Platelet transfusion and anticoagulation in haematological cancer-associated thrombosis and thrombocytopenia

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Platelet transfusion and anticoagulation in haematological cancer-associated thrombosis and thrombocytopenia: the CAVEaT multi-centre prospective cohort.

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Essentials:

- There is very limited prospective data to guide management of patients with cancer, thrombosis and severe thrombocytopenia
- We present a prospective multicentre UK cohort of 105 patients with haematological cancer, thrombosis, and severe thrombocytopenia.
- Data from this cohort demonstrate wide variation in management with high rates of bleeding (7% major bleeding and 25% clinically relevant bleeding at 28 days).
- There is a need for randomized data in this area.

Abstract:

Background: Venous thromboembolism (VTE) in patients with thrombocytopenia represents a complex management challenge.

Objectives: describe practice, document outcomes, and compare management to national guidelines.

Methods: We present a prospective multicentre cohort of 105 patients with haematological cancer, VTE within 28 days and platelets < $50x10^9$/L from 14 May 2019 to 24 April 2021 from 20 sites.

Results: median age was 64 and median initial platelet count 28 x 10^9/L. Thromboses were: 46% catheter-associated, 11% lower limb, 33% pulmonary emboli (PE) and 10% other sites. Management was according to International Society for Thrombosis and Haemostasis (ISTH) guidance in 30 (47%) of 64 patients with high-risk thrombosis and 2 (5%) of low-risk thrombosis (catheter-associated or asymptomatic subsegmental PE). 12 patients (11%) received no anticoagulation. At 28 days Mortality was 15%, 8% experienced VTE progression, 7% experienced major bleeding, and 25% experienced clinically relevant non-major bleeding. 4 inferior vena cava filters were placed, 2 were later removed. The median number of platelet units transfused was 5 (range 0-53). 27% of patients had a change of management strategy by 28 days. There was no clear relationship between platelet transfusion threshold, anticoagulant dose reduction threshold and risk of thrombosis progression or major bleeding.

Conclusions: This data set demonstrates the heterogeneity of approaches used in patients presenting with severe thrombocytopenia and acute thrombosis and confirms the high rates of bleeding in this cohort with thrombosis progression rates similar to the wider cancer-associated thrombosis population. Randomized data is required in order to inform the optimal management.

Key Words:

Thrombosis

Thrombocytopenia

Platelet transfusion

Anticoagulants

Hematologic Neoplasms

Introduction:

Venous Thromboembolism (VTE) in patients with malignancy and thrombocytopenia presents a unique and complex set of management challenges given the need to balance anti-thrombotic therapy with heightened risk of bleeding. There is considerable variability in practice. A survey of Canadian Haematologists and Internal Medicine specialists reported significant variation in the use of platelet transfusion, platelet thresholds for transfusion, and the doses of anticoagulants used(1). A multinational vignette-based survey of 168 physicians regarding management of anticoagulation in patients with haematological malignancy and thrombocytopenia identified that a complex decision making process is often used with numerous relevant factors including time since thrombosis, prior bleeding, practice setting, and haematological diagnosis and treatment(2).

This variability in practice reflects a limited evidence base, with guideline recommendations based on consensus. A recently published prospective cohort from the Venous thromboembolism Network US describing management and outcomes of 121 patients with any malignancy, thrombosis within 7 days and platelet count < 100 x 10^9/L has described marked variation in practice and frequent changes in the anticoagulation strategy for individual patients over time, reporting high rates of bleeding (24% by 60 days), and a rate of VTE recurrence of 5.6% by 60 days(3). A systematic review examined the important question of whether it is preferable in the presence of severe thrombocytopenia to use platelet transfusion to support full dose anticoagulation, or to reduce or withhold anticoagulation(4): the authors identified only two relevant retrospective observational studies including a total of 121 patients with cancer-associated thrombosis and thrombocytopenia.

Published retrospective cohorts including patients with acute VTE and thrombocytopenia have confirmed the high bleeding risk of patients with severe thrombocytopenia managed with anticoagulation (5) and suggest that anticoagulation is a superior strategy to no anticoagulation or inferior vena cava (IVC) filter placement only(6).

The British Society for Haematology (BSH) and International Society on Thrombosis and Haemostasis (ISTH) have issued guidance regarding the management of acute VTE, whilst acknowledging the limited supporting data (7, 8). A summary of the guidelines is presented in Supplementary Table 1. Platelet transfusion is recommended to maintain a platelet count of > 40-50x10^9/L and full dose anticoagulation with low molecular weight heparin (LMWH) for the first month of anticoagulation from the date of the VTE (ISTH guideline) or the first three months from the date of the VTE (BSH guideline). Where this platelet level is not practically achievable, reduced doses of LMWH are recommended.

The ISTH guidelines additionally suggest a less intensive strategy without platelet transfusion for patients more than 1 month from VTE or with lower risk thrombosis using reduced dose LMWH or omitting for platelets < 25 x 10^9/L. Lower risk thrombosis is defined by the ISTH guideline as upper limb line associated deep vein thrombosis (DVT) or asymptomatic sub-segmental pulmonary embolism (PE). Both guidelines recommend against the use of IVC filters unless there is an absolute contraindication to anticoagulation.

A recent Canadian consensus committee has suggested preferring LMWH to direct oral anticoagulants (DOACS) in the setting of thrombocytopenia < 50x10^9/L, and to apply clinical judgement regarding dose reductions(9).

The aims of the Cancer Associated Venous Thromboembolism and Thrombocytopenia (CAVEaT) multicentre prospective audit of patients with haematological malignancy, thrombosis and thrombocytopenia were to describe UK practice and management, document the outcomes, and compare practice to recommendations in national guidelines. A secondary objective was to inform the development of the research agenda. The numbers of these cases of thrombosis and thrombocytopenia are low, and therefore only a multi-centre cohort would be expected to provide sufficient meaningful data.

