REVIEW

Bleeding risk in endoscopic retrograde cholangiopancreatography. Impact of the use of antithrombotic drugs

Fernando Alberca-de-las-Parras, Juan Egea-Valenzuela and Fernando Carballo-Álvarez

Department of Digestive Diseases. Endoscopy Unit. Hospital Clínico Universitario Virgen de la Arrixaca. IMIB. Murcia, Spain

ABSTRACT

Aims: To analyze the risk factors for hemorrhage during endoscopic retrograde cholangiopancreatography and the impact of antithrombotic drugs.

Material and methods: *Data sources:* papers indexed in PubMed have been reviewed, as well as those found during the analysis of the bibliography of meta-analysis and reviews. *Selection criteria:* the references have been firstly evaluated by review of the abstract. After selecting the most significant articles (mainly randomized trials and well-designed case series) these have been deeply analyzed. *Evaluation of the studies and synthesis:* criteria by the Oxford Centre for Evidence-Based Medicine have been used for the analysis of the references and elaboration of evidence levels.

Results: Seven hundred and sixty-five references were found, 753 in PubMed and the Cochrane Library. Twelve studies were selected during the analysis of other published articles (systematic reviews, meta-analysis and clinical practice guidelines). After analyzing the title or the abstract, 655 studies were excluded. Finally, 83 high quality trials or descriptive studies have been included in the analysis.

Conclusions: Seven conclusions regarding the risk factors for bleeding and the impact of antithrombotic drugs have been defined.

Key words: Antithrombotic drugs. Clopidogrel. Aspirin. Anticoagulants. Sphincterotomy. Bleeding.

INTRODUCTION

Bleeding risk in endoscopic procedures has been stratified by expert consensus and this is how it is defined in clinical practice guidelines (1), with two risk levels (Table I). However, this risk stratification could be much more exhaustive as it is difficult to compare, for example, an endoscopic sphincterotomy (ES) in a patient with multi-morbidity with a pedunculated polyp resection. This could be an endless complication, and this is why the opinion of the endoscopist is important and should always be taken into consideration when deciding whether certain drugs should be discontinued or altered coagulation should be treated. Endoscopists should be familiar with the real bleeding risk of the different endoscopic procedures and the real impact of antithrombotic drugs on hemorrhagic risk.

Another important point is the severity of the hemorrhage: it is considered severe when hospital admission, red cell transfusion or surgical management is required (2).

METHODS

Search strategy and study selection

One author (FAP) searched Cochane Lybrary and MEDLINE database by using the following search strategy: (ENDOSCOPIC SPHINCTEROTOMY OR PRECUT SPHINCTEROTOMY OR ENDOSCOPIC PAPILLARY BALLOON DILATION OR BILIARY BALLOON DILATATION) BLEEDING, (ENDOSCOPIC SPHINCTEROTOMY OR PRECUT SPHINCTEROTOMY OR BILIARY BALOON DILATATION) SPHINCTEROTOMY COMPLICATIONS, SPHINCTEROTOMY AND ANTITHROMBOTIC DRUGS, (ENDOSCOPIC SPHINCTEROTOMY OR PRECUT SPHINCTEROTOMY OR BILIARY BALOON DILATATION) AND THIOPURINES, (ENDOSCOPIC SPHINCTEROTOMY OR PRECUT SPHINCTEROTOMY OR BILIARY BALOON DILATATION) AND ANTIPLATELETS, (ENDOSCOPIC SPHINCTEROTOMY OR PRECUT SPHINCTEROTOMY OR BILIARY BALLOON DILATATION) AND ANTICOAGULANTS). Filters activated: clinical trial, controlled clinical trial, meta-analysis, randomized controlled trial, review, guideline, practice guideline, publication date from 1968/01/01 to 2014/11/22.

References from the selected studies were also reviewed, emphasizing the most significant papers, guidelines and meta-analysis, discarding those previously detected.

Table I. Bleeding risk during endoscopic procedures

Low bleeding risk (< 1%)	High bleeding risk (1-6%)
Diagnostic endoscopic procedures with or without biopsies	Polypectomy
Diagnostic endoscopic retrograde cholangiopancreatography	Electrocoagulation (laser or ablation)
Placement of biliary stents without sphincterotomy	Sphincterotomy
Diagnostic endoscopic ultrasound	Dilation of malignant stenosis
Push enteroscopy	Percutaneous endoscopic gastrostomy
	Endoscopic ultrasound guided fine needle punction
	Treatment of varices
	Device assisted enteroscopy

Data selection

Once search was completed, the selected references were analyzed according to the following topics: a) year of publication and inclusion of cases; b) country; c) type of study, specifying whether the study was prospective or retrospective and identifying the randomized studies; d) data with regard to the use of antithrombotic drugs in the case series; and e) bleeding events described during the main endoscopic procedures.

Outcome and analysis

Our aim was to identify those factors associated with bleeding risk during endoscopic retrograde cholangiopancreatography (ERCP) and the role of antithrombotic drugs by applying evidence-based medicine criteria.

We performed a narrative review of the literature and classified the references. We have defined the bleeding risk of the different procedures associated with ERCP (ES, endoscopic papillary balloon dilation [EPBD], precut sphincterotomy [PS], and morbidities) and other associated factors, especially regarding published data about the use of antiplatelet and anticoagulant agents.

RESULTS

Search results and study description

This was a qualitative review of the literature regarding bleeding during endoscopic procedures and the role of antithrombotic drugs.

Seven hundred and sixty-five references were found, from which 753 were obtained from searching PubMed following the previously described strategy. Twelve papers were selected from the analysis of other published studies, systematic reviews, meta-analysis (MA) and guidelines.

After analyzing the title or the abstract of the studies, 655 papers were discarded due to inadequate referencing, duplicity, exclusively abstract availability, obvious low quality studies or lack of availability.

One hundred and ten papers have been full text assessed, being randomized and non-randomized trials, as well as high quality case series, meta-analysis, systematic reviews

or clinical practice guidelines. Eighty-three clinical trials or high quality descriptive studies have been identified.

A diagram of results (Fig. 1) is provided.

In order to analyze the references and elaborate the different evidence levels, the criteria by the Centre for Evidence-Based Medicine (CEBM - Oxford University) have been applied in this study (3).

