



# Management of anticoagulant and antiplatelet therapy in patients undergoing interventional pulmonary procedures

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**Available studies suggest some antithrombotic agents may be used in interventional pulmonary procedures** <http://ow.ly/vSF030bRqjt>

**Cite this article as:** Pathak V, Allender JE, Grant MW. Management of anticoagulant and antiplatelet therapy in patients undergoing interventional pulmonary procedures. *Eur Respir Rev* 2017; 26: 170020 [<https://doi.org/10.1183/16000617.0020-2017>].

**ABSTRACT** There has been great progress in antithrombotic therapy over the past several years. Its use has increased with the advent of novel anticoagulants, as these medications do not require frequent blood tests for monitoring. Antithrombotic therapy is aimed at reducing the risk of thromboembolic events in patients with atrial fibrillation, coronary artery disease, deep vein thrombosis, valvular heart disease and pulmonary embolism. These patients are often critically ill and frequently undergo urgent interventions requiring discontinuation of anticoagulant or antiplatelet therapy which can increase the risk of thrombosis; however, continuing these agents can lead to increased risk of haemorrhage.

The purpose of this article is to summarise the literature surrounding the safety of using antiplatelet and anticoagulant therapies in patients undergoing interventional pulmonary procedures.

## Introduction

Interventional pulmonology is an evolving field that encompasses the management of pulmonary diseases through a minimally invasive approach [1]. Interventional pulmonology entails endoscopic management of lung parenchymal diseases, central airway diseases and pleural diseases. More specifically, lung mass, lung nodules, mediastinal and hilar lymphadenopathy, central airway obstruction, pleural effusion and pneumothorax are diseases managed endoscopically by interventional pulmonologists.

The number of interventional pulmonary procedures has grown several fold over the past few years. Given the growth of these procedures and availability of newer cancer treatments, diagnostic and therapeutic applications have expanded. This growth means more procedures in medically complex patients, including those with cardiovascular diseases. Antiplatelet therapy is commonly administered for the primary and secondary prevention of cardiovascular diseases [2, 3]. Surprisingly, statements on interventional pulmonology from the American College of Chest Physicians [4] and the European Respiratory Society/American Thoracic Society [5] do not discuss the management of these medications in the peri-procedural

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Received: March 11 2017 | Accepted after revision: May 05 2017

Conflict of interest: None declared.

Provenance: Submitted article, peer reviewed.

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setting. There are some guidelines on management of antithrombotic and antiplatelet agents in patients undergoing endoscopic procedures [6, 7] as well as those undergoing diagnostic flexible bronchoscopy [8], but there are no specific guidelines to date regarding the management of antithrombotic agents in patients undergoing interventional pulmonary procedures.

We discuss interventional pulmonary procedures and the supporting literature individually.

### Selection criteria

We searched PubMed, MEDLINE and the Cochrane Library using combinations of words that included bronchoscopy, endobronchial ultrasound guided transbronchial needle aspiration, percutaneous dilatational tracheostomy, central airway obstruction, tracheobronchial stent, pleural effusion, pneumothorax, pleuroscopy, tube thoracostomy, antiplatelet, anticoagulation and antithrombotic therapy. Non-English literature was excluded. Articles that were pertinent to this topic were included (table 1). Half-lives and reversal methods of antithrombotic agents are listed in table 2.

### Percutaneous dilatational tracheostomy

Percutaneous dilatational tracheostomy (PDT) has gained widespread acceptance compared to surgical tracheostomy because it can be performed relatively quickly at the bedside, does not carry the risks of transporting a critically ill patient to the operating room and saves costs and resources of operating room staff [9]. However, bleeding is a common complication of such procedures. Several small studies have evaluated the safety of undergoing PDT in patients on anticoagulant and antiplatelet therapy.

