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Direct oral anticoagulants in cancer-associated venous thromboembolism: It is high time for a change of therapeutic paradigm

Running title: Anticoagulants in cancer

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Giancarlo Agnelli and colleagues have recently revealed results of the CARAVAGGIO study at the American College of Cardiology and World Congress of Cardiology's virtual scientific sessions. The outcomes of this trial, simultaneously published in the *The New England Journal of Medicine* [1], support the inclusion of apixaban as another direct oral anticoagulant (DOAC) for cancer patients with newly diagnosed incidental or symptomatic proximal deep vein thrombosis (DVT) or pulmonary embolism (PE). This study seems to finish the ongoing discussion on the possibility of using DOACs in cancer-associated thrombosis (CAT) and change the paradigm, setting the low-molecular-weight heparin (LMWH) as a drug of choice and gold standard in this indication.

Venous thromboembolism (VTE) is the second-leading cause of mortality in cancer patients receiving chemotherapy [2]. The adjusted occurrence of VTE is a significant predictor of limited survival within the first year for all cancer types (HR 1.6–4.2; $p < 0.01$) [3]. Moreover, the risk of VTE varies depending on the type of cancer, the stage of metastatic

disease, and receipt of some anti-cancer therapy [4]. The highest risk refers to pancreatic cancer, hematological malignancies, lung, gastric, and brain cancer. The CLOT trial, published in 2003, showed superior efficacy of dalteparin compared to vitamin K antagonist in the prevention of recurrence of cancer-associated VTE and similar bleeding rate in both groups [5]. It was the basis for explicit recommendations for initial and long-term CAT treatment with LMWH in the following years. Recently the European Society of Cardiology Guidelines suggested that “edoxaban or rivaroxaban should be considered as an alternative LMWH, with a word of caution for patients with gastrointestinal cancer due to the increased bleeding risk with DOACs” [6]. The latter was added to underline that the increased risk of bleeding may counterbalance the benefits of anticoagulation therapy in cancer patients. The risk of bleeding in patients treated with DOACs is an essential problem in “mucosal” types of cancer occurring in the gastrointestinal tract and urinary system. Last but not least is the possibility of unfavorable interactions of DOACs with chemotherapy, which may occur during concomitant use.

In the Hokusai VTE Cancer study, oral edoxaban was confirmed to be noninferior to subcutaneous dalteparin concerning the composite outcome of recurrent VTE or major bleeding, but the rate of major bleeding was higher with edoxaban than with dalteparin [7]. Similarly, SELECT-D trial rivaroxaban has shown low VTE recurrence and but the results for major bleeding was 4% for dalteparin and 6% for rivaroxaban. Unfortunately, the adequate rates for clinically relevant non-major bleeding were 4% for dalteparin and 13% for rivaroxaban [8]. Of note, both studies did not exclude patients with cerebral metastases and brain tumors.

The newly published CARAVAGGIO study is a multinational, randomized, open-label, investigator-initiated study to compare efficacy and safety of apixaban and dalteparin in 1170 cancer patients with VTE [1]. Patients with basal-cell or squamous-cell carcinoma of the skin, primary brain tumor, brain metastases, and acute leukemia were excluded, but all other types neoplastic disease may have been included in the study. Approximately one-third of patients presented cancer at gastrointestinal sites. 585 patients were assigned to receive apixaban at a dose of 10 mg twice daily for the first week and 5 mg twice daily subsequently and 585 patients were assigned to receive dalteparin at a dose of 200 IU/kg of body weight subcutaneously once daily for the first month and 150 IU/kg of bodyweight subsequently over a period of 5 months. The primary efficacy end-point was defined as the recurrence of VTE.

The principal safety outcome was defined as major bleeding. Finally, 1155 patients were included in further analysis. Patients with PE accounted for 52.8% and 57.7% in the apixaban and dalteparin groups, respectively. Approximately 20% of the cases were individuals with incidental DVT or PE who were diagnosed during diagnostic procedures performed for reasons other than clinical suspicion of VTE. Ninety-seven percent of cases presented active cancer at enrollment.

The primary efficacy end-point occurred in 5.6% patients in the apixaban group (32 patients: 13 recurrent DVTs, 19 recurrent PE, including 4 cases of fatal PE) compared to 7.9% (46 patients: 15 recurrent DVT, 32 recurrent PE, including 3 cases of fatal PE) in the dalteparin group ($p < 0.001$ for noninferiority; $p = 0.09$ for superiority in favor of apixaban).

