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Anticoagulation in Patients with Platelet Disorders

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Abstract

Platelet disorders comprise heterogeneous diseases featured by reduced platelet counts and/or impaired platelet function causing variable bleeding symptoms. Despite their bleeding diathesis, patients with platelet disorders can develop transient or permanent prothrombotic conditions that necessitate prophylactic or therapeutic anticoagulation. Anticoagulation in patients with platelet disorders is a matter of concern because the bleeding risk could add to the hemorrhagic risk related to the platelet defect. This review provides an overview on the evidence on anticoagulation in patients with acquired and inherited thrombocytopenia and/or platelet dysfunction. We summarize tools to evaluate and balance bleeding— and thrombotic risks and describe a practical approach on how to manage these patients if they have an indication for prophylactic or therapeutic anticoagulation.

Keywords

- thrombocytopenia
- platelet dysfunction
- anticoagulation
- thrombotic risk
- bleeding risk

Introduction

Platelet disorders (PDs) comprise acute and chronic conditions resulting from reduced platelet count and/or impaired platelet function. Typical bleeding symptoms include petechiae, ecchymoses, prolonged bleeding after injury, epistaxis, or menorrhagia. Bleeding severity ranges from almost trivial to very severe.[1–3]

Patients with PDs can coincidently acquire transient or permanent prothrombotic conditions, which necessitate prophylactic or therapeutic anticoagulation. Prophylactic anticoagulation is usually administered in hospitalized medical patients, after surgery, or in outpatients at increased risk of thrombosis (e.g., some cancer patients).[4–6] Therapeutic anticoagulation is indicated to treat and prevent venous thromboembolism (VTE),[7,8] to prevent stroke in patients with atrial fibrillation (AF),[9,10] and to reduce the risk of thromboembolism in patients with mechanical heart valves.[11,12]

Anticoagulation in PD patients is a matter of great concern because it increases the risk of bleeding. This could add to the hemorrhagic risk related to the platelet defect. Therefore, each decision to provide anticoagulation must be balanced by tailoring bleeding and thrombotic risks at an individual level. In this review, we provide a summary of how to approach patients with PD who have an indication for anticoagulation.

Platelet Disorders

Thrombocytopenia

Thrombocytopenia is defined as reduced blood platelets less than 150×10^9/L.[13] For intensive care patients[14] and for patients with immune thrombocytopenia,[15] thrombocytopenia is defined as platelets less than 100×10^9/L, as bleeding symptoms unlikely occur if platelet counts are above this threshold. Platelet counts less than 50×10^9/L is further specified as severe thrombocytopenia.[16] Confirmed thrombocytopenia results from (1) increased platelet consumption (e.g., immune-mediated platelet destruction, bleeding, disseminated intravascular coagulation [DIC]); (2) decreased platelet production (e.g., bone marrow failure, myelodysplasia, and chemotherapy); and (3) increased sequestration of platelets

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(e.g., due to splenomegaly). A standardized workup is required to diagnose primary thrombocytopenia, or secondary thrombocytopenias due to an underlying disease.[17]

Platelet Dysfunction

Acquired platelet function defects (PFDs) mainly occur due to drug therapies and/or complicating systemic disease.[18] Antiplatelet agents, nonsteroidal anti-inflammatory drugs, β-lactam antibiotics, anticonvulsants, antidepressants, and angiotensin 2 inhibitors impair platelet function.[19] Alcohol, flavonoids-rich foods (e.g., red wine, cocoa, and green tea), spices (e.g., cumin), or herbal products (e.g., ginkgo biloba, garlic) also reduce platelet function.[20–24] Myelodysplastic and myeloproliferative syndromes, diseases with paraproteinemia, liver and/or renal failure, and severe trauma are associated with platelet dysfunction and/or additional thrombocytopenia.[25–27] Moreover, ventricular assist devices and extracorporeal circulations frequently cause PFDs in addition to other hemostasis defects such as acquired von Willebrand syndrome.[28] Of note, platelet hyperactivity can also occur increasing the risk of thrombosis (e.g., in patients with myeloproliferative neoplasms).[29] PFDs are diagnosed by means of platelet function tests.[30]

