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Original article

Anticoagulation in thrombocytopenic patients with hematological malignancy: A multinational clinical vignette-based experiment

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ABSTRACT

Background: Thrombocytopenia in cancer patients with an indication for anticoagulation poses a unique clinical challenge. There are guidelines for the setting of venous thromboembolism but not atrial fibrillation (AF). Evidence is lacking and current practice is unclear.

Objective: To identify patient and physician characteristics associated with anticoagulation management in hematological malignancy and thrombocytopenia.

Methods: A clinical vignette-based experiment was designed. Eleven hematologists were interviewed, identifying 5 relevant variable categories with 2–5 options each. Thirty hypothetical vignettes were generated. Each physician received 5 vignettes and selected a management strategy (hold anticoagulation; no change; transfuse platelets; modify type/dose). The survey was distributed to hematologists and thrombosis specialists in 3 countries. Poisson regression models with cluster robust variance estimates were used to calculate relative risks for using one management option over the other, for each variable in comparison to a reference variable.

Results: 168 physicians answered 774 cases and reported continuing anticoagulation for venous thromboembolism or AF in 607 (78%) cases, usually with dose reduction or platelet transfusion support. Overall, management was affected by platelet count, anticoagulation indication, time since indication, type of hematological disease and treatment, and prior major bleeding, as well as physician demographics and practice setting. The CHA_2DS_2-VASc score and time since AF diagnosis affected anticoagulation management in AF.

Conclusion: This study indicates what the widely accepted management strategies are. These strategies, and possibly others, should be assessed prospectively to ascertain effectiveness. The decision process is intricate and compatible with current venous thromboembolism guidelines.

1. Introduction

Thrombocytopenia in cancer patients with an indication for anticoagulation is not uncommon [1], and poses a unique clinical challenge. Clinical trials evaluating anticoagulants for treatment of venous thromboembolism (VTE) excluded patients with thrombocytopenia [2-4]. As a result, management is informed mainly by expert opinion [5] and limited retrospective cohort studies on VTE, as recently reviewed [6]. In this setting, anticoagulation can be held or continued at full or reduced doses, with or without platelet transfusion support. Holding anticoagulation appears to increase the risk of VTE recurrence, especially in patients with acute VTE [7, 8]. On the other hand, there is a

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high risk of clinically significant bleeding (13.5–27%) [7-10] and a varying risk of major bleeding [10, 11], particularly when anticoagulation is continued. Accordingly, the thrombotic risk should be sufficiently high to justify anticoagulation in patients with a high risk of bleeding. Specific recommendations on management of anticoagulation in thrombocytopenic cancer patients with VTE, but not with atrial fibrillation, are provided by several guidelines [12-14]. These guidelines use VTE acuity (e.g. ≤1 month vs. >1 month since VTE) [12-14], platelet count (e.g. <25,000/μL vs. ≥25,000/μL) [12, 13] and VTE burden (lower vs. higher risk of thrombus progression) [12] to guide management once platelets are below 50,000/μL. Whether these VTE guidelines are implemented in daily practice is unknown.

Two physician surveys provide descriptive data on physician choices in response to case vignettes and selected questions regarding management of anticoagulation prescribed for VTE [15, 16] and other indications [15] in patients with thrombocytopenia and hematological malignancies. Both surveys showed a predominant threshold of 50,000/μL for initial management changes and variation in management across anticoagulation indications. However, other aspects of management differ between the two surveys. For instance, the North American survey (n = 24) indicates a greater tendency to hold or reduce anticoagulation intensity in various scenarios with various depths of thrombocytopenia [16], while in the French survey (n = 98) physicians held therapy infrequently [15]. Importantly, these surveys do not account for effects of other clinical variables on management choice, and do not detail the rationale and methodology of variable selection. The current study aimed to identify the patient and physician characteristics associated with anticoagulation management in patients with thrombocytopenia and hematological malignancy.

2. Methods

2.1. Design

2.1.1. Vignette experiment

We designed a clinical vignette-based experiment that would mimic the clinical setting in which decision-making occurs, similar to a recent study by Ten Cate et al. [17, 18]. Each vignette was intended to represent a fictitious but realistic patient with disease or treatment-related thrombocytopenia and an indication for anticoagulation. This approach was selected since the costs and time associated with studying real-life treatment patterns in this population were significant, and because traditional surveys have several limitations, as detailed above.

2.1.2. Selecting case variables

In order to identify which patient variables should be evaluated in this study, 11 Israeli and Dutch hematologists were interviewed about the management of patients with hematological malignancy, disease or treatment related thrombocytopenia and an indication for anticoagulant therapy. These physicians had varying levels of seniority and experience, and different fields of expertise (Supp. Table 1). The two lines of questioning used were: 1) ``What are the variables influencing anticoagulation management in this setting?"; 2) ``What are the management options that should be considered?". The interviews were recorded and the content was broken down into a list of equally-weighted case variables and management options. The selection process (Supp. Table 2) was influenced by the following factors: 1) a literature review identifying context-specific variables [6]; 2) each variable's cumulative weight (i.e. number of physicians selecting this variable in the interview phase), whereby only variables selected at least twice were considered; 3) the variable's specificity to this setting, meaning that variables specific to cancer and thrombocytopenia were prioritized since this was the topic of the study; 4) variability of levels within a given attribute, whereby lack of variability precluded selection.

The final list included five attributes (i.e. variable categories), each with two to five levels (representing the actual variables) as shown in Fig. 1A. For example, one of the five attributes was ``depth of thrombocytopenia" and the corresponding levels were ``20,000/μL" or ``40,000/μL". Six additional attributes with the potential to influence management were chosen as case constants which comprised the fixed medical history for all cases (e.g. renal function = normal), as shown in Fig. 1B. This was done to improve clarity for the physician and remove ambiguity over variables which could confound decision making.

2.1.3. Creating the vignettes

Each case was comprised of one level from each of the five attributes. Using computer algorithms, as previously described [18], a balanced set of 30 variable combinations (i.e. case vignettes) was selected, as depicted in Supp. Table 3. This fractional factorial design retained sufficient information compared to the full design (270 cases) as shown by its D-efficiency of 99.5% and G-efficiency of 94.7% (Supp. Figure 1). Fig. 1B demonstrates how these variables were used to create case vignettes, and gives examples of two of the 30 vignettes used in this survey. The 30 vignettes were algorithmically subdivided into six diagonal blocks of five vignettes each (Supp. Table 3), meaning that there were six survey versions (A thru F). Each survey participant was randomly assigned to one block of five vignettes and was required to assess bleeding and thrombotic risk and to select an anticoagulation management strategy for each case. Physicians used a visual analog scale from 0 (negligible risk of thrombosis/bleeding) to 10 (highest risk) to subjectively assess bleeding and thrombosis risk based on the clinical variables of a given case [18]. These scores were used as a measure of variability and to explore how physician-assessed bleeding and thrombosis risks affect management.

