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ORIGINAL ARTICLE

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Platelet transfusion and tranexamic acid to prevent bleeding in outpatients with a hematological disease: A Dutch nationwide survey

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Abstract

Objectives: There is scarce evidence about the effectiveness of anti-bleeding measures in hematological outpatients experiencing persistent severe thrombocytopenia. We aim to describe clinical practice and clinicians' considerations on the administration of prophylactic platelet transfusions and tranexamic acid (TXA) to outpatients with acute leukemia, myelodysplastic syndrome (MDS), or aplastic anemia (AA) in the Netherlands.

Methods: We conducted an online survey among members of the Dutch Society for Hematology.

Results: The survey was filled out by 73 respondents. Prophylactic platelet transfusions are widely used in acute leukemia and MDS outpatients receiving disease-modifying treatments (87%-98% of respondents). TXA is predominantly prescribed in case of bleeding (tendency) (71%-88% of respondents). Conditions potentially increasing bleeding risks highly variably influence clinicians' decision making on anti-bleeding regimens, which includes a wide range in adhered platelet thresholds.

Conclusion: Considering that both the contribution of prophylactic platelet transfusions as well as TXA to limiting bleeding is insufficiently evidence-based, there is an urgent need for trials on optimal anti-bleeding strategies in this outpatient population, which should encompass efficacy, logistic, financial, and quality-of-life aspects.

KEYWORDS

acute myeloid leukemia, aplastic anemia and bone marrow failure, myelodysplastic syndromes, socioeconomics and ethics, supportive care, thrombocytes

1 | INTRODUCTION

Thrombocytopenia due to bone marrow disease and/or myelotoxic treatments is a common phenomenon in hematological patients. In order to prevent clinically relevant bleeding, prophylactic platelet transfusions (ie, indicated by a platelet count threshold, in the absence of bleeding) are administered.[1,2] Indeed, randomized controlled trials demonstrated reduced bleeding incidences with such a strategy in hospitalized patients undergoing intensive chemotherapy and/or allogeneic stem cell transplantations.[3,4] Nevertheless,

clinically relevant bleeding is not eliminated and alternative anti-bleeding strategies are nowadays explored, including alternative treatments and the identification of reliable bleeding predictors.[5,6]

Next to this intensively treated patient population, a subgroup of hematological outpatients suffers from persistent severe thrombocytopenia due to, for example, refractory bone marrow disease, inducing chronic bone marrow failure. Actual bleeding risks for this specific outpatient population are unknown, but one may argue those to be relatively low compared to the intensively treated hospitalized patients. Conversely, due to the chronic state of their low platelet counts, a large fraction of this population may eventually experience significant bleeding. One Canadian registry for patients with myelodysplastic syndrome (MDS) and secondary acute myeloid leukemia (AML) indeed reported bleeding in 83% of patients during a median follow-up period of 27 weeks, with 12% of patients experiencing WHO grade 3 or 4 bleeding.[7,8] However, the attributive effect of platelet transfusion in this outpatient setting is unknown, although a few small observational studies suggested safety, logistical, and financial advantages of a stringent platelet transfusion policy.[7,9] One randomized trial, which could have gained important insights into the efficacy of prophylactic transfusions in outpatients, was unfortunately terminated early because of poor recruitment.[10] Therefore, so far high-quality evidence on any potential benefits weighted against adverse risks of a prophylactic versus therapeutic platelet transfusion regimens in this outpatient population is lacking.

Consequently, current guidelines are based on expert opinion and mainly advice to only transfuse the thrombocytopenic (out) patient population suffering from chronic bone marrow failure on a therapeutic rather than on a prophylactic base.[11-13] Other guidelines suggest to consider an adjusted platelet count threshold,[14] while the recently updated Dutch transfusion guideline in this respect lacks any recommendations.[15]

In addition to platelet transfusions, preventative anti-bleeding measures may also include the use of the anti-fibrinolytic drug tranexamic acid (TXA).[11] Compared to platelet transfusions, TXA has the advantage of oral administration, thereby overcoming the necessity of intramural care. Outside the hematological setting, the use of TXA has proven to be beneficial in therapeutic settings, reducing blood loss, and limiting morbidity and mortality during, for example massive trauma, surgery, and obstetric bleeding. Evidence to justify its use for hematological thrombocytopenic patients is scarce and inconclusive.[16] Remarkably, the aforementioned Canadian MDS registry study did not find differences in grade 3-4 bleeding frequencies among patients treated with TXA versus TXA and/or prophylactic platelet transfusions versus neither of those, although confounding by indication should be considered.[7] Hopefully several ongoing large-scaled randomized studies in hospitalized patients will clarify the possible prophylactic role of TXA, with or without additional platelets.[5,17]

However, the present lack of knowledge is likely to result in a high variability of practices on how best to prevent bleeding in hemato-oncologic outpatients.

To assess this, we performed nationwide survey among hematology clinicians across the Netherlands regarding the extent of use, and considerations on indications of platelet transfusions and TXA in hematological outpatients suffering from persistent severe thrombocytopenia due to underlying bone marrow disease.

Summary statements

1. What is the new aspect of your work?

   It is currently unknown how to best prevent bleedings in acquired persistent severe thrombocytopenia, and this survey provides insight in current clinical practices of anti-bleeding strategies among hematological outpatients in the Netherlands.

2. What is the central finding of your work?

   Currently applied preventive anti-bleeding strategies for patients with acquired persistent thrombocytopenia lack uniformity; platelet transfusions are the mainstay of prophylactic strategies in this setting, but there is a large interphysician variability in decisions made on indications and agents used, both being strongly but heterogeneously influenced by various clinical conditions.

3. What is (or could be) the specific clinical relevance of your work?

   These results underline the current gap in knowledge and emphasize the need for further research, including a RCT on the effectiveness, safety and patients' burdens of various anti-bleeding strategies, ultimately aiming to improve supportive care in this specific stage of disease.

