REVIEW ARTICLE

The Periprocedural Management of Anticoagulation and Platelet Aggregation Inhibitors in Endoscopic Interventions

Christian M. Lange, Stephan Fichtlscherer, Wolfgang Miesbach, Stefan Zeuzem, Jörg Albert

SUMMARY

Background: In Germany, more than half a million persons, most of them elderly, are under long-term treatment with anticoagulants. The approval of new oral anticoagulants and platelet aggregation inhibitors, as well as new data on periprocedural bridging with heparins, have introduced marked complexity to the management of treatment with anticoagulants and platelet aggregation inhibitors for endoscopic interventions in visceral surgery.

Method: This review is based on pertinent publications retrieved by a selective literature search in PubMed, as well as on the relevant guidelines.

Results: Robust data are available on the management of vitamin K antagonists (VKA) and platelet aggregation inhibitors for endoscopic procedures; on the other hand, the data on the periprocedural management of non-VKA oral anticoagulants (NOAC) are still inadequate. Endoscopic procedures that carry a low risk of bleeding can be performed under treatment with anticoagulants or platelet aggregation inhibitors. Before any procedure with a high risk of bleeding (≥ 1.5%) oral anticoagulants of any type and P2Y12 inhibitors should generally be discontinued. Patients in whom VKA are temporarily discontinued for this reason need bridging treatment with heparin only if they are at high risk of thromboembolic events (≥ 10% per year). For patients who are anticoagulated with NOAC, timely discontinuation of the drug depending on renal function is of key importance, and bridging is usually unnecessary.

Conclusion: Adequate scientific evidence supports the current recommendations and treatment algorithms for the periprocedural management of oral anticoagulants and platelet aggregation inhibitors in endoscopic procedures. Larger-scale studies are still needed to provide a sound basis for the corresponding recommendations about NOAC.

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Gastroenterology and Hepatology, Department of Medicine 1, Frankfurt University Hospital, Frankfurt am Main: PD Dr. Lange, Prof. Zeuzem, Prof. Albert

Cardiology, Department of Medicine 3, Frankfurt University Hospital, Frankfurt am Main: Prof. Fichtlscherer

Hemostaseology, Department of Medicine 2, Frankfurt University Hospital, Frankfurt am Main: PD Dr. Miesbach

Intestinal bleeding is one of the most frequently occurring complications after endoscopic procedures (1). The risk may be aggravated by treatment with anticoagulants or platelet aggregation inhibitors (1). Whenever a patient being treated with any such medication is scheduled for an endoscopic intervention, the benefit of reducing the bleeding risk by interrupting treatment—or by switching temporarily to treatment with heparins, known as bridging—has to be weighed against the increased danger of thromboembolic complications. Before every endoscopy, therefore, the bleeding risk associated with the procedure, the importance of the treatment with anticoagulants or platelet aggregation inhibitors, and the urgency of the intervention must be carefully considered.

This review summarizes the available evidence on management of anticoagulants and platelet aggregation inhibitors before endoscopic interventions, placing emphasis on recent advances in knowledge.

Methods

A selective literature search was carried out in PubMed with the search terms "bridging therapy," "endoscopy," "complications," "bleeding risk," "anticoagulants," "antiplatelet agents," "antithrombotic," "clopidogrel," "periprocedural management," "NOACs," and combinations thereof. Relevant guidelines from professional bodies (German Society of Gastroenterology, Digestive and Metabolic Diseases [*Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten*], American Society for Gastrointestinal Endoscopy, American College of Chest Physicians, European Society of Gastrointestinal Endoscopy, European Society of Cardiology) were included.