ABOUZGHEIB *et al.* [10] conducted a retrospective study assessing the safety of patients undergoing percutaneous tracheostomy on antiplatelet therapy. 20 patients who underwent tracheostomy during the study period received antiplatelet therapy, while 137 patients did not and constituted a control group. Patients in the antiplatelet therapy group received either clopidogrel with or without aspirin or dipyridamole with or without aspirin. Patients who had clopidogrel discontinued within 3 days of the procedure were included in the study group and patients who had not been on clopidogrel for 4 days were eligible for inclusion in the control group. Major complications were defined as reduction in haemoglobin  $>2$  g-dL<sup>-1</sup>, any reduction in haemoglobin requiring transfusion or need for surgical procedure to control bleeding. In the antiplatelet group, mean $\pm$ SD pre- and post-procedure haemoglobin was 8.7 $\pm$ 1.55 g-dL<sup>-1</sup> and 8.6 $\pm$ 1.41 g-dL<sup>-1</sup>, respectively. One patient had oozing from the tracheostomy site that stopped after application of pressure. In the control group, mean $\pm$ SD pre- and post-procedure haemoglobin was 9.5 $\pm$ 1.32 g-dL<sup>-1</sup> and 9.5 $\pm$ 1.34 g-dL<sup>-1</sup>, respectively. Five (3.6%) patients had minor oozing for  $>10$  min after

TABLE 1 Summary of the research studies

	Type of study	Patients n	Antithrombotic agents used	Outcomes
<b>Thoracentesis/tube thoracostomy</b>				
MAHMOOD <i>et al.</i> [13]	Prospective	25	Clopidogrel, aspirin	One patient had haemothorax
PUCHALSKI <i>et al.</i> [14]	Prospective	73	Clopidogrel, LMWH, UH, warfarin	No bleeding
ZALT <i>et al.</i> [15]	Prospective	30	Clopidogrel	No bleeding
ABOUZGHEIB <i>et al.</i> [16]		18	Clopidogrel	No bleeding
DAMMERT <i>et al.</i> [17]	Retrospective	30	Clopidogrel	No bleeding
<b>EBUS-TBNA</b>				
STATHER <i>et al.</i> [23]	Retrospective	12	Clopidogrel	No bleeding
<b>Transbronchial biopsy</b>				
ERNST <i>et al.</i> [25]	Prospective	30	Clopidogrel	Study stopped at 6 months due to high rate of bleeding
<b>Tracheostomy (PDT)</b>				
ABOUZGHEIB <i>et al.</i> [10]	Retrospective	20	Clopidogrel, dipyridamole, aspirin	One with minor <sup>#</sup> bleeding
BRAUNE <i>et al.</i> [11]	Retrospective	118	UH	Two patients with major <sup>¶</sup> bleeding
PASIN <i>et al.</i> [12]	Retrospective	36	Bivalirudin, UH	Three minor <sup>#</sup> and two major <sup>¶</sup> bleedings
<b>Percutaneous thoracic aspiration</b>				
PIEPER <i>et al.</i> [26]	Retrospective	12	Clopidogrel	One patient with major <sup>¶</sup> bleeding

EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; PDT: percutaneous dilatational tracheostomy; LMWH: low molecular weight heparin; UH: unfractionated heparin. <sup>#</sup>: patients who did not require administration of blood products or surgical correction; <sup>¶</sup>: patients who required administration of blood products or surgical correction.

