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Editorial

The hidden side of oral thrombin inhibitors

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The management of patients suspected of acute coronary syndromes (ACS) with atrial fibrillation (AF) remains a clinical challenge. Four novel anticoagulants and three different antiplatelet agents at different doses lead to a dizzying number of potential regimen. New oral anticoagulants (NOACs) have been shown not to be inferior to vitamin K antagonists (VKAs) in reducing thromboembolic events in patients with non-valvular AF and venous thrombo-embolism. However, the ones that directly inhibit thrombin (OTI) have been associated with greater risk of myocardial infarction (MI) [1]. Recent meta-analysis with dabigatran was associated with an increased absolute risk of major acute cardiovascular events (MACE) [2]. It was suggested that a group-specific effect for OTI should be responsible [3]. Nevertheless, observational studies such as Danish [4] and American [5] registries of dabigatran use have not confirmed these results. This discrepancy could be explained by the propensity matching [6].

Recently, RE-DUAL PCI trial with dabigatran [7] supported the superior safety on bleeding events of dual therapy with a dabigatran plus clopidogrel over conventional triple therapy with warfarin, aspirin and clopidogrel in patients with AF undergoing percutaneous coronary intervention with stent (PCI).

Regarding the efficacy, the occurrence of MACE, including death or thromboembolic events, or unplanned revascularization, was comparable with dual (110 and 150 mg twice daily doses of dabigatran combined) and triple therapy. Analysis of the occurrence of individual thromboembolic endpoints, including all-cause death, stroke, unplanned revascularization, MI and stent thrombosis, which was performed separately for each doses of dabigatran and compared with corresponding patients on triple therapy, did not highlight significant difference. However, the absolute incidence of stent thrombosis and MI with dual therapy of dabigatran 110 mg twice daily, was approximately two-fold higher than with corresponding triple therapy (Table 1).

This slight increase of acute coronary syndromes might be related to pro-thrombotic activity of OTI. No definitive conclusion can be drawn regarding the small sample size of the evaluated population and the low absolute incidence of MACE. This causative observation with dabigatran treatment remains controversial. Recently, Rubboli et al. [8] suggested that the possible significance of increased cardiovascular events should be in relation with the design of RE-DUAL PCI. Indeed, two periods could be evaluated: the first three months and up to 3 months. The initial comparison was based on the first 3 months for which two treatment strategies were proposed (dual versus triple therapy). The duration of aspirin was limited to 1 or 3 months maximum depending on the type of stent implantation. Up to 3 months, comparison concerned the two different drugs. If MACE occurred during the first period, it might be related to the non-efficacy of the dual therapy. If MACE occurred after the 3 months where both dabigatran and warfarin arms were on dual antithrombotic regimen, it might be speculated that dabigatran 110 mg twice a day did not provide enough intensity of anticoagulation to prevent ischemics events. In the RE-DUAL- PCI, as there was no information about the period over which the event occurs, no conclusion should currently be attributed to the efficacy of dabigatran.

Recently we published the safety and efficacy of dual therapy with dabigatran 110 mg twice a day plus clopidogrel in AF-ACS patients [9]. Because RE-DUAL-PCI trial suggests dropping aspirin, aspirin was not given in our study after PCI in the two arms. In the field of ACS-AF PCI, our daring study is the first trial to compare two dual therapy regimens (dabigatran 110 mg + clopidogrel versus VKAs + clopidogrel) confirm that the omission of aspirin didn't increase ischemic event in the two dual therapy regimen. Interestingly, most of the MACE occurred at 6 months and it appears that the curve separation occurs at distance of PCI. In particular, all the MACE referring to ischemic events (stent thrombosis, MI and ischemia-driven revascularization) occurred after the first 6 months period [9]. Moreover, high on platelet reactivity (HPR) can't be the etiology of this excess of ischemics events because we took into account HPR in this study. As far as we know, it is the first time that tailoring of antiplatelet therapy was used for patients on dual therapy (OAC + clopidogrel) undergoing PCI for ACS-AF. So, our results are in agreement with REDUAL-PCI regarding ischemic events. Numerical increase in stent thrombosis and repeated PCI in the dabigatran group (110 mg twice a day) was observed. Despite more favorable patient features (stent thrombosis criteria, HAS-BLED,

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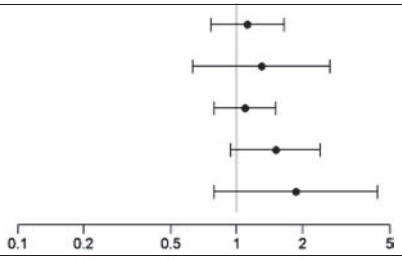
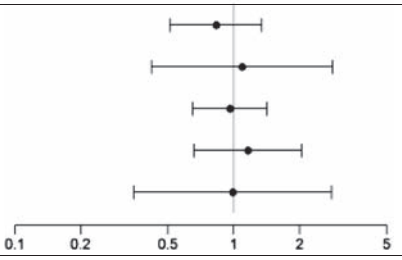
Table 1
Individual efficacy end-points of dual therapy including dabigatran 110 and 150 mg compared with triple therapy in the RE-DUAl PCI trial.

Endpoint	DT Dabigatran 110 mg (N = 981) n (%)	TT (N = 981) n (%)	HR plot (log scale)
All-cause death	55 (5.6)	48 (4.9)	
Stroke	17 (1.7)	13 (1.3)	
Unplanned revascularization	76 (7.7)	69 (7.0)	
Myocardial infarction	44 (4.5)	29 (3.0)	
Stent thrombosis	8 (0.8)	8 (0.8)	



Forest plot Dabigatran 110

Endpoint	DT Dabigatran 150 mg (N = 763) n (%)	TT (N = 764) n (%)	HR plot (log scale)
All-cause death	30 (3.9)	35 (4.6)	
Stroke	9 (1.2)	8 (1.0)	
Unplanned revascularization	51 (6.7)	52 (6.8)	
Myocardial infarction	26 (3.4)	22 (2.9)	
Stent thrombosis	7 (0.9)	7 (0.9)	



Forest plot Dabigatran 150

CRUSADE, CHA2DS2-VASc and GRACE scores) we noticed an increase in the rate of MACE in the dabigatran group, with and without adjustment on the propensity score.

Therefore, the increase in the absolute incidence of MACE observed with dual therapy of dabigatran 110 mg twice a day and clopidogrel might be currently attributed to inadequate intensity of oral anticoagulation and not with REDUAL PCI design. In accordance most studies employing OTIs have shown an association with myocardial infarction occurrence [10], our results can shed further light on the less efficacy of dabigatran in preventing ischemic MACE in ACS-FA patients treated by PCI.

1. Conclusion

The safety of oral anticoagulants keeps being discussed, particularly regarding the risk of MI. We believe that further studies are necessary to clear out the doubts on prothrombotic activity in the dual therapy (dabigatran 110 mg twice a day plus clopidogrel) after PCI. Because there is a considerable heterogeneity regarding cardiovascular safety, a specific trial comparing NOAC should be driven with ischemic events as primary endpoint.

While waiting for such a trial, analysis of the available dataset remains the only option to elucidate these questions. In our opinion a close monitoring is necessary in high-risk patients on a direct thrombin inhibitor, and an alternative NOAC or VKAs could be a better choice in ACS patient.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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