Results

Bleeding risk in endoscopic procedures

Clinically meaningful bleeding is a very rare (<0.1%) complication of diagnostic endoscopy with or without mucosal biopsy, even in patients being treated with anticoagulants or platelet aggregation inhibitors (2–5). International guidelines classify endoscopy as a low-risk intervention for bleeding if the latter can be anticipated in fewer than 1.5% of cases, while a bleeding

TABLE 1

Stratification of gastroenterological endoscopic procedures according to risk

Interventions with high bleeding risk (≥ 1.5%)	Interventions with low bleeding risk (<1.5%)
– Polypectomy	– Diagnostic endoscopy ± biopsy or ± removal of small polyps?*
– Papillotomy (ERCP)	– Stent change (ERCP)
– EUS with fine-needle aspiration	– Diagnostic EUS
– Treatment of varices	– Capsular endoscopy
– Dilatation/bouginage	– Diagnostic balloon enteroscopy
– Implantation of a metal stent in the gastrointestinal tract with dilatation/bouginage	– Implantation of a metal stent in the gastrointestinal tract without dilatation/bouginage
– Endoscopic submucosal dissection	
– Endoscopic mucosa resection	
– Gastropexy, PEG	
– Liver biopsy	

* Controversial; ERCP, endoscopic retrograde cholangiopancreaticography; EUS, endoscopic ultrasound ; PEG, percutaneous endoscopic gastrostomy

risk of ≥ 1.5% is classified as high *(Table 1)* (2, 6, 7). The studies discussed below help to put these figures into the context of treatment with anticoagulants or platelet aggregation inhibitors.

Polypectomy

The removal of small colonic polyps (<1 cm) carries a low risk of bleeding (<1%) (5), whereas excision of larger or sessile colonic polyps is associated with high bleeding risk. For example, removal of polyps >20 mm was followed by slight bleeding in 5.2% and by severe hemorrhage in 1.5% of cases (8). Excision of polyps from the stomach and duodenum is usually associated with a high risk (≥ 1.5%), endoscopic removal of sessile polyps from the duodenum with a very high risk of bleeding (>10%) (1).

The risk that polypectomy in the colon will be followed by bleeding is not substantially increased by acetylsalicylic acid (ASA) (9). In contrast, a meta-analysis showed an elevated rate of delayed hemorrhage after polypectomy in patients who had taken clopidogrel, whether alone or in combination with ASA (dual platelet aggregation inhibition) (6.5% with, 1.7% without clopidogrel) (10). Some studies showed no significant increase in bleeding risk after removal of small colonic polyps in patients being treated with anticoagulants (11, 12). For larger colonic polyps, however, anticoagulation—even when bridging with heparin—increased the bleeding rate (2.2% versus 0.2%) (13, 14).

Endoscopic retrograde cholangiopancreaticography

Diagnostic endoscopic retrograde cholangiopancreaticography (ERCP) is associated with a low risk of bleeding (<0.1%), whereas the bleeding risk with papillotomy is high (15). A bleeding rate of 2 to 6% following papillotomy has been observed in prospective studies (16, 17). ASA seems not to increase the risk of bleeding after this intervention to any great degree (18).

Percutaneous endoscopic gastrostomy

A recently published meta-analysis found a bleeding rate of 2. 7% after insertion of a stomach tube by means of percutaneous endoscopic gastrostomy (PEG) (19). Only dual platelet aggregation inhibition, not monotherapy with either ASA or clopidogrel, was associated with a meaningful increase in bleeding risk (19).

Bronchoscopy

Bronchoscopy is distinguished from gastroenterological endoscopic interventions by the potentially grave consequences (aspiration) even in the absence of hemodynamically relevant bleeding. Bronchoscopy with or without biopsy can be carried out under ASA, but clopidogrel and anticoagulants should be discontinued before any bronchoscopy with biopsy (mucosal or transbronchial) (20).

