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REVIEW

Periprocedural antithrombotic therapy during various types of percutaneous cardiovascular interventions

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Percutaneous catheter-based interventions became a critically important part of treatment in modern cardiology, improving quality of life as well as saving many life. Due to the introduction of foreign materials to the circulation (either temporarily or permanently) and due to a certain damage to the endothelium or endocardium, the risk of thrombotic complications is substantial and thus some degree of antithrombotic therapy is needed during all these procedures. The intensity (dosage, combination, and duration) of periprocedureal antithrombotic treatment largely varies based on the type of procedure, clinical setting, and comorbidities. This manuscript summarizes the current therapeutic approach to prevent clotting (and bleeding) during a large spectrum of interventions: acute and elective coronary interventions, acute stroke interventions and elective carotid stenting, electrophysiology procedures, interventions for structural heart disease, and peripheral arterial interventions.

Keywords Percutaneous interventions • Antithrombotic therapy • Anticoagulants • Antiplatelet drugs • Thrombolytics • Stents • Ablation • Device implantation

Introduction

Percutaneous catheter-based interventions became a critically important part of treatment in modern cardiology, improving quality of life as well as saving many lifes. Due to the introduction of foreign materials to the circulation (either temporarily or permanently) and due to a certain damage to the endothelium or endocardium, the risk of thrombotic complications is substantial and thus some degree of antithrombotic therapy is needed during all these procedures. The intensity (dosage, combination, and duration) of periprocedureal antithrombotic treatment largely varies based on the type of procedure, clinical setting, and comorbidities. The aim of this manuscript is to review the current therapeutic approach (including guidelines whenever available) and to discuss the existing gaps of evidence and unresolved questions.

Percutaneous coronary interventions for acute myocardial infarction

The antithrombotic treatment in patients with ST-elevation myocardial infarction (STEMI) as well as in those with ongoing myocardial ischaemia[1] in the absence of STE should include three classes of drugs: (i) acetylsalicylic acid (ASA), (ii) intravenous anticoagulant, and (iii) P2Y12 inhibitor. These agents should be given as soon as the diagnosis is certain, frequently in the pre-hospital phase when the clinical presentation and electrocardiogram are typical and diagnostic, i.e. before coronary angiography.[2,3] Controversy exists only in the optimal timing of P2Y12 inhibitors—the evidence for their upfront (pre-hospital) use is still lacking for the primary PCI strategy. It is even more controversial for the thrombolytic strategy.

Pre-/periprocedural oral antiplatelet therapy

An oral loading dose of ASA 150–300 mg (or i.v. 80–150 mg) should be given to all patients. The preferred P2Y12 inhibitors are prasugrel (60 mg p.o. loading dose) or ticagrelor (180 mg p.o. loading dose).[4,5] In the STEMI subgroup of the TRITON–TIMI 38 trial, prasugrel was superior to clopidogrel (primary endpoint prasugrel 10.0% vs. clopidogrel 12.4%), without a significant increase in non-CABG-related bleeding (2.4% vs. 2.1%). There was a lower risk of stent thrombosis (1.6% vs. 2.8%), as well as of cardiovascular mortality (1.4% vs. 2.4%)[6] in favour of prasugrel. Prasugrel is

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contraindicated in patients with prior stroke or TIA and not recommended for patients aged 75 years or more. In patients with body weight <60 kg, a maintenance dose of 5 mg is recommended.

In the STEMI subgroup of the PLATO trial, ticagrelor was superior to clopidogrel (primary endpoint 9.4% vs. 10.8%)[7] without higher risk of bleeding (TIMI non-CABG major 2.5% vs. 2.2%) but with a trend towards a lower risk of cardiovascular mortality at 1 year (4.7% vs. 5.4%).

In a pooled analysis of 48 599 patients, novel P2Y12 inhibitors prasugrel or ticagrelor have been associated with a mortality benefit and no significant excess of major bleeding among STEMI patients.[8] Importantly, the more potent agents (prasugrel and ticagrelor) should not be used in patients with prior haemorrhagic stroke or with moderate-to-severe liver disease.

When neither of these agents is available (or if they are contraindicated), clopidogrel 600 mg p.o. should be given instead[9] to fulfil the requirement for dual antiplatelet therapy (DAPT).

Intravenous antiplatelet therapy

Trials (mostly using abciximab) performed before the era of thienopyridines pre-loading documented clinical benefits from GP IIb/IIIa inhibitors as adjunct to primary PCI performed with UFH including a significant 1-year survival benefit that was revealed in a meta-analysis of GP IIb/IIIa inhibitors with abciximab.[10] However, the benefits of GPIIb/IIIa inhibitors in the era of potent novel P2Y12 inhibitors are questionable and there is a high likelihood of bleeding complications when four antithrombotic agents (aspirin, P2Y12 inhibitor, injectable anticoagulant, and GPIIb/IIIa inhibitor) are be combined simultaneously.

