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Randomised trial of first-line bronchial artery embolisation for non-severe haemoptysis of mild abundance

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ABSTRACT

Background Whereas first-line bronchial artery embolisation (BAE) is considered standard of care for the management of severe haemoptysis, it is unknown whether this approach is warranted for non-severe haemoptysis.

Research question To assess the efficacy on bleeding control and the safety of first-line BAE in non-severe haemoptysis of mild abundance.

Study design and methods This multicentre, randomised controlled open-label trial enrolled adult patients without major comorbid condition and having mild haemoptysis (onset <72 hours, 100–200 mL estimated bleeding amount), related to a systemic arterial mechanism. Patients were randomly assigned (1:1) to BAE associated with medical therapy or to medical therapy alone.

Results Bleeding recurrence at day 30 after randomisation (primary outcome) occurred in 4 (11.8%) of 34 patients in the BAE strategy and 17 (44.7%) of 38 patients in the medical strategy (difference –33%; 95% CI –13.8% to –52.1%, $p=0.002$). The 90-day bleeding recurrence-free survival rates were 91.2% (95% CI 75.1% to 97.1%) and 60.2% (95% CI 42.9% to 73.8%), respectively (HR=0.19, 95% CI 0.05 to 0.67, $p=0.01$). No death occurred during follow-up and no bleeding recurrence needed surgery.

Four adverse events (one major with systemic emboli) occurred during hospitalisation, all in the BAE strategy (11.8% vs 0%; difference 11.8%, 95% CI 0.9 to 22.6, $p=0.045$); all eventually resolved.

Conclusion In non-severe haemoptysis of mild abundance, BAE associated with medical therapy had a superior efficacy for preventing bleeding recurrences at 30 and 90 days, as compared with medical therapy alone. However, it was associated with a higher rate of adverse events.

Trial registration number NCT01278199

INTRODUCTION

Although rare, haemoptysis is a potentially life-threatening condition. In a recent 5-year French national study,¹ haemoptysis

Key messages

- To assess the efficacy on bleeding control and the safety of first-line bronchial artery embolisation (BAE) in patients with non-severe haemoptysis of mild abundance.
- In non-severe haemoptysis of mild abundance, BAE associated with medical therapy has a superior efficacy for preventing bleeding recurrences at 30 and 90 days, as compared with medical therapy alone.
- A first-line interventional radiology should be considered in the management of patients with haemoptysis, whichever its severity, bearing in mind the risk of adverse events associated with the procedure.

accounted for 0.2% of all hospitalisations. Haemoptysis was associated with a substantial posthospital morbidity and health services consumption, in large part due to a 3-year bleeding recurrence rate of 16.3%, as well as with a high subsequent mortality rate of 21.6% and 27% at 1 and 3 years after the index hospitalisation.¹

The therapeutic management of haemoptysis requires determining the most appropriate treatment, according to a rigorous assessment of the severity of haemoptysis, based on (1) the bleeding amount and the need for respiratory support, (2) the presence of comorbidities and (3) the cause and mechanism of bleeding.^{2,3} The therapeutic options may include medical measures,^{4–7} interventional radiology^{8,9} or emergency surgical lung resection.^{10–12} Bronchial artery embolisation (BAE) has gradually emerged as the first-line therapeutic measure in severe haemoptysis, achieving control of bleeding in 80%–90% of cases, with an acceptable risk:benefit ratio.^{9,13–15} Conversely, it is not known whether BAE is warranted in non-severe haemoptysis,

whose prognosis may be less pejorative either spontaneously or with therapeutic interventions. In this context, the current therapeutic approach is guided by physicians' preference integrating the risk:benefit ratio estimate and resources availability.

To date, no controlled study has compared the efficacy on bleeding control and the safety of a strategy using interventional radiology to medical therapy alone. The Arterio-embolisation in Hemoptysis of Mild Severity trial aimed to investigate the efficacy on the rate of bleeding recurrence of adding early first-line BAE to medical therapy in non-severe acute haemoptysis of mild abundance, as compared with medical therapy alone.

METHODS

Study design and participants

The ARTEMHYS trial was an open-label multicenter, randomised controlled trial conducted in the intensive care unit (ICU) or intermediate care ward (ICW) of seven French university teaching hospitals.

