The Current View of Endoscopic procedures and Antithrombotic Therapies

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Abstract

In recent years, treatment of pathologies related to hypercoagulation has advanced significantly as the result of the use of old and new drugs. In addition, significant advances have been achieved in diagnostic and therapeutic methods in digestive endoscopy. On the other hand, the life expectancy of the world population has increased considerably, so gastroenterologists must perform endoscopic procedures more frequently in older patients who present comorbidities for which they receive antithrombotic therapies, especially for cardiovascular diseases.

Many treatment guides produced by important medical associations are available. They are oriented to the performance of endoscopic procedures in patients undergoing antithrombotic therapies. These patients are at risk of bleeding during or after these procedures, and they are at risk of thrombosis when medication is suspended. Nevertheless, no prospective or controlled studies have been performed to guide formulation of protocols for the various diagnostic and therapeutic endoscopic techniques that might be used for these patients. Gastroenterologists must balance the risks of bleeding and embolism to determine the most appropriate time to perform an endoscopic procedure in these patients. Therefore, it is of great importance that you have knowledge of this topic.

We present an updated review of the literature and the most recent recommendations of the European society of gastroenterology.

Keywords

Antithrombotic therapy, digestive endoscopy, antiplatelet drug (antiaggregant), anticoagulants.

INTRODUCTION

Life expectancy of the world's population has increased considerably as a result of health care systems improved in part by advances in diagnostic and therapeutic methods. One result is that gastroenterologists must perform endoscopic procedures in older patients more and more frequently. These patients often present comorbidities related to antithrombotic therapies, especially for cardiovascular diseases. At the beginning of this decade, according to a study published in the American literature, about 70% of patients with cardiovascular disease received acetylsalicylic acid (ASA). Up to 18% required the use of double antiplatelet therapy and 6% had indications for combination therapy of ASA and an oral anticoagulant. (1)

In this group of patients, the risk of digestive bleeding is associated with factors such as the use of antiplatelet agents, anticoagulants, advanced age, female gender, histories of peptic ulcers, histories of cardiogenic shock and failure to prescribe proton pump inhibitors (PPI) when indicated. According to some studies, in-hospital mortality due to thrombotic cardiovascular events is close to 4%, and gastrointestinal (GI) bleeding is considered to be 0.15%. (2, 3)

What is the best time to perform an endoscopic procedure in patients being treated with antithrombotic therapy? Gastroenterologists should balance the risk of hemorrhaging

with the risk of and embolism and should rely on support from hematologists, cardiologists, and cardiovascular surgeons to determine the best time to perform the procedure.

Despite the importance of this topic, there have been no prospective or controlled studies that allow formulation of protocols for performing various diagnostic and therapeutic endoscopy procedures in patients using antithrombotic therapies even though there are many management guides formulated by the most important scientific societies that guide the care of this type of patients. (4, 5)

NEW COAGULATION CASCADE

Increasingly frequent prescription of antiplatelet agents and anticoagulants has greatly increased the importance of awareness of the physiology of coagulation and the pharmacodynamics of the drugs used for gastroenterologists.

In 1964, MacFarlane described the cascade of coagulation. The intrinsic pathway of factors XII, XI, IX, VIII and V and the extrinsic pathway of the [tissue factor and Factor VII unite in a common pathway with Factor X. Various coagulation factors interact to finally convert prothrombin to thrombin and, through the latter, from fibrinogen to fibrin. In the classical cascade, platelets are not as important and function independently. (6)

In 1994, two studies were published at almost the same time. They introduced a new process of coagulation in which the classical cascade is modified and the two coagulation pathways are linked almost from the onset of the process. This occurs because the tissue factor-Factor VIII complex also participates in the activation of factor IX and because the process occurs in three consecutive phases almost simultaneously, rather than in a cascade. During the initial phase, formation of the tissue factor-Factor VII complex activates factors IX and X, and small amounts of thrombin are produced from direct and indirect activation of Factor X. In the second or amplification phase, platelets release acid phospholipids which, together with calcium in the blood, activate factors XI, IX, VIII and V. Through chemotactic mechanisms, they are attracted to the surface of the platelets where feedback and multiplication processes occur. The third phase consists of propagation. Large amounts of Factor X are activated, the prothrombin complex is formed, prothrombin is converted into thrombin and, through the latter, fibrinogen is converted into fibrin. All of this occurs on the surface of the platelet at an exponentially accelerating rate. In this new process, the role of platelets and thrombin, especially in the two final phases, is particularly important. This new process of coagulation has been accepted since 2007 by the European Society of Cardiology. (7-9)

