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

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

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 multimorbidity 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 Cochrane Library and MEDLINE database by using the following search strategy: (ENDOSCOPIC SPHINCTEROTOMY OR PRECUT SPHINCTEROTOMY OR ENDOSCOPIC PAPILLARY BALLOON DILATATION 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 BALOON 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.

**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 extravasation 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); 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; 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 periampullary 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).
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.*
Ampulllectomy 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 (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


60. 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


### Table I. Bleeding risk during endoscopic procedures

<table>
<thead>
<tr>
<th>Low bleeding risk (&lt;1%)</th>
<th>High bleeding risk (1-6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Diagnostic endoscopic procedures with or without biopsies</td>
<td>- Polypectomy</td>
</tr>
<tr>
<td>- Diagnostic endoscopic retrograde cholangiopancreatography</td>
<td>- Electrocoagulation (laser or ablation)</td>
</tr>
<tr>
<td>- Placement of biliary stents without sphincterotomy</td>
<td>- Sphincterotomy</td>
</tr>
<tr>
<td>- Diagnostic endoscopic ultrasound</td>
<td>- Dilation of malignant stenosis</td>
</tr>
<tr>
<td>- Push enteroscopy</td>
<td>- Percutaneous endoscopic gastrostomy</td>
</tr>
<tr>
<td></td>
<td>- Endoscopic ultrasound guided fine needle puncture</td>
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<tr>
<td></td>
<td>- Treatment of varices</td>
</tr>
<tr>
<td></td>
<td>- Device assisted enteroscopy</td>
</tr>
</tbody>
</table>

### Table II. Risk factors for bleeding during ERCP

<table>
<thead>
<tr>
<th>Bleeding risk</th>
<th>Possible bleeding risk</th>
<th>No bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Altered coagulation or low platelets</td>
<td>- Cirrhosis</td>
<td>- Aspirin or NSAIDs</td>
</tr>
<tr>
<td>- Anticoagulants intake three days before sphincterotomy</td>
<td>- Dilated bile duct</td>
<td>- Ampuloma</td>
</tr>
<tr>
<td>- Acute cholangitis before ERCP</td>
<td>- Choledocholithiasis</td>
<td>- Long</td>
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<tr>
<td>- Bleeding during sphincterotomy</td>
<td>- Periampullary diverticula</td>
<td>sphincterotomy</td>
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<tr>
<td>- Low case volume endoscopist</td>
<td>- Precut sphincterotomy</td>
<td>- Length of previous sphincterotomy</td>
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</table>
Table III. Systematic reviews and meta-analysis on endoscopic papillary balloon dilation

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Author</th>
<th>Year</th>
<th>Studies</th>
<th>Patients</th>
<th>Outcome</th>
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</thead>
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<tr>
<td>24</td>
<td>Baron</td>
<td>2004</td>
<td>ES vs EPDB</td>
<td>8</td>
<td>EPDB &lt; bleeding 0% vs 2%</td>
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<td>25</td>
<td>Weinberg</td>
<td>2006</td>
<td>ES vs EPDB</td>
<td>15</td>
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<td></td>
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<td></td>
<td>EPDB &lt; bleeding 0.1% vs 4.8% RR: 0.15</td>
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<td>26</td>
<td>Zhao</td>
<td>2013</td>
<td>ES vs EPDB</td>
<td>12</td>
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<td>EPDB &lt; bleeding 0.1% vs 4.8%</td>
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<td>27</td>
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<td>28</td>
<td>Feng</td>
<td>2012</td>
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<td>EPDB &lt; bleeding 0.2% vs 4.6%, OR: 0.14</td>
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<td>30</td>
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<td>32</td>
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<td>ES vs EPBD</td>
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<td>NS (1.7% vs 2.8%)</td>
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<td>36</td>
<td>Gurusamy</td>
<td>2011</td>
<td>ES-BS vs ES-DS</td>
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<td></td>
<td>ES-BS no differences</td>
</tr>
<tr>
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<td>Wang</td>
<td>2013</td>
<td>ES-BS vs ES-DS</td>
<td>6</td>
<td>631</td>
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<tr>
<td></td>
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<td></td>
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<td></td>
<td>ES-BS no differences</td>
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<tr>
<td>41</td>
<td>Navaneethan</td>
<td>2014</td>
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AC: Anticoagulants; AP: Antiplatelets; ASA: Aspirin; NS: Non-significant; P: Prospective; R: Retrospective; RA: Randomized; NRA: Non-randomized.

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.

Table IV. ERCP and antithrombotic drugs
Fig. 1. Flow chart.