In the event of angiographic evidence of large thrombus, slow- or no-reflow, and other thrombotic complications, use of GP IIb/IIIa inhibitors as bail-out therapy appears reasonable, although this has not been tested in a randomized trial.

The FINESSE study[11] randomized STEMI patients to upstream abciximab at the first medical contact vs. in-cath-lab abciximab and found no significant effect on the primary endpoint (death, recurrent myocardial infarction, and heart failure), but significantly increased bleeding risk after upstream abciximab.

Cangrelor, an intravenous rapidly acting P2Y12 inhibitor (dose 30 μg/kg bolus followed by infusion of 4 μg/kg/min), was compared with a 600-mg loading dose of clopidogrel either before or early after PCI in patients with ACS undergoing PCI in The CHAMPION PLATFORM and PCI studies. A minor benefit from cangrelor was observed, however, it is not known whether this benefit would apply also if cangrelor would be compared with prasugrel or ticagrelor.

Injectable anticoagulants

Heparin

Despite the lack of large randomized trials, unfractionated heparin (UFH) remains the cornerstone of anticoagulation treatment in STEMI patients planned to undergo primary PCI. Several other drugs have been compared with heparin, but none of them was proven to be superior. There is however one critically important issue in heparin treatment: the dose MUST be adapted to the patient body weight: if no GPIIb/IIIa inhibitors are planned (what is the current routine practice in most centres), the dose of UFH should be 70–100 units kg^{-1} (lower dose preferred in elderly patients especially fragile females with low body weight). A frequent mistake in the real life practice is the use of an arbitrary UFH dose (e.g. 5000 or 10 000 units) for all patients, irrespective of body weight. An arbitrary 5000 unit dose will certainly be ineffective for a 95-kg middle-aged smoker and on the other hand arbitrary 10 000 units may be an extremely dangerous overdose (risk of intracranial bleeding) for an elderly 55 kg female.

Bivalirubin

Bivalirubin was assessed in several randomized trials. In the HORIZONS-AMI trial,[12] bivalirudin alone (with bail-out GP IIb/IIIa inhibitors in 7.2% of patients) was superior to combined therapy with UFH plus systematic GP IIb/IIIa inhibitor (mostly abciximab). However, the net adverse clinical endpoint (9.2% vs. 12.1%) included major bleeding (4.9% vs. 8.3%). Thus, it is not surprising that combination of two potent antithrombotic drugs was more harmfull than a single drug. There was no significant difference in the ischaemic endpoints, even there was a higher incidence of stent thrombosis in the bivalirudin group (1.3% vs. 0.3%).

The same problem was in the design of the EUROMAX trial,[13] comparing a single drug strategy (pre-hospital bivalirudin) vs. a combination strategy (heparin with optional—69% patients—GPIIb/IIIa inhibitors). The primary endpoint (death or non-CABG major bleeding at 30 days) again included bleeding (2.6% vs. 6.0%) and was significantly lower with pre-hospital administration of bivalirudin (5.1% vs. 8.5%). Again, similarly to the HORIZONS-AMI trial, there were no differences in ischaemic endpoints: death (2.9% vs. 3.1%), stent thrombosis (1.6% vs. 0.5%), and re-infarction (1.7% vs. 0.9%).

The HEAT-PCI study[14] compared bivalirudin vs. UHF with similar rates (15%) of GPIIb/IIIa inhibitors in both arms. The study better represents contemporary practice (restriction of GP IIb/IIIa inhibitors to bail-out situations, the use of novel P2Y12 inhibitors, radial approach and drug-eluting stent, DES, implantation). The primary efficacy endpoint (all-cause mortality, stroke, recurrent infarction, and unplanned target lesion revascularization) was higher in the bivalirudin than in the UFH group (8.7% vs. 5.7%) including an increase in stent thrombosis (3.4% vs. 0.9%), but no significant difference in mortality (5.1% vs. 4.3%). The primary safety outcome (major BARC 3–5 bleeding) was 3.5% in the bivalirudin group vs. 3.1% in the UFH group.

Thus, the entire treatment benefit of bivalirudin demonstrated in HORIZONS-AMI and EUROMAX trials was caused by the study design (low use of GPIIb/IIIa inhibitors in the bivalirudin arm) and cannot answer the question whether bivalirudin is superior to heparin or vice versa. The results of HEAT-PCI study suggest, that heparin may be even superior to bivalirudin when the same rate of GPIIb/IIIa inhibition is used. A problem with bivalirudin is also that results were better in subject at low risk (no troponin) but not in those with high troponin (high risk); therefore, bivalirudin seems to provide no advantages high-risk patients.

