

The Outcome of Fall in the Elderly on Anticoagulation: Direct Oral Anticoagulants versus Warfarin

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ABSTRACT

Background: Aging is associated with increased prevalence of multiple pathologies including atrial fibrillation (AF), thrombophlebitis and predisposition to fall. Anticoagulation can decrease the burden of thrombophlebitis disorders and thromboembolic events. However, due to concerns associated with bleeding risk, possible fall related injuries, and the lack of reversing agents for Direct oral anticoagulants (DOACs), elderly patients have been undertreated with anticoagulation.

Methods: We performed a systematic search of electronic medical records of two teaching hospitals and selected elderly patients (≥ 65 years old) who presented to the emergency departments with the complaint of fall and had been treated with DOACs or warfarin prior to admission.

Results: 322 patients met inclusion criteria for the study (warfarin = 204 and DOACs = 118). Major bleeding, intracranial bleeding, ICU admission, bleeding related death/hospice and length of stay at the hospital was 21.5%, 4.9%, 16.7%, 2.5% and 4.7 ± 3.1 days in the warfarin group and 17.8%, 4.2%, 11%, 0% and 4.3 ± 3.9 days in the DOACs group, respectively (p -value = 0.46, 1, 0.19, 0.16 and 0.53). The length of stay in ICU was 2.5 ± 2.3 days in the warfarin group vs 1.7 ± 0.6 days in the DOACs group (p -value = 0.7). Anticoagulation was continued in 87.6% of patients upon discharge. Warfarin use, INR more than 3, major bleeding, intracranial bleeding and ICU admission were associated with stopping anticoagulation upon discharge from the hospital.

Conclusion: There were no statistically significant differences in health outcome between patients on warfarin and DOACs.

Keywords

Direct oral anticoagulant (DOAC), Elderly, Fall, Warfarin.

Introduction

It is estimated that the elderly population (ages 65 and older) will double from 46 million in 2016 to over 98 million by 2060 in the United States [1]. Aging is associated with changes in the function of organs and increases in incidence of atrial fibrillation

and thrombophlebitis. Anticoagulants are the main therapeutic measures which decrease the mortality and morbidity of atrial fibrillation and venous thromboembolism [2]. For more than 60 years, vitamin K antagonists have been the primary anticoagulant [3]. However, vitamin K antagonists have disadvantages like a narrow therapeutic window, significant food and drug interactions and frequent lab monitoring [4,5]. Large randomized clinical trials showed that direct oral anticoagulants (DOACs) could be a good

alternative to warfarin for treatment of venous thromboembolism and preventing stroke in non-valvular atrial fibrillation [6,7].

Falls are a common cause of death and hospital admission among the elderly population. Approximately 3 in 4 fall-related deaths in the United States occur in the elderly population. It is estimated that among elderly who are living at home, 40% will fall at least once each year [8]. Moreover, elderly patients have been undertreated with anticoagulation due to concerns about the higher risk of bleeding, fall-related injuries and lack of a reversible agent for DOACs [2].

It has been challenging for physicians to weigh the benefits of anticoagulation versus the risk of bleeding and complications after fall, and select appropriate anticoagulation strategies in the elderly population. Data on real-life outcomes of elderly patients, who presented with fall while being anticoagulated, is limited. This study was designed to compare the in-hospital outcomes of fall in elderly patients who have been anticoagulated with warfarin or DOACs.

Methods

A retrospective study was conducted at two teaching hospitals in the Chicago, IL, area: 1) Presence Saint Francis Hospital and 2) Presence Saint Joseph Hospital. This study was approved by the institutional review board of both hospitals. We performed a systematic computerized search of the hospitals' databases from August 2014 to September 2017 using ICD 9 and 10 coding and selected elderly patients (≥ 65 years old) who were admitted for fall and had been on non-vitamin K oral anticoagulants (DOACs) including dabigatran, rivaroxaban, apixaban, or warfarin prior to admission. ICD-9 coding V58.61 for chronic anticoagulant use and E880 to E888 for fall were used in the period of August 2014 to September 2015. ICD-10 coding Z79.01 for chronic anticoagulant use and W00 to W19 for fall were used for search in the database from October 2015 to September 2017.

