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Antiplatelet Drugs and Risk of Bleeding After Bedside Pleural Procedures

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1 **Title:** Antiplatelet drugs and risk of bleeding after bedside pleural procedures: a national multicenter cohort
2 study

3
4 **Short title:** Antiplatelet drugs and bleeding after pleural procedures

5
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10

1 **Abstract**

2 **Background.** The decision making on antiplatelet drug withdrawal or continuation before performing a
3 pleural procedure is based on the balance between the risk of bleeding associated with the antiplatelet
4 therapy and the risk of arterial thrombosis due to its interruption. Knowledge on antiplatelet therapy-
5 associated risk of bleeding after pleural procedure is lacking.

6 **Research Question.** Is the risk of bleeding associated with antiplatelet drugs increased in patients
7 undergoing pleural procedures?

8 **Study Design and Methods.** We conducted a French multicenter cohort study in 19 centers. The main
9 outcome was the occurrence of bleeding, defined as hematoma, hemoptysis or hemothorax, during the 24
10 hours following the pleural procedure. Serious bleedings were defined as bleeding requiring blood
11 transfusion, respiratory support, endotracheal intubation, embolization, surgery or death.

12 **Results.** A total of 1124 patients was included (66% of men, median age of 62.6 ± 27.7 years), of whom 182
13 were on antiplatelet therapy and 942 were not. Fifteen patients experienced a bleeding event including
14 eight serious bleedings. The 24-hour incidence of bleeding was 3.23% (95% CI, 1.08 to 5.91) in the
15 antiplatelet group and 0.96% (95% CI, 0.43 to 1.60) in the control group. The occurrence of bleeding events
16 was significantly associated with antiplatelet therapy in univariate (OR, 3.44; 95% CI, 1.14 to 9.66; $p=0.021$)
17 and multivariate analysis (OR, 4.13; 95% CI, 1.01 to 17.03; $p=0.044$) after adjusting for demographic data
18 and the main risks factors for bleeding. Likewise, antiplatelet therapy was significantly associated with
19 serious bleeding in univariate (OR, 8.61; 95% CI, 2.09 to 42.3; $p=0.003$) and multivariate analysis (OR, 7.27;
20 95% CI, 1.18 to 56.1; $p=0.032$) after adjusting for the number of risk factors for bleeding.

21 **Interpretation.** Antiplatelet therapy was associated with an increased risk of post-pleural procedure
22 bleeding and serious bleeding. Future guidelines should take into account these results for patient safety.

23

24 **Key words:** antiplatelet drug; bleeding risk; pleural procedure; thoracentesis; chest tube insertion; closed
25 pleural biopsy.

1 **Introduction**

2 Pleural disorders affect over 3000 people per million population each year in developed countries (1),
3 caused by a wide range of pathologies, in particular congestive heart failure, infection, and cancer. Pleural
4 procedures (thoracentesis, closed pleural biopsy, or chest tube insertion) are key to diagnosis (2) and may
5 also be the main therapeutic approach in conditions such as pneumothorax (3). All of these procedures
6 entail a risk of bleeding, which is infrequent but may be life-threatening (4). Patients taking concomitant
7 antiplatelet drugs would usually be considered at higher risk for this complication, raising the question
8 antiplatelet therapy discontinuation before pleural procedures. However, withdrawing antiplatelet drugs
9 may have adverse consequences in patients with coronary (5) or cerebral (6) vascular diseases at high risk
10 of thrombosis. Long-term antiplatelet therapy is now commonly prescribed and the risk of thrombosis after
11 their withdrawal well known. In contrast, data on the risk of post-pleural procedure bleeding associated
12 with antiplatelet therapy are scant. Previous studies have reported low rates of hemorrhagic complications
13 after pleural procedures in patients receiving antiplatelet therapy. However, they were single-center
14 studies and included few patients (7)(8)(9), in particular the size of study populations was below the
15 number of procedures necessary to observe even one bleeding event after pleural procedures. In other
16 areas, the increased risk of bleeding in patients receiving antiplatelet drugs after chest surgery,
17 bronchoscopy, or interventional pulmonary procedures is well established and has led to guidelines on the
18 management of antiplatelet drugs before procedures (10)(11)(12). In contrast, the current international
19 guidelines for pleural procedures do not address the question of antiplatelet drug management (2)(13). The
20 general guidance on all percutaneous procedures in patients taking antiplatelet drugs noted that its
21 recommendations for pleural procedures were limited due to the weakness of available data (14). In
22 consequence, clinical decision making is heterogeneous (15) and patient safety potentially compromised.
23 The current study was conceived to assess the risk of bleeding and serious bleeding associated with
24 antiplatelet drugs in patients undergoing pleural procedures.

