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Participate in Protocol Critique?

Y es/No

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Title: Safety and efficacy of direct oral anticoagulants for venous thromboembolism treatment and atrial fibrillation in hematologic malignancy patients

Hypothesis: DOACs will be associated with less major bleeding than LMWH while having a non-significant difference in efficacy when used in heme/BMT patients.
The retrospective study will include adult patients with hematologic malignancy treated with a DOAC/LMWH between July 1, 2012 and May 18, 2021 at UC San Diego Health, UC Davis Health and UCSF Health. All the information will be accessed from pre-existing medical records. The precise number of current participants is unknown but estimated to be atleast 200 participants. As a retrospective study, there will not be blinding or randomization of participants.

As this is a retrospective chart review, risk for harm is minimized.
We aim to utilize the results of this study to direct medical therapy for VTE or Afib patients with concomitant hematological malignancies who undergo a bone marrow transplant.
Background Review:

Cancer patients have a seven-fold increase in risk of developing venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism.[1] VTE is the second leading cause of death in this patient population. According to current guidelines, low-molecular-weight heparin (LMWH) is the recommended antithrombotic therapy in cancer patients.[2] While there is evidence to show that LMWH is more effective and causes fewer bleeding events than vitamin K antagonists (VKA) for the prevention of recurrent malignancy-related VTE, the evidence for giving LMWH or VKA over direct oral anticoagulants (DOACs) to this patient population is modest.[3]

DOACs, which are also known as novel oral anticoagulants or target-specific oral anticoagulants, are indicated for VTE treatment and for thromboembolism prophylaxis in patients with non-valvular atrial

fibrillation. While dabigatran directly inhibits thrombin to produce its anticoagulation effects, rivaroxaban, apixaban, and edoxaban, work by inhibiting Factor Xa. DOACs are favorable alternatives for antithrombotic therapy because close laboratory monitoring is not routinely recommended as with VKA and LMWH.[4] However, clinical practice guidelines established by CHEST and the American Society of Clinical Oncology continue to recommend LMWH over DOACs for the treatment and prevention of cancer-related thromboembolism.[2,5]

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Unfortunately, few clinical studies address DOAC use for VTE treatment and prevention in cancer patients. A randomized, controlled trial of 5,365 adult patients with a confirmed VVTE concluded that apixaban was non-inferior to conventional therapy with LMWH followed by dose-adjusted warfarin for the treatment of acute VTE.[6] However, patients with malignancy only comprised about 3% of the study population. This matches other studies comparing the different DOACs and VKA, in which cancer patients represented only 2-10% of the population.[7] As seen in current literature, the proportion of cancer patients in these study populations is very limited. This is especially true for patients with hematologic malignancies, such as myeloma, lymphoma, and leukemia. In addition to the limited representation of cancer patients within these trials, there are no significant studies that compare DOACs to LMWH, the current recommended anticoagulation therapy for cancer-related VTE.

A recent single center retrospective study conducted by Man et al. studied bleeding rates in patients with hematologic malignancy receiving immunomodulatory agents concomitantly with warfarin or a DOAC.[8] Over two-thirds of the study population were myeloma patients, and the study found similar bleeding rates between the warfarin group and DOAC group (17% and 16%). To further explore the use of DOACs in a specialized patient population, we are conducting a retrospective chart review at our institution to evaluate the safety of DOACs for VTE treatment and stroke prevention in atrial fibrillation in patients with a hematologic malignancy.

A search through UC San Diego Health, UC Davis Health, and UCSF Health's electronic medical records will be performed for the period of July 1, 2012 to May 18, 2021. The institution's electronic medical record system was launched in February of 2012; therefore, the study period will begin several months after the start to account for patient profiles that were not yet transitioned to the electronic system. A retrospective chart review will be performed of adult patients with hematologic malignancies who received at least one FDA-approved dose of a DOAC/LMWH for VTE treatment and/or stroke prevention for atrial fibrillation.

Patient data will be extracted from medical records and compiled in a secure database. Nominal data will be analyzed against various patient demographics by utilizing chi-square tests, and continuous variables will be analyzed with two-sample t-tests.

Inclusion Criteria:

- Age of 18 years or older
- Have a diagnosis of a hematologic malignancy as defined by the 2016 revision of the World Health Organization classification of lymphoid and myeloid neoplasms and acute leukemia[9,10]
- Received at least one dose of a DOAC or LMWH from July 1, 2012 to May 18, 2021
- Treatment for VTE and/or stroke prevention for atrial fibrillation

Exclusion Criteria:

- Solid tumor malignancy without active hematologic malignancy
- Patients receiving non-FDA approved doses of DOAC/LMWHs for VTE and/or stroke prevention for atrial fibrillation
- Prescribed DOAC/LMWH but therapy was never initiated

Clinical Data: All measurements will be extracted from patient's medical records by the study investigators and include patient demographics, DOAC/LMWH data, and bleeding outcomes.

1. Patient data: gender, ethnicity, date of birth
2. Type of hematologic malignancy
3. History of blood/marrow transplantation (BMT)
4. Type of BMT
5. Date of BMT
6. Conditioning regimen for BMT
7. Immunosuppression used for BMT
8. Donor and recipient CMV status
9. Concomitant drugs used post-BMT that have potential drug-drug interactions with DOACs
10. Concomitant chemotherapy while on DOAC/LMWH
11. Specific DOAC/LMWH used
12. Indication for using DOAC/LMWH
13. Date of VTE event (if applicable)
14. Date of VTE event while on a DOAC/LMWH (if applicable)
15. Concomitant antiplatelet therapy
16. Clinical characteristics when DOAC/LMWH therapy was started: baseline platelet count, baseline serum creatinine, baseline creatinine clearance, baseline hemoglobin
17. Anti-Xa levels (if applicable)
18. Previous use of VKA
19. Previous use of LMWH

20. Date that DOAC/LMWH was started
21. Date that DOAC/LMWH was permanently discontinued
22. Reason for discontinuation of DOAC/LMWH
23. Correct starting dose was started
24. Major bleeding events
25. Minor bleeding events (i.e. gastrointestinal, hematuria, bruising, epistaxis, extremity hematoma)
26. Fatal bleeding events
27. Transfusions required and the number of units of packed red blood cells received
28. History of receiving a lumbar puncture while on the DOAC/LMWH and if the drug was appropriately held according to our institution's guideline
29. HAS-BLED score
30. Use of concomitant medications increasing VTE risk (estrogens, progestins, epoetin-stimulating agents, bevacizumab, immunomodulators, lenalidomide, pomalidomide, thalidomide, or tamoxifen)
31. Current smoker status
32. History of coagulation deficiency disorder.
33. Deceased or not deceased
34. Cause of death (if known)
35. Date of last follow-up or death

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