The primary management (and secondary management) could be one of the following: 1) hold anticoagulation (inferior vena cava [IVC] filter?); 2) continue anticoagulation with no change; 3) no change in anticoagulation but transfuse platelets (platelet transfusion threshold: 30,000/μL vs. 50,000/μL); 4) modify anticoagulation type or dose (type of modification?). The term ``hold" meant temporarily or permanently stopping anticoagulation. We piloted the survey in Italy and no implausible cases or missing management options were identified. The survey was designed as a website which included functionality enabling the responders to contact the study team. Missing data was prevented by way of design, whereby participants could not progress to the next case before all questions were answered. The above process is shown schematically in Supp. Figure 2. The introduction to the questionnaire is shown in the supplemental material and was designed to remove ambiguity.

Each survey containing five cases of anticoagulation and thrombocytopenia was followed by a questionnaire with three cases of antiplatelet therapy (APT) and thrombocytopenia (published recently [19]) which was created using the same methodology. Since the patient variables and management options differed, the anticoagulation and APT cases were created and analyzed separately. These questionnaires were distributed together on the same website for convenience, since the case setting and target population were the same.

2.1.4. Sample and setting

The target population was hematologists, thrombosis specialists and specialists in transfusion medicine. These physicians are often the case managers and likely to make the final management decisions in this setting. An invitation to participate and a link to the survey website was distributed by e-mail to members of national hematology and/or thrombosis societies in Israel, the Netherlands and Italy (n = 886), using societal mailing lists. The survey was anonymous and voluntary, and no compensation was offered. Data on physician characteristics, practice setting and relevant practice patterns were collected from each physician prior to answering the vignettes.

2.1.5. Randomization and blinding

The website assigned consecutive participants with sequential

A: List of selected attributes and levels

Attribute	Level 1 §	Level 2	Level 3	Level 4	Level 5
Hematological malignancy and treatment ¶, ‡	• Diffuse large B cell lymphoma • R-CHOP treatment	• ALL • Asparaginase-based intensive chemotherapy	**• AML** **• High dose cytarabine consolidation**		
Depth of Thrombocytopenia	**40,000/μL**	20,000/μL			
Indication and type of antithrombotic regimen ¶, †	• Atrial fibrillation; CHA_2DS_2-VASc = 2 • Anticoagulation	• Atrial fibrillation; CHA_2DS_2-VASc = 6 • Anticoagulation	• Catheter-related UE-DVT • Anticoagulation	**• Symptomatic PE** **• Anticoagulation**	• Symptomatic PE • Anticoagulation • Aspirin (due to ischemic stroke 4 months earlier)
Time since the anticoagulation indication-defining event	6 months	2 months	**2 weeks**		
Major GI bleeding from an unidentified source	Never	**4 months earlier**	3 weeks earlier		

B: Case vignette examples

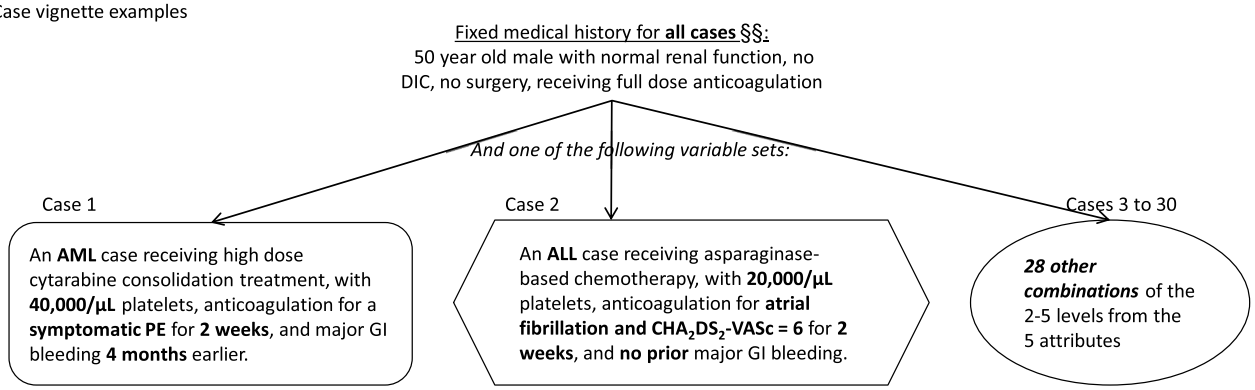


Fig. 1. This figure depicts the attributes and levels which were selected for evaluation in this study (panel A) and shows how case vignettes were built from these variables (panel B) In panel A, attributes represent the variable category (e.g. platelet count) while the levels are the actual variables (e.g. 20,000/μL or 40,000/μL). Each of the 30 selected case vignettes are comprised of one level from each of the 5 attributes. Panel B shows that all cases are comprised of a shared set of case constants§§, as well as 1 of the 30 variable combinations. Case example 1 and 2 are comprised of the 5 levels marked by the rectangle and hexagon, respectively, in panel A. § Level 1 is the reference level for statistical comparisons within each attribute group. Levels with lower thrombotic or bleeding risk were chosen. ¶ This is a composite attribute linking two individual attributes which depend on each other. This was done to prevent implausible variable combinations. ‡ This attribute is a composite of ``duration of thrombocytopenia" (represented by type of disease and treatment) and ``drug-specific thrombotic risk". † This attribute is a composite of ``type of antithrombotic treatment" and ``indication for antithrombotic treatment". §§ Six additional attributes with single levels were chosen as case constants which comprised the fixed medical history for all cases, as shown here. These attributes were: age, sex, renal function, DIC, surgery and anticoagulation dose. This was done to improve clarity for the physician and remove ambiguity over variables which could confound decision making. ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; DIC, disseminated intravascular coagulation; UE-DVT, upper extremity deep vein thrombosis; GI, gastrointestinal; PE, pulmonary embolism; R-CHOP, rituximab cyclophosphamide doxorubicin vincristine prednisone.

questionnaire versions (Supp. Table 3). The questionnaire could only be accessed once at each internet protocol (IP) address, preventing manipulation of questionnaire allocation by the responders. The surveys were anonymous and the IP location was neither linked to the questionnaire data nor included in the data file. Therefore, the study investigators were blinded to allocation.

2.2. Statistical analysis

For analysis, primary management choices were grouped to enable stepwise comparisons between two management strategies at each step. This resulted in three consecutive management steps (A→B→C) as shown in Fig. 2. First, (step A) we compared continuing anticoagulation with holding all anticoagulation. Next, when anticoagulation was continued (step B), we compared any additional intervention to no additional management changes. Last, when additional interventions were chosen (step C), platelet transfusion support alone was compared with modification in type/dose of anticoagulation. At each step, Poisson regression models with cluster-robust variance estimates (to account for the physician-clustered design) [20], were used to calculate the relative risk (RR) and corresponding confidence interval (CI) for choosing one management option (over the other) for each physician or patient variable compared to the reference variable. In addition, physician-assessed bleeding and thrombotic risk scores were analyzed using mixed effects binomial logistic regression, to facilitate interpretation of between-physician variability in how subjective risk assessments translate into clinical decisions. Random intercepts and random slopes were specified for these scores, but omitted if the associated variance was zero. Predicted probability plots, incorporating 15 curves representing physician choices by risk assessment equidistantly distributed across the full range of percentiles, were used to visualize the random components of these models.