Eligible patients were those presenting with non-severe acute haemoptysis of mild abundance, likely related to a systemic arterial mechanism. Acute haemoptysis of mild abundance was defined as an estimated cumulative bleeding amount ranging from 100 to 200 mL within 72 hours, using the following scale: a teaspoonful (5 mL), a spittoon (120 mL) and a large filled glass (200 mL).^{4 16} Non-severe haemoptysis was characterised by the absence of all of the following criteria related to (1) bleeding amount: acute respiratory failure with the need for mechanical ventilation; haemorrhagic shock, need for blood products transfusion, cardiac arrest; (2) bleeding aetiology or mechanism: mycetoma, pulmonary arterial vasculature involvement according to a pre-enrolment multidetector CT-angiography (MDCTA); and (3) severe baseline comorbid conditions: advanced chronic heart failure; chronic pulmonary disease (chronic obstructive pulmonary diseases Gold 3,^{3 17} pneumonectomy, tracheostomy, cystic fibrosis); chronic renal failure (creatinin clearance <30 mL/min or dialysis). Patients with the following conditions were also not eligible: traumatic haemoptysis; time to referral beyond 72 hours from bleeding onset; formal indication for anticoagulant therapy at therapeutic dosage; pregnant or lactating women, or patients having do-not-resuscitate order (moribund patient, life expectancy of <24 hours).^{2 4}

Prior to enrolment, a MDCTA was required to identify the site, the cause and the mechanism of bleeding, and map the bronchial and non-bronchial systemic arteries.⁸

Randomisation and masking

Randomisation was performed within the first 16 hours of ICU/ICW admission, using a secure web-response system available in each study centre. Patients were randomly assigned in a 1:1 ratio to BAE with medical therapy (interventional strategy) or medical therapy alone. Randomisation was stratified on centre and the permuted-block

(different sizes of blocks) randomisation list was established by an independent statistician. Investigators had no access to the randomisation list and were blinded to the size of blocks.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of the research.

Interventions

Patients allocated to the interventional strategy received medical therapy as per current routine practice in each centre, in combination with BAE performed within 12 hours after randomisation, and at least 6 hours after intravenous infusion of terlipressin, if administered (online supplemental file). Those allocated to the medical strategy received medical therapy alone. Medical therapy included bed rest and fasting, continuous monitoring of oxygen saturation, respiratory rate, heart rate and arterial blood pressure in all patients regardless of the randomisation arm, as described elsewhere.⁴ The BAE procedure was performed by experienced radiologists and standardised in all centres.^{8 18}

Outcomes

The percentage of bleeding recurrence at day 30 after randomisation was the primary efficacy endpoint, since two-thirds of bleeding recurrences occur within the month following initial management.⁴ Bleeding control was defined by bleeding cessation or bleeding of less than 50 mL during follow-up after the intervention, given that limited amount of bloody sputum that do not justify any additional therapeutic measure may be observed after effective initial management. Conversely, bleeding of 50 mL or more was considered as a failure of the intervention, as it would more likely lead to intensification or change in therapy. Patients allocated to the interventional strategy in whom the embolisation was technically impossible were also considered as failure.

The secondary endpoints were efficacy and safety endpoints: the rate of in-hospital adverse events related to the intervention, categorised into minor or major events (online supplemental file); the length of hospital stay; the percentage of bleeding recurrence at day 90 after randomisation; the 90-day rates of secondary hospitalisation or invasive interventions (BAE or surgery) for controlling bleeding recurrence after randomisation; and the overall death rates at 30 and 90 days after admission.

Statistical analysis

Assuming a bleeding recurrence rate of 26% at 30 days in the group treated with medical therapy alone,⁴ 210 patients were needed to achieve 80% power to detect a 15% difference in the bleeding recurrence rate at 30 days between the two groups (ie, a reduction from 26% to 11% with BAE), considering a two-sided alpha of 5% and an

expected dropout rate of 2%. Given the expected recruitment in each centre, the study was initially planned for 27 months' duration, including a 3-month follow-up period.

Baseline characteristics were reported using frequencies and percentages or median and IQRs. The primary outcome was compared using Pearson χ^2 test in the intention-to-treat (ITT) population, including all patients randomised who did not withdraw consent. Patients with missing outcome data at day 30 were considered as failure in both groups, as well as patients for whom the embolisation was technically impossible in the intervention group. Those assumptions were adopted in a conservative approach to avoid favouring the intervention group. Sensitivity analyses were performed on the population with no missing primary outcome and on the per-protocol population, thus excluding patients with a missing primary outcome, or for whom the embolisation was technically impossible, as well as crossovers of the randomised strategy.

Bleeding recurrence at day 90 was analysed in the same way as the primary endpoint, including the aforementioned missing value dealing strategy. Other missing values were not replaced. A sensitivity analysis was performed on the per-protocol population. Time from randomisation to the first bleeding recurrence or to censoring was compared using a Cox proportional hazard model stratified by centre. Bleeding recurrence-free 90-day survival was represented using Kaplan-Meier survival curves. Ninety-day rate of rehospitalisation or invasive interventions for bleeding recurrence and in-hospital complications rate were compared using Pearson χ^2 tests, and differences between groups were estimated with their 95% CI. Hospital length of stay was compared using Wilcoxon rank-sum test.

All analyses were performed with the SAS V.9.4 statistical software. All tests were two-sided and a p value of less than 0.05 indicated statistical significance. No adjustment for multiple comparisons was made.

RESULTS

From 1 November 2011 to 30 November 2016, 679 patients with haemoptysis were screened in the participating centres; 606 (89%) patients were non-eligible, mostly (70%) because of bleeding amount outside of the targeted range (figure 1). Initially planned for 2 years, the study duration was extended by 2 years and terminated because of low enrolment rate and lack of additional funding after 73 patients had been randomised, with follow-up ending on 28 February 2017.