Over the years, many studies of how to prevent coagulation when indicated have been carried out. Inhibition of prothrombin by vitamin K antagonists such as warfarin and acenocumarol is the most commonly used therapy for prevention of chronic thrombotic processes. Inhibition of Factor VIII, through varoius forms of heparin, continues to be successfully used because of its easy control and low risk of hemorrhaging. The new oral anticoagulants (NOACs) act on Factor X and directly on thrombin. Currently, it is also clear that the combination of thrombin inhibitors and platelet activity in doses corresponding to the lower level of the therapeutic range can achieve an effective antithrombotic effect without the risk of bleeding (6).

ANTITHROMBOTIC DRUGS

- Antiplatelet agents
  - Enzyme Inhibitors
    - Cyclooxygenase inhibitors (ASA)
    - Phosphodiesterase inhibitors (dipyridamole)
  - Specific receptor inhibitors
    - Adenosine diphosphate (ADP) receptor inhibitors: clopidogrel, ticagrelor, prasugrel
    - Factor IIb and IIIa antagonists: tirofiban, abciximab and trigramin
- Anticoagulants
  - Heparins
    - Unfractioned heparin (UFH)
    - Low molecular weight heparin (LMWH): enoxaparin, dalteparin, fondaparinux
  - Oral anticoagulants
    - Vitamin K antagonist: warfarin
    - Selective inhibitors of Factor Xa: rivaroxaban, apixaban
    - Direct thrombin inhibitor: dabigatran

Antiplatelet agents

Acetylsalicylic acid (ASA)

Acetylsalicylic acid is one of the best known pharmacodynamic drugs and has been one of the most frequently used drugs throughout history. It has wide indications for cardiovascular pathologies. It acts by inhibiting cyclooxygenase 1, so it selectively blocks platelets from synthesizing thromboxane A2 and irreversibly blocks platelet functioning. Its effect is counteracted by the administration of platelets. (10)

Thienopyridines

Thienopyridines are ADP receptor antagonists that selectively and irreversibly prevent platelet aggregation and activation. They have not antidote, so suspension is recommen-

ded before any type of endoscopic procedure, independent of the risk of thromboembolism. When the patient has a high risk of thromboembolism risk, it is recommended that thienopyridine be replaced with ASA at doses of 100 mg/day until thienopyridine can be restarted.

When the patient receives double therapy, thienopyridine should be discontinued and ASA continued. Thienopyridines do not have an antidote. Therefore, in view of the need to reverse its effect, platelet transfusion should be considered according to the risk of hemorrhage entailed by the endoscopic procedure to be performed. (11)

Clopidogrel

Clopidogrel is given at a dose of 75 mg/day, achieves inhibition of 25% to 30% on the second day, and reaches maximum inhibition between the fifth and seventh day. These times are shortened if higher doses are given. Each day after administration of clopidogrel is discontinued, a platelet regeneration of 10% to 14% is achieved. It should be discontinued five days before the endoscopic procedure.

Ticagrelor

Ticagrelor inhibits platelets faster than does clopidogrel, is given at doses of 90 mg/12 hours, and achieves a peak at two to four hours. Its action decreases rapidly after 72 hours but lasts up to five days. It should be discontinued five days before the endoscopic procedure.

Prasugrel

Prasugrel is 10-100 times more potent than clopidogrel, is given in a single daily dose of 10 mg, and should be discontinued seven to ten10 days before the endoscopic procedure.

It should be remembered that high-risk endoscopic procedures require platelet counts above 50,000 units, while low-risk patients require platelet values greater than 20,000. Platelets should be administered before and during the procedure at a recommended dose of one unit per 10 kg of weight. For each unit of platelets to be administered, an increase of 5,000 to 10,000 platelets should be achieved. This is called the platelet yield. (12)

Oral Anticoagulants

Oral Anticoagulants inhibit vitamin K-dependent factors and require anti-thrombin to act. They have a small therapeutic margin so therefore require continuous monitoring of the international normalized index (INR). For cases with low risks of hemorrhaging, it is recommended that their use be continued, but oral anticoagulants should be suspended for high-risk procedures. When performing procedures with low risks of thrombosis, they should be suspended three to five days before the procedure when INR is less than 1.5. When there is a high risk of thrombosis, the patient should receive bridge therapy with LMWH. (13, 14)