These analyses were performed for the three primary management steps (A→B→C) and for the secondary management choice of 50% reduction in therapeutic dose low molecular weight heparin (LMWH) vs. prophylactic dose, when dose modification was chosen (step C.1). Since we expected a limited sample size due to attrition after the primary management choice, other secondary management choices are shown descriptively as the number of cases in which a specific management strategy was selected. Bleeding and thrombotic risk scores for these cases are shown as mean (± standard deviation). Continuous variables were standardized (mean subtracted and scaled by their standard deviations) before inclusion in analyses.

R (*R* Foundation for Statistical Computing, Vienna, Austria) version

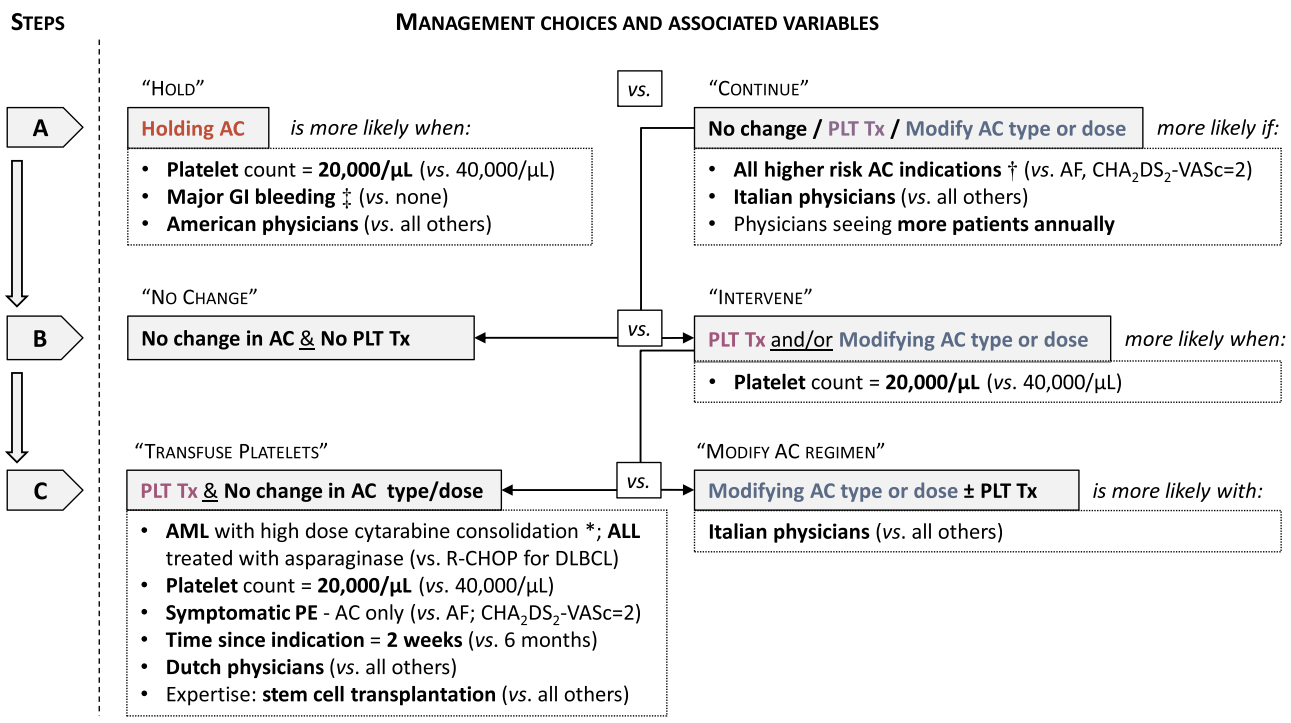


Fig. 2. This figure shows how management choices were grouped and summarizes the variables associated with each management choice, in this case vignette study. The 3 consecutive steps of anticoagulation management (A→B→C) are depicted in and above the gray boxes, which also show how individual management choices are grouped. At each step, there is a choice between 2 actions. The white boxes summarize variables with statistically significant higher odds of choosing a management strategy over the competing one, compared to the reference variable in parentheses ($p < 0.05$, unless otherwise specified). † Higher risk AC indications included the following: AF, CHA_2DS_2-VASc = 6; catheter-related upper extremity deep vein thrombosis; symptomatic PE; symptomatic PE and ischemic stroke with additional aspirin treatment. ‡ Major GI bleeding 4 months or 3 weeks earlier from an unidentified source * $p = 0.056$ AC, anticoagulation; AF, atrial fibrillation; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; DLBCL, diffuse large B cell lymphoma; GI, gastro-intestinal; PE, pulmonary embolism; PLT, platelet; R-CHOP, rituximab cyclophosphamide doxorubicin vincristine prednisone; Tx, transfusion.

3.4.1 was used for all analyses. The `AlgDesign' package was used to create the fractional factorial design. Cluster robust empirical variance estimates were calculated with the `sandwich' package. Mixed effects models were implemented using the package `lme4′. Random effects were visualized using the `visreg' package. Statistical significance was set at a two-sided p value < 0.05.

3. Results

3.1. Sample

The survey was answered by 168 subjects, mainly from Israel (52), Italy (59) and the Netherlands (47), between 21/3/2017 and 29/5/2017. This represents 18% of the 886 physicians directly invited to participate in these countries. Table 1 shows the participants' demographics, practice setting and practice patterns. Briefly, 69 (41%) reported expertise in thrombosis, 140 (83%) were senior physicians and 134 (80%) worked at academic medical centers. Physicians estimated seeing a median of 5 patients [interquartile ratio, IQR = 8] with thrombocytopenia and antithrombotic medication per month.

3.2. Case vignettes

In total, management and bleeding/thrombotic risk were reported for 774 cases amounting to 4.6 cases per physician, on average. Physicians took a median of 71.5 s [IQR, 66.6] to complete each vignette. There were 464 cases with VTE and 310 cases with atrial fibrillation. Overall, modification of anticoagulation type/dose was the management strategy selected most often, chosen by 141 (84%) of unique responders at least once, followed by holding anticoagulation ($n = 93$; 55%) and continuing anticoagulation without platelet transfusion ($n = 71$; 42%). Finally, 62 physicians (37%) selected platelet transfusion support in at least one of the cases.

3.3. Primary management

Fig. 3 shows the distribution of management choices for each of the primary management steps (A→B→C), for all cases. The management among the 310 atrial fibrillation cases was as follows: For CHA_2DS_2-VASc scores of 6 ($n = 151$) and 2 ($n = 159$), respectively, anticoagulation was modified in 71 (47%) and 60 (38%) cases, held in 33 (22%) and 59 (37%), continued with platelet transfusion in 27 (18%) and 13 (8%), and continued without change in 20 (13%) and 27 (17%), respectively.

3.3.1. Associations with patient and physician variables

Fig. 3 shows Forest plots with adjusted RRs (95% CI), derived from the multivariate model, for choosing one management strategy over the other at each step, for every variable compared to its reference. For example, major gastrointestinal (GI) bleeding 3 weeks earlier makes it 52% more likely that a physician would hold anticoagulation than in cases without major GI bleeding (95% CI: 1.03–2.24), as denoted by the arrow in Fig. 3A.