One patient withdrew consent immediately after randomisation and 72 patients were analysed, including 38 allocated to the medical strategy and 34 to the interventional strategy. Five crossovers occurred within groups: three (7.9%) patients in the medical strategy also received BAE during the 72 hours period after randomisation, whereas two (5.9%) patients randomised to the interventional strategy did not receive BAE (figure 1). In the primary

ITT analysis, these crossovers were all analysed according to their randomisation group.

Characteristics of patients

Baseline characteristics did not differ between groups (table 1). Ground-glass opacities (37.5%) and alveolar consolidation (31.9%) accounted for the most frequent bleeding-related lung parenchymal findings on thoracic CT scan. The aetiology of bleeding was identified in 37 (51.4%) patients altogether and was dominated by bronchiectasis (25%) and active tuberculosis (5.6%) or tuberculosis sequels (8.3%); lung cancer accounted for only 5.6% of cases, and pneumonia or lung abscess accounted for 1.4%, with a similar distribution in both groups. Haemoptysis was cryptogenic in 48.6% of patients.

Cointerventions

Supplemental oxygen was administered in 35 (49.3%) patients to obtain a pulse oxymetry of >90%. Bronchoscopic techniques were used in 32 (44.4%) patients, at a comparable rate in both groups (table 2). Intravenous terlipressin was administered at a dose of 1 mg every 4–6 hours to five and six patients in the medical strategy and interventional strategy, respectively, for a median total dosage of 2.5 (2.0–3.0) mg and 1.0 (1.0–1.0) mg, respectively.

Primary outcome

At day 30, the bleeding recurrence status was unknown for two patients allocated to the medical strategy, with respective follow-up of 2 and 29 days (figure 1 and online supplemental e-Table 1). Altogether, the randomised strategy failed in 21 (29.2%) patients, including 17 (44.7%) of 38 patients in the medical strategy, and 4 (11.8%) of 34 patients in the interventional strategy (difference 33%, 95% CI 13.8% to 52.1%, p=0.002) (table 3). These results were consistent in the sensitivity analyses restricted to patients with available data (n=70, difference 29.9%, 95% CI 10.5% to 49.3%, p=0.005) and on the per-protocol population (n=63, difference 26.4%, 95% CI 6.7% to 46%, p=0.014).

Secondary outcomes

The length of hospital stay did not differ among groups. No death occurred during follow-up (crude median duration 92 days, IQR 90–99.25) (table 3). At day 90, the bleeding recurrence status was unknown for two additional patients (one in each group, figure 1). Altogether, the treatment failed in 23 patients (31.9%). The percentage of bleeding recurrence was higher in the medical strategy than in the interventional strategy (47.4% vs 14.7%; difference 32.7%, 95% CI 12.8% to 52.5%, p=0.003) (table 3) and remained such in the per-protocol population (difference 27.5%, 95% CI 7.6% to 47.4%, p=0.012).

