatinine clearance <40 ml min^{-1}.[77] Prospective, randomized trials involving large numbers are difficult because of the ubiquitous use of statins in patients with cardiovascular co-morbidities. However, the randomized trials in patients undergoing coronary angiography, using high dose statins seem beneficial.[78–81]

In a trial involving 241 statin-naive patients with acute coronary syndrome undergoing PCI, 120 patients were randomized to receive atorvastatin (80 mg+40-mg) before the procedure, compared with 121 placebo controls, with all patients receiving atorvastatin 40 mg daily post-procedure. The treatment group had a significantly lower rate of CIN compared with placebo (5 vs 13.2%, P=0.046) and were independently associated with a decreased risk of CIN (OR=0.34, CI=0.12 to 0.97, P=0.043) and a shorter hospital stay (p=0.007).[79] Similar results were reported by the Protective Effect of Rosuvastatin and Antiplatelet Therapy on Contrast-Induce Acute Kidney Injury and Myocardial Damage in Patients With Acute Coronary Syndrome (PRATO-ACS) Study. In this study, consecutive statin-naive patients with non-ST elevation ACS undergoing early invasive intervention, were randomly assigned to receive rosuvastatin (40+20 mg per day; n=252) or no statin treatment control group (n=252). The results showed a beneficial effect of statins on CIN (6.7 vs. 15.1%; adjusted OR=0.38; CI=0.20 to 0.71, P=0.003). There was also a lower 30-day

incidence of adverse cardiovascular and persistent renal damage (3.6 vs. 7.9%, P=0.036).[80] Conversely, there is contrary evidence in one single-centre prospective study enrolling patients with chronic renal disease, where statins did not confer additional benefits over standard preventative measures.[82] On balance, although the data are promising, it would be premature to recommend high dose statins for the sole purpose of preventing CIN. However, given the favourable side-effect profile, it may be argued that escalation of dose in those already on statins and starting statin-naïve patients on the medication (if it is otherwise indicated) for the perioperative period, is a reasonable approach for reducing CIN. Table 3 summarize the trials involving statins in the prevention of CIN.

Remote ischaemic preconditioning

Remote ischaemic preconditioning (RIPC) involves the application of series of intermittent non-lethal ischaemic stimuli, to a particular region of the body (often a limb), in order to mitigate ischaemic damage to an organ in another region. In practice the preconditioning stimulus may be applied to either an upper or lower limb, using a non-invasive BP cuff. Recent clinical trials have shown a potential beneficial renal effect from this technique when used in cardiac surgery.[83 84] Several small single-centre prospective trials showed a reduced rate of CIN in patients undergoing coronary angiography or percutaneous interventions,[85–87] with further research in progress (Table 4[88]). However, patients in the control groups of these studies had unusually high event rates, which raises concerns over the generalizability of the results to other lower risk patient groups. Nevertheless, when the preconditioning stimulus is being applied to upper or lower limbs using non invasive BP cuffs, the reported complication rates are very low to nil in the vast majority of studies, and the potential protection may spread beyond the kidneys.[89] Thus there appears to be little downside to using RIPC and this technique warrants further study in patients at risk of CIN.

Renal replacement therapy (RRT)

As CM can be effectively removed by haemodialysis (HD) or haemofiltration (HF), these interventions have been proposed as a means of preventing CIN. Although earlier trials on high risk patients using HF held promise, there were some methodological weaknesses that may have influenced the results, such as differential medical management in the intervention group.[90 91] In a meta-analysis that examined the use of HD or HF, RRT vs standard medical therapy was shown not to affect the incidence of CIN. This meta-analysis suffered from significant heterogeneity in terms of patient background, treatment protocols and types of contrast used. Interestingly, in a subgroup analysis that examined only HD (n=6 trials), where the heterogeneity was significantly reduced, the relative risk of developing CIN was actually higher in HD than in the comparator groups.[92] This was similar to the findings of an earlier meta-analysis.[93] A trend towards a reduction in temporary rescue RRT in the HD/HF groups was reported, but again heterogeneity between the included trials was significant. When limited to only the HF studies (n=3 trials), the heterogeneity was substantially reduced and the difference in temporary RRT requirements was significantly less in the treatment groups. Looking at individual trials, it would appear that HD might have more benefit in those with a lower baseline renal function[94] than in those with slightly more reserve.[95] On balance, given the resource implications, risks associated with RRT and the marginal benefits over less invasive measures, the prophylactic use of RRT cannot be recommended.

Agents acting on the renal circulation

Renal vasoconstriction has been implicated in the pathogenesis of CIN[29] although much of the evidence comes from animal studies. As such, agents with renal vasodilating effects have been investigated and, disappointingly, there is no strong evidence for their efficacy in CIN prophylaxis across several classes of agents tested. Trials involving dopamine mostly did not demonstrate any benefit with its use.[96–99] Similarly patients given fenoldopam also did not experience any benefits in terms of reduction in CIN.[100 101] Calcium channel antagonists did not fare any better, with only one small trial showing some benefits[102] whilst others showed less favourable results.[103 104] Owing to both its renal vasodilatory and diuretic effects, the adenosine antagonist theophylline and, to a lesser degree, aminophylline have also been investigated for protective effects. Dai and colleagues[105] systematically analysed 13 prospective, randomized trials involving theophylline and three involving aminophylline and showed an overall odds ratios of 0.48 in reducing the incidence of CIN in favour of theophylline, but with moderate statistical heterogeneity.[105] There was also no impact on mortality or need for dialysis. There were also no benefits seen in subgroup analyses of patients with poorer baseline renal function or of trials of higher quality.

A relative newcomer to the family of renal vasodilators to be tested for the prevention of CIN is the prostacyclin analogue iloprost. To date there is a single-centre randomized, double-blind, placebo-controlled study of iloprost involving 208 patients. The drug was well tolerated and resulted in a reduction of CIN from 22% in the control group to 8% in the treatment group, with the latter demonstrating a slight increase in eGFR. Further larger confirmatory trials are required before a recommendation can be given for the use of iloprost.

Peri-procedural management

The cornerstone of successful prevention and management of CIN is vigilance of the clinical team; the first step is to identify patients at risk. These comprise patients who have received CM in the days leading up to surgery and those having known risk factors, which include increased serum creatinine, diabetes mellitus, dehydration, congestive heart failure, age more than 70 yr and concurrent administration of nephrotoxic drugs.[26] The limitations of serum creatinine in reflecting renal function are well known and, therefore, estimation of GFR using one of the established formulas would be preferable in identifying those with reduced renal reserve,[29] and an eGFR of <60 mls min^{-1} 1.73 m^{-2} should raise concern.[26]

As the vast majority of the trials on preventative measures for CIN have been performed during diagnostic or minimally invasive procedures, we have concentrated on a small number of interventions to maintain academic rigour. However, the kidneys of surgical patients may face several concurrent or sequential insults in the perioperative period and minimizing the occurrence of CIN is just one part of management aimed at preventing AKI. Close communication within the operating team is essential and concerns regarding any potential nephrotoxic drugs or interventions (such as manipulations likely to compromise renal blood flow) should be discussed.

Given the recent evidence regarding forced diuresis, it is inappropriate to expose dehydrated patients to contrast in the

Table 3 Summary of the effect of statins on contrast induced nephropathy. Adj OR, Adjusted odds ratio; CKD, chronic kidney disease; CI, 95% confidence interval; Cr, creatinine; NAC, N acetylcysteine; NS, normal saline; NTSE-ACS, non ST elevation acute coronary syndrome; PRCT, Prospective Randomized Control Trial

Author & Yr	Study Type & Number of patients	Procedure	Primary Outcome	Treatment & Incidence	Comparator & Incidence	Statistical Significance	Effect size	Comments
Khanal *et al.* (2005)[76]	Prospective multicentre audit (*n*=29409)	PCI	Cr ↑ 0.5 mg dl^{-1}	Pre - procedural statins (*n*=10831); 4.37%	Statin naïve patients (*n*=18040); 5.93%	P<0.0001	Adj. OR 0.87 (0.77-0.99, P=0.03)	Preprocedural renal failure patients excluded
Patti *et al.* (2008)[77]	Prospective cohort study; (*n*=434)	PCI	Cr ↑ 0.5 mg dl^{-1} or 25% from baseline	Pre - procedural statins (*n*=260); 3%	Statin naïve patients (*n*=174); 27%	P<0.0001	90% risk decrease	4 year follow up
Xinwei *et al.* (2009)[78]	RCT (*n*=228)	ACS patients PCI	Cr ↑ 0.5 mg dl^{-1} or 25% from baseline	Simvastatin 80 mg (S80) (*n*=113)	Simvastatin 20 mg (S20) (*n*=115)	CIN incidence not stated Cr returned to normal in S80 but not S20	Not given	Cotreatment NS hydration
Toso *et al.* (2010)[82]	Single centre PRCT (*n*=304)	Patients with pre-existing CKD for PCI	Cr ↑ 0.5 mg dl^{-1} within 5 days	Atorvastatin 80 mg day^{-1} *n*=151; 10%	Placebo (*n*=152); 11%	P=0.86		Cotreatment NS hydration plus NAC
Patti *et al.* (2011)[79]	Multi-centre PRCT (*n*=241)	ACS patients PCI	Cr ↑ 0.5 mg dl^{-1} within 5 days	Atorvastatin 80 mg then 40 mg day^{-1} (*n*=120); 5%	Placebo (*n*=121); 13.2%	P=0.046	OR=0.34 CI=0.12 to 0.97, P=0.043	
Han *et al.* (2014)[81]	Multi-centre PRCT (*n*=2998)	DM and CKD patients for PCI, peripheral angiography	Cr ↑ 0.5 mg dl^{-1} or 25% from baseline at 72h	Rosuvastatin10 mg day^{-1} for 5 days (*n*=1,498); 2.3%	Standard care (*n*=1,500); 3.9%	P=0.01		NS hydration for both groups
Leoncini *et al.* (2014)[80]	Single centre PRCT	NSTE-ACS patients	Cr ↑ 0.5 mg dl^{-1} or 25% from baseline within 72h	Rosuvastatin 40+20 mg day^{-1} (*n*=252); 6.7%	Standard care (*n*=252); 15.1%		Adj OR=0.38 CI=0.2 to 0.71, P=0.003	

Table 4 Summary of evidence for remote ischaemic preconditioning and renal protection. AKI, Acute Kidney Injury; CABG, Coronary Artery Bypass Graft; CI, 95% confidence interval; KDIGO, Kidney Disease Improving Global Outcome; MCRCT, Multi-Centre Randomized Control Trial; OR, Odds Ratio; PCI, Percutaneous Coronary Intervention; PRCT, Prospective Randomized Control Trial; RCT, Randomized Control Trial; RIPC, Remote ischaemic preconditioning

Study	Type	Procedure	RIPC (N)	Control (N)	Outcome (RIPC vs CON)	Effect size	Comments
Venugopal *et al.* (2010)[83]	Secondary analysis	CABG*	38	40	AKI stages: I: 3 vs 25% II: 3 vs 0% III: 0 vs 0%	P=0.005	data from 2 prospective trials
Zarbock *et al.* (2015)[8]	MCRCT	Cardiac surgery*	120	120	KDIGO AKI 37.5 vs 52.5%	ARR, 15%; CI=2.56-27.44%; P=0.02	
Er *et al.* (2012)[85]	PRCT	Coronary angiography	50	50	12 vs 40%	OR=0.21 CI=0.07 – 0.57 P=0.002	
Deftereos *et al.* (2013)[86]	PRCT	PCI	113	112	12.4 vs 29.5%	*p*=0.002; OR=0.34; CI=0.16 to 0.71	
Yamanaka *et al.* (2014)[87]	RCT	PCI	63	62	10 vs 36%	P=0.003 OR=0.18 CI 0.05-0.64; P=0.008	

elective setting. At a minimum the patient should receive pre hydration either with 0.9% saline or isotonic bicarbonate.

