

# Tranexamic acid versus adrenaline for controlling iatrogenic bleeding during flexible bronchoscopy (TAVA): a double blind, randomized control trial

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## Original Research

# Tranexamic acid versus adrenaline for controlling iatrogenic bleeding during flexible bronchoscopy (TAVA): a double blind, randomized control trial

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Short Title: Tranexamic acid versus adrenaline in bronchoscopy (TAVA)

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## Abstract

Background: The most commonly used topical haemostatic agents during flexible bronchoscopy (FB) are cold saline and adrenaline. Data on usage of other agents such as tranexamic acid (TXA) for this purpose are limited.

Research question: is TXA effective and safe in controlling iatrogenic bleeding during FB compared to adrenaline?

Study design and methods: we conducted a cluster-randomized, double blind, single centre trial in a tertiary teaching hospital. Following haemostasis failure after 3 applications of cold saline (4°C, 5ml), patients were randomized to receive up to 3 applications of TXA (100mg, 2ml) or adrenaline (0.2mg, 2ml). If bleeding persisted, crossover was allowed (for up to 3 further applications) before proceeding with other interventions. Bleeding severity was graded by the bronchoscopist using a visual analogue scale (VAS; 1 - very mild, 10 - severe).

Results: During the study period 2033 FB were performed and 130 patients were successfully randomized to adrenaline (N=65) or TXA (N=65), while 12 had to be excluded for protocol violations (2 from the adrenaline and 10 from TXA arm). There were no differences in the bleeding control rate - bleeding was stopped in 83.1% (54/65) of patients in both groups (p=1). The severity of bleeding and number of applications needed for bleeding control (N) were similar in both groups (adrenaline mean VAS= 4.9±1.3, N=1.8±0.8; TXA mean VAS=5.3±1.4, N=1.8±0.8). Both adrenaline and TXA were more successful in controlling moderate than severe bleeding (p=0.008 and p=0.012, respectively), and required more applications for severe bleeding control (p=0.006 and p=0.002, respectively). We observed no drug related adverse events in both groups.

Interpretation: We found no significant difference between adrenaline and TXA for controlling iatrogenic endobronchial bleeding, thus adding to the body of evidence that TXA can be used safely and effectively during FB.

Clinical Trial Registration: ClinicalTrials.gov; No.: NCT04771923; URL: www.clinicaltrials.gov


Keywords: tranexamic acid, adrenaline, endobronchial bleeding, bronchoscopy

## Abbreviations

CTCAE – Common Terminology Criteria for Adverse Events

DAPT – dual antiplatelet therapy

DOAC – direct oral anticoagulant

FB – flexible bronchoscopy

IP – interventional pulmonology

LMWH – low molecular weight heparin

SAE – serious adverse event

TXA – tranexamic acid

VAS – visual analogue scale

Flexible bronchoscopy (FB) is one of the most fundamental diagnostic procedures for airway examination and sampling. The procedure is safe with a reported mortality between 0 and 0.1%, and a complication rate ranging from <0.1 to 11%.[1–3] The most common complication of diagnostic FB is bleeding that can occur in 0.26 – 5% of cases, mostly depending on the procedures performed and patient characteristics.[4] The most widely used topical haemostatic agents for bleeding during diagnostic FB are cold saline and adrenaline. The proposed mechanism of action of both drugs is vasoconstriction of pulmonary vessels with consequent blood flow reduction and haemostasis promotion.[5]

Tranexamic acid (TXA) is an antifibrinolytic drug that competitively inhibits the activation of plasminogen. Both parenteral and topical TXA are widely used for haemostasis in trauma and various surgical settings after several randomized controlled trials confirmed their efficacy and safety.[6,7] A large retrospective Japanese nationwide study concluded that intravenous TXA may reduce the mortality, length of hospital stay and healthcare costs of patients with haemoptysis.[8] Furthermore, several small prospective studies investigated the use of TXA in airway bleeding with mostly positive results. TXA was used in a wide range of different forms, from prophylactic intratumoral injection, application via FB for airway bleeding after topical cold saline and adrenaline failure to TXA inhalations for haemoptysis.[9–12] To our knowledge, only one small randomized trial evaluated the role of TXA for bleeding control during FB. A total of 50 patients with haemoptysis or iatrogenic bleeding during diagnostic FB were randomized to either adrenaline or TXA after haemostasis failure of cold saline lavage. Although there was no significant difference in time to bleeding control between the two groups, only 1 patients in the TXA group versus 8 patients in the adrenaline group required additional medication for bleeding control.[13]

Based on these data we hypothesized that topical TXA is a safe and effective therapy for bleeding management during diagnostic FB. The aim of our study was to evaluate the effectiveness of topical TXA in iatrogenic airway bleeding and compare it to topical adrenaline in a prospective, double blind, cluster randomized controlled trial.

