## 2019 international clinical practice guidelines for the treatment of venous thromboembolism

We read with interest the article by Dominique Farge and colleagues[1] The authors stated that, for ambulatory patients, primary pharmacological prophylaxis of venous thromboembolism (VTE) with low-molecular-weight heparin (LMWH) is indicated for those with locally advanced or metastatic pancreatic cancer treated with systemic anticancer therapy and who have a low risk of bleeding, and primary prophylaxis with direct oral anticoagulant is recommended for those who are receiving systemic anticancer therapy at intermediate-to-high risk of VTE, identified by cancer type (ie, pancreatic) or by a validated risk assessment model (ie, Khorana score of ≥2), and not actively bleeding or not at a high risk of bleeding. We believe those recommendations are premature and would like to make a few comments.

Substantial heterogeneity in dosing regimens (prophylactic *vs* intermediate *vs* therapeutic) and duration of low-molecular-weight heparin therapy existed among studies evaluating primary outpatient thromboprophylaxis in advanced pancreatic cancer.[2]

The option of direct oral anticoagulants in the primary outpatient thromboprophylaxis of cancer-associated thrombosis is exciting. However, caution is needed in interpreting the AVERT and CASSINI trial results owing to different trial designs and patient populations (table).[3,4] In the AVERT trial, apixaban decreased VTE events but increased the major bleeding events.[3] In the CASSINI trial, rivaroxaban did not reduce VTE events on intention-to-treat analysis.[4]

The American Society of Clinical Oncology (ASCO) guidelines take a cautious approach to primary outpatient thromboprophylaxis (by use of the term "may offer thromboprophylaxis") in solid malignancies.[5] Considering the quality of life, cost burden, and absence of strong evidence, the International Initiative on Thrombosis and Cancer recommendations are still premature, and more randomised controlled studies are required to resolve the uncertainties.

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*Kyaw Zin Thein, *Thein Hlaing Oo*
**THOo@mdanderson.org**

Department of Investigational Cancer Therapeutics (KZT), and Section of Thrombosis and Benign Hematology (THO), The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

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| | Patients | VTE events (%) | Major bleeding (%) | Clinically relevant non-major bleeding (%) | NNT to prevent one VTE event |
|---|---|---|---|---|---|
| **AVERT**[3] | | | | | |
| Cancer type | | | | | |
| Gynaecological and genitourinary (26%), lymphoma (26%), pancreas (12%), lung (10%), stomach (8%), brain (5%), myeloma (3%), others (10%) | Apixaban (n=288); placebo (n=275) | 4·2% for apibaxan *vs* 10·2% for placebo; p<0·001 | 3·5% for apibaxan *vs* 1·8% placebo | 7·3% for apibaxan *vs* 5·5% for placebo; HR 1·28 (95% CI 0·89–1·84) | 17 |
| **CASSINI**[4] | | | | | |
| Cancer type | | | | | |
| Pancreas (32%), gastric and gastro-oesophageal junction (21%), lung (16%), breast (9%), lymphoma (7%), others (15%) | Rivaroxaban (n=420); placebo (n=421) | 6·0% for rivaroxaban *vs* 8·8% for placebo; p=0·10 | 2·0% for rivaroxaban *vs* 1·0% for placebo | 2·7% for rivaroxaban *vs* 2·0% for placebo; HR 1·34 (95% CI 0·54–3·32); p=0·53 | 35 |

VTE=venous thromboembolism. NNT=number needed to treat. HR=hazard ratio.

***Table:*** **Patient characteristics and results of the AVERT and CASSINI trials**