1 **Methods**

2 **Setting and patients**

3 We conducted a multicenter cohort study involving 19 French centers (eight respiratory care departments
4 and 11 intensive care units in 14 university teaching hospitals and five general hospitals). All patients
5 undergoing bedside thoracentesis, closed pleural biopsy or chest tube insertion from November 2011 to
6 January 2014 were considered for inclusion. We excluded patients aged less than 18, those with
7 hemothorax, recent chest surgery, receiving full anticoagulation or under extracorporeal membrane
8 oxygenation. Participants were considered to be in the exposed (or antiplatelet) group if they were
9 receiving antiplatelet drugs at the time of the procedure and at least five days before the procedure. They
10 were considered to be in the unexposed (or control) group if they had never been under antiplatelet
11 therapy or were free from antiplatelet drugs during at least five days before the pleural procedure (16) (17)
12 (18) (19). To avoid confusion regarding the evaluation of bleeding risk, patients in whom antiplatelet drugs
13 had been interrupted for any reason during the five days preceding the pleural procedure were not
14 included in the study.

15 The study was approved by the Institutional Review Board of the French Language Respiratory Society
16 (Société de Pneumologie de Langue Française, CEPRO 2011-051) and was declared to the National
17 Commission on Informatics and Liberty (CNIL 911367). Study information was included in an information
18 booklet routinely given to all patients prior to thoracentesis, closed pleural biopsy or chest tube insertion
19 during the study period. French legislation on noninterventional studies requires collecting non-opposition
20 of patients but does not require written consent. As such, non-opposition was obtained from each patient
21 included in the study for the use of their deidentified medical records data. Participants did not receive
22 financial compensation.

23 **Outcomes**

24 The main outcome was the occurrence of "bleeding", defined as the occurrence of hematoma, hemoptysis
25 or hemothorax, during the 24 hours following the pleural procedure. The secondary outcome was the
26 occurrence of "serious bleeding" during the 24 hours post pleural procedure, defined as bleeding requiring
27 blood transfusion, respiratory support, endotracheal intubation, embolization or surgery, or when death
28 occurred. In the event of bleeding, the interventions required (follow-up, blood transfusion, respiratory
29 support, endotracheal intubation, embolization or surgery) were recorded, as was the occurrence of death.

30 **Other measurements and risk factor for bleeding**

31 We documented demographic (age, gender, body mass index) and biological data (platelets count,
32 prothrombin time (PT), activated partial thromboplastin time (APTT) ratio, creatinine clearance, measured
33 the day or the day before the procedure), as well as procedure characteristics (operator experience,
34 diameter of pleural device, and radiographic guidance). Radiographic guidance included both
35 ultrasonographic and Computed Tomography (CT) scan guidance, the latter one consisting in marking the
36 puncture site using a felt tip pen during a chest CT scan; then, pleural procedure was performed at bedside

1 without real-time guidance. We determined risk factors for bleeding for each patient. Intrinsic risk factors
2 for bleeding were defined as age > 65 years, platelet count < 100 10⁹/L, PT < 50%, APTT > 1.4, and
3 moderate and severe renal failure (creatinine clearance < 60 and 30 L.min⁻¹ as assessed with Cockcroft-
4 Gault formula (2)(12)(13)). Extrinsic risk factors for bleeding were defined as junior operator (resident or
5 medical student), experience of operator < 50 procedures, no image-guidance for pleural procedure, and
6 pleural device diameter > 14F.

7 **Statistical analysis**

8 Study group characteristics were described using mean ± standard deviation, or median ± interquartile
9 range in case of non-normality, for quantitative variables and number (percentage) for qualitative variables.
10 Comparison between groups was performed using Student's *t*-test, or Wilcoxon tests in case of non-
11 normality, for quantitative variables and Fisher exact tests for qualitative variables. The 24-hour incidence
12 of bleeding (and serious bleeding) was calculated in the whole population, in the exposed to antiplatelet
13 therapies group and in the control group. Because the number of events was low, the 95% confidence
14 intervals (CI) were computed using a bias-corrected accelerated bootstrap method with 10,000 replications
15 (20).