Inherited PDs represent a peculiar group of rare conditions involving only platelets or presenting as syndromes with additional clinical manifestations.[1,31] For instance, patients with *MYH9*-related thrombocytopenia—the most frequent inherited PD—may develop sensorineural deafness, nephropathy, juvenile cataracts, and chronic elevation of liver enzymes.[32] Inherited PD can present with thrombocytopenia, alterations of platelet size, platelet dysfunction, or as a combination of these findings.[1,33] Inherited PDs featured by platelet dysfunction such as Bernard–Soulier syndrome or Glanzmann thrombasthenia have more severe bleeding symptoms than those with thrombocytopenia only.[1,34] Diagnostic tools involve clinical evaluation, immune-morphologic assessment on blood smears, platelet function assays, and genetic testing.[1,2,35,36]

Treatment of Platelet Disorders

Therapeutic goals include the treatment of underlying diseases, prophylaxis, and management of bleeding episodes. Avoidance of drugs impairing platelet function or contact sports, providing regular dental cares, and hormonal therapy to reduce menorrhagia in women of childbearing age can reduce bleeding episodes. If sideropenic anemia is present, iron should be substituted. Pharmacological treatment of bleedings mainly rely on tranexamic acid and desmopressin.[1,37,38] In certain acquired (e.g., immune thrombocytopenia) and inherited PD, thrombopoietin-receptor agonists can transiently increase platelet counts and facilitate invasive procedures.[39–41] Against more severe bleeding, platelet transfusions and/or recombinant-activated factor VII can be applied.[42] Importantly, platelet concentrates should be avoided whenever possible in Glanzmann thrombasthenia or Bernard–Soulier syndrome to reduce the risk for isoantibody formation against the glycoproteins absent on patients' and expressed on blood donors' platelets, which render further platelet transfusions ineffective.[43]

Bleeding Risk Assessment

Various bleeding assessment tools (BATs) based on history-taking questionnaires have been created to assess the bleeding tendency, guide treatment, and predict future bleedings in patients with different hemorrhagic diatheses.[44] Two frequently used BATs for PD are the World Health Organization (WHO)[45] and the International Society of Thrombosis and Haemostasis (ISTH) BAT.[34,46] The WHO scale is a global, nonstructured tool that categorizes bleeding into four groups: grade 0, no bleeding; grade 1, petechiae; grade 2, mild blood loss; grade 3, gross blood loss; and grade 4, debilitating blood loss. The ISTH-BAT sums 14 distinct scores corresponding to specific graduated bleeding manifestations (►**Supplementary Table S1** [online only]).

Recent studies on patients with inherited PD showed that the degree of basal bleeding symptoms predicts the risk of spontaneous and provoked future bleedings.[34] Particularly, a substantial bleeding history (WHO grade ≥ 2 or ISTH-BAT score ≥ 6), female sex, and certain procedures (i.e., cardiovascular or urological interventions) predict a higher risk of surgery-related hemorrhagic complications.[39] Women with PD have a higher risk of postpartum hemorrhage when a history of maternal bleeding and/or platelet count lower than 50×10^9/L is present.[47,48]

Both BATs have not been evaluated for acquired PD. However, even these subjects—particularly those with persisting symptoms—are likely at higher bleeding risk when having a WHO bleeding scale of ≥ 2 or an ISTH-BAT total score of ≥ 6. Sometimes, their primary diseases carry additional hemorrhagic risks due to a compromised plasmatic coagulation (e.g., due to chronic liver disease).[49] We therefore recommend investigating platelet function *and* plasmatic coagulation to judge the risks and benefits of anticoagulation in patients with PD.

Thrombotic Risk Assessment

Thrombotic risk assessment varies with clinical settings. The *Caprini* score assesses the risk of surgery-associated VTE. In the general population not undergoing thromboprophylaxis, the incidence rates of thrombotic events correlated with this model were <0.5, 3, ≥ 5, and ≥ 6% when the scores were 0, 1 to 2, ≥ 3, and ≥ 5, respectively.[4,50,51]

The American College of Chest Physicians (ACCP) classified three surgical categories with a VTE risk: <10% (minor surgery), 10 to 40% (moderate-risk surgery), and up to 80% for high-risk procedures (e.g., knee or hip arthroplasty).[52]

The *Khorana* score assesses the VTE risk for ambulatory and hospitalized cancer patients including clinical and laboratory criteria: type of neoplasia (pancreatic and stomach cancer account for the highest risk), prechemotherapy platelet and leukocyte count, hemoglobin concentration, use of red cell growth factors, and body mass index. Scores ≥ 2 qualify patients worthy of prophylactic anticoagulation.[53]