ERCP procedure

The risk of bleeding during ERCP is related in most of the cases with ES, as ERCP does not present a risk by itself unless severe comorbidities or altered coagulation are present. Bleeding rates reported in ERCP are between 0.5-5% (4-8), and in most cases the bleeding is referred as mild (6). However, in a large multicenter case series, some severe bleeding episodes were reported (including fatal cases), with hemorrhage rates of up to 33% (9).

Bleeding due to ES has been defined as the presence of clinical symptoms (melena or hematemesis) or the extrav-
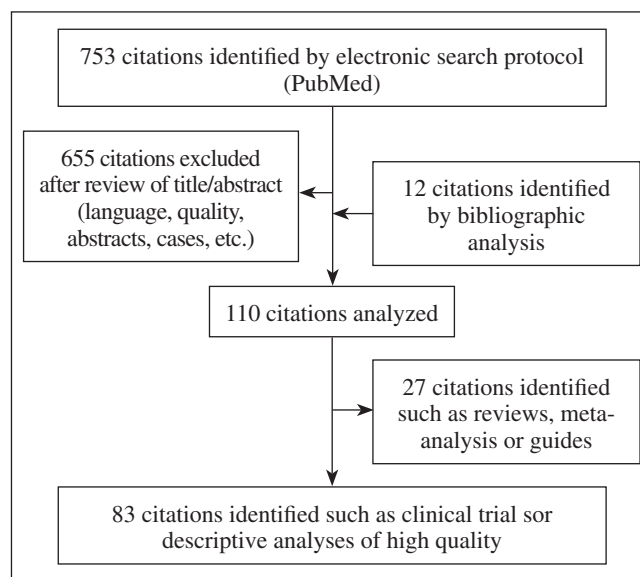

Fig. 1. Flow chart.

asation of blood into the gastrointestinal lumen after ES observed endoscopically (10). Oozing after ES is not considered as significant and, in fact, it has been reported in up to 20-30% of the ES with spontaneous cessation (11). In a study analyzing bleeding rates after precut ES, this was reported in 7% of patients. In all of the cases, bleeding was mild and controlled endoscopically (12). This is why elapsed time is important and it is important to wait for 2-3 minutes after ES to estimate if the bleeding is significant (13). Many studies were difficult to interpret as the characteristics of the bleeding episodes were not always correctly reported or explained. In addition, performance of ES was not always reported although we should consider that bleeding is basically related to this procedure as a multicenter prospective Norwegian study has shown (OR: 4.09 [CI: 2.12-7.91] p < 0.001) (9).

Based on elapsed time, hemorrhage can be classified as: a) immediate, defined as bleeding 2-3 minutes after ES (50-60% of the cases); and b) delayed, defined as bleeding after completion of the ERCP, from some hours to 7-10 days after the procedure (10,13-16).

Based on the severity of the post-ES hemorrhage, this can be classified as: a) mild, when there is clinical evidence but the drop in hemoglobin levels is less than 3 g/dL and transfusion is not required; b) moderate, when endoscopic but not angiographic or surgical treatment is needed and transfusion requirement is up to four red-cell units; c) severe, when transfusion requirement is five or more units and/or surgery or angiographic treatment is needed; and d) fatal (4,7).

Several risk factors for bleeding after ES have been described and can be divided into three main groups (4,17) (Table II).

It is important to highlight some aspects of this classification: low volume case or lack of experience by the endoscopist have been defined as the performance of less than one ES per week (11), and the risk of bleeding in this case is usually related to uncontrolled cutting when performing ES ("zipper cut") (7). An inverse relationship between post-ES hemorrhage episodes and case volume has been shown (8,14). Prolonged procedure time (41-60 minutes) also predicts higher bleeding rates (p = 0.22) (9). Periampullary diverticula have been considered to be a possible risk factor of bleeding but there is some controversy and recent studies point to the fact that, in these cases, the real risk of bleeding is probably the same as in non-diverticular papilla, and not related to the performance of ES or endoscopic papillary balloon dilation (EPBD) (18,19).

In a multicenter retrospective study including 956 consecutive patients, authors analyzed factors related to complications during ERCP. In those cases with bleeding episodes (n = 56: 51 mild, four moderate, one severe and fatal), multivariate analyses showed that cirrhosis (OR: 8.03; p = 0.003), length of ES (full ES: OR: 6.22; p < 0.001) and lithiasis size > 16 mm (OR: 4.00; p < 0.001) were associated with increased bleeding rates. In the case of stones bigger than 16 mm, the completion of ES before EPBD is not recommended (20).

In a prospective study, the endocut system was compared to the blended cut mode when performing ES, with no differences observed in the risk of bleeding (7.8% *vs* 9.9%) (21). Some authors suggest that the use of blended current via automated current delivery cautery systems could reduce the risk of immediate bleeding (11,15), and others report the use of blended cut for biliary sphincterotomy and pure cutting current for pancreatic sphincterotomy, although this procedure may increase the rate of bleeding episodes (13).

Special situations

EPBD has been proposed as an alternative technique in patients needing an urgent aperture of the bile duct and presenting with altered coagulation.

Two MA compare ES alone with ES + EPBD: one of them, including six randomized trials (835 patients), showed similar bleeding rates after ES alone and ES + EPBD (1.7% *vs* 3.1%; OR = 0.50 [0.20-1.23]), although studies were heterogeneous (I^2 = 22%) (22); the other includes 30 published studies (2,511 patients) and the conclusions are that bleeding after ES + EPBD (1.9%) did not present significant differences with ES alone (3.6%), although there were differences when performing EPBD alone (0.1% of bleeding events; p < 0.001) (23), so authors recommend EPBD without ES in patients with altered coagulation or periampullary diverticula, and EPBD with limited ES in the rest of the cases.

The use of EPBD is safe and could be performed alone (without ES) in patients with altered coagulation or peri-

---

Table II. Risk factors for bleeding during ERCP

Bleeding risk	Possible bleeding risk	No bleeding risk
Altered coagulation or low platelets	Cirrhosis	Aspirin or NSAIDs
Anticoagulants intake three days before sphincterotomy	Dilated bile duct	Ampuloma
Acute cholangitis before ERCP	Choledocholithiasis	Long sphincterotomy
Bleeding during sphincterotomy	Periampullary diverticula	Length of previous sphincterotomy
Low case volume endoscopist	Precut sphincterotomy	

ampullary diverticula. Evidence level 1a. Recommendation grade A.

