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Higher risk of stent thrombosis with double therapy with direct oral anticoagulants: cherry picking the populations of interest does not help

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This commentary refers to 'Appropriate cohort selection and its impact on a meta-analysis evaluating the efficacy of direct oral anticoagulants post-percutaneous coronary intervention', by P. Agasthi *et al.*, 2020;41:1700.

We thank Dr Agasthi and colleagues for their interest in our meta-analysis[1,2] and for drawing our attention to the finding that double antithrombotic therapy with direct oral anticoagulants (DOAC-DAT) is associated to an increased risk of stent thrombosis (ST) as compared to triple antithrombotic therapy with vitamin K antagonists. Their argumentations are two-fold:

(1) We included all patients participating in the AUGUSTUS study irrespective of whether they received percutaneous coronary intervention (PCI) at index event.
(2) A signal suggesting higher ST risk was observed with dabigatran 110 mg but less so with dabigatran 150 mg within the RE-DUAL PCI study.

The rationale for including all study participants and not just those who received PCI shortly before study inclusion arises from the need to respect the randomization process, while avoiding arbitrary selection of a post-randomization subgroup for which randomization was not stratified for. It is noteworthy emphasizing that even patients who did not receive PCI or stent implantation at the time of qualifying event were exposed to the risk of ST because of stent-assisted procedure performed in the past. Indeed, two of the overall 32 definite/probable ST cases observed during the study occurred in patients allocated to DAT who received stent implantation prior to but not at the time of qualifying event. Restricting the analysis to patients within the AUGUSTUS trial who had stent implantation at the time of qualifying event yields entirely consistent results with respect to the pooled relative risk increase for the endpoint definite/probable ST with DOAC-DAT, with 80% of the events occurring within 30 days from randomization as recently published.[3]

An arbitrary selection of patients who received only one of the two tested dabigatran doses within the RE-DUAL PCI trial would even be more questionable. All patients in the USA and non-elderly patients in other countries were randomly assigned to the 110-mg DAT group, the 150-mg DAT group, or the TAT group in a 1:1:1 ratio. Elderly patients outside the USA were randomly assigned to the 110-mg DAT group or the TAT group in a 1:1 ratio; they were not eligible to be assigned to the 150-mg DAT group, in accordance with the recommendations of the dabigatran label in those countries. Based on this asymmetric randomization process and limited statistical power, the statistical analysis plan of the trial pre-specified that both dabigatran doses had to be analysed together and contrasted with TAT. As such, the observation that numerical higher rates of ST occurred mainly in patients taking the low but not the high dabigatran regimen can be subject to a considerable play of chance. Finally, a numerical excess of ST occurred in the DOAC-DAT arm of the AUGUSTUS trial despite the use of apixaban at full and approved regimen for stroke prevention (i.e. 5 mg b.i.d.). Hence, whether the use of a full non-vitamin K antagonist oral anticoagulant regimen helps mitigate the ST risk observed consistently across all DOAC-DAT trials remains currently speculative.

We therefore stand with our prior conclusion and believe that the higher risk of ST is real as it comes consistently across all included studies without heterogeneity.

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CARDIOVASCULAR FLASHLIGHT

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Vasospastic angina following immune checkpoint blockade

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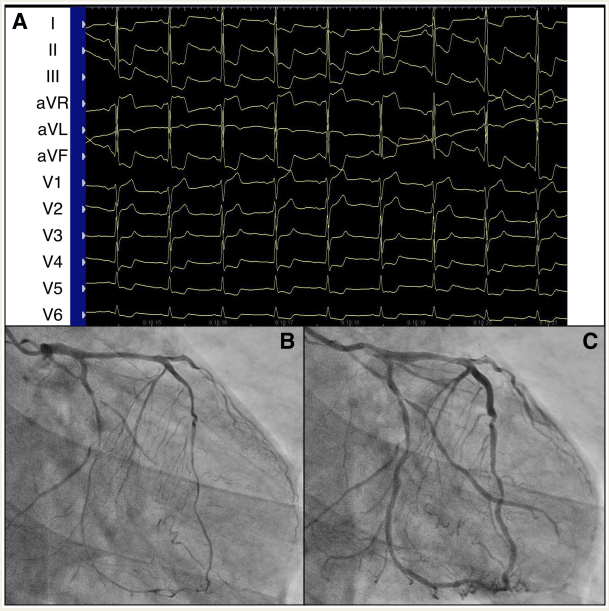
A 57-year-old man had renal cell carcinoma with lung and bone metastases and had undergone 2 cycles of anticancer treatment with an immune checkpoint inhibitor, nivolumab (3 mg/kg, every 2 weeks). Two weeks after the last administration of nivolumab, he was admitted to our hospital due to several episodes of rest angina, especially at night and in the early morning. Resting chest pain, which lasted for 5–20 min, appeared 3 days after the first nivolumab administration and gradually worsened. He had no history of heart disease. Previous management of his renal cell carcinoma involved chemotherapy with sunitinib and axitinib. He had never received radiation therapy to his chest. After admission, he had spontaneous episodes of rest angina with transient ischaemic electrocardiographic (ECG) changes that promptly resolved with nitrate. He underwent coronary angiography 3 days after admission. Immediately after entering the catheterization laboratory, he complained of chest pain, and his ECG showed ST depression in multiple leads (*Panel A*). Coronary angiography revealed multiple spasms throughout the coronary bed (*Panel B*), which was resolved after intracoronary nitroglycerine administration (*Panel C*). He was diagnosed with vasospastic angina, and the symptoms disappeared gradually with the up-titration of a calcium channel blocker and a nitrate. He was able to continue nivolumab treatment without recurring chest pain under coronary vasodilator medication.



In summary, this is a rare case of vasospastic angina following immune checkpoint blockade. Cardiologists and oncologists should be vigilant for vasospasm as a possible immune-related adverse event.