16 To assess the association between bleeding events, as the dependent variable, and antiplatelet drugs as the
17 explanatory variable, we first conducted univariate analyses using univariate logistic regression. The main
18 logistic multivariate model was constructed considering baseline characteristics for adjustment: (i)
19 excluding the collinear covariates (highly associated each other, e.g. pleural procedure and pleural device
20 diameter); (ii) choosing the covariates most associated with the dependent variable in univariate analysis
21 when the quantitative or qualitative covariate was available (e.g. PT); and (iii) assessing the linearity
22 between the dependent variable and quantitative covariates using cubic splines in adjusted generalized
23 additive models. The main model was then adjusted for gender, age, platelet count, PT, APTT ratio,
24 moderate renal failure, department, pleural procedure, operator experience and radiographic guidance.
25 Because the number of events was small relative to the number of covariates, we have taken care to verify
26 the convergence of the model (control of the number of iterations, stability of the coefficients and standard
27 errors during the successive addition of the covariates). Interaction terms between antiplatelet drugs and
28 the covariates were tested one at a time in multivariate logistic models. In addition, we conducted
29 sensitivity analyses: (i) using a backward stepwise selection; and (ii) using the Firth's bias-Reduced
30 penalized-likelihood logistic regression adapted to rare events (21), adjusted for the same covariates that
31 within the main model. Finally, to assess the center effect, we added the center as a random-effect in a
32 univariate generalized linear mixed-effects model; adjustments were not possible because of problems of
33 convergence of the model. Results were expressed as odds ratios (OR) with 95% confidence interval (CI).
34 Given the rarity of the events, the association between serious bleeding events and antiplatelet drugs was
35 study using a univariate logistic regression, and a multivariate analysis only adjusted for the number of total
36 (intrinsic and extrinsic) bleeding risk factors per patient.

- 1 All statistical analyses were performed using R software, version 3.5.2 (22). The threshold for statistical
- 2 significance was 0.05.

1 **Results**

2 **Patients and procedures**

3 The study population consisted of 1124 patients, 737 (66%) men and 387 (34%) women, whose median age
4 was 62.6 ± 27.7 years. Among them, 182 were taking antiplatelet drugs (142 treated by aspirin, 17 by
5 clopidogrel, 22 by aspirin and clopidogrel, and one by aspirin and prasugrel), and 942 were not. Pleural
6 procedures consisted of 377 thoracenteses, 130 closed pleural biopsies and 617 chest tube insertions
7 (including 343 surgical and 270 percutaneous chest tube insertions; four missing values). The procedure
8 was indicated for pleural effusion in 80% and pneumothorax in 20% of the whole population (**Table 1**).
9 Patients taking antiplatelet drugs were more likely to be men (73% vs 64%, $p=0.028$) and older (76% vs 39%
10 over 65 years, $p<0.001$), and to have a higher body mass index (24.4 ± 6.5 vs 22.7 ± 5.7 $\text{kg}\cdot\text{m}^{-2}$, $p<0.001$) and
11 a poorer renal function (50% vs 27% for moderate renal failure, $p<0.001$). They were less likely to have
12 thrombopenia (2% vs 8%, $p=0.004$). Differences in PT and APTT ratio between groups did not reach
13 significance. The indication for pleural effusion was higher in the antiplatelet group (89% vs 78%, $p<0.001$).
14 In the antiplatelet group, the rate of image-guidance was higher (77% vs 68%, $p=0.01$). The rate of image
15 guidance was significantly higher when pleural procedure was performed for pleural effusion than for
16 pneumothorax (82% vs 21%, $p<0.001$). Among the 781 patients having radiologic guidance, 689 were
17 ultrasonographic guidance and 92 were CT scan guidance. We did not observe significant difference
18 between groups for operator experience and pleural device diameter (**Table 1**). The kind of pleural
19 procedure was highly associated with the indication ($p<10^{-9}$) and the pleural device diameter ($p<10^{-9}$).
20 Likewise, the experience of the operator was highly associated with the senior or junior doctor status
21 ($p<10^{-9}$).

22 **Description of bleeding events**

23 Fifteen bleeding events occurred, six in the antiplatelet group and nine in the control group, including nine
24 hemothorax, two hemoptysis, and three hematomas. In one case, the nature of the bleeding event was not
25 documented in the electronic form. Nine events occurred after chest tube insertion (two after surgical and
26 six after percutaneous chest tube insertions ($p=0.15$); one missing value), five after thoracentesis and one
27 after closed pleural biopsy. It means that 1.5% of chest tube insertions, 1.3% of thoracenteses and 0.8% of
28 closed pleural biopsies led to bleeding ($p>0.99$). The 24-hour incidence of bleeding was 1.33% (95% CI, 0.71
29 to 2.05) in the whole population, 3.23% (95% CI, 1.08 to 5.91) in the antiplatelet group and 0.96% (95% CI,
30 0.43 to 1.60) in the control group. In the antiplatelet group, all bleeding events occurred in patients taking
31 aspirin monotherapy.