Management of platelet aggregation inhibitors in visceral endoscopic procedures

Treatment with platelet aggregation inhibitors need not be interrupted for interventions with low bleeding risk such as diagnostic esophagoduodenoscopy, colonoscopy, or ERCP without papillotomy *(Table 1)* (7, 21). In preparation for high-risk interventions *(Table 1)*, patients should discontinue the intake of P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor), provided interruption is justifiable (see stratification of the risk of arterial thrombosis/stent thrombosis in *Table 2*) (7, 21–23). ASA can generally continue to be given to patients who have been on dual platelet aggregation inhibition, or can be temporarily administered instead of monotherapy with a P2Y12 inhibitor (7, 21). Clopidogrel, ticagrelor, and prasugrel should generally be discontinued 7 days before the endoscopic intervention (7, 21). In the event of an emergency intervention, it may be possible to lower the bleeding risk by transfusion of platelets. This procedure is not applicable in patients on ticagrelor, because the active ingredient circulates in the blood (24). In cases where intervention carries a high risk of bleeding and of arterial occlusion or stent thrombosis, the individual benefits and risks of ASA monotherapy must ultimately be discussed in an interdisciplinary team in consultation with the patient *(Table 2)*. Help in weighing up the risk may be provided by the placebo-controlled POISE-2 study, which included risk patients with non-cardiac surgical interventions. The authors found that perioperative administration of ASA led to an increased bleeding risk (4.6% versus 3.8%), but not to a reduced rate of myocardial infarction (25). However, only 4% of POISE-2

participants had a coronary stent in place. Other studies observed a high rate (ca. 10%) of cardiac and cerebrovascular complications in patients with coronary stents whose intake of aggregation inhibitors was interrupted (26).

Management of anticoagulants in gastroenterological endoscopic procedures

To help determine whether treatment with anticoagulants can be interrupted and whether bridging with heparin is feasible, evaluation of the bleeding risk associated with the procedure must be accompanied by assessment of the patient's individual risk for thromboembolism. *Table 3* summarizes the risk of thromboembolism entailed by the principal entities in the absence of adequate anticoagulation. The risk of a thromboembolic event over a 12-month period is generally stratified into high (≥ 10 %), moderate (ca. 4–10 %), and low (<4%) (22, 23). However, the data for estimation of the risk of thromboembolic complications were gathered without consideration of interventional procedures. Temporary discontinuation of anticoagulants in patients at low and moderate risk of thromboembolism is followed in around 0.1 to 0.7% of cases by thromboembolism within 30 days after the intervention. The (surgical) trauma may pathophysiologically favor thrombus formation (27–29).

The periprocedural management of vitamin K antagonists (VKA) and non-VKA oral anticoagulants (NOAC) is summarized in *Table 4* and *Table 5*, respectively.

Periprocedural interruption of treatment with VKA in elective endoscopy

In endoscopic procedures with a low risk of bleeding (*Table 1)*, treatment with VKA should be continued as usual (2, 6, 22). In most cases this applies equally to patients with high or low risk of thromboembolism (2, 6, 22). For indications with a high target international normalized ratio (INR), e.g., an artificial mitral valve with a target INR of 2.5–3.5, one can consider letting the INR sink to the lower end of the range, because the data on the safety of endoscopic interventions at INR values >2.5 are sparse (2). Administration of vitamin K should, however, be avoided in these circumstances (22, 23).

In the case of endoscopic procedures with a high risk of bleeding (*Table 1)*, treatment with VKA should generally be temporarily discontinued (2, 6, 21–23). Assessment of the individual risk of thromboembolism *(Table 3)* is crucial in deciding whether bridging with heparin is necessary or whether the VKA treatment should simply be interrupted with no bridging. Patients with a low risk of thromboembolism (group C in *Table 3*) can go without bridging (2, 6, 21–23), but bridging should be the rule in those at high risk of thromboembolism (group A in *Table 3*). The procedure for patients with a moderate risk of thromboembolism (group B in *Table 3*) has not yet been clearly

TABLE 2

Stratification of risk of arterial thrombosis/stent thrombosis*[1]