Where patients are admitted on the day of surgery they should be instructed to drink oral fluids liberally the night before. Preoperative anaemia should be sought and treated where time permits, as anaemia is correlated with the incidence of CIN.[106–108] One should be aware that patients taking beta blockers are more likely to develop anaphylactoid reactions to CM and are, in turn, potentially more resistant to treatment.[109]

Apart from incorporating measures that are directed specifically at minimizing CIN, one must not forget other common sense measures to preserve renal function. These include maintenance of renal blood flow and renal perfusion pressure, avoidance of nephrotoxic agents, judicious glycaemic control, and the appropriate management of any postoperative complications.[110] With respect to perioperative management of medications, one must not overlook the potential for a postoperative decrease in renal clearance of drugs such as metformin, with the potential to cause lactic acidosis. Other drugs that undergo renal excretion may also need closer monitoring.

There is a scarcity of robust data regarding the influence of anaesthetic technique on CIN/AKI incidence. Multivariate analyses of patients from the EUROSTAR data in 2007, indicated a lower incidence of systemic complications, including renal outcomes, from the use of loco-regional techniques compared with general anaesthesia in EVAR, especially in the higher risk patients.[111] However in another single centre retrospective analysis of 302 patients undergoing EVAR, there was no statistically significance difference between the two techniques in terms of all complications and all-cause mortality.[112]

Alternatives to iodinated contrast media

For those who are allergic or at very high risk of developing CIN, alternatives may be considered. The most practical alternative in endovascular surgery is carbon dioxide (CO_2) but because of its cumbersome delivery, inferior image quality and potential for embolism, it has not gained popularity. Carbon dioxide is a highly soluble gas that briefly displaces the blood, before being rapidly dissolved and excreted through exhalation.[113] Being non-allergenic, non-nephrotoxic and of low viscosity relative to blood, makes CO_2 a safe contrast medium.[114 115] Even though CO_2 possesses these favourable characteristics, the risk of neurotoxicity, limiting its use to infra-diaphragmatic arteriography has been recommended.[116 117] Other limitations include being less user-friendly and the complication of vapour lock that may risk impeding blood flow and result in tissue ischaemia.[117 118] Notwithstanding these limitations, practitioners have successfully used CO_2 digital subtraction angiography (CO_2 -DSA) either to assist or as an alternative to CM for EVAR in high-risk patients, with similar results.[119–121] It has also been investigated for the detection of endoleaks post graft placement, where it has shown moderate sensitivity and specificity for type I but not type 2 endoleaks and the authors have suggested that it may have a potential for initial evaluation of endoleak in order to minimize CM exposure.[122] Therefore, this technique is gaining acceptance as a credible alternative to CM in endovascular procedures. Needless to say, its use requires careful planning and good communication between members of the operating team.

Gadolinium

Gadolinium was once thought to be a suitable alternative to CM. This was disproved after the report of its association with nephrogenic systemic sclerosis (NSF).[123] NSF is a serious fibrosing dermatopathy associated with hardened skin nodules, joint contractures and multi-organ involvement in its severe form, but no effective treatment is currently available.[124] Furthermore, gadolinium is more nephrotoxic than CM in equivalent doses that produce the same x-ray attenuating function.[125] Therefore, the European Society of Urogenital Radiology (ESUR) does not recommend its use for angiography and CT.[26]

Concluding remarks

CIN prevention is continually evolving. The data regarding N-acetyl cysteine, and to lesser extent, bicarbonate, theophylline and renal replacement therapy, is illustrative of the problems that physicians face in their endeavour to minimize patient harm. Multiple small trials with different designs and co-treatments, spanning over a long time have predominated in the literature and limited interpretation of the efficacy of

treatments, even with meta-analysis. Thankfully, some better quality evidence, especially with regards to hydration and NAC, is beginning to emerge attributable, in part, to standardization of definitions and more rigorous study design. Maintaining a high urinary flow rate around the time of contrast exposure is pivotal in minimizing harm from the CM. However, evidence is equivocal at best for the strategy of reducing oxidative damage, by either antioxidants or urinary alkalinization. The renal vasodilator iloprost is promising but further data are awaited. Patients taking statins should be maintained on therapy and there is evidence that initiation of treatment may have other benefits also.[75] Intraoperative remote ischaemic preconditioning is simple and safe but requires further validation before it can be recommended as a prophylaxis.

Authors' contributions

Writing paper: G.T.C.W., E.Y.P.L.
Revising paper: all authors

Declaration of interest

None declared.

References

1. Wong GT, Irwin MG. Contrast-induced nephropathy. *Br J Anaesth* 2007; **99**: 474–83
2. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med* 1997; **103**: 368–75
3. Mehran R, Aymong ED, Nikolsky E, *et al*. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004; **44**: 1393–9
4. Rihal CS, Textor SC, Grill DE, *et al*. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002; **105**: 2259–64
5. McDonald JS, McDonald RJ, Comin J, *et al*. Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. *Radiology* 2013; **267**: 119–28
6. Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. *Clinical Kidney Journal* 2013; **6**: 8–14
7. Media ACoRCoDaC. ACR Manual on Contrast Media – Version 10.1. 2015
8. Newhouse JH, Kho D, Rao QA, Starren J. Frequency of serum creatinine changes in the absence of iodinated contrast material: implications for studies of contrast nephrotoxicity. *AJR Am J Roentgenol* 2008; **191**: 376–82
9. Rundback JH, Nahl D, Yoo V. Contrast-induced nephropathy. *J Vasc Surg* 2011; **54**: 575–9
10. Carpenter JP, Fairman RM, Barker CF, *et al*. Endovascular AAA repair in patients with renal insufficiency: strategies for reducing adverse renal events. *Cardiovasc Surg* 2001; **9**: 559–64
11. Nguyen BN, Neville RF, Rahbar R, Amdur R, Sidawy AN. Comparison of outcomes for open abdominal aortic aneurysm repair and endovascular repair in patients with chronic renal insufficiency. *Ann Surg* 2013; **258**: 394–9
12. Biancari F, Catania A, D'Andrea V. Elective endovascular vs. open repair for abdominal aortic aneurysm in patients aged 80 years and older: systematic review and meta-analysis. *Eur J Vasc Endovasc Surg* 2011; **42**: 571–6
13. Rashid ST, Salman M, Myint F, *et al*. Prevention of contrast-induced nephropathy in vascular patients undergoing angiography: a randomized controlled trial of intravenous N-acetylcysteine. *J Vasc Surg* 2004; **40**: 1136–41
14. Investigators ACT. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized Acetylcysteine for Contrast-induced nephropathy Trial (ACT). *Circulation* 2011; **124**: 1250–9
15. Lawlor DK, Moist L, DeRose G, *et al*. Prevention of contrast-induced nephropathy in vascular surgery patients. *Ann Vasc Surg* 2007; **21**: 593–7
16. Zaraca F, Wiedermann CJ, Ebner H. Contrast media-induced nephropathy in patients undergoing angiography prior to or during vascular surgery: a systematic review. *Minerva Chir* 2011; **66**: 553–60
17. Rudnick M, Feldman H. Contrast-induced nephropathy: what are the true clinical consequences? *Clin J Am Soc Nephrol* 2008; **3**: 263–72
18. Gruberg L, Mintz GS, Mehran R, *et al*. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with preexistent chronic renal insufficiency. *J Am Coll Cardiol* 2000; **36**: 1542–8
19. Mitchell AM, Joones AE, Tumlin JA, Kline JA. 1-Year Mortality Following Contrast-Induced Nephropathy. *American Journal of Internal Medicine* 2013; **1**: 1–6
20. Abe M, Morimoto T, Akao M, *et al*. Relation of contrast-induced nephropathy to long-term mortality after percutaneous coronary intervention. *Am J Cardiol* 2014; **114**: 362–8
21. Fleischmann D, Kamaya A. Optimal vascular and parenchymal contrast enhancement: the current state of the art. *Radiol Clin North Am* 2009; **47**: 13–26
22. Thomsen HS, Morcos SK. Radiographic contrast media. *BJU Int* 2000; **86**: 1–10
23. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1990; **175**: 621–8
24. Owen RJ, Hiremath S, Myers A, Fraser-Hill M, Barrett BJ. Canadian Association of Radiologists consensus guidelines for the prevention of contrast-induced nephropathy: update 2012. *Can Assoc Radiol J* 2014; **65**: 96–105
25. Bucher AM, De Cecco CN, Schoepf UJ, *et al*. Is contrast medium osmolality a causal factor for contrast-induced nephropathy? *Biomed Res Int* 2014; **2014**: 931413
26. Stacul F, van der Molen AJ, Reimer P, *et al*. Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines. *Eur Radiol* 2011; **21**: 2527–41
27. Seeliger E, Becker K, Ladwig M, Wronski T, Persson PB, Flemming B. Up to 50-fold increase in urine viscosity with iso-osmolar contrast media in the rat. *Radiology* 2010; **256**: 406–14
28. Jost G, Pietsch H, Lengsfeld P, Hutter J, Sieber MA. The impact of the viscosity and osmolality of iodine contrast agents on renal elimination. *Invest Radiol* 2010; **45**: 255–61
29. Seeliger E, Sendeski M, Rihal CS, Persson PB. Contrast-induced kidney injury: mechanisms, risk factors, and prevention. *Eur Heart J* 2012; **33**: 2007–15
30. McCullough PA, Bertrand ME, Brinker JA, Stacul F. A meta-analysis of the renal safety of isosmolar iodixanol compared