32 Eight serious bleeding events occurred, five in the antiplatelet group and three in the control group.
33 Overall, 83.3% of bleeding events occurring in patients on antiplatelet therapy were serious vs 33.3% in
34 controls. No death occurred. Five serious bleeding events occurred after chest tube insertion, two after
35 thoracentesis, and one after closed pleural biopsy. In other terms, 0.8% of chest tube insertions, 0.5% of
36 thoracenteses and 0.8% of closed pleural biopsies led to serious bleeding ($p = 0.89$). The 24-hour incidence

1 of serious bleeding was 0.71% (95% CI, 0.27 to 1.25) in the overall study group, 2.69% (95% CI, 0.54 to 5.38)
2 in the antiplatelet group and 0.32% (95% CI, 0 to 0.75) in the control group.

3 **Association between bleeding events and antiplatelet therapy**

4 In univariate analysis, the occurrence of bleeding events was significantly associated with antiplatelet
5 therapy (OR, 3.44; 95% CI, 1.14 to 9.66; p=0.021). It was also significantly associated with platelet count
6 (OR, 0.44; 95% CI, 0.25 to 0.73 per 100 G.L-1 increase; p=0.002), PT level (OR, 0.76; 95% CI, 0.61 to 0.97 per
7 10% increase; p=0.020), APTT ratio (OR, 3.18; 95% CI, 1.26 to 6.81 per one unit increase; p=0.006),
8 increased APTT ratio > 1.4 (OR, 3.28; 95% CI, 1.01 to 9.39; p=0.033), and severe renal failure (OR, 4.68; 95%
9 CI, 1.01 to 16.60; p=0.025) (**Table 2**). In multivariate analysis, after adjusting for gender, age, platelet count,
10 PT, APTT ratio, moderate renal failure, department, pleural procedure, operator experience and
11 radiographic guidance, the occurrence of bleeding events was significantly associated with antiplatelet
12 therapy (OR, 4.13; 95% CI, 1.01 to 17.03; p=0.044) (**Table 2**). The analysis showed no significant interaction
13 of any covariable with antiplatelet therapy (data not shown). In sensitivity analyses, we also observed an
14 association between the occurrence of bleeding events and antiplatelet therapy using (i) the stepwise
15 procedure (OR, 5.16; 95% CI, 1.41 to 18.36; p=0.010) (**Table 2**); and (ii) the Firth's bias-Reduced penalized-
16 likelihood logistic regression (OR, 4.02; 95% CI, 2.62 to 8.44). Finally, the univariate association between the
17 occurrence of bleeding and antiplatelet therapy was similar and remained significant when adding the
18 center as a random-effect (OR, 3.40; 95% CI, 1.11 to 9.72; p=0.024).

19 Likewise, antiplatelet therapy was significantly associated with the risk of serious bleeding (OR, 8.61; 95%
20 CI, 2.09 to 42.3; p=0.003) in univariate analysis. This association remained statistically significant after
21 adjustment for the number of bleeding risk factors per patient (OR, 7.27; 95% CI, 1.18 to 56.1; p=0.032).

1 Discussion

2 In our study, antiplatelet therapy was identified as an independent risk factor for post-pleural procedure
3 bleeding (OR, 4.13; 95% CI, 1.01 to 17.03; after adjustment for the main risk factors of bleeding) and
4 serious bleeding (OR, 7.27; 95% CI, 1.18 to 56.1; p=0.032; after adjustment for the number of risk factors of
5 bleeding). These findings are the first to firmly demonstrate the relationship between antiplatelet therapy
6 and post-pleural procedures bleeding events and to give an estimation of the rate of bleedings in patients
7 taking antiplatelet therapy at the time of the procedure. They are consistent with a previous study, which
8 reported one case of severe hemothorax after thoracentesis among twenty-five patients treated with
9 clopidogrel while none of the fifty controls experienced bleeding (9). In contrast, two other studies, limited
10 by small study sample and design, did not find any significant bleeding after pleural procedure in patients
11 taking antiplatelet therapy (7)(8).

12 Overall, antiplatelet therapy is associated with an increased risk of bleeding and blood product usage after
13 all kinds of surgery (10). In the pulmonary interventional field, *Ernst and al.* reported in a prospective
14 cohort study of 604 patients undergoing transbronchial lung biopsy, including 30 patients on clopidogrel,
15 that the rate of bleeding was dramatically increased in patients taking clopidogrel (88% vs 3.4% in controls,
16 including 34% of moderate and 27% of major bleeding) (23). In contrast, in a large retrospective analysis of
17 15,181 percutaneous core biopsies, including 1,174 lung biopsies, *Atwell and al.* reported a similar rate of
18 bleeding in patients taking aspirin (0.6%, n=3,195) and controls (0.4%, n=11,986; p=0.34) (24). However,
19 this later study was highly limited by the definition of aspirin use based on the ingestion of aspirin within
20 the 10 days preceding the biopsy but not specifically at the time of the procedure.