The *Padua* score is a well-known model to identify medical patients at high risk of VTE (score > 4) and guide prophylactic anticoagulation. This score includes a previous history of VTE,

immobilization, the presence of thrombophilia, active cancer, recent trauma or surgery, elderly, heart or respiratory failure, acute infarction or stroke, acute infection or rheumatologic disorder, ongoing hormonal treatments, and obesity.[54]

Regarding therapeutic anticoagulation, the CHA_2DS_2-VASc score was established to stratify patients with AF according to their risk of stroke or other arterial thromboembolism (2 points for previous embolic event and age $\geq$75 years; 1 point each for congestive heart failure, hypertension, diabetes mellitus, age 65–74 years, vascular disease, and female sex).[55] Patients with scores $\geq$2 should start anticoagulation if no high bleeding risk is present.

Patients with acute VTE and implanted mechanical heart valve prosthesis have a high risk of thrombosis and stringently require therapeutic anticoagulation.[5,7,8] However, the risk of recurrence after an acute VTE event is considered to be highest during the first 30 days after the VTE has occurred,[56,57] being the minimum time where therapeutic anticoagulation is mandatory.[58] For mechanical heart valves, the kind and position of the valve play a role. Mechanical mitral valves or replacement of multiple valves bear the highest thromboembolic risk, whereas the risk is lower for aortic valves.[59] Moreover, biological valves have a much lower thrombotic risk and do not necessitate long-term anticoagulation.[11] Some systemic disorders necessitate therapeutic anticoagulation such as the antiphospholipid syndrome,[60] DIC,[61] or heparin-induced thrombocytopenia,[62] even if platelet counts are very low. Finally, treatments to prevent bleeding such as recombinant factor VIIa or platelet transfusions may increase the venous and arterial thrombotic risk.[3,63]

While none of the described stratification tools have been validated to assess the risk of thrombosis in patients with PD, they provide a solid basis to identify subjects with an increased thromboembolic risk. Therefore, we include them into a benefit–risk assessment for PD patients to decide if anticoagulation is indicated.

Alternatives to Anticoagulation

Despite significantly less effective than prophylactic anticoagulation, mechanical prophylaxis is indicated for PD patients with very high bleeding risk.[64] Here, intermittent pneumatic compression is more effective than elastic compressive stockings.[65] However, patients who can receive pharmacoprophylaxis do not benefit from adjunctive mechanical prophylaxis.[66]

Patients with acute VTE not tolerating therapeutic anticoagulation may receive an inferior vena cava filter. Because of possible complications of this approach, the indication should be evaluated individually.[67]

Thromboprophylaxis

Thrombocytopenia

Most guidelines on thromboprophylaxis rely on studies that excluded patients with platelets less than 50×10^9/L. However, above this threshold, prophylactic anticoagulation appears safe if no other hemorrhagic risk factors are present.[68] For oncology patients with platelet counts between 25 and 50×10^9/L, the ISTH suggests prophylactic anticoagulation after acute thrombotic episodes with low risk of progression or subacute or chronic thrombosis.[58] Patients with platelets below 25×10^9/L require an individual decision weighing thrombotic and bleedings risks.

The anticoagulant of choice depends on the clinical setting. A meta-analysis of 20 studies including approximately 10,000 cancer patients undergoing surgery revealed no difference between perioperative thromboprophylaxis with low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH), and LMWH compared with fondaparinux on mortality, thromboembolic outcomes, and bleeding. A lower incidence of wound hematoma occurred with LMWH compared with UFH.[69] Direct oral anticoagulants (DOACs) apixaban and rivaroxaban may serve as alternatives for LMWH for thromboprophylaxis in ambulatory patients starting chemotherapy, including those with mild thrombocytopenia.[70,71] Here, a high risk of gastrointestinal or urogenital bleeding should be excluded.[72] Eventually, a randomized study with more than 3,000 intensive care patients including those with mild thrombocytopenia revealed a better safety profile of LMWH over UFH.[73]