Overall, 322 patients met the criteria for our study. All patients were more than 65 years old and had fallen within 2 days prior to their admission and were either on warfarin or DOACs. Exclusion criteria were: 1) age less than 65 at the time of admission, 2) admission for a cause other than fall or fall-related injuries, 3) fall incidence occurred more than 2 days prior to admission or during hospitalization, 4) patient was on other anticoagulation medications like enoxaparin or fondaparinux or were on two or more anticoagulant agents or on bridge therapy with heparin or enoxaparin, 5) patient was not taking anticoagulation agent at the time of admission, 6) patient was transferred out to another hospital. Anticoagulation use at the time of admission was determined based on electronic medical record and physician notes. Baseline characteristics, living place, BMI, indication for anticoagulation, CHA2DS2-VASc score for patients with history of atrial fibrillation, medical history, medications, fracture, major bleeding, intracranial bleeding, blood product transfusion, reversal factor administration, length of stay, intensive care unit (ICU) admission, inpatient mortality, and discharge destination

were collected for each patient. Major bleeding defined as fatal bleeding, symptomatic bleeding in a critical area or organ, (such as intracranial, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), drop in hemoglobin level of ≥ 2 g/dL or transfusion of ≥ 2 units of whole blood or red cells.

Statistical analysis was performed using SPSS version 21 (SPSS Inc., Chicago, IL) and R v. 3.5.0 (cran.r-project.org). Numerical variables were compared using the unpaired student's t-test (using the Levene test to test for equal variance) and associations between categorical variables were tested using the chi-square test. In cases where the chi-square approximation was not appropriate, Monte Carlo simulation was used. A significance level of $\alpha=0.01$ was used throughout the study. Because of the large number of independent comparisons, results were corrected using the Benjamini-Hochberg method. The 95% confidence interval for proportion data was calculated with the Agresti-Coull method.

Results

322 patients met the criteria for our study, of which 204 (63.4%) patients were on warfarin and 118 patients (36.6%) were on DOACs. The baseline characteristics of patients are presented in Tables 1 and 2. The mean age of patients was 81.6 ± 8.3 years and 51.2% were female. Of the patients with a history of preceding use of DOACs, 15.3% were on dabigatran, 39.8% on apixaban, and 44.9% on rivaroxaban. A total of 57 (17.7%) patients were older than 90, 18 (5.6%) patients had a history of valve replacement and 8 (2.5%) patients had a history of end-stage renal disease (ESRD). Only one patient with a history of ESRD was treated with apixaban for atrial fibrillation. 18% of patients were referred from a nursing home and 51.6% had history of previous fall.

| | Warfarin (n=204) | DOACs (n=118) | p-value |
|------------------------------------|------------------|----------------|---------|
| Age | 81.2 ± 8.3 | 82.2 ± 8.2 | 0.37 |
| Female sex | 52.9% | 48.3% | 0.49 |
| Caucasian race | 80.9% | 83.9% | 0.55 |
| Alcohol | 24.5% | 39% | 0.012 |
| Diabetes mellitus | 35.8% | 28% | 0.17 |
| Hypertension | 85.3% | 82.2% | 0.53 |
| Chronic kidney disease | 23% | 20.3% | 0.68 |
| End-stage renal disease | 3.4% | 0.8% | 0.27 |
| Coronary artery disease | 40.2% | 39.8% | 1 |
| Congestive heart failure | 35.3% | 32.2% | 0.63 |
| Valve replacement | 8.8% | 0% | <0.001 |
| Osteoporosis | 14.7% | 17.8% | 0.76 |
| Dementia | 26.5% | 21.2% | 0.35 |
| Stroke | 17.2% | 26.3% | 0.065 |
| History of fall | 51% | 52.5% | 0.82 |
| Nursing home resident | 18.6% | 16.9% | 0.77 |
| Body mass index, kg/m ² | 26.5 ± 6.1 | 26.4 ± 6.3 | 0.63 |
| CHADS2VASc score | 4.4 ± 1.4 | 4.4 ± 1.8 | 0.84 |

