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Reduced doses of direct oral anticoagulation are safe in atrial fibrillation patients with mild thrombocytopenia

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ABSTRACT A critical appraisal and clinical application of Janion-Sadowska A, Papuga-Szela E, Łukaszuk R, et al. Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation and Thrombocytopenia. *Journal of Cardiovascular Pharmacology*. 2018;72(3):153-160. doi: [10.1097/fjc.0000000000000607](https://doi.org/10.1097/fjc.0000000000000607)

Keywords: atrial fibrillation, anticoagulation, thrombocytopenia, noac

Clinical Context

Patricia Clark (pseudonym) is a 66 year old Caucasian female with a past medical history of diabetes, hypertension, hepatitis C, and chronic mild thrombocytopenia due to hepatitis C who was admitted to our medicine team one day after losing vision in her right eye. The ophthalmologists diagnosed her cause of blindness as central retinal artery occlusion, but during workup she was incidentally found to have an internal jugular thrombosis and atrial fibrillation. Anticoagulation is proposed as the cornerstone of treatment for both venous thrombosis and atrial fibrillation, however, the risk of bleeding due to concurrent thrombocytopenia complicated our treatment approach. Furthermore, Mrs. Clark told us that her husband was once on warfarin but suffered a stroke as a complication of the therapy. She voiced a strong desire to never take warfarin herself. We questioned if a direct oral anticoagulant (DOAC) would be a proper therapy for her condition.

Clinical Question

Would a DOAC be a safe and effective therapy for a patient with atrial fibrillation and concurrent mild thrombocytopenia?

Research Article

Janion-Sadowska A, Papuga-Szela E, Łukaszuk R, Chrapek M, Undas A. Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Thrombocytopenia. *Journal of Cardiovascular Pharmacology*, 2018;72(3):153-160. doi: [10.1097/FJC.0000000000000607](https://doi.org/10.1097/FJC.0000000000000607)

Related Literature

A literature review of the pubmed database was performed using the following “all fields” topics: [atrial fibrillation] AND [thrombocytopenia] AND [platelet aggregation inhibitors OR anticoagulants]. This yielded 72 search results. References were also

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reviewed in articles on atrial fibrillation and thrombocytopenia on UpToDate and DynaMed as well as systematic reviews on the topic.¹

Five cohort studies were found during the search. No randomized control trials could be found assessing the use of DOACs for treating atrial fibrillation with thrombocytopenia.

The Kiviniemi paper assessed efficacy and bleeding risks of patients with atrial fibrillation and thrombocytopenia on vitamin K antagonists undergoing percutaneous coronary intervention. However, in addition to our patient not undergoing PCI, she explicitly stated she did not want to be put on warfarin, the main drug used in this study. Furthermore, patients were only followed for 12 months.²

The Houghton paper is a retrospective cohort study assessing safety and efficacy of anticoagulation treatment of venous thromboembolism during thrombocytopenia in patients with hematologic malignancy. However, patients in this study had a severe thrombocytopenia defined as a platelet count less than 50 x 10⁹/L. Our patient's thrombocytopenia was more moderate with a count of 63 x 10⁹/L. Additionally, our patient's mechanism of thrombocytopenia was different than the patients in this study and not complicated by the cancer treatments patients were receiving.³

The Khanal paper is another retrospective cohort study assessing safety and efficacy of anticoagulation treatment of venous thromboembolism during thrombocytopenia in patients with hematologic malignancy. Patients in this study had an even more severe thrombocytopenia (median nadir of 10 x 10⁹/L) than patients in the Houghton paper. Furthermore, the majority of patients were treated with low molecular weight heparin or heparin (77%). This drug was not feasible for an outpatient, long-term use in our patient.⁴

Aside from this critical appraisal's chosen publication, the Wang paper is the only other study examining anticoagulation in atrial fibrillation patients with thrombocytopenia. However, it is a retrospective cohort study assessing safety and efficacy of DOAC vs warfarin therapy in atrial fibrillation patients with thrombocytopenia. Our patient had already established that she did not want warfarin therapy. Of note, the study did find that DOACs were associated with a lower rate of major bleeding with no significant difference in stroke or systemic embolism when compared to warfarin in patients with thrombocytopenia. Even though warfarin treatment was not an option, the study provided our medical team reassurance that DOAC would be an appropriate treatment for her.⁵

Critical Appraisal

To the best of my knowledge, no randomized control trial exists assessing the safety and effectiveness in DOACs for treating atrial fibrillation with concurrent thrombocytopenia. The 2018 Janion-Sadowska study is a prospective observational cohort study with SORT evidence level 2B. It aimed at estimating the effectiveness and risk of bleeding events associated with reduced doses of DOACs in atrial fibrillation patients with thrombocytopenia.