Platelet Dysfunction

So far, only one study has systematically explored the risk of VTE in patients with PD undergoing surgery.[74] Out of more than 200 procedures performed in 133 subjects affected by 22 inherited PDs, the risk of postsurgical VTE was lower than in the general population but not negligible, and correlated with the *Caprini* score and the ACCP procedure-related risk stratification. Both mechanical and pharmacologic prophylaxis reduced the occurrence of VTE. Most of the anticoagulated patients received enoxaparin at a median daily dosage of 4,000 IU (interquartile range [IQR]: 2,000–5,000) starting from the day of surgery for a median duration of 15 days (IQR: 7–18). Of note, the rate of postsurgical bleedings did not significantly differ between anticoagulated and non-anticoagulated patients. The study also showed that patients with substantial platelet dysfunction were not exempt from postsurgical VTE. In fact, two patients affected with Glanzmann thrombasthenia and biallelic Bernard–Soulier syndrome developed postprocedural VTE. Despite a high individual VTE risk (*Caprini* scores of 8 and 12, respectively), both subjects did not receive anticoagulation, presumably because of the perceived high bleeding risk. Selleng et al. also reported on a patient with *MYH9*-related thrombocytopenia not receiving prophylactic anticoagulation who developed postsurgical VTE.[75] These cases show that postsurgical thromboprophylaxis should not be withhold in inherited PD patients, when prothrombotic risk factors are present. This concept is reasonably transferrable to persistent acquired PD.

Therapeutic Anticoagulation

Thrombocytopenia

For thrombocytopenia and cancer-associated acute VTE, the ISTH suggests full-dose anticoagulation at platelet counts greater than 50×10^9/L, and to consider an adapted regimen if platelets fall below that level. This includes platelet transfusion support to maintain platelet counts at 40 to 50×10^9/L, if

patients have high-risk features of cancer-associated VTE such as symptomatic segmental or proximal pulmonary embolism, proximal deep vein thromboses, or a history of recurrent/progressive thrombosis. Lower risk thromboses such as distal deep vein thromboses, incidental subsegmental pulmonary embolism, and catheter-related thromboses may be anticoagulated with half therapeutic doses. Prophylactic-dose LMWH may be considered for patients with platelets of 25 to 50×10^9/L. Anticoagulation is stopped for patients with platelets less than 25×10^9/L, although prophylactic dosage might be reasonable as long as platelet counts exceed 10×10^9/L.[58] The minimum treatment duration should cover 6 months or longer, if the tumor persists and the VTE risk remains high.[76]

Thrombocytopenia is also common in AF patients with greater than 10% being affected.[77] AF guidelines acknowledge low platelet counts as a risk factor for bleeding,[9] but do not recommend specific platelet thresholds to adjust or withhold anticoagulation. However, AF patients with mild or moderate thrombocytopenia may safely be anticoagulated and DOACs may be as safe and effective as in non thrombocytopenic patients. A cohort study including 367 patients with thrombocytopenia (platelets $<100 \times 10^9$/L) found that DOAC therapy ($n = 181$) was associated with a lower tendency for major bleeding with no significant difference in ischemic stroke/systemic embolism or death when compared with warfarin ($n = 186$).[78] A retrospective study compared AF patients treated with either warfarin ($n = 6{,}287$) or DOACs ($n = 5{,}240$). DOAC patients with reduced platelet counts ($<150 \times 10^9$/L) had significantly lower mortality rates during a median follow-up of 40.6 months compared with warfarin controls.[79] Caro and Navada reported one patient with more severe thrombocytopenia associated with myelodysplastic syndrome and two with acute myeloid leukemia and AF, who did not develop major bleeding despite anticoagulation (1 rivaroxaban, 2 warfarin) during an average follow-up of 203 days.[80]

A proof-of-concept study revealed that AF patients with mild thrombocytopenia might benefit from DOACs at reduced doses. Sixty-two patients with AF and platelet counts from 50 to 100×10^9/L were treated with rivaroxaban 15 mg once daily (33.9%), dabigatran 110 mg twice daily (54.8%), or apixaban 2.5 mg twice daily (11.3%) and compared with matched AF subjects with normal platelet counts being treated with the recommended doses of DOACs. Thrombocytopenic patients had similar rates of major bleeding (1.8 vs. 2.7%/year, $p = 0.49$), clinically relevant non-major bleeding (1.5 vs. 1.1%/year, $p = 0.74$), ischemic stroke and transient ischemic attacks (1.8 vs. 1.5%/year, $p = 0.8$), and death (1.06 vs. 1.11%/year, $p = 0.96$). The risk of bleeding and stroke was unaffected by the type of DOAC.[81]

Finally, cancer patients on chemotherapy with newly diagnosed AF are suggested to take a DOAC over vitamin K antagonist or LMWH, if no contraindications (e.g., gastrointestinal cancers) are present and no relevant drug-to-drug interactions are expected.[82] We therefore conclude that AF patients with platelets greater than 50×10^9/L should receive therapeutic anticoagulation, preferably with DOACs. For patients with lower platelet counts, reduced dose regimens may be appropriate to reduce the bleeding risk based on an individual benefit–risk evaluation. An individual management is also necessary for patients with mechanical heart valves or other high-risk situations, who develop thrombocytopenia.