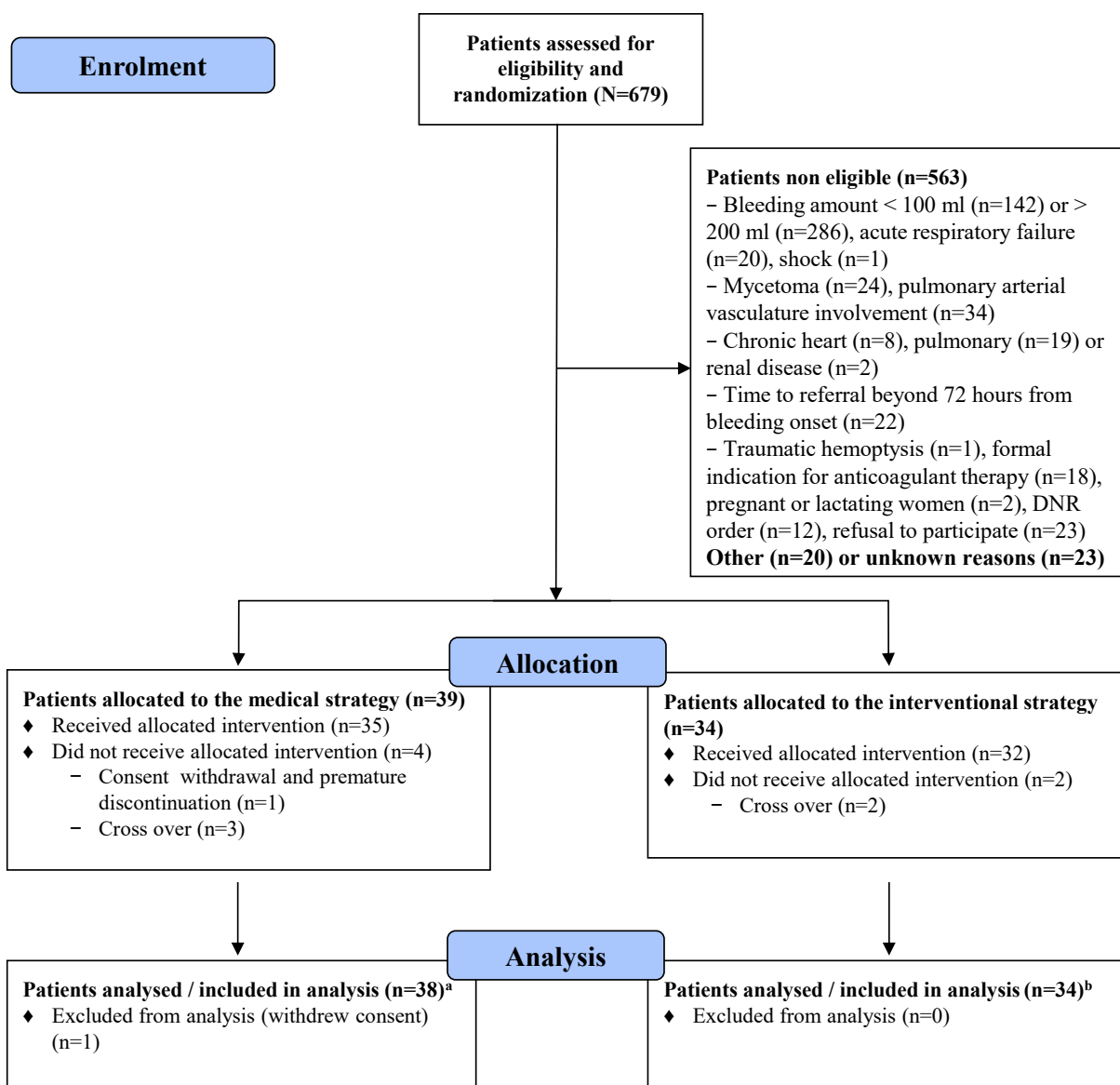


Figure 1 Flow diagram of the study population in the Arterio-embolisation in Hemoptysis of Mild Severity trial of medical management of mild-to-moderate haemoptysis with or without bronchial artery embolisation. ^aBleeding recurrence status was missing for two patients on day 30 (respective follow-up durations, 2 and 29 days) and for one other patient on day 90 (follow-up duration, 74 days); ^bbleeding recurrence status was missing for one patient on day 90 (follow-up duration, 67 days).

In the whole population, the 90-day bleeding recurrence-free survival rate was 74.9% (95% CI 63.1% to 83.4%). The risk of bleeding recurrence was more than fivefold lower in the interventional strategy than in the medical strategy (HR=0.19, 95% CI 0.05 to 0.67, $p=0.01$) (figure 2).

Failures of the intervention and management of recurrent bleeding episodes are detailed in online supplemental e-Table 1, together with the duration of follow-up. Five failures occurred in the interventional strategy, including one due to technical failure of BAE, one due to unknown status of bleeding recurrence, and three to recurrent bleedings, two of which required repeated BAE. Of the 18 failures in the medical strategy, 3 were due to unknown status of bleeding recurrence, and 15

were due to recurrent bleeding, 9 of which were treated with BAE. All documented recurrent bleedings ($n=18$) occurred during the first 8 days of the index hospitalisation. No hospital readmission occurred. None required emergent surgical lung resection. The rate of invasive treatment for bleeding recurrence (ie, BAE) in patients followed up to day 90 was 25.7% (9/35) in the medical strategy and 6.3% (2/32) in the interventional strategy (difference 19.5%, 95% CI 2.7% to 36.2%, $p=0.032$) (table 3).

The overall in-hospital complication rate related to the interventions was 5.6% (95% CI 1.8% to 14.4%). All adverse events ($n=4$) occurred in the interventional strategy (11.8% vs 0%; difference 11.8%, 95% CI 0.9% to 22.6%, $p=0.045$) and were considered to be related to

Table 1 Baseline characteristics of patients enrolled in the Arterio-Embolisation in Hemoptysis of Mild Severity trial of first-line bronchial artery embolisation or medical therapy alone for management of mild acute haemoptysis