## Study Design and Methods

We conducted a pragmatic, cluster-randomized, double blind, single centre trial in a tertiary teaching hospital during a one-year period from February 22nd 2021 to February 4th 2022. The trial was approved by the University Hospital Centre Zagreb institutional ethical review board (approval number: 8.1-21/20-2; 02/21AG) and registered with ClinicalTrials.gov (NCT04771923) prior to trial start. There were no changes to trial protocol, material and methods after trial commencement.

Participants

All patients requiring diagnostic FB during the study period were assessed for eligibility and signed informed consent prior to the start of diagnostic FB. Patients requiring mediastinal staging with convex probe EBUS or peripheral bronchoscopy with radial probe EBUS were also screened and included in the study. Exclusion criteria included all relevant relative and absolute contraindications for FB and topical use of adrenaline: coagulopathy (PV INR >1.3), thrombocytopenia ($<50x10^9$) or anaemia (Hgb <80 g/L), ongoing treatment with direct oral anticoagulant agents (DOAC), low molecular weight heparin (LMWH) or dual antiplatelet therapy (DAPT) - unless appropriately discontinued before the scheduled bronchoscopy, thrombophilia, history of pulmonary embolism or deep vein thrombosis, uncontrolled coronary heart disease, uncontrolled cerebrovascular disease, history of tachyarrhythmia, uncontrolled pulmonary hypertension, hemodynamic instability and severe hypoxemia (PaO2 <60 mmHg and SaO2 <90% with a FiO2 of 60% or higher). DOAC therapy was discontinued 48 hours, LMWH 24 hours, and DAPT at least 5 days prior to bronchoscopy.

Interventions

Patients with bleeding during FB that was not successfully controlled after 3 applications of 5ml of cold (4°C) saline were randomized to receive up to 3 applications of TXA (2ml of 50mg/ml solution; a total of 100mg of TXA per application) or adrenaline (2 ml of 1:10000 solution; a total of 0.2mg of adrenaline per application). The adrenaline concentration and dose was determined as per usual institution protocol since there is no official consensus between different guidelines and publications on the optimal dose of adrenaline.[14] The drug solutions were prepared and prefilled into identical 2ml syringes and labelled “1” and “2”, depending on the weekly randomization. Each drug application was at least 60 seconds apart to allow time for visual assessment of clot formation and to standardize workflow between different bronchoscopists. If bleeding persisted, crossover was allowed (for up to 3 further applications, 60 seconds apart) before proceeding with other interventions, thus ensuring that all patients receive adrenaline as the current standard of care at our

institution. At the end of each procedure, the bronchoscopist noted the number of drug applications and severity of bleeding in the written bronchoscopy report.

Outcomes

The primary outcome was proportion of patients with successfully controlled bleeding in each arm. Bleeding control was assessed by the bronchoscopist by visual confirmation of clot formation. Secondary outcomes included the mean number of TXA or adrenaline applications necessary to control bleeding, number of recurrent bleeding episodes in each group, proportion of successfully controlled bleeding in relation to the severity of bleeding, indications for diagnostic FB, sampling methods during FB and the number of adverse events in each group. The bleeding severity was graded by the bronchoscopist at the end of the procedure using a visual analogue scale (VAS; 1 - very mild, 10 – very severe).

Sample size

In a previously published randomized trial comparing endobronchial TXA to adrenaline there was a 96% (24/25) bleeding control rate in the TXA group and 68% (17/25) in the adrenaline group. [13] Based on these data a group sample size of 40 is required to detect this difference with 90% power and a significance level of 5%. However, given our previous clinical experience with adrenaline, we hypothesized that the bleeding control rate of adrenaline is at least 75% thus requiring a group sample size of 61 to detect the difference with the same power and significance level.