2 | METHODS

A nationwide Web-based survey of hematology clinicians was conducted in the Netherlands between October 2019 and February 2020.

The questionnaire was accessible via a weblink and distributed via email by the Dutch Society for Hematology. Members comprise the large majority of registered hematologists in the Netherlands as well as a proportion of hematology residents and physician assistants. All are involved in treatment decisions on bleeding prevention in the Netherlands, either completely independent or following consultation of a senior hematologist. Reminders were sent out via the newsletter of the society and via personal communication by members of the benign working party of the society to colleagues in their region. Prior to distribution, the survey was piloted among the study team and three other hematologists to assess content and time required for survey completion.

Study data were collected in a Web-based database (Castor) and securely stored at the Leiden University Medical Center.

The survey (translation available via the Supplementary Material) focused specifically on acute leukemia, myelodysplastic

syndrome (MDS), and aplastic anemia (AA) outpatients. Since we expected that the disease stage, and appurtenant treatment, might influence the chosen prophylactic bleeding policies, we specified several patient groups. With regard to acute leukemia and MDS, questions were subdivided based on whether patients were 1. in between or shortly after curatively intended induction chemotherapy courses; 2. receiving hypomethylating agents with a palliative intention; and 3. ineligible for any disease-modifying treatment. Questions on AA involved all patients outside the context of a hematopoietic allogeneic stem cell transplantation. Specific domains of the questionnaire involved: 1. clinician practices' demographics; 2. use of a prophylactic platelet transfusion policy and its thresholds; 3. clinical conditions determining the use of a prophylactic platelet transfusion policy; 4. prophylactic use of TXA; 5. clinical conditions determining the use of TXA; 6. clinicians' estimations on bleeding risks with a prophylactic versus therapeutic platelet transfusion policy.

The survey used the following definitions: prophylactic platelet transfusions, that is transfusions prescribed based on a certain platelet count threshold which may differ per patient or physician; therapeutic platelet transfusions, that is transfusions prescribed in case of (clinically relevant) bleeding or preceding an intervention; clinically relevant bleeding, that is bleeding events that lead to (additional) medical care, for example visit to the emergency department or additional outpatient clinic visit on short term, therapeutic transfusions, admission to the hospital, additional diagnostics, or treatments. Any tendency to bleeding referred to minor, clinically non-relevant bleeding, for example petechiae.

Due to the descriptive nature of our survey, no formal statistics were performed but results are presented descriptively.

3 | RESULTS

Of the 562 members contacted, 73 (13%) responded at least to one domain (Table 1). Of these 73 respondents, 55% completed the entire questionnaire. The majority of respondents were hematologists (81%), working in hospitals which perform both allogeneic and autologous stem cell transplantations (45%, ie academic hospitals), with a median working experience of 10.5 years. Respondents represented 38 out of 89 (43%) Dutch hospitals.

A minority of respondents worked at hospitals that do not treat some of the patient categories covered by this survey (Table 1). In those instances, these respondents were excluded from these particular calculations.

TABLE 1 Characteristics of respondents

	Total n = 73	
Function[a]		
Hematologist	59	(81%)
Resident hematology	4	(6%)
Other[b]	10	(14%)
Years of working experience in hematology[c]	10.5	(5-19)
Echelon classification of hospital[d]		
Level A	33	(45%)
Level B	7	(10%)
Level C-HIC	6	(8%)
Level C-SCT	6	(8%)
Level C-HIC + C-SCT	8	(11%)
Level D	9	(12%)
Unknown	4	(6%)
Outpatient population that is treated per respondent[e]		
Myelodysplastic syndrome with chemotherapy	60	(82%)
Myelodysplastic syndrome with hypomethylating agents	69	(95%)
Myelodysplastic syndrome without disease-modifying treatment	68	(93%)
Leukemia with chemotherapy	58	(80%)
Leukemia with hypomethylating agents	68	(93%)
Leukemia without disease-modifying treatment	71	(97%)
Aplastic anemia	51	(70%)

[a]Values are numbers (percentage of total of respondents).

[b]Physician assistants (n = 7), pediatric hematologist (n = 1), resident not in training for hematologist (n = 1), oncologist with hematology care (n = 1).

[c]Median (IQR), 72 participants responded.

[d]Level A hospitals are allowed to perform allogeneic and autologous stem cell transplantations (SCT); Level B hospitals are allowed to perform autologous SCT; Level C-HIC hospitals deliver intensive hematological care, for example acute leukemia treatment; Level C-SCT hospitals deliver postautologous stem cell transplantation care; Level D hospitals deliver non-intensive hematological care, that is treatment that is not expected to induce intense and long-lasting pancytopenia.

[e]Values are numbers (percentage of total of respondents) of those who treat the specific patient population at their clinical practice.

3.1 | Use of prophylactic anti-bleeding therapies

Figure 1 describes numbers and percentages of respondents who routinely use prophylactic platelet transfusions or TXA per patient category. Almost all actively treated MDS and acute leukemia outpatients are offered prophylactic platelet transfusions (87%-98%), while this is only considered for the minority of patients ineligible for or refractory to any disease-modifying treatment (35% and 34%). Similarly, the vast majority of aplastic anemia patients receive prophylactic platelet transfusions (82%). Oppositely, TXA is hardly routinely prescribed in any of these patient populations (0%-7%), but is generally regarded as supportive care in situations of clinically relevant bleeding or bleeding tendency (71%-88%). Here, TXA is mostly used as an additive to prophylactic platelet transfusions in patients receiving any type of treatment (74% to 100%), while in the