High risk of arterial thrombosis or stent thrombosis (>0.5%)	Low risk of arterial thrombosis
– Status post acute coronary syndrome (STEMI and NSTEMI) within first 12 months	– PAOD without stent
– Coronary stents within first 6 months after implantation (particularly in first 3 months for drug-eluting stents, particularly in first 4 weeks for bare metal stents)*[2]	– Primary and secondary prophylaxis of non-cardioembolic stroke
	– CHD without the above conditions

STEMI, ST-segment-elevation myocardial infarct; NSTEMI, non-ST-segment-elevation myocardial infarct; PAOD, peripheral arterial occlusion disease; CHD, coronary heart disease

*[1] Modified from (23)

*[2] With considerable variation depending on size, type, and location of stent and nature of medicinal coatings. In risk constellations, therefore, an interdisciplinary decision together with the treating cardiologist is advisable.

TABLE 3

Stratification of risk of thromboembolism with various diagnoses*

	High risk of thromboembolism (≥ 10%/year)
Group A	– DVT or PAE within past 3 months – AFF and stroke or TIA within past 3 months – Certain mechanical heart valves (artificial mitral valve, some older models of artificial aortic valves, double valve replacement, any mechanical heart valves after thromboembolism) – AF with CHA2DS2-VASc score of 6–9 points, valvular AF, with thrombus in atrium – Severe thrombophilia (factor V Leiden homozygous, antiphospholipid syndrome, severe protein C/protein S/antithrombin deficiency)
	Moderate risk of thromboembolism (ca. 4–10%/year)
Group B	– Idiopathic DVT or PAE within past year, but at least 3 months ago – AF with CHA2DS2-VASc score of 4–5 points – Heart valves (bioprosthetic valves within first 3 months, most artificial mitral valves)
	Low risk of thromboembolism (< 4 %/year)
Group C	– Secondary DVT or PAE within the past year, but at least 3 months ago – AF with CHA2DS2-VASc score of 1–3 points – Bioprosthetic valves after 3 months

DVT, deep vein thrombosis; PAE, pulmonary artery embolism; TIA, transitory ischemic attack; AF, atrial fibrillation

*Modified from (22, 23)

TABLE 4

Recommended procedure in the case of elective endoscopy in patients being treated with vitamin K antagonists (VKA)

	Risk of thromboembolism	
Bleeding risk	Low (Group C in *Table 3*)	High (Group A in *Table 3*)
Low (<1.5%)	Continue VKA treatment unchanged	Continue VKA treatment unchanged
High (≥ 1.5%)	Interrupt VKA treatment, no bridging with heparin	Interrupt VKA treatment, bridging with heparin indicated

Table adapted from Müller-Lissner et al. (40). Individual decisions are necessary in patients with moderate risk of thromboembolism (group B in *Table 3*) undergoing a procedure with high bleeding risk (see text).

established. The guidelines also give no clearcut recommendation in this regard (2, 6, 21–23). The recently published studies discussed in the following, however, show that here too bridging can be dispensed with in most cases.

Even non-randomized prospective trials in patients with minor surgical or interventional procedures and meta-analyses of such studies suggested that bridging with heparin leads to an increased rate of bleeding (major hemorrhage: 4.2% versus 0.9%) without lowering the risk of thromboembolic complications (30, 31). A prospective randomized trial confirmed these findings, showing that bridging with low-molecular heparin compared with continuation of warfarin treatment during implantation of a pacemaker or defibrillator was associated with a significantly higher rate of bleeding complications (16% [n = 56] versus 3.5% [n = 12]). Overall, however, very few thromboembolisms occurred (n = 2) (32). A large placebo-controlled study of bridging before surgery in patients with atrial fibrillation was published in 2015 (33). Five days before operation, warfarin was replaced by either dalteparin or placebo. The patients with no bridging did not have a higher rate of thromboembolic complications (<0.5% in both groups), but showed a significantly lower rate of periprocedural bleeding (1.3 versus 3.2%). In analogy, dispensing with bridging treatment should not lead to an increase in thromboembolic complications for endoscopic procedures.