Randomization

To minimize workflow interruption, instead of randomizing each patient separately, we randomized patients in weekly clusters. Each week during the study period was randomly assigned to TXA or adrenaline as the first medication to be used during that week. All patients with haemostasis failure after 3 applications of cold saline during the given week received the same first medication and the same second medication in case of haemostasis failure. The random allocation sequence was generated and supervised by a medical doctor in our institution who has no contact with the bronchoscopy suite and communicated to the supervising nurse. The supervising nurse prepared the drug solutions during the whole week and prefilled identical 2ml syringes with adrenaline and TXA labelling them with the number “1” or “2”. If the week was randomly assigned to TXA, syringes containing TXA were labelled “1” and those containing adrenaline were labelled “2”, and vice versa if the week was randomly assigned to adrenaline. When bleeding requiring drug application occurred, the bronchoscopist ordered drug “1” up to 3 times and, if necessary, drug “2” for up to 3 further applications, as described previously.

Blinding

The operating bronchoscopists, bronchoscopy nurses, patients and the staff collecting data and assessing outcomes were blinded. The allocation was available only to the supervising medical doctor and nurse who were not involved in performing the bronchoscopies or patient care in any way. The treating bronchoscopist could break blinding and continue haemostasis as per usual institutional protocol at his own discretion if concerned about patient safety during the procedure and those patients were excluded from the analysis.

Statistical methods

Microsoft Excel (Microsoft, Redmond, WA, USA) was used to tabulate data and calculate frequencies and percentages. Medcalc (v20.027, MedCalc Software, Ostend, Belgium) was used to calculate summary statistics as well to perform Chi square, t-test and Mann-Whitney tests as appropriate. P value <0.05 was considered statistically significant.

## Results

A total of 2033 FB were performed during the study period between February 22nd 2021 and February 4th 2022, with 575 bleeding episodes with a mean VAS of 3.6±1.3. Bleeding was successfully stopped with cold saline in 432 patients (75.1%). One patient refused further treatment and was excluded while the remaining 142 patients were randomized to either TXA or adrenaline (75 and 67 patients, respectively). Final analysis was performed in 130 patients - 11 patients were excluded from the final analysis due to protocol violation and 1 was unblinded during the procedure by the operating bronchoscopist due to the severity of bleeding (shown in Fig.1). Patient, sampling and operator characteristics were similar for both groups, as shown in Table 1.

There was no difference in the primary outcome between tranexamic acid and adrenaline – bleeding was successfully stopped in 54/65 (83.1%) of patients in both groups. Both drugs stopped the bleeding after an average 1.8±0.8 applications (p=1.00). There was a non-significant difference in the number of applications needed after crossover - 2.00±0.8 applications of TXA were needed to control the bleeding after adrenaline failure, and 2.2±0.98 applications of adrenaline were needed to control the bleeding after TXA failure (p=0.57). Out of the overall 575 bleeding episodes, 367 (63.8%) were scored as mild (VAS 1-3), 184 (32.0%) moderate (VAS 4-6) and 24 (4.2%) as severe (VAS 7+). The severity of bleeding was similar in both finally examined groups (N=130) – mean VAS was 4.94±1.31 in the adrenaline group and 5.25±1.44 in the TXA group. However, there were more severe bleeding episodes in the TXA group (12/65; 18.5%) then in the adrenaline group (5/65; 7.7%, p= 0.069). There was no significant difference in the bleeding control rate between adrenaline and TXA in patients with moderate (VAS 4-6; p=0.75) and severe (VAS 7+; p=0.50) bleeding. Both drugs were significantly more successful in controlling moderate bleeding than severe bleeding and required more applications for severe bleeding control (shown in Fig. 2). Overall, haemostasis was successfully achieved with cold saline in 367/367 (100%) of patients with mild bleeding (VAS 1-3), 62/184 (33.7%) of patients with moderate bleeding (VAS 4-6) and 3/24 (12.5%) of patients with severe bleeding (VAS 7+) (p<0.0001). When examining the finally included bleeding episodes (N=130), more experienced interventional pulmonologists gave lower VAS bleeding scores compared to less experienced general pulmonologists (p=0.0025). The mean difference, however, was only 0,6 points of the VAS scale (95% CI 0,13 to 1,08) which is most likely clinically irrelevant.

A total of 9 serious adverse events (SAE) occurred during the study period on the 2033 FB performed. Patients randomized to adrenaline had a total of 3 SAE: the first patient developed acute respiratory failure, the second experienced a transitory ischemic attack while the third patient had recurrent bleeding after early termination of the procedure on patient request. Patients randomized to TXA

had 2 SAE – both required hospitalization due to recurrent bleeding but were excluded from the analysis due to study protocol violation. Other SAE that occurred during the study period were one episode of new onset atrial fibrillation, one respiratory arrest during FB with successful resuscitation and one episode of recurrent bleeding after initial successful haemostasis with 2 cold saline applications. Only one patient required ICU admission due to massive bleeding following renal cell carcinoma endobronchial metastasis biopsy, but was not included in the study at the operators discretion.