Several MA and systematic reviews compare ES and EPBD (Table III). In some of these, lower bleeding rates are reported when performing EPBD compared with ES. In one study that included eight prospective randomized trials, although similar overall complication rates were reported, bleeding events were less frequent in the EPBD group (0% *vs* 2%) (24). A Cochrane review analyzed 12 randomized trials (1,363 patients) and found lower rates of hemorrhagic complications in patients where EPBD was performed (0.1% *vs* 4.8%) (RR: 0.15, 95% [CI: 0.06 - 0.39]) (25). One more MA including 12 randomized controlled trials (1,865 patients) showed lower bleeding rates in EPBD (RR: 0.12, 95% CI: 0.04-0.34, p = 0.00) recommending EPBD as the election technique in patients with altered coagulation (26), and similar results are reported in the systematic reviews and MA by Liao (OR: 0.15, 95% CI: 0.04-0.50, p = 0.002) (27), Liu (three randomized trials [OR: 0.10 95%, CI: 0.03-0.30, p < 0.0001]) (28), Feng (OR: 0.67%, 95% IC: 0.04-0.50, p = 0.002) (29), Liu (ten randomized controlled trials [0.2% *vs* 4.6%, Peto OR: 0.14, 95% CI: 0.06-0.31; p = 0.00001]) (30) and He (20 randomized trials, OR: 0.12) (31). But in the MA by Jin (five studies including 621 patients), no significant differences were found between the two techniques (1.7% *vs* 2.8%; p = 0.32) (32).

There are no significant differences in the risk of bleeding when EPBD is performed for 30 or 60 seconds (3.1% *vs* 6.6%; p = 0.17) (42). And there are no differences either when EPBD lasts one or five minutes (34).

One retrospective study shows that EPBD is safe and effective, with no significant bleeding rates, for the treatment of lithiasic recurrence after ES (35).

When analyzing preoperative *vs* intraoperative endoscopic sphincterotomy, two MA find conflicting results. In one including four randomized trials with 532 patients, the authors report lower complication rates when intraoperative ES is performed, although the risk of bleeding is similar (36). In the second study, the authors conclude that there are no significant differences in bleeding when ES is carried out for lithiasis extraction during preoperative or intraoperative ES (37).

In a large series of therapeutic ERCP performed in 2,087 patients, bleeding rates of 2.1% were reported. In this series authors analyzed the cases in which bleeding occurred during cholangioscopy, and did not find significant differences (38).

The use of temporary biliary stents without ES has shown lower bleeding rates than stenting after ES (OR = 9.70, 95% [CI: 1.21-77.75], p = 0.03) in one MA including three trials and 338 patients (39). Moreover, auto-expandable metallic stents do not seem to present an increased risk of bleeding during placement or removal (40).

Table III. Systematic reviews and meta-analysis on endoscopic papillary balloon dilation

Ref.	Author	Year		Studies	Patients	
24	Baron	2004	ES *vs* EPDB	8		EPDB < bleeding 0% *vs* 2%
25	Weinberg	2006	ES *vs* EPDB	15	1,768	EPDB < bleeding 0.1% *vs* 4.8% RR: 0.15
26	Zhao	2013	ES *vs* EPDB	12	1,865	EPDB < bleeding RR: 0.12
27	Liao	2012	ES *vs* EPDB	11	923	EPDB < bleeding RR: 0.15
37	Liu	2013	ES *vs* EPDB	11	1,295	EPDB < bleeding RR: 0.10
28	Feng	2012	ES *vs* EPDB	7	790	EPDB < bleeding RR: 0.67
30	Liu	2012	ES *vs* EPDB	10	1,491	EPDB < bleeding 0.2% *vs* 4.6%, OR: 0.14
32	Jin	2014	ES *vs* EPBD	5	621	NS (1.7% *vs* 2.8%)
36	Gurusamy	2011	ES-BS *vs* ES-DS	4	532	ES-BS no differences
37	Wang	2013	ES-BS *vs* ES-DS	6	631	ES-BS no differences
41	Navaneethan	2014	PS *vs* RAC	7	1039	NS, 6.2% *vs* 6.7%
42	Cennamo	2010	PS *vs* RAC	6	966	NS
39	Cui	2014	Stenting with no ES	3	338	Stent with no ES < bleeding OR: 9.70
22	Yang	2013	EPDB *vs* EPDB + ES	6	835	NS, OR: 0.50
23	Kim	2013	EPDB *vs* EPDB + ES	30	2,511	EPBD < bleeding 0.1% *vs* 1.9%
31	He	2013	ES *vs* EPDB	20	1,865	EPBD < bleeding RR: 0.12

ES: Endoscopic sphincterotomy; EPDB: Endoscopic papillary balloon dilation; RR: Relative risk; NS: Non-significant; PS: Precut sphincterotomy; RAC: Repeated attempts at cannulation; BS: Before surgery; DS: During surgery.

The risk of bleeding during pre-cut sphincterotomy (PS) has been analyzed in two MA: in one which included seven randomized trials with a total of 1,039 patients, the authors compared the risk of bleeding related to PS (6.2%) and multiple cannulation attempts (6.9%) and did not find statistically significant differences (OR = 0.85, 95% [CI: 0.51-1.41]) (41). In the second MA (six randomized trials and 966 patients), differences in the risk of bleeding when performing ES or PS were not found either (42). The risk of bleeding in PS ranges from 1.8% (12) to 5.5% (43), which is slightly higher than in ES, but without a statistically significant difference.

In one retrospective study, two different PS techniques have been compared (pancreatic sphincterotomy and pre-cut with a needle knife), and no differences in terms of bleeding between them were found (12), although in a short series including 20 patients, pancreatic sphincterotomy caused bleeding in 15% of the cases (44). Katsinelos et al. (45) have analyzed differences in one retrospective study that included 274 patients among three types of PS. Bleeding occurred during the procedure in five out of 129 sphincterotomies with needle knife (3.9%); in all there was bleeding in four out of 78 needle knife fistulotomies (5.2%), two of them during the procedure and two delayed hemorrhages, and there were no bleeding events in 67 pancreatic sphincterotomies (0%). In all cases the bleeding was mild with no transfusional requirements.

In one prospective study the authors have compared the complications when performing pre-cut after placement of a pancreatic plastic stent ("layer by layer" method) or pre-cut alone, and they find higher bleeding rates in the latter procedure (0/98 [0%] *vs* 3/36 [8.3%]; p = 0.0036) (46).

There are not concrete published data about the use of antithrombotic drugs and PS.

PS is not related to increased risk of bleeding in any of its modalities. Evidence level 1a. Recommendation grade A.
The use of pancreatic plastic stents could decrease the risk of bleeding. Evidence level 2b. Recommendation grade B.

