Pfizer Internal Medicine
Medical Affairs

Newsletter of November 2023

Oral anticoagulant insights

Welcome to the second edition of Oral Anticoagulant Insights, your go-to newsletter for valuable information and updates on the use of direct oral anticoagulants (DOACs) for stroke prevention in atrial fibrillation (AF) and the treatment of venous thromboembolism (VTE). We are thrilled to bring you a collection of insights based on the latest research and practical guidelines to ensure you stay at the forefront of knowledge.

In the November edition, we have meticulously curated a plethora of valuable information and updates that we are confident will pique your interest. The highlights of this edition encompass:

1 Patients with ischemic stroke attributed to large-artery atherosclerotic or small-vessel occlusive disease face an increasing risk of AF over time

Three-year results of the randomized STROKE AF trial show the risk of AF detection after stroke attributed to large-artery atherosclerotic (LAD) or small-vessel occlusive disease (SVD) continues to rise beyond one year in patients monitored with an insertable cardiac monitor (ICM), from 12.5% at one year to 21.7% at three years. In contrast, the detection rate in patients undergoing standard monitoring remained low at 2.4% despite the performance of numerous intermittent recordings. Most AF episodes in the ICM group were asymptomatic, and most patients with AF had at least 1 episode longer than an hour. The study findings have several clinical implications. First, AF is common in patients after stroke attributable to non-cardioembolic mechanisms. Second, clinicians should not be reassured after one year of AF-negative monitoring that the patient's risk for developing AF will continue to remain low, as the risk continues to increase for at least three years after stroke. Third, AF is essentially not detected by patients, and AF-negative intermittent episodic rhythm monitoring should not be reassuring. Lastly, even if the initial episode of AF is short and of questionable clinical significance, most patients with AF will experience an increasing burden over time with a likely corresponding increase in the risk of stroke. Notably, there was no reduction in recurrent stroke in the ICM vs. control groups. However, the study had insufficient power to detect such a difference. Besides, 24% of patients with AF in the ICM group were not anticoagulated, limiting the clinical impact of AF detection on stroke prevention.

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2 An elevated international normalized ratio on admission is associated with a higher risk for in-hospital death and mortality in the year following discharge of DOAC-treated patients

A study from Israel shows that the international normalized ratio (INR) is of prognostic significance in patients receiving DOACs. Findings indicate that an elevated INR (above 1.5) is associated with a 57% increase in the risk of death in the year following discharge, a 180% increased risk of in-hospital mortality, and a 15% increase in length of hospitalization, regardless of anticoagulation indication, co-morbidities, and liver function. Subgroup analyses show similar results in patients treated with dabigatran, rivaroxaban, and apixaban. Increases in INR levels associated with the use of DOACs are well-documented in the literature. However, the use of INR to monitor DOAC levels or activity is not recommended due to inappropriate sensitivity and lack of a definite dose-response relationship. To date, the clinical significance of elevated INR in patients treated with DOACs is unclear. The researchers state that while one of the proclaimed advantages of DOACs is eliminating the need for drug monitoring, the study findings suggest that examining the INR level can be beneficial for assessing patients' prognosis, as used in patients not treated with DOACs. A possible explanation for the study results is that, in addition to its reflection of the coagulation system, INR may also serve as a surrogate marker for patients' hemodynamic and metabolic reserve. Altogether, this study emphasizes that a heightened INR at admission in patients treated with DOACs should not be dismissed as solely a consequence of the DOAC treatment; it may indicate an increased risk of adverse outcomes.

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3 Apixaban may be preferred for older adults with AF, particularly for patients with frailty

A US Medicare claims data comparing warfarin, rivaroxaban, and apixaban in older patients with AF finds that apixaban was associated with lower home time lost (defined as >14 days in 12 months) and fewer clinical events (a composite of ischemic stroke, systemic embolism, major bleeding, or death) than rivaroxaban and warfarin, with more significant reductions among patients with frailty, reflecting the higher background risks and disease burden in patients with frailty. The main strengths of this study include the generalizability of results based on a nationally representative database of older adults in the US, new-user, active comparator design, and propensity score overlap weighting that minimizes confounding. Yet, the study is subject to certain limitations, including residual confounding and a relatively short follow-up truncated at 365 days. An invited commentary on this study underscores the importance and relevance of its findings, considering the persisting treatment gaps for AF patients who are frail, the overall under-prescription of OAC, and the high risk of adverse outcomes, including thromboembolism. Taken together, the study findings, according to the researchers, support apixaban as the preferred OAC for older adults with AF, particularly for older adults with frailty.