with low-osmolar contrast media. *J Am Coll Cardiol* 2006; **48**: 692–9
31. Aspelin P, Aubry P, Fransson SG, *et al*. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 2003; **348**: 491–9
32. Liss P, Persson PB, Hansell P, Lagerqvist B. Renal failure in 57 925 patients undergoing coronary procedures using iso-osmolar or low-osmolar contrast media. *Kidney Int* 2006; **70**: 1811–7
33. Katzberg RW. Urography into the 21st century: new contrast media, renal handling, imaging characteristics, and nephrotoxicity. *Radiology* 1997; **204**: 297–312
34. Rapoport SI, Levitan H. Neurotoxicity of X-ray contrast media. Relation to lipid solubility and blood-brain barrier permeability. *Am J Roentgenol Radium Ther Nucl Med* 1974; **122**: 186–93
35. Pasternak JJ, Williamson EE. Clinical pharmacology, uses, and adverse reactions of iodinated contrast agents: a primer for the non-radiologist. *Mayo Clin Proc* 2012; **87**: 390–402
36. Madsen TE, Pearson RR, Muhlestein JB, *et al*. Risk of nephropathy is not increased by the administration of larger volume of contrast during coronary angiography. *Crit Pathw Cardiol* 2009; **8**: 167–71
37. Hiremath S, Akbari A, Shabana W, Fergusson DA, Knoll GA. Prevention of contrast-induced acute kidney injury: is simple oral hydration similar to intravenous? A systematic review of the evidence. *PLoS One* 2013; **8**: e60009
38. Group IGOKAKIW. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney International Supplements* 2012; **2**: 1–138
39. Weisbord SD, Palevsky PM. Prevention of contrast-induced nephropathy with volume expansion. *Clin J Am Soc Nephrol* 2008; **3**: 273–80
40. Briguori C, Visconti G, Focaccio A, *et al*. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury. *Circulation* 2011; **124**: 1260–9
41. Marenzi G, Ferrari C, Marana I, *et al*. Prevention of contrast nephropathy by furosemide with matched hydration: the MYTHOS (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) trial. *JACC Cardiovasc Interv* 2012; **5**: 90–7
42. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 1994; **331**: 1416–20
43. Weinstein JM, Heyman S, Brezis M. Potential deleterious effect of furosemide in radiocontrast nephropathy. *Nephron* 1992; **62**: 413–5
44. Stevens MA, McCullough PA, Tobin KJ, *et al*. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the P.R.I.N.C.E. Study. Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. *J Am Coll Cardiol* 1999; **33**: 403–11
45. Lynch RM, Robertson R. Anaphylactoid reactions to intravenous N-acetylcysteine: a prospective case controlled study. *Accid Emerg Nurs* 2004; **12**: 10–5
46. Wang T, Mao X, Li H, *et al*. N-Acetylcysteine and allopurinol up-regulated the Jak/STAT3 and PI3K/Akt pathways via adiponectin and attenuated myocardial postischemic injury in diabetes. *Free Radic Biol Med* 2013; **63**: 291–303
47. Amini M, Salarifar M, Amirbaigloo A, Masoudkabir F, Esfahani F. N-acetylcysteine does not prevent contrast-induced nephropathy after cardiac catheterization in patients with diabetes mellitus and chronic kidney disease: a randomized clinical trial. *Trials* 2009; **10**: 45
48. Azmus AD, Gottschall C, Manica A, *et al*. Effectiveness of acetylcysteine in prevention of contrast nephropathy. *J Invasive Cardiol* 2005; **17**: 80–4
49. Briguori C, Colombo A, Airoldi F, *et al*. N-Acetylcysteine versus fenoldopam mesylate to prevent contrast agent-associated nephrotoxicity. *J Am Coll Cardiol* 2004; **44**: 762–5
50. Carbonell N, Blasco M, Sanjuan R, *et al*. Intravenous N-acetylcysteine for preventing contrast-induced nephropathy: a randomised trial. *Int J Cardiol* 2007; **115**: 57–62
51. Carbonell N, Sanjuan R, Blasco M, Jorda A, Miguel A. N-acetylcysteine: short-term clinical benefits after coronary angiography in high-risk renal patients. *Rev Esp Cardiol* 2010; **63**: 12–9
52. Coyle LC, Rodriguez A, Jeschke RE, Simon-Lee A, Abbott KC, Taylor AJ. Acetylcysteine In Diabetes (AID): a randomized study of acetylcysteine for the prevention of contrast nephropathy in diabetics. *Am Heart J* 2006; **151**: 1032 e9–12
53. Diaz-Sandoval LJ, Kosowsky BD, Losordo DW. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). *Am J Cardiol* 2002; **89**: 356–8
54. Ferrario F, Barone MT, Landoni G, *et al*. Acetylcysteine and non-ionic isosmolar contrast-induced nephropathy–a randomized controlled study. *Nephrol Dial Transplant* 2009; **24**: 3103–7
55. Fung JW, Szeto CC, Chan WW, *et al*. Effect of N-acetylcysteine for prevention of contrast nephropathy in patients with moderate to severe renal insufficiency: a randomized trial. *Am J Kidney Dis* 2004; **43**: 801–8
56. Goldenberg I, Shechter M, Matetzky S, *et al*. Oral acetylcysteine as an adjunct to saline hydration for the prevention of contrast-induced nephropathy following coronary angiography. A randomized controlled trial and review of the current literature. *Eur Heart J* 2004; **25**: 212–8
57. Gomes VO, Poli de Figueredo CE, Caramori P, *et al*. N-acetylcysteine does not prevent contrast induced nephropathy after cardiac catheterisation with an ionic low osmolality contrast medium: a multicentre clinical trial. *Heart* 2005; **91**: 774–8
58. Gulel O, Keles T, Eraslan H, Aydogdu S, Diker E, Ulusoy V. Prophylactic acetylcysteine usage for prevention of contrast nephropathy after coronary angiography. *J Cardiovasc Pharmacol* 2005; **46**: 464–7
59. Kay J, Chow WH, Chan TM, *et al*. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. *JAMA* 2003; **289**: 553–8
60. Kim BJ, Sung KC, Kim BS, *et al*. Effect of N-acetylcysteine on cystatin C-based renal function after elective coronary angiography (ENABLE Study): a prospective, randomized trial. *Int J Cardiol* 2010; **138**: 239–45
61. MacNeill BD, Harding SA, Bazari H, *et al*. Prophylaxis of contrast-induced nephropathy in patients undergoing coronary angiography. *Catheter Cardiovasc Interv* 2003; **60**: 458–61
62. Miner SE, Dzavik V, Nguyen-Ho P, *et al*. N-acetylcysteine reduces contrast-associated nephropathy but not clinical events during long-term follow-up. *Am Heart J* 2004; **148**: 690–5
63. Ochoa A, Pellizzon G, Addala S, *et al*. Abbreviated dosing of N-acetylcysteine prevents contrast-induced nephropathy after elective and urgent coronary angiography and intervention. *J Interv Cardiol* 2004; **17**: 159–65

64. Oldemeyer JB, Biddle WP, Wurdeman RL, Mooss AN, Cichowski E, Hilleman DE. Acetylcysteine in the prevention of contrast-induced nephropathy after coronary angiography. *Am Heart J* 2003; **146**: E23
65. Sadat U, Walsh SR, Norden AG, Gillard JH, Boyle JR. Does oral N-acetylcysteine reduce contrast-induced renal injury in patients with peripheral arterial disease undergoing peripheral angiography? A randomized-controlled study. *Angiology* 2011; **62**: 225–30
66. Sandhu C, Belli AM, Oliveira DB. The role of N-acetylcysteine in the prevention of contrast-induced nephrotoxicity. *Cardiovasc Intervent Radiol* 2006; **29**: 344–7
67. Seyon RA, Jensen LA, Ferguson IA, Williams RG. Efficacy of N-acetylcysteine and hydration versus placebo and hydration in decreasing contrast-induced renal dysfunction in patients undergoing coronary angiography with or without concomitant percutaneous coronary intervention. *Heart Lung* 2007; **36**: 195–204
68. Shyu KG, Cheng JJ, Kuan P. Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. *J Am Coll Cardiol* 2002; **40**: 1383–8
69. Thiele H, Hildebrand L, Schirdewahn C, *et al*. Impact of high-dose N-acetylcysteine versus placebo on contrast-induced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate Percutaneous Coronary Intervention Acute Myocardial Infarction N-ACC) Trial. *J Am Coll Cardiol* 2010; **55**: 2201–9
70. Hoffmann U, Fischereder M, Kruger B, Drobnik W, Kramer BK. The value of N-acetylcysteine in the prevention of radiocontrast agent-induced nephropathy seems questionable. *J Am Soc Nephrol* 2004; **15**: 407–10
71. Briguori C, Colombo A, Violante A, *et al*. Standard vs double dose of N-acetylcysteine to prevent contrast agent associated nephrotoxicity. *Eur Heart J* 2004; **25**: 206–11
72. Marenzi G, Assanelli E, Marana I, *et al*. N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med* 2006; **354**: 2773–82
73. Haase M, Haase-Fielitz A, Bagshaw SM, *et al*. Phase II, randomized, controlled trial of high-dose N-acetylcysteine in high-risk cardiac surgery patients. *Crit Care Med* 2007; **35**: 1324–31
74. Hynninen MS, Niemi TT, Poyhia R, *et al*. N-acetylcysteine for the prevention of kidney injury in abdominal aortic surgery: a randomized, double-blind, placebo-controlled trial. *Anesth Analg* 2006; **102**: 1638–45
75. Chan WW, Wong GT, Irwin MG. Perioperative statin therapy. *Expert Opin Pharmacother* 2013; **14**: 831–42
76. Khanal S, Attallah N, Smith DE, *et al*. Statin therapy reduces contrast-induced nephropathy: an analysis of contemporary percutaneous interventions. *Am J Med* 2005; **118**: 843–9
77. Patti G, Nusca A, Chello M, *et al*. Usefulness of statin pretreatment to prevent contrast-induced nephropathy and to improve long-term outcome in patients undergoing percutaneous coronary intervention. *Am J Cardiol* 2008; **101**: 279–85
78. Xinwei J, Xianghua F, Jing Z, *et al*. Comparison of usefulness of simvastatin 20 mg versus 80 mg in preventing contrast-induced nephropathy in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Am J Cardiol* 2009; **104**: 519–24
79. Patti G, Ricottini E, Nusca A, *et al*. Short-term, high-dose Atorvastatin pretreatment to prevent contrast-induced nephropathy in patients with acute coronary syndromes undergoing percutaneous coronary intervention (from the ARMYDA-CIN [atorvastatin for reduction of myocardial damage during angioplasty–contrast-induced nephropathy] trial. *Am J Cardiol* 2011; **108**: 1–7
80. Leoncini M, Toso A, Maioli M, Tropeano F, Villani S, Bellandi F. Early high-dose rosuvastatin for contrast-induced nephropathy prevention in acute coronary syndrome: Results from the PRATO-ACS Study (Protective Effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome). *J Am Coll Cardiol* 2014; **63**: 71–9
81. Han Y, Zhu G, Han L, *et al*. Short-term rosuvastatin therapy for prevention of contrast-induced acute kidney injury in patients with diabetes and chronic kidney disease. *J Am Coll Cardiol* 2014; **63**: 62–70
82. Toso A, Maioli M, Leoncini M, *et al*. Usefulness of atorvastatin (80 mg) in prevention of contrast-induced nephropathy in patients with chronic renal disease. *Am J Cardiol* 2010; **105**: 288–92
83. Venugopal V, Laing CM, Ludman A, Yellon DM, Hausenloy D. Effect of remote ischemic preconditioning on acute kidney injury in nondiabetic patients undergoing coronary artery bypass graft surgery: a secondary analysis of 2 small randomized trials. *Am J Kidney Dis* 2010; **56**: 1043–9
84. Zarbock A, Schmidt C, Van Aken H, *et al*. Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. *JAMA* 2015; **313**: 2133–41
85. Er F, Nia AM, Dopp H, *et al*. Ischemic preconditioning for prevention of contrast medium-induced nephropathy: randomized pilot RenPro Trial (Renal Protection Trial). *Circulation* 2012; **126**: 296–303
86. Deftereos S, Giannopoulos G, Tzalamouras V, *et al*. Renoprotective effect of remote ischemic post-conditioning by intermittent balloon inflations in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2013; **61**: 1949–55
87. Yamanaka T, Kawai Y, Miyoshi T, *et al*. Remote ischemic preconditioning reduces contrast-induced acute kidney injury in patients with ST-elevation myocardial infarction: A randomized controlled trial. *Int J Cardiol* 2014; **178C**: 136–41
88. Sterenborg TB, Menting TP, de Waal Y, *et al*. Remote ischemic preconditioning to reduce contrast-induced nephropathy: study protocol for a randomized controlled trial. *Trials* 2014; **15**: 1–19
89. Pei H, Wu Y, Wei Y, Yang Y, Teng S, Zhang H. Remote ischemic preconditioning reduces perioperative cardiac and renal events in patients undergoing elective coronary intervention: a meta-analysis of 11 randomized trials. *PLoS One* 2014; **9**: e115500
90. Marenzi G, Marana I, Lauri G, *et al*. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med* 2003; **349**: 1333–40
91. Marenzi G, Lauri G, Campodonico J, *et al*. Comparison of two hemofiltration protocols for prevention of contrast-induced nephropathy in high-risk patients. *Am J Med* 2006; **119**: 155–62
92. Cruz DN, Goh CY, Marenzi G, Corradi V, Ronco C, Perazella MA. Renal replacement therapies for prevention of radiocontrast-induced nephropathy: a systematic review. *Am J Med* 2012; **125**: 66–78 e3