Methods:

Participating sites were identified through a UK national network of haematology trainees, HaemSTAR. Data on consecutive patients were recorded prospectively. Inclusion criteria were: a haematological malignancy, current platelet count of less than 50 x 10^9/L and radiologically confirmed DVT or PE diagnosed within 28 days. Patients with distal lower limb DVT were not eligible for inclusion.

Data collection:

A pre-piloted series of forms were used to record anonymised routinely available data at registration, 28 days and three months from the diagnosis of VTE. Patients were registered and followed up from the date of thrombocytopenia with platelet count < 50 x 10^9/L until 3 months from the date of VTE. Data collected included: patient characteristics (malignancy type, ani-cancer treatment, inpatient or outpatient setting, height and weight, pre-chemotherapy blood count); VTE characteristics (site, method of diagnosis, whether catheter associated thrombosis (CAT)); and treatment strategy. The presence of recent clinically significant bleeding as judged by the investigator was recorded. From April 2020 COVID-19 infection was

also recorded. Outcomes were mortality, thrombosis progression, clinically relevant non-major bleeding and major bleeding as defined by the ISTH (10)(11), inferior vena cava (IVC) filter placement, and any changes to management strategy. The recruitment target was set at 100 patients with at least 28 days of follow up. CAVEaT was conducted using fully anonymised routinely available data. All sites were required to obtain appropriate local institutional approvals. The protocol required no changes to patient care.

Analysis plan:

Data are presented descriptively. Continuous data are described as median and range, with interquartile range supplied where relevant. Dichotomous data are described as N (%).

Thromboses were categorised as high-risk or low-risk according to the ISTH guidelines on management of cancer-associated thrombosis in patients with thrombocytopenia (8): upper limb catheter associated thrombosis and incidental subsegmental PE were considered low-risk, all other DVT or PE was considered high-risk. Treatment strategies for every patient were categorised with reference to the ISTH guideline (8), and BSH guideline (7) as strategies with platelet transfusion thresholds 40-50 x 10^9/L or strategies with lower platelet transfusion thresholds ≤ 30 x 10^9/L. Additionally, the platelet count threshold at which anticoagulant dose was reduced from full dose was also recorded and categorised as 40-50 x 10^9/L or lower. Patients managed without anticoagulation were considered separately.

Outcomes are presented for the whole population with outcome data at any time point. A sensitivity analysis was performed to compare the whole population with complete cases only (not died or lost to follow up). Patients were not censored on occurrence of VTE progression or major bleeding.

Results:

Baseline Characteristics

106 eligible patients were registered from 20 UK hospital trusts from 14 May 2019 to 24 Apr 2021: of these 105 had follow up at 28 days and 94 had follow up at 90 days, as shown in Supplementary Figure 1. The one patient with no outcome data was excluded from the analysis. Baseline characteristics of the patients are shown in Table 1. The median time from thrombosis to registration was 2 days (range 0-20). The median age was 64 years and median platelet count at registration 28 x 10^9/L. The cohort were predominantly inpatients (79%), acute leukaemia was the most common diagnosis (51%) and the most common treatment type was intensive induction / consolidation chemotherapy (39%). The proportion of patients with recent clinically significant bleeding before the diagnosis of VTE was 21%, with 7% having

recent major bleeding, with a median time from the episode of bleeding to registration of 12 days (range 1-95 days).

Details of the index thromboses are shown in Table 2. The most common thrombosis site was catheter-associated upper limb thrombosis, accounting for 40 (38%) of thromboses, followed by pulmonary emboli affecting segmental or larger pulmonary arteries in 29 patients (27% of thromboses). Isolated lower limb proximal DVT was less common, affecting 16 (15%) patients. 91 (86%) of VTEs were diagnosed on imaging to investigate attributable symptoms, the remainder noted incidentally on imaging for other indications. Most patients (79%) were not receiving thromboprophylaxis or anticoagulation prior to the index VTE.

Initial management

The approaches at registration to anticoagulation and platelet transfusion with 28 day outcomes are shown in Table 3 according to initial anticoagulation intensity and platelet transfusion threshold. 56 (53%) of patients were managed with full intensity LMWH or unfractionated heparin, 30 (28%) with 50% dose LMWH, 3 (3%) with prophylactic dose LMWH heparin, 4 (4%) with DOACs and 12 (11%) with no anticoagulation. In view of the small number of patients treated with prophylactic LMWH these are grouped with reduced dose LMWH in the table. Of 4 patients treated with DOACs, 3 were given reduced doses compared to the licensed VTE treatment dose.

The platelet transfusion threshold was 40-50 x 10^9/L in 65 (62%) patients and ≤ 30 x10^9/L in 38 (36%) patients. The anticoagulation used was reduced from full dose if the platelet count was less than a threshold of 40-50 x 10^9/L in 60 (57%) patients, and reduced at a threshold < 40 x 10^9/L in 33 (31%) of patients. It was notable that patients managed with strategies with less intense anticoagulation or lower platelet transfusion thresholds had lower initial platelet counts and those managed without anticoagulation had the lowest platelet counts: platelet transfusion threshold 40-50 x 10^9/L median platelet count 35, interquartile range (IQR) 25-43; platelet transfusion threshold ≤ 30 x 10^9/L median platelet count 22 x 10^9/L , IQR 17-33.5; no anticoagulation, median platelet count 15.5 x 10^9/L, IQR 12.5-21. Data on platelet increments following transfusions were available for 70 (67%) of patients: the median increment was 20 x 10^9/L, IQR 13 – 28 x 10^9/L.

In total 46 (43%) patients were managed using the BSH guideline approach or ISTH guideline high-risk thrombosis approach (see Supplementary with the use of platelet transfusions to maintain a platelet count of > 40-50 x 10^9/L in order to permit anticoagulation with LMWH. 64 patients had ISTH-defined high-risk thrombosis, of whom 30 (47%), were managed with the ISTH high-risk or BSH approach. 42

patients had ISTH-defined low-risk thrombosis, of whom two (5%) were managed using the ISTH low-risk approach without the use of platelet transfusion. 12 patients (11%) received no anticoagulation.