| Reason for anticoagulation\$\$ | | | |
|---|-----------|------------|--------|
| Atrial fibrillation/atrial flutter | 76% | 89% | <0.001 |
| PE/DVT\$ | 21.6% | 9.3% | 0.076 |
| Valve replacement | 9.3% | 0% | 0.3 |
| Atrial fibrillation and valve replacement | 6.8% | 0% | 0.001 |
| Atrial fibrillation and DVT/PE | 7.4% | 1.7% | 0.49 |
| Others/ unknown | 2.5% | 2.5% | 1 |
| Number of medications | 9.7 ± 4.8 | 10.4 ± 5.1 | 0.2 |
| Antiplatelet medications | | | |
| Aspirin | 22.1% | 15.3% | 0.15 |
| Plavix | 5.9% | 9.3% | 0.27 |
| Aspirin and plavix | 2.5% | 2.5% | 1 |
| Anti-hypertensive medications | 80% | 78.8% | 0.77 |
| Calcium channel blocker | 26.3% | 28% | 0.8 |
| ACEI/ARB\$ | 32.7% | 45.8% | 0.024 |
| Diuretic | 45.1% | 46.6% | 0.82 |
| Beta blocker | 52.9% | 54.2% | 0.9 |
| Alpha blocker | 9.3% | 11% | 0.7 |
| Vitamin D | 34.3% | 33.1% | 0.9 |
| Corticosteroid | 8.8% | 5.1% | 0.27 |
| Selective serotonin reuptake inhibitors | 25.9% | 23.7% | 0.69 |
| Sedative/antipsychotic Medications | 32.4% | 36.4% | 0.47 |

Table 1: Baseline Characteristics.

\$ ACEI/ARB= angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker, DOACs= Direct oral anticoagulants, PE/DVT= Pulmonary emboli/ Deep vein thrombosis, \$\$ Patients could have more than one reason for oral anticoagulation therapy.

| | Warfarin (n=204) | DOACs\$ (n=118) | p-value |
|------------------------------------|------------------|-----------------|---------|
| Creatinine (mg/dl) | 1.4 ± 1.1 | 1.2 ± 0.6 | 0.22 |
| Creatinine >2 | 13.5% | 3.7% | 0.02 |
| Hemoglobin (g/dL) | 12.2 ± 1.9 | 12.6 ± 1.9 | 0.74 |
| Platelet count x10 ⁹ /L | 206.5 ± 74.4 | 205.8 ± 61.2 | 0.2 |
| INR\$ | 2.4 ± 1.4 | Not applicable | |
| Sub therapeutic INR (<2) | 40.7% | Not applicable | |
| Super therapeutic INR (>3) | 13.7% | Not applicable | |
| Albumin (g/dL) | 3.7 ± 0.5 | 3.5 ± 0.4 | 0.09 |

Table 2: Baseline lab data. \$INR= International Normalized Ratio.

A total of 187 (58.07%) patients were admitted to inpatient services. The health outcomes of patients in each group are shown in Table 3. Major bleeding occurred in 21.5% of warfarin group vs 17.8% of DOAC patients (p-value=0.46), intracranial bleeding occurred in 4.9% of warfarin group vs 4.2% of DOAC patients (p-value=1). 18.6% of warfarin patients were admitted to the ICU vs 11% (p-value= 0.19) of DOAC patients. (Figure 1) Two patients on warfarin treatment required surgical intervention for intracranial bleeding. Fresh frozen plasma, vitamin K, and prothrombin complex concentrate were administered in 9.3%, 7.4% and 2.5% in patients treated with warfarin compared to 0%, 0% and 1.7% of patients who were treated with DOACs (p-value=

0.003, 0.004 and 0.72 respectively). Transfusion of more than 1 unit and fresh frozen plasma transfusion more than 3 units were not statistically significant between patients who were treated with warfarin or DOACs 4.4% vs 3.4% (p-value= 0.77) and 1.5% vs 0% (p-value=0.3).

| | Warfarin (n=204) | DOACs\$ (n=118) | p-value |
|--|------------------|-----------------|---------|
| Hospitalization | 59.8% | 55.1% | 0.41 |
| Fracture on admission | 33.3% | 28.8% | 0.45 |
| Major bleeding\$\$ | 21.5% | 17.8% | 0.46 |
| Intracranial bleeding | 4.9% | 4.2% | 1 |
| Blood transfusion ≥ 2 Units | 4.4% | 3.4% | 0.77 |
| FFP administration | 9.3% | 0% | 0.003 |
| FFP administration ≥ 4 Units | 1.5% | 0% | 0.3 |
| Vitamin K administration | 7.4% | 0% | 0.004 |
| Prothrombin complex concentrate administration | 2.5% | 1.7% | 0.72 |
| Length of stay | 4.7 ± 3.1 | 4.3 ± 3.9 | 0.53 |
| ICU admission | 16.7% | 11% | 0.19 |
| ICU stay duration (Days) | 2.5 ± 2.3 | 1.7 ± 0.6 | 0.7 |
| Continue anticoagulant on discharge | 87.8% | 94.9% | 0.048 |
| New Discharge to nursing home | 31.4% | 26.3% | 0.38 |
| Bleeding related death | 1.5% | 0% | 0.30 |
| Hospice | 1% | 0% | 0.53 |
| Bleeding related death/ Hospice | 2.5% | 0% | 0.16 |

Table 3: In-hospital Course.