TABLE 2 Half-life and reversal of selected antithrombotic agents

	Agent	Half-life with normal renal function	Reversal prior to elective procedure	Reversal prior to urgent procedure
<b>Oral antiplatelet agents</b>				
Cyclo-oxygenase inhibitor	Aspirin	20 min	NA	Platelet transfusion
Irreversible P2Y <sub>12</sub> ADP receptor inhibitor	Clopidogrel	6–8 h	Withhold drug 5–10 days prior to procedure	Platelet transfusion, desmopressin in severe cases
Irreversible P2Y <sub>12</sub> ADP receptor inhibitor	Prasugrel	2–15 h	Withhold drug 5–10 days prior to procedure	Platelet transfusion, desmopressin in severe cases
Irreversible P2Y <sub>12</sub> ADP receptor inhibitor	Ticlopidine	12 h	Withhold drug 10–14 days prior to procedure	Platelet transfusion, desmopressin in severe cases
Reversible P2Y <sub>12</sub> ADP receptor inhibitor	Ticagrelor	7 h	Withhold drug 5–10 days prior to procedure	Platelet transfusion, desmopressin in severe cases
<b>Oral anticoagulant agents</b>				
Vitamin K antagonist	Warfarin	20–60 h	Withhold drug 5 days prior to procedure, monitor INR	<i>i.v.</i> vitamin K, four-factor PCC, three-factor PCC or activated PCC
Direct factor Xa inhibitor	Rivaroxaban	5 h	Withhold drug ≥24 h prior to procedure	Consider three- or four-factor PCC or activated PCC
Direct factor Xa inhibitor	Edoxaban	10–14 h	Withhold drug ≥24 h prior to procedure	Consider three- or four-factor PCC or activated PCC
Direct factor Xa inhibitor	Apixaban	12 h	Withhold drug ≥48 h prior to procedures with high bleed risk; withhold drug ≥24 h prior to procedures with low bleed risk	Consider three- or four-factor PCC or activated PCC
Direct thrombin inhibitor	Dabigatran	12–17 h	Withhold drug 1–2 days prior to procedure (CrCl ≥50 mL·min <sup>-1</sup> ); withhold drug 3–5 days prior to procedure (CrCl <50 mL·min <sup>-1</sup> ); longer for patients undergoing spinal puncture or major surgery	Idarucizumab
<b>Parenteral anticoagulant agents</b>				
Anti-Xa, antithrombin III inhibitor	UFH	60–90 min	Withhold drug 4–6 h prior to procedure	Protamine sulfate
LMWH	Enoxaparin	4.5 h	Withhold drug 24 h prior to procedure	Protamine sulfate
LMWH	Dalteparin	2.5 h	Withhold drug 24 h prior to procedure	Protamine sulfate

ADP: adenosine diphosphate; LMWH: low molecular weight heparin; NA: not applicable; INR: international normalised ratio; PCC: prothrombin complex concentrate; CrCl: creatinine clearance; UFH: unfractionated heparin.

the procedure, four of whom required local cauterisation to control the bleeding. There were several limitations to this study. First, this was a small, retrospective study with only 20 patients evaluated in the intervention cohort. Additionally, only aspirin with or without clopidogrel therapy was evaluated (dipyridamole therapy was included in the study protocol, but no patients undergoing tracheostomy received this agent). Finally, not all patients were at steady-state serum concentrations of clopidogrel, as patients in the study group could have been included if they had discontinued clopidogrel within the past 3 days. Despite these limitations, the authors of this study concluded that it was safe to proceed with PDT without stopping clopidogrel in patients with a strong indication for antiplatelet therapy.

Studies have evaluated use of anticoagulation in patients undergoing percutaneous tracheostomy. A retrospective, observational study [11] of 118 patients receiving systemic heparin infusions while on extracorporeal membrane oxygenation (ECMO) was conducted to assess safety of PDT. Major and minor complications were assessed. 48 (40.7%) patients received red blood cell transfusions within 24 h before PDT, 17 (14.4%) patients received platelet transfusions and eight (6.8%) patients received fresh frozen plasma prior to the procedure. The heparin infusions were stopped 1 h prior to tracheostomy and restarted immediately after completion of the procedure at the previous rate. No procedure-related deaths occurred. Major complications occurred in five (4.2%) patients. Two (1.7%) patients had procedure-related bleeding, two (1.7%) patients had peri-procedural pneumothoraces and one (0.8%) patient had sedation-related hypotension requiring brief cardiopulmonary resuscitation without neurologic sequelae. The incidence of

minor bleeding from the tracheostomy site was 31.4%, all of which were either self-limiting (78.4%) or responded to peri-stomal compression (10.8%), topical vasoconstrictive agents (8.1%) or electrocauterisation (2.7%). Based upon the low rates of major bleeding observed in this study, the authors concluded that PDT is not a contraindication to patients receiving ECMO who require full-dose anticoagulation; however, larger studies are needed to confirm these findings. Limitations of this study include its retrospective design, which relied on information documented in the medical record for review and analysis; small sample size, which reduced the power of the study to detect rare complications; and the potential for limited applicability, since the centres included in this study were highly experienced in both ECMO and PDT [11].