Ampullectomy is an endoscopic procedure with high complication rates in which bleeding is variable as reported in different series (2-18%). In most of the cases surgery is not needed and these complications can be managed endoscopically (47-49). Early bleeding has been reported to be more common than delayed hemorrhage (6 *vs* 1 case in 28 patients) (49).

In liver transplant recipients who undergo ERCP, the reported bleeding rates are variable. In one series of biliary complications after transplantation, no bleeding was reported in ERCP procedures (50). In a retrospective series including 292 cases the rate of hemorrhagic complications was 1.7% (51), and in one series with 150 patients bleeding occurred in eight cases (8.5%), but the authors did not report the severity of these events and did not find differences when compared with their general series of ERCP in patients with no transplantation (n = 13 [6.9%]) (OR: 1.34, CI: 0.50-3.57, p = 0.55) (52). In a short case series, higher rates of delayed bleeding have been reported, but not immediate hemorrhagic events (53). Placement and removal of metallic stents do not seem to increase the risk of bleeding in these patients (one complication in 22 cases) (54).

Primary sclerosing cholangitis is not a risk factor for bleeding during ERCP as only four bleeding episodes have been reported in 294 patients (0.7%) (55).

Management of pancreatic diseases during ERCP seems to have lower bleeding rates than biliary procedures as reported in a retrospective series including 2,753 patients with pancreas divisum, in which only 0.7% presented with bleeding during ERCP (56), and in one case series of patients who underwent endoscopic minor papilla balloon dilation (57).

Liver cirrhosis has been defined as a risk factor for bleeding, but a prospective study in patients with coagulopathy associated with chronic hepatopathy has shown that suprapapillary puncture does not increase the risk of bleeding compared to standard cannulation techniques (58).

Age is a controversial risk factor, as some studies show higher bleeding rates in individuals over 50 years old (especially in individuals older than 90 years) (9). However, no differences in terms of bleeding were found in other studies when stratifying by age (59). Several authors have reported their experience of ERCP in children and have reported no differences in the risk of bleeding (60-62).

Hemodialysis patients present a higher risk of bleeding, especially when the duration of dialysis is long (bleeding events in 19% of ES) (63). These data are not confirmed when EPBD is performed (64).

It is worth highlighting that submucosal adrenaline injection before ES can prevent bleeding, but the results from a prospective study (9/60 *vs* 1/60; p = 0.017) (65) have not been confirmed in other studies.

Antiplatelets

Some retrospective studies have analyzed the effect of antiplatelet agents (66,67) with generally inconclusive results. However, a higher risk of bleeding is described in one study when taking aspirin (ASA), reporting rates of acute bleeding of 9.7% *vs* 3.9% (ASA *vs* control, p < 0.001), and 6.5% *vs* 2.7% in delayed hemorrhage (p = 0.04) (66). These data suggest that, except in emergency situations, antiplatelets should be discontinued at least seven days before ERCP.

In a case-control prospective study including 308 patients taking ASA or non-steroidal anti-inflammatory drugs (NSAIDs), bleeding was observed in 74 cases (24%), but only eight of these (2.6%) were clinically significant (68).

The length of ES, the enlargement of previous ES or ASA/NSAIDs intake do not seem to increase the risk of bleeding (20,23). Specific use of rectal indomethacin as

post-ERCP pancreatitis prophylaxis does not increase the risk of bleeding when compared to placebo as shown in a recent randomized trial (8% *vs* 9.4%). No differences in bleeding were found between patients taking ASA or clopidogrel, and even in a small group of patients with double antiplatelet therapy (69).

Risks related to clopidogrel and new antiplatelet agents remains uncertain, with a clear lack of evidence about these drugs (70). A retrospective study included data from ERCP performed in 50 patients who presented with acute coronary syndrome in the previous months and were undergoing antiplatelet therapy. The authors reported seven bleeding events during ERCP treated endoscopically (14%); one patient on monotherapy and five patients with double antiplatelet therapy who had discontinued clopidogrel five days before the ERCP, and two delayed hemorrhages (4%) (71).

In the large and recent retrospective study by Lee et al. (72), the authors included 762 patients and analyzed the cases of bleeding after ES and the influence of antiplatelet therapy. One hundred and thirty-two individuals were undergoing treatment with antiplatelets; in 29 cases these drugs were discontinued and 601 patients were not receiving treatment. They did not find differences among the three groups, nor in the global bleeding rates (9.8%, 10.3% and 10.5%, respectively; p = 0.977), nor in the rates of early or delayed hemorrhage (3.0%/6.8%, 3.4%/6.9% and 3.7%/6.8%, respectively; p = 0.998) or the severity of the bleeding episode (7.6%/2.3%, 6.9%/3.4% and 8.0%/2.5% of mild/severe bleeding, respectively; p = 0.490). The only difference found in this study was that between patients taking antiplatelets and those who discontinued these drugs at least seven days before ERCP, with a lower risk of bleeding in this latter group (16.3% *vs* 6%; p = 0.071), thus the authors suggest that maintained antiplatelet intake increases the risk of bleeding.

Katsinelos et al., in a study including 2,715 therapeutic ERCPs with 122 bleeding events (4.5%), do not find antiplatelet or anticoagulant agents as an independent risk factor for bleeding (5).

In a short retrospective series including nine patients with a high risk of thrombosis and a need for urgent ERCP

(eight cases of acute cholangitis and one case of obstructive jaundice secondary to neoplasm), ES was performed in all cases with dual antiplatelet therapy, and no bleeding events were reported (73).

A retrospective case-control study demonstrated that antiplatelets do not significantly increase the risk of bleeding (OR: 0.41; 95% CI: 0.13-1.31). In this series, 21 out the 40 patients on antiplatelet therapy presented early bleeding (53%), and half of the episodes were moderate or severe. A limited number of patients were taking clopidogrel, thus no recommendations could be made in this group (74).

As the evidence is scarce and mainly based on retrospective studies, the different published guidelines (75-80) consider ERCP as a high risk technique and recommendations are that it can be performed in patients on ASA (dose dependent) and not on clopidogrel or new generation antiplatelets. These recommendations are based on poor evidence, without any prospective or randomized trials.

The use of aspirin has not shown to increase the risk of bleeding when performing endoscopic sphincterotomy. Evidence level 2c. Recommendation grade B.