## Discussion

We found no significant difference between TXA and adrenaline, the currently most widely used drug for controlling bleeding during FB, in this randomized clinical trial. This finding is in concurrence with previous studies, thus further strengthening the evidence base indicating that TXA could be a valid therapeutic option in bleeding control during FB.[12,13] In addition, there were no significant differences between the drugs in the secondary outcomes including the number of applications needed for bleeding control and severity of bleeding.

FB is one of the most commonly used diagnostic procedures for airway examination and sampling. The procedure is safe, with a low complication and morality rate. Endobronchial bleeding is one of the most common complications of FB. Although most bleeding episodes during FB are mild and self-limiting, serious or fatal bleeding can occur even in the absence of obvious precipitating factors.[15,16] We recorded a total of 575 bleeding episodes during the 2033 FB performed, most of which were classified as mild (367/575, 63.8%) and moderate (184/575, 32.0%) with a mean VAS of 3.6±1.3. Out of the 2033 patients, 142 (6.98%) required at least one drug application for bleeding control during FB and only 20 (0.98%) experienced severe (VAS 7+) bleeding. No deaths occurred during the study period, 4 patients (0.19%) required hospitalization for recurrent bleeding and only 1 patient (0.05%) experienced massive bleeding requiring ICU admission. The majority of moderate and severe bleeding occurred after biopsies of visible endobronchial lesions, followed by transbronchial biopsies, both of which are known to be most associated with clinically significant bleeding. While the incidence of severe bleeding was similar to the incidence reported in previous studies [17–19], we observed a higher incidence of mild and moderate bleeding in our cohort. This could be explained by several factors, including patient, procedure and operator characteristics and bleeding definitions, which are not standardized in the literature.[20] A standardized bleeding scale was recently proposed to define bleeding severity after transbronchial lung biopsy by grading the required response - the Nashville Bleeding Scale. Using this scale the vast majority of our randomized patients would be classified as grade 2 bleeding.[20] Similarly, the Common Terminology Criteria for Adverse Events (CTCAE) that was used to assess bleeding in the NAVIGATE study, is also based on the intervention needed to control the bleeding.[19] Furthermore, despite promising attempts, no methods to objectively quantify bleeding are widely used and definitions of “massive” bleeding vary in the literature.[5,21] Thus, we decided to use a simple VAS scale to assess the severity of bleeding from minor (1) to very severe (10). Although subjective, similar subjective assessments of bleeding were used in previous studies and were adapted by the BTS guidelines for diagnostic flexible bronchoscopy.[22,23] As expected, we found that more experienced interventional pulmonologists (IP)

graded bleeding lower than general pulmonologists (p=0.0025). Despite this, the mean VAS, VAS distribution and number of procedures performed by IP and non-IP were similar in both groups, allowing us to conclude that there was no significant bias due to perceived bleeding severity. The groups were also well balanced regarding other important factors such as procedure type, medication, platelet counts and coagulation parameters.

Despite the fact that bleeding is one of the most common complications of FB, there is a lack of strong recommendations from guidelines on bleeding management. There is a narrow pallet of topical medications used in everyday practice with missing evidence from high quality trials supporting their use [22]. The most used substances are cold saline and adrenaline, but despite their widespread use in everyday clinical practice, there is no standardization of doses and dilutions used during FB. The amount of cold saline recommended by the literature ranges from large volume iced saline lavage using 50ml aliquots, with an average volume up to 500ml in some series [24], to small aliquots of 5-10ml.[22] In our trial, we used 5ml aliquots as per usual institutional protocol. Although topical therapies are usually considered similar in potency, particularly when grading bleeding [20], we observed a significant drop in cold saline efficacy with increasing bleeding severity. TXA and adrenaline successfully controlled most bleeding that could not be stopped with cold saline. Additionally, despite reports of successful control of massive bleeding with cold saline[25], only 3/20 episodes of severe bleeding were controlled by cold saline in our study. This difference could be explained by the smaller volume of saline used in our protocol.