PASIN *et al.* [12] published a single-centre, retrospective study of critically ill patients undergoing percutaneous tracheostomy in a 14-bed cardiothoracic and vascular intensive care unit (ICU). 36 patients in the ICU underwent PDT during the study period, 26 of whom were on an anticoagulant. The primary end-point was major and minor bleeding episodes. Bivalirudin was the most common anticoagulant used ( $n=22$ ), and four patients were on a heparin infusion. Of the patients who received bivalirudin, 15 had the drug interrupted 6 h prior to the procedure, two patients had the drug interrupted 3 h prior to the procedure and five did not have the drug interrupted. None of the patients who received heparin had the drug interrupted prior to tracheostomy. The mean $\pm$ SD pre-procedure haemoglobin concentration was  $10.1 \pm 1.15$  g·dL<sup>-1</sup> and the mean $\pm$ SD platelet count was  $128\,000 \pm 89\,500$  platelets· $\mu$ L<sup>-1</sup>. No patients in the study were deemed to have had procedure-related death, however 10 intra- and post-procedural complications occurred. Three patients had minor intra-procedural bleeding, two of whom were on bivalirudin at the time of the procedure. The third, who was not on anticoagulation at the time of the procedure, had minor posterior tracheal wall injury. Six patients had post-procedural complications. Three of the six post-procedure complications were due to minor bleeding, one was due to fever and two were due to major bleeding. Of note, seven out of these 10 patients with bleeding complications had a platelet count  $<100\,000$  platelets· $\mu$ L<sup>-1</sup> and four had platelets  $<50\,000$  platelets· $\mu$ L<sup>-1</sup>. Two patients required transfusion. Overall, rates of severe bleeding were low in this study despite anticoagulant therapy with bivalirudin and heparin.

Limitations of this study include its retrospective design, small sample size and lack of power to detect a difference in rates of procedure-related death. Additionally, since the half-life of bivalirudin in patients with normal renal function is only 25 min, withholding the drug 6 h prior to the procedure would have allowed for the drug to be completely cleared. In addition, since several patients had thrombocytopenia at baseline, they were already at a high risk of PDT-related bleeding.

Overall, these studies demonstrated low rates of major bleeding in patients who underwent percutaneous tracheostomy while receiving antiplatelet therapy with clopidogrel with or without aspirin or anticoagulant therapy with bivalirudin or heparin. However, anticoagulation was withheld for several hours prior to the procedure for many patients, potentially allowing for partial or full elimination of the medication. Additionally, clopidogrel was stopped for as many as 3 days, which may have contributed to a low incidence of bleeding. In contrast, the risk of minor bleeding may be increased with peri-procedural use of anticoagulants and antiplatelet agents, although most bleeds could be successfully managed with electrocauterisation, compression or application of topical vasoconstrictors. Patients with pre-existing thrombocytopenia appear to be at greater risk of bleeding.