Platelet Dysfunction

Anticoagulation in inherited PD was reported for patients with Glanzmann thrombasthenia,[74,83–88] Bernard–Soulier syndrome[74] and *MYH9*-related thrombocytopenia[75,89] who developed VTE. The thrombotic manifestations were often provoked by a transient risk factor such as surgery or a central venous catheter, which highlights the relevance of thromboprophylaxis. In acute VTE, therapeutic dose anticoagulation with UFH or LMWH was administered at most. None of the reported patients received DOACs as first choice. Long-term anticoagulation was mainly performed with vitamin K antagonists or LMWH, and anticoagulation-related bleeding was rare. In the SPATA-DVT study, a patient with Glanzmann thrombasthenia and deep vein thrombosis received therapeutic dose enoxaparin for 3 months without bleeding complications.[74] Only one severe hemorrhagic episode due to gastrointestinal angiodysplasia was reported in a Glanzmann thrombasthenia patient receiving anticoagulation with rivaroxaban. This patient had a severe bleeding phenotype even before anticoagulation, which had likely aggravated but not *caused* the hemorrhage.[85]

Thus, a limited course of anticoagulation appears feasible in patients with PD without a dramatic increase of the bleeding risk. However, long-term anticoagulation might overproportionally increase the bleeding risk. We therefore propose to administer therapeutic anticoagulation during the first month after an acute VTE. Further course of treatment should consider the type of thrombosis, the bleeding tendency of each patient, the treatment effectiveness, and the individual risk of VTE recurrence to adapt the anticoagulation regimen. The indication for anticoagulation in AF patients should be based on the CHA_2DS_2-VASc score and treatment should be managed similar to patients with thrombocytopenia. Reduced doses of LMWH or DOACs may be appropriate for long-term anticoagulation, if intolerable bleeding symptoms occur during therapeutic dose anticoagulation.

Few reports deal with patients receiving prosthetic heart valves, mainly addressing their perioperative management. Garcia-Villarreal et al described a Glanzmann thrombasthenia patient undergoing prosthetic mitral valve replacement who developed severe bleeding complications during postsurgery anticoagulation including severe hematuria and gastrointestinal bleeds.[90] Only the shift to a biologic valve prosthesis could control the situation as anticoagulation could be stopped afterward. This case illustrates the relevance to accurately plan such procedures and to ascertain whether less thrombogenic cardiac or arterial devices can be implanted to avoid long-term anticoagulation after the procedure. In addition, acquired von Willebrand syndrome can occur in patients with prosthetic heart valves and complicate postprocedural bleedings.[91]

Table 1 Approach to postsurgical VTE prophylaxis in patients with inherited and persistent acquired platelet disorders

VTE risk assessment	Advisable postsurgical VTE prophylaxis	Adjustment in case of postsurgical excessive bleeding
Low (*Caprini* score: 0–2)	Mechanical prophylaxis[a]	–
Moderate (*Caprini* score: 3–4)	Mechanical prophylaxis[a] Consider pharmacologic prophylaxis[b] in case of expected prolonged immobilization *and* low individual bleeding risk[c]	Start mechanical prophylaxis[a] and *consider to switch* to pharmacologic one[b] as soon as bleeding has been stopped and adequate hemostatic balance has been restored
High/very high (*Caprini* score: ≥ 5)	Pharmacologic prophylaxis[b]	Start mechanical prophylaxis[a] and *switch* to the pharmacologic one[b] as soon as bleeding has been stopped and adequate hemostatic balance has been restored

Abbreviation: BAT, bleeding assessment tool; ISTH, International Society of Thrombosis and Haemostasis; LMWH, low-molecular-weight heparin; WHO, World Health Organization; VTE, venous thromboembolism.
[a]Pneumatic compression (preferably) or compression stockings should be started immediately after surgery and continued for 2 weeks.
[b]LMWH at a prophylactic dosage, to be started within 6 hours after surgery and continued for 2 weeks.
[c]WHO bleeding scale < 2 or ISTH-BAT < 6.