For urgent cases when a patient's INR is between 1.5 and 2.5, vitamin K (10 mg of phytomenadione), should be administration to try to reverse anticoagulation. Prothrombin complex concentrate is the second option. Recombinant Factor VII and fresh plasma at doses of 10 to 30 mL/kg are an option only when other therapeutics are not available. (12)

New Oral Anticoagulants (NOAC)

Some studies have demonstrated that the new oral anticoagulants (NOAC) are better for prevention of stroke sand embolic-systemic events than is warfarin. They act directly action without any need for anti-thrombin, do not require monitoring because their action is more stable, and the dose does not require adjustment. The anticoagulant effect is achieved and ceases faster after administration or suspension than is the anticoagulant effect of warfarin. There are no antidotes to reverse their action. Some studies mention an increased risk of bleeding with the use of NOACs, especially with dabigatran. (11, 15)

The European Society of Anesthesiology says that it is not necessary to suspend NOACs for upper endoscopies or for colonoscopies, even if biopsies are scheduled. (16)

When a procedure is performed on patients receiving drugs such as dabigatran and apixaban that are administered in two daily doses, endoscopy should be performed more than 10 hours after the last dose. For patients who receive rivaroxaban, which is given once daily, administration should be suspended at least one day before the procedure. For high-risk procedures, evaluation of creatinine clearance is recommended. If it is greater than 50 mL/min, suspend the drug one to two days prior to the procedure. If it is lower, suspend the drug three to five days days before. It is recommended that medication be restarted the day after the procedure. (17)

Dabigatran

Dabigatran acts directly on thrombin (Factor IIa), has a half-life of 9-17 hours which varies according to age and renal function, is administered in doses of 75 mg every 12 hours, is absorbed in the proximal intestine and is eliminated by the kidneys.

Rivaroxaban

Rivaroxaban prevents the formation of thrombin by directly inhibiting Factor Xa, has a half-life of five to nine hours in young patients and eleven to thirteen hours in elderly patients, and is administered in doses of 10 mg/day. Its absorption in the gastrointestinal tract is not altered by

food consumption. It is metabolized by the liver and excreted by the kidneys, so its use is contraindicated in patients with advanced cirrhosis and/or severe renal insufficiency.

Apixaban

Apixaban irreversibly inhibits Factor Xa, has a half-life of 8 to 15 hours, and is given every 12 hours at doses of 2.5 mg. It is absorbed in the gastrointestinal tract and is metabolized by the liver. A third of the drug is eliminated through the feces without being absorbed and a fourth is eliminated by renal excretion. It is not recommended in patients with renal or liver pathologies. (11)

Bridge Therapy

Bridge Therapy is indicated for:

- Patients with prosthetic valves including mitral valve replacements, two or more mechanical valves, double valve replacements or aortic valve replacements with other risk factors.
- Patients with nonvalvular atrial fibrillation with antecedent of thrombosis or embolism and/or a CHADS2 score over four.
- Patients with venous thromboembolism within the three previous months or severe thrombophilia evidenced by protein C deficiency, protein S or antithrombin deficiency, antiphospholipid syndrome, homozygous for Leiden factor V, homozygous for mutation of prothrombin gene G20210A, or heterozygous component for both genes. (18)

CONSIDERATIONS IN CASES OF BLEEDING

Performing endoscopy of the digestive tract should be considered urgently in patients whose hemoglobin (Hb) has decreased by more than 2 g and in patients with obvious signs of bleeding such as hematemesis, hematochezia and melena. When these patients receive antithrombotic therapy, the risk of bleeding following endoscopy increases by more than 1.5% including when there is a history of renal failure, liver disease or cancer.

When patients receive ASA and present bleeding that requires performance of endoscopy, the patient must first be hemodynamically compensated by the use of intravenous fluids, inotropes, and platelet transfusions when necessary. Increased risk of bleeding has not been observed in patients undergoing endoscopy. However, an increase in 30-day mortality has been observed in high-risk cardiovascular patients who have had ASA discontinued.

For patients receiving warfarin, administration of vitamin K and fresh frozen plasma may be necessary; it is considered that endoscopy can be performed when INR values are less than 2.5, although for reasons of safety it is better if the INR level is less than 1.5.