93. Cruz DN, Perazella MA, Bellomo R, *et al*. Extracorporeal blood purification therapies for prevention of radiocontrast-induced nephropathy: a systematic review. *Am J Kidney Dis* 2006; **48**: 361–71
94. Lee PT, Chou KJ, Liu CP, *et al*. Renal protection for coronary angiography in advanced renal failure patients by prophylactic hemodialysis. A randomized controlled trial. *J Am Coll Cardiol* 2007; **50**: 1015–20
95. Reinecke H, Fobker M, Wellmann J, *et al*. A randomized controlled trial comparing hydration therapy to additional hemodialysis or N-acetylcysteine for the prevention of contrast medium-induced nephropathy: the Dialysis-versus-Diuresis (DVD) Trial. *Clin Res Cardiol* 2007; **96**: 130–9
96. Weisberg LS, Kurnik PB, Kurnik BR. Dopamine and renal blood flow in radiocontrast-induced nephropathy in humans. *Ren Fail* 1993; **15**: 61–8
97. Kapoor A, Sinha N, Sharma RK, *et al*. Use of dopamine in prevention of contrast induced acute renal failure–a randomised study. *Int J Cardiol* 1996; **53**: 233–6
98. Hans SS, Hans BA, Dhillon R, Dmuchowski C, Glover J. Effect of dopamine on renal function after arteriography in patients with pre-existing renal insufficiency. *Am Surg* 1998; **64**: 432–6
99. Gare M, Haviv YS, Ben-Yehuda A, *et al*. The renal effect of low-dose dopamine in high-risk patients undergoing coronary angiography. *J Am Coll Cardiol* 1999; **34**: 1682–8
100. Stone GW, McCullough PA, Tumlin JA, *et al*. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA* 2003; **290**: 2284–91
101. Ng TM, Shurmur SW, Silver M, *et al*. Comparison of N-acetylcysteine and fenoldopam for preventing contrast-induced nephropathy (CAFCIN). *Int J Cardiol* 2006; **109**: 322–8
102. Neumayer HH, Junge W, Kufner A, Wenning A. Prevention of radiocontrast-media-induced nephrotoxicity by the calcium channel blocker nitrendipine: a prospective randomised clinical trial. *Nephrol Dial Transplant* 1989; **4**: 1030–6
103. Khoury Z, Schlicht JR, Como J, *et al*. The effect of prophylactic nifedipine on renal function in patients administered contrast media. *Pharmacotherapy* 1995; **15**: 59–65
104. Spangberg-Viklund B, Berglund J, Nikonoff T, Nyberg P, Skau T, Larsson R. Does prophylactic treatment with felodipine, a calcium antagonist, prevent low-osmolar contrast-induced renal dysfunction in hydrated diabetic and nondiabetic patients with normal or moderately reduced renal function? *Scand J Urol Nephrol* 1996; **30**: 63–8
105. Dai B, Liu Y, Fu L, Li Y, Zhang J, Mei C. Effect of theophylline on prevention of contrast-induced acute kidney injury: a meta-analysis of randomized controlled trials. *Am J Kidney Dis* 2012; **60**: 360–70
106. Nikolsky E, Mehran R, Lasic Z, *et al*. Low hematocrit predicts contrast-induced nephropathy after percutaneous coronary interventions. *Kidney Int* 2005; **67**: 706–13
107. Murakami R, Kumita S, Hayashi H, *et al*. Anemia and the risk of contrast-induced nephropathy in patients with renal insufficiency undergoing contrast-enhanced MDCT. *Eur J Radiol* 2013; **82**: e521–4
108. Li WH, Li DY, Han F, Xu TD, Zhang YB, Zhu H. Impact of anemia on contrast-induced nephropathy (CIN) in patients undergoing percutaneous coronary interventions. *Int Urol Nephrol* 2013; **45**: 1065–70
109. Morcos SK, Thomsen HS, Exley CM, Members of Contrast Media Safety Committee of European Society of Urogenital R. Contrast media: interactions with other drugs and clinical tests. *Eur Radiol* 2005; **15**: 1463–8
110. Webb ST, Allen JSD. Perioperative renal protection. *Continuing Education in Anaesthesia, Critical Care & Pain* 2008; **8**: 176–80
111. Ruppert V, Leurs LJ, Rieger J, *et al*. Risk-adapted outcome after endovascular aortic aneurysm repair: analysis of anesthesia types based on EUROSTAR data. *J Endovasc Ther* 2007; **14**: 12–22
112. Bakker EJ, van de Luijtgaarden KM, van Lier F, *et al*. General anaesthesia is associated with adverse cardiac outcome after endovascular aneurysm repair. *Eur J Vasc Endovasc Surg* 2012; **44**: 121–5
113. Huber PR, Leimbach ME, Lewis WL, Marshall JJ. CO(2) angiography. *Catheter Cardiovasc Interv* 2002; **55**: 398–403
114. Seeger JM, Self S, Harward TR, Flynn TC, Hawkins IF Jr. Carbon dioxide gas as an arterial contrast agent. *Ann Surg* 1993; **217**: 688–97; discussion 97-8
115. Hawkins IF, Cho KJ, Caridi JG. Carbon dioxide in angiography to reduce the risk of contrast-induced nephropathy. *Radiol Clin North Am* 2009; **47**: 813–25, v-vi
116. Coffey R, Quisling RG, Mickle JP, Hawkins IF Jr, Ballinger WB. The cerebrovascular effects of intraarterial CO2 in quantities required for diagnostic imaging. *Radiology* 1984; **151**: 405–10
117. Nadolski GJ, Stavropoulos SW. Contrast alternatives for iodinated contrast allergy and renal dysfunction: options and limitations. *J Vasc Surg* 2013; **57**: 593–8
118. Caridi JG, Hawkins IF Jr. CO2 digital subtraction angiography: potential complications and their prevention. *J Vasc Interv Radiol* 1997; **8**: 383–91
119. Gahlen J, Hansmann J, Schumacher H, Seelos R, Richter GM, Allenberg JR. Carbon dioxide angiography for endovascular grafting in high-risk patients with infrarenal abdominal aortic aneurysms. *J Vasc Surg* 2001; **33**: 646–9
120. Lee AD, Hall RG. An evaluation of the use of carbon dioxide angiography in endovascular aortic aneurysm repair. *Vasc Endovascular Surg* 2010; **44**: 341–4
121. Chao A, Major K, Kumar SR, *et al*. Carbon dioxide digital subtraction angiography-assisted endovascular aortic aneurysm repair in the azotemic patient. *J Vasc Surg* 2007; **45**: 451–8; discussion 8-60
122. Huang SG, Woo K, Moos JM, *et al*. A prospective study of carbon dioxide digital subtraction versus standard contrast arteriography in the detection of endoleaks in endovascular abdominal aortic aneurysm repairs. *Ann Vasc Surg* 2013; **27**: 38–44
123. Grobner T. Gadolinium–a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006; **21**: 1104–8
124. Sadowski EA, Bennett LK, Chan MR, *et al*. Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology* 2007; **243**: 148–57
125. Elmstahl B, Nyman U, Leander P, Chai CM, Frennby B, Almen T. Gadolinium contrast media are more nephrotoxic than a low osmolar iodine medium employing doses with equal X-ray attenuation in renal arteriography: an experimental study in pigs. *Acad Radiol* 2004; **11**: 1219–28

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Special Issue

New antiplatelet drugs and new oral anticoagulants

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Abstract

In our daily anaesthetic practice, we are confronted with an increasing number of patients treated with either antiplatelet or anticoagulant agents. During the last decade, changes have occurred that make the handling of antithrombotic medication a challenging part of anaesthetic perioperative management. In this review, the authors discuss the most important antiplatelet and anticoagulant drugs, the perioperative management, the handling of bleeding complications, and the interpretation of some laboratory analyses related to these agents.

Key words: antiplatelet agents; anticoagulants and haemorrhage; blood coagulation tests

Editor's key points

- Antiplatelet agents significantly increase the risk of bleeding in high-risk surgery.
- A number of anticoagulant drugs that either inactivate factor Xa or directly inhibit thrombin have become available in recent years.
- Current data do not support the use of peripherative bridging therapy to cover the withdrawal of oral anticoagulants in patients at low risk of thromboembolism.
- Standard coagulation tests together with assay of factor Xa activity can be used to guide the managment of new anticoagulant drugs in the perioperative setting.

Arterial and venous thrombosis have an important impact on worldwide morbidity and mortality. Worldwide, >10 million deaths per annum are caused by arterial thrombotic events (ischaemic stroke, heart disease, and peripheral gangrene).[1 2] Platelets are the key prothrombotic element in arterial thrombosis, forming aggregates interconnected by fibrin. Antiplatelet treatment can counteract this process. For decades, aspirin has been the first-line antiplatelet drug of choice; recently, however, alternative antiplatelet substances have been introduced.

Half a million deaths related to venous thromboembolism occur in the European Union per year.[1] Venous thrombi consist primarily of fibrin with some cells trapped in between. Anticoagulants are the drugs of choice to prevent or treat these conditions. For decades, warfarin and heparin were the mainstay of treatment, but the development of new anticoagulant drugs is constantly enlarging the pharmaceutical armamentarium.

In this review, the pharmacological properties of the new antiplatelet and new oral anticoagulant drugs, their usage in the perioperative setting, and the management of bleeding complications are discussed.

Antiplatelet agents (Table 1)

Platelet adhesion, activation, and aggregation are mediated by numerous adhesive proteins. The reactions of these proteins underpin the physiological responses to endothelial damage or rupture of atherosclerotic plaques. Amplification of these mechanisms and excessive thrombus formation endanger vascular flow, leading to occlusion of arteries and temporary or persistent ischaemia.[3] Blocking such thrombus formation can prevent ischaemic events.