### Tube thoracostomy and thoracentesis

Although small, several studies have been published evaluating chest tube placement (tube thoracostomy) and thoracentesis in patients on clopidogrel therapy. MAHMOOD *et al.* [13] conducted a prospective cohort study to assess the safety of therapeutic thoracentesis and small-bore chest tube placement in patients taking clopidogrel. 25 patients consented to continuation of their home clopidogrel regimens. This group was compared to a control group of 50 patients for whom clopidogrel was withheld prior to either pulmonary procedure. Patients were excluded if they had an international normalised ratio (INR)  $>2$ , or a platelet count  $<50\,000$  platelets· $\mu$ L<sup>-1</sup>. Full-dose anticoagulation was withheld for all procedures. Procedural complications were defined as a decrease in haemoglobin  $>2$  g·dL<sup>-1</sup>, evidence of reaccumulation of pleural fluid on the chest radiograph within 24 h for the procedure, or haemothorax. Of the 25 patients taking clopidogrel, 22 (88%) were on concomitant aspirin therapy. The mean $\pm$ SD pre- and post-procedural haemoglobin in the clopidogrel group was  $9.7 \pm 1.3$  g·dL<sup>-1</sup> and  $9.6 \pm 1.5$  g·dL<sup>-1</sup>, respectively ( $p=0.49$ ). The mean $\pm$ SD pre- and post-procedure haemoglobin in the control group was  $10.3 \pm 1.4$  g·dL<sup>-1</sup> and  $10.4 \pm 1.3$  g·dL<sup>-1</sup>, respectively ( $p=0.38$ ). In addition, there was no significant difference in the rate of reaccumulation of pleural effusion after the procedures. One (4%) patient on clopidogrel experienced a haemothorax after thoracentesis and required two units of packed red blood cells and small-bore chest tube placement.

Limitations of this study include the small sample size and lack of statistical power to detect a significant difference in bleeding between clopidogrel and control groups given the low reported incidence of

haemothorax. In addition, all procedures were performed with ultrasound guidance and by interventional pulmonologists, or physicians under training (fellows) under close supervision, which may have impacted the low incidence of adverse events. Additionally, since this trial was not randomised, it is possible that only patients who consented to continue antiplatelet therapy prior to these procedures were at low bleed risk. The authors concluded that the bleeding outcomes seen in this trial were low enough to warrant a larger randomised trial to further assess the safety of clopidogrel continuation during these procedures.

PUCHALSKI *et al.* [14] conducted a prospective single-centre observational study of 312 patients undergoing thoracentesis, 130 (42%) of whom had a bleeding risk. Out of these 130 patients, 15 were on clopidogrel, 14 were on either low molecular weight heparin or unfractionated heparin and 44 patients had an INR >1.5 due to liver disease or warfarin. The authors did not find any increased risk of bleeding in these patients and concluded that thoracentesis may be safe to perform in patients receiving anticoagulants such as warfarin, heparin and clopidogrel.

ZALT *et al.* [15] conducted a prospective study of 30 patients who received clopidogrel within 24 h of an emergent, therapeutic ultrasound-guided thoracentesis and continued therapy after the procedure. 46 procedures were completed over the course of 26 months. The primary outcome was to determine whether clopidogrel increased the risk of bleeding during and after thoracentesis. Patients were excluded if they had platelet counts <100 000 platelets· $\mu\text{L}^{-1}$  or an INR >1.5. Only one patient developed procedure-related bleeding, defined as a small subcutaneous haematoma at the puncture site. Haemostasis was achieved with manual compression and no decline in haemoglobin was observed. As with prior studies, this study was limited by its small sample size and lack of a comparator group.

Another retrospective study [16] was conducted to assess the safety of therapeutic chest tube placement in patients on clopidogrel therapy. Major complications were defined as reduction in haemoglobin >2 g·dL<sup>-1</sup>, need for transfusion, bleeding necessitating admission to the ICU or need for another procedure to stop the bleeding. Minor complications were defined as a reduction in haemoglobin 1–2 g·dL<sup>-1</sup> within 24 h of chest tube insertion and/or local bleeding lasting >10 min. 18 patients who underwent 24 ultrasound-guided chest tube insertions while on clopidogrel therapy were included. 13 out of the 18 patients were on concomitant aspirin. No major or minor complications were documented in any patient. As with prior studies, limitations include the small sample size and lack of comparator group.

DAMMERT *et al.* [17] conducted a retrospective review of 30 patients who underwent 43 small-bore (8, 14 or 16 Fr) chest tube insertions (Seldinger technique) while on clopidogrel. The primary end-point was any significant bleeding complication defined as a reduction in haemoglobin >2 g·dL<sup>-1</sup> after chest tube insertion, haemothorax, development of a chest wall haematoma or any bleeding requiring blood transfusion, surgery, additional chest tube insertion or ICU admission. 91% of patients were receiving concomitant aspirin. All patients had a platelet count >50 000 platelets· $\mu\text{L}^{-1}$  and an INR <1.5, with the exception of one patient with an INR of 1.7. No significant bleeding complications were noted in any patient and no patient experienced a decrease in pre- or post-haemoglobin concentrations >1.2 g·dL<sup>-1</sup>.