In patients receiving NOAC and bleeding with the requirement of endoscopy, and as much as possible due to the patient's conditions, an abundance of intravenous fluids should be administered since these drugs are eliminated renally. The administration of Factor VIIa or activated prothrombin complex concentrates, especially in case of consumption of dabigatran) should be considered. In cases of consumption of rivaroxaban or apixaban inactivate prothrombin complex concentrates should be considered. (18, 19)

Once the bleeding is controlled, administration of antithrombotic treatment should be resumed, if possible on the same day of the procedure. The recommendation for patients receiving double antiplatelet therapy is that ASA should never be discontinued, thienopyridines should be discontinued five to seven days before the procedure and resumed once the bleeding has been controlled. LMWH can be restarted within 24 hours if the procedure has low risk of bleeding or 72 hours later in procedures with high risk of bleeding. (20)

Risk of Bleeding from Thromboembolism

At the time an endoscopic procedure is performed in a patient with antithrombotic therapy, a balance must be made between the risk of discontinuing medication which could lead to thromboembolism in the patient, and the possibility of increased risk of bleeding if treatment is not discontinued. According to the literature, the main pathologies that produce high risks for thromboembolism are the following (11):

- Nonvalvular atrial fibrillation: Anticoagulation in these patients is indicated with only one of the following criteria:
  - Recent congestive heart failure [1]
  - Arterial hypertension [1]
  - Patient over the age of 75 years [2]
  - Diabetes mellitus [1]
  - Stroke [1]
  - Transient ischemia [2]
  - History of vascular disease [1]
  - Female gender [1]
  - Patients between the age of 65 and 75 [1]

  These criteria are grouped in the CHADS 2 and CHA2DS 2-VASc levels that determine the risk of stroke in patients without antithrombotic therapy. The value of each criterion is in brackets. Higher numbers indicate higher risks of thromboembolism. (21, 22)
- Valvulopathies treated with metallic prosthetic valves with no other associated factors have annual risks of thromboembolic events of less than 5%. If the patient also has atrial fibrillation, the risk rises to 5% to 10%

which is considered to be moderate. When a patient has any mitral, tricuspid, aortic, or bivalve metal prosthesis, multiple prosthesis or a history of a cardiac embolism the risk is considered to be high (over 10%). (23)

- Patients who have had conventional coronary stents placed have increased risk of thrombosis if double antiplatelet therapy is discontinued during the first 6 weeks. If a medicated stent has been placed, the greatest risk of thrombosis exists during the first three to six months. Nevertheless, there is a high risk of thrombosis if medication is suspended within the first year after stent placement. (24)
- Within three months of deep venous thrombosis, there is a high risk (over 10%) of new thromboembolic events occurring. Between three and twelve months the risk is between 5% and 10%, and when more than a year has passed the risk falls to 5%. (25)

Risk of Bleeding

Several associations and societies have classified diagnostic and therapeutic endoscopic procedures according to the risk of bleeding in patients receiving antithrombotic therapies and have formulated recommendations regarding the management of anticoagulation.

Tables 1 and 2 show endoscopic procedures and the risks of bleeding in patients receiving anti-embolic therapy according to the classification of the Spanish Society of Digestive Pathology (Sociedad Española de Patología Digestiva - SEPD) and the European Society of Gastrointestinal Endoscopy (ESGE).

Table 1. Risk of bleeding according to the SEPD procedure, Spanish Society of Digestive Endoscopy (Sociedad Española de Endoscopia Digestiva - SEED), Spanish Society of Thrombosis and Hemostasis (Sociedad Española de Trombosis y Hemostasia - SETH) and the Spanish Society of Cardiology (Sociedad Española de Cardiología - SEC), 2015.

Low risk of hemorrhage	High risk of hemorrhage
Diagnostic endoscopy with or without biopsy	Polypectomy
Diagnostic ERCP	Laser coagulation and ablation
Insertion of biliary stent without sphincterotomy	Sphincterotomy
Echoendoscopy	Dilation of benign or malignant stenosis
Pulsed Enteroscopy	PEG Placement
	Echoendoscopy with puncture of cyst
	Balloon Enteroscopy
	Mucosal resection, submucosal dissection, ampullectomy

ERCP: endoscopic retrograde cholangiopancreatography; PEG: Percutaneous endoscopic gastrostomy. Taken from: Alberca de las Parras F et al. Rev Esp Enferm Dig. 2015; 107 (5): 289-306.