\$DOACs= Direct oral anticoagulants.

\$\$Fatal bleeding, symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in hemoglobin level of ≥ 2 g/dL or leading to the transfusion of ≥ 2 units of whole blood or red cells were used for definition of major bleeding

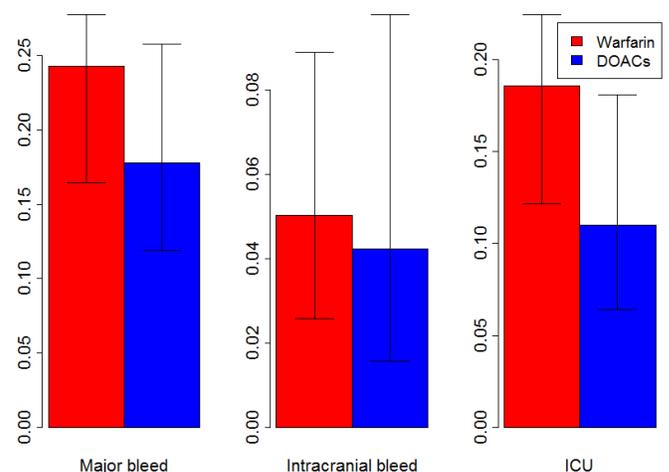


Figure 1: Proportion of patients on warfarin and DOACs that had major bleed, intracranial bleed, and ICU admission.

31.4% of patients on warfarin and 26.3% of patients on DOACs who lived at home or assisted living prior to admission were discharged to a nursing home (p-value= 0.38). The anticoagulation agent was discontinued in 12.3% of patients on warfarin versus 5.1% of patients in the DOACs group (p-value= 0.048) (Figure 2). Bleeding associated death happened in 3 patients (1.5%) in the warfarin group versus 0% in the DOACs group, (p-value=0.3). Total 5 patients either died or enrolled into hospice, all of which were in the warfarin group (2.5% of the warfarin group versus 0% in the DOACs patients (p-value= 0.16).

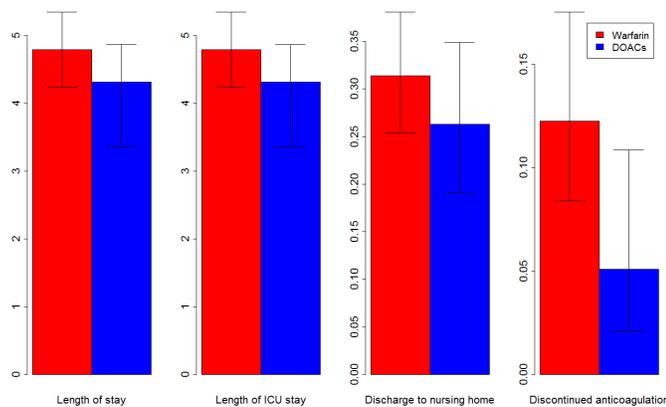


Figure 2: Length of hospital stay, Length of ICU stay, fraction of patients discharged to nursing home, and fraction of patients who discontinued coagulation upon discharge. Error bars represent 95% confidence intervals.

Further analysis showed that stroke (P value<0.05), fracture (p-value<0.001), major bleeding (p-value<0.001) were associated with new discharge to nursing home. Warfarin use (p-value<0.05), intracranial bleeding (p-value<0.001), INR greater than 3 (p-value<0.05), ICU admission (p-value<0.001), Major bleeding (P value<0.001) were associated with stopping anticoagulation at discharge.

Discussion

This study compares the in-hospital outcome of elderly patients who had been on anticoagulant agents, warfarin or DOACs and presented to the emergency department with mechanical fall. Our findings showed that the rate of intracranial bleeding and mortality were not significantly different in patients who were on DOACs compared to patients who were on warfarin.