21 The risk of bleeding following a percutaneous procedure is arbitrarily classified as high when the rate of
22 bleeding is over 1.5% in the general population or when they are performed in vital organs (14). In our
23 study, we found a low rate of bleeding after pleural procedure in the overall study population, evaluated at
24 1.33% (95% CI, 0.71 to 2.05). Previous studies have reported variable rates of post-pleural procedures
25 bleeding ranging from 0 to 3.8% for thoracentesis (25)(26)(27)(28), 0 to 12.5% for closed pleural biopsy
26 (2)(29)(30)(31), and 0 and 4.2% for chest tube insertion (32)(33)(34). These studies were not designed to
27 specifically address the question of hemorrhagic complications related to pleural procedures and they
28 predate the publication of guidelines for pleural procedures (2)(13). A more recent audit conducted in the
29 United Kingdom found results similar to ours with 1.1% of hemothorax and 1% of chest wall hematomas
30 among 1162 thoracenteses, and 1.3% iatrogenic hemothorax among 1394 chest tube insertions (4). In this
31 study, the impact of antiplatelet therapy on bleeding events was not analyzed. Although hemorrhagic
32 complications of pleural procedures were infrequent in the UK study and ours, they can be life-threatening.
33 In our study, we found a rate of severe bleeding at 0.71% (95% CI, 0.27 to 1.25) in the overall population.
34 Fortunately, there were no deaths among our patients, however post-pleural hemorrhagic complications
35 are known to be possibly fatal (4). The rate of bleeding might have been lower if all the patients had
36 received radiological guidance, as recommended (4). Indeed, we observed that only 69% of the procedures

1 were realized under radiologic guidance. However, at the beginning of the study, the BTS guidelines were
2 relatively recent and we hypothesize that practices in the centers involved in this study had not been
3 modified yet. One patient with severe bleeding in the antiplatelet group had no radiologic guidance.
4 Altogether, these data suggest that antiplatelet therapy should be systematically stepped down to the
5 minimum acceptable relative to the patient's thrombotic risk before any pleural procedure is undertaken.
6 These results are of particular importance since they represent a change to current practice in pulmonology
7 (15).

8 Our study was not designed to evaluate the risk of thrombosis in patients who had stopped antiplatelet
9 therapy for the procedure. However, we know from previous studies that, in patients at high risk of
10 thrombosis, discontinuation of antiplatelet therapy is an independent predictor of death, transient
11 ischemic attack, and acute coronary syndromes (35)(36)(37)(38)(39). In our study, we found a frequency of
12 bleeding at 3.23% (95% CI, 1.08 to 5.91) and of severe bleeding at 2.69% (95% CI, 0.54 to 5.38) in patients
13 undergoing pleural procedures while receiving antiplatelet therapy; and none led to death. This risk may be
14 considered as acceptable when balanced with the risk of a serious cardiovascular event associated with
15 antiplatelet drug withdrawal in patients at high risk of thrombosis. If pleural procedures must be performed
16 under antiplatelet therapy, a personalized approach should be performed including a comprehensive
17 bleeding risk assessment, correction of all additional risk factors for bleeding and a particular attention to
18 all aspects of the technique.

19
20 The main limit of the study is the presence of missing data, especially concerning renal function. In
21 addition, the low number of events limited the multivariate analysis. However, we could construct a
22 converging multiple linear model adjusted for the main risk factors of bleeding. Furthermore, this low
23 number of events resulted in low statistical power that possibly explained that usual risk factors for
24 bleeding were not associated with bleeding in the multivariate model. In addition, our study was not design
25 to evaluate the risk of bleeding according to the antiplatelet agent. All bleedings occurred in patients
26 treated by aspirin in monotherapy. No extra precautions were taken in patients receiving dual antiplatelet
27 therapy, the absence of bleeding was probably due to the small number of patients in this group. Doses of
28 aspirin were not recorded but supposed to be low (between 75 mg to 160mg per day) according to the
29 French guidelines that recommend low doses of aspirin in cardiovascular diseases. Finally, our study
30 pertains to bedside procedures only; the corresponding observations and interpretation cannot be
31 extrapolated to CT-guided or surgical procedures.

32

33 **Conclusion**

34 Antiplatelet therapy was associated with an increased risk of post-pleural procedure bleeding and serious
35 bleeding that should be taken into account in the benefice/risk balance when considering a pleural

1 procedure in a patient taking antiplatelet drugs. However, the rates of bleeding and severe bleeding were
2 low, advocating that pleural procedures may be performed with an acceptable risk when antiplatelet
3 therapy cannot be interrupted.