Treatment strategies for prevention or therapy of arterial thrombosis are changing constantly. The duration of treatment,

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Table 1 Summary of the characteristics of currently available antiplatelet drugs

Characteristic	Aspirin	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor	Abciximab	Eptifibatide	Tirofiban
Route of administration	Oral once daily, (i.v.)	Oral once daily, (i.v. under investigation)	Oral once daily	Oral twice daily	i.v.	i.v.	i.v.	i.v.
Bioavailability	68%	50%	80%	36%				
Plasma peak concentration	30–40 min	1 h	30 min	1.5 h	Seconds	Dose dependent	Dose dependent	Dose dependent
Time to plasma steady state		2–8 h	30 min to 4 h	30 min to 2 h	Seconds	Initial bolus and continuous application	Initial bolus and continuous application 4–6 h	Initial bolus and continuous application 10 min
Plasma half-life	15–30 min	8 h	7 h	7 h	2–5 min	10–15 min	2.5 h	2 h
Plasma protein binding	Strong	Strong	Strong	Strong				
Time from last dose to offset	7–10 days	7–10 days	7–10 days	5 days	60 min	12 h	2–4 h	2–4 h
Reversibility of platelet inhibition	No	No	No	Yes	Yes	Yes	Yes	Yes
Recommended period of discontinuation before surgical intervention (see Fig. 2)	0–5 days	7 days	10 days	7 days	1–6 h	48 h	8 h	8 h

especially of dual or triple antiplatelet therapy, is highly dependent on the indication for treatment and, for percutaneous coronary intervention, the chemical constitution of any coronary stents (Table 2).[4–6]

Acetylsalicylic acid (aspirin)

For >50 yr, aspirin has been known to have antithrombotic and anti-inflammatory properties.[7] Aspirin is a cyclooxygenase (COX) inhibitor that irreversibly inhibits COX1 and, in higher doses, COX2. Inhibition of COX1 is the main antithrombotic mechanism; the formation of prostaglandin H_2 is blocked, thus thromboxane A2 cannot be synthesized. Thromboxane A2 activates platelets and stimulates their aggregation.[8] The irreversibility of the effect of aspirin causes inhibition for the lifespan of a platelet (7–10 days). After the discontinuation of aspirin intake by a patient, their platelet function can be expected to increase by 10–15% per day as a result of new platelet formation.[8 9] Aspirin is a key component of antiplatelet treatment to reduce death attributable to myocardial infarction or stroke.[10] Bleeding risk is smaller with low doses (75–100 mg), which deliver an equivalent antithrombotic impact to higher doses (300 mg).[11] Drug interactions with aspirin are scarce, but co-administration of non-selective COX1 inhibitors may impair its efficacy. Owing to potential aggravation of ischaemic heart diseases attributable to selective COX2 inhibitors, these drugs should be avoided in patients with coronary artery disease. About one-third of patients receiving aspirin manifest treatment failure (thrombotic complication or death). Non-compliance is a substantial problem but difficult to quantify, with estimates ranging between 3 and 40%. Adverse events resulting from rebound thrombocyte activation after aspirin withdrawal are frequent. Some patients show biochemical resistance or high platelet reactivity, detected by platelet function assays. Diabetes, cardiac surgery, or acute coronary syndromes, all of which are associated with an inflammatory response, are associated with high platelet reactivity. In addition, genetic polymorphisms (COX1, COX2 alleles, platelet glycoprotein receptors), or increased platelet turnover (bone marrow diseases) can reduce the effect of aspirin. The fact that aspirin has only a single binding site and does not influence

Table 2 Treatment recommendations for antiplatelet agents.[4–6] BMS, bare metal stent; DES, drug-eluting stent; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease

Condition	Treatment recommendations
Primary prevention	Aspirin Risk *vs* benefit evaluation
Acute coronary syndrome	PCI: aspirin lifelong plus ticagrelor, prasugrel, or clopidogrel ≥12 months Non-PCI: aspirin lifelong plus clopidogrel or ticagrelor ≥12 months
Stable angina or former myocardial infarction	Aspirin lifelong plus clopidogrel BMS ≥1 month DES ≥6 months
Recent stroke	Aspirin in high-risk situation plus clopidogrel 90 days
Past stroke	Aspirin or clopidogrel
PVD	Aspirin or clopidogrel

other thrombocyte receptors results in aspirin having less antithrombotic effect than many other agents.[9 12 13]

$P2Y_{12}$ receptor antagonists

$P2Y_{12}$ receptors are adenosine diphosphate (ADP) receptors expressed on the surface of thrombocytes, which can be blocked chemically. The overall effect of ADP on platelets, the change of conformation, emergence of pseudopodia, platelet aggregation, and interaction with other cellular or plasma components to promote coagulation, is reduced.[14] Currently, clopidogrel, prasugrel, and ticagrelor are in use, and cangrelor has recently been licensed. Those substances are often prescribed in conjunction with aspirin, i.e. dual antiplatelet therapy (DAPT).[15]

Clopidogrel

Clopidogrel is a thienopyridine and a prodrug, of which 85% is hydrolysed to an inactive metabolite. The remaining part is activated via cytochromes P3A4/3A5 and P2B6/1A2/2C9/2C19.6. The active metabolite binds irreversibly to $P2Y_{12}$. For rapid onset of platelet inhibition, an initial loading dose is necessary.[8 16] The pharmacological effect lasts for the lifespan of the affected thrombocytes.[15] The CYP450 dependency makes clopidogrel susceptible to drug interactions. Proton-pump inhibitors can also reduce its effect. No studies have been published proving sufficient evidence that any other drug interactions have any impact on its therapeutic effect.[17] Thirty per cent of patients treated with clopidogrel do not show adequate platelet inhibition. Genetic polymorphisms (CYP2C19, $P2Y_{12}$ receptor) or altered intracellular signal pathways seem to be causative. Patients, especially if diabetic, may show high platelet reactivity even when receiving dual antiplatelet therapy. However, non-compliance, discontinuation of drug intake, or lack of access to clopidogrel are more frequent causes of inadequate platelet inhibition than pharmacological high platelet reactivity.[15]

Prasugrel

Prasugrel, a third-generation oral thienopyridine, is a prodrug, converted by CYP450 enzymes to its active metabolite. It binds irreversibly to $P2Y_{12}$, inhibiting platelet function for the lifespan of the affected platelets. Prasugrel shows a more reliable conversion to the active drug and more rapid onset of action than clopidogrel. Prasugrel produces more effective platelet inhibition than clopidogrel. Genetic polymorphisms (CYP2C9, CYP2C19) do not influence the metabolism of prasugrel. Drug interactions attributable to CYP-dependent conversion have not been described.[9]

Ticagrelor

Ticagrelor is an oral non-thienopyridine reversible $P2Y_{12}$-blocking agent. CYP3A4 and CYP3A5 are the enzymes involved in the hepatic metabolism of ticagrelor. One of its active metabolites also has an important platelet-inhibiting effect. Twenty-four hours after the last intake, the antiplatelet effect of ticagrelor has declined by 50%, and 20% of the antiplatelet activity remains after 3 days. CYP3A4, CYP3A5, and CYP2D6 are moderately inhibited by ticagrelor, and drug interactions associated with this effect have been reported. Digoxin concentrations should be monitored in the event of concomitant use. Serum concentrations of some statins (lovastatin and simvastatin) are increased. Concomitant use of CYP3A4 inhibitors (ketoconazole, ritonavir, and clarithromycin) or inducers (rifampicin, phenytoin, carbamazepine, and dexamethasone) should be avoided.[18]

Cangrelor

Cangrelor is the most recently (June 2015) approved i.v. non-thienopyridine, reversible $P2Y_{12}$-blocking agent. Steady-state concentrations are achieved after 18–24 h of i.v. infusion without a loading dose or a preliminary bolus being recommended. Platelet inhibition is >90%. Cangrelor is inactivated by plasma enzymes, and within 60 min of stopping the infusion the platelet function has recovered to normal.[19] These favourable pharmacokinetic properties make cangrelor a promising agent for bridging of high-risk patients in the perioperative setting.[20]

Glycoprotein IIb/IIIa inhibitors

Glycoprotein IIb/IIIa (GpIIb/IIIa) receptors are the most numerous proteins on the platelet surface. Glycoprotein IIb/IIIa inhibitors block the adhesion of fibrinogen to the activated platelet, preventing the building of interplatelet bridges. Adhesion of fibronectin, von Willebrand factor, and vitronectin are inhibited. The activation of the GpIIb/IIIa receptor is one of the final steps in platelet activation, building cross-linked platelet–fibrinogen complexes. Glycoprotein IIb/IIIa receptors also contribute to a positive feedback mechanism with thrombin and collagen, producing a sustained prothrombotic effect.[21 22] Abciximab, tirofiban, and eptifibatide are i.v. GpIIb/IIIa inhibitors that are currently in use.

Abciximab

Abciximab is a humanized monoclonal mouse antibody. It reversibly binds to thrombocytes within 1 min of adminstration. A loading dose is necessary to achieve a >80% receptor blockage. It shows the highest affinity to the GpIIb/IIIa receptor of the three licensed drugs.[23] It has a short plasma half-life, but a long biological activity.

Tirofiban and eptifibatide

Tirofiban and eptifibatide are synthetic GpIIb/IIIa inhibitors that reversibly bind and rapidly dissociate (10–15 s) from the GpIIb/IIIa receptor. The plasma concentration of these drugs determines the receptor occupancy and extent of platelet inhibition. Both molecules compete with fibrinogen for the binding of the GpIIb/IIIa receptor. The affinity for the receptor is greater for tirofiban than for eptifibatide.[23]

Other antiplatelet agents

Cilostazol and dipyridamole are phosphodiesterase inhibitors that interfere with degradation of cyclic adenosine monophosphate and cyclic guanosine monophosphate. In addition to their antiplatelet action, they cause vasodilation because of an effect on vascular smooth muscle.

The protease-activated receptor-1 antagonists, agents such as vorapaxar and atopaxar, inhibit platelet activation through alternative routes, including thrombin-mediated platelet aggregation. Numerous other platelet surface proteins (glycoprotein VI, glycoprotein Ib, prostaglandin E, nitrous oxid, and thromboxane A) are potential targets for inhibitory drugs currently under investigation.[3 8]

Management of antiplatelet therapy in the perioperative setting (Fig. 1)[24 25]

Dual antiplatelet therapy is known to reduce significantly the number of arterial thrombotic events in the perioperative period. Discontinuation of antiplatelet agents is associated with a risk of myocardial infarction, stent thrombosis, and death attributable

Risk of a cardiovascular event / Risk of perioperative Bleeding	Low to moderate cardiovascular risk	High cardiovascular risk ACS >12 months preop PCI/DES >6 months preop PCI/BMS >1 month preop CABG >6 weeks preop CVA/TIA >1 month preop Peripheral vascular disease	Very high cardiovascular risk ACS <12 months preop PCI/DES <6 months preop PCI/BMS <1 month preop CVA/TIA <1month preop CABG <6 weeks preop
Low bleeding risk e.g. endoscopy, body surface surgery	Discontinue aspirin 5 days before surgery – to 7 days after surgery	Continue aspirin Discontinue $P2Y_{12}$ inhibitors	Delay elective surgery to allow management of cardiovascular condition Urgent surgery e.g. cancer surgery requires multidisciplinary dicussion of management. Consider: - continuation of aspirin - discontinuation of $P2Y_{12}$ inhibitors with/without bridging with tirofiban or cangrelor
Moderate bleeding risk e.g. biopsy, therapeutic endoscopy; cardiothoracic, urologic, orthopedic, vascular, visceral, ENT and surgery			
High bleeding risk e.g. hepatobiliary and vertebrospinal surgery Very high i.e. intracranial surgery		Discontinue aspirin 5 days before surgery to 1–2 days after surgery Discontinue $P2Y_{12}$ inhibitors	

Fig 1 Perioperative management of antiplatelet drugs. ACS, acute coronary syndrome; BMS, bare metal stent; CABG, coronary artery bypass graft; CVA, cerebrovascular accident; DES, drug-eluting stent; PCI, percutaneous coronary intervention; postop, postoperative; preop, preoperative; PVD, peripheral vascular disease; TIA, transient ischaemic attack.[24 25]

to inflammatory-mediated rebound effects of platelet adhesion. Persistent perioperative application is associated with higher risk of bleeding (2.5–20 *vs* 30–50%) and a 30% higher rate of blood cell transfusion; however, mortality linked to these circumstances is hardly increased. The necessity of elective surgery should be assessed on a patient-by-patient basis. Antiplatelet therapy and treatment for other co-morbidities should be optimized. The relative risks of a thromboembolic event and of bleeding should be weighed. Postoperative restarting of antiplatelet therapy depends on the individual patient's cardiovascular risk profile, the bleeding risks associated with the particular operation, and the pharmacokinetics of each drug. The aim should be to re-establish the antiplatelet regimen as early as is reasonably possible. Hospital discharge without restarting treatment carries substantial risks.[19 26]

For operations with a low bleeding risk, antiplatelet therapy does not need to be interrupted. In procedures with a high risk of bleeding, aspirin should be maintained and other antiplatelet substances discontinued long enough before surgery to allow the antiplatelet effect to have waned. If possible, for example after percutaneous coronary angioplasty, the operation should be delayed until the patient has a lower risk of cardiovascular complications. In patients with a low risk of thromboembolic events who require surgery that carries a high risk of haemorrhage, antiplatelet therapy should be interrupted in the perioperative period. The continuous evaluation of the bleeding should guide intra- and postoperative therapeutic strategies.[8 9 27] The management of bleeding is discussed below.