Similarly, there is a variety of doses and concentrations of adrenaline recommended by the literature (from 0.5ml up to 20ml of 1:20,000 solution) with no high quality data favouring one or the other, or supporting the use of adrenaline for endobronchial bleeding in general.[14] In this study, we used 2ml aliquots of 1:10:000 adrenaline as per usual institutional protocol. Adrenaline was effective in bleeding control, stopping 83.1% of bleeding successfully. This success rate was better than we expected based on the study by Fekri et al which reported a success rate of 68%, a difference that could be explained by different study design and sample size.[13] Adrenaline has the potential of causing arrhythmia, and should be used with caution in elderly patients, patients with known heart disease, carcinoid tumours or a history of arrhythmias. Several existing case reports raise the concern of the safety of adrenaline, even in previously healthy adults with no known risk factors for malignant arrhythmia.[14,26] We observed no SAE that could be definitely associated with adrenaline, and no malignant arrhythmias during the study period. However, all patients with serious cardiovascular comorbidities and risk factors for arrhythmia were excluded from our study.

After the affirmation of TXA in different trauma and surgical indications, several small trials explored the role of tranexamic acid in the setting of endobronchial bleeding management. Marquez et al conducted a pilot study that included patients with both non-iatrogenic and iatrogenic bleeding. TXA was applied after cold saline and adrenaline failure. All patients in the iatrogenic group (N=20) achieved haemostasis.[12] In the study by Fekri et al, TXA achieved an equally impressive success rate, stopping 24 out of 25 (96%) of bleeding episodes[13] We observed a 83.1% total success rate of TXA in our study, and a 100% (11/11) success rate when used after crossover. Although our total success rate was lower, we observed an equally impressive success rate after adrenaline and cold saline failure. This observation is limited by the very small number of patients but could be a consequence of a synergistic effect of adrenaline and TXA which have different mechanisms of action. Importantly, in addition to design differences between our and the above-mentioned studies, we used a different dose and dilution of TXA which could have also contributed to the observed difference in efficacy. The most important concern of TXA use, which was previously emphasized in the literature, was the theoretical increased risk of thrombotic complications.[4] We observed no thrombotic events related to the application of TXA in our study.

Although many potential sources of bias are eliminated from our trial due to the double blind, randomized control trial design, it has several limitations. Firstly, the single centre design and the usage of doses and concentrations of the investigated drugs as per usual institutional protocol limit the generalizability of our findings. Secondly, we decided to exclude non-iatrogenic bleeding due to concerns for patient safety and inability to provide informed consent for trial participation in emergency situations, thus excluding an important patient group from analysis. Thirdly, although a placebo-controlled trial would better determine the efficacy and safety of topical TXA in bleeding during FB, we used adrenaline as a comparator because it is the standard of care at our institution and not providing it could negatively impact patient safety, despite the lack of high-quality evidence supporting its use. Furthermore, we consider using a placebo for a potentially life threatening complication unethical.

## Interpretation

We found no significant difference between adrenaline and TXA for controlling iatrogenic endobronchial bleeding. Our results add to the body of evidence that topical TXA can be used safely and effectively during FB, providing an important additional therapeutic option, especially for situations when adrenaline raises safety concerns.

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### Guarantor statement

SB and GG take full responsibility for the content of the manuscript, including the data and analysis.

### Author Contributions

SB and GG conceptualized and designed the study, collected and curated the data, drafted and revised the manuscript and provided final approval of the version to be published. IS, FDž, MJM, DB, MK, FP, DS and MS made substantial contributions to the collection and interpretation of data, critical revision of the manuscript and provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolve

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None declared.

### Other contributions

We are grateful for the contribution by the hospital medical staff performing the procedures as well as the patients agreeing to participate in the study.

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## Take-Home Point

Study Question: is tranexamic acid effective and safe in controlling iatrogenic bleeding during flexible bronchoscopy compared to adrenaline?

Results: There were no differences in the bleeding control rate between tranexamic acid and adrenaline - bleeding was stopped in 83.1% (54/65) of patients in both groups (p=1).

Interpretation: We found no significant difference between adrenaline and tranexamic acid for controlling iatrogenic bleeding, thus adding to the body of evidence that tranexamic acid can be used safely and effectively during flexible bronchoscopy.