1 **REFERENCES**

- 2 1. Du Rand I, Maskell N. Introduction and methods: British Thoracic Society Pleural Disease Guideline 2010.
3 Thorax. 2010;65 Suppl 2: ii1-3.
- 4 2. Maskell N. British Thoracic Society Pleural Disease Guidelines--2010 update. Thorax 2010; 65:667-9.
- 5 3. MacDuff A, Arnold A, Harvey J. Management of spontaneous pneumothorax: British Thoracic Society
6 Pleural Disease Guideline 2010. Thorax 2010;65 Suppl 2: ii18-31.
- 7 4. Hooper CE, Welham SA, Maskell NA, British Thoracic Society. Pleural procedures and patient safety: a
8 national BTS audit of practice. Thorax 2015; 70:189-91.
- 9 5. Charlot M, Nielsen LH, Lindhardsen J, and al. Clopidogrel discontinuation after myocardial infarction and
10 risk of thrombosis: a nationwide cohort study. Eur Heart J 2012; 33:2527-34.
- 11 6. Sibon I, Orgogozo J-M. Antiplatelet drug discontinuation is a risk factor for ischemic stroke. Neurology
12 2004; 62:1187-9.
- 13 7. Zalt MB, Bechara RI, Parks C, and al. Effect of routine clopidogrel use on bleeding complications after
14 ultrasound-guided thoracentesis. J Bronchol Interv Pulmonol 2012; 19:284-7.
- 15 8. Dammert P, Pratter M, Boujaoude Z. Safety of ultrasound-guided small-bore chest tube insertion in
16 patients on clopidogrel. J Bronchol Interv Pulmonol 2013; 20:16-20.
- 17 9. Mahmood K, Shofer SL, Moser BK, and al. Hemorrhagic complications of thoracentesis and small-bore
18 chest tube placement in patients taking clopidogrel. Ann Am Thorac Soc 2014; 11:73-9.
- 19 10. Ferraris VA, Saha SP, Oestreich JH, and al. 2012 update to the Society of Thoracic Surgeons guideline on
20 use of antiplatelet drugs in patients having cardiac and noncardiac operations. Ann Thorac Surg. 2012;
21 94:1761-81.
- 22 11. Trosini-Désert V, Vergnon JM, Collet JP, and al. Fiberoptic bronchoscopy and anti-platelet agents: a risk-
23 benefit analysis. Rev Mal Respir 2007; 24:48-56.
- 24 12. Ernst A, Silvestri GA, Johnstone D. Interventional pulmonary procedures: Guidelines from the American
25 College of Chest Physicians. Chest 2003; 123:1693-717.
- 26 13. Havelock T, Teoh R, Laws D, and al. Pleural procedures and thoracic ultrasound: British Thoracic Society
27 Pleural Disease Guideline 2010. Thorax 2010;65 Suppl 2: ii61-76.
- 28 14. Baron TH, Kamath PS, McBane RD. Management of antithrombotic therapy in patients undergoing
29 invasive procedures. N Engl J Med 2013; 368:2113-24.
- 30 15. Dangers L, Similowski T, Chenivresse C. [Pleural procedures in patients treated by platelet aggregation
31 inhibitors: An opinion survey]. Rev Mal Respir 2016;33:41-6.
- 32 16. Patrono C, Baigent C, Hirsh J, and al. Antiplatelet drugs*: American college of chest physicians evidence-
33 based clinical practice guidelines (8th edition). Chest 2008;133(6_suppl):199S-233S.
- 34 17. Gogarten W, Vandermeulen E, Van Aken H, and al. Regional anaesthesia and antithrombotic agents:
35 recommendations of the European Society of Anaesthesiology. Eur J Anaesthesiol 2010 ;27 :999-1015.