Enoxaparin

Enoxaparin (0.5 mg/kg i.v. bolus followed by subcutaneous treatment, dose adjustment to impaired renal function is essential) was compared with UFH in the ATOLL trial. The primary composite endpoint (30-day death, complication of myocardial infarction, procedural failure, and major bleeding) was not significantly different, but secondary endpoints suggested possible benefit from enoxaparin. In the

per-protocol analysis, enoxaparin was superior to UFH in reducing mortality (RR 0.36) and major bleedings (RR 0.46) in patients undergoing primary PCI. Based on these considerations, enoxaparin may be considered as an alternative to UFH in primary PCI.[15]

Fondaparinux

Fondaparinux in the context of primary PCI is potentially harmfull (risk of catheter thrombosis) and is therefore not recommended.[16]

Elective percutaneous coronary interventions for stable coronary artery disease

Ad hoc percutaneous coronary intervention

Most patients with stable coronary artery disease nowadays undergo elective coronary angiography immediately followed by *ad hoc* PCI. In such situation, pretreatment with aspirin is widely used (usually due to a known diagnosis of coronary artery disease and not specifically due to the diagnostic angiography) and possibly is appropriate (albeit was never tested in a randomized trial). Anticoagulation with UFH (i.v. bolus of 70–100 U/kg) remains the standard anticoagulant treatment for elective PCI.[3] Heparin is usually given in the cath-lab in two separate doses: initial small dose at the beginning of diagnostic angiography and second dose after the decision for *ad hoc* PCI is taken. The total UFH dose should be ALLWAYS calculated per the patient body weight: 70–100 units kg^{-1} (see also the previous chapter). The second antiplatelet drug (P2Y12 inhibitor) is usually added in the cath-lab just prior to PCI, i.e. between angiography and PCI.

Planned elective percutaneous coronary intervention

Patients with known coronary angiography scheduled for elective PCI should be pretreated with DAPT at least few hours before the procedure and UFH should be used in the way described above as well. In patients not using any chronic antiplatelet therapy, the oral loading dose of ASA should be 150–300 mg (or 80–150 mg i.v.) and clopidogrel loading dose 300–600 mg.[17–19] In patients on chronic aspirin and/or clopidogrel therapy, the loading dose before an elective procedure is not needed. There is no evidence of benefit for systematic clopidogrel pre-loading before diagnostic coronary angiography in SCAD.[20]

Recent trials did not demonstrate additional benefit from GP IIb/IIIa inhibitors after a clopidogrel loading dose of 600 mg.[21–23] Anecdotal experience, however, suggests that GP IIb/IIIa inhibitors may be beneficial in 'bail-out' situations (intraprocedure thrombus formation, slow flow, and threatened vessel closure).[24]

Percutaneous coronary interventions in patients with atrial fibrillation

Approximately 10% of patients undergoing PCI have another indication for long-term oral anticoagulation (OAC)—most frequently concomitant atrial fibrillation. There is an ongoing debate about the optimal antithrombotic medication in these patients theoretically requiring triple therapy: OAC permanently and DAPT for 1 year. In practice, the best approach is individual decision based on the concrete bleeding risk vs. stent thrombosis risk. Patients with increased bleeding risk should receive triple therapy during the first month after stent implantation followed by long-term dual therapy (OAC + clopidogrel or OAC + aspirin). Patients at low-bleeding risk may receive triple therapy up to 6 months, followed by long-term OAC + aspirin.

Interventions for structural heart disease

Structural heart interventions are a heterogeneous mixture of usually elective procedures ranging from the technically simple and short patent foramen ovale closure to long and complex interventions on mitral valve. Most of structural heart interventions involve rather large devices. These devices are typically metallic (stainless steel and nitinol are the most common); Dacron type polyester fabric to promote tissue growth or pericardial tissue made valve prosthesis are often present.