Variable	Medical strategy (n=38)	Interventional strategy (n=34)
Age (years)	54.5 (44–69)	51.0 (40–66)
Sex (male)	26 (68.4)	25 (73.5)
Current smokers*	23 (60.5)	23 (69.7)
Never smokers	11 (28.9)	7 (21.2)
Referral from		
Home	3 (7.9)	1 (2.9)
Emergency department	28 (73.7)	22 (64.7)
Out-of-hospital emergency services	4 (10.5)	6 (17.6)
Hospital ward	3 (7.9)	5 (14.7)
Performance status†		
0	25 (89.3)	25 (86.2)
1	2 (7.1)	2 (6.9)
2	1 (3.6)	1 (3.4)
3	0	1 (3.4)
4	0	0
Pre-existing respiratory illness		
At least one	12 (31.6)	13 (38.2)
Bronchiectasis	4 (10.5)	3 (8.8)
Lung cancer	3 (7.9)	1 (2.9)
Active tuberculosis	2 (5.4)	0
Sequels of tuberculosis	3 (7.9)	7 (20.6)
Cardiovascular		
Hypertension	15 (39.5)	9 (26.5)
Valvular disease	1 (2.6)	0
Ischaemic heart disease	1 (2.6)	3 (8.8)
Clinical physiological data during the first 24 hours of admission (minimal and maximal values)		
Core temperature (°C)‡	36.6 (36.2–36.8) 37.1 (37.0–37.4)	36.6 (36.3–36.9) 37.1 (36.9–37.4)
Heart rate (beats/min)§	66 (57–80) 88 (77–97)	69 (61–79) 86 (72–95)
Systolic blood pressure (mm Hg)¶	121 (105–134) 154 (138–171)	125 (112–147) 160 (142–177)
Respiratory rate (breaths/min)**	15 (14–20) 23 (20–30)	15 (14–20) 25 (22–31)

Continued

Table 1 Continued

Variable	Medical strategy (n=38)	Interventional strategy (n=34)
Pulse oxymetry (%)††	96 (93–97) 99 (98–100)	95 (93–97) 99 (97–100)
Bleeding on admission and persistence		
Cumulated bleeding amount on admission (mL)‡‡	120 (110–150)	150 (120–150)
Persistent bloody expectoration after admission§§		
Laboratory data on admission	34 (91.9)	27 (93.1)
Platelet count (giga/L)¶¶	233 (195–256)	219 (184–258)
Haemoglobin (g/dL)***	13.7 (12.2–15.0)	14.0 (12.5–15.1)
Prothrombin time (%)†††	95 (84–100)	97 (89.5–100.0)
Blood urea nitrogen (mmol/L)‡‡‡	5 (4–6)	5 (4–6)
Serum creatinine (µmol/L)§§§	67 (59–87)	72 (64–1)

Data are n (%) or median (IQR 25%–75%).

*Data are available for 71 patients (n1=38, n2=33).

†57 patients (n1=28, n2=29).

‡70 patients (n1=37, n2=33).

§71 patients (n1=38, n2=33).

¶70 patients (n1=37, n2=33).

**64 patients (n1=35, n2=29).

††68 patients (n1=36, n2=32).

‡‡71 patients (n1=38, n2=33).

§§66 patients (n1=37, n2=29).

¶¶70 patients (n1=37, n2=33).

***70 patients (n1=37, n2=33).

†††65 patients (n1=33, n2=32).

‡‡‡67 patients (n1=36, n2=31).

§§§70 patients (n1=37, n2=33).

the procedure (online supplemental eTable 2). Three patients (9%) had minor complications which resolved without further intervention; one patient (3%), however, had a paresis and several systemic emboli, which eventually resolved without long-term sequel.

DISCUSSION

In this randomised trial, we aimed to investigate whether early first-line BAE had beneficial effects compared with medical therapy alone in the management of non-severe acute haemoptysis of mild abundance related to a systemic bronchial artery hypervascularisation. As compared with the medical strategy alone, the addition of early BAE

Table 2 Medical interventions performed in the medical or interventional strategy group

Variable	Medical strategy (n=38)	Interventional strategy (n=34)
Medical treatment		
None	4 (10.5)	11 (32.4)
Topical alone	1 (2.6)	1 (2.9)
General alone	16 (42.1)	9 (26.5)
Both topical and general	17 (44.7)	13 (38.2)
Topical therapy*		
Endobronchial suctioning	18 (47.4)	14 (41.2)
Chemical tamponade†	4 (10.5)	5 (14.7)
Mechanical tamponade‡	0	0
General measures§		
Supplemental oxygen	22 (57.9)	13 (39.4)
Intravenous terlipressin	5 (13.2)	6 (18.2)
Cough suppression	0	0
Antimicrobial treatment	15 (39.5)	14 (42.4)

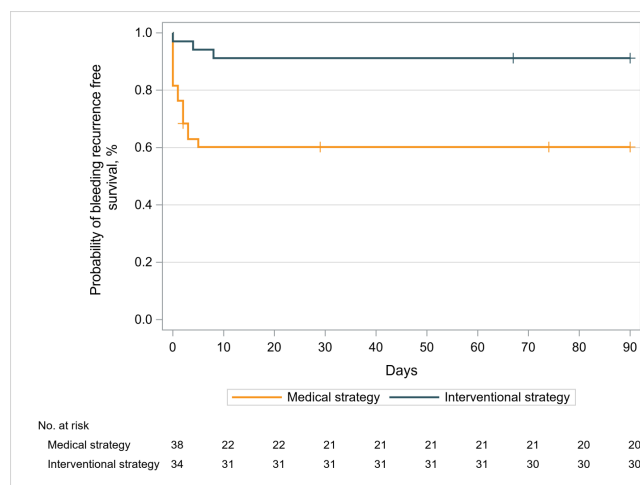
Data are n (%).