- 1 18. HAS Antiagrégants plaquettaires: prise en compte des risques thrombotique et hémorragique pour les
2 gestes percutanés chez le coronarien Novembre 2013
- 3 19. Godier A., Fontana P., Motte S., and al. Management of antiplatelet therapy in patients undergoing
4 elective invasive procedures. *Anaesth Crit Care Pain Med* .2018 Aug;37(4):379-389
- 5 20. Efron B. Estimation and Accuracy after Model Selection. *J Am Stat Assoc*. 2014;109(507):991–1007.
- 6 21. Firth D. Bias Reduction of Maximum Likelihood Estimates. *Biometrika* 1993;80(1):27-38.
- 7 22. R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: R
8 Foundation for Statistical Computing 2008. <http://www.R-project.org>.
- 9 23. Ernst A, Eberhardt R, Wahidi M, and al. Effect of routine clopidogrel use on bleeding complications after
10 transbronchial biopsy in humans. *Chest* 2006; 129:734–737.
- 11 24. Atwell TD, Smith RL, Hesley GK, and al. Incidence of bleeding after 15,181 percutaneous biopsies and
12 the role of aspirin. *AJR Am J Roentgenol*. 2010; 194:784–789.
- 13 25. Spanuchart I, Gallacher S. Hemothorax after thoracentesis. *N Engl J Med* 2016; 375:1878
- 14 26. Jones PW. Ultrasound-Guided Thoracentesis: Is It a Safer Method? *Chest* 2003; 123:418–23.
- 15 27. Colt HG, Brewer N, Barbur E. Evaluation of patient-related and procedure-related factors contributing to
16 pneumothorax following thoracentesis. *Chest* 1999; 116:134–8.
- 17 28. Grogan DR, Irwin RS, Channick R, and al. Complications associated with thoracentesis. A prospective,
18 randomized study comparing three different methods. *Arch Intern Med* 1990; 150:873–7.
- 19 29. Chang DB, Yang PC, Luh KT, and al. Ultrasound-guided pleural biopsy with Tru-Cut needle. *Chest* 1991;
20 100:1328–33.
- 21 30. McLeod DT, Ternouth I, Nkanza N. Comparison of the Tru-cut biopsy needle with the Abrams punch for
22 pleural biopsy. *Thorax* 1989; 44:794–6.
- 23 31. Morrone N, Algranti E, Barreto E. Pleural biopsy with Cope and Abrams needles. *Chest* 1987; 92:1050–2.
- 24 32. Cho S, Lee EB. Management of primary and secondary pneumothorax using a small-bore thoracic
25 catheter. *Interact Cardiovasc Thorac Surg* 2010; 11:146–9.
- 26 33. Horsley A, Jones L, White J, Henry M. Efficacy and complications of small-bore, wire-guided chest drains.
27 *Chest* 2006 ;130 :1857–63.
- 28 34. Marquette C-H, Marx A, Leroy S, and al. Simplified stepwise management of primary spontaneous
29 pneumothorax: a pilot study. *Eur Respir J* 2006 ;27 :470–6.
- 30 35. Collet JP, Montalescot G, Blanchet B, and al. Impact of prior use or recent withdrawal of oral
31 antiplatelet agents on acute coronary syndromes. *Circulation*. 2004;110(16):2361-7.
- 32 36. Maulaz AB, Bezerra DC, Michel P, Bogousslavsky J. Effect of discontinuing aspirin therapy on the risk of
33 brain ischemic stroke. *Arch Neurol*. 2005;62(8):1217-20.
- 34 37. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a
35 special risk for late stent thrombosis. *J Am Coll Cardiol*. 2005;45(3):456-9.

- 1 38. Biondi-Zoccai GG, Lotrionte M, Agostoni P. A systematic review and meta-analysis on the hazards of
2 discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur*
3 *Heart J.* 2006;27(22):2667-74.
- 4 39. Rodríguez LA, Cea-Soriano L, Martín-Merino E, Johansson S. Discontinuation of low dose aspirin and risk
5 of myocardial infarction: case-control study in UK primary care. *BMJ.* 2011;343: d4094.

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2 Authors' role

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7 Gilles Mangiapan contributed to the acquisition and interpretation of data, revised the work critically for
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Table 1: Description of patients and pleural procedures.

Characteristics	N	All patients (n = 1124)	Antiplatelet group (n = 186)	Control group (n = 938)	p value
Male gender — no. (%)	1124	737 (66%)	135 (73%)	602 (64%)	0.028
Age (year) — median ± IQR	1115	62.6 ± 27.7	75.8 ± 17.1	60.1 ± 28.4	< 0.001
Age > 65 years — no. (%)	1115	499 (45%)	139 (76%)	360 (39%)	< 0.001
BMI (kg.m ⁻²) — median ± IQR	868	23.0 ± 5.7	24.4 ± 6.5	22.7 ± 5.7	< 0.001
Platelets count (G.L ⁻¹) — median ± IQR	1111	261 ± 156	263 ± 150	260 ± 158	0.35
Platelets < 100 G.L ⁻¹ — no. (%)	1111	75 (7%)	4 (2%)	71 (8%)	0.004
PT (%) — median ± IQR	1048	83 ± 23	79 ± 24	83 ± 22	0.05
PT < 50% — no. (%)	1048	61 (6%)	7 (4%)	54 (6%)	0.37
APTT ratio — median ± IQR	975	1.03 ± 0.30	1.06 ± 0.32	1.03 ± 0.28	0.08
APTT > 1.4 — no. (%)	975	132 (14%)	25 (15%)	107 (13%)	0.62
Creatinine Cl. (L.min ⁻¹) — median ± IQR	955	82.0 ± 61.5	60.3 ± 47.4	87.1 ± 61.3	< 0.001
Creatinine Cl. < 60 L.min ⁻¹ — no. (%)	955	296 (31%)	77 (50%)	219 (27%)	< 0.001
Creatinine Cl. < 30 L.min ⁻¹ — no. (%)	955	73 (8%)	24 (15%)	49 (6%)	< 0.001
Indication for pleural procedure — no. (%)	1124				< 0.001
Pleural effusion		899 (80%)	166 (89%)	733 (78%)	
Pneumothorax		225 (20%)	20 (11%)	205 (22%)	
Pleural procedure — no. (%)	1124				0.14
Chest tube insertion		617 (55%)	94 (50%)	523 (56%)	
Thoracentesis		377 (33%)	74 (40%)	303 (32%)	
Closed pleural biopsy		130 (12%)	18 (10%)	112 (12%)	
Type of department — no. (%)	1124				0.52
Respiratory Medicine		614 (55%)	106 (57%)	508 (54%)	
Intensive Care Medicine		510 (45%)	80 (43%)	430 (46%)	
Senior operator — no. (%)	1124	524 (47%)	86 (46%)	438 (47%)	0.89
Experience of operator < 50 procedures — no. (%)	1124	596 (53%)	95 (51%)	501 (53%)	0.62
Image-guidance — no. (%)	1124	781 (69%)	144 (77%)	637 (68%)	0.011
Pleural device diameter > 14F — no. (%)	1063	329 (31%)	45 (26%)	284 (32%)	0.15