Major bleeding occurred in 3.8% (22) of patients in the apixaban group and 4% (23) of patients in the dalteparin group. Moreover, major gastrointestinal bleeding occurred in 1.9% (11) of patients in the apixaban group and 1.7% (10) patients in the dalteparin group. There were two fatal bleeding episodes in the dalteparin group compared to 0 in the apixaban group. Moreover, the rates of clinically relevant non-major bleeding were not significantly higher with apixaban versus dalteparin (9% and 6%). The incidence of death was similar in both groups — 23.4% in the apixaban versus 26.4% in the dalteparin arm. Most deaths were related to cancer — 85.2% and 88.2%, respectively.

The key finding of this study was that oral apixaban is non-inferior to subcutaneous dalteparin for the treatment of VTE in cancer patients since diagnosis up to 6 months. Not similar to previous studies involving other DOACs, the occurrence of major bleedings, either general or gastrointestinal, were similar in apixaban and dalteparin groups. The clinical benefit of treatment prolonged for more than half-year should be assessed in additional studies.

Cancer patients need to have the possibility to use a convenient and safe drug. The treatment regimen for VTE with apixaban and rivaroxaban allows for the administration of oral medications from the first day of therapy, what is exceptionally convenient in cases of DVT and low-risk incidental PE. However, it also requires a physician to make the right decision regarding the choice of DOAC or LMWH based on the type of cancer, comorbidities, bleeding risk, concomitant chemotherapy and patient preference. As a satisfactory safety profile of apixaban showed in the CARAVAGGIO trial, it makes that

selection easier. However, the work is not yet completed. More extensive research is still needed to allow this heterogeneous group of patients to be treated in a more individualized way allowing all therapies to be more effective and safer.

Conflict of interest: None declared

References

1. Agnelli G, Becattini C, Meyer G, et al. Caravaggio Investigators. Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med*. 2020; 382(17): 1599–1607, doi: [10.1056/NEJMoa1915103](https://doi.org/10.1056/NEJMoa1915103), indexed in Pubmed: [32223112](https://pubmed.ncbi.nlm.nih.gov/32223112/).
2. Kuderer NM, Ortel TL, Francis CW. Impact of venous thromboembolism and anticoagulation on cancer and cancer survival. *J Clin Oncol*. 2009; 27(29): 4902–4911, doi: [10.1200/JCO.2009.22.4584](https://doi.org/10.1200/JCO.2009.22.4584), indexed in Pubmed: [19738120](https://pubmed.ncbi.nlm.nih.gov/19738120/).
3. Chew HK, Wun T, Harvey D, et al. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med*. 2006; 166(4): 458–464, doi: [10.1001/archinte.166.4.458](https://doi.org/10.1001/archinte.166.4.458), indexed in Pubmed: [16505267](https://pubmed.ncbi.nlm.nih.gov/16505267/).
4. Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. *PLoS Med*. 2012; 9(7): e1001275, doi: [10.1371/journal.pmed.1001275](https://doi.org/10.1371/journal.pmed.1001275), indexed in Pubmed: [22859911](https://pubmed.ncbi.nlm.nih.gov/22859911/).
5. Lee AYY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med*. 2003; 349(2): 146–153, doi: [10.1056/NEJMoa025313](https://doi.org/10.1056/NEJMoa025313), indexed in Pubmed: [12853587](https://pubmed.ncbi.nlm.nih.gov/12853587/).
6. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020; 41(4): 543–603, indexed in Pubmed: [31504429](https://pubmed.ncbi.nlm.nih.gov/31504429/).
7. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med*. 2018; 378(7): 615–624, doi: [10.1056/NEJMoa1711948](https://doi.org/10.1056/NEJMoa1711948), indexed in Pubmed: [29231094](https://pubmed.ncbi.nlm.nih.gov/29231094/).
8. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol*. 2018; 36(20): 2017–2023, doi: [10.1200/JCO.2018.78.8034](https://doi.org/10.1200/JCO.2018.78.8034), indexed in Pubmed: [29746227](https://pubmed.ncbi.nlm.nih.gov/29746227/).