28 day outcomes

Outcome data at 28 days from the date of VTE are presented in Table 3 according to the intended management strategy recorded at registration. Overall mortality was 15% with 8% having progression of thrombosis, 7% major bleeding and 22% clinically relevant non-major bleeding. The median units of platelets transfused in the first 28 days was 5. Four IVC filters were placed. Comparison of patients with ISTH-defined high-risk or low-risk thrombosis demonstrated similar management strategies and outcomes as shown in Supplementary Tables 2 and 3: therefore these groups are not distinguished in the main analysis. For example the rate of thrombosis progression was 6% in the ISTH high-risk group and 7% in the ISTH low-risk group despite a smaller proportion of the ISTH high-risk patients being managed with full intensity anticoagulation (31% vs 52%).

Amongst the 56 patients initially managed with full dose LMWH / UFH 4 (7%) had thrombosis recurrence and 3 (5%) had major bleeding. Amongst the 33 patients initially managed with reduced dose LMWH 4 (13%) had thrombosis progression 4 (13%) had major bleeding.

Patients managed with a higher platelet transfusion threshold received more platelets and were inpatients for a higher proportion of the first 28 days: transfusion threshold 40-50 x 10^9/L *N* = 65, median platelet count 35, IQR 25-43; threshold ≤ 30x 10^9/L *N* =28, median platelet count 22 , IQR 17-33.5; no anticoagulation *N* = 12, median platelet count 15.5, IQR 12.5-21. Figure 1 shows all patients according to whether they experienced major bleeding, progression of thrombosis or neither of these events according to baseline platelet count plotted against platelet transfusion threshold or anticoagulant dose reduction platelet threshold. There was no relationship evident between choice of platelet transfusion threshold or anticoagulant dose reduction threshold and the distribution of major bleeding or thrombosis progression events observed. The majority of thrombosis progression events (5 of 7) occurred in patients with baseline platelet counts above the median platelet count of 28 x 10^9/L.

90 day outcomes

Outcomes at 90 days from the VTE are shown in Table 4. Between 28 days and 90 days there were only 2 further events of thrombosis progression and 1 further event of major bleeding, no further IVC filters were placed and the median number of units of platelets transfused in this period was 1.5. A further 14 deaths occurred giving a 90-day mortality of 28%. Amongst the patients who died, 1 patient had

experienced thrombosis progression, which was not a causal factor in the death, and 2 patients had experienced major bleeding, of which the bleeding was reported to be a relevant factor in their death for both. No patients experienced both thrombosis and major bleeding.

Four of the eight patients with major bleeding experienced central nervous system bleeding all of whom had been managed with platelet transfusion thresholds of 40-50x10^9/L: three patients had received LMWH and one had received a DOAC. The most common sites of clinically relevant non-major bleeding were epistaxis (13), haematuria (5) and lower gastrointestinal. Site of bleeding are shown in supplementary table 2.

Of four IVCs placed, two were removed after 8-12 weeks, and for two removal was not attempted. No complications were reported from the IVCs placed.

Changes to management during follow-up

28 (27%) patients had a change of treatment strategy during the first 28 days from the date of VTE, increasing to 48 (51%) by 90 days from the date of VTE. The categories of strategy changes made and reasons for the changes are shown in Figure 2. The most common change was to stop anticoagulation before 90 days (21 patients, 6 treated with only 6 weeks' anticoagulation for catheter-associated thromboses). The reason for stopping anticoagulation before day 28 was most often bleeding (4 of 7 patients), and between day 28 and 90 was most often impracticality of maintaining platelets > 40-50x10^9 /L (6 of 13 patients). The second most common change was to change from LMWH to a DOAC (6 patients, 3 changing before day 28 and 3 after day 28). 6 patients experienced progression of thrombosis, which was managed in 4 cases by increasing the LMWH dose and in 2 cases by converting from DOAC to LMWH.

A sensitivity analysis was performed to compare the results of the whole population to complete cases (those without mortality or loss to follow up), as shown in Supplementary Table 4 demonstrating the results were robust between these analysis groups (for example 28 day thrombosis rates of 8% and major bleeding rates of 7% in both analysis groups).

Discussion:

Severe thrombocytopenia in the setting of acute thrombosis presents a complex management challenge with risks of both thrombosis progression and major bleeding, often occurring in the context of life threatening malignancy and complex therapies. Use of multiple platelet transfusions is common in this patient cohort, but is associated with significant resource implications, burden of administration on clinical services and patients as well as risks of alloimmunisation and transfusion reactions. Data from the

CAVEaT cohort confirm the heterogeneity of management approaches used in practice, high rates of bleeding and similar rates of thrombosis recurrence or progression to non-thrombocytopenic patients with cancer associated VTE. Only 47% of patients with high-risk thrombosis were managed in line with published guidelines from the ISTH(8) or BSH(7), with lower platelet transfusion thresholds often used and only 5% of patients with ISTH low risk thromboses managed with the ISTH recommended approach for low risk thrombosis, principally because 84% patients with catheter-associated thrombosis or asymptomatic subsegmental PE were managed with the use of platelet transfusion to support anticoagulation. This finding may relate to the study reflecting UK practice, which might be more likely to be influenced by the BSH guidelines than in some other countries, as well as the limited evidence base underpinning the ISTH guidelines and inherent heterogeneity of the patient group. The platelet count transfusion threshold chosen appeared to be influenced by the initial platelet count with patients with lower initial platelet counts more likely to be managed with lower platelet transfusion thresholds.

These data also demonstrate the high frequency of changes to the anticoagulant strategy with 51% having a change by 90 days, and highlight the importance of bleeding, difficulty in practically maintaining a platelet count of > $50x10^9$/L and the value of oral anticoagulation for patients as reasons for changing strategy. Both the CAVEaT and VENUS cohorts and previous retrospective cohorts describe similar numbers of patients (11-14%) managed without anticoagulation(3, 4), with this group having the lowest initial median platelet counts of 15.5 x 10^9/L and highest mortality (30% at 28 days), most likely reflecting that patients with thrombosis and thrombocytopenia include a group in the terminal stages of their malignancy.