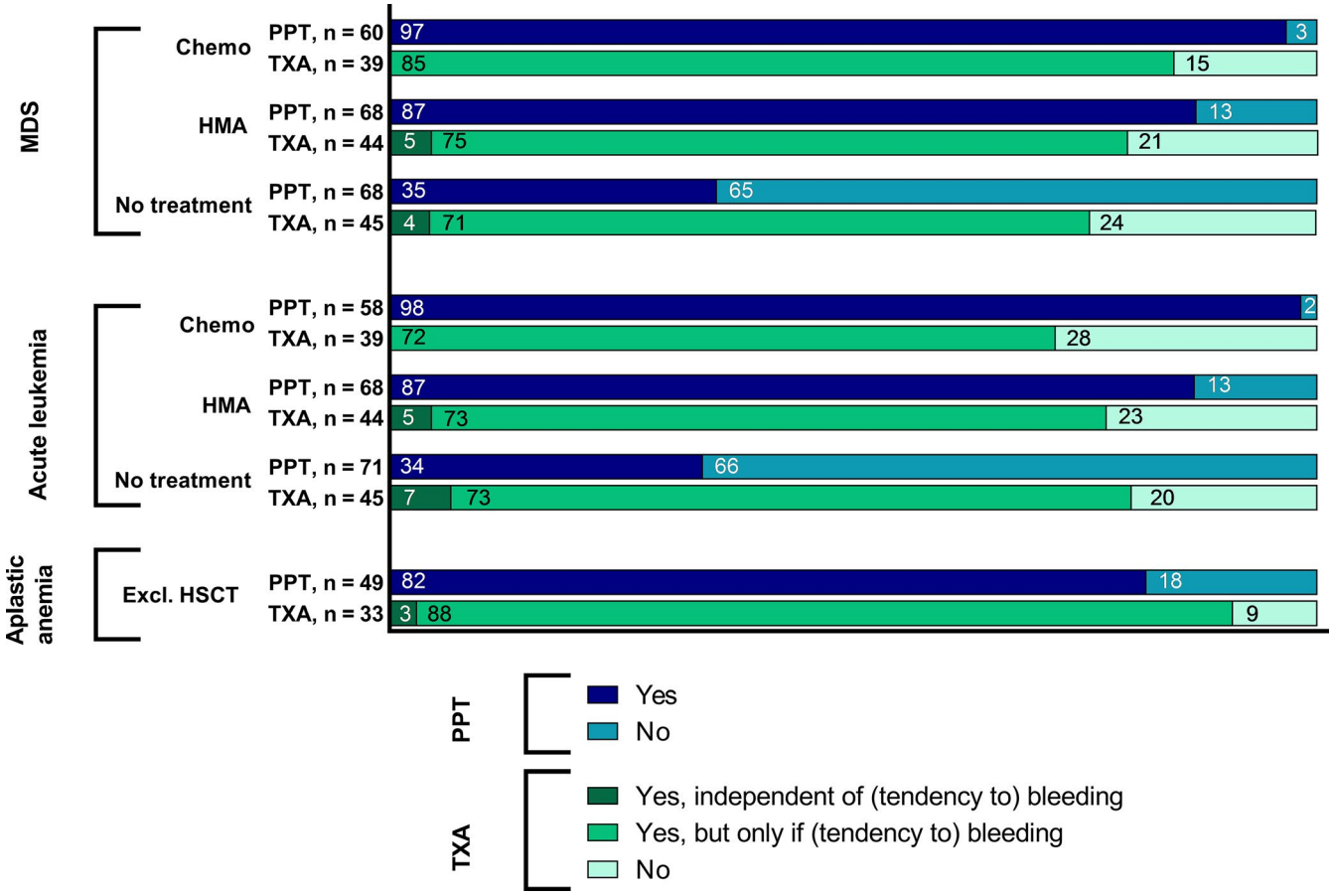


FIGURE 1 **Prophylactic anti-bleeding options considered per diagnosis and treatment modality**. Values in bars indicate percentages of respondents. Absolute numbers of respondents per question are presented at the left side of the bar. Chemo: outpatients in between or shortly after intensive chemotherapy courses. HMA: outpatients treated with hypomethylating agents, for example azacitidine or decitabine. No treatment: outpatients not receiving any disease-modifying treatment, that is refractory disease, treatment ineligible, palliative setting. Aplastic anemia excl. HSCT: outpatients excluding those in work-up for or having received an allogeneic hematopoietic stem cell transplantation. Data represent questions 1 and 6a of survey, see Supplementary Material. Abbreviations: HMA: hypomethylating agents; HSCT: hematopoietic stemcell transplantation; MDS: myelodysplastic syndrome; PPT: prophylactic platelet transfusion; TXA: tranexamic acid

palliative setting without any disease-modifying treatment, TXA is also chosen as solitary regimen (MDS 47% and acute leukemia 44%, Table S1).

3.2 | Clinical conditions modifying prophylactic anti-bleeding treatment

Several clinically related conditions may modulate anti-bleeding preventative measures. The most likely ones were assessed in this survey (Figure 2, Table S2).

Figure 2 illustrates the strong heterogeneity in how clinicians value certain clinical conditions as determinants for anti-bleeding strategies. In general, recent clinically relevant bleeding (<3 months), and continuous use of platelet aggregation inhibitors or therapeutically dosages of anticoagulant medication are valued most important, especially for the regimen of prophylactic platelet transfusions. In addition, clinicians are quite reluctant to start TXA in patients with a medical history of cerebral or coronary ischemic events.

Furthermore, presence of fever, red blood cell transfusion dependency, and low hematocrit levels are considered as important clinical factors when deciding to give prophylactically platelet transfusions (25%-43%). Such conditions are considered hardly relevant for TXA decision making (Table S2).