According to some studies, a procedure is considered to have low risk if the probability of bleeding is less than 1.5%, (18) but for other groups the risk of bleeding should be less than 1.0% to consider that a procedure has low risk of bleeding. (11)

Generally, the various guidelines recommend that when a patient with a pathology considered to be high risk for thromboembolism requires a procedure considered to be at low risk of bleeding, medications can be continued even if biopsies are required. The incidence of bleeding does not vary much compared to that of patients whose antithrombotic therapy is discontinued. (27)

Table 2. Risk of bleeding for procedures according to guidelines of the British Society of gastroenterology (BSG) and ESGE 2016 (26)

Low risk of hemorrhage	High risk of hemorrhage
Diagnostic endoscopy with or without biopsy	Endoscopic polypectomy
Placement of biliary or pancreatic stent	ERCP with sphincterotomy
Enteroscopy without polypectomy	Sphincterotomy plus biliary dilation with balloon
	Ampullectomy
	Mucosal resection, submucosal dissection
	Dilation of stenosis
	Treatment of esophageal varices
	Stent placement
	PEG
	Echoendoscopy with puncture

PEG: Percutaneous endoscopic gastrostomy. Taken from: Veitch AM et al. Gut. 2016; 65 (3): 374-89.

The recommendation in procedures with a high risk of hemorrhage and low thromboembolic risk is to suspend thromboembolic treatment. For procedures that have high risk of hemorrhage and thromboembolism the ASGE and ESGE recommend continuing therapy with ASA only. Elective procedures for this group of patients should be postponed until completion of treatment (18).

RECOMMENDATIONS OF THE ESGE 2016 GUIDELINES FOR ENDOSCOPY IN PATIENTS UNDERGOING ANTIPLATELET OR ANTICOAGULANT THERAPY

The following is a summary of the main recommendations in the 2016 ESGE guidelines. (26)

Using ASA

It is recommended to continue ASA administration in all endoscopic procedures except endoscopic submucosal

dissection (ESD), colonic endoscopic mucosectomy that is more than two cm deep, upper GI mucosectomy and ampullectomies. In these cases, a risk-benefit analysis of suspension of the drug should be evaluated done (poor quality evidence or weak recommendation).

Procedures with low risks of bleeding

- Continue administration of thienopyridines alone or in double anticoagulation therapy (poor quality evidence, strong recommendation).
- Continue administration of (poor quality evidence, weak recommendation). INR should be checked to make sure that it is not above the therapeutic range for a week prior to the procedure (poor quality evidence, strong recommendation).
- NOACs should not be administered on the day of the procedure (very low quality evidence, weak recommendation) (Figure 1).

Procedures with high risks of bleeding

- For patients with low risk of thrombosis discontinue warfarin 5 days before the procedure (high quality evidence, strong recommendation). Always check that the INR is below 1.5 (evidence of low quality, strong recommendation). Suspend thienopyridine 5 days prior to the procedure (moderate quality evidence, strong recommendation).
- For patients with dual therapy suspend thienopyridine and continue ASA (poor quality evidence, weak recommendation).
- For patients with risk of thrombosis continue ASA and seek the support of a cardiologist to establish the risks and benefits of suspending thienopyridines (high quality evidence, strong recommendation).
- For patients with risk of thrombosis, warfarin should be temporarily replaced by LMWH (poor quality evidence, strong recommendation).
- Administration of NOACs should be stopped at least 48 hours before the procedure (very low quality evidence, strong recommendation). Medication should be withdrawn three days before the procedure for patients receiving dabigatran who have creatinine clearances between 30 and 50 mL/min (poor quality evidence, strong recommendation).
- Suspended medications should not be restarted until at least 48 hours have passed. Decision to restart depends on the risk of thrombosis or bleeding (moderate quality evidence, strong recommendation) (Figure 2).

Bridge Therapy

Bridge therapy is recommended only for patients receiving warfarin, since it does not decrease the risk of embolism for patients receiving NOAC but significantly increases the risk of bleeding.