Our data confirm the high rates of bleeding in patients with thrombosis and thrombocytopenia with clinically relevant bleeding in 29% of patients and major bleeding in 8% by 90 days, demonstrating a similar pattern to the VENUS cohort of patients with acute thrombosis, any malignancy and platelets < 100 $x10^9$/L in which there was bleeding in 24% and major bleeding in 9% by 60 days(3). The rate of thrombosis progression was slightly higher than reported in the VENUS cohort at 8% by 28 days and 11% at 90 days, which may have been related to differences in methodology between the studies. We observed an overall rate of thrombosis progression of 10% at 90 days, similar to that reported in previous studies of cancer associated thrombosis managed with LMWH(12-15). In this cohort we did not observe a difference in outcomes between patients with high-risk as compared to low-risk thromboses as defined in the ISTH guidelines, although larger patient numbers would be required to explore the relevance of these risk groups in patients with severe thrombocytopenia.

Our data also demonstrate that it remains uncommon in UK practice to use DOACs in patients with cancer associated thrombosis and thrombocytopenia, with only 4 (4%) of patients initially managed with DOACs and 6 further patients converted to DOACs by 3 months' follow up. The use of IVC filters was also uncommon with only 4 IVC filters placed in this cohort in accordance with published guidance.

The main strengths of this data set are the prospective data collection of consecutive cases within the setting of a large national healthcare system with similar approaches between centres to management of the haematological malignancy. There are, however, several important limitations. Firstly the observational non-randomised nature of the data greatly limits any potential comparison of the efficacy of the different management strategies, which is also limited by the relatively small total number of patients and heterogeneity of management strategies. Additionally the study resources and design did not allow for central adjudication of bleeding and thrombosis events or longitudinal assessment of compliance to the intended strategy. Time-to-event data were not collected for bleeding or thrombosis progression, preventing cumulative incidence analysis to formally account for death as a competing factor, although the sensitivity analysis performed suggests the main findings are nevertheless robust despite this limitation. Platelet count data over time were not collected because the frequency of measurement was highly variable. There are also inherent limitations associated with interpretation of medical record data, particularly given that management strategies for this cohort were frequently changed from the initial strategy.

In conclusion the CAVEaT data set confirms the heterogeneity of management approaches used in patients presenting with severe thrombocytopenia in the context of acute thrombosis and haematological malignancy and confirms the high rates of bleeding in this cohort as well as thrombosis recurrence / progression rates similar to the general cancer-associated thrombosis population. There is a need for larger scale prospective and particularly randomised data in this area in order to provide clinicians and patients with higher quality evidence to guide difficult management decisions in what are often complex clinical scenarios.

Author contributions: SB, NC and SS conceived the study. SB wrote the protocol with NC, SS and MD. HaemSTAR collaborators identified sites and collected data. SB and MD analysed data. SB drafted the manuscript. All authors reviewed the manuscript.

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Conflict of Interest: MD: speakers or advisory board fees from Amgen, Sanofi, Takeda, Portola and Takeda all unrelated to this project Other authors: no conlfict of interest to declare.

References:

1. Kopolovic I, Conter HJ, Kuo KHM. Management of Cancer-Associated Venous Thromboembolism in Patients with Concomitant Thrombocytopenia: A Survey of Canadian Practitioners. Blood. 2014;124(21):2174-2174. doi:10.1182/blood.V124.21.2174.2174.

2. Leader A, Ten Cate V, Ten Cate-Hoek AJ, Beckers EAM, Spectre G, Giaccherini C, Gurevich-Shapiro A, Krashin E, Raanani P, Schouten HC, Falanga A, Ten Cate H. Anticoagulation in thrombocytopenic patients with hematological malignancy: A multinational clinical vignette-based experiment. Eur J Intern Med. 2020 Jul;77:86-96. eng. Epub 2020/03/17. doi:10.1016/j.ejim.2020.03.005. Cited in: Pubmed; PMID 32173172.

3. Carney BJ, Wang TF, Ren S, George G, Al Homssi A, Gaddh M, Connolly GC, Shah V, Bogue T, Bartosic A, Neuberg D, Baumann Kreuziger L, Zwicker JI. Anticoagulation in cancer-associated thromboembolism with thrombocytopenia: a prospective, multi-center cohort study. Blood Adv. 2021 Oct 18. eng. Epub 2021/10/19. doi:10.1182/bloodadvances.2021005966. Cited in: Pubmed; PMID 34662892.

4. Samuelson Bannow BR, Lee AYY, Khorana AA, Zwicker JI, Noble S, Ay C, Carrier M. Management of anticoagulation for cancer-associated thrombosis in patients with thrombocytopenia: A systematic review. Research and Practice in Thrombosis and Haemostasis. 2018;2(4):664-669. doi:10.1002/rth2.12111.

5. Houghton DE, Key NS, Zakai NA, Laux JP, Shea TC, Moll S. Analysis of anticoagulation strategies for venous thromboembolism during severe thrombocytopenia in patients with hematologic malignancies: a retrospective cohort. Leukemia & lymphoma. 2017;58(11):2573-2581. eng. Epub 2017/04/09. doi:10.1080/10428194.2017.1306644. Cited in: Pubmed; PMID 28393576.

6. Khan M, Cox TM, Nassif M, Alzubaidi MA, Garg N, Qiao W, Aung FM, Oo TH, Rojas-Hernandez CM. Comparative outcomes of thrombocytopenic acute leukemic patients with venous thromboembolism at a Comprehensive Cancer Center. J Thromb Thrombolysis. 2018 Apr;45(3):377-385. eng. Epub 2018/02/09. doi:10.1007/s11239-018-1621-6. Cited in: Pubmed; PMID 29417408.

