Oral Anticoagulant Treatment in Patients with Atrial Fibrillation and Cancer

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Oral anticoagulant therapy is recommended for the majority of patients with atrial fibrillation (AF) to reduce their risk of stroke.[1,2] Nonvitamin K antagonists (NOACs) are generally preferred over vitamin K antagonists (VKAs) in AF patients because they have been shown in randomized trials and observational cohorts to be at least as effective for stroke prevention while reducing the risk of life-threatening bleeding.[3–5] NOACs are also more convenient to use because they do not require routine coagulation monitoring and have a lower potential for food and drug interactions.

Patients with cancer are at increased risk of both thromboembolism and bleeding.[6] Cancer patients with venous thromboembolism (VTE) have long been preferentially treated with low-molecular-weight heparin (LMWH) because it is more effective than warfarin to prevent recurrent VTE in these patients.[7] More recently, NOACs have begun replacing LMWH for this indication based on the results of randomized trials (Hokusai-VTE-Cancer, SELECT-D, and ADAM-VTE) demonstrating similar efficacy and safety, and superior convenience.[8–10] Patients with cancer who have AF may be at higher risk of stroke and bleeding than AF patients who do not have cancer,[11,12] but the role of NOACs in AF patients with cancer remains uncertain. Very few patients with cancer were included in trials comparing a NOAC with warfarin in AF,[3] and until recently treatment guidelines did not provide recommendations about the use of NOACs in this population.[13]

In this issue of Thrombosis and Haemostasis, Cavallari and colleagues[14] report the results of a systematic review and meta-analysis of randomized ($n = 3$) and observational ($n = 3$) studies comparing the efficacy and safety of NOACs (rivaroxaban, edoxaban, or apixaban) with warfarin in the subgroup of AF of patients with cancer. The three randomized trials[15–17] included a combined total of 2,661 patients with AF and a history of cancer (mean age 75 years, males 69%, active cancer 37%) who were followed for a mean 2.2 years. The pooled analyses of these trials showed no significant differences between NOACs and warfarin for stroke or systemic embolism (2.8 vs. 4.0%, $p = 0.11$), VTE (0.8 vs. 0.9%, $p = 0.86$), mortality (16.1 vs. 15.6%, $p = 0.93$), or major bleeding (7.8 vs. 9.5%, $p = 0.13$), although NOACs were associated with significantly lower rates of intracranial hemorrhage (0.1 vs. 1.6%, $p = 0.01$). The three observational studies[18–20] included 21,112 patients with AF and a history of cancer (mean age 74 years, males 60%, proportion with active cancer not reported) who were followed for a mean of 1.6 years. The pooled analyses of these studies showed that NOACs compared with warfarin were associated with significantly lower rates of stroke or systemic embolism (2.3 vs. 10.3%, $p< 0.0001$), VTE (2.9 vs. 4.0%, $p = 0.00001$), and mortality (10.6 vs. 23.9%, $p< 0.0001$), but there were no significant differences in major bleeding (2.4 vs. 3.6%, $p = 0.18$) or intracranial hemorrhage (0.3 vs. 0.6%, $p = 0.01$). Pooling of data from the three randomized trials with data from the one observational study that reported outcomes separately in AF patients with and without cancer demonstrated that the rates of stroke or systemic embolism rates were similar (3.6 vs. 3.9%, $p = 0.50$), but cancer compared with noncancer patients had significantly higher rates of VTE (1.4 vs. 0.74%, $p< 0.001$), mortality (17.7 vs. 8.5%, $p< 0.001$), and major bleeding (9.0 vs. 5.1%, $p< 0.001$). The latter findings contrast with those of Deng and colleagues who restricted their analyses to data from randomized trials and found no difference in rates of stroke, major bleeding and death between AF patients with or without cancer.[21]

The report by Cavallari and colleagues is one of the most comprehensive to date examining the effects of NOACs compared with warfarin in AF patients with cancer,[14] but we believe that the results should be cautiously interpreted. First, very large benefits of NOACs compared with warfarin were found in observational studies, but these are prone to confounding. It is unclear whether Cavallari and colleagues adjusted these analyses for potential confounders, but the 8% absolute reduction in stroke/systemic embolism and 13.3%

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absolute reduction in mortality with NOACs compared with VKAs are implausibly large. Second, although randomized trials generally provide higher quality evidence than observational studies, the three randomized trials involved only modest numbers of patients and events, resulting in wide confidence intervals. Third, the randomized trials excluded patients with reduced life expectancy, thereby presumably excluding patients with more advanced cancers. Restricting inclusion to patients with early-stage cancer, many of whom did not have active cancer at the time of enrolment, limits the applicably of the results.