Conclusions

There is clear evidence that patients with PD can develop thrombosis in the presence of prothrombotic risk factors despite their bleeding phenotype. Moreover, the additional risk of bleeding resulting from prophylactic anticoagulation is substantially lower compared with the risk of bleeding during longer-term therapeutic dose anticoagulation whenever a VTE has developed. As a consequence, prophylactic anticoagulation should be considered if the thrombotic risk is high.

In ►Table 1, we propose how to guide perioperative thromboprophylaxis in patients with PD according to the *Caprini* score. Briefly, we suggest mechanical prophylaxis when the thrombotic risk is only low or intermediate, and prophylactic anticoagulation with LMWH when the VTE risk is high. In case of postsurgical excessive bleeding, LMWH should be postponed until effective hemostasis has been achieved. These principals can be applied likewise for other medical conditions with an increased thrombotic risk adapting the described tools for risk stratification.

Therapeutic dose anticoagulation may be feasible for a defined duration without an inacceptable high bleeding risk. However, dose reductions or withhold of anticoagulation should be considered as soon as the VTE risk declines and if bleeding symptoms worsen. ►Table 2 summarizes

Table 2 Approach to adapt therapeutic anticoagulation in patients with inherited and persistent acquired platelet disorders

Bleeding risk	Thrombotic risk	Indication for anticoagulation	Considerations for anticoagulation
High[a]	High	Venous thromboembolism < 3 mo Atrial fibrillation (CHA_2DS_2-VASc score ≥ 2) Heart valve prosthesis (mechanical valves, multiple valve prosthesis)	Consider short-acting intravenous or oral drugs (UFH, DOACs), with dose reduction after the first month if the VTE has resolved Weigh bleeding against thrombotic risk and consider short-acting oral drugs (DOACs) with close monitoring of bleeding symptoms Whenever possible, consider biologic prosthesis before implantation. If a mechanical valve has been implanted and bleeding in a patient undergoing anticoagulation cannot be managed otherwise, switch to biologic valve
High[a]	Low	Venous thromboembolism > 3 mo Atrial fibrillation (CHA_2DS_2-VASc score < 2) Heart valve prosthesis (biologic prosthesis)	Consider to stop therapeutic dose anticoagulation Consider not to start anticoagulation Consider not to provide long-term anticoagulation
Low[b]	High	Venous thromboembolism < 3 mo Atrial fibrillation (CHA_2DS_2-VASc score ≥ 2) Heart valve prosthesis (mechanical valves, multiple valve prosthesis)	Consider a usual course of anticoagulation and plan a reevaluation of thrombotic risk after 3 mo Consider usual course of anticoagulation with periodic evaluation of bleeding symptoms Consider usual course of anticoagulation with periodic evaluation of bleeding symptoms
Low[b]	Low	Venous thromboembolism > 3 mo Atrial fibrillation (CHA_2DS_2-VASc score < 2) Heart valve prosthesis (biologic prosthesis)	Consider to stop therapeutic dose anticoagulation Consider not to start anticoagulation Consider to stop postinterventional anticoagulation early

Abbreviations: BAT, bleeding assessment tool; DOACs, direct oral anticoagulants; ISTH, International Society of Thrombosis and Haemostasis; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; WHO, World Health Organization; VTE, venous thromboembolism.
[a]WHO BS ≥ 2 or ISTH-BAT total score ≥ 6 or platelet counts $< 50 \times 10^9$/L.
[b]WHO BS < 2 or ISTH-BAT total score < 6 or platelet counts $> 50 \times 10^9$/L.

considerations for therapeutic anticoagulation in PD patients and lists potential treatment options.

Although most experience exists with LMWH, the advantages of DOACs may indicate this treatment in specific situations such as AF or VTE.

Due to the scanty evidence, caution is mandatory for treatment decisions and physicians should carefully assess and document bleeding events and thrombosis risks before and during anticoagulation on a regular schedule to optimize individual therapy. A close follow-up is highly recommended to provide the safest and most efficient anticoagulation in patients with PD.

Conflicts of Interest

C.Z. has no conflicts to report. T.T. reports personal fees and other from Bristol Myers Squibb, personal fees and other from Pfizer, personal fees from Bayer, personal fees and other from Chugai Pharma, other from Novo Nordisk, personal fees from Novartis, and other from Daiichi Sankyo, outside the submitted work.

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