Fig. 2 summarizes case and physician variables which had a statistically significant association with management choices at each of these management steps, based on data in Fig. 3. For instance, holding anticoagulation was preferred over continuing (step A) when platelet counts were 20,000/µL, in case of prior major bleeding and by American physicians. In summary, Figs. 2 and 3 show that physicians usually continue anticoagulation with strategies aimed at mitigating the bleeding risk (i.e. platelet transfusion or change in dose), and that management is affected by multiple patient and physician variables.

Table 1
Characteristics of participating physicians.

Category	Variable group	Level	Number of participants (%) (n = 168)
Physician demographics	Rank	Senior physician with management role	54 (32)
		Senior physician	86 (51)
		Resident	12 (7)
		Fellow [a]	16 (10)
	Primary clinical expertise	General hematology [a]	35 (21)
		Leukemia	4 (2)
		Malignant hematology	28 (17)
		Stem cell transplantation	5 (3)
		Thrombosis	69 (41)
		Transfusion medicine	20 (12)
		Other	7 (4)
	Years of clinical experience	*Median, years [IQR]*	*15 [17]*
	Estimated number of patients [b] seen per month	*Median [IQR]*	*5 [8]*
Practice setting	Country	Israel [a]	52 (31)
		Italy	59 (35)
		Netherlands	47 (28)
		Other [d]	10 (6)
	Hospital type	Academic tertiary referral center [a]	77 (46)
		Academic community hospital	57 (34)
		Community hospital	34 (20)
	Institutional guidelines [c]	Yes	63 (38)
		No [a]	105 (62)
Practice patterns	Multidisciplinary discussion before deciding patient management [b,e]	Yes	133 (79)
		No [a]	35 (21)
	Discussion with patient prior management decision [b]	Yes, and influences management	111 (66)
		Yes, but doesn't influence management	45 (27)
		No [a]	12 (7)

This table shows the demographics, practice setting and relevant practice patterns of the physicians participating in this survey.
[a] This was the reference level for statistical comparisons within this categorical variable group.
[b] Patients with thrombocytopenia and an indication for anticoagulation or antiplatelet medication.
[c] Guidelines for managing patients with thrombocytopenia and an indication for anticoagulation or antiplatelet medication.
[d] This included physicians from the United States (5), Spain (4) and Haiti (1).
[e] Multidisciplinary discussion was defined by asking the following question: Do you usually discuss such cases in a multidisciplinary capacity with the malignant hematology case manager, the physician who prescribed the antithrombotic therapy (or a colleague from the same discipline) and/or a thrombosis and hemostasis specialist?
IQR, inter-quartile range.

Since the primary analysis demonstrated that the anticoagulation was managed differently in VTE and atrial fibrillation cases, a sensitivity analysis was performed in which both types of cases were analyzed separately (Fig. 4). This was performed only for the first management step (i.e. continue vs. hold) due to attrition and diminished power at the subsequent steps. This analysis shows that, for the most part, patient and physician characteristics influence management choices similarly for both types of indications, with the exception of two notable differences. First, physicians were more likely to continue anticoagulation in VTE patients with acute lymphoblastic leukemia receiving asparaginase-based intensive chemotherapy, while the type of hematological disease and treatment regimen did not influence this management step in the atrial fibrillation cases or overall. Second, the time since the anticoagulation indication was significantly related to the management choice in VTE and atrial fibrillation cases separately, albeit in opposite directions, which was obscured in the overall analysis. Specifically, physicians were more likely to continue anticoagulation when a VTE occurred 2 months or 2 weeks earlier (than 6 months earlier), while holding anticoagulation was preferred when the indication was atrial fibrillation diagnosed 2 months earlier (compared to 6 months earlier).

3.4. Secondary management

Secondary management is shown below, according to the primary management choice:

3.4.1. When anticoagulation was held

Physicians chose to hold anticoagulation in 75 VTE cases, 41 of which were pulmonary embolism (PE) cases and 34 were upper extremity deep vein thrombosis. IVC filter placement was pursued in 10 of the 41 PE cases (24.4%), and the corresponding mean bleeding and thrombotic risk scores were 7.30 (± 2.11) and 6.40 (± 1.78), respectively (on a scale of 0 to 10). When physicians opted against an IVC filter, the bleeding and thrombotic risk scores were 6.51 (± 1.85) and 3.75 (± 1.92), respectively. In summary, IVC filters seem to be reserved for cases with higher thrombotic, but not bleeding risk.

3.4.2. When platelets were transfused

Platelet transfusion was chosen in 119 cases to enable full dose anticoagulation. The platelet transfusion target was 30,000/μL in 54 cases (45%), 50,000/μL in 57 (48%) and not predefined in 8 (7%) cases. The mean bleeding and thrombotic risk scores were 5.52 (± 2) and 5.69 (± 2.21), respectively, with a target of 30,000/μL, and 6.02 (± 1.82) and 6.16 (± 2.31), respectively, when 50,000/μL was targeted. Thus, it appears that neither the thrombotic nor the bleeding risk influences the platelet transfusion target.

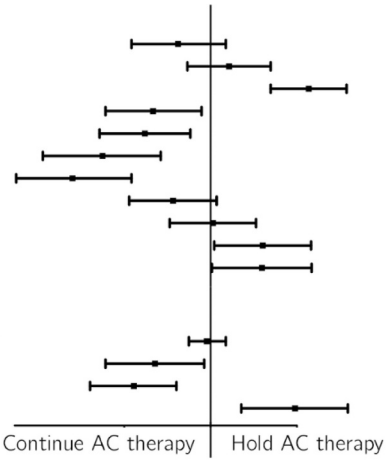
3.4.3. When type or dose of anticoagulation was modified

Anticoagulation dose or type was modified in 277 case vignettes that had anticoagulation only. When the type of pre-thrombocytopenia anticoagulation was a vitamin K antagonist (VKA), 255 (92%) changed to LMWH, 9 (3%) chose a direct oral anticoagulant (DOAC), while 13 (5%) continued VKAs. When baseline anticoagulation was a DOAC, LMWH was chosen in 240 (87%), DOAC dose was halved in 29 (10%) while full dose DOACs were continued in 8 (3%). When LMWH was the baseline anticoagulant, 116 (42%) reduced the dose by 50% (i.e. intermediate dose), 112 (40%) selected prophylactic doses and 49 (18%)

A

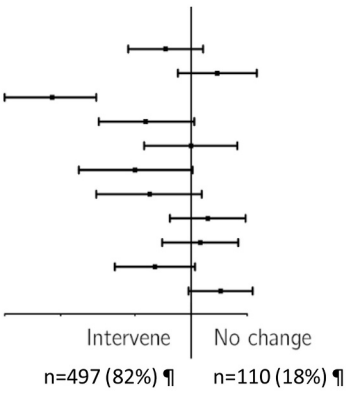
Patient attributes		RR (95% CI)	P
ALL. Asparaginase-based intensive chemotherapy	*	0.77 (0.53-1.13)	0.1881
AML.High dose Cytarabine consolidation	*	1.16 (0.83-1.62)	0.3740
Platelets: 20,000/microliter	†	2.20 (1.62-2.98)	<0.0001
AF; CHA_2DS_2-VASc = 6. AC only	‡	0.63 (0.43-0.93)	0.0185
Symptomatic UE Catheter-related DVT. AC only	‡	0.59 (0.41-0.85)	0.0053
Symptomatic pulmonary embolism. AC only	‡	0.42 (0.26-0.67)	0.0003
Symptomatic PE. AC. Aspirin treatment	‡	0.33 (0.21-0.53)	<0.0001
Time since indication: 2 weeks	§	0.74 (0.52-1.05)	0.0914
Time since indication: 2 months	§	1.02 (0.72-1.44)	0.9034
→ Major GI bleeding 3 weeks earlier	‖	1.52 (1.03-2.24)	0.0341
Major GI bleeding 4 months earlier	‖	1.51 (1.01-2.25)	0.0438

