Association of Adding Aspirin to Warfarin Therapy Without an Apparent Indication with Bleeding and Other Adverse Events

BACKGROUND:

- Warfarin sodium and aspirin are two medications commonly used for the treatment or prevention of thrombotic and atherosclerotic disease
- Combination warfarin and aspirin use is recommended in a few situations, such as acute coronary syndrome (ACS), mechanical heart valve replacement, and recent percutaneous coronary intervention

OBJECTIVE:

- To determine the frequency and outcomes of patients on warfarin and aspirin without a clear therapeutic indication for the combination therapy

METHODS

- **Study Design:** A registry-based Michigan Anticoagulation Quality Improvement Initiative (MAQI) registry cohort study gathered data from 6 outpatient anticoagulation clinics, both community and academic practices, throughout the state of Michigan
- **Study Enrollment:** January 1, 2010 to December 31, 2017
- **Inclusion Criteria:** Adult patients, newly initiated on warfarin therapy for atrial fibrillation (AF) or venous thromboembolism (VTE) between January 1, 2010 and December 31, 2016
- **Exclusion Criteria:** Receiving direct oral anticoagulants**,** fewer than 3 months of warfarin therapy, experienced a myocardial infarction (MI) within 6 months before initiation of warfarin therapy, history of heart valve replacement (mechanical or bioprosthetic)
- **Primary Outcome:**
    - Rates of any bleeding, major bleeding events, emergency department visits, hospitalizations, and thrombotic events at years 1, 2, and 3
- **Study Duration**: Patients were included in the study from the time of enrollment to the first event in each category or to the last follow-up if no events occurred

RESULTS

- 6539 patients were included within the study before Propensity Score Matching
    - 2453 patients received combination warfarin and aspirin treatment
    - 4086 patients received warfarin monotherapy
- 3688 patients were included after Propensity Score Matching
    - 1844 patients received combination warfarin and aspirin
    - 1844 patients received warfarin monotherapy
- **Primary Outcome Measure**:
    - Patients treated with combination warfarin and aspirin therapy experienced more overall bleeding events compared with those receiving warfarin monotherapy (cumulative incidence at 1 year: 26.0% [95% CI 23.8%-28.3%] vs. 20.3% [95% CI 18.3%-22.3%] (P<0.001)
    - The number of major bleeding events was also higher for the combination warfarin and aspirin therapy groups, with a cumulative incidence of 5.7% [95% CI, 4.6-7.1%] at 1 year compared with 3.3% [95% CI, 2.4%-4.3%] at 1 year for patients receiving warfarin alone (P<0.001)
    - Hospital admission related to bleeding were higher in the combination warfarin and aspirin group compared to the warfarin monotherapy group [8.1%, 95% CI, 6.8-9.6% vs 5.2%; 95% CI 4.1%-6.4%] (P=0.001)
    - 2.3% of patients [95% CI, 1.6%-3.1%] had a thrombotic event at 1 year while receiving combination warfarin and aspirin therapy compared with 2.7% of patients [95% CI, 2.0%-3.6%] receiving warfarin alone (P=0.40)

    - 1.8% [95% CI 1.2%-2.6%] of combination warfarin and aspirin-treated patients had an ED visit related to thrombosis at year 1 compared with 1.9% [95% CI, 1.3%-2.7%] of patients receiving warfarin alone (P=0.84)

- **Authors Stated Conclusion:**
    - An increased risk of bleeding and recent hospitalizations is associated with the use of warfarin and aspirin therapy in patients without a heart valve replacement or recent ACS

STRENGTHS

- While enrolled in the anticoagulation clinics, patients were closely followed up and data was collected using predefined forms that included relevant clinical outcomes
- Population-based cohort may have been more likely to reflect real-world practice
- All patients had received standard anticoagulation care and the findings are possibly generalizable to other settings (including anticoagulation clinics and high quality care outside of anticoagulation clinics)
- Sensitivity analysis was conducted to determine that other factors did not influence the results

LIMITATIONS

- Unknown confounding variables could influence results
- Analysis did not adjust for severity of comorbid conditions
- Results cannot be extrapolated to patients receiving direct oral anticoagulants with aspirin
- Generalizability due to geographically limited patient population followed up at anticoagulation clinics
- Observed event rates may have underestimated true event rates if patients received care from outside from the study's facilities
- Few thrombolytic events occurred during the study period, making it difficult to detect differences for this outcome
- Other medications the patients were taking and diet could have affected increased bleeding or clotting risk
- Approximately 60% of patients were within the therapeutic INR range of 2 to 3; however, supratherapeutic INRs or subtherapeutic INRs can have an impact on bleeding or clotting
- Data was not analyzed for years 2 and 3, even though stated in the primary outcome they were measuring outcomes in years 1, 2, and 3
- Other possible risk factors, such as genetic mutations, are not taken into consideration which could develop thrombosis

CONCLUSIONS

- Because this study suggests that combined use of warfarin and aspirin therapy in patients without a clear therapeutic indication is associated with an increased risk of bleeding and hospitalizations, warfarin and aspirin therapy should be used with caution
- However, few thrombolytic events had occurred in both the warfarin and aspirin combination therapy versus the warfarin monotherapy groups; aspirin possibly does not need to be prescribed with warfarin for patients without a clear therapeutic indication
- Randomized, clinical trials should be conducted, if necessary, to determine if the findings in this study are reflected in the real world

Reference: Schaefer JK, Li Y., Gu X., Souphis NM, Haymart B., Kline-Rogers E., et al. Association of Adding Aspirin to Warfarin Therapy Without an Apparent Indication with Bleeding
and Other Adverse Events. JAMA Intern Med. 2019;179(4):533-541.

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