Fall for elderly can be a life-altering event. Increasing age is a risk factor for falls and nearly 40 percent of the elderly population have at least 1 fall episode per year. In 2014, older Americans experienced 29 million falls causing seven million injuries and costing an estimated \$31 billion in annual Medicare costs. Nearly 2/3rds of elderly patients who sustain an injury from a fall do not recover to their baseline activity [9,10]. In our study, 29.5% of the patients were discharged to a nursing home/subacute rehab facility after a fall episode, which shows the significant burden of fall on the health care system. Fall while being on anticoagulation can increase the risk of complications and morbidity. Many physicians and patients consider risk of fall before starting anticoagulation in

elderly patient. Inui et al. showed that the mortality of patients on oral anticoagulation after the first fall is 6% compared with 3.1% in elderly patients who are not anticoagulated. They only evaluated fall in elderly patients who were anticoagulated with warfarin and suggested that patients with low CHA2DS2-VASc scores should have a discussion regarding the benefits of anticoagulation versus the risk of fall while they are anticoagulated [11]. Other studies show the overall benefit of anticoagulation in patients with history of fall who needed to be anticoagulated [11-13]. However, there is no data available comparing the rate of complication in groups who were on DOACs to patients who were not anticoagulated or were treated by warfarin. In our study, there were a total of 5 cases of bleeding related death or hospice in patients who had fall and were anticoagulated. Two cases of death occurred secondary to intracranial bleeding and 1 case was secondary to major bleeding and cardiac arrest. All cases of death and hospice happened in the warfarin group; however, this finding was not statistically significant. Two previous studies on anticoagulation related intracranial hemorrhage failed to show any association between mortality of intracerebral hemorrhage and type of anticoagulant which could be due to the small number of patients in those studies [14,15]. A recent study in the Journal of the American Medical Association showed increase in mortality of patients with intracerebral hemorrhage who were on warfarin compared with patients who were on DOACs [16]. The average age of patients in this study was 68.3 ± 15.38 and the mechanism of intracranial hemorrhage was not specified. The average age in our study was 81.55 ± 8.29 and intracranial hemorrhage was secondary to fall. Our study also showed that there is no statistically significant difference in other health outcomes between warfarin and DOAC patients in term of hospitalization, ICU admission and major bleeding.

The major concern about DOACs is the lack of reversal agent and delay in procedures in patients who have been on DOACs. Idarucizumab is commercially available to reverse lethal bleeding in patients on dabigatran [17]. Andexanet alfa has been introduced as an agent to reverse and decrease bleeding in patients who are on rivaroxaban and apixaban and this agent has just approved by FDA for reversing other factor Xa inhibitor [18,19]. In our study, 9.3% of total patients received at least a form of reversal agent in the warfarin group compared to 1.6% of patients in DOACs group. Despite increased rate of reversal factor administration in patients who were on warfarin, mortality rate did not increase in patients who were on DOACs.

Elderly patients with AF usually have more concurrent conditions that affect compliance and adherence to anticoagulation therapy [20]. In our study, only 45.20% of patients on warfarin had therapeutic INR. A meta-analysis of 45 studies involving 71,065 individuals receiving a vitamin K antagonist (VKA) showed that half of the thromboembolic events occurred at INRs below the therapeutic range while 44 percent of hemorrhages occurred at INRs above the therapeutic range [20]. Some studies have shown that in comparison to warfarin, DOACs had significantly lower risk of discontinuation of anticoagulation and better adherence

[20-22]. Our study showed that anticoagulation was more likely to be discontinued in patients who were on warfarin.

Multiple factors increase the risk of fall and fall-related complications. Impaired vision, lack of balance, numerous medications, sedatives, orthostatic hypotension, and alcohol use are among factors which make elderly patients prone to fall [23,24]. In our study, 33.8% of patients had been taking sedatives and 50.6% of patients were taking more than 10 medications prior to admission. The meta-analysis published recently in JAMA showed that exercise, vision assessment and treatment and environment safety can decrease the risk of fall [25]. These measures and minimizing polypharmacy should be emphasized especially in elderly patients who are candidate for anticoagulant agents.

This study has some limitations; It is a retrospective study and data was collected through chart review, sample size was small and we were not able to do subgroup analysis and head to head comparison of different DOACs. In conclusion, our study demonstrated that DOACs does not have worse outcome in elderly suffering fall even with lack of reversal agents at the time of study.

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