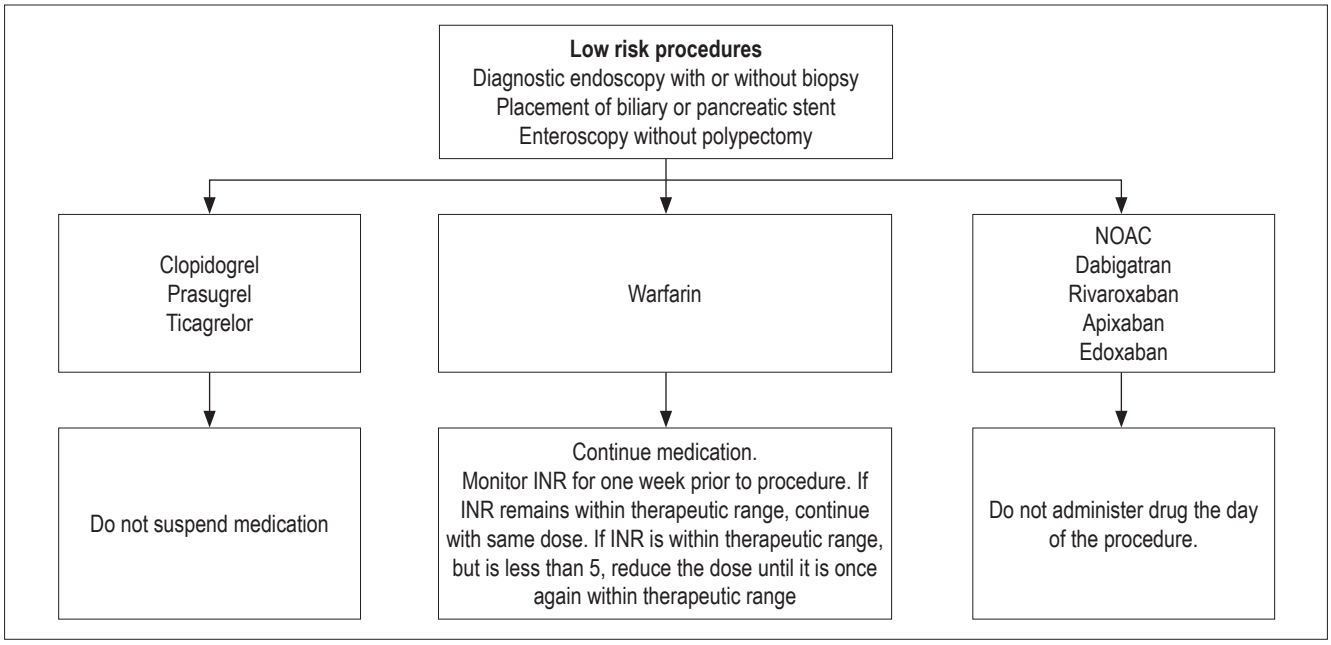

Figure 1. Use of medications in low-risk procedures. Modified from (26).

