Long-Term Care Updates

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Anticoagulant-related GI bleeds and cancer diagnosis in atrial fibrillation patients

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Introduction

Patients with atrial fibrillation (AF) are commonly treated with oral anticoagulants (OACs) for stroke prevention. OACs carry a risk for gastrointestinal (GI) bleeding. As GI bleeding can be a marker for malignancy, initiating OAC therapy may hypothetically reveal malignancy in the GI tract.[1] Considering patients with early-stage GI cancer or precancerous lesions are usually asymptomatic and survival is closely related to the stage of cancer diagnosis, early detection via GI bleeding as a consequence of OAC therapy may lead to better prognosis and survival.[2]

In this newsletter, we will discuss the evidence correlating GI bleeds and GI cancer diagnosis in AF patients on OACs.

Clinical Evidence

The first study examining this relationship was a retrospective observational study that focused on the link between non-VKA oral anticoagulants (NOACs), GI bleeding, and GI cancer incidence. Researchers retrieved the preferred terms on GI bleeding and GI cancer reported as adverse events (AEs) from phase III studies in patients with AF for each NOAC (dabigatran, rivaroxaban, and apixaban) on ClinicalTrials.gov and analyzed information from the RELY clinical trials database on GI malignancy cases. Analysis was restricted to the first 6 months of treatment in order to describe malignancies that existed pre-treatment. Researchers found results from three phase III studies: RELY, ROCKET AF, and

Table. Incidence of GI bleeding and GI cancer (reported as adverse effects)[2]

Phase III Study	RELY			ROCKET AF		ARISTOTLE	
Drug	**Dabigatran 110 mg BID**	**Dabigatran 150 mg BID**	**Warfarin**	**Rivaroxaban 15 mg or 20 mg**	**Warfarin**	**Apixaban 5 mg or 2.5 mg BID**	**Warfarin**
Total # of subjects	5983	6059	5998	7111	7125	9052	9088
Total - GI bleeding	85 (1.42%)	117 (1.93%)	82 (1.37%)	250 (3.52%)	191 (2.68%)	175 (1.93%)	145 (1.59%)
Total - GI cancer	47 (0.79%)	37 (0.61%)	22 (0.37%)	58 (0.83%)	52 (0.73%)	63 (0.69%)	52 (0.57%)

ARISTOTLE. AE GI bleeding incidence and AE GI cancer incidence for each trial from ClincalTrials.gov are outlined in the table above.[2]

Evaluation of the RELY clinical trials database showed the same pattern as ClinicalTrials.gov, with significantly more GI bleeding and malignancy events in the pooled dabigatran groups compared to warfarin over the complete study period. A total of 199 GI cancer events were reported in 181 subjects, with a majority being diagnosed within the first year of the study and the most frequently reported tumors being colon cancer (n=83). Researchers also found an association between GI bleeding and GI cancer incidence in all AF subjects on dabigatran or warfarin, where 85.4% had GI bleeding before diagnosis of GI malignancy. They concluded that GI bleeding events with OACs can identify GI cancers at an early stage if proper diagnostic procedures are carried out immediately after GI bleeding.[2]

Further research involving real-world evidence from Denmark also evaluated the relationship between GI bleeds and cancer diagnosis. Researchers performed a retrospective study to estimate the absolute risk of colorectal cancer in AF patients treated with OAC therapy with and without lower GI bleeding. Nationwide healthcare registers were utilized to identify adult patients with AF or atrial flutter who picked up a prescription for any OAC (warfarin, rivaroxaban, dabigatran, or apixaban). The primary study outcome was diagnosis of colorectal cancer. A total of 125,418 subjects were identified, and, after a maximum of 3 years of treatment, 2,576 cases of lower GI bleeding were discovered. Of those patients who experienced lower GI bleeding, 140 were diagnosed with colorectal cancer within one year. Researchers found that the absolute 6-month risk of lower GI bleeding increased with age,