IQR: interquartile range; BMI: Body Mass Index; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; APTT ratio: patient/control APTT ratio; Cl: clearance.

Table 2: Associations for bleeding in univariate and multivariate analyses.

Variable	Univariate analysis		Multivariate analysis			
			Main model ^a		Stepwise model ^b	
	Odds ratio (95% CI)	<i>p</i> value	Odds ratio (95% CI)	<i>p</i> value	Odds ratio (95% CI)	<i>p</i> value
Antiplatelet drug therapy	3.44 (1.14-9.66)	0.021	4.13 (1.01-17.03)	0.044	5.16 (1.41-18.36)	0.010
Male gender	1.27 (0.42-3.56)	0.65	1.89 (0.48-7.19)	0.34	—	—
Age (per 5 years increase)	1.07 (0.93-1.24)	0.37	1.06 (0.86-1.32)	0.63	—	—
Age > 65	1.42 (0.51-4.07)	0.50	—	—	—	—
Platelet count (per 100 G.L ⁻¹ increase)	0.44 (0.25-0.73)	0.002	0.57 (0.28-0.97)	0.08	0.59 (0.30-0.97)	0.08
Platelet count < 100 G.L ⁻¹	3.56 (0.80-11.5)	0.05	—	—	—	—
PT (per 10% increase)	0.76 (0.61-0.97)	0.020	0.93 (0.64-1.37)	0.70	—	—
PT < 50%	2.54 (0.39-9.47)	0.23	—	—	—	—
APTT ratio (per 1 unit increase)	3.18 (1.26-6.81)	0.006	2.72 (0.53-12.10)	0.20	3.23 (0.93-9.11)	0.038
Increased APTT ratio > 1.4	3.28 (1.01-9.39)	0.033	—	—	—	—
Creatinine Cl. < 60 L.min ⁻¹	1.87 (0.53-6.63)	0.304	—	—	—	—
Creatinine Cl. < 30 L.min ⁻¹	4.68 (1.01-16.60)	0.025	1.85 (0.33- 8.43)	0.45	—	—
Indication for pleural procedure (pneumothorax vs pleural effusion)	1.00 (0.23-3.18)	> 0.99	—	—	—	—
Department (intensive care vs respiratory medicine)	2.44 (0.86-6.79)	0.106	1.01 (1.94-5.81)	0.99	—	—
Pleural procedure						
Closed pleural biopsy	ref		ref		ref	
Chest tube insertion	1.91 (0.35-35.37)	0.54	0.59 (0.05-14.17)	0.69	—	—
Thoracentesis	1.73 (0.28-33.38)	0.62	0.93 (0.10-20.31)	0.96	—	—
Operator (junior vs senior physician)	2.43 (0.83-8.80)	0.13	—	—	—	—
Experience < 50 procedures	1.78 (0.63-5.76)	0.29	3.88 (0.91-27.01)	0.10	3.88 (0.96-26.06)	0.09
Radiographic guidance	0.83 (0.23-2.43)	0.74	0.94 (0.18-3.79)	0.93	—	—
Pleural device diameter > 14F	0.40 (0.06-1.51)	0.24	—	—	—	—

CI: confidence interval; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; APTT ratio: patient/control APTT ratio; Cl: clearance

^a n = 826; AIC = 121.6; number of Fisher Scoring iterations = 8

^b n = 826; AIC = 108.4; number of Fisher Scoring iterations = 8