*Topical measures performed using flexible fiberoptic bronchoscopy.

†Topical tamponade including cold saline solution lavage or epinephrine instillation.

‡Mechanical tamponade including bronchial blockers or Fogarty catheters at the segment or subsegment bronchial levels.

§Data are available for 71 patients (missing for one patient in the interventional strategy).

**Figure 2** Ninety-day bleeding recurrence-free survival after initiating therapy in patients with mild-to-moderately severe haemoptysis (Kaplan-Meier estimate). The 90-day bleeding recurrence-free survival rate was 91.2% (95% CI 75.1 to 97.1) in the interventional strategy and 60.2% (95% CI 42.9 to 73.8) in the medical strategy (HR=0.19, 95% CI 0.05 to 0.67, p=0.0101, by Cox proportional hazard model stratified by centre).

achieved a higher efficacy in bleeding control at 1 and 3 months, but was associated with a higher rate of in-hospital complications.

The most difficult issues in the initial management of haemoptysis is to assess its severity and estimate the risk of bleeding recurrence, which condition the therapeutic decision and the time to its implementation. Life-threatening haemoptysis associated with high bleeding amounts, acute respiratory failure requiring mechanical ventilation or shock, which involve 10% of the patients with haemoptysis, mandate prompt management in an intensive care setting.^{1 2} In this context, the therapeutic management include the administration of inhaled or

Table 3 Primary and secondary outcomes of patients

Endpoints	Medical strategy (n=38)	Interventional strategy (n=34)	Absolute difference, % (95% CI)	P value
30-day bleeding recurrence	17 (44.7)	4 (11.8)	33.0 (13.8 to 52.1)	0.002
90-day bleeding recurrence	18 (47.4)	5 (14.7)	32.7 (12.8 to 52.5)	0.003
In-hospital complications rate	0	4 (11.8)	11.8 (0.9 to 22.6)	0.045
90-day rate of rehospitalisation or invasive treatment for bleeding recurrence, n (%)*	9/35 (25.7)	2/32 (6.3)	19.5 (2.7 to 36.2)	0.032
Length of hospital stay (days)	4.0 (3.0–7.0)	4.0 (3.0–9.0)	–	0.75†
Mortality rate of 30 and 90 days‡	0	0	–	–

Data are n (%) or median (IQR 25%–75%).

*Analysis restricted to patients followed up to day 90. Bleeding recurrence status was missing at day 90 for four patients; invasive treatment was missing for one patient with bleeding recurrence during hospitalisation.

†Wilcoxon test.

‡Two patients in the medical strategy group were lost to follow-up at day 30 (at days 2 and 29, respectively); four other patients were lost to follow-up at day 90 (one patient in the medical strategy at day 74 and three patients in the interventional strategy at days 40, 48 and 67, respectively; see the online supplemental 2, e-Table 1). The mean/median duration of follow-up was 94.6±22.6 days/92 (90–99) days.

systemic vasoconstrictors or antifibrinolytic drugs, and the use of bronchoscopy-guided tamponade by flexible or rigid bronchoscope.^{7 19} The place of emergency surgery has gradually decreased because of high operative mortality rates,^{11 12} whereas interventional radiology has emerged worldwide as the most effective non-surgical first-line treatment, despite the lack of strong evidence from randomised trials. BAE results in immediate bleeding control in most of these severe cases with a satisfactory risk:benefit ratio.^{2 4 11 12 18}

On the other hand, most patients presenting with mild-to-moderate haemoptysis are in the 'grey zone' of severity, considering the lack of usual severity criteria (bleeding amount or need for mechanical ventilation or vasopressors), although they unpredictably may progress to acute respiratory failure and ultimately die from massive bleeding recurrence.^{2 4} As a consequence, the most appropriate management of these patients at intermediate risk is still a matter of debate and the literature is scarce on this topic.^{3 4} In this study, which is to our knowledge the first randomised trial performed on the management of haemoptysis of mild severity, we focused on that latter population of patients by selecting those having haemoptysis of mild abundance (ie, bleeding amount ranging from 100 to 200 mL) on admission, not associated with acute respiratory failure or shock, and in whom the mechanism of bleeding involved the systemic bronchial artery vasculature. The main aetiologies were chronic inflammatory lung diseases and infectious illnesses, after excluding mycetomas. In this selected population, the use of BAE achieved a 33% absolute reduction of bleeding recurrence rate at 30 days, as compared with the medical strategy (11.8% vs 44.7%). These findings are consistent with a previous observational study from our group,⁴ which indicated a 11% recurrence rate at 1 month in the subset of patients admitted to the ICU and receiving a BAE for haemoptysis of mild abundance not related to mycetoma or pulmonary arterial vasculature involvement, as compared with a 26% rate with medical management alone.