## Tables

| Patient characteristics | Adrenaline (N=65) | Tranexamic acid (N=65) | p value[a] |
|---|---|---|---|
| Age, Median (IQR) | 68 (63-77) | 67 (56-75) | 0.09 |
| Gender - female, N (%) | 24 (36.9) | 23 (35.4) | 0.86 |
| male | 41 (63.1) | 42 (64.6) | |
| BMI (kg/m2), mean±SD | 25.7±5.3 | 26.7±4.8 | 0.39 |
| **Therapy N (%)** | | | |
| DOAC | 8 (12.3) | 3 (4.6) | 0.12 |
| LMWH | 3 (4.6) | 1 (1.5) | 0.31 |
| Aspirin | 12 (18.5) | 12 (18.5) | 0.52 |
| DAPT | 1 (1.5) | 2 (3) | 0.56 |
| **Lab values, mean±SD or median (IQR)** | | | |
| Hb (g/L) | 130.3±22.4 | 129.4±16.8 | 0.80 |
| Platelet count (x10^9/L) | 299.7±107.9 | 308.6±123.4 | 0.95 |
| INR | 1.02 (0,97-1,05) | 1.01 (0.99-1.05) | 0.92 |
| APTT (s) | 23.9 (22.2-26) | 24.2 (22.07-26.73) | 0.74 |
| Fibrinogen (g/L) | 4.78±1.43 | 4.92±1.93 | 0.79 |
| BUN (mmol/L) | 5.9 (5.1-7.7) | 5 (4.05-7.45) | 0.17 |
| Creatinine (µmol/L) | 70.5 (60-85) | 75 (56-89.5) | 0.68 |
| **Operator characteristics and procedures, N (%)** | | | |
| Operator experience – IP | 28 (43) | 30 (46.2) | 0.73 |
| - non IP | 37 (56.9) | 35 (53.8) | |
| EBB | 40 (61.5) | 37 (56.9) | 0.59 |
| TBB | 12 (18.5) | 10 (15.4) | 0.64 |
| TBNA | 22 (33.8) | 21 (32.3) | 0.85 |
| Brush | 32 (49.2) | 29 (44.6) | 0.60 |
| **Indication, N (%)** | | | |
| Lung cancer | 59 (90.8) | 57 (87.7) | 0.42 |
| ILD | 5 (7.7) | 8 (12.3) | |
| Other | 1 (1.5) | 0 (0) | |
| **Final diagnosis N (%)** | | | |
| NSCLC - adenocarcinoma | 22 (33.8) | 19 (29.2) | 0.34 |
| NSCLC - suqmous cell carcinoma | 13 (20) | 12 (18.5) | |
| SCLC | 4 (6.2) | 6 (9.2) | |
| Pulmonary metastasis | 1 (1.5) | 2 (3) | |
| Other | 4 (6.2) | 12 (18.5) | |
| Overall diagnostic yield (%) | 69.2 | 78.5 | 0.23 |