Physician attributes	RR (95% CI)	P
Practicing years	0.97 (0.84-1.13)	0.7295
Number of unique patients seen annually	0.64 (0.43-0.95)	0.0278
Country: Italy (vs, all others)	0.54 (0.38-0.76)	0.0005
Country: United States (vs. all others)	1.97 (1.28-3.01)	0.0019



B

Patient attributes		RR (95% CI)	P
ALL. Asparaginase-based intensive chemotherapy	*	0.73 (0.46-1.16)	0.1810
AML.High dose Cytarabine consolidation	*	1.38 (0.85-2.25)	0.1878
Platelets: 20,000/microliter	†	0.18 (0.10-0.31)	<0.0001
AF; CHA_2DS_2-VASc = 6. AC only	‡	0.57 (0.32-1.04)	0.0657
Symptomatic UE Catheter-related DVT. AC only	‡	1.00 (0.56-1.77)	0.9892
Symptomatic pulmonary embolism. AC only	‡	0.50 (0.25-1.02)	0.0565
Symptomatic PE. AC. Aspirin treatment	‡	0.60 (0.31-1.14)	0.1162
Time since indication: 2 weeks	§	1.23 (0.77-1.96)	0.3800
Time since indication: 2 months	§	1.12 (0.70-1.79)	0.6450
Major GI bleeding 3 weeks earlier	‖	0.64 (0.39-1.05)	0.0776
Major GI bleeding 4 months earlier	‖	1.44 (0.97-2.14)	0.0725



C

Patient attributes		RR (95% CI)	P
ALL. Asparaginase-based intensive chemotherapy	*	1.60 (1.05-2.45)	0.0291
AML.High dose Cytarabine consolidation	*	1.63 (0.99-2.70)	0.0566
Platelets: 20,000/microliter	†	2.15 (1.46-3.17)	0.0001
AF; CHA_2DS_2-VASc = 6. AC only	‡	1.56 (0.84-2.87)	0.1581
Symptomatic UE Catheter-related DVT. AC only	‡	1.62 (0.84-3.12)	0.1509
Symptomatic pulmonary embolism. AC only	‡	2.25 (1.17-4.30)	0.0145
Symptomatic PE. AC. Aspirin treatment	‡	0.95 (0.46-1.96)	0.8940
Time since indication: 2 weeks	§	1.68 (1.05-2.66)	0.0294
Time since indication: 2 months	§	0.99 (0.65-1.50)	0.9584
Major GI bleeding 3 weeks earlier	‖	0.97 (0.62-1.52)	0.8905
Major GI bleeding 4 months earlier	‖	0.93 (0.61-1.42)	0.7207

Physician attributes	RR (95% CI)	P
Country: Italy (vs. all others)	0.51 (0.31-0.84)	0.0086
Country: Netherlands (vs. all others)	1.91 (1.26-2.91)	0.0026
Specialty: stem cell (vs. all others)	3.33 (2.23-4.98)	<0.0001

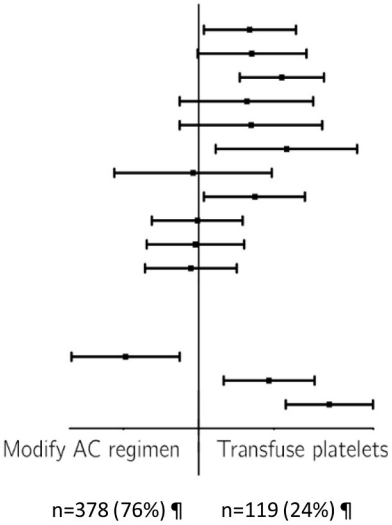
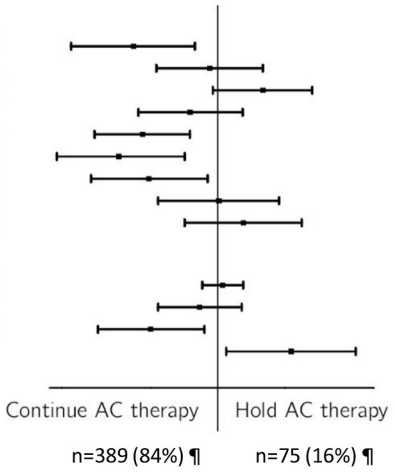


Fig. 3. This figure shows forest plots with RRs (95% CI, p value), derived from a cluster robust Poisson regression model, for selecting a management strategy (over the other) for each patient or physician variable in comparison to reference variables. These plots depict only the variables that remained in the final multivariable models. Plots A, B and C show management steps A, B and C, respectively. The arrow to the left of plot A denotes an example discussed in the manuscript. Patient variables were compared to reference variables signified by adjacent symbols, while physician variables were compared to all other levels within that attribute. The patient and physician attributes are detailed in Fig. 1 and Table 1, respectively. * Diffuse large B cell lymphoma, R-CHOP treatment. † 40,000/μL. ‡ AF, CHA_2DS_2-VASc = 2, AC only. § 6 months. ‖ No prior GI bleeding. ¶ Number of cases in which the management strategy was selected (%). AC, anticoagulation; AF, atrial fibrillation; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; DVT, deep vein thrombosis; GI, gastro-intestinal; PE, pulmonary embolism; R-CHOP, rituximab cyclophosphamide doxorubicin vincristine prednisone; RR, relative risk; UE, upper extremity.

A Venous thromboembolism cases

Patient attributes		RR (95% CI)	P
ALL. Asparaginase-based intensive chemotherapy	*	0.42 (0.22-0.79)	0.0077
AML.High dose Cytarabine consolidation	*	0.92 (0.53-1.59)	0.7592
Platelets: 20,000/microliter	†	1.59 (0.95-2.65)	0.0778
Symptomatic pulmonary embolism. AC only	‡	0.75 (0.44-1.29)	0.2990
Symptomatic PE. AC. Aspirin treatment	‡	0.46 (0.28-0.75)	0.0020
Time since indication: 2 weeks	§	0.36 (0.19-0.71)	0.0028
Time since indication: 2 months	§	0.49 (0.27-0.90)	0.0218
Major GI bleeding 3 weeks earlier	‖	1.01 (0.54-1.88)	0.9862
Major GI bleeding 4 months earlier	‖	1.30 (0.71-2.38)	0.4012
Physician attributes		**RR (95% CI)**	**P**
Practicing years		1.05 (0.85-1.30)	0.6599
Number of unique patients seen annually		0.83 (0.54-1.28)	0.3931
Country: Italy (vs, all others)		0.50 (0.29-0.87)	0.0141
Country: United States (vs, all others)		2.13 (1.09-4.15)	0.0265