If short-term discontinuation of VKA is indicated, the interruption should be as brief as possible—as a rule 5 days, occasionally as long as 8 days. It must be remembered that the half-life of warfarin is shorter than that of phenprocoumon (Marcumar). Heparin bridging in therapeutic dosage is commenced as soon as the target INR of <2 has been reached (ca. 36 h after the last dose of VKA) and ends 4–6 h (unfractionated heparin) or 12–24 h (low-molecular heparin) before the procedure (2, 22, 23). As a rule the previous maintenance dosage of VKA can be resumed on the evening of the day of intervention. If the bleeding risk is high, as in the case of papillotomy, bridging should not give way to therapeutic heparin dosage until 48–72 h after the procedure (6). If anticoagulation is a high priority, e.g., in the case of an artificial mitral valve, treatment can also be resumed earlier with due consideration of the benefits and risks. Particularly in patients with mechanical artificial valves, the best way to proceed should be discussed with the treating cardiologist before the endoscopic intervention.

Periprocedural interruption of treatment with NOAC in elective endoscopy

The immediate effect and the short half-life of NOAC mean that bridging with heparins is unnecessary (34). Instead, NOAC intake can in principle simply be temporarily interrupted before the procedure and then resumed as soon as adequate hemostasis has been attained. One problem is that the NOAC approved for use are eliminated to a greater or lesser extent via the kidneys and can thus accumulate in a patient with renal insufficiency. In patients with restricted renal function, therefore, NOAC should be discontinued for a longer period, regardless of creatinine clearance and the substance used, to ensure complete restoration of hemostasis (21). *Table 5* contains recommendations for interruption of NOAC treatment before endoscopic procedures adapted from Baron et al. (21), based essentially on the product data together with a certain amount of information from licensing studies, particularly for dabigatran. Because the data are so sparse, *Table 5* should currently be regarded as no more than a rough guide.

To date there are no robust data on the safety of endoscopic procedures in patients being treated with NOAC. It is striking, however, that in the licensing studies NOAC treatment was generally associated with a lower rate of bleeding than VKA treatment, but the rate of gastrointestinal hemorrhage was sometimes higher for NOAC than for VKA (35, 36). This is attributed to a local action of NOAC, particularly dabigatran and rivaroxaban, in the gastrointestinal tract. NOAC can be resumed 24 h and 48–72 h after interventions with low and high bleeding risk, respectively (21). These long intervals are necessary because NOAC exert their full therapeutic effect within a few hours after intake. If a longer interruption seems necessary, short-term postprocedural administration of heparins must be considered.

Emergency endoscopy in patients on anticoagulants or platelet aggregation inhibitors

Gastrointestinal hemorrhage in a patient being treated with anticoagulants or P2Y12 inhibitors is often a high-risk clinical situation. After initial stabilization of the patient, endoscopy must be performed to detect and treat the source of the bleeding. Endoscopic hemostasis is safe and effective even under total