The investigators screened 924 white atrial fibrillation patients to prospectively enroll 67 patients with a persistent mild thrombocytopenia defined as a platelet count from 50 to 100 x 10⁹/L, who were referred to the Centre for Coagulation Disorders in Cracow, Poland. Patients were excluded if they had significant mitral disease, any valve prosthesis, antiphospholipid syndrome, cancer, or a glomerular filtration rate below 30 mL/min. In the center, DOACs were started on patients with reduced doses of rivaroxaban, dabigatran, or apixaban. The decision to use reduced DOAC doses was made arbitrarily based on moderate-to-severe bleeding risk concerns at full doses in patients with reduced platelet counts. A reference group comprised of 65 atrial fibrillation patients with normal platelet counts matched for age and sex, were treated with the full recommended DOAC dose according to 2012 ESC guidelines for atrial fibrillation management. The choice of a DOAC in both patient groups was at the physician's and patient's discretion.

The majority of study participants were Caucasian women with an average age of 70 and an average platelet count of 78 x 10⁹/L. This is similar to our patient, a 66 year old Caucasian female with a platelet count of 63 x 10⁹/L. The main cause of mild thrombocytopenia in study participants was liver cirrhosis (n=35), which is similar to our patient's hepatitis C cause for thrombocytopenia. Other causes of mild thrombocytopenia were autoimmune disease (n=9), immune thrombocytopenia (n=5), or



had an unidentified cause (n=18). Only 14.5% of study participants had diabetes, whereas our patient had poorly controlled diabetes, which could increase her risk of bleeding compared to study participants. Nonetheless, our patient should be sufficiently similar to the study population.

Patients were followed from 23 to 64 months. Five patients with thrombocytopenia and three control patients were lost to follow-up, leading to a total of 62 thrombocytopenic vs 62 control patients studied. The authors combined major bleeding and clinically relevant non-major bleeding (CRNMB) as the primary end point for analysis. Major bleeding was defined according to the International Society of Haemostasis recommendations and included fatal or symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, pericardial, intraarticular, or compartment syndrome), bleeding causing a fall in hemoglobin of 20g/L or more, or bleeding resulting in 2 or more units of red blood cell transfusion. CRNMB was defined as non-major bleeding that resulted in hospitalization, medical intervention, or prompted face-to-face evaluation. All other bleeding complications were classified as minor bleeding. At the end of follow-up, the number of all kinds of bleeding, stroke, and death were similar in both groups. Major bleeding occurred in 5 of 62 (8.1%) patients with thrombocytopenia compared to 7 of 62 (11.3%) patients with normal platelet counts. CRNMB occurred in 4 of 62 (6.4%) thrombocytopenic patients compared to 3 of 62 (4.8%) control patients. Minor bleeding occurred in 30 of 62 (48.4%) of patients with thrombocytopenia compared with 24 of 62 (38.7%) patients with normal platelets. Stroke/TIA occurred in 5 of 62 (8.1%) thrombocytopenic patients vs 4 of 62 (6.5%) control patients. Mortality was the same between thrombocytopenic patients and patients with normal platelet count (3 of 62, 4.8% in both groups). Because the incidence of strokes/TIA and deaths were similar in both groups, the study suggests that treating patients with atrial fibrillation and concurrent thrombocytopenia with reduced doses of DOACs is an efficacious way of reducing thromboembolic events without significantly increasing the risk of bleeding complications. It should be noted, however, that the study is underpowered to find a statistically significant difference between groups that might otherwise exist.

When selecting patients for the control group, the investigators selected patients based on demographics, but did not account for the form of DOAC medication being received. Therefore, the majority of thrombocytopenic patients ended up being treated with dabigatran (54.8%) whereas the majority of patients with a normal platelet count were treated with rivaroxaban (53.2%). As a result, the clinical outcomes between groups may be skewed by the different DOACs taken between patients. Furthermore, a larger percentage of thrombocytopenic patients were on ACEI compared to normal platelet count patients (20% vs 7%). While the study does not mention any other blood pressure control medications, it is possible thrombocytopenic patients had better controlled blood pressure, thus reducing their chances of bleeding. Lastly, although the study observed similar stroke/TIA rates in both groups, the study was underpowered to assess the efficacy of the treatments tested.⁶

Clinical Application

Mrs. Clark was initially hesitant to start any type of "blood thinners". Her husband died of complications following an intracranial hemorrhage while being on warfarin. We acknowledged her concerns, but also discussed her reason for current admission and the risks of not receiving anticoagulation therapy. We explained that DOACs do not operate through an identical mechanism as warfarin and require less monitoring than patients on warfarin. Mrs. Clark ultimately agreed to treatment with rivaroxaban. Her CHA₂DS₂-VASc score was calculated to be 5. Because of this, as well as the incidental finding of internal jugular vein thrombosis, our team thought it was best for Mrs. Clark to be on long term therapy. Because the Janion-Sadowska study did not differentiate between DOACs, the specific type of DOAC was chosen based on Mrs. Clark's insurance coverage as well as her preference to take the medication only once daily.

Learning points:

1. Currently, limited research shows that DOACs in reduced doses are safe in patients with atrial fibrillation and mild thrombocytopenia needing anticoagulation to prevent stroke or embolic events.
2. Current guidelines for atrial fibrillation or venous thromboembolism prophylaxis are based on randomized clinical trials that exclude subjects with a high bleeding risk, including patients with thrombocytopenia.



3. More research is needed to evaluate the safety and efficacy of treatment options for patients with atrial fibrillation or venous thrombosis in the setting of thrombocytopenia.

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