In situations where there is a high chance of bleeding and withdrawal of antiplatelet therapy carries a high risk of cardiovascular events, bridging of antiplatelet therapy can be considered. Bridging therapies involve replacing antiplatelet therapy using long-acting $P2Y_{12}$ antagonists with a short-acting anticoagulant or antiplatelet agent that can be discontinued shortly before surgery. The use of tirofiban and eptifibate has been described. More recently, cangrelor has become available and is recommended as a suitable drug because of its pharmacokinetic profile. In the situation of bridging, treatment with aspirin should be continued and the other oral agent stopped 5–7 days before surgery. A short-acting i.v. agent should be started no more than 72 h after the discontinuation of DAPT. Four to six hours (or 1 h for cangrelor) before surgery, the i.v. drug is discontinued and is restarted 6 h after surgery. The patient's usual DAPT is restarted as soon as the risk of perioperative haemorrhage is negligible.[28–32]

Heparinoids are sometimes used for bridging. This is based on their known effect in unstable angina and Non-ST-elevation myocardial infarction (NSTEMI); they do not have any protective effect against coronary or stent thrombosis. Heparin is not an appropriate substitute for antiplatelet agents. Non-steroidal

anti-inflammatory agents and, in particular, reversible COX1 inhibitors can be considered as short-term substitutes.[8 26 27]

The management of bleeding

Antiplatelet drugs have haemorrhage as a common side-effect. Several factors associated with a higher risk of bleeding have been identified, including female sex, advanced aged (>75 yr), impaired renal function, anaemia, low body weight (<60 kg), and a history of transient ischaemic attack or stroke. In a surgical context, complex or urgent operations are considered as high-risk situations for bleeding.

Major surgical bleeding in patients treated with antiplatelet agents increases perioperative morbidity and mortality, as do blood transfusions. A restrictive transfusion management strategy is widely recommended, with transfusion thresholds of the order of a haemoglobin <80 g litre^{-1} or a haematocrit <25%.[33] No antagonists for antiplatelet agents are available. Management of significant haemorrhage is based on the administration of tranexamic acid, fibrinogen, factor XIII, desmopressin, platelets, and activated factor VIIa. The prothrombotic properties of these agents may pose a risk of major thrombotic complications.[8 9 34]

Drug monitoring and laboratory tests

Numerous platelet function tests are available (e.g. turbidometric light transmittance, VerifyNow, Thrombelastogram, Multiplate, or Platelet Function Analyser-100). These were often initially designed to identify platelet function disorders (either dysfunction or hyperactivity). With the increasing armamentarium of platelet-inhibiting drugs, many of which display significant intra-individual variation in their efficacy, these assays have become more relevant to drug monitoring, the design of individualized pharmacotherapy, perioperative evaluation, and the planning of surgery. The results of platelet function tests vary between assays and depend on the cut-off values used to define a normal test. A further limitation is the dependency of these assays on haematocrit and platelet count.[35–37]

Anticoagulant agents (Table 3)

Anticoagulants inhibit the initiation and progress of coagulation and fibrin-clot formation and propagation. Their uses include the treatment or prevention of venous thromboembolism and atrial fibrillation. For acute treatment of venous thromboembolism and during revascularization therapy, immediately acting parenteral anticoagulants are used. Low molecular weight heparins and, recently, parenteral anti-factor Xa agents (fondaparinux) have widely replaced unfractionated heparin.[38 39] Oral anticoagulants are indicated for long-term treatment or prevention of thromboembolic complications of different cardiovascular diseases, such as venous thromboembolism, myocardial infarction, or atrial fibrillation, and after implantation of mechanical valves.[38]

Parenteral anticoagulants

Unfractionated heparin and low molecular weight heparin

Heparins are indirectly acting anticoagulants that bind to and activate antithrombin. After inducing a conformational change in antithrombin, the heparins dissociate and bind to further antithrombin molecules. Activated antithrombin accelerates the inactivation of coagulation factors IIa, IXa, Xa, Xia, and XIIa. Unfractionated heparin dosing depends on the indication for its

Table 3 Summary of the characteristics of currently available anticoagulant drugs

Characteristic	Warfarin	Oral				Parental				
		Dabigatran	Apixaban	Edoxaban	Rivaroxaban	Unfractionated heparin (s.c./i.v.)	Low molecular weight heparins (s.c.)	Fondaparinux (s.c.)	Argatroban (i.v.)	Bivalirudin (i.v.)
Mechanism of action	Vitamin K antagonist	Direct inhibition IIa	Direct inhibition Xa	Direct inhibition Xa	Direct inhibition Xa	Direct inhibition Xa=IIa	Direct inhibition Xa>IIa	Direct inhibition Xa	Direct inhibition IIa	Direct inhibition IIa
Bioavailability (%)	80	6	66	62	80	30	90	100	100	100
Plasma half-life	20–60 h	12–14 h	8–15 h	10–14 h	7–10 h	1 h	4 h	17 h	50 min	24 min
Duration of action from last dose	48–96 h	48 h	24 h	24 h	24 h	Dose dependent (s.c.)	Dose dependent	48–96 h	2–4 h	1 h
Peak plasma concentration	Variable	2 h	2.5–4 h	1–2 h	1–3 h	4 h (s.c.)	3 h	2 h		0.25–2 h
Elimination	Metabolism	80% renal	25% renal	50% renal	50% renal, 50% hepatic	Reticulo-endothelial system	Hepatic metabolism, renal excretion 10%	Renal	65% faeces, 22% urine	20% renal
Drug interaction	CYP2C9, CYP3A4, CYP1A2	P-glycoprotein inhibitors	CYP3Y4, P-glycoprotein inhibitors	P-glycoprotein inhibitors	Strong CYP3A4 inhibitors or inducers and P-glycoprotein inhibitors					

use and is highly variable. Low molecular weight heparins can be used at a fixed dose for prophylaxis and in a weight-adjusted dose for therapeutic anticoagulation.[40]

Fondaparinux

Fondaparinux selectively and irreversibly binds to antithrombin III, thus inactivating factor Xa and, in turn, interrupting thrombin formation and thrombus propagation.[40]

Direct thrombin inhibitors

Parenteral direct thrombin inhibitors bind directly, selectively, and reversibly to the active site of thrombin. Fibrin formation and propagation of clot formation are inhibited. Currently, desirudin, argatroban, and bivalirudin are licensed direct thrombin inhibitors. They are the main alternative therapeutic agents in heparin-induced thrombocytopenia.[40 41]

Oral anticoagulants

Vitamin K antagonists

For more than 80 yr, vitamin K antagonists have been known to have anticoagulant properties and were the most frequently used oral anticoagulant drugs. After the identification of dicoumarol warfarin, phenprocoumon and acenocoumarol were synthesized.[42] These drugs, the latter mainly used in Europe, hinder the synthesis of vitamin K-dependent clotting factors; vitamin K reductase is blocked, causing a depletion of reduced vitamin K. This is needed for the γ-carboxylation and activation of vitamin K-dependent clotting factors II, VII, IX, and X. Additionally, they inhibit the carboxylation of the anticoagulant proteins C, S, and Z, causing a transient procoagulant state.[43 44]

Although vitamin K antagonists are highly effective agents they do have numerous limitations.

1. Genetic polymorphisms producing variation in patients' sensitivity.
   - Drugs such as warfarin act on the vitamin K epoxide reductase complex 1 (VKORC1). People with the A allele of VKORC1 produce less VKORC1 subunit than those with the more common G allele and require less VKA to produce an anticoagulant effect.
   - Warfarin is metabolized in the liver by CYP2C9. People with the CPY2C9*2 and CPY2C9*3 variants metabolize warfarin less effectively than those with wild-type CPY2C9*1 and require a lower dose to warfarin to achieve effective anticoagulation.
2. Non-genetic factors, including age, body weight, dietary vitamin K intake, concomitant diseases, and alcohol consumption, modulate the required dose.
3. Vitamin K antagonist drugs show variable pharmacodynamic properties, with slow onset and slow offset of action.
4. Vitamin K antagonists are subject to interactions with drugs metabolized by CYP2C9, CYP3A4, and CYP1A2.
5. They have a narrow therapeutic window, with the need for constant monitoring.

A >10-fold interpatient variation in the dose necessary to reach the desired anticoagulant effect is observed, leading to a risk of under- or overdosing and causing haemorrhage or thromboembolism. This made the development of alternative drugs attractive.[38 42 45]

New oral anticoagulants

In 2004, ximelagatran was licensed by the European Medical Agency, thus becoming the first oral thrombin inhibitor to reach the market. As a result of potential hepatotoxicity, it was withdrawn soon after.[46] Since 2008, further new oral anticoagulants have been introduced. These include the direct thrombin inhibitor, dabigatran, and the direct factor X inhibitors, such as rivaroxaban, apixaban, and edoxaban. Other new oral antiocoagulants (NOACs) are currently being tested in clinical trials.

Dabigatran etexilate

Dabigatran etexilate, a low molecular weight prodrug, is a direct thrombin inhibitor. It is converted to its active form, dabigatran, by non-specific esterases in the liver and plasma. It binds directly to the active site of thrombin via ionic interactions. Fibrin-bound thrombin and free thrombin are inactivated competitively and reversibly. Unlike heparins, which cannot inhibit clot-bound factor II, dabigatran can inhibit thrombus expansion triggered by thrombin. The following events in the coagulation cascade are prevented by dabigatran: conversion of fibrinogen into fibrin, positive feedback amplification of coagulation activation, cross-linking of fibrin monomers, platelet activation, and inhibition of fibrinolysis. Co-medication with P-glycoprotein inhibitors, including ketoconazole, amiodarone, verapamil, or quinidine, may increase its plasma concentration. Rifampicin may reduce the plasma concentration because of induction of P-glycoprotein.[47 48]

Apixaban

Apixaban is a direct, selective factor Xa inhibitor that inhibits free and prothrombinase complex-bound factor Xa. It is rapidly absorbed in the stomach and small bowel, independently of food intake. Absorption is mediated by P-glycoprotein, and P-glycoprotein inhibitors can increase absorption. Metabolism is mediated by CYP3A4, and concomitant use of CYP3A4 and P-glycoprotein inducers (carbamazepine, phenobarbital, phenytoin, St John's wort, and rifampicin) cause a decreased concentration of apixaban.[42 48 49]

Rivaroxaban

Rivaroxaban is a direct, highly selective, reversible, competitive inhibitor of free and complex-bound factor Xa. The bioavailability of this lipophilic drug is increased by concomitant food intake, causing more predictable plasma concentrations. Co-treatment with CYP3A4 inhibitors or inducers and P-glycoprotein inhibitors is (relatively) contraindicated, because it may lead to altered plasma concentrations of rivaroxaban.[42 48 50]

Edoxaban

Edoxaban is a direct, highly selective and competitive inhibitor of factor Xa. It has a bioavailability of 62%. Co-administration of strong P-glycoprotein inhibitors (e.g. ketoconazole, amiodarone, verapamil, or quinidine) cause an increased effect of edoxaban, necessitating a dose reduction of 50%. Dose adjustment in patients with low body weight (<60 kg) or moderate renal impairment is also necessary.[51]