Intravenous heparin is the dominant periprocedural anticoagulant because of familiarity to all operators, availability of antidote and low cost. Level of anticoagulation can be adjusted according to activated clotting time (ACT). However, the optimal target ACT is mostly not clear. Intriguingly, one single centre study elegantly demonstrated abnormal baseline ACT values prior to transcatheter aortic valve implantation (TAVI) in typical elderly and frail population and heparin dosing adjustment lead to less bleeding.[25] Access site bleeding is obviously more common after arterial puncture than venous one; it is clear from TAVI data that arterial bleeding complications lead to a significant increase in early mortality. Many structural interventions involve catheter manipulation of right and left atria (i.e. thin-walled structures) with 1–2% risk of perforation and resulting cardiac tamponade. On the other hand, the longer procedure duration and the slower blood circulation around catheters both increase the risk of thrombus formation with possible embolization leading to disabling stroke or other organ embolization. Reversal of heparin activity with protamine is generally not recommended but can be very useful in case of bleeding. Bivalirudin has been compared with heparin in a randomized BRAVO 3 study of TAVI. There was no reduction in bleeding and heparin remains the standard of periprocedural care.[26]

Patients on OAC have this therapy interrupted for the procedure to minimize bleeding complications. Bridging with unfractionated or low-molecular heparin should be individualized based on every patient risk of bleeding and thrombosis.[27] Suitable timing of OAC restart after the procedure is not well defined and is probably best left at discretion of attending physician. The role of new oral anticoagulants (NOACs) for structural heart interventions is not yet defined; dabigatran caused harm in patients with mechanical heart valves[28] and ongoing Atlantis study currently evaluates apixaban after TAVI.

Antiplatelet therapy is commonly prescribed just before and continued after structural heart interventions with the aim to prevent thrombotic complications until endothelization of implanted device is completed. Only aspirin and clopidogrel have been studied in this

setting. The timing is empirical and any recommendations are based on expert consensus. Even a systematic review of antiplatelet and anticoagulation medication after TAVI did not provide any clear conclusions except the need for larger studies.[29] Atrial fibrillation can occur in the post-operative period and could be one of the leading causes of stroke during the first 30 days after procedure.

Table 1 provides summary of the most common structural heart interventions and data extracted from the major studies. For less common interventions, the scientific evidence is even more difficult to obtain due to small numbers.

Electronic device implantation

As with any small surgery, also implantation of cardiac implantable electronic devices (CIED) is also associated with a risk of bleeding. Hematomas following CIED implantation are quite frequent (2.9–9.5% of the cases). Although bleeding following CIED implantation is typically small and only very rarely life threatening, it prolongs hospitalization, increases the costs and surgical haematoma evacuation is associated with 15 times higher risk of infection.

Unfortunately, many patients indicated for CIED implantation are also indicated for antithrombotic or anticoagulant treatment. Data on contemporary populations from clinical studies and surveys indicate a rate of use of anticoagulant therapy ranging from 15% in patients with pacemakers, to 35% in patients with ICDs, reaching almost 50% in patients with cardiac resynchronization therapy. Moreover, ~50% of these patients have an indication for single or dual antiplatelet treatment.[30] Typical examples are patients with a history of atrial fibrillation (either with slow ventricular response or as a part of sick sinus syndrome) or patients after valve surgery. Moreover, antithrombotic and anticoagulant treatment has changed within last 10 years with new and more potent drugs present on the market, such as prasugrel, ticagrelor or NOAC, and some patients requires a combination of anticoagulant and antiplatelet treatment, which makes the situation even more complicated.

Cardiac implantable electronic devices implantation and anticoagulation

The management of anticoagulation and antiplatelet treatment during CIED implantation has changed substantially within last ten years. According to the ESC guidelines for cardiac pacing from 2007, anticoagulation treatment should have been interrupted 3–8 days pre-operatively and replaced with heparin. This is in complete contradiction with the ESC guidelines from 2013. According to these recent guidelines, the use of heparin bridging to OAC has been shown to increase the risk of bleeding and continuation of warfarin is recommended instead.[30–32]

The first study reporting the feasibility of implantation with ongoing warfarin was a study by Goldstein *et al.*[31] However, the majority of the 37 patients in this study underwent generator replacement and not leads and pacemaker de novo implantation. Since then a number of observational studies and recent randomized studies have confirmed the superiority of warfarin continuation to bridging to heparin. In the BRUISE CONTROL study,[32] i.e. the largest randomized study comparing ongoing warfarin to bridging to heparin strategy, warfarin continuation was associated with significantly

Table 1 Comparison of the most common structural heart interventions from antithrombotic therapy perspective

Procedure	Typical access	Main catheter size (French)	Procedure time (min)	Left atrium manipulation	Atrial fibrillation (%)	Heparin	Guideline or IFU target ACT (s)	Authors target ACT (s)	Periprocedural stroke or embolism (%)	Aspirin (months)	Clopidogrel (months)	Warfarin new indication (months)	NOAC (months)	References
PTMV	Venous	9–12	40–50	Yes	Frequent	Yes	None	300	0.5–5	–	–	–	To be tested	6–8
PFO closure	Venous	7–9	10–50	Yes	Excluded in PC and Respect trials	Yes	200	Not measured	Very low	6 to 24	1–6	–	–	9,10
ASD closure	Venous	7–12	65	Yes	3–5	Yes	200	Not measured or 250	Very low	6	–	–	–	11,12
LAA occlusion	Venous	12	30–60	Yes	Always	Yes	250	300	2–3	Lifelong	0–6	0–1.5	–	13,14
TAVI	2 × arterial and 1 × venous	18	60–133	No	33–47	Yes	250	250	4.6–6.7	Lifelong	3–6	–	Currently tested	15–19
MitraClip	Venous	24	100	Yes	34–68	Yes	250	300	0.7–2.1	6	1	–	To be tested	20–22