B Atrial fibrillation cases

Patient attributes		RR (95% CI)	P
ALL. Asparaginase-based intensive chemotherapy	*	0.68 (0.30-1.52)	0.3470
AML.High dose Cytarabine consolidation	*	0.75 (0.40-1.41)	0.3763
Platelets: 20,000/microliter	†	1.86 (0.96-3.58)	0.0645
AF; CHA_2DS_2-VASc = 6. AC only	‡‡	0.62 (0.42-0.93)	0.0219
Time since indication: 2 weeks	§	1.82 (0.96-3.44)	0.0658
Time since indication: 2 months	§	2.30 (1.15-4.60)	0.0181
Major GI bleeding 3 weeks earlier	‖	1.68 (0.94-2.98)	0.0786
Major GI bleeding 4 months earlier	‖	1.35 (0.74-2.46)	0.3238
Physician attributes		**RR (95% CI)**	**P**
Practicing years		0.90 (0.73-1.11)	0.3301
Number of unique patients seen annually		0.53 (0.32-0.90)	0.0181
Country: Italy (vs, all others)		0.57 (0.36-0.91)	0.0187
Country: United States (vs, all others)		1.62 (0.87-3.03)	0.1314

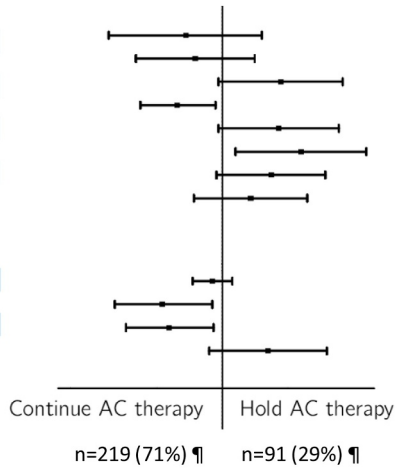


Fig. 4. This figure shows forest plots with RRs (95% CI, p value), derived from a cluster robust Poisson regression model, for holding AC (over continuing AC) for each patient or physician variable in comparison to reference variables, stratified according to type of AC indication. Plot A depicts cases with venous thromboembolism and plot B shows AF cases. Patient variables were compared to reference variables signified by adjacent symbols, while physician variables were compared to all other levels within that attribute. The patient and physician attributes are detailed in Fig. 1 and Table 1, respectively. * Diffuse large B cell lymphoma, R-CHOP treatment. † 40,000/μL. ‡ Catheter-related upper extremity deep vein thrombosis, AC only. § 6 months. ‖ No prior GI bleeding. ¶ Number of cases in which the management strategy was selected (%). ‡‡ AF, CHA_2DS_2-VASc = 2, AC only. AC, anticoagulation; AF, atrial fibrillation; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; GI, gastro-intestinal; PE, pulmonary embolism; R-CHOP, rituximab cyclophosphamide doxorubicin vincristine prednisone; RR, relative risk.

continued full dose LMWH. As shown in Supp. Figure 3, intermediate LMWH doses (over prophylactic doses) was more likely in case of symptomatic PE than in atrial fibrillation with CHA_2DS_2-VASc = 2 and when there were institutional management protocols, while prophylactic doses were preferred when the platelet count was 20,000/μL (vs. 40,000/μL).

3.5. Subjective assessment of bleeding and thrombotic risk

Across all cases, physicians subjectively assessed a mean thrombotic risk of 5.4 (± 2.2) and a mean bleeding risk of 6.1 (± 1.9), on a scale of 0–10.

3.5.1. Associations with management

The ORs (95% CI) for choosing one management strategy over the other for increasing bleeding and thrombotic risks are shown in Table 2. Stepwise, increasing bleeding risk was associated with holding anticoagulation (step A), platelet transfusion support or modifying the regimen (step B), and modifying anticoagulation dose/type (step C). Increasing thrombotic risk correlated with continuing anticoagulation (step A) and intermediate LMWH doses (over prophylactic does, step C.1). Thus, physicians' decisions appear to be driven by a complex interaction between perceived bleeding and thrombotic risks.

3.5.2. Variability between physicians

The variability between physicians yielded 15 distinct approaches, which represent the full spectrum of variability between physicians. Fig. 5 depicts the relationship between management and physician-assessed thrombotic risk selected by individual physicians. For example, at step A, the change in management preference occurred at thrombotic risk scores of two to five, whereby at scores below this threshold holding anticoagulation was more probable, and at scores above this

Table 2
Associations between increasing bleeding or thrombotic risk [a] and management choice.

Step	Management choice	Increasing bleeding risk, OR (95% CI) [a]	Increasing thrombotic risk, OR (95% CI) [a]
A	Hold anticoagulation (*over continuing* [b])	1.57 (1.34–1.83) [e]	0.50 (0.42–0.59) [e]
B [c]	Platelet transfusion support or modify the regimen (*over continuing without change*)	1.97 (1.59–2.44) [e]	1.08 (0.92–1.28)
C	Platelet transfusion support (*over modifying anticoagulation*)	0.75 (0.60–0.93) [e]	0.96 (0.78–1.19)
C.1 [d]	Reduce therapeutic LMWH dose by 50% (*over using prophylactic dose*)	0.87 (0.70–1.08)	1.43 (1.15–1.79) [e]

This table shows the odds ratio for selecting a specific management strategy (over the other) by increasing bleeding or thrombotic risk.

[a] Subjective physician assessment of bleeding and thrombotic risk associated with a given case vignette, using separate scales of 0 (negligible risk of thrombosis/bleeding) to 10 (highest). ORs indicate the change in odds of the outcome (e.g., holding anticoagulation) per unit increase in the scale (e.g., going from a bleeding risk of 6/10 to 7/10 increases the likeliness of holding anticoagulation by 57%).

[b] with or without platelet transfusion support or change in anticoagulant dose/type.

[c] When anticoagulation was continued.

[d] When anticoagulation was modified.

[e] $p < 0.05$

CI, confidence interval; *LMWH*, low molecular weight heparin; *OR*, odds ratio.

range continuing anticoagulation was more probable. In plots A and D, the differing intercepts indicate that the average response to a given risk differs slightly by physician, while the similarity in the slopes indicate that the rate at which a given management strategy is pursued is virtually the same for all physicians. In contrast, in plots B and C, although the rate at which a given management strategy is pursued across cases differs widely between physicians, most physicians consistently preferred one management strategy over the other.

