Study: Afib patients on low doses of blood thinners have more bleeding episodes than those on standard doses

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Patients with atrial fibrillation (Afib) who took low doses of blood-thinning medications known as direct oral anticoagulants (DOACs) experienced more bleeding episodes during the first three months of treatment and about one in five had high blood levels of the medications,

compared with similar patients who took standard doses of the same medications, according to a study published in Blood Advances.

Patients with Afib, a common type of arrhythmia, or irregular heart rhythm, face a five-fold risk of stroke and are therefore often prescribed blood-thinning medications (anticoagulants) to slow blood clotting.

To reduce the risk of unwanted and sometimes dangerous bleeding and other adverse effects associated with these medications, doctors may opt to prescribe lower doses to patients deemed high risk for bleeding. In the United States, Afib affects up to 6 million people and causes an estimated 450,000 hospitalizations annually. Risk for Afib increases with age.

"We found that 58% of bleeding complications occurred in patients who were treated with low doses of DOACs," said Gualtiero Palareti, MD, of the Arianna Anticoagulation Foundation in Bologna, Italy, and the study's coordinator, who noted that people with Afib often need these medications lifelong.

"Not only did the use of low doses not reduce bleeding risk, it also did not prevent patients from developing high blood levels of the medication ."

Four DOACs are approved in the United States and Europe: apixaban, dabigatran, edoxaban, and rivaroxaban. DOACs are prescribed at fixed doses based on a patient's age, weight, and other health conditions.

To reduce the risk of bleeding and blood-clotting complications, doctors may prescribe lower doses of the medications to patients who are older or who have other health conditions that might increase their risk for

these complications.

Observational studies have shown that patients with Afib who are treated with DOACs have fewer strokes and blood clots than patients with Afib who are treated with warfarin, an older blood-thinning medication.

Unlike with warfarin, most patients treated with DOACs do not undergo regular tests to measure blood levels of the medication. However, recent studies have suggested that blood levels of DOACs can vary considerably between patients and that levels that are too low or too high may increase patients' risk for blood clots and bleeding episodes.

Dr. Palareti and his colleagues designed the "Measure and See" study, or MAS, to examine whether a relationship existed between blood levels of DOACs, measured soon after initiating the drugs to treat Afib, and the occurrence of blood clots and bleeding episodes.

In a paper published in *Blood Advances* in April, they reported that patients with the lowest blood levels of their DOAC medication, measured soon after initiating treatment, experienced the most blood clots during a one-year follow-up period. The current study looked at the relationship between measured blood levels of DOACs and bleeding events.

The MAS study involved 1,657 patients with Afib (median age 80, 54% men); the choice of DOAC prescribed was left up to the treating physician.

The patients had blood drawn within two to four weeks of beginning treatment with a DOAC and immediately before they were to take their next pill, when blood levels of the drug were expected to be at their lowest. Patients were evaluated during the first month of treatment and received check-ups every three to four months for a year.

All patient blood samples were analyzed in the same laboratory. An independent committee, whose members did not know the patients' identities or blood-draw results, assessed and recorded all bleeding events, blood clots, strokes, heart attacks, deaths due to a stroke or heart disease, and other adverse events during the 12-month follow-up period. Primary endpoints for the current study were major bleeding and bleeding requiring medical intervention, hospitalization, or evaluation.

Results showed that 50 patients (3.1%) experienced bleeding events, of which 29 (58%) occurred in patients treated with low doses of a DOAC. About 30% of all recorded bleeding events occurred in patients who had the highest blood levels of their medication.

During the first three months of treatment, bleeding events occurred significantly more frequently in patients who had the highest blood levels of their medication.

"Our findings indicate that treatment with low doses of a DOAC does not necessarily prevent the occurrence of high blood levels of the drug," said Dr. Palareti. "This predisposes patients to a higher risk of bleeding during the first three months of treatment—a period when the risk of bleeding due to oral anticoagulants is already elevated."

After the first three months, the risk of bleeding events was not associated with either low-dose treatment or blood levels of the medication. "This suggests that the risk of bleeding events during anticoagulant treatment is multicausal," Dr. Palareti said.

Alongside the results of the study published in April, these findings suggest that measuring medication levels in patient's blood shortly after initiating DOAC treatment and tailoring the medication dose accordingly might help to avoid excessively low or high blood levels and reduce bleeding and clotting complications, especially in patients who are

prescribed low-dose treatment, Dr. Palareti said. He and his colleagues are now planning a pilot clinical trial to test this approach.

The researchers noted a few limitations to their study. Study enrollment was adversely affected by the COVID-19 pandemic. While 27 centers in Italy participated in the study, 75% of the patients were recruited at just one center, potentially limiting the results' generalizability. Medication levels in a patient's blood were tested only once, in one central laboratory, within a month of entering the study and beginning DOAC treatment.

More information: *Blood Advances* (2024). doi.org/10.1182/bloodadvances.2024013126

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