3.3 | Platelet thresholds

In general, a platelet threshold of ≤10×10^9/L is routinely applied for all acute leukemia, MDS and AA outpatients (Figure 3, Panel A; 77%-100%). Though, when clinical conditions that potentially increase bleeding risks are present, a wide range of thresholds between 10×10^9/L up to 50×10^9/L is applied (Figure 3, Panel B). In case of use

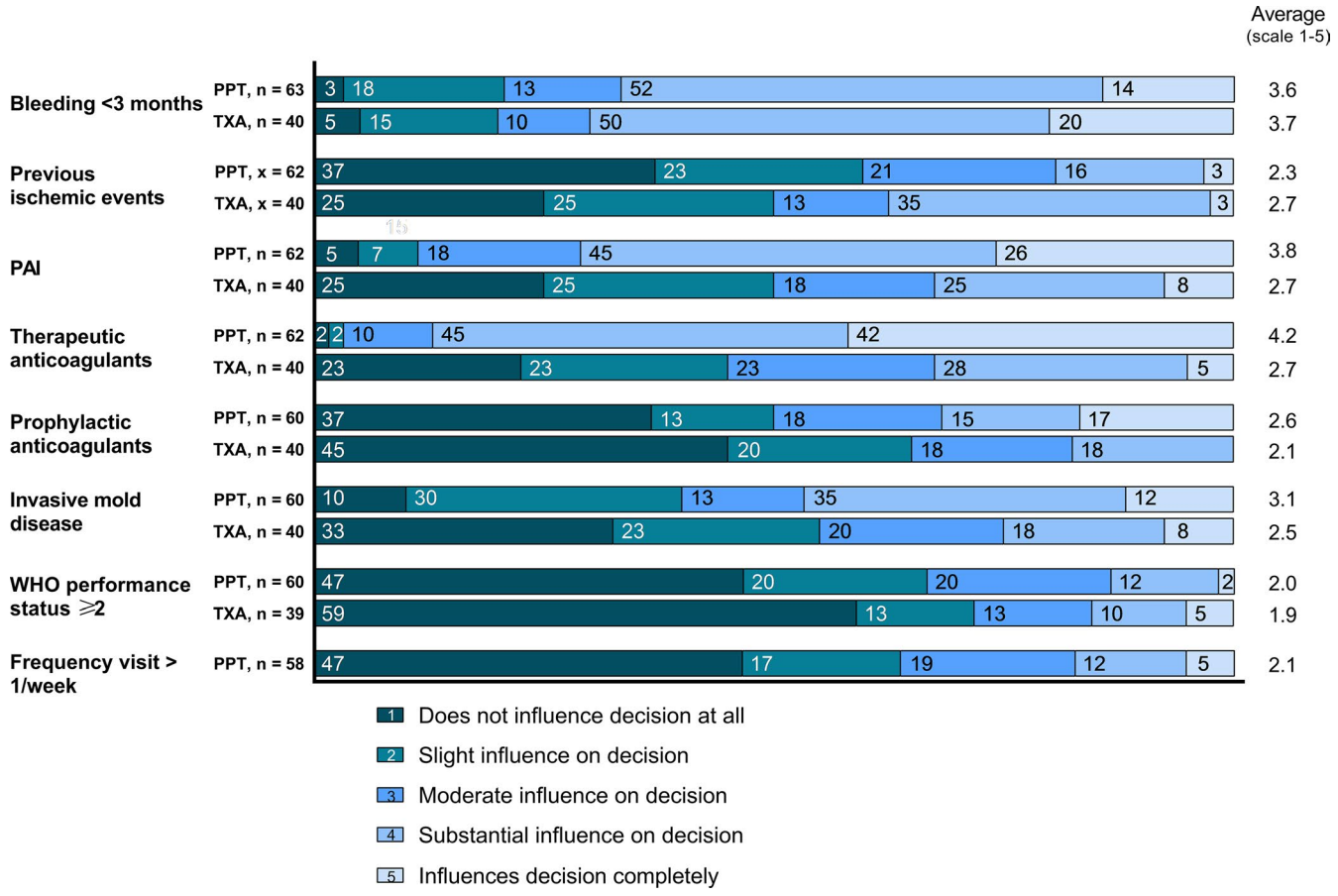


FIGURE 2 Clinical conditions considered in decision making on prophylactic anti-bleeding treatments. Values in bars indicate percentages of respondents. Absolute numbers of respondents per question are presented at the left side of the bar. The average score per clinical condition is reported at the right side of the bar (minimum score 1, maximum score 5). Bleeding <3 mo: clinically relevant bleedings in the past 3 months. Previous ischemic events: medical history of cardiac or cerebral ischemic event. PAI: the need or wish to continue platelet aggregation inhibitors. Therapeutic anticoagulants: the need or wish to continue therapeutic dosage of low molecular weight heparin, vitamin K antagonist or direct oral anticoagulant. Prophylactic anticoagulants: the need or wish to continue prophylactic dosage of low molecular weight heparin. Invasive mold disease: presence of cerebral or pulmonary invasive mold disease. WHO, performance status of 2: ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours. Frequency visit >1/wk: need to visit the outpatient clinic with a frequency of more than once weekly – only surveyed for platelet transfusions, not for tranexamic acid. Data represent question 3 and 6c of survey, see Supplementary Material. Abbreviations: PAI: platelet aggregation inhibitors; PPT: prophylactic platelet transfusions; TXA: tranexamic acid; WHO: World Health Organisation

of platelet aggregation inhibitors (PAI) or therapeutic anticoagulants, over 90% of respondents increased standard platelet transfusion thresholds above 10×10^9/L, the majority to 20×10^9/L to 30×10^9/L.