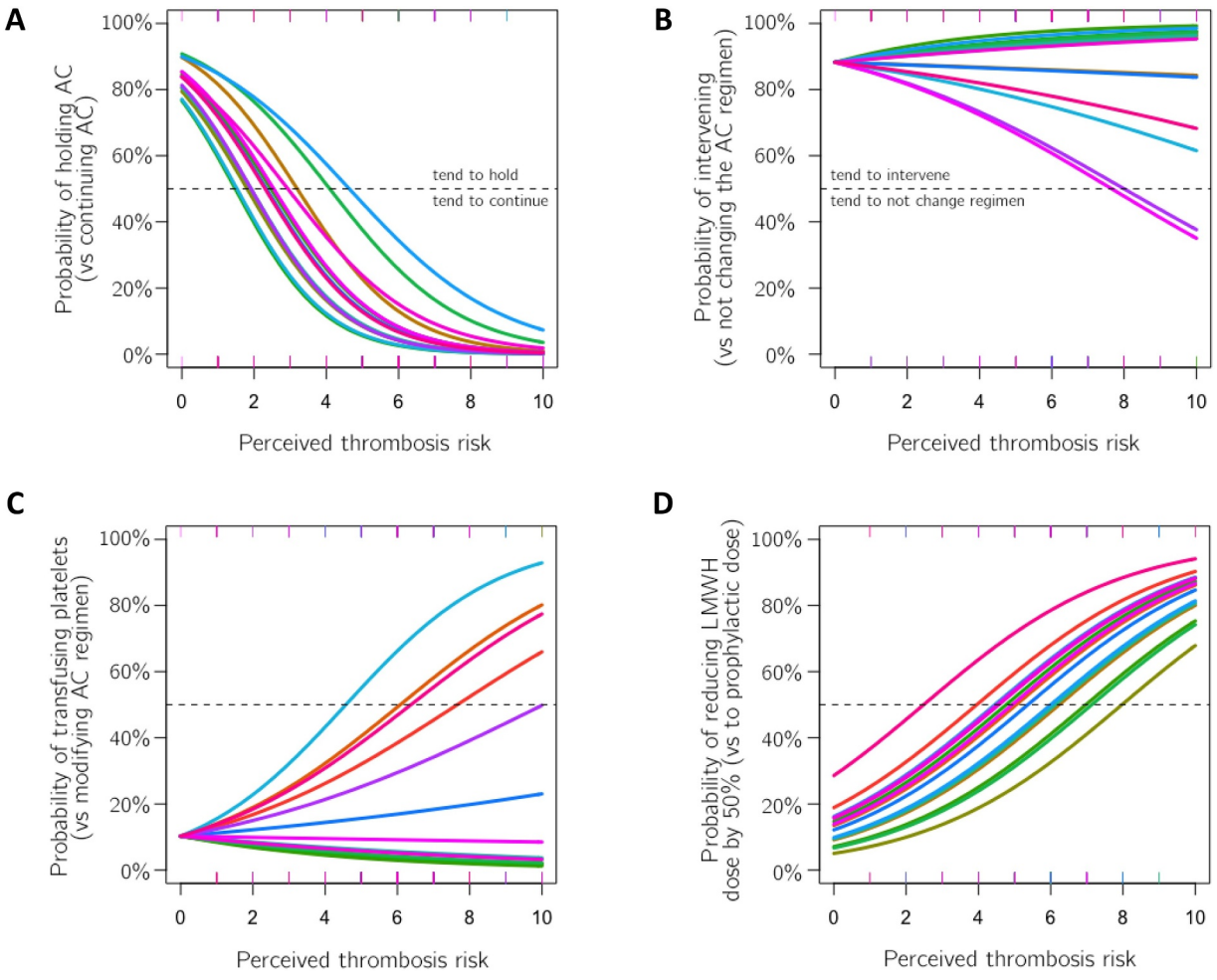


Fig. 5. This figure shows the physician-assessed thrombosis risk and its variable impact on clinical decision making in this case vignette study. The relationship between thrombosis risk perception and clinical decisions was allowed to vary between physicians both in terms of intercept and slope, unless either or both were associated with close to zero between-participant variance. Random intercepts are indicated by varying starting points (i.e. different position on *y*-axis when *x* is equal to 0), while random slopes are visualized as differential slopes between curves (i.e. differences in direction and/or intensity of change). Each panel (A-D) shows a different management step. Each curve represents all the cases answered by one physician and shows the probability of choosing a given management over another (*y* axis) according to the thrombotic risk assessed by physicians on a scale of 0 to 10 (*x* axis). 15 curves are shown in each panel, representing the full spectrum of variability between physicians. These curves are equidistantly distributed across the full range of risk assessment percentiles. AC, anticoagulation; LMWH, low molecular weight heparin.

4. Discussion

This clinical vignette-based experiment provides comprehensive data on factors influencing management in patients with hypoproliferative thrombocytopenia, hematological malignancy and an indication for anticoagulation, shedding light on current practice as reported by 168 physicians working in different settings. Management is affected by platelet count, anticoagulation indication, time since indication, prior major GI bleeding, and the type and treatment of the underlying hematological disease, as well as physician demographics and practice setting. This study indicates what the widely accepted management strategies are. These strategies, and possibly others, should be assessed prospectively to ascertain effectiveness. In fact, the current study was a preparatory phase in planning a prospective observational study in this field, which is currently recruiting patients [21]. Furthermore, the variables identified in the current analysis should be considered as potential confounders when analyzing clinical outcomes.

The first step in the decision process is to decide whether to suspend anticoagulation or to continue. In this study, 78% of all cases had anticoagulation continued. Continuing anticoagulation was preferred in cases with higher risk anticoagulation indications, while holding was more likely with lower platelet counts and prior major GI bleeding. IVC filters were recommended in one in four patients with PE whose anticoagulation was held, especially in those with higher perceived thrombotic risk. This is congruent with guidelines advising that IVC filters be considered in thrombocytopenic cancer patients with VTE and a high thrombotic risk, in whom platelet transfusions cannot facilitate anticoagulation [12, 13].

The management of cases with atrial fibrillation and thrombocytopenia is of special interest since there are scarce patient data and no guidelines. In the current study, almost two thirds of lower risk atrial fibrillation cases (CHA_2DS_2-VASc = 2), had anticoagulation continued during thrombocytopenia. This is in contrast to hypothesis-generating data that support withholding anticoagulation in atrial fibrillation when platelets are $<50{,}000/\mu L$, unless justified by a high thrombotic risk [6, 24, 25]. If this is confirmed in ongoing prospective studies [21, 26], guidance statements ought to be drafted and implemented in order to change clinical practice. Since the risk of arterial thrombosis is higher in cancer [27], the risk-benefit ratio may favor anticoagulation in patients with high CHA_2DS_2-VASc scores. Indeed, patients with atrial fibrillation and higher thrombotic risk (CHA_2DS_2-VASc = 6) were more likely to have anticoagulation continued (over holding) than in cases with CHA_2DS_2-VASc = 2. Nonetheless, anticoagulation was held in over one in five cases with CHA_2DS_2-VASc = 6. Furthermore, atrial fibrillation necessitating long term anticoagulation presents different thrombotic challenges than VTE in cancer patients, as recently reviewed and addressed in society guidelines [22, 23]. This is reflected by differences in approach to management of VTE and atrial fibrillation cases in this study, especially regarding how time since the anticoagulation indication affects management. The preference of continuing anticoagulation in acute and sub-acute VTE patients is generally in line with society guidelines [12]. In contrast, in atrial fibrillation cases, holding anticoagulation was more likely with more acute indications than with long-standing ones (i.e. 6 months earlier). This is in line with practice in a recent retrospective cohort study of this patient population [27]. Accordingly, the rationale and safety of this approach to atrial fibrillation acuity needs to be studied. In addition, future thrombocytopenia-specific guidelines should suggest how time since diagnosis of atrial fibrillation should influence management.