PTMV, percutaneous transvenous mitral valvuloplasty; PFO, patent foramen ovale; ASD, atrial septal defect; LAA, left atrial appendage; TAVI, transcatheter aortic valve implantation; IFU, instructions for use; ACT, activated clotting time; NOAC, new oral anticoagulant.

lower risk of bleeding (RR 0.16, 95% CI 0.08–0.32) and no difference in the risk of thromboembolic events. Recently, observational and small randomized trials have shown similar incidences of bleeding complications during CIED implantation with uninterrupted novel anticoagulants (NOACs) or warfarin.[33]

In patients with moderate or even high risk (such as in patients with artificial valves, recent pulmonary embolisms or in patients with history of AF and higher CHADS2VASc scores), the implantation of CIED should be done while on p.o. anticoagulation, with careful haemostasis during surgery.

Cardiac implantable electronic devices and antiplatelet treatment

Compared with untreated patients, aspirin carries a two-fold risk of bleeding and DAPT (aspirin plus thienopyridine) carries a four-fold or according some authors even a six-fold risk of bleeding during the peri-operative period. This risk was reduced by withholding clopidogrel 4–7 days before implantation. In most cases, dual antiplatelet medications can safely be discontinued, for a period of 5–7 days.

Ablation of cardiac arrhythmias

Ablation and anticoagulant treatment

Left-sided ablations present a high risk of periprocedural thromboembolic events due to (i) the disease itself (typically atrial fibrillation), (ii) the differences in the clot formation in the right- and left-sided atria and ventricles, and (iii) the difference in the clinical manifestation in case of the embolization of right- and left-sided cardiac chambers. While thrombi from the right-sided cardiac chambers remain mostly asymptomatic, even small thrombus from the left atrium can lead to stroke with severe neurologic disability.

All left-sided ablations were previously performed on heparin and the same was true of CIED implantation, patients were bridged to heparin from p.o. warfarin. The development of ongoing warfarin during ablation has followed a similar path to its use with CIED implantation Recently, according to non-randomized observational studies and randomized trials, ongoing uninterrupted warfarin has been shown to be safe and associated with lower rates of bleeding events, and lower rate of thromboembolic events compared with bridging to heparin.[34] In these trials, target international normalized ratio (INR) before and during ablation was 2.0–3.0 and was checked one day before the procedure. In patients with uninterrupted warfarin, periprocedurally heparin was given to all of them with similar target ACT values. Not surprisingly, patients on uninterrupted warfarin had lower stroke events compared with bridging strategy (OR 0.17, 95% CI 0.08–0.35) according to the meta-analysis of 12 observational and randomized trials comparing this two strategies.[35] Surprisingly, the rates of major (OR 0.72, 95% CI 0.54–0.95) and minor bleedings (OR 0.33, 95% CI 0.21–0.52) were also reduced in the uninterrupted warfarin strategy. It has become clear that holding warfarin and bridging with heparin/low-molecular-weight heparin creates a gap in which thrombotic complications are increased.

Recently, similar and quite robust data have been published comparing uninterrupted NOAC to warfarin. The ablation on uninterrupted NOAC was associated with similar rate of stroke and bleeding as the ablation with uninterrupted warfarin.[36,37] With respect to total bleeding, no significant difference was observed between dabigatran, rivaroxaban and apixaban and warfarin according to the meta-analysis of the randomized trials.[37]

Ablation and antiplatelet treatment

There is only a few reports regarding the risk and complications of catheter ablation if performed with concomitant dual antiplatelet and anticoagulant treatment. However, available reports indicate higher incidence of bleeding and vascular complications in ablation performed with clopidogrel.[38] Catheter ablation present mostly elective procedure, and so discontinuation of clopidogrel or other thienopyridines is recommended.

Catheter-based interventions for acute ischaemic stroke

There is lack of scientific evidence and complete absence of official guidelines recommending any specific protocol for periprocedural antithrombotic treatment during acute stroke interventions. Possibly, the most comprehensive document on this subject—the American guidelines for the management of acute stroke[39,40]—describe the reperfusion strategies and the use (or rather no use) of anticoagulant and antiplatelet agents as the potential primary therapy for stroke (when no reperfusion strategies are used), but not as periprocedural therapy during catheter-based thrombectomy (CBT).