7. Watson HG, Keeling DM, Laffan M, Tait RC, Makris M, the British Committee for Standards in Haematology. Guideline on aspects of cancer-related venous thrombosis. British Journal of Haematology. 2015;170(5):640-648. doi:10.1111/bjh.13556.

8. Samuelson Bannow BT, Lee A, Khorana AA, Zwicker JI, Noble S, Ay C, Carrier M. Management of cancer-associated thrombosis in patients with thrombocytopenia: guidance from the SSC of the ISTH. Journal of Thrombosis and Haemostasis. 2018;16(6):1246-1249. doi:10.1111/jth.14015.

9. Carrier M, Blais N, Crowther M, Kavan P, Le Gal G, Moodley O, Shivakumar S, Suryanarayan D, Tagalakis V, Wu C, Lee AYY. Treatment Algorithm in Cancer-Associated Thrombosis: Updated Canadian Expert Consensus. Current Oncology. 2021;28(6):5434-5451. Cited in: Pubmed; PMID doi:10.3390/curroncol28060453.

10. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 2015 Nov;13(11):2119-26. eng. Epub 2016/01/15. doi:10.1111/jth.13140. Cited in: Pubmed; PMID 26764429.

11. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005 Apr;3(4):692-4. eng. Epub 2005/04/22. doi:10.1111/j.1538-7836.2005.01204.x. Cited in: Pubmed; PMID 15842354.

12. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI, Investigators A-E. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013 Feb 21;368(8):699-708. Epub 2012/12/12. doi:10.1056/NEJMoa1207541. Cited in: Pubmed; PMID 23216615.

13. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, Rickles FR, Julian JA, Haley S, Kovacs MJ, Gent M. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003 Jul 10;349(2):146-53. eng. Epub 2003/07/11. doi:10.1056/NEJMoa025313. Cited in: Pubmed; PMID 12853587.

14. Lee AYY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, Khorana AA. Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial. Jama. 2015 Aug 18;314(7):677-686. eng. Epub 2015/08/19. doi:10.1001/jama.2015.9243. Cited in: Pubmed; PMID 26284719.

15. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, Hale D, Dunn JA, Lyman GH, Hutchinson C, MacCallum P, Kakkar A, Hobbs FDR, Petrou S, Dale J, Poole CJ, Maraveyas A, Levine M. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). J Clin Oncol. 2018 Jul 10;36(20):2017-2023. eng. Epub 2018/05/11. doi:10.1200/jco.2018.78.8034. Cited in: Pubmed; PMID 29746227.

Appendix

HaemSTAR Collaborators:

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Table 1: Baseline Characteristics of 105 patients with haematological malignancy, thrombosis and thrombocytopenia.

Variable	Median (Range)
Age/years	64 (15-91)
BMI	26 (13-66)
Pre-chemotherapy Full Blood Count	
Hb (g/L)	99 (60-157)
WCC (10^9/L)	5.25 (0.1-118)
Platelets (10^9/L)	81 (9-480)
Platelets at registration	
Platelets (10^9/L)	28 (5-49)
Variable	*N* (%)
Sex	
Male	61 (58%)
Female	44 (42%)
Care setting	
Inpatient	83 (79%)
Outpatient	22 (21%)
Previous VTE	
Yes	3 (3%)
No	102 (97%)
History of SARS-CoV-2 infection	
Yes	1 (1%)
No	104 (99%)
History of recent bleeding*	
Major bleeding	6 (7%)
CRNMB	15 (14%)
Haematological malignancy	
Acute Myeloid Leukaemia†	37 (35%)
Acute Promyelocytic Leukaemia	3 (3%)
Acute Lymphoblastic Leukaemia	14 (13%)
MDS	8 (8%)
CML/MPD	2 (2%)
High grade B-cell NHL	14 (13%)
Low grade B-cell NHL	13 (12%)
T-cell NHL	7 (7%)
Myeloma	7 (7%)
Systemic Anti-Cancer Treatment	
Intensive induction / consolidation	42 (40%)
Intermediate intensity induction	4 (4%)

Curative non-intensive outpatient	3 (3%)
Non-curative outpatient	23 (22%)
Allogeneic HSCT	11 (10%)
Autologous HSCT	6 (6%)
CAR-T	4 (4%)
Supportive care	12 (1%)
Asparaginase within 8 weeks	11 (10%)

BMI Body Mass index; Hb haemoglobin; WCC white cell count; HSCT haematopoietic stem cell transplant; CAR-T chimeric antigen receptor T-cell therapy; MDS myelodysplastic; CML chronic myeloid leukaemia; MPD Myeloproliferative disorder; NHL non-Hodgkin lymphoma;

* Time frame determined by investigator, see text.

† Excluding Acute Promyelocytic Leukaemia.

Table 2 Baseline Characteristics of VTE in 105 patients with haematological malignancy, thrombosis and thrombocytopenia.

VTE Characteristics	*N* (%)
VTE site	
Upper limb not catheter-associated	4 (4%)
Upper limb catheter-associated*	40 (38%)
Lower limb proximal DVT†	16 (15%)
PE, segmental or larger	29 (27%)
PE, symptomatic subsegmental	4 (4%)
PE, asymptomatic subsegmental*	2 (2%)
IJV	6 (6%)
Abdominal vein	2 (2%)
Other	2 (2%)
Diagnostic radiology	
Routine CT/MRI	15 (14%)
CT/MRI for suspected VTE	64 (60%)
US doppler for suspected VTE	26 (25%)
Anticoagulation prior to VTE	
LMWH prophylaxis	17 (16%)
LMWH treatment	2 (2%)
DOAC	2 (2%)

Warfarin	0 (0%)
Nil	84 (80%)

DVT deep vein thrombosis; PE pulmonary embolism; VTE venous thromboembolism; IJV internal jugular vein; LMWH low molecular weight heparin; DOAC direct oral anticoagulant; CT computed tomography; US ultrasound

* ISTH defined low risk thrombosis

† Denotes proximal DVT without PE. Cases with concomitant DVT and PE are categorised as PE