The perioperative setting (Table 4)

Of all patients receiving oral anticoagulant treatment, 10% have to interrupt it for invasive procedures at some point.[52] In current clinical practice, bridging therapy is widely used to cover the temporary withdrawal of oral anticoagulation. Recent data (e.g. BRIDGE Trial, ORBIT-AF) suggest that this approach increases

Table 4 Recommendations for perioperative omission or new oral antiocoagulants

Drug	Glomerular filtration rate (ml min^{-1})	Bleeding risk	Duration of omission before surgery (h)	Recommendations for restarting
Dabigatran	>50	Moderate	36	Decisions on restarting these agents depend on surgical bleeding risk (see Fig. 1), renal function, the indication for anticoagulation, and the presence or otherwise of a neuroaxial catheter. A pause of at least 6 h after the surgical intervention is recommended
	50–30		48–72	
	<30		Minimum 72	
	>50	High	48–72	
	50–30		96	
	<30		Minimum 120	
Rivaroxaban <10 mg		Moderate	18	
		High	24	
Rivaroxaban >15 mg	>50	Moderate	24	
	50–30		48	
	<30		Minimum 72	
	>50	High	36	
	50–30		48	
	<30		Minimum 72	
Apixaban	>50	Moderate	24	
	50–30		48	
	<30		Minimum 72	
	>50	High	48	
	50–30		72	
	<30		Minimum 72	
Edoxaban	>50	Moderate	24	
	50–30		48	
	<30		Minimum 72	
	>50	High	48	
	50–30		72	
	<30		Minimum 72	

the risk of perioperative haemorrhage but with little beneficial effect on thromboembolic complications in patients with atrial fibrillation.[53 54] Most importantly, two major aspects need to be considered, as follows: (i) the risk of intervention related haemorrhage (as subdivided in Fig. 1); and (ii) the risk of perioperative thromboembolism, classified as low, medium, or high (as in Table 5).[55]

A low-risk procedure in a low-risk patient does not require discontinuation of oral anticoagulation. In patients with lone atrial fibrillation or a CHA_2DS_2-VASc ≤4 ($CHADS_2$, $CHADS_2$ risk score for stroke in atrial fibrillation based on congestive heart failure, hypertension, age >75 yr, diabetes, and stroke or transient ischaemic attack; CHA_2DS_2- VASc, updated risk score for stroke in atrial fibrillation including $CHADS_2$ risk factors plus vascular disease age 65–75 yr and female sex), bridging is of questionable value because haemorrhagic risks exceed the risk of thromboembolic complications in these patients. High-risk procedures or high-risk patients do need bridging therapy to cover withdrawal of vitamin K antagonists. All intermediate-risk patients (CHA_2DS_2-VASc >4) and interventions carrying an intermediate risk of bleeding are likely to require patient-by-patient estimation of the individual bleeding and thromboembolic risk.[56]

In contrast to the periopertive management of vitamin K antagonists, current data do not support preoperative bridging therapy to cover the perioperative withdrawal of NOACs.[28 29 57 58] The advice for interruption of NOACs depends on their plasma half-life and the patient's co-morbidities, especially renal function. Two half-lives (remaining drug concentration <25%) are considered as an adequate compromise between the reduction of bleeding risk and the prevention of a thromboembolic event. If there is reduced elimination or a high risk of perioperative haemorrhage, the time of discontinuation should be increased. For minor surgical procedures, treatment with NOACs can be continued without interruption. Usual haemostatic measures are undertaken, and an awareness of the risk of bleeding is important. For major surgical procedures that carry a high bleeding risk and interventions near delicate structures or in enclosed spaces (e.g. neurosurgery), NOACs should be discontinued.[59 60]

If emergency surgery is needed, an evaluation of the indication for treatment with a NOAC, and the daily dose, last intake, and renal function allows a rough estimation of the pharmacological activity at the time of planned surgery. If feasible, a delay for at least 24 h from the last dose is advisable. New oral antiocoagulant ingestion less than 2–6 h previously may be treated with activated charcoal. Haemodialysis may be used for dabigatran elimination. The treatment of bleeding is discussed in the next section.[59 60]

Postoperative resumption depends on the risk of bleeding, the renal function, and the presence of neuroaxial catheters.

Management of bleeding

Bleeding risk is increased in patients aged >75 yr, with concomitant aspirin intake, diabetes mellitus, low body weight (<50 kg), or an elevated plasma concentration of the anticoagulant.[61] Minor bleeding can be treated with basic measures, including compression, sclerotherapy, blood-pressure regulation, and so forth. It usually does not require pharmacological correction of coagulation. Anticoagulation should be interrupted until no further bleeding is detected.[58]

In the event of major bleeding (>20% of patient's blood volume), potential causes should be identified without delay. General measures should be undertaken, including the avoidance

Table 5 An approach to classifying arterial and venous thromboembolic risk in surgical patients. $CHADS_2$, $CHADS_2$ risk score for stroke in atrial fibrillation based on congestive heart failure, hypertension, age >75 yr, diabetes, and stroke or transient ischaemic attack; CHA2DS2-VASc, updated risk score for stroke in atrial fibrillation including $CHADS_2$ risk factors plus vascular disease age 65–75 yr and female sex;[55] VTE, venous thromboembolic event

Thromboembolic risk	Risk factors
Low risk	VTE >12 months previously without risk factors for further event
	$CHADS_2$ ≤2 without cerebrovascular disease
	CHA_2DS_2-VASc <4
	Bileaflet aortic valve without further risk factors (e.g. diabetes, atrial fibrillation, or congestive heart failure)
Intermediate risk	Recurrent VTE
	Active cancer
	VTE 3–12 months
	Factor V Leiden carrier
	Prothrombin mutation carrier
	$CHADS_2$ score 3–4
	CHA_2DS_2-VASc score 4–5
	Bileaflet aortic valve disease with further risk factors
High risk	VTE <3 months, severe thrombophilia
	Cerebrovascular accident <6 months previously
	$CHADS_2$ score 5–6
	CHA_2DS_2-VASc score >5
	Prosthetic cardiac valve
	Aortic valve replacement with cage ball valve

and correction of acidosis, hypothermia, and hypocalcaemia. Specific reversal agents for NOACs are not yet available. Research on the development of specific reversal agents is in progress (e.g. idarucizumab for dabigatran, andexanet alfa for factor Xa inhibitors, and PER977 for factor Xa and thrombin inhibitors).[62]

Procoagulant agents may be required. Options include prothrombin complex concentrate (25–50 U kg^{-1}) or activated prothrombin complex concentrate (50–100 U kg^{-1}); the latter is more efficient but also more likely to cause thromboembolic complications. Recombinant factor VIIa may be used as rescue medication, but carries a high risk of thromboembolism. Adjuncts such as tranexamic acid or desmopressin may be considered, but there are few clinical data regarding their efficacy.[59 60 63]

Drug monitoring and laboratory tests (Fig. 2)[64]

One advantage of NOACs over vitamin K antagonists is the avoidance of the necessity of routine laboratory monitoring. The most frequently used coagulation tests (activated partial thromboplastin time and international normalized ratio) are influenced by NOACs, because they directly inhibit factor IIa or Xa, the end points of these assays. The degree of alteration of clotting assays depends on the plasma concentration of the NOAC. Moreover, normal test results indicate a lack of a significant NOAC effect. This is particularly true for the activated partial thromboplastin time test in patients taking dabigatran.[65–67] Interpretation of drug plasma concentration is difficult because there is no defined range that reflects optimal treatment levels or bleeding risk. In daily clinical practice, routine laboratory testing during NOAC treatment is currently not recommended. A better understanding of their influence on laboratory coagulation tests might allow optimization and individualization of treatment in the future.[68] Laboratory testing is advisable in patients requiring urgent surgery, those with a rapid decline in renal function, or in bleeding patients. Test results should be interpreted in the context of the time of last drug administration. At present, our ability to state that there is no NOAC effect is probably greater than our ability to quantify any NOAC effect.

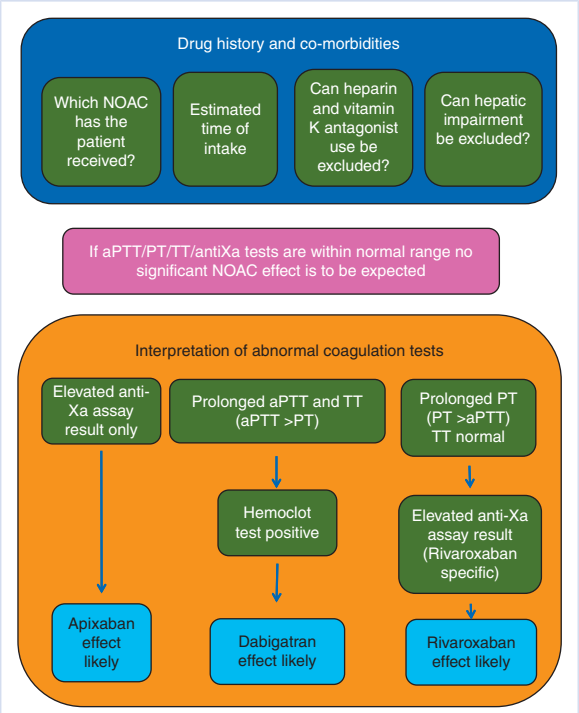

Fig 2 Interpretation of laboratory coagulation tests in patients with suspected new oral antiocoagulant treatment. anti-Xa, anti-Xa assay; aPTT, activated partial thromboplastin time; Hemoclot test, Hemoclot® thrombin inhibitor assay; PT, prothrombin time; TT, thrombin time.[64]

Concomitant use of antiplatelet agents and new oral antiocoagulants

In clinical routine, the number of patients receiving antiplatelet therapy and NOAC therapy is increasing. Data suggest that

NOACs offer benefit in ischaemic events when used concomitantly with a single antiplatelet regimen. Patients on DAPT (aspirin and clopidogrel) who additionally receive a NOAC show a 3-fold increase in the risk of haemorrhage without further reduction of adverse cardiac events. Potentially, the bleeding risk is higher with more potent antiplatelet agents (ticagrelor and prasugrel), although data to confirm this are lacking. An individualized approach is necessary in patients who might be favourably treated with a combination of DAPT (including prasugrel and ticagrelor) and NOACs, balancing the potential benefit against the increased risk of haemorrhage. A dose reduction may be a potential strategy, but research to confirm this is required. The indication for long-term use of NOACs and DAPT in an individual patient should be re-evaluated regularly.[69]

Conclusion

It is essential for anaesthetists to know the properties of new antiplatelet agents and NOACs because their management in the perioperative period or the bleeding patient is crucial. The perioperative period is associated with significant prothrombotic risk because of the inflammatory response to surgery. This risk must be balanced with the likelihood of haemorrhage in patients treated with antiplatelet or anticoagulant drugs. Both situations carry a significant burden of morbidity and mortality. With the increasing use of a broad range of antiplatelet and anticoagulant drugs, most anaesthetists face these dilemmas on a regular basis.

Guidelines are published and updated regularly to enable appropriate, up-to-date treatment, and the anaesthetist should ensure that they are familiar with relevant local and national guidance.[28 29 67]

Sophisticated laboratory assays are unevenly accessible in emergency situations, but standard laboratory tests, such as activated partial thromboplastin time, international normalized ratio, or basic platelet function tests, are not. These allow adaptation and guidance of treatment strategies (Fig. 2). Multidisciplinary discussion to plan the best treatment in high-risk patients undergoing surgery is essential.