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4 OAC use is associated with 53% lower ischemic stroke risk in AF patients at intermediate risk of stroke compared to no OAC use

In a nationwide study from Norway comprising more than 1.1 million individuals with a CHA_2DS_2-VASc risk score of 1, OAC use was associated with favorable clinical outcomes in AF patients at intermediate risk of stroke. Non-anticoagulated AF patients had higher stroke risk compared to anticoagulated AF patients, and the risk of intracranial hemorrhage (ICH) associated with OAC treatment was generally low. Also, there was 2.5 times increased risk of stroke in non-anticoagulated AF patients compared to non-AF individuals with a comparable, intermediate CHA_2DS_2-VASc risk profile. The optimal strategy for the prevention of thrombo-embolism in AF patients at an intermediate stroke risk is debated. Bleeding risk is one of the driving reasons for physicians and patients to avoid OAC therapy. It was suggested that a thromboembolic rate of 1.0 events per 100 person-years, equivalent to a 1-year risk of ~1%, should be the threshold for the benefit of OAC therapy to outweigh the bleeding risk. Findings from this study, with an ischemic stroke rate of 1.05%/person-years in non-anticoagulated AF patients at intermediate stroke risk, may suggest that OAC may be beneficial in this group of patients, although confirmation in large randomized controlled trials is warranted.

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5 With OACs, patients aged ≥85 benefit from lower mortality and stroke, with no increase in major bleeding in comparison to no OAC use

An analysis of the GARFIELD-AF registry shows that OACs reduced the risk of death and stroke in very old AF patients, with no evidence of an increase in the risk of bleeding. The researchers point out that this finding underscores that OACs appear safe in very old AF patients who would typically not receive appropriate dosing due to frailty and bleeding risk concerns. The American AF guidelines do not recommend utilizing a specific bleeding risk score. European AF guidelines recommend using the HAS-BLED score, and the NICE guidelines prefer the ORBIT bleeding risk score. Generally, guidelines emphasize that a high bleeding risk score should not discourage OAC use; instead, it should be used to identify and prompt changes in modifiable risk factors for bleeding. All in all, the results from this study would help inform the physician community in providing effective anticoagulation therapy to older AF patients.

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6 In AF patients aged ≥75 years, dabigatran, apixaban, and edoxaban are associated with lower risks of intracranial hemorrhage compared to vitamin K antagonist and rivaroxaban

A network meta-analysis of 7 randomized controlled trials comparing the efficacy and safety of DOACs in older patients with AF finds that in patients aged ≥75 years, all DOACs showed similar efficacies in preventing stroke and systemic embolic events, except for edoxaban, which showed nominally decreased efficacy compared with other DOACs. All DOACs had similar bleeding risks to vitamin K antagonist (VKA), and rivaroxaban was the only DOAC with no significant difference in risk of intracranial hemorrhage to VKA, whereas all other DOACs had reduced risks. Compared with VKA, the risk of all bleeding events was nominally higher with rivaroxaban, whereas it was lower with apixaban. Furthermore, high-dose DOAC regimens of dabigatran and edoxaban prevented more embolic events without increased bleeding risk than low-dose regimens or VKA. Lastly, factor Xa inhibitors (apixaban and edoxaban) were associated with lower risks of major bleeding in very old patients (aged ≥80 years) compared with factor IIa inhibitors and VKA.

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7 Patients with active cancer and AF undergoing periprocedural interruption of DOAC therapy for invasive procedures are at increased risk of postprocedural major bleeding

Data to guide periprocedural anticoagulation management in patients with active cancer, specifically DOAC-treated patients with AF, are limited. Analysis of the PAUSE study identified active cancer as an independent predictor of surgical major bleeding events in patients with AF who underwent periprocedural interruption of DOACs for elective surgeries or procedures according to the PAUSE study protocol (DOAC interruption 1 day before a low-bleed-risk procedure and 2 days before a high-bleed-risk procedure; DOAC resumption ~24 hours after low-bleed-risk procedures and ~48 to 72 hours after high-bleed-risk procedures). Patients with active cancer had longer DOAC-interruption and -resumption intervals than those without active cancer, reflecting management according to the PAUSE study protocol for high-bleed-risk procedures. These findings could, in part, reflect the increased bleed risk of cancer-related procedures or from the cancer itself and associated patient comorbidities, as well as the cautious reintroduction of anticoagulation on the part of clinicians. Moreover, residual DOAC levels were low among patients with active cancer and below the lower reported limit in all active cancer patients who experienced a major bleeding event, except for two patients for whom no DOAC level was measured. Altogether, these findings suggest that the increased risk of surgical bleeding observed in patients with active cancer might be attributable to the extent and invasiveness of cancer-related procedures rather than the residual DOAC anticoagulant effect. More importantly, this analysis identified no arterial thromboembolic events and only 2 VTE events in patients with active cancer, suggesting that delaying resumption of DOAC therapy for 2 to 3 days and the use of a short course of postprocedural prophylactic LMWH/UFH appears to be safe with respect to thromboembolic risk.