Table 3 Initial management strategies and outcomes at 28 days from VTE of 105 patients with haematological malignancy, thrombosis and thrombocytopenia according to platelet transfusion thresholds and anticoagulation intensity

Anticoagulant treatment	Platelet transfusion threshold (10^9/L)	*N*	Platelet count at registration (10^9/L) Median (range)	Follow up (patient-days)	Mortality	Thrombosis Progression	Major bleeding	CRNMB	Platelet units transfused Median (range)	Inpatient days Median (range)
All patients	Any	105 (100%)	28 (5-49)	2139	15 (14%)	8 (8%)	7 (7%)	26 (25%)	5 (0-53)	14 (0-28)
Full dose LMWH /	40-50	39 (37%)	39 (5-49)	915	5 (13%)	2 (5%)	3 (8%)	10 (26%)	6 (0-46)	19 (0-28)
UFH*	≤ 30	17 (16%)	31 (7-49)	371	1 (6%)	2 (12%)	0 (0%)	3 (18%)	4 (0-24)	18 (0-28)
Reduced dose	40-50	24 (23%)	27.5 (13-48)	560	2 (8%)	3 (13%)	3 (13%)	7 (29%)	4.5 (0-53)	10 (0-28)
LMWH†	≤ 30	9 (8%)	22 (17-38)	197	3 (33%)	1 (11%)	1 (11%)	2 (22%)	1.5 (0-13)	13 (0-25)
DOAC	40-50	2 (2%)	38 (35-41)	52	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4.5 (0-9)	0 (0-0)
	≤ 30	2 (2%)	41.5 (40-43)	52	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (0-10)	14 (0-28)
No anticoagulant	≤ 30	12 (11%)	15.5 (7-32)	267	4 (33%)	0 (0%)	0 (0%)	4 (33%)	3 (0-23)	8 (0-28)

BSH British Society for Haematology; DOAC direct oral anticoagulant; CRNMB clinically relevant non-major bleeding; ISTH International Society on Thrombosis and Haemostasis; LMWH Low molecular weight heparin; UFH unfractionated heparin

*3 patients received UFH

†30 patients received 50% dose and 3 patients received prophylactic dose LMWH

Table 4 Initial management strategies and outcomes at 90 days from VTE of 105 patients with haematological malignancy, thrombosis and thrombocytopenia according to platelet transfusion thresholds and anticoagulation intensity

Anticoagulant treatment	Platelet transfusion threshold (10^9/L)	*N*	Platelet count at registration (10^9/L) Median (range)	Follow up (patient-days)	Mortality	Thrombosis Progression	Major bleeding	CRNMB	Platelet units transfused Median (range)	Inpatient days Median (range)
All patients	Any	105 (100%)	28 (5-49)	7139	21 (20%)	10 (10%)	8 (8%)	30 (29%)	6.5 (0-53)	21 (0-84)
Full dose LMWH /	40-50	39 (37%)	39 (5-49)	2590	7 (18%)	3 (8%)	3 (8%)	10 (26%)	7 (0-46)	22 (0-56)
UFH†	≤ 30	17 (16%)	31 (7-49)	1186	2 (12%)	3 (18%)	0 (0%)	4 (24%)	5.5 (0-34)	24 (0-69
Reduced dose	40-50	24 (23%)	27.5 (13-48)	1822	5 (21%)	3 (13%)	3 (13%)	9 (38%)	6.5 (0-53)	26 (0-84)
LMWH‡	≤ 30	9 (8%)	22 (17-38)	569	3 (33%)	1 (11%)	1 (11%)	2 (22%)	7 (0-18)	16 (0-31)
DOAC	40-50	2 (2%)	38 (35-41)	180	0 (0%)	0 (0%)	1 (50%)	1 (50%)	12 (0-24)	3.5 (0-7)
	≤ 30	2 (2%)	41.5 (40-43)	114	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (0-15)	29.5 (0-59)
No anticoagulant	≤ 30	12 (11%)	15.5 (7-32)	806	4 (33%)	0 (0%)	0 (0%)	4 (33%)	6.5 (0-26)	16.5 (0-47)

BSH British Society for Haematology; DOAC direct oral anticoagulant; CRNMB clinically relevant non-major bleeding; ISTH International Society on Thrombosis and Haemostasis; LMWH Low molecular weight heparin; UFH unfractionated heparin

*3 patients received UFH

†30 patients received 50% dose and 3 patients received prophylactic dose LMWH

Figure 1 Key outcomes (thrombosis progression and major bleeding) at 28 days from date of VTE for 105 patients with haematological malignancy, thrombosis and platelet count < 50 x 109/L shown according to baseline platelet count and A) Platelet transfusion threshold or B) Anticoagulant dose reduction threshold

Figure 2: Changes to VTE management and the reasons for those changes in the first 28 days from thrombosis (A and B) and between days 28-90 from thrombosis (C and D) in 105 patients with haematological malignancy and thrombocytopenia. DOAC direct oral anticoagulant; LMWH low molecular weight heparin; VTE venous thromboembolism.