anticoagulation (37). In one study the rebleeding rate after upper gastrointestinal hemorrhage was 23% in patients with INR >2 and 21% when INR was in the normal range during initial endoscopic hemostasis (37). Interruption of anticoagulation to facilitate prevention of rebleeding achieved only a non-significant reduction in the rebleeding risk (ca. 15% versus 20%) but greatly increased the risk of thromboembolism (8% versus 0.8%) (38). Patients at high risk of thromboembolism or stent thrombosis should have their treatment with anticoagulants or platelet aggregation inhibitors interrupted only in very well founded cases, i.e., life-threatening bleeding. In such a case it may also be advisable to antagonize anticoagulants or platelet aggregation inhibitors before an endoscopic procedure. Heparins can be antagonized with protamine (which, however, antagonizes low-molecular heparins insufficiently), VKA with vitamin K and/or prothrombin complex preparations, and platelet aggregation inhibitors (except ticagrelor) with transfusions of platelets. It must be borne in mind, however, that fatal thromboembolisms have been observed, particularly in patients with artificial mitral valves—even in cases where an abnormal INR was merely brought down to the normal therapeutic range with vitamin K (22). Antagonists for NOAC have now been developed, e.g., idarucizumab (licensed in 2015) for dabigatran, andexanet alfa (phase III) for apixaban, rivaroxaban, and possibly edoxaban. Until these agents become available, antagonization of dabigatran with recombinant factor VIIa and of rivaroxaban, apixaban, or edoxaban with prothrombin complex preparations can be considered in life-threatening circumstances (21). This is of limited effect, however, and also associated with a meaningful risk of thromboembolism (39). Furthermore, dabigatran can be removed by hemodialysis in the presence of renal insufficiency, while plasmapheresis or elimination by means of extracorporeal liver replacement procedures (Prometheus, MARS) can be considered as a last resort in patients being treated with rivaroxaban, apixaban, or edoxaban (39).

Conclusion

Robust data show that endoscopic interventions with a low risk of periprocedural bleeding can be carried out in patients being treated with VKA or platelet aggregation inhibitors, whereas administration of anticoagulants and P2Y12 inhibitors should be interrupted for interventions with a high risk of bleeding. Bridging with heparin in the case of VKA treatment is now indicated only in a small number of patients with very high risk of thromboembolism. Bridging is usually not necessary in the case of NOAC, where timely interruption of medication, depending on renal function, plays a greater role. However, the recommendations on management of NOAC in endoscopic procedures are based essentially on expert opinion. Prospective studies to confirm these recommendations are urgently required.

TABLE 5

Time for which direct oral anticoagulation should be discontinued before elective endoscopy*

Substance	Renal function (GFR in mL/min)	Bleeding risk	
		Standard	High
Dabigatran	≥ 80	1 day	2 days
	≥ 50 to <80	1–2 days	2–3 days
	30 to%50	2–3 days	4–5 days
Rivaroxaban	>50	1 day	2 days
	30 to 50	1–2 days	3–5 days
	15 to < 30	2–3 days	4–7 days
Apixaban	>50	1 day	2 days
	30 to 50	1–2 days	3–4 days
	15 to < 30	2–3 days	4–5 days
Edoxaban	>80	1 day	2 days
	50 to 80	1–2 days	3–4 days
	15 to < 50	2–3 days	4–5 days

The term "standard risk" derives from the product information. GFR, glomerular filtration rate
*Modified from (21, 39)

Conflict of interest statement
Prof. Fichtlscherer has received payments for lectures on acute coronary syndrome/platelet aggregation inhibitors from AstraZeneca and Daiichi Sankyo.

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KEY MESSAGES

- Treatment with vitamin K antagonists (VKA), non-VKA oral anticoagulants (NOAC) and platelet aggregation inhibitors can be continued unchanged in gastrointestinal endoscopic interventions with a low risk of periprocedural bleeding, e.g., in diagnostic colonoscopy.
- Bridging with heparin is unnecessary in most patients in whom VKA or NOAC have to be interrupted before endoscopic procedures with a high risk of bleeding.
- Bridging with heparin is now recommended only in a small number of patients with a very high risk of thromboembolism, e.g., those with an artificial mitral valve.
- The recent (idarucizumab) and impending (andexanet alfa) licensing of specific antidotes to NOAC represents a considerable advance in the safe use of these anticoagulants.
- To optimize the use of NOAC, it is essential to time the periprocedural interruption of treatment precisely on an individual basis, depending on the creatinine clearance.

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Corresponding author
PD Dr. med. Christian M. Lange
Medizinische Klinik 1
Goethe Universitätsklinikum Frankfurt
Theodor-Stern-Kai 7
60590 Frankfurt am Main, Germany
Christian.Lange@kgu.de