Thrombolysis

These 2013 guidelines only describe thrombolysis use in acute ischaemic stroke. Intravenous thrombolysis is indicated for all eligible (per guidelines) stroke patients irrespective whether subsequent endovascular intervention is planned. The 2015 update[40] and the Canadian guidelines[41] further specify that endovascular intervention is indicated for all eligible acute ischaemic stroke patients including patients with contraindications to thrombolysis. When i.v. thrombolysis is used, the endovascular intervention should commence immediately, without waiting for the effect of thrombolysis. Nowadays, when stent-retrievers are much faster and much more effective, i.a. use of rtPA is reserved only for patients with more distal occlusions, not accessible with stent-retrievers and as a primary therapy is abandoned. *Table 2* presents the current indications for acute stroke interventions according to the use of bridging thrombolysis.

Anticoagulants

As mentioned above, no information is given in these three guideline documents about the use of anticoagulants during CBT in patients with contraindications for thrombolysis. In general, urgent anticoagulation with the goal of preventing early recurrent stroke or improving stroke outcomes or for the management of non-cerebrovascular conditions is not recommended due to the risk of serious intracranial haemorrhage (IIIA recommendation). Anticoagulant therapy within 24 h after rtPA is not recommended (IIIB).

Antiplatelet agents

Similarly, no recommendation is given for periprocedural use of antiplatelet agents. Acetylsalicylic acid is not recommended as a substitute for other acute interventions (IIIB), ASA is not recommended

Table 2 Indications for acute stroke interventions with and without bridging thrombolysis

	Facilitated intervention (bridging thrombolysis)[a]	Direct intervention (thrombolysis not used)
Moderate or severe stroke	NIHSS ≥6	NIHSS ≥6
Stroke onset—treatment delay[b]	0–4.5 h	0–6 h (6–12 h in selected patients with significant penumbra)
Contraindications for the use of thrombolytics	Bridging thrombolysis not possible	Remains the only option for reperfusion
Native CT (ASPECTS score)	≥6	≥6
Angiographic finding (CT-A, MR-A, or invasive angiography)[c]	ICA, MCA-M1, BA, or VA occlusion	ICA, MCA-M1, BA, or VA occlusion

NIHSS, National Institutes of Health Stroke Score; CT-A, computed tomography angiogram; MR-A, magnetic resonance angiogram; ICA = internal carotid artery; MCA-M1, M1 segment of the middle cerebral artery; BA, basilar artery; VA, vertebral artery.
[a]When i.v. t-PA is used, patient should proceed immediately to interventional lab (waiting for the effect of thrombolysis is not anymore acceptable in 2015!).
[b]Start of CT scan—groin puncture time (including e.v. thrombolysis) should be <60 min in 90% of patients!
[c]When native CT scan shows the hyperdense MCA sign, no angiography is necessary, patient should proceed directly to the interventional lab.

as adjunctive therapy within 24 h of i.v. rtPA (IIIC). Oral ASA should be initiated within 24–48 h after stroke onset (IA recommendation). The usefulness of clopidogrel in acute ischaemic stroke is not well established and further research is required (IIbC). Intravenous GPIIb/IIIa inhibitors are not recommended (IIIB).

Similar to AHA/ASA guidelines, no information about periprocedural anticoagulation or antiplatelet treatment is provided in the important multisociety consensus paper on catheter-based interventions in acute stroke.[42]

Periprocedural therapy in published trials and registries

Most published trials or registries do not mention periprocedural antithrombotic therapy at all.[43–45] A small single centre registry of 23 consecutive cases of emergency carotid stenting followed by mechanical thrombectomy found successful carotid stenting in all cases, and establishment of TICI flow 2a/2b/3 in 91%. Symptomatic intracranial haemorrhage occurred in 5/23 patients (22%). Of 13 patients receiving an intravenous loading dose of abciximab during the procedure, 4/13 had SICH (31%) compared with 1/10 (10%) of those who did not. Of seven patients who received intravenous tissue plasminogen activator prior to the procedure, none had SICH. 90-day mortality was 9/23 (39%). All patients who had SICH were above the median age.[46] In the TREVO study, it was recommended that administration of anticoagulants and antiplatelets be suspended for 24 h post-thrombectomy in patients who were not in direct need of these agents. Exclusion criteria: Heparin use within previous 48 h with aPTT >2 times normal was even an exclusion criterion. Intravenous thrombolysis was used in 60% of patients prior to the endovascular procedure. Periprocedural antithrombotic treatment included i.a. rtPA in 10% and GP IIb/IIIa inhibitors in 5%.[47] One study[48] used neither i.v. heparin nor intra-arterial fibrinolytics at any time during the mechanical thrombectomy procedure, even if the recanalization attempt was unsuccessful. When stent placement was needed, antiplatelet management consisted of 500 mg of aspirin i.v. during the procedure, and double antiplatelet was discussed after the 24-h CT control in view of any serious haemorrhagic complications. Patients treated by direct CBT in a Turkish study[49] received 100 mg ASA before CBT in the emergency department. During interventional stroke procedure, 2000 units of bolus heparin were given routinely. No further antiplatelet or heparin was administered within 24 h of procedure. A CT or MRI was performed 24 h after the procedure. If no haemorrhage was present, aspirin 300 mg/day was given.