There is no evidence about the role of clopidogrel and other thienopyridines on the risk of bleeding when performing endoscopic sphincterotomy, but the general recommendation is the previous discontinuation of these agents. Evidence level 2c. Recommendation grade B.

Anticoagulant agents

ERCP without ES, with or without stent placement, is considered to be a technique with a low bleeding risk and it could be performed in patients undergoing anticoagulant therapy (81).

Some studies have been carried out with low-molecular-weight heparin (LMWH) as it was thought to have protective effects on post-ERCP pancreatitis and the reported rate of bleeding does not seem to be increased (2.3% in 438 patients) (82). However, in a study including 598 ERCPs

Table IV. ERCP and antithrombotic drugs

No.	Author	Year	P/R	RA/NRA	n	Bleeding	Characteristics
66	Hui	2002	R	NRA			ASA > bleeding, NS
74	Hussain	2007	R	NRA	126	40	Case-control with AP
69	Onal	2012	R	NRA	308	74	NSAIDs > bleeding, but mild bleeding
73	Abdel-Samie	2013	R	NRA	8	0	Double AP therapy
69	Patai	2014	P	RA	637	50	Rectal Indomethacin no > bleeding
71	Koh	2014	R	NRA	50	9	AC and AP, NS
72	Lee	2014	R	NRA	762	77	AP > bleeding
5	Katsinelos	2014	R	NRA	2715	122	AC and AP, NS

AC: Anticoagulants; AP: Antiplatelets; ASA: Aspirin; NS: Non-significant; P: Prospective; R: Retrospective; RA: Randomized; NRA: Non-randomized.

(206 ES and 88 PC) the rate of bleeding in the group of patients on LMWH was 10.3%, significantly higher than in non-anticoagulated patients (83).

Different guidelines define anticoagulants as a risk factor for bleeding after ES and promote the withdrawal of these agents and protection under LMWH as a standard practice. Recommending a last dose 24 hours before the endoscopic procedure (1,76,77,80,84) and maintaining them as a bridging therapy in patients at high thrombotic risk (80,85). However, the protective effects of LMWH on thrombosis remain unclear, but an MA has shown a greater risk for bleeding during endoscopic and non-endoscopic procedures (not specifically ERCP) in patients undergoing this therapy (86).

In table IV the literature on ERCP and antithrombotic drugs is summarized.

Anticoagulant agents increase the risk of bleeding after ES. Evidence level 1c. Recommendation grade A.

In patients with a high thrombotic risk, withdrawal of anticoagulant agents and bridging therapy with LMWH before ES are recommended. Evidence level 4. Recommendation grade D.

REFERENCES

1. Eisen GM, Baron TH, Dominitz JA, et al. Guideline on the management of anticoagulation and antiplatelet therapy for endoscopic procedures. Gastrointest Endosc 2002;55:775 DOI: 10.1016/S0016-5107(02)70402-1
2. Cancer therapy evaluation program: Common Terminology Criteria for Adverse Events. Available at: http://ctep.cancer.gov/protocolDevelopment/ electronic_applications/ctc.htm
3. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: An attempt at consensus. Gastorintest Endosc 1991;37:383-93. DOI: 10.1016/S0016-5107(91)70740-2
4. Katsinelos P, Lazaraki G, Chatzimavroudis G, et al. Risk factors for therapeutic ERCP-related complications: An analysis of 2,715 cases performed by a single endoscopist. Ann Gastroenterol 2014;27(1):65-72.
5. Anderson MA, Fisher L, Jain R, et al. Complications of ERCP. Gastrointest Endosc 2012;75(3):467-73. DOI: 10.1016/j.gie.2011.07.010
6. Mergener K. Complications of endoscopic and radiologic investigation of biliary tract disorders. Curr Gastroenterol Rep 2011;13:173-81. DOI: 10.1007/s11894-011-0179-7
7. Loperfido S, Angelini G, Benedetti G, et al. Major early complications from diagnostic and therapeutic ERCP: A prospective multicenter study. Gastrointest Endosc 1998;48:1-10. DOI: 10.1016/S0016-5107(98)70121-X
8. Glomsaker T, Hoff G, Kvaløy JT, et al; Norwegian Gastronet ERCP Group. Patterns and predictive factors of complications after endoscopic retrograde cholangiopancreatography. Br J Surg 2013;100(3):373-80. DOI: 10.1002/bjs.8992. E-pub: 6 Dic 2012.
9. Huibregtse K, Katon RM, Tytgat GN. Precut papillotomy via fine-needle knife papillotome: A safe and effective technique. Gastrointest Endosc 1986;32:403-5. DOI: 10.1016/S0016-5107(86)71921-4
10. Freeman ML. Complications of endoscopic retrograde cholangiopancreatography: Avoidance and management. Gastrointest Endosc Clin N Am 2012;22:567-86. DOI: 10.1016/j.giec.2012.05.001
11. Jamry A. Comparative analysis of endoscopic precut conventional and needle knife sphincterotomy. World J Gastroenterol 2013;19(14):2227-33. DOI: 10.3748/wjg.v19.i14.2227
12. Balmadrid B, Kozarek R. Prevention and management of adverse events of endoscopic retrograde cholangiopancreatography. Gastrointest Endosc Clin N Am 2013;23(2):385-403. DOI: 10.1016/j.giec.2012.12.007
13. Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996;335:909-18. DOI: 10.1056/NEJM199609263351301
14. Freeman ML. Adverse outcomes of ERCP. Gastrointest Endosc 2002;56:S273-82. DOI: 10.1067/mge.2002.129028
15. Ferreira LE, Fatima J, Baron TH. Clinically significant delayed post-sphincterotomybleeding: A twelve year single center experience. Minerva Gastroenterol Dietol 2007;53:215-23.
16. Kapral C, Duller C, Wewalka F, et al. Case volume and outcome of endoscopic retrograde cholangiopancreatography: Results of a nationwide Austrian benchmarking project. Endoscopy 2008;40(8):625-30. DOI: 10.1055/s-2008-1077461
17. Kim KH, Kim TN. Endoscopic papillary large balloon dilation in patients with periampullary diverticula. World J Gastroenterol 2013;19(41):7168-76. DOI: 10.3748/wjg.v19.i41.7168. Disponible en URL: http://www.wjgnet.com/1007-9327/full/v19/i41/7168.htm
18. Zippi M, Traversa G, Pica R, et al. Efficacy and safety of endoscopic retrograde cholangiopancreatography (ERCP) performed in patients with periampullary duodenal diverticula (PAD). Clin Ter 2014;165(4):e291-4. DOI: 10.7417/CT.2014.1745
19. Park SJ, Kim JH, Hwang JC, et al. Factors predictive of adverse events following endoscopic papillary large balloon dilation: Results from a multicenter series. Dig Dis Sci 2013;58(4):1100-9. DOI: 10.1007/s10620-012-2494-8. E-pub: 8 Dic 2012.
20. Tanaka Y, Sato K, Tsuchida H, et al. A prospective randomized controlled study of endoscopic sphincterotomy with the endocut mode or conventional blended cut mode. Clin Gastroenterol 2015;49(2):127-31. DOI: 10.1097/MCG.0000000000000096
21. Yang XM, Hu B. Endoscopic sphincterotomy plus large-balloon dilation vs. endoscopic sphincterotomy for choledocholithiasis: A meta-analysis. World J Gastroenterol 2013;19(48):9453-60. DOI: 10.3748/wjg.v19.i48.9453
22. Kim JH, Yang MJ, Hwang JC, et al. Endoscopic papillary large balloon dilation for the removal of bile duct stones. World J Gastroenterol 2013;19(46):8580-94. DOI: 10.3748/wjg.v19.i46.8580
23. Baron TH, Harewood GC. Endoscopic balloon dilation of the biliary sphincter compared to endoscopic biliary sphincterotomy for removal of common bile duct stones during ERCP: A metaanalysis of randomized, controlled trials. Am J Gastroenterol 2004;99:1455-60. DOI: 10.1111/j.1572-0241.2004.30151.x
24. Weinberg B, Shindy W, Lo S. Endoscopic balloon sphincter dilation (sphincteroplasty) versus sphincterotomy for common bile duct stones. Cochrane Database Syst Rev 2006;4:CD004890.
25. Zhao HC, He L, Zhou DC, et al. Meta-analysis comparison of endoscopic papillary balloon dilatation and endoscopic sphincteropapillotomy. World J Gastroenterol 2013;19(24):3883-91. DOI: 10.3748/wjg.v19.i24.3883
26. Liao WC, Tu YK, Wu MS, et al. Balloon dilation with adequate duration is safer than sphincterotomy for extracting bile duct stones: A systematic review and meta-analyses. Clin Gastroenterol Hepatol 2012;10(10):1101-9. DOI: 10.1016/j.cgh.2012.05.017. E-pub: 27 Mayo 2012.
27. Liu Y, Su P, Lin Y, et al. Endoscopic sphincterotomy plus balloon dilation versus endoscopic sphincterotomy for choledocholithiasis: A meta-analysis. J Gastroenterol Hepatol 2013;28(6):937-45. DOI: 10.1111/jgh.12192
28. Feng Y, Zhu H, Chen X, et al. Comparison of endoscopic papillary large balloon dilation and endoscopic sphincterotomy for retrieval of choledocholithiasis: A meta-analysis of randomized controlled trials. J Gastroenterol 2012;47(6):655-63. DOI: 10.1007/s00535-012-0528-9. E-pub: 24 Feb 2012.
29. Liu Y, Su P, Lin S, et al. Endoscopic papillary balloon dilatation versus endoscopic sphincterotomy in the treatment for choledocholithiasis: A meta-analysis. J Gastroenterol Hepatol 2012;27(3):464-71. DOI: 10.1111/j.1440-1746.2011.06912.x
30. He L, Geng XP, Zhao HC, et al. Endoscopic papillary balloon dilatation vs endoscopic sphincteropapillotomy for common bile duct stones: A meta-analysis. Zhonghua Wai Ke Za Zhi 2013;51(6):556-61.
31. Jin PP, Cheng JF, Liu D, et al. Endoscopic papillary large balloon dilation vs. endoscopic sphincterotomy for retrieval of common bile duct