3.4 | Estimated bleeding risks

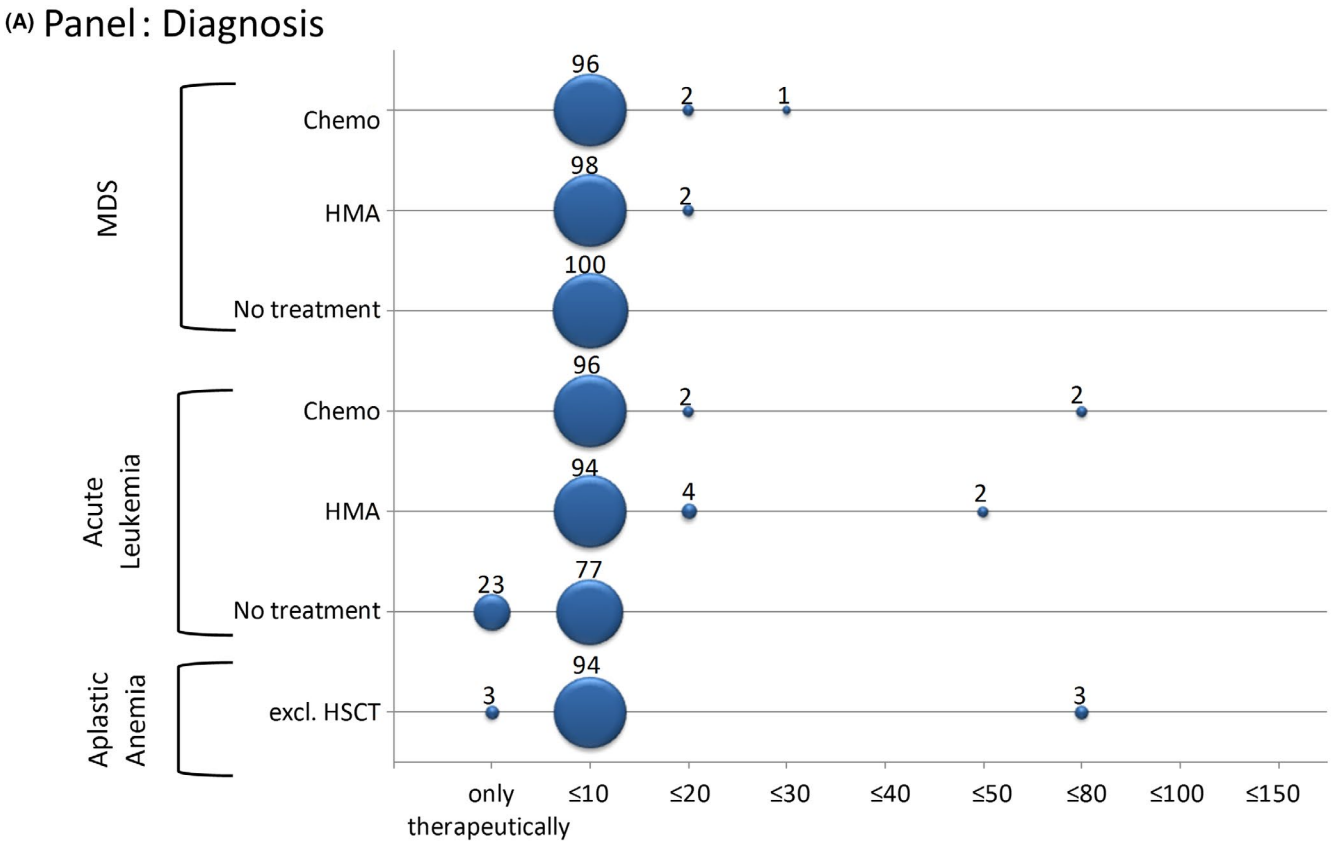
Figure 4 illustrates estimated six months of incidences of clinically relevant bleeding under a prophylactic versus therapeutic-only platelet transfusion strategy. The vast majority of clinicians estimate the likelihood of a bleeding event under a prophylactic regimen to be low, that is <10% over six months of time. Switching to a therapeutic-only regimen (Panel B) is expected to increase the risk of bleeding according to most clinicians. However, estimates on the magnitude of this increase again are widely variably, with some estimating even bleeding risks over 50%.

4 | DISCUSSION

This nationwide survey among hematology clinicians identified a heterogeneous practice of and considerations on the use of prophylactic platelet transfusions and TXA among acute leukemia, MDS, and AA outpatients in the Netherlands.

First, our results indicate the stage of the disease to be an important determinant of prophylactic anti-bleeding strategies. Hence, prophylactic platelet transfusions are widely applied in patients receiving disease-modifying treatment, and far less in patients without active treatment options. Oppositely, TXA, although orally available and cheap, is seldom applied on a prophylactic base. This wide use of a prophylactic platelet transfusion strategy may not come as a surprise, since the 2011 version of the Dutch transfusion guideline recommended so for all thrombocytopenic patients originating from an acquired bone

marrow failure.[18] This guideline was recently updated, now restricting this advice to patients with a transient rather than chronic bone marrow failure.[15] Importantly, these advices are extrapolated from studies performed in intensively treated (in) patients. Indeed, it is completely unknown whether the observed protective anti-bleeding results of platelet transfusions similarly apply to outpatient settings where mucosal-damage and extensive inflammation are uncommon clinical conditions.[11,19] Yet, with benefits per platelet transfusion to potentially