The superior efficacy of the interventional strategy on bleeding control was sustained at 90 days, with a 91.2% bleeding recurrence-free survival rate compared with 60.2% with the medical strategy. This rate is in the higher range of those reported in uncontrolled series of severe haemoptysis treated with BAE.^{4 18 20 21} Bleeding recurrences mostly occur in lung cancer, mycetoma or cavitory lesions, and may be related to incomplete embolisation, recanalisation of previously embolised arteries, as well as to the recruitment of new collaterals due to the progression of the underlying disease.^{4 18} In the present study, lung cancer accounted for only 5.6% of all etiologies. This low rate may be explained by our selection criteria that targeted non-severe acute haemoptysis of mild abundance related to a systemic arterial mechanism. Haemoptysis related to lung cancer usually involve high bleeding amounts, high rate of acute respiratory failure and shock, as well as high rate of pulmonary arterial vasculature

involvement.^{2 4 11 22} Altogether, the spectrum of the aetiologies of haemoptysis in the present study was similar to that recently described in two large European series of haemoptysis of mild severity, including bronchiectasis, pneumonia/lung abscess, acute tuberculosis and post-tuberculosis sequels, and differed from that of haemoptysis of large abundance or associated with other severity criteria.^{1 2 4 21-24} Cryptogenic haemoptysis also accounted for a large part of our population, and BAE has been shown to provide immediate control of bleeding in most of these cases, with few recurrences at both short and long terms.^{16 25 26}

The overall rate of in-hospital complications related to the randomised strategy was 5.6%. All were reported in patients receiving BAE, including three minor complications and one major complication, all of which had favourable outcomes. These findings are in accordance with other series of the literature^{4 9 18 27}: BAE should be performed by experienced personnel after a rigorous and multidisciplinary evaluation of the benefit:risk ratio. Guiding the procedure with imaging, specifically MDCTA, and the use of modern ionic contrast media and superselective catheterisation of bronchial arteries are essential to decrease the rate of complications related to the procedure.^{9 18 28-30} There were no complications related to the medical measures, particularly intravenous terlipressin. A recent Israeli study suggested that inhaled tranexamic acid may be helpful for controlling haemoptysis of low abundance.¹⁹ Its place in the treatment of moderate-to-severe abundance haemoptysis should be investigated.

Limitations of this study are related to the following: first, the achieved sample size matched to less than half of the expected sample. This discrepancy is in large part due to the fact that the targeted population was representative of less than 20% of the patients screened in the participating units, as most these patients had criteria favouring a first-line interventional radiology. However, to assess the applicability of a first-line interventional strategy outside of the intensive care environment was considered unrealistic. Despite the low recruitment rate, the effect size recorded in this trial, including the consistent results at 30-day and 3-month follow-up, strongly supports the efficacy of the interventional strategy tested. Second, the medical interventions were non-standardised to match routine practice in each centre, which may have favoured the interventional arm, but the use of these different interventions did not differ between groups. Last, due to the relatively small sample size and numbers of events, the trial lacks the power to confidently assess the risk:benefit ratio of BAE in patients with non-severe acute haemoptysis of mild abundance involving the systemic bronchial artery vasculature.

To summarise, BAE added to medical treatment reduced the risk of recurrent bleeding at 30 and 90 days in patients with non-severe acute haemoptysis of mild abundance involving the systemic bronchial artery vasculature, as compared with medical measures alone. In

such a selected population presenting with haemoptysis revealing or complicating the course of bronchiectasis, pneumonia/lung abscess, acute tuberculosis and post-tuberculosis sequels, and cryptogenic haemoptysis, the indication of interventional radiology should be weighed with the estimate of the risk associated with the procedure, the risk estimate of bleeding recurrence and information from thoracic imaging.

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AR and TS drafted the article. All authors participated in the critical revision of the manuscript and provided final approval to submit this version of the manuscript and have agreed to be accountable for all aspects of the work.

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On-line Supplement**Randomized trial of first-line bronchial artery embolization for non-severe hemoptysis of mild abundance**

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Content

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- Potential adverse events of the interventions
- e-Table 1: Failures of the intervention, bleeding recurrence and follow-up at 30 and 90 days.
- e-Table 2: Adverse events occurring in the interventional strategy and outcome

Interventions

Patients allocated to the interventional strategy received medical therapy as per current routine practice in each center, in combination with BAE performed within 12 hours after randomization, and at least 6 hours after any intravenous infusion of terlipressin, if administered. Those allocated to the medical strategy received medical therapy alone.

General medical measures - Medical therapy administered to all patients, regardless of the randomization arm, included bed rest and fasting, continuous monitoring of oxygen saturation, respiratory rate, heart rate and arterial blood pressure, as described elsewhere (1). Oxygen was delivered to obtain a pulse oxymetry >90%. No attempt was made to suppress cough. Additional measures aiming at controlling persistent bleeding were left at the discretion of the attending physicians. When deemed necessary, bronchoscopic techniques used cold saline solution lavage or topical vasoconstrictive agents, and systemic terlipressin was administered at a dose of 1 mg intravenously every 4 to 6 hours. As the indications of these additional procedures were likely homogeneous in each participating center, the randomization by center was expected to limit potential bias related to their use.