stones: A meta-analysis. World J Gastroenterol 2014;20(18):5548-56. DOI: 10.3748/wjg.v20.i18.5548

32. Paspatis GA, Konstantinidis K, Tribonias G, et al. Sixty versus thirty seconds papillary balloon dilation after sphincterotomy for the treatment of large bile duct stones: A randomized controlled trial. Dig Liver Dis 2013;45(4):301-4. DOI: 10.1016/j.dld.2012.10.015. E-pub: 26 Nov 2012.

33. Liao WC, Lee CT, Chang CY, et al. Randomized trial of 1-minute versus 5-minute endoscopic balloon dilation for extraction of bile duct stones. Gastrointest Endosc 2010;72(6):1154-62. DOI: 10.1016/j.gie.2010.07.009. E-pub: 25 Sep 2010.

34. Tsai TJ, Lai KH, Lin CK, et al. Role of endoscopic papillary balloon dilation in patients with recurrent bile duct stones after endoscopic sphincterotomy. J Chin Med Assoc 2014;pii:S1726-4901(14)00208-1. DOI: 10.1016/j.jcma.2014.08.004

35. Gurusamy K, Sahay SJ, Burroughs AK, et al. Systematic review and meta-analysis of intraoperative versus preoperative endoscopic sphincterotomy in patients with gallbladder and suspected common bile duct stones. Br J Surg 2011;98(7):908-16. DOI: 10.1002/bjs.7460. E-pub: 7 Abr 2011.

36. Wang B, Guo Z, Liu Z, et al. Preoperative versus intraoperative endoscopic sphincterotomy in patients with gallbladder and suspected common bile duct stones: System review and meta-analysis. Surg Endosc 2013;27(7):2454-65. DOI: 10.1007/s00464-012-2757-7. E-pub: 26 Ene 2013.

37. Hammerle CW, Haider S, Chung M, et al. Endoscopic retrograde cholangiopancreatography complications in the era of cholangioscopy: Is there an increased risk? Dig Liver Dis 2012;44(9):754-8. DOI: 10.1016/j.dld.2012.04.024. E-pub: 21 Jun 2012.

38. Cui PJ, Yao J, Zhao YJ, et al. Biliary stenting with or without sphincterotomy for malignant biliary obstruction: A meta-analysis. World J Gastroenterol 2014;20(38):14033-9. DOI: 10.3748/wjg.v20.i38.14033

39. Canena J, Liberato M, Horta D, et al. Short-term stenting using fully covered self-expandable metal stents for treatment of refractory biliary leaks, postsphincterotomy bleeding, and perforations. Surg Endosc 2013;27(1):313-24. DOI: 10.1007/s00464-012-2368-3. E-pub: 18 Jul 2012.