Despite our reservations about the data from observational studies, the totality of the evidence suggests that NOACs are a reasonable option in the majority of patients with cancer who require anticoagulation, including those with cancer who have AF. This conclusion reflects the consistent evidence presented by Cavallari and colleagues[14] from subgroups of patients with cancer in the AF trials,[15–17] and is further supported by the results of trials comparing NOACs and LMWH for the treatment of cancer-related VTE (►**Table 1**).[8–10] Similar results were reported from subgroups of cancer patients enrolled in trials comparing NOACs and warfarin for VTE treatment (EINSTEIN, Hokusai, RECOVER, AMPLIFY).[22–25]

Several issues remain unresolved. All of the NOACs are substrates of P-glycoprotein (P-gp), and both rivaroxaban and apixaban are metabolized via the CYP3A4 enzyme.[26] Many chemotherapeutic agents are substrates, inhibitors, or inducers of P-gp and/or CYP3A4, and their concomitant use with NOACs may increase or reduce anticoagulant blood levels, potentially leading to less than expected efficacy or safety.[13,26] We recommend that clinicians consult relevant drug information before prescribing NOACs in cancer patients with AF undergoing chemotherapy. Clinicians should also be aware that trials in cancer patients with VTE have demonstrated that NOACs compared with warfarin produce more gastrointestinal (GI) bleeding in those with cancer of the GI tract.[8,9] It is likely that this also applies in AF patients with cancer of the GI tract.

Our conclusions are consistent with recently updated International Society on Thrombosis and Haemostasis guidelines suggesting that NOACs should be used in preference to warfarin in newlydiagnosed AF who have active cancer, except if the patients have GI cancer or history of GI-bleeding.[27] The

Table 1 Randomized comparisons between nonvitamin K antagonist oral anticoagulants and standard treatment in patients with cancer and venous thromboembolism or with cancer and atrial fibrillation

Patients with cancer and atrial fibrillation						
	NOAC		VKA		HR (95% CI)	Reference
	Events	Patients	Events	Patients		
Stroke/systemic embolism						
ENGAGE AF-TIMI 48[a]	14	390	24	395	0.60 (0.31–1.15)	15
ARISTOTLE	15	615	14	621	1.09 (0.53–2.26)	16
ROCKET-AF	8	307[b]	16	329[b]	0.52 (0.22–1.21)	17
Major bleeding						
ENGAGE AF-TIMI 48[a]	56	390	63	395	0.98 (0.68–1.40)	15
ARISTOTLE	24	615	32	621	0.76 (0.45–1.29)	16
ROCKET-AF	23	309	33	331	0.71 (0.42–1.21)	17
Patients with cancer and venous thromboembolism						
	NOAC		LMWH		HR (95% CI)	
	Events	Patients	Events	Patients		
Venous thromboembolism						
Hokusai-VTE cancer	41	522	59	524	0.71 (0.48–1.06)	8
SELECT-D	8	203	18	203	0.43 (0.19–0.99)	9
ADAM-VTE	1	145	9	142	0.10 (0.01–0.78)	10
Major bleeding						
Hokusai-VTE cancer	36	522	21	524	1.77 (1.03–3.04)	8
SELECT-D	11	203	6	203	1.83 (0.68–4.96)	9
ADAM-VTE	0	145	2	142	Not calculable[c]	10

Abbreviations: AF,atrial fibrillation; CI, confidence interval; HR, hazard ratio; LMWH, low molecular weight heparin; NOAC, nonvitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; VTE, venous thromboembolism.
[a]Results reported on higher-dose edoxaban regimen (60 mg once-daily).
[b]Efficacy outcome analyzed using the intention-to-treat population.
[c]Not able to calculate as there were no events in the apixaban arm.

guidelines do not recommend changing from one OAC to another in patients with AF undergoing cancer treatment unless there are potential drug-drug interactions that preclude the use of a particular agent.

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Conflict of Interest
K.K.W.O. reports personal fees from Bayer, outside the submitted work. J.W.E reports honoraria and grant support from Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb/Pfizer, Daiichi Sankyo, Glaxo Smith Kline, Janssen, sanofi aventis and Eli Lilly as well as a personnel award from the Heart and Stroke Foundation. M.W.has nothing to disclose.

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