Figure 1

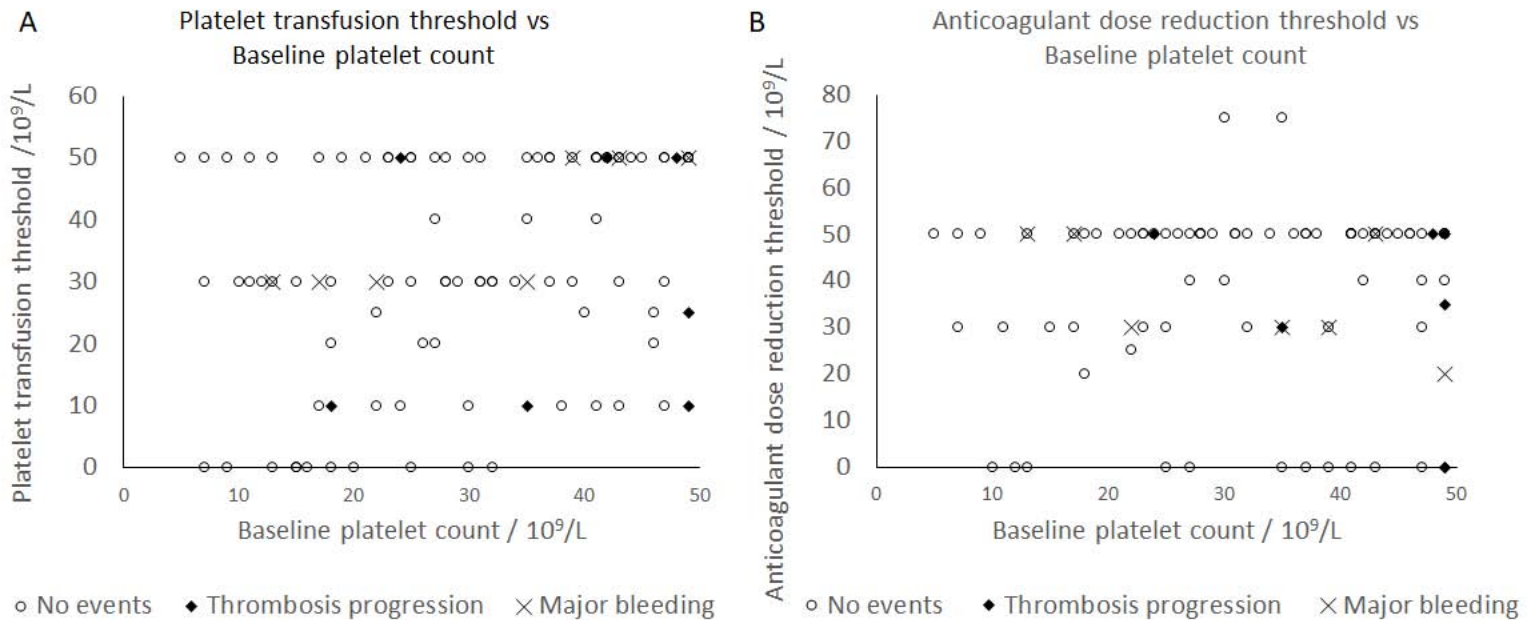
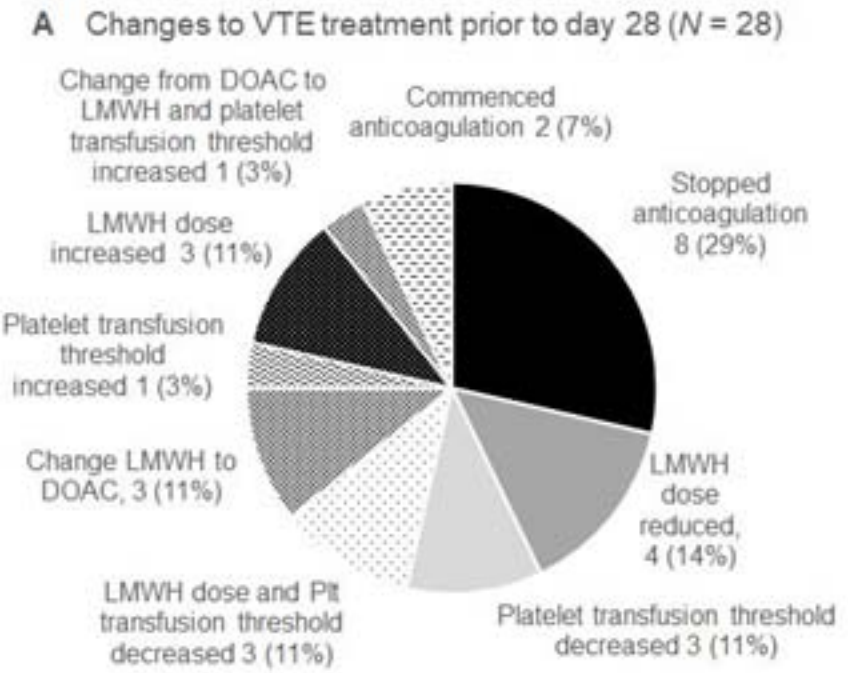
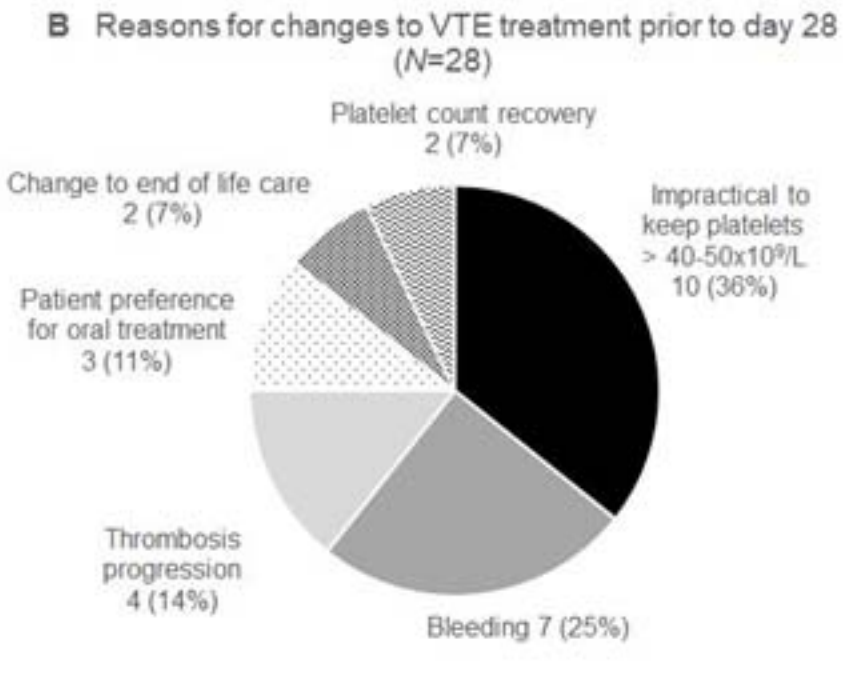
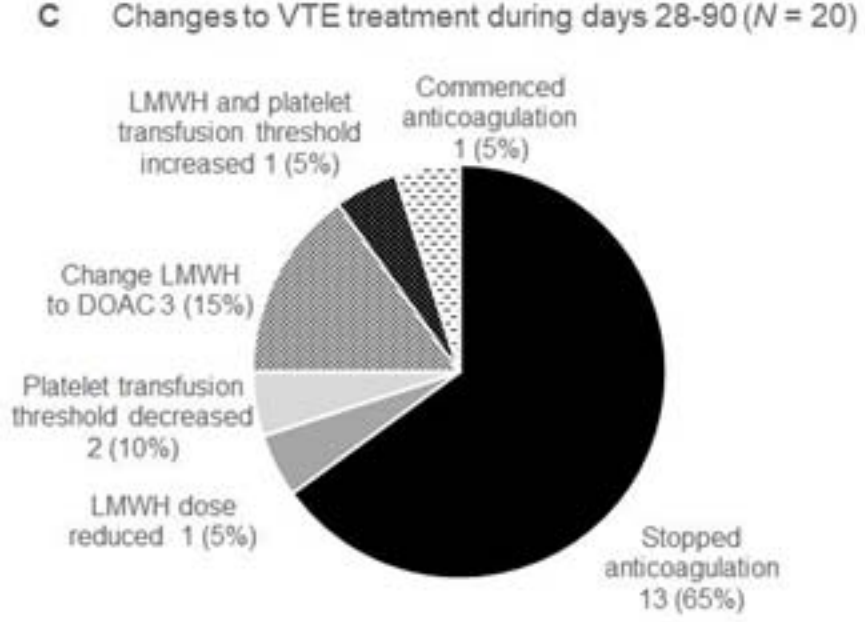
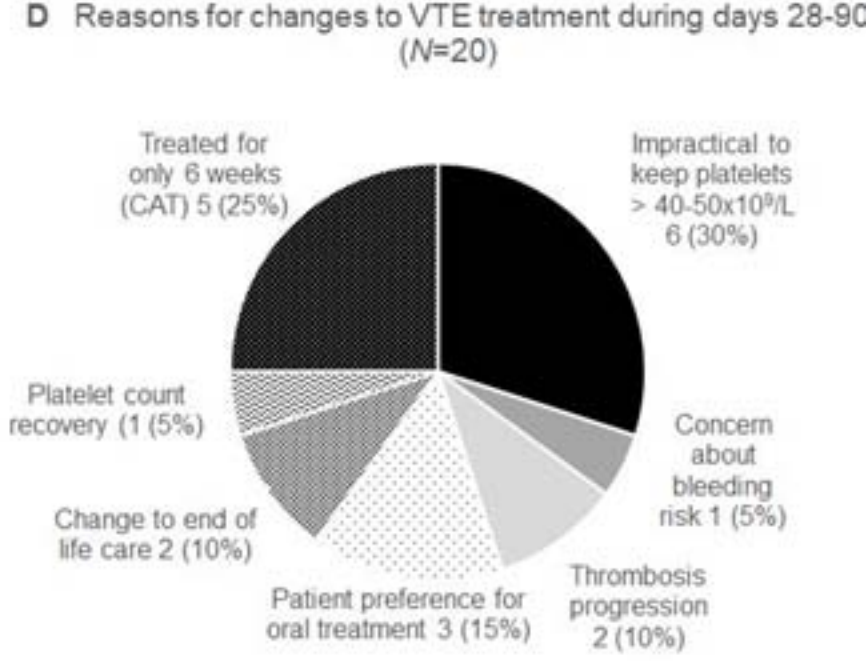