was highest within the first month of OAC therapy, and ranged from 0.29% (95% CI 0.24–0.36) to 0.95% (95% CI 0.79–1.14) in subjects 65 to 85 years old. After lower GI bleeding, the absolute 1-year risk of colorectal cancer was 3.7% (95% CI 2.2–6.2) to 8.1% (95% CI 6.1–10.6) in subjects ≤65 and 76 to 80 years old. Such risk was irrespective of age or time in OAC treatment. In subjects who had not yet bled, the risk ranged from 0.16% (95% CI 0.15–0.16) to 0.53% (95% CI 0.55–0.87). When comparing those who had lower GI bleeds to those who did not, those who bled had increased risk ratios of colorectal cancer at 24.2 (95% CI 14.5–40.4) and 12.3 (95% 7.9–19.0) regardless of age. Additionally, most cancer events in all ages occurred within 2 months of lower GI bleeding. The researchers concluded that anticoagulated AF patients with lower GI bleeding had high absolute 1-year risk and risk ratios of colorectal cancer compared to patients without GI bleeding and that lower GI-bleeding in such patients should not be dismissed as an adverse effect of anticoagulation treatment. Rather, timely examination could potentially provide early detection of malignant colorectal lesions.[1]

Most recently, one prospective cohort study added more evidence to support this conclusion. Researchers followed AF patients receiving NOACs to determine whether bleeding was a predictor of new-onset cancers after NOAC use. Nonvalvular AF patients who received NOAC (dabigatran, rivaroxaban, apixaban, and edoxaban) treatment at cardiology and neurology clinics of Taipei Veterans General Hospital in Taiwan were followed every 3 to 6 months through medical records, clinic visits, and phone interviews to evaluate the incidence of bleeding, stroke, and new-onset cancers. New-onset cancer was defined as diagnosis after starting the NOAC. Major bleeding episodes were defined as fatal bleeding, symptomatic bleeding in a critical area or organ, or bleeding that caused a reduced hemoglobin level of 20 g/L. A total of 395 AF patients on NOACs were followed for an average of 2.8 years. Researchers found 18 (4.5%) patients were diagnosed with new-onset cancer 584 ± 372 days after starting a NOAC, with most being GI cancers (n=7). Those with new-onset cancer had a statistically significant higher incidence of bleeding events (66.7%, $p<0.001$) compared to those with pre-existing cancer (33.3%) and no cancer at all (20.2%). Of all the bleeding events that occurred (n=94), 12 patients (12.8%) were diagnosed with new-onset cancer. All bleeding events began prior to new-onset cancer diagnosis and were independently correlated with new-onset cancers (OR: 7.89, $p=0.001$). Researchers concluded that bleeding in AF patients on NOACs could be an alerting sign of new-onset cancer and should prompt the initiation of early cancer surveillance.[3]

While each study above has its own distinctions, all three are of observational design, which comes with inherent limitations. The main limitation being that none of them can prove GI bleeding as a consequence of OAC therapy is a sign of GI cancer. Their results only help understand the incidence of GI bleeding and GI cancer diagnosis in AF patients on OACs and can suggest there is an association between them. Therefore, other risk factors for GI bleeds such as alcohol consumption and dietary habits could have also

described the association between GI bleeding and cancer incidence. The results from the studies are limited to the data available at the cardiology and neurology clinics of Taipei Veterans General Hospital and on ClinicalTrials.gov, the RELY clinical trials database, and the Denmark healthcare registers. Additionally, adherence to OAC therapy can only be assumed. The retrospective nature of the first two studies in particular also increases the potential for missing data compared to the prospective cohort study. Nevertheless, all three studies came to the same conclusion: GI bleeding in AF patients on OACs may not be just an adverse effect and can potentially serve as an sign of GI cancer and suggest the need for cancer surveillance.

Conclusion

GI bleeding is a common adverse effect associated with OAC therapy in patients with AF. Given that GI bleeding is a well-known marker of GI malignancy, it is rational to theorize that GI bleeding as result of OAC therapy might help healthcare providers identify and diagnose GI cancer earlier. Research supports a strong association between the incidence of GI bleeding and GI cancer in these patients. Therefore, when caring for AF patients on OAC therapy who experience GI bleeds, healthcare workers should not see it as simply a complication of anticoagulant therapy. They should consider it as a potential sign of GI cancer and perform the proper diagnostic tests.

References

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