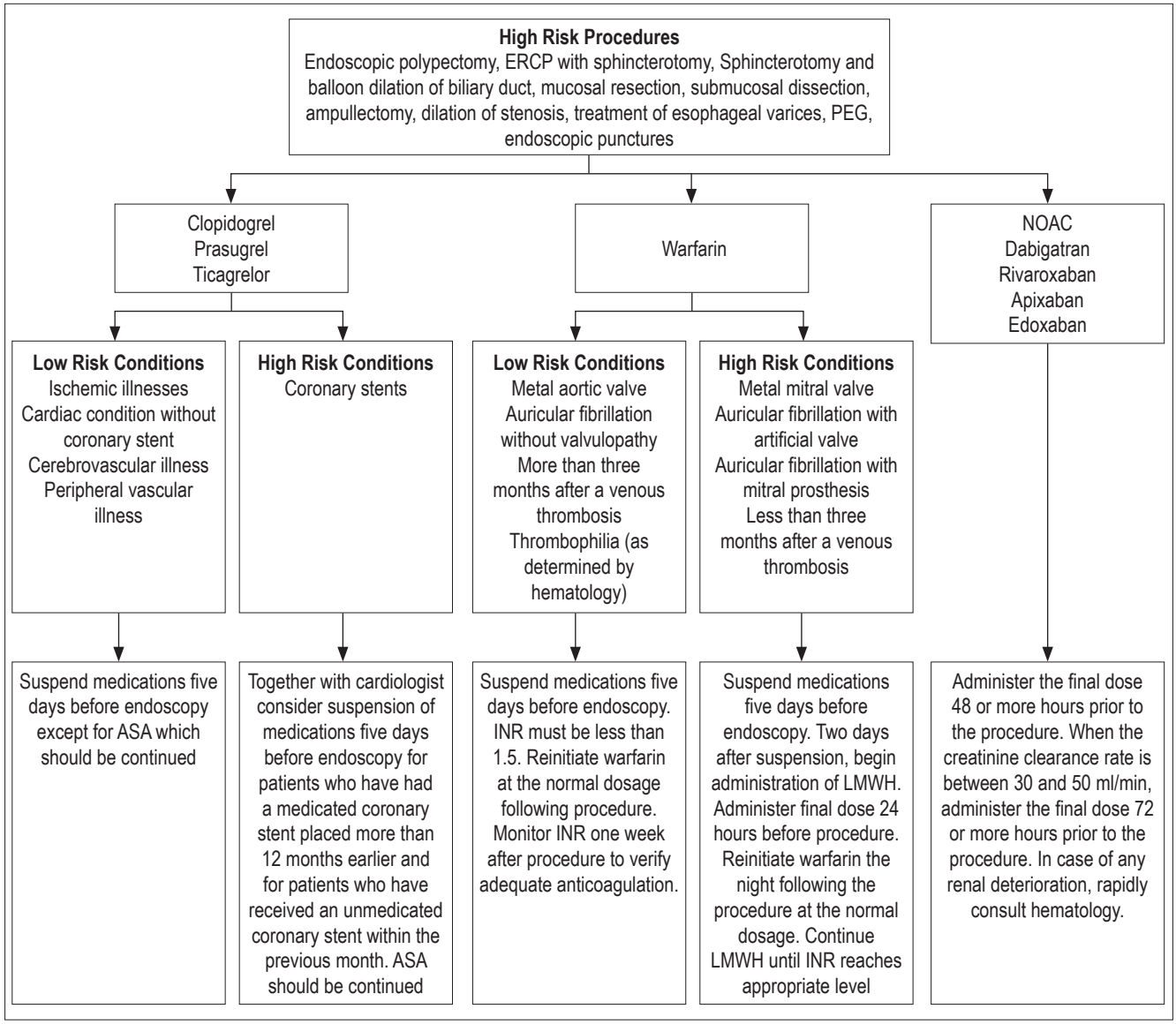

Figure 2. Use of medications in high-risk procedures. Modified from (26).

Triple antithrombotic therapy

Triple antithrombotic therapy is especially indicated for two groups of patients: those with coronary stents who are receiving dual therapy and who may develop atrial fibrillation with warfarin or NOAC, and those with chronic atrial fibrillation who are anticoagulated and who may develop an acute coronary syndrome requiring dual antiplatelet therapy. These patients are at high risk of bleeding during any endoscopic procedure, so they should be evaluated by a cardiologist or other relevant specialist.

Treatment of bleeding in patients receiving NOAC

Temporary suspension of a NOAC is sufficient for patients with mild bleeding, but for patients with severe bleeding, endoscopic hemostasis, red blood cell administration and even correction of coagulopathy with transfusion of platelets and other blood products may be necessary. The most recent use of NOAC and the half-life from serum creatinine to clearance should be determined.

Fresh frozen plasma does not significantly reverse the anticoagulant effect of NOACs and no clinical benefits have been demonstrated from its use.

Similarly, protamine sulfate and vitamin K do not reverse the anticoagulant effects of NOACs, but the effect of antifibrinolytics on bleeding due to NOACs is not known. The use of tranexamic acid appears to be a reasonable alternative.

Although prothrombin complex concentrate and recombinant Factor VIIa have not been evaluated in clinical trials, prothrombin complex concentrate in doses of 40 to 50 IU/kg can be used when bleeding compromises the life of a patient.

Diagnostic endoscopy and Eiopsies

No increased risk of bleeding has been observed for patients who have biopsies taken while they are using ASA, clopidogrel or warfarin. Nevertheless, serious studies of patients who use NOACs and have biopsies or multiple biopsies taken (such as in follow-up of Barrett's esophagus) have yet to be conducted. For these reasons, and since there is no reliable evidence to determine the status of anticoagulation in patients who use NOACs, it is suggested that an adequate safety margin consists of omitting administration of the drug on the morning of the procedure. This applies both to once-a-day and twice-a-day regimens.