A
Platelet transfusion threshold vs
Baseline platelet count
Platelet transfusion threshold /10⁹/L
Baseline platelet count / 10⁹/L
No events
Thrombosis progression
Major bleeding
B
Anticoagulant dose reduction threshold vs
Baseline platelet count
Anticoagulant dose reduction threshold / 10⁹/L
Baseline platelet count / 10⁹/L
No events
Thrombosis progression
Major bleeding

Figure 2


A Changes to VTE treatment prior to day 28 (N = 28)
Change from DOAC to LMWH and platelet transfusion threshold increased 1 (3%)
Commenced anticoagulation 2 (7%)
Stopped anticoagulation 8 (29%)
LMWH dose increased 3 (11%)
Platelet transfusion threshold increased 1 (3%)
Change LMWH to DOAC, 3 (11%)
LMWH dose reduced, 4 (14%)
LMWH dose and Plt transfusion threshold decreased 3 (11%)
Platelet transfusion threshold decreased 3 (11%)


B Reasons for changes to VTE treatment prior to day 28 (N=28)
Platelet count recovery 2 (7%)
Change to end of life care 2 (7%)
Impractical to keep platelets > 40-50x10⁹/L 10 (36%)
Patient preference for oral treatment 3 (11%)
Thrombosis progression 4 (14%)
Bleeding 7 (25%)


C Changes to VTE treatment during days 28-90 (N = 20)
LMWH and platelet transfusion threshold increased 1 (5%)
Commenced anticoagulation 1 (5%)
Change LMWH to DOAC 3 (15%)
Platelet transfusion threshold decreased 2 (10%)
LMWH dose reduced 1 (5%)
Stopped anticoagulation 13 (65%)


D Reasons for changes to VTE treatment during days 28-90 (N=20)
Treated for only 6 weeks (CAT) 5 (25%)
Impractical to keep platelets > 40-50x10⁹/L 6 (30%)
Platelet count recovery (1 (5%)
Concern about bleeding risk 1 (5%)
Change to end of life care 2 (10%)
Thrombosis progression 2 (10%)
Patient preference for oral treatment 3 (15%)