[a] t-test, Mann Whitney test or Chi square test as appropriate

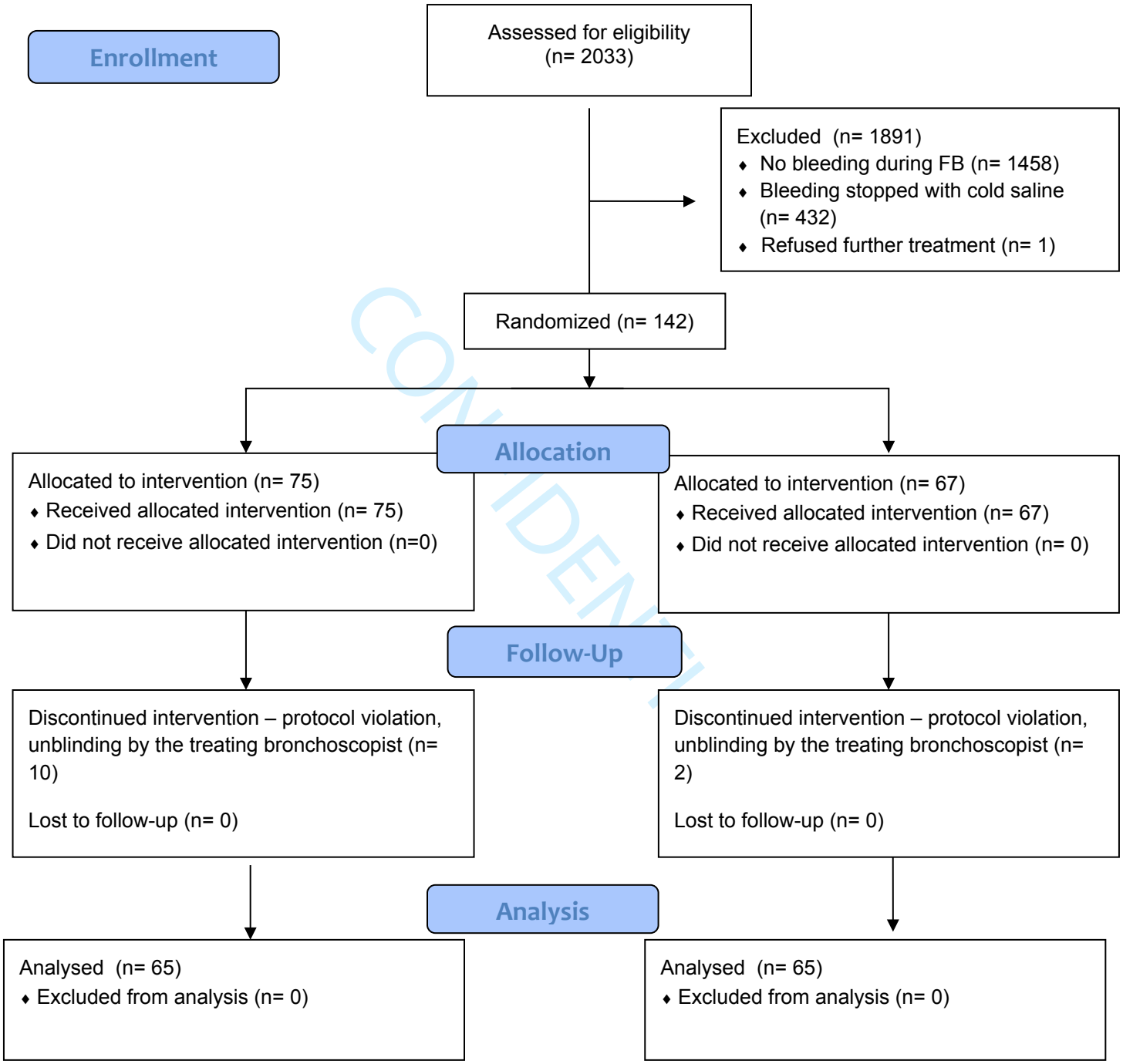
Table 1. Patient, sampling and operator characteristics. BMI= body mass index, DOAC = direct oral anticoagulant, LMWH = low molecular weight heparin, DAPT = dual antiplatelet therapy, Hb = hemoglobin, INR = international normalized ratio, APTT = activated partial thromboplastin clotting time, BUN = blood urea nitrogen, IP = interventional pulmonologist, EBB = endobronchial biopsy, TBB = transbronchial biopsy, TBNA = transbronchial needle aspiration, ILD = interstitial lung disease, NSCLC = non small cell lung cancer, SCLC= small cell lung cancer