Polypectomies, Endoscopic Mucosal Resection (EMR) and ESD

The most important risk factor for patients with colonic polyps is the size of the polyp. The use of electric current for cutting has also been implicated as a risk factor because, when coagulation or mixture of currents is used, the risk of bleeding is lower. For polypectomies, the use of mechanical techniques such as endoloops or clips is considered to be better than the use of an adrenaline mixture which in turn is better than the use of adrenaline alone. There are no prospective studies about use of antiplatelet or anticoagulant agents and resection of polyps, although their use is considered to increase risk of bleeding from mild to moderate depending on the type of resection to be performed (polypectomy, EMR or ESD).

ERCP

In clinical practice, the risk of early or late bleeding associated with performance of ERCP and sphincterotomy is 0.1% to 2%. Coagulopathy, the initiation of anticoagulants during the three days following the procedure, cholangitis and the inexperienced endoscopists have been identified as factors associated with risks of bleeding. Only a few inconclusive studies have been done on the relation of thienopyridines to bleeding. No studies have been performed on patients using NOAC. Some studies suggest that balloon dilation of the biliary tract is safer than performance of a sphincterotomy.

Endoscopic ultrasonography (EUS) and fine needle aspiration (FNA)

A prospective study has determined that, in terms of bleeding by patients who have EUS guided FNA, there is no significant difference between those who receive ASA and those who do not. There are no studies regarding use thienopyridines or NOAC and EUS guided FNA.

Endoscopic Dilation

Several studies that have evaluated the use of pneumatic and/or mechanical dilations have not found significant rates of bleeding among patients who have undergone this procedure. No studies have been designed to directly assess the risk of bleeding associated with dilations. There have been no studies evaluating endoscopic dilations in the GI tract and risk of bleeding in patients receiving thienopyridines or NOACs.

Stent Placement

There are no studies of patients taking thienopyridines or NOACs who have stents placed endoscopically in the GI tract. The risk of bleeding during stent placement is considered to be 0.5% to 1%.

PEG

Some studies report that administration of ASA does not increase the risk of bleeding when PEG is performed. No studies have been conducted to analyze the risk of bleeding in patients treated with prasugrel, ticagrelor or NOAC who undergo PEG.

Endoscopies and Esophageal Varices

One study observed no increased risk of bleeding during endoscopy of patients treated with ASA who had esophageal varices. No studies of the risk of bleeding have been performed of patients with variceal ligation who receive thienopyridines or NOAC. Nevertheless, the recommendation is that these drugs should be discontinued prior to the procedure if possible.

The recommendations above summarize the most important of the recently published ESGE 2016 guidelines.

Coagulation and Cancer

In the 1960s, the French physician Armand Trousseau described the syndrome that currently bears his name. It is defined as any unexplained thrombotic event that precedes or is simultaneous to the diagnosis of a hidden malignant tumor.

The onset of cancer is generally associated with several clinical thrombotic syndromes including local and systemic venous and arterial thrombosis. Thrombosis is often the first clinical manifestation of a neoplasm and is the second leading cause of death in cancer patients. In-vitro coagulation test anomalies are found in more than 90% of cancer patients.

Several authors have shown a significant correlation between the incidence of thromboembolic events and poor prognosis of neoplastic disease which supports the idea that activation of the coagulation system contributes to tumor aggressiveness. (28)

Tumor cells activate tissue factor III and phosphatidylserine (PS) thus promoting activation of extravascular coagulation. This has been correlated with the potential of tumor cells to metastasize. Activation of coagulation enzymes in the tumor's microenvironment may lead to activation of protease-activated receptors (PARs), in particular PAR1 and PAR2, which have been associated with establishment of tumor cells at sites distal to the primary tumor. This has been demonstrated in melanoma, breast cancer and fibrosarcoma.

Long ago it was proposed that coagulation proteins may play an important role in the development of new antitumor therapies given the role that they play in the progression of tumors. These therapeutic strategies are oriented toward blocking some molecules involved in activation of coagulation. This could attenuate tumor growth, angiogenesis and metastases. (28)

Importance of endoscopy and anticoagulation

Significant progress has been made in the treatment of pathologies related to thrombosis and coagulation with new and old drugs. There have also been significant advances in diagnostic and therapeutic endoscopy. Consequently, it is of great importance for today's gastroenterologists to have up-to-date knowledge of this topic.

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