In all these studies, thoracentesis was performed using ultrasound. Either 6 Fr or 8 Fr catheters were inserted using a modified Seldinger technique (over the needle). Chest tube placements were also performed using ultrasound in all the above-mentioned studies; Seldinger technique (over a guidewire) was used to insert the chest tube and the size of the chest tube varied from 8 Fr to 16 Fr in diameter. Chest tube diameter >20 Fr is considered to be large bore [18, 19]. These studies, although small, demonstrate that continuation of clopidogrel may be safe in patients undergoing ultrasound-guided thoracentesis or small-bore chest tube insertion.

### Medical thoracoscopy/pleuroscopy

Despite an exhaustive search, we could not find any literature on peri-operative management of antithrombotic therapy in patients undergoing medical pleuroscopy.

### Video-assisted thoracic surgery

CERFOLIO *et al.* [20] conducted a prospective case-control study of 33 patients undergoing general thoracic procedures who were on antiplatelet therapy at the time of the procedure. These patients were matched to 132 controls not on antiplatelet therapy. 14 patients were on clopidogrel plus aspirin and 19 patients were on clopidogrel alone. There was no increased risk of bleeding in patients who underwent primary thoracotomy; however, two patients required “redo” thoracotomies and both had clinically significant bleeding on aspirin and clopidogrel. The authors recommended discontinuing aspirin and continuing clopidogrel monotherapy based on these results. A retrospective study [21] of 164 patients undergoing thoracoscopic surgery for lung cancer compared bleeding events in 106 patients who had interruptions of their antiplatelet therapy (median time of antiplatelet interruption was 9 days) to 58 patients who had no

interruptions in antiplatelet therapy. Patients taking both aspirin and clopidogrel (n=11) compared to those on other antiplatelet regimens had more post-operative bleeding (p=0.005), more chest tube drainage over a 3-day period (median (range) 1140mL (430–2280 mL) *versus* 690mL (140–2030 mL)), and required more red blood cell transfusions (p=0.003). Changes in haemoglobin were not significantly different between groups. Based on these findings, the authors recommended discontinuing clopidogrel and continuing aspirin alone. Limitations of this study include retrospective design, small sample size and lack of assessment of long-term oncologic outcomes of peri-operative use of antiplatelet agents. Both of these studies recommended discontinuation of dual antiplatelet therapy and continuation of a single agent. Since prior studies have shown that aspirin may not increase the risk of bleeding complications to the extent that clopidogrel does, it may be safest to recommend continuation of aspirin alone in these patients [22].

### Endobronchial ultrasound-guided transbronchial needle aspiration

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive pulmonary procedure used to diagnose pulmonary diseases by enabling highly accurate biopsies of intrathoracic structures during bronchoscopy. STATHER *et al.* [23] reported 12 cases of patients on clopidogrel therapy in whom the risk of stopping therapy before EBUS-TBNA was thought to outweigh the theoretical risk of bleeding. Significant bleeding was defined as blood loss >5mL and/or requiring interruption of the procedure and/or another specific intervention, such as a topical iced saline/epinephrine application. 24 lymph node stations and two lung masses were aspirated. One patient required repeat bronchoscopy after discontinuation of clopidogrel so that transbronchial biopsies could be performed. No significant bleeding was noted in any of the cases at the time of biopsy or ≤4 weeks after the procedure.