Elective carotid stenting

The optimal anticoagulation regimen for carotid artery stenting (CAS) remains unknown.[50] Periprocedural UHF is commonly used. Dual antiplatelet therapy with aspirin and clopidogrel is recommended. Two small, randomized trials comparing aspirin alone with double antiplatelet therapy for CAS were terminated prematurely due to high rates of stent thrombosis and neurological events in the aspirin-alone group.[51,52] In patients with proven intolerance to DAPT, CEA should be preferred to CAS. Newer antiplatelet agents such as prasugrel or ticagrelor have not yet been adequately tested in CAS.

A recent survey among the Dutch interventional radiologists showed that almost all continue acetyl salicylic acid till the time of percutaneous interventions. Clopidogrel is stopped in 40% peripheral interventions, but not before CAS. A flushing solution on the sideport of the sheath was used routinely by 50% of radiologists during CAS, but only a minority of them (28%) used a heparinized flushing solution. Unfractionated heparin was used by almost all radiologists as a bolus (5000 IU was the most used dosage, additional smaller bolus usually repeated after 1 h in longer procedures).[53]

Interventions for peripheral arterial disease

Antiplatelet therapy with aspirin (or clopidogrel) is recommended to reduce overall cardiovascular risk in chronic symptomatic lower extremity artery disease (LEAD) patients.[50,54] Data on periprocedural antithrombotic therapy in LEAD interventions are spare. Most published data deal with pharmacological treatment following revascularization procedures, but not during such procedures. Recommendations are based on expert consensus only. Acetylsalicylic

Table 3 **Summary on the periprocedural use of antithrombotic drugs**

	PCI for AMI	Elective PCI	Structural interventions	Electronic device implantation	Arrhythmias ablation	Acute stroke (thrombectomy)	Elective carotid stenting	Peripheral arterial interventions
Thrombolytics	NO (exception: pre-hospital thrombolysis in patients with very long delays to PCI)	NO	NO	NO	NO	YES as bridging therapy in eligible patients	NO	NO for most cases. YES (local thrombolysis) in selected cases
Injectable anticoagulants	YES (heparin or enoxaparin or bivalirudin, dosage of anticoagulant must be adopted to body weight!)	YES (heparin or enoxaparin, dosage of anticoagulant must be adopted to body weight!)	YES (heparin, dosage adopted to body weight and to ACT!)	NO	YES for patients who are not on chronic OAC. NO for temporary replacement of OAC	NO for patients who received bridging rtPA. YES (low dose heparin) for patients treated with direct thrombectomy without rtPA	YES	YES
Oral anticoagulants	NO If patient with AMI is on chronic OAC, no or lower dose heparin should be used.	NO If chronic use, OAC should be interrupted before PCI	NO If chronic use, OAC should be interrupted before PCI	NO If patient is on chronic OAC, therapy should continue (careful timing of implantation with respect to OAC dosage)	YES for patients who are on chronic OAC—they should not interrupt treatment	NO If patient with acute stroke is on chronic OAC, no anticoagulants should be added during mechanical intervention	NO	NO
Acetylsalicylic acid	YES	YES	YES	NO (If chronic use should be discontinued 5–7 days before implantation)	NO (If chronic use should be discontinued 5–7 days before implantation)	NO (Exception: YES just prior to carotid stenting in the acute phase of stroke)	YES	YES
P2Y12 inhibitors	YES	YES	YES	NO (If chronic use, should be discontinued 5–7 days before implantation)	NO (If chronic use, should be discontinued 5–7 days before implantation)	NO (If carotid stenting was part of the acute procedure, P2Y12 inhibitors should be initiated after control CT scan post-thrombectomy procedure)	YES	YES if stent implantation
GPIIb/IIIa inhibitors	Routine upfront use not indicated. Selective (bail-out) use in cath-lab only	NO	NO	NO	NO	NO	NO	NO