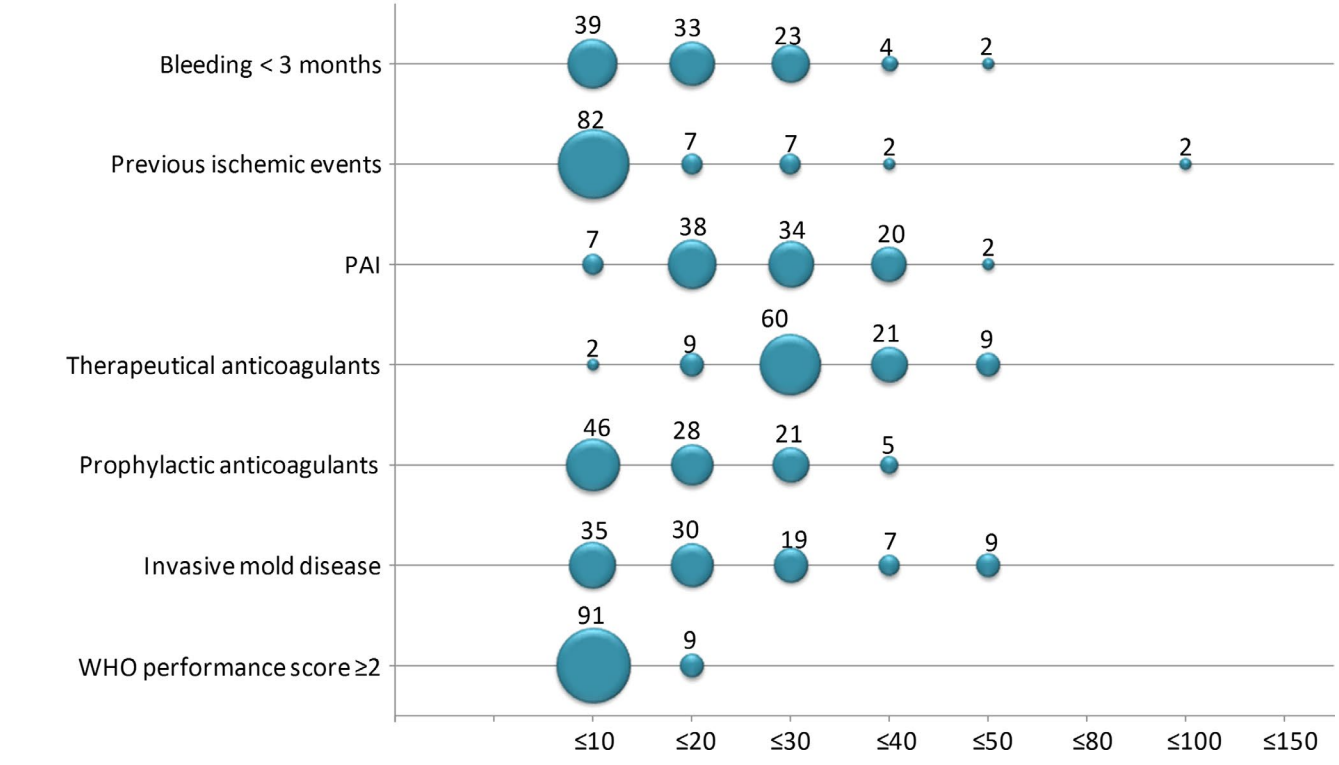


FIGURE 3 Applied platelet count thresholds. The size of and numbers in the bubbles indicate percentages of respondents routinely adhering to a specific platelet threshold. Panel A: platelet thresholds per patient category. Chemo: outpatients in between or shortly after intensive chemotherapy courses. HMA: outpatients treated with hypomethylating agents, for example azacitidine or decitabine. No treatment: outpatients not receiving any disease-modifying treatment, that is refractory disease, treatment ineligible, palliative setting. Aplastic anemia excl. HSCT: outpatients excluding those in work-up for or having received an allogeneic hematopoietic stem cell transplantation. Panel B: platelet thresholds specified per clinical condition. Bleeding <3 mo: clinically relevant bleedings in the past three months. Previous ischemic events: medical history of cardiac or cerebral ischemic event. PAI: the need or wish to continue platelet aggregation inhibitors. Therapeutic anticoagulants: the need or wish to continue therapeutic dosage of low molecular weight heparin, vitamin K antagonist or direct oral anticoagulant. Prophylactic anticoagulants: the need or wish to continue prophylactic dosage of low molecular weight heparin. Invasive mold disease: presence of cerebral or pulmonary invasive mold disease. WHO = World Health Organization, performance status of 2: ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours. Data represent question 2 and 4 of survey, see Supplementary Material. Abbreviations: HMA: hypomethylating agents; HSCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndrome; PAI: platelet aggregation inhibitors; WHO: World Health Organisation

be less, adverse effects of longer-term platelet transfusions are not abandoned, including a cumulative risk of transfusion reactions,[20] financial costs, and logistic challenges for the patient and the hospital. The few studies performed so far indeed questioned the effectiveness and net benefit of prophylactic platelet transfusions in the setting of persistent thrombocytopenia, although the size and design of these studies warrants firm conclusions.[7,9] Despite the fact that some international guidelines have taken these arguments into account and nuanced advices to a therapeutic-only transfusion strategy for patients with chronic bone marrow failure,[11-13] our survey illustrates a general reluctance to a therapeutic-only transfusion strategy for hematological outpatients, as clinicians believe such a strategy to substantially increase bleeding risks.

Second, our survey illustrates that several clinical conditions modulate the decision to initiate preventive anti-bleeding strategies, especially with regard to prophylactic platelet transfusion strategy. Remarkably, in situations believed to be associated with increased bleeding risks, a wide range of platelet thresholds is applied. Again, this seems to reflect an extrapolation of evidence on additional bleeding risk factors available from intensively treated hospitalized patients.[11,12,18] However, such evidence is lacking for hematological outpatients with chronic bone marrow failure.

Some limitations of this survey need to be taken into consideration. The survey was sent out to all Dutch hematological clinicians, thereby aiming for a representative overview of clinical practices in the Netherlands. Despite our efforts, the response (13%) was moderate and overrepresented by clinicians working in academic hospitals (45%). This may have biased our outcomes to policies mainly applied within the academic setting. On the other hand, hematologists working in the field of clinical transfusion medicine completed this survey (verified by personal communication). While they are responsible for transfusion policies across their hospital and geographic region, their responses increase the validity of our results.