40. Navaneethan U, Konjeti R, Venkatesh PGK, et al. Early precut sphincterotomy and the risk of endoscopic retrograde colangiopancreatography related complications: An updated meta-analysis. World J Gastrointest Endosc 2014;6(5):200-8. DOI: 10.4253/wjge.v6.i5.200

41. Cennamo V, Fuccio L, Zagari RM, et al. Can early precut implementation reduce endoscopic retrograde cholangiopancreatography-related complication risk? Meta-analysis of randomized controlled trials. Endoscopy 2010;42(5):381-8. DOI: 10.1055/s-0029-1243992. E-pub: 19 Mar 2010.

42. Bruins Slot W, Schoeman MN, Disario JA, et al. Needle-knife sphincterotomy as a precut procedure: A retrospective evaluation of efficacy and complications. Endoscopy 1996;28:334-9. DOI: 10.1055/s-2007-1005476

43. Lin LF. Transpancreatic precut sphincterotomy for biliary access: The relation of sphincterotomy size to immediate success rate of biliary cannulation. Diagn Ther Endosc 2014;2014:864082. DOI: 10.1155/2014/864082. E-pub: 10 Mar 2014.

44. Katsinelos P, Gkagkalis S, Chatzimavroudis G, et al. Comparison of three types of precut technique to achieve common bile duct cannulation: A retrospective analysis of 274 cases. Dig Dis Sci 2012;57(12):3286-92. DOI: 10.1007/s10620-012-2271-8. E-pub: 20 Jun 2012.

45. Kubota K, Sato T, Kato S, Watanabe S, et al. Needle-knife precut papillotomy with a small incision over a pancreatic stent improves the success rate and reduces the complication rate in difficult biliary cannulations. J Hepatobiliary Pancreat Sci 2013;20(3):382-8. DOI: 10.1007/s00534-012-0552-4

46. Ismail S, Marianne U, Heikki J, et al. Endoscopic papillectomy, single-centre experience. Surg Endosc 2014;28(11):3234-9. DOI: 10.1007/s00464-014-3596-5. E-pub: 14 Jun 2014.

47. De Palma GD. Endoscopic papillectomy: Indications, techniques, and results. World J Gastroenterol 2014;20(6):1537-43. DOI: 10.3748/wjg.v20.i6.1537

48. Ito K, Fujita N, Noda Y, et al. Impact of technical modification of endoscopic papillectomy for ampullary neoplasm on the occurrence of complications. Dig Endosc 2012;24(1):30-5. DOI: 10.1111/j.1443-1661.2011.01161.x. E-pub: 1 Jun 2011.

49. Torres V, Martínez N, Lee G, et al. How do we manage post-OLT redundant bile duct? World J Gastroenterol 2013;19(16):2501-6. DOI: 10.3748/wjg.v19.i16.2501

50. Ambrus RB, Svendsen LB, Hillingsø JG, et al. Post-endoscopic retrograde cholangiopancreaticography complications in liver transplanted patients, a single-center experience. Scand J Surg 2014. DOI: 10.1177/1457496914529274

51. Sanna C, Giordanino C, Giono I, et al. Safety and efficacy of endoscopic retrograde cholangiopancreatography in patients with post-liver transplant biliary complications: Results of a cohort study with long-term follow-up. Gut Liver 2011;5:328-34. DOI: 10.5009/gnl.2011.5.3.328

52. Tenca A, Pugliese D, Consonni D, et al. Bleeding after sphincterotomy in liver transplanted patients with biliary complications. Eur J Gastroenterol Hepatol 2011;23(9):778-81. DOI: 10.1097/MEG.0b013e32834928e8

53. García-Pajares F, Sánchez-Antolín G, Pelayo SL, et al. Covered metal stents for the treatment of biliary complications after orthotopic liver transplantation. Transpl Proceed 2010;42:2966-9. DOI: 10.1016/j.transproceed.2010.07.084

54. Navaneethan U, Jegadeesan R, Nayak S, al. ERCP-related adverse events in patients with primary sclerosing cholangitis. Gastrointest Endosc 2014;pii:S0016-5107(14)01878-1. DOI: 10.1016/j.gie.2014.06.030

55. Yamamoto N, Isayama H, Sasahira N, et al. Endoscopic minor papilla balloon dilation for the treatment of symptomatic pancreas divisum. Pancreas 2014;43(6):927-30. DOI: 10.1097/MPA.0000000000000148

56. Moffatt DC, Coté GA, Avula H, et al. Risk factors for ERCP-related complications in patients with pancreas divisum: A retrospective study. Gastrointest Endosc 2011;73(5):963-70. DOI: 10.1016/j.gie.2010.12.035. E-pub: 9 Mar 2011.

57. Artifon EL, Da Silveira EB, Aparicio D, et al. Management of common bile duct stones in cirrhotic patients with coagulopathy: A comparison of supra-papillary puncture and standard cannulation technique. Dig Dis Sci 2011;56(6):1904-11. DOI: 10.1007/s10620-011-1593-2. E-pub: 12 Feb 2011.

58. Yun DY, Han J, Oh JS, et al. Is endoscopic retrograde cholangiopancreatography safe in patients 90 years of age and older? Gut Liver 2014;8(5):552-6. DOI: 10.5009/gnl13310. E-pub: 24 Feb 2014.

59. Troendle DM, Barth BA. ERCP can be safely and effectively performed by a pediatric gastroenterologist for choledocholithiasis in a pediatric facility. J Pediatr Gastroenterol Nutr 2013;57(5):655-8. DOI: 10.1097/MPG.0000000000000124

60. Lü T, Zhang XF. Analysis of clinical application of endoscopic retrograde cholangiopancreatography for the pancreatic diseases in children. Zhonghua Er Ke Za Zhi 2013;51(5):367-70.