### Endoscopic ultrasound

Current guidelines on the use of antiplatelet and anticoagulant agents for patients undergoing endoscopic ultrasound (EUS) [7] recommend no interruption in therapy for patients on clopidogrel, prasugrel or ticagrelor who are undergoing diagnostic EUS. For patients undergoing high-risk procedures, including EUS with fine needle aspiration (FNA) it is recommended to discontinue therapy 5 days prior to the procedure for patients without coronary stents. For high-risk patients such as those with coronary stents, it is recommended to seek cardiologist consultation prior to discontinuing P2Y<sub>12</sub> receptor antagonist antiplatelet therapy. It is not necessary to discontinue aspirin. With regard to oral anticoagulants, patients undergoing diagnostic EUS on warfarin may continue warfarin as long as the INR is within the therapeutic range. For patients on direct anticoagulants such as dabigatran, rivaroxaban, apixaban and edoxaban, it is recommended to omit the dose the day of the procedure. For patients undergoing EUS with FNA it is recommended to stop warfarin 5 days prior to the procedure in low-risk patients and to bridge with low molecular weight heparin in high-risk patients. Direct oral anticoagulants should be held ≥48 h prior to EUS with FNA for patients with normal renal function.

### Bronchoalveolar lavage/endobronchial biopsy/bronchial brushing

British Thoracic Society (BTS) guidelines [8] state that minor bleeding occurs in 0.19% of patients undergoing bronchoscopy and severe bleeding occurs in 0.26% of cases. A prior study showed that clinically significant bleeding occurred in 0.83% of patients, which was increased to 1.9% with biopsy [24]. The guidelines currently recommend holding clopidogrel for 7 days prior to all bronchoscopies, and holding warfarin for 5 days prior. Low-dose aspirin can be continued. Bleed risk should be balanced with the potential benefit from such procedures. Per the BTS guidelines, clopidogrel should be held for 7 days prior to endobronchial biopsy. No guidelines exist regarding antithrombotic management before bronchial brushing specifically, hence we recommend following BTS guidelines on holding the anticoagulation prior to bronchial brushing.

### Transbronchial biopsy

ERNST *et al.* [25] conducted a prospective cohort study of 604 patients who underwent transbronchial lung biopsy over a 13-month period. The clopidogrel group consisted of 30 (5%) patients who had used clopidogrel within 24 h of the bronchoscopy. The control group consisted of the remaining 574 patients who were not using clopidogrel within 24 h of the study. The primary end-point was to determine whether clopidogrel increased risk of bleeding after transbronchial biopsy. Patients were excluded if they had received warfarin or heparin with 2 weeks of the endoscopic procedure or had a platelet count of <80 000 platelets· $\mu\text{L}^{-1}$ . The study was stopped after 6 months due to excessively high rates of bleeding in the clopidogrel group. 88% of patients in the clopidogrel group experienced bleeding. Of these bleeding episodes, 27% were considered minor bleeds, 34% were considered moderate bleeds and 27% were considered major bleeds. Additionally, 100% of patients who received both clopidogrel and aspirin experienced bleeding (50% moderate bleeding and 50% severe bleeding), compared to only 3.4% of control

patients who did not receive antiplatelet therapy ( $p < 0.001$  for all comparisons). Based on these results, the authors concluded that clopidogrel should be stopped 5–7 days before transbronchial biopsy per the manufacturer's recommendations to decrease risk of bleeding. The recommendations from this study are supported in the current BTS guidelines, which recommend discontinuation of clopidogrel therapy 7 days prior to transbronchial biopsy and discontinuation of warfarin 5 days prior to the procedure. For patients on warfarin, INR should be checked prior to the procedure to ensure it is  $< 1.5$ . Low-dose aspirin therapy can be continued [8].

### Transthoracic needle aspiration and lung biopsy

PIEPER *et al.* [26] performed a retrospective review of image-guided percutaneous core needle biopsies performed in patients with clopidogrel use within 5 days. They reported total of 63 deep biopsies performed in 63 patients with recent use of clopidogrel. Mean  $\pm$  SD time of clopidogrel abstinence before biopsy was  $2.9 \pm 1.9$  days (median 3 days). Lung biopsy was performed in 12 (19%) out of 63 patients. Biopsy was performed using 19-gauge introducer and a 20-gauge Bard biopsy needle (Bard Biopsy Systems, Tempe, AZ, USA). Nine patients underwent computed tomography-guided biopsy and three patients underwent ultrasound-guided biopsy. Only one patient out of 12 was reported to have clinically significant bleeding, after injury to an intercostal artery during lung biopsy (computed tomography-guided), which was successfully treated with coil embolisation.