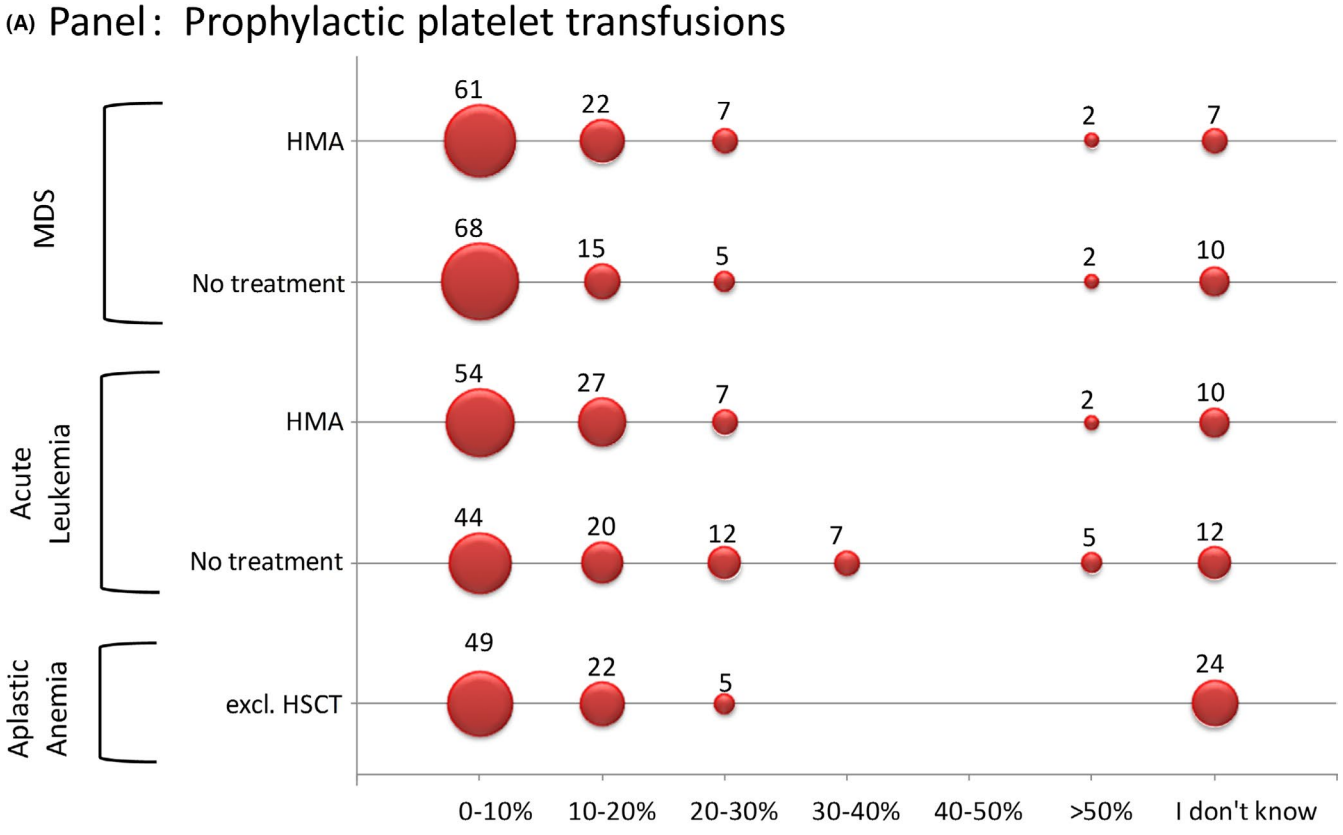
By having the survey spread via the Dutch Society for Hematology, we were able to send our survey request to the majority of our intended population. Unfortunately, due to privacy regulations, provision of a personalized weblinks and thereby filling out individual sections of the questionnaire at different time points was not possible. This probably explains why only 55% completed the entire survey including the final part on TXA use. However, as the use of TXA and the likelihood of a responder to complete the survey are unrelated, it seems unlikely that this biased results on TXA.

Further, one may argue whether opinions on prophylactic platelet transfusion indications also reflect underlying practical considerations. Although our survey did not verify any existence of such considerations, absence of constraints in infrastructural resources of both the Dutch blood supply organization as well as hospitals' outpatient departments should at all times enable facilitation of platelet transfusions whenever deemed indicated. We thus reckon capacity issues not to have skewed our results to a specific prophylactic strategy.

Finally, this survey was only sent out in the Netherlands. The objectified heterogeneity of practices likely relates to the absence of advices in the Dutch nationwide transfusion guideline on how to manage persistent severe thrombocytopenia in chronic bone marrow failure.[15] In contrast, some international guidelines specifically suggest against prophylactic platelet transfusions,[11-13] or to adjust thresholds.[14] None of these guidelines specifically comment on use of TXA in the absence of bleeding. Consequently, it seems likely that practices differ per country.

In conclusion, in the Netherlands, prophylactic platelet transfusions in contrast to TXA use are highly integrated in routine care to hematological outpatients suffering from persistent severe thrombocytopenia, despite the lack of any evidence in this clinical setting. Clinical practice is furthermore characterized by a large heterogeneity in decision reasoning and its outcomes with regard to clinical conditions generally assumed to increase bleeding risks.

The results of this survey underline the current gap in knowledge on bleeding and preventive strategies in hematological patients with chronic bone marrow failure. Further research should focus on (cumulative) bleeding incidences and bleeding predictors in this specific patient population. Second, there is a need to set up a large-scaled comparative RCT on the effectiveness, safety, and patients' burdens of various anti-bleeding strategies for these patients. Finally, these outcomes would need to be incorporated into existing guidelines.