61. Cerezo-Ruiz A, Casáis-Juanena LL, Naranjo-Rodríguez A, et al. Colangiopancreatografía retrógrada endoscópica en pacientes menores de 18 años: nuestra experiencia. Gastroenterol y Hepatol 2008;31(08):490-3. DOI: 10.1157/13127090

62. Hori Y, Naitoh I, Nakazawa T, et al. Feasibility of endoscopic retrograde cholangiopancreatography-related procedures in hemodialysis patients. J Gastroenterol Hepatol 2014;29(3):648-52. DOI: 10.1111/jgh.12336

63. Takahara N, Isayama H, Sasaki T, et al. Endoscopic papillary balloon dilation for bile duct stones in patients on hemodialysis. J Gastroenterol 2012;47(8):918-23. DOI: 10.1007/s00535-012-0551-x. E-pub: 22 Feb 2012

64. Matsushita M, Takakuwa H, Shimeno N, et al. Prophylactic injection of hypertonic saline-epinephrine oral to the papilla for prevention of postsphincterotomy bleeding. J Clin Gastroenterol 2010;44(8):e167-70. DOI: 10.1097/MCG.0b013e3181e5ceca

65. Hui CK, Lai KC, Yuen MF, et al. Does withholding aspirin for one week reduce the risk of post-sphincterotomy bleeding? Aliment Pharmacol Ther 2002;16:929-36.

66. Nelson DB, Freeman ML. Mayor hemorrhage from endoscopic sphincterotomy: Risk factor analysis. J Clin Gastroenterol 1994;19:283-7. DOI: 10.1097/00004836-199412000-00004

67. Onal IK, Parlak E, Akdogan M, et al. Do aspirin and non-steroidal anti-inflammatory drugs increase the risk of post-sphincterotomy hemorrhage: A case-control study. Clin Res Hepatol Gastroenterol 2013;37(2):171-6. DOI: 10.1016/j.clinre.2012.04.010. E-pub: 5 Jun 2012.

68. Patai A, Solymosi N, Patai AV. Does rectal indomethacin given for prevention of post-ERCP pancreatitis increase bleeding after biliary endoscopic sphincterotomy or cardiovascular mortality?: Post hoc analysis using prospective clinical trial data. Med 2014;93(26):e159. DOI: 10.1097/MD.000000000000015

69. Rustagi T, Jamidar PA. Endoscopic retrograde cholangiopancreatography-related adverse events: General overview. Gastrointest Endosc Clin N Am 2015;25(1):97-106. DOI: 10.1016/j.giec.2014.09.005

70. Koh HR, Park CH, Chung MW, et al. Endoscopic retrograde cholangiopancreatography in patients with previous acute coronary syndrome. Gut Liver 2014;8(6):674-9. DOI: 10.5009/gnl13301. E-pub: 15 Nov 2014.

71. Lee MG, Kim J, Lee SH, et al. Effect of sustained use of platelet aggregation inhibitors on post-endoscopic sphincterotomy bleeding. Dig Endosc 2014;26(6):737-44. DOI: 10.1111/den.12271. E-pub: 27 Mar 2014.

72. Abdel Samie AA, Sun R, Vöhringer U, et al. Safety of endoscopic sphincterotomy in patients under dual antiplatelet therapy. Hepatogastroenterol 2013;60(124):659-61. DOI: 10.5754/hge12356. E-pub: 28 Dic 2012.

73. Hussain N, Alsulaiman R, Burtin P, et al. The safety of endoscopic sphincterotomy in patients receiving antiplatelet agents: A case-control study. Aliment Pharmacol Ther 2007;25:579-84. DOI: 10.1111/j.1365-2036.2006.03225.x

74. Boustière C, Veitch A, Vanbiervliet G, et al. ESGE Guideline: Endoscopy and antiplatelet agents. Endoscopy 2011;43:445-58. DOI: 10.1055/s-0030-1256317

75. Zuckerman MJ, Hirota WK, Adler DG, et al. ASGE guideline: The management of low-molecular-weight heparin and nonaspirin antiplatelet agents for endoscopic procedures. Gastrointest Endosc 2005;61(2):189-94. DOI: 10.1016/S0016-5107(04)02392-2

76. Alberca-de-las-Parras F. Clinical practice guidelines for managing coagulation in patients undergoing endoscopic procedures. Rev Esp Enferm Dig 2010;102(2):124-38. DOI: 10.4321/S1130-01082010000200007

77. Veitch AM, Baglin TP, Gershlick AH, et al. Guidelines for the management of anticoagulant endoscopic procedures and antiplatelet therapy in patients undergoing endoscopic procedures. Gut 2008;57;1322-9. DOI: 10.1136/gut.2007.142497

78. Becker RC, Scheiman J, Dauerman HL, et al; American College of Cardiology and the American College of Gastroenterology. Management of platelet-directed pharmacotherapy in patients with atherosclerotic coronary artery disease undergoing elective endoscopic gastrointestinal procedures. Am J Gastroenterol 2009;104:2903-17. DOI: 10.1038/ajg.2009.667

79. Alberca de las Parras F, Marín F, Roldán Schilling V, et al. Manejo de los fármacos antitrombóticos asociados a los procedimientos endoscópicos. Rev Esp Enferm Dig 2015;107:289-306.

80. Hittelet A, Devière J. Management of anticoagulants before and after endoscopy. Can J Gastroenterol 2003;17(5):329-32. DOI: 10.1155/2003/182398

81. Rabenstein T, Schneider HT, Bulling D, et al. Analysis of the risk factors associated with endoscopic sphincterotomy techniques: Preliminary results of a prospective study, with emphasis on the reduced risk of acute pancreatitis with low-dose anticoagulation treatment. Endoscopy 2000;32(1):10-9. DOI: 10.1055/s-2000-138

82. Oren A, Breumelhof R, Timmer R, et al. Abnormal clotting parameters before therapeutic ERCP: Do they predict major bleeding? Eur J Gastroenterol Hepatol 1999;11(10):1093-7. DOI: 10.1097/00042737-199912000-00086

83. Ross I Baker, Paul B Coaughlin, Alex S Gallus, et al; the Warfarin Reversal Consensus Group. Warfarin reversal: Consensus guidelines, on behalf of the Australasian Society of Trombosis and Haemostasis. Med J Australia 2004;181(9):492-7.

84. Acosta RD, Abraham NS, Chandrasekhara V, et al. The management of antithrombotic agents for patients undergoing GI endoscopy. Gastrointest Endosc 2016;83:3-16. DOI: 10.1016/j.gie.2015.09.035

85. Siegal D, Yudin J, Kaatz S, et al. Periprocedural heparin bridging in patients receiving vitamin K antagonists. Circulation 2012;126:1630-9. DOI: 10.1161/CIRCULATIONAHA.112.105221012;126:1630-9. DOI: 10.1161/CIRCULATIONAHA.112.105221

86. Siegal D, Yudin J, Kaatz S, et al. Periprocedural heparin bridging in patients receiving vitamin K antagonists. Circulation 2012;126:1630-9. DOI: 10.1161/CIRCULATIONAHA.112.105221