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8 In DOAC–treated AF patients, the relationship between body mass index and mortality and major bleeding appears to be U-shaped

A nationwide Swedish study of DOAC-treated patients with AF reveals a U-shaped relationship between body mass index (BMI) and mortality and major bleeding but no significant association between a higher BMI and the risk of ischemic stroke or systemic embolism. Patients with pre-obesity and obesity class I had the lowest risk of mortality, a phenomenon known as the obesity paradox. Possible explanations for this obesity paradox might be that these patients more frequently have comorbidities (e.g., hypertension, hyperlipidemia, and diabetes) that are earlier and more often aggressively treated with pharmacologic drugs, such as angiotensin-converting enzyme inhibitors, ß-blockers, and statins (as observed in the present study), which might be beneficial. Another explanation could be a greater capacity to manage metabolic stress from chronic illness because of better metabolic reserves. In extremely obese patients, on the other hand, the benefits of high BMI may not exceed the disadvantages of additional adiposity (e.g., organ dysfunction, prothrombotic state, and cardiovascular burden). The higher risk of mortality in underweight patients could be related to residual confounding factors, and underweight is often associated with older age, frailty, comorbidities, and a lack of reserves to handle possible catabolic states. Overall, the findings of this study underscore the importance of carefully managing and closely monitoring patients with extremely low or high BMIs.

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9 Standard and reduced DOAC regimens have comparable thromboembolism risk and significantly lower bleeding risk compared to warfarin in frail AF patients

A Danish nationwide cohort study examined the one-year safety and effectiveness of DOACs compared with warfarin in a large cohort of frail AF patients with a median age of 80 years. Findings demonstrate no significant difference in thromboembolic risk and lower risk of major bleeding with DOAC standard and reduced dose regimens, with the most pronounced difference in bleeding-free survival observed for highly frail patients (Hospital Frailty Risk Score >15). Age and frailty are potent risk factors for thromboembolic events in AF patients. Despite this, these patients are often untreated, under-dosed, or treated with aspirin in routine clinical practice. Reluctance to initiate oral anticoagulation therapy in frail AF patients may stem from concerns about cognitive impairment, frailty, comorbidity, and polypharmacy. The European Heart Rhythm guideline explicitly states that frail patients with an indication for OAC therapy should receive treatment. The lack of evidence to guide optimal care for frail AF patients might, in part, explain the gap between guidelines and clinical practice. Given the limited data from randomized trials, evidence from observational studies, like the current investigation, may inform decision-making about anticoagulation in frail patients and provide physicians with added confidence in prescribing DOACs in this challenging clinical setting.

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10 Expert panel proposes recommendations on the management of cancer-associated thromboembolism in vulnerable population

An expert panel releases recommendations on the management of challenging cases of patients with cancer-associated thrombosis (CAT), underscoring that in older patients, age is not per se a critical factor for choice of treatment, but frailty is. Patients over 70 years of age with CAT should undergo a systematic frailty evaluation before choosing treatment, and modifiable bleeding risk factors should be addressed. In patients with renal impairment, creatine clearance should be assessed and monitored regularly thereafter. In patients with an eGFR < 30 mL/min/1.72 m^2, the anticoagulant treatment may need to be adapted. Similarly, platelet count should be assessed prior to treatment and monitored regularly. In patients with grade 3-4 thrombocytopenia (< 50,000 platelets/μL), treatment with a low molecular weight heparin at a reduced dose should be considered. For patients with CAT and low body weight, standard anticoagulant treatment recommendations are appropriate, whereas in obese patients, apixaban may be preferred.

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We believe that knowledge and collaboration are the driving forces behind advancement in healthcare. Thus, we encourage you to actively engage with the newsletter by sharing your thoughts, experiences, and questions. Your contributions are invaluable and shape the direction of our content, ensuring it remains relevant and tailored to your needs.

For more medical information on DOACs, AF or VTE, please visit the website of the internal medicine department of Pfizer Israel, Pfizer Science.

Pfizer Science

Sending you sincere regards for a prosperous month and hoping for better days ahead.
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