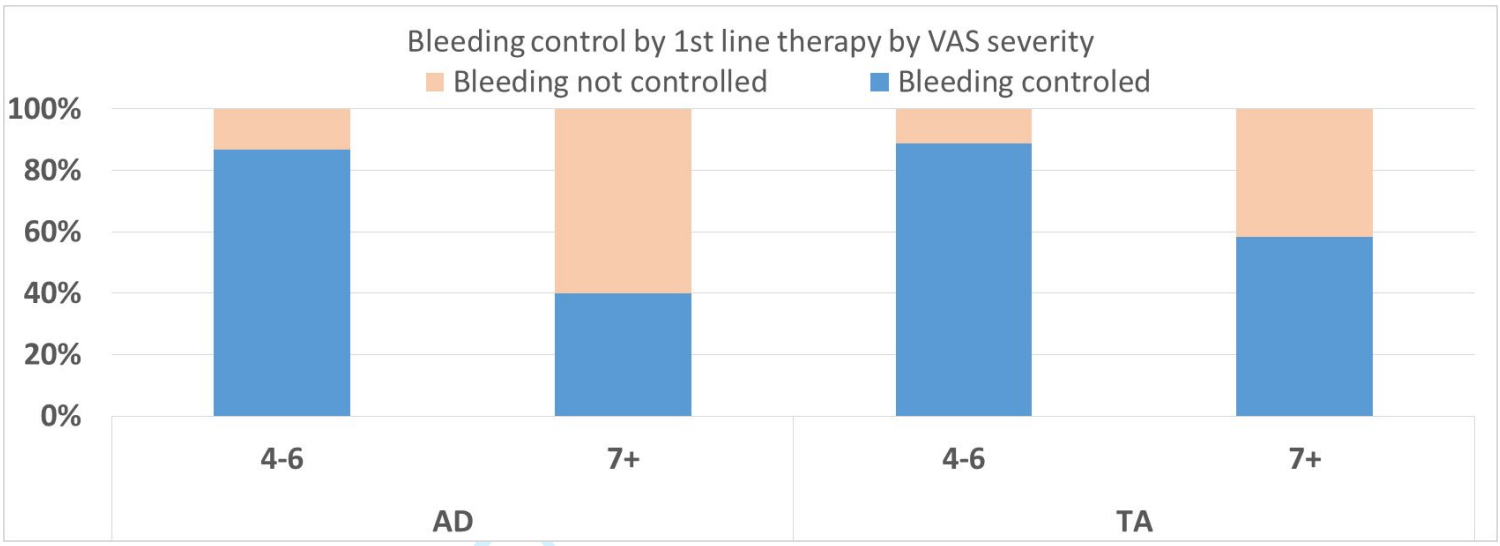
## Figure Legends

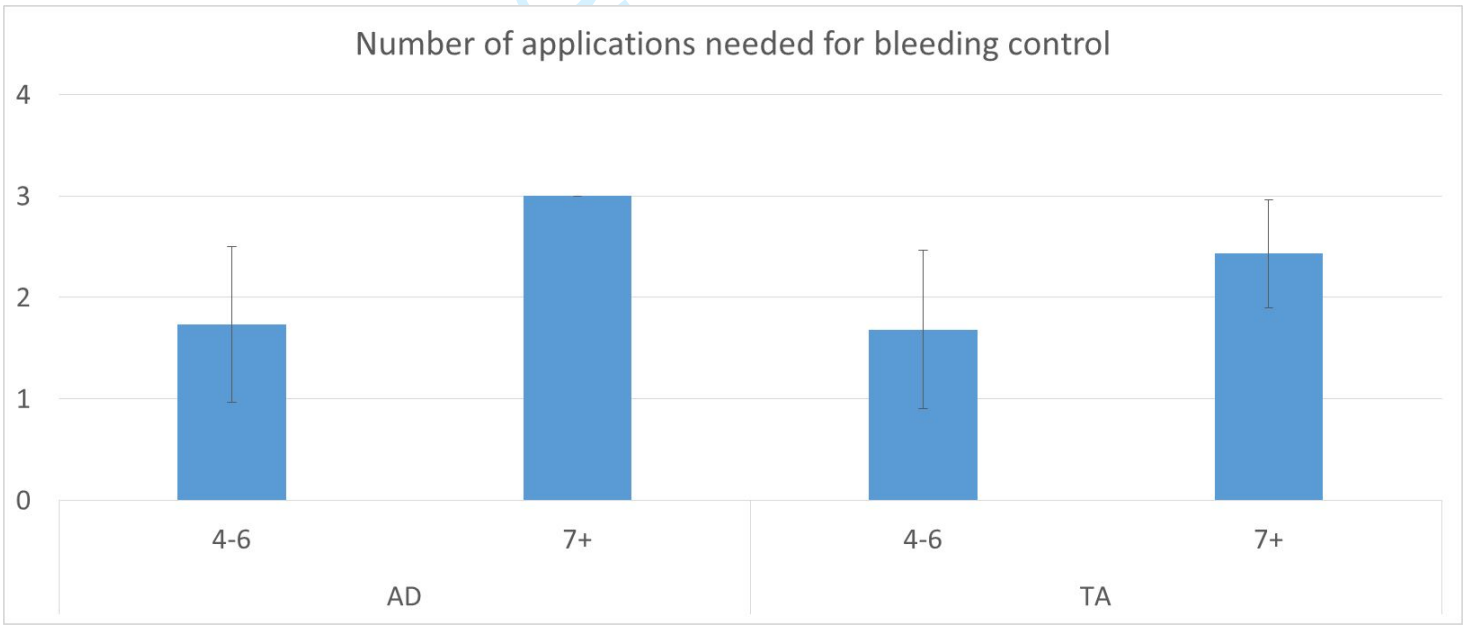
Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. FB = flexible bronchoscopy

Figure 2. Both adrenaline (AD) and tranexamic acid (TXA) were significantly more successful in controlling moderate bleeding (p=0.008 and p=0.012, respectively) and required significantly more drug applications for controlling severe bleeding (p=0.006 and p=0.002, respectively).

## CONSORT 2010 Flow Diagram




Bleeding control by 1st line therapy by VAS severity
Bleeding not controlled
Bleeding controled
100%
80%
60%
40%
20%
0%
4-6
7+
4-6
7+
AD
TA


Number of applications needed for bleeding control
4
3
2
1
0
4-6
7+
4-6
7+
AD
TA