(A) Panel: Prophylactic platelet transfusions
MDS
HMA
61
22
7
2
7
No treatment
68
15
5
2
10
Acute Leukemia
HMA
54
27
7
2
10
No treatment
44
20
12
7
5
12
Aplastic Anemia
excl. HSCT
49
22
5
24
0-10%
10-20%
20-30%
30-40%
40-50%
>50%
I don't know

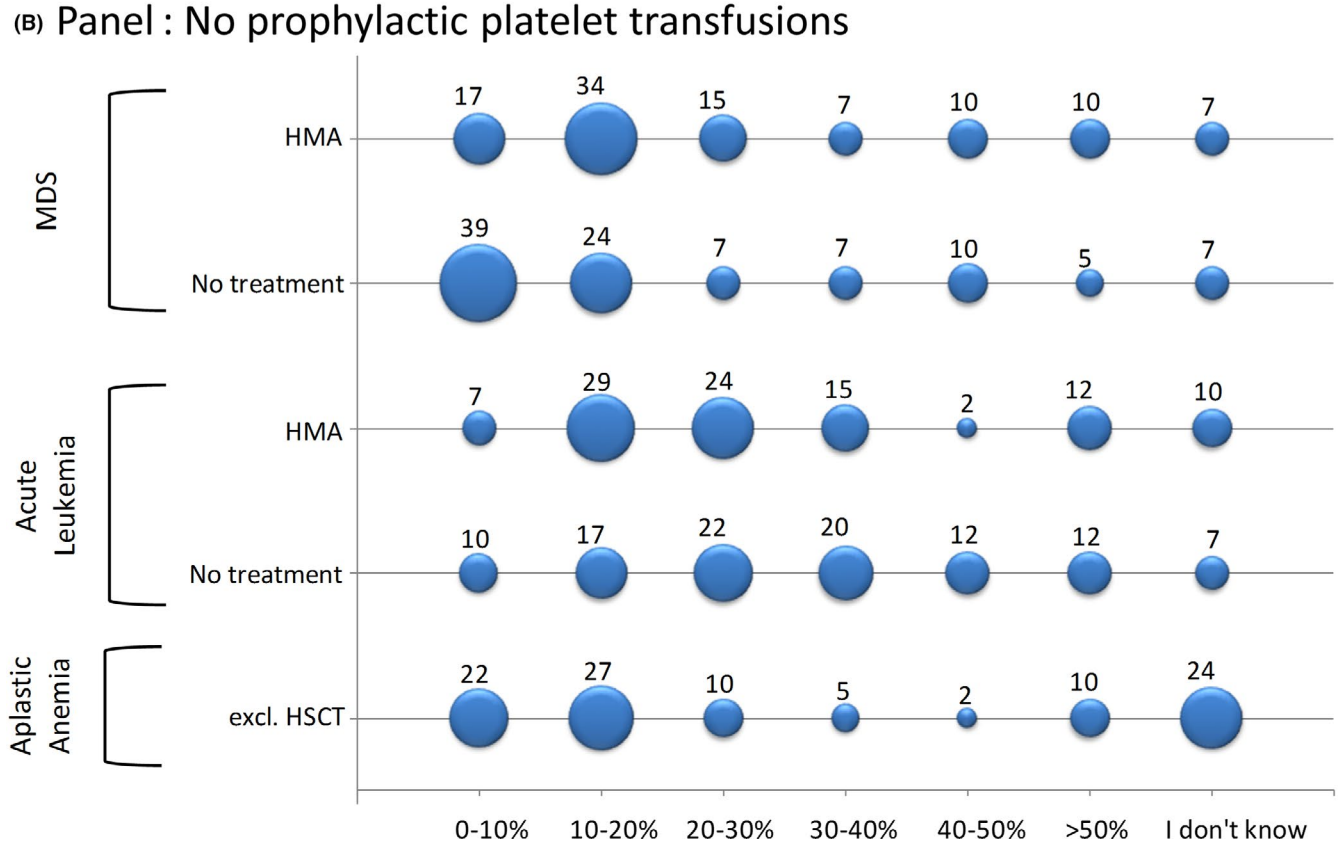

(B) Panel : No prophylactic platelet transfusions
MDS
HMA
17
34
15
7
10
10
7
No treatment
39
24
7
7
10
5
7
Acute Leukemia
HMA
7
29
24
15
2
12
10
No treatment
10
17
22
20
12
12
7
Aplastic Anemia
excl. HSCT
22
27
10
5
2
10
24
0-10%
10-20%
20-30%
30-40%
40-50%
>50%
I don't know

FIGURE 4 Estimated 6-month cumulative incidence of clinically relevant bleeding. The size of and numbers in the bubbles indicate percentages of respondents per patient category. Panel A: estimated 6 mo bleeding incidence with prophylactic platelet transfusion. Panel B: estimated 6 mo bleeding incidence with therapeutic-only platelet transfusions. HMA: outpatients treated with hypomethylating agents, for example azacitidine or decitabine. No treatment: outpatients not receiving any disease-modifying treatment, that is refractory disease, treatment ineligible, palliative setting. Aplastic anemia excl. HSCT: outpatients excluding those in work-up for or having received an allogeneic hematopoietic stem cell transplantation. Data represent question 8 of survey, see Supplementary Material. Abbreviations: HMA: hypomethylating agents; HSCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndrome

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AUTHOR CONTRIBUTIONS

LLC designed the study, performed the research, analyzed the data, and wrote the manuscript. CCD and RTM designed tables and figures and revised the manuscript. JJZ and DE designed the study and revised the manuscript.

DATA AVAILABILITY STATEMENT

The data, without any direct identifying information, that support the findings of this study are available from the corresponding author upon reasonable request, under the conditions that there must at least be an approved statistical analysis plan and a legal data sharing agreement is arranged.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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