### Rigid bronchoscopy/airway stents

Despite exhaustive literature review, no studies were found addressing these procedures, probably because they, like rigid bronchoscopy and laser therapies, are used to diagnose and treat massive haemoptysis. Other indications for rigid bronchoscopy includes foreign body retrieval, dilation of airway strictures, relief of airway obstruction, insertion of stents, laser therapy or other mechanical tumour ablation. American College of Chest Physicians guidelines [4] describe coagulopathy as a contraindication to the procedure. Many of the interventional pulmonary procedures are similar in nature to advanced gastroenterology procedures. Guidelines published by the British Society of Gastroenterology [27] on management of antithrombotic therapy in patients undergoing endoscopic procedures recommend that low-risk diagnostic procedures such as oesophagogastroduodenoscopy can be undertaken on warfarin and clopidogrel, while high-risk procedures such as biopsy and dilatation of strictures should be performed after normalising coagulopathy.

### Endoscopic lung volume reduction

Lung volume reduction coil treatment is a minimally invasive procedure designed to reduce hyperinflation and improve elastic recoil in patients with severe emphysema. A recent multicentre study [28] published on coil treatment for lung volume reduction found that this strategy led to improved clinical outcomes that were sustained for  $\leq 1$  year; however, this study excluded patients who were on antiplatelet or anticoagulant therapy at the time of the procedure. Therefore, erring on the side of caution for these patients is advised.

### Bronchial thermoplasty

Bronchial thermoplasty is a procedure used to reduce the mass of airway smooth muscle and reduce the incidence of bronchoconstriction. The Asthma Intervention Research (AIR) Trial Study group [29] has conducted two studies assessing bronchial thermoplasty for asthma control, which have shown improved clinical outcomes for up to 5 years post-procedure [30]. While neither of these studies specifically addressed the use of antiplatelet or anticoagulant therapy, the manufacturer currently recommends withholding antiplatelet and anticoagulant therapy prior to the procedure, as with other bronchoscopic procedures.

### Conclusion

Although available studies surrounding the use of antiplatelet and anticoagulant therapy in patients undergoing pulmonary procedures are small in size, the findings suggest that use of these agents does not significantly increase the risk of major bleeding, with the exception of transbronchial biopsy and patients on dual antiplatelet therapy with aspirin and clopidogrel undergoing video-assisted thoracic surgery; however, larger studies are needed to confirm whether these practices are safe. Additionally, current studies have yet to identify whether these procedures can safely be performed in patients on other antiplatelet agents such as ticagrelor and prasugrel or direct oral anticoagulants such as dabigatran, apixaban, rivaroxaban or edoxaban. Until further studies are available, clinicians should be advised to err on the side of caution with regard to performing interventional pulmonology procedures. Continuation of aspirin alone is generally accepted for patients undergoing interventional pulmonology procedures; however, in the absence of larger studies, our recommendation would be to discontinue P2Y<sub>12</sub> ADP

receptor inhibitors including clopidogrel, prasugrel and ticagrelor 5–7 days prior to the procedure. In addition, we recommend discontinuing warfarin 5 days prior to the procedure and monitoring the INR to ensure that it has normalised. In the event that urgent reversal is needed, we recommend normalising the coagulopathy with use of reversal agents [31–35] if clinically possible before the procedure. However, clinical discretion, urgency of the procedure and benefit *versus* risk should be taken into account before the decision is made to proceed with or forgo these procedures.

### Acknowledgements

Author contributions were as follows. Vikas Pathak: conception and design, data accumulation and manuscript preparation; J. Erin Allender: manuscript preparation; Mollie W. Grant: data accumulation and manuscript preparation.

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