Once anticoagulation was continued, additional actions aimed at mitigating the bleeding risk were taken in most (82%) cases. One strategy, used in one in five cases, was to transfuse platelets at increased platelet thresholds in order to enable anticoagulation. There was no clear preference towards either of the transfusion targets in our survey (i.e. 50,000/μL or 30,000/μL). The other approach, used in most cases, was to reduce the dose of LMWH, although there is scarce data to support this practice [28]. Prophylactic and intermediate doses, which are considered equally acceptable dose reductions [12], were used in a similar proportion of cases. DOAC doses were reduced in one in 10 cases in this study, although there is currently no data on DOAC dose reduction due to thrombocytopenia [4, 29-31].

Overall, platelet count and the type and acuity of the indication for anticoagulation were associated with management, in a manner that was compatible with current VTE guidelines [12-14]. DOACs were changed to LMWH in the vast majority of cases, in line with a recent guidance statement indicating that DOACs may not be appropriate when platelets are $<50{,}000/\mu L$ [12]. There is indeed no evidence supporting the safety of DOACs in thrombocytopenia since patients with platelet counts below 50,000–100,000/μL were excluded from the clinical trials [4, 29-31]. Moreover, there is reason to exercise caution because of an increase in clinically-relevant bleeding with edoxaban and rivaroxaban compared to dalteparin for treatment of cancer-associated thrombosis [4, 29]. Of note, the type of malignancy and prior GI bleeding influence management but are not reflected in current guidelines, but there is some data suggesting the clinical importance of this attribute in these patients [7, 9]. We suggest that these variables be addressed in future guidelines since they influence reported practice.

Another important finding is that practice setting (i.e. country, having institutional protocols guiding management, type of hospital) and physician demographics (i.e. primary clinical expertise, volume of patients seen) influenced management choices. Compared to all others, American physicians were more likely to hold anticoagulation, while their Italian counterparts preferred continuing anticoagulation. When anticoagulation was continued, Italian physicians (compared to all others) selected dose reduction over platelet transfusion, which is compatible with an Italian expert consensus statement [5]. Dutch physicians were more likely to transfuse platelets than modify anticoagulation, in line with the institutional protocol employed at the primary Dutch study center, which was the only primary study center that had an institutional protocol (Supp. Table 4). The absolute frequencies of management choices underlying these relative risks, stratified by country, are shown in Supp. Table 5. The differences in management across the participating countries resemble the contrasting approaches seen between recently published North American and French surveys [15, 16]. Based upon self-assessed thrombotic risk, the main variability in decision-making lies with managing patients in whom anticoagulation was continued. This variability in management could be the result of uncertainty stemming from lack of high-quality evidence. Finally, almost all physicians employed a discussion with the patient, which is encouraging given the complexity of these decisions and lack of conclusive evidence. However, 1 in 4 physicians said that this discussion would not influence management.

This study has a number of unique strengths. The sample included physicians with a wide range of clinical expertise from different types of hospitals across at least 36 geographical regions. The methodology enabled us to provide estimates on the magnitude and statistical significance of the effect that each factor has on management, in contrast to prior descriptive surveys [15, 16]. Moreover, the multivariate analysis accounts for associations between variables, while the mixed effects model considers different types of variance. In addition, when answering conventional surveys, physicians may adapt their response to match what is perceived to be the desirable answer. In the current study, the use of case vignettes that are composed of varying patient characteristics and the lack of suggestive questions in favor of a set of standardized options, minimize the potential for this bias and provide a much richer dataset that more closely approximates actual practice. Importantly, our study has no clinically implausible findings, supporting the validity and reliability of the study findings.

There are several limitations that warrant discussion. First, the management process was assessed in an artificial setting and not with real patients. While the optimal management strategy is the most important factor driving decisions, there is a lack of prospective high-

quality evidence to inform management in this setting. Management varied greatly between prior retrospective studies, possibly explaining contrasting bleeding and thrombosis rates [6]. The methodology of the current study is typically used to assess practice when the costs, time and logistics associated with studying real-life treatment patterns in this population are deemed prohibitive. Second, we can only discuss the variables and management strategies chosen for investigation. It must be emphasized that variables not evaluated in this study may still affect management of these patients in clinical practice. Several variables identified as predictors of bleeding in cancer patients receiving anticoagulation, such as older age and renal failure, were not evaluated in this study [32, 33]. Nonetheless, these variables and others were included as case constants, meaning that they were the same across all cases and would not affect decisions in this study. Incorporating these additional variables in the cases would have created too much variability and an unfeasible sample size. Of note, variables not represented at all in the study cases, such as body weight, may have introduced some degree of ambiguity. Furthermore, certain relevant physician characteristics may not have been documented, which could have led to some degree of residual confounding. Third, the management choices reported by physicians may not reflect actual practice. However, the survey's anonymous nature reduces the potential for this bias. Fourth, only 18% of the target population answered the survey, potentially affecting the generalizability of the study. We could not evaluate selection bias since demographic data on the target population were not available. In this respect, a disproportionate number of responders were senior physicians with a management role, suggesting some degree of selection bias. The potential influence of sampling and selection bias on the study results is reduced by incorporating multiple physician demographics and practice settings into the multivariate model. Nonetheless, there may be residual confounding by variables that were not considered. Accordingly, the results may not be generalizable to all countries and practice settings. Last, the target population included hematologists, thrombosis specialists and specialists in transfusion medicine but not cardiologists who are often consulted in this context and in some instances, are the primary case managers. This population was chosen since the majority of the cases presented in this study are managed as inpatients on the hematology ward. Therefore, we considered hematologists to be most likely to make the final management decision, possibly after consulting with other disciplines, such as cardiologists, as specified in the introduction to the questionnaire (shown in the supplemental material). Reassuringly, the vast majority indicated that their management decision would be made after a discussion with a multidisciplinary team. We recognize that in some settings cardiologists may make the final management decision, especially in the context of atrial fibrillation. Therefore, future research elucidating the management approach employed by cardiologists is warranted.

In conclusion, anticoagulation is continued in most thrombocytopenic patients with hematological malignancy and anticoagulation, usually with additional measures to reduce bleeding risk. The management process is clinically reasonable for VTE cases and compatible with current guidelines, however some factors influencing practice are not reflected in these guidelines. The practice of continuing anticoagulation in most cases with low risk atrial fibrillation and the preference towards holding anticoagulation in recently diagnosed atrial fibrillation warrant investigation. Ongoing studies will determine how these approaches affect clinical outcomes.

Declaration of Competing Interest

Dr. Leader reports personal fees from Bayer and Pfizer outside the submitted work. Dr.. Spectre reports personal fees from Bayer, personal fees from Pfizer, personal fees from Sanofi, personal fees from Boeringer Ingelheim, outside the submitted work. Dr. Falanga reports personal fees from LEO Pharma, personal fees from Bayer, outside the submitted work. Dr. ten Cate reports grants and personal fees from Bayer, grants from Pfizer, grants from Bristol-Myers Squibb, outside the submitted work. None of the other authors have any actual or potential conflicts of interest capable of influencing judgment.

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Supplementary materials

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