Rolandas Urbstonaitis
Mentor: Maithili Deshpande
Title*: Bleeding events, morbidity and mortality associated with DOAC's compared to warfarin in patients with atrial fibrillation and venous thromboembolism age 50 and older.*

Purpose: There is a lack of post market safety evidence on use of direct oral anticoagulants (DOACs) in patients ages 50 and older who have a diagnosis of venous thromboembolism or atrial fibrilation. The purpose of this study is to review and summarize reports of bleeding and subsequent morbidity and mortality associated with each DOAC and warfarin in patients 50 and older who have a diagnosis of atrial fibrillation or venous thromboembolisms (VTE).

Methods: This study used the FDA Adverse Event Reporting System (FAERS) data for the period from January 2015 to January 2018. Adults diagnosed with venous thromboembolism or atrial fibrillation, using a DOAC (dabigatran, apixaban, rivaroxaban) or warfarin, and age 50 and older were included in the study. Reports of bleeding were identified by using search terms from standardized quarries in the medical dictionary for regulatory activities (MedDRA). Outcomes related to morbidity and mortality were compared from the documented reports. A case/non-case methodology was used to evaluate the association between bleeding and the use of the drugs of interest. The reporting odds ratio (ROR) was utilized to compare the effects of DOACs and warfarin on bleeding/hemorrhagic events.

Results: A total of 1,881 patient ADR reports were identified with the DOACs or Warfarin. Of the 1,881 ADR reports, 894 were unique bleed reports of which 187 were linked to apixaban, 184 were linked to rivaroxaban, 67 were linked to dabigatran, and 456 bleed reports linked warfarin to bleeding. The RORs (95% CI) of hemorrhage associated with apixaban, rivaroxaban, dabigatran, and warfarin across all indications were 0.693 (0.560 - 0.857), 0.718 (0.579 - 0.890), 0.962 (0.685 - 1.353), 1.723 (1.435 - 2.070), respectively. The RORs for bleeding cases in warfarin treated patients aged 50-64, 65-80, and ≥80 were 2.765 (1.7839 - 4.2857), 1.460 (1.1138 - 1.8803), and 1.635 (1.1574 - 2.3088), respectively. The RORs for bleeding cases in apixaban treated patients aged 50-64, 65-80, and ≥80 were 0.3505 (0.1930 - 0.6365), 0.6825 (0.5057 - 0.9210), 0.8452 (0.5800 - 1.2319), respectively. The RORs for bleeding cases in dabigatran treated patients aged 50-64, 65-80, and ≥80 were 0.6328 (0.2839 - 1.4150), 1.1710 (0.7371 - 1.8601), and 0.9430 (0.4701 - 1.8915), respectively. The RORs for bleeding cases in rivaroxaban treated patients aged 50-64, 65-80, and ≥80 were 0.7800 (0.4886 - 1.2452), 0.8130 (0.6042 - 1.0940), and 0.5911 (0.3844 - 0.9090), respectively. When looking at morbidity and mortality outcomes, only 4.8% of all bleeding events with warfarin lead to death. Contrarily, the percentage of bleeding events leading to death with the DOACs was much higher with apixaban, rivaroxaban, and dabigatran having 10.8%, 8.1%, and 6.3% of their bleed events leading to death respectively.

Conclusion: Out of all the anticoagulants in the study, warfarin associated hemorrhages were significantly increased across all the age groups (50-64, 65-80, and ≥80) and both indications (venous thromboembolism and atrial fibrilation) when compared to the reference anticoagulants. In contrast, when it came to apixaban and rivaroxaban the RORs were significant for the decreased risk of reporting bleeding rather than any other event, this trend was significant across both indications for apixaban while only significant in the VTE group for

rivaroxaban. All of the DOACs from the study had a greater percentage of reports leading to death or life-threatening outcomes when compared to warfarin.