BAE procedure - The BAE procedure was performed by experienced radiologists and standardized in all centers (2,3). A catheter was introduced into the right femoral artery using the Seldinger technique. Selective catheterization of systemic (bronchial and non-bronchial) arteries was performed, using 4 to 5 French catheters, according to etiology and bleeding site identified on MDCTA (alveolar or ground glass opacities, intra-bronchial materials), vascular mapping and abnormal findings on angiography (enlarged or tortuous arteries), or when arteries had a near-normal aspect but supplied the bleeding site. The use of microcatheter (2.4 or 2.7F) was encouraged for embolization, which mainly used acrylic beads of 500 to 1100 μm and polyvinyl alcohol particles of 400 to 1000 μm (2,3).

Potential adverse events recorded

Potential complications expected to be related to the interventions were categorized into minor and major complications.

Complications related to the interventional radiological strategy could be associated with arterial catheterization, administration of contrast medium or the embolisation procedure *per se*. Minor complications were local groin puncture hematoma, vasospasm, arterial dissection or perforation, hyperthermia, dysphagia, or chest pain. Major complications included neurological events (spinal cord ischemia leading to transient or permanent paraparesis or paraplegia; transient cerebral ischemia/stroke); vascular non-neurological events (myocardial infarction, systemic ischemia other than cerebral, pulmonary infarction); hemorrhagic events (overt bleeding with one of the followings: fall in hemoglobin of ≥ 2 g/100 mL compared to the initial value, need for red blood cells transfusion; need for surgical cure of hematoma); metabolic events (acute renal failure); and others (contrast media hypersensitivity, diaphragmatic paralysis; femoral artery aneurysm at puncture site).

Minor complications related to the medical management included acrocyanosis, abdominal cramps, diarrhea, headache, and symptomatic hyponatremia; major complications included systemic hypertension, myocardial ischemia, ventricular and supraventricular arrhythmia, and limb hypoperfusion.

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eTable 1

Failure of the initial strategy, including bleeding recurrence at 30 and 90 days, and duration of follow-up in patients with mild-to-moderate hemoptysis allocated to a medical management strategy alone (M) or to the interventional strategy (I) with bronchial artery embolisation (BAE) in addition to medical management.

	Patient No.	Treatment arm*	Initial bleeding amount, mL	Bleeding recurrence			Follow-up
				Date, d	Amount, ml	Treatment	Days, no
Failure of the initial strategy (n=1)	1	I†	120	-	-	-	103
30-day bleeding recurrence, (n=18)	2	M	150	D0	50	Intravenous terlipressin	130
	3	M	150	D0	50	BAE	138
	4	M	110	D0	70	BAE	90
	5	M	100	D0	80	Supplemental oxygen	99
	6	M	120	D0	90	Supplemental oxygen	90
	7	M	200	D0	180	Supplemental oxygen	97
	8	M	120	D0	180	BAE	164
	9	M	120	D1	80	BAE	90
	10	M	120	D1	300	BAE	95
	11	M	120	D2	55	BAE + supplemental oxygen	98
	12	M	120	D2	80	Supplemental oxygen	91
	13	M	140	D2	210	BAE	90
	14	M	120	D3	290	Intravenous terlipressin + BAE	122
	15	M	150	D3	1000	Mechanical ventilation	90
	16	M	200	D5	100	BAE	92
	17	I	200	D0	100	Supplemental oxygen	48
	18	I	150	D4	50	BAE	104
	19	I	120	D8	100	BAE	40
Bleeding recurrence status unknown at day 30, (n=2)‡	20	M	110	-	-	-	29
	21	M	160	-	-	-	2
Bleeding recurrence status unknown at day 90, (n=2)‡	22	M	200	-	-	-	74
	23	I	100	-	-	-	67

Abbreviations: d day; BAE: bronchial artery embolization

D0 is the day on which the strategy was applied

* Treatment arm: I, interventional (BAE); M: medical

† technical failure of BAE

‡ None of these patients had recurrent bleeding documented at time of loss to follow-up.

The rate of hospital readmission or invasive treatment for bleeding recurrence in patients followed-up to day 90 was 25.7% (9/35) in the medical strategy group and 6.3% (2/32) in the interventional strategy group (difference 19.5%, 95% CI 2.7 to 36.2, $P=.032$).

e-Table 2. In-hospital complications related to the intervention

Complication	Date of diagnosis	Intensity	Management and follow-up
local groin puncture hematoma	D0	minor	none spontaneous resolution (D18)
bronchial artery dissection	D0	minor	none
acute renal dysfunction	D2	minor	none spontaneous resolution (D6)
spinal cord ischemia; splenic, renal and pancreatic infarction	D1	major	- paresis, resolving with rehabilitation care - splenic, renal and pancreatic infarction, resolution at 6-month follow-up

D0 = day on which the strategy was applied.