Authors' contributions

The review was conceived by V.K.-O. and M.F.

Declaration of interest

None declared.

References

1. Raskob GE, Rosendaal FR. On World Thrombosis Day. *Lancet* 2014; **384**: 1653–4
2. World Health Organisation. Deaths from cardiovascular diseases and diabetes. WHO 2016. Available from http://www.who.int/gho/ncd/mortality_morbidity/en/ (accessed 26 December 2014)
3. Patrono C, Andreotti F, Arnesen H, *et al*. Antiplatelet agents for the treatment and prevention of atherothrombosis. *Eur Heart J* 2011; **32**: 2922–32
4. Choudhry NK, Desai NR, Fischer MA *et al*. 2012. Alosa Foundation, Inc. Available from http://www.alosafoundation.org/wp-content/uploads/2013/03/Antiplatelet_UnAd.pdf (accessed 21 February 2016)
5. Windecker S, Kolh P, Alfonso F, *et al*. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014; **35**: 2541–619
6. Kernan WN, Ovbiagele B, Black HR, *et al*. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; **45**: 2160–236
7. Fuster V, Sweeny JM. Aspirin: a historical and contemporary therapeutic overview. *Circulation* 2011; **123**: 768–78
8. Oprea AD, Popescu WM. Perioperative management of antiplatelet therapy. *Br J Anaesth* 2013; **111**(Suppl 1): i3–17
9. Hall R, Mazer CD. Antiplatelet drugs: a review of their pharmacology and management in the perioperative period. *Anesth Analg* 2011; **112**: 292–318
10. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Br Med J* 2002; **324**: 71–86
11. Ferraris VA, Saha SP, Oestreich JH, *et al*. 2012 update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations. *Ann Thorac Surg* 2012; **94**: 1761–81
12. Michelson AD. Advances in antiplatelet therapy. *Hematology Am Soc Hematol Educ Program* 2011; **2011**: 62–9
13. Weitz JI, Eikelboom JW, Samama MM, American College of Chest Physicians. New antithrombotic drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; **141**(2 Suppl): e120S–51S
14. Topol EJ, Byzova TV, Plow EF. Platelet GPIIb-IIIa blockers. *Lancet* 1999; **353**: 227–31
15. Wijeyeratne YD, Heptinstall S. Anti-platelet therapy: ADP receptor antagonists. *Br J Clin Pharmacol* 2011; **72**: 647–57
16. Lins R, Broekhuysen J, Necciari J, Deroubaix X. Pharmacokinetic profile of 14C-labeled clopidogrel. *Semin Thromb Hemost* 1999; **25**(Suppl 2): 29–33
17. Giorgi MA, Di Girolamo G, González CD. Nonresponders to clopidogrel: pharmacokinetics and interactions involved. *Expert Opin Pharmacother* 2010; **11**: 2391–403
18. Dobesh PP, Oestreich JH. Ticagrelor: pharmacokinetics, pharmacodynamics, clinical efficacy, and safety. *Pharmacotherapy* 2014; **34**: 1077–90
19. Ortel TL. Perioperative management of patients on chronic antithrombotic therapy. *Hematology Am Soc Hematol Educ Program* 2012; **2012**: 529–35
20. Angiolillo DJ, Firstenberg MS, Price MJ, *et al*. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *JAMA* 2012; **307**: 265–74
21. Patrono C, Bachmann F, Baigent C, *et al*. Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European society of cardiology. *Eur Heart J* 2004; **25**: 166–81
22. Armstrong PC, Peter K. GPIIb/IIIa inhibitors: from bench to bedside and back to bench again. *Thromb Haemost* 2012; **107**: 808–14
23. Schneider DJ. Anti-platelet therapy: glycoprotein IIb-IIIa antagonists. *Br J Clin Pharmacol* 2011; **72**: 672–82
24. Filipovic M, Korte W, Rickli H. Thromboseprophylaxe und periinterventionelle antithrombotische Therapie, 5.

Auflage 2014. Available from http://www.kardiologie.kssg.ch/content/dam/dokument_library/container_kardiologie/Gerinnungskarte/Thromboembolieprophylaxe%20in%20der%20Chirurgie%2026%2005%202014.pdf.ocFile/Thromboembolieprophylaxe%20in%20der%20Chirurgie%2026%2005%202014.pdf (accessed 29 February 2016)
25. Douketis JD, Spyropoulos AC, Spencer FA, *et al*. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines (9th edition). *Chest* 2012; **141**: e326S–50S
26. Chassot PG, Marcucci C, Delabays A, Spahn DR. Perioperative antiplatelet therapy. *Am Fam Physician* 2010; **82**: 1484–9
27. Benzon HT, Avram MJ, Green D, Bonow RO. New oral anticoagulants and regional anaesthesia. *Br J Anaesth* 2013; **111** (Suppl 1): i96–113
28. The Cardiac Society of Australia and New Zealand. Guidelines for the use of antiplatelet therapy in patients with coronary stents undergoing non-cardiac surgery. 2009. Available from www.csanz.edu.au (accessed 26 October 2015)
29. Österreichische Gesellschaft für Anästhesiologie, Reanimation und Intensivmedizin Perioperatives Management von PatientInnen mit Koronarstents unter dualer Antiplättchentherapie bei nicht-kardiochirurgischen Eingriffen. Empfehlungen der Arbeitsgruppe perioperative Gerinnung der ÖGARI. 2013. Available from www.oegari.at (accessed 25 October 2015)
30. Kyo S, Imanaka K, Kurosawa H, *et al*. Guidelines for Perioperative Cardiovascular Evaluation and Management for Noncardiac Surgery. *Circ J* 2011; **75**: 989–1009
31. Douketis J, Spyropoulos AC, Spencer FA *et al*. Perioperative Management of Antithrombotic Therapy 2016. Available from www.chestnet.org (accessed 8 December 2014)
32. Rossini R, Musumeci G, Visconti LO, *et al*. Perioperative management of antiplatelet therapy in patients with coronary stents undergoing cardiac and non-cardiac surgery: a consensus document from Italian cardiological, surgical and anaesthesiological societies. *EuroIntervention* 2014; **10**: 38–46
33. Carson JL, Grossman B, Kleinman S, *et al*. Red blood cell transfusion: a clinical practice guideline from the AABB. *Ann Intern Med* 2012; **157**: 49–58
34. Gresele P. Antiplatelet agents in clinical practice and their haemorrhagic risk. *Blood Transfus* 2013; **11**: 349–56
35. Wolf Z, Mani H, Lindhoff-Last E. Significance of platelet function tests. *Internist* 2010; **51**: 1095–6
36. Sambu N, Curzen N. Monitoring the effectiveness of antiplatelet therapy: opportunities and limitations. *Br J Clin Pharmacol* 2011; **72**: 683–96
37. Mahla E, Höchtl T, Prüller F, Freynhofer MK, Huber K. Platelet function: new drugs, new assays: possible impacts on operative medicine? *Anaesthesist* 2012; **61**: 483–96
38. Weitz JI, Eikelboom JW, Samama MM; American College of Chest Physicians. New antithrombotic drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141(2 Suppl)**: e120S–51S
39. Eikelboom JW, Weitz JI. New anticoagulants. *Circulation* 2010; **121**: 1523–32
40. Garcia DA, Baglin TP, Weitz JI, Meyer M. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; **141**: e24S–43S
41. Lee CJ, Ansell JE. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Br J Clin Pharmacol* 2011; **72**: 581–92
42. Scaglione F. New oral anticoagulants: comparative pharmacology with vitamin K antagonists. *Clin Pharmacokinet* 2013; **52**: 69–82
43. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**(6 Suppl): 160S–98S
44. 2005. Available from http://www.drugbank.ca/drugs/DB00682 (accessed 25 October 2015))
45. Bauer KA. Pros and cons of new oral anticoagulants. *Hematology Am Soc Hematol Educ Program* 2013; **2013**: 464–70
46. Keisu M, Andersson TB. Drug-induced liver injury in humans: the case of ximelagatran. *Handb Exp Pharmacol* 2010; **196**: 407–18
47. Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. *Circulation* 2011; **123**: 1436–50
48. Dempfle CE. Direct oral anticoagulants—pharmacology, drug interactions, and side effects. *Semin Hematol* 2014; **51**: 89–97
49. Nutescu E. Apixaban: a novel oral inhibitor of factor Xa. *Am J Health Syst Pharm* 2012; **69**: 1113–26
50. Gulseth MP, Michaud J, Nutescu EA. Rivaroxaban: an oral direct inhibitor of factor Xa. *Am J Health Syst Pharm* 2008; **65**: 1520–9
51. Lip GYH, Agnelli G. Edoxaban: a focused review of its clinical pharmacology. *Eur Heart J* 2014; **35**: 1844–55
52. Douketis JD, Woods K, Crowther MA. Anticoagulant Management of Patients Undergoing Elective who Require Temporary Interruption of Warfarin Therapy. 2005. Available from http://fhs.mcmaster.ca/surgery/documents/Handout2forVTEProphylaxisof02Sep2009byDr.M.Crowther.pdf (accessed 2 October 2015)
53. Douketis JD, Spyropoulos AC, Kaatz S, *et al*. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med* 2015; **373**: 823–33
54. Steinberg BA, Peterson ED, Kim S, *et al*. Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circulation* 2015; **131**: 488–94
55. January CT, Wann LS, Alpert JS, *et al*. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014; **130**: 2071–104
56. Rechenmacher SJ, Fang JC. Bridging anticoagulation: primum non nocere. *J Am Coll Cardiol* 2015; **66**: 1392–403
57. CoaguSave 2015. Available from http://www.girard.li/girardDev/index_light_slider.html (accessed 25 October 2015)
58. Beyer-Westendorf J, Gelbricht V, Förster K, *et al*. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. *Eur Heart J* 2014; **35**: 1888–96
59. Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in patients undergoing invasive procedures. *N Engl J Med* 2013; **368**: 2113–24
60. Kozek-Langenecker SA. Perioperative management issues of direct oral anticoagulants. *Semin Hematol* 2014; **51**: 112–20

61. Palareti G. Direct oral anticoagulants and bleeding risk (in comparison to vitamin K antagonists and heparins), and the treatment of bleeding. *Semin Hematol* 2014; **51**: 102–11
62. Vanden Daelen S, Peetermans M, Vanassche T, *et al*. Monitoring and reversal strategies for new oral anticoagulants. *Expert Rev Cardiovasc Ther* 2015; **13**: 95–103
63. Siegal DM, Cuker A. Reversal of novel oral anticoagulants in patients with major bleeding. *J Thromb Thrombolysis* 2013; **35**: 391–8
64. Tran H, Joseph J, Young L, *et al*. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. Australasian Society of Thrombosis and Haemostasis. *Intern Med J* 2014; **44**: 525–36
65. van Ryn J, Baruch L, Clemens A. Interpretation of point-of-care INR results in patients treated with dabigatran. *Am J Med* 2012; **125**: 417–20
66. Thrombosis Canada. New/Novel Oral Anticoagulants (NOACs) Perioperative Management 2015. Available from http://thrombosiscanada.ca/wp-content/uploads/2015/01/NOACs-Peri-Operative-Management-2015Jan22-FINAL.pdf (accessed 25 October 2015)
67. Heidbuchel H, Verhamme P, Alings M, *et al*. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J* 2013; **34**: 2094–106
68. Ten Cate H. New oral anticoagulants: discussion on monitoring and adherence should start now! *Thromb J* 2013; **11**: 8
69. Oldgren J, Wallentin L, Alexander JH, *et al*. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. *Eur Heart J* 2013; **34**: 1670–80

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