PCI, percutaneous coronary intervention; AMI, acute myocardial infarction; GP, glycoprotein; OAC, oral anticoagulants.

acid together with heparin (UFH) is commonly used during peripheral artery interventions. Heparin is used at the doses of 50–70 IU/kg (up to 100 IU/kg). Continuous anticoagulation therapy (UFH, low-molecular-weight heparin, LMWH) following intervention (24–48hrs) is sometimes recommended after procedures with suboptimal results, complex lesions, and infrapopliteal arteries. Acetylsalicylic acid monotherapy after balloon angioplasty (without stenting) was used in the femoropopliteal region in the Basil trial.[55] This trial demonstrated non-inferiority of the interventional treatment of severe lower limb ischaemia to surgical treatment. After intervention with bare metal stent (BMS) in infrainguinal region DAPT (i.e. combination of ASA and thienopyridine) is recommended for 1 month.[50] The DES, that proved superiority over BMS in femoropopliteal region, was in Zilver PTX (paclitaxel) trial using DAPT for 2 months.[56] In Sirocco trial with implant sirolimus eluting stents in femoropopliteal regions DAPT was used for 1 month and no benefit was seen comparing BMSs.[57] It has been proven that anticoagulation therapy with Warfarin after infrainguinal balloon PTA is not superior over ASA, but has higher bleeding risk.[50] Due to the lacking data regarding antithrombotic treatment in LEAD interventions, some centres adjust their protocols adapting data from coronary interventions (PCI) and prolong DAPT therapy. Individualized therapy taking into account the diffuseness of the disease, the quality of the inflow and the outflow, the presence of critical limb ischaemia, the extent of stenting, the use of covered stents, and the stent fracture risk is reasonable.[58]

The survery of the British Society of Interventional Radiology was summarized with the following recommendation: heparinized saline should be used at a recognized standard concentration of 1000 IU/l as a flushing concentration in all arterial vascular interventions and that 3000 IU bolus is considered the standard dose for straightforward therapeutic procedures and 5000 IU for complex, crural, and endovascular aneurysm repair work. The bolus should be given after arterial access is obtained to allow time for optimal anticoagulation to be achieved by the time of active intervention and stenting. Further research into clotting abnormalities following such interventional procedures would be an interesting quantifiable follow-up to this initial survey of opinions and practice.[59]

Antithrombotic strategies in cardiac patients undergoing non-cardiac surgery

Aspirin and P2Y12 inhibitors

The timing of non-cardiac surgery should always be weighted individually based on the nature of surgical illness vs. the cardiac illness. Early (4 weeks) after stent implantation DAPT should be continued in all patients unless the risk of life-threatening surgical bleeding is unacceptably high. Continuation of aspirin may be considered in the peri-operative period. Stopping aspirin therapy should be considered if haemostasis may be difficult to control during surgery. In patients treated with P2Y12 inhibitors, who need to undergo surgery, postponing surgery for 5–7 days after P2Y12 inhibitor cessation should be considered unless the patient is at high risk of an ischaemic event.[60]

Anticoagulants

The bleeding risk should be individually weighed against the benefit of anticoagulants. Patients treated with vitamin K antagonists (VKAs) should have the INR <1.5 to undergo surgery safely. In patients with a high risk of thrombo-embolism (atrial fibrillation with a CHA2DS2-VASc score ≥ 4 or mechanical prosthetic valves or recent venous thrombo-embolism) discontinuation of VKAs is hazardous and these patients will need bridging therapy with a therapeutic-dose of LMWH. Vitamin K antagonist treatment should be stopped 3–5 days before surgery, with daily INR measurements, until ≤ 1.5 is reached, and LMWH should be started 1 day after discontinuation of VKA. Low-molecular-weight heparin is resumed at the pre-procedural dose 1–2 days after surgery, depending on the patient's haemostatic status, but at least 12 h after the procedure. Vitamin K antagonists should be resumed on Day 1 or 2 after surgery—depending on adequate haemostasis—with the pre-operative maintenance dose plus a boosting dose of 50% for two consecutive days. Low-molecular-weight heparin should be continued until the INR returns to therapeutic levels.

Direct oral anticoagulants

Direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, or edoxaban) have a well-defined 'on' and 'off' action, 'bridging' to surgery is in most cases unnecessary, due to their short biological half-lives.

Summary

The periprocedural antithrombotic strategies vary between different types of percutaneous cardiovascular interventions. Heparin remains the key drug for most of these interventions. Oral antiplatelet drugs are essential when stents are implanted. Oral anticoagulants used chronically are not interrupted during most interventions in electrophysiology. Thrombolysis remains important part of acute stroke treatment. Overview on the use of antithrombotic drugs in different settings is summarized in *Table 3*.

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