LETTER TO THE EDITOR

What Could be the Most Advantageous Therapeutic Approach to Avoid both Arterial and Venous Thrombosis in Hyperhomocysteinemia?

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Dear Editor,

Thrombophilia is the tendency to form blood clots both in arteries and veins [1]. Inherited and acquired high plasma homocysteine (HHcy) levels are judged as thrombophilic agents because they can induce both arterial and venous thrombosis [2-5]. But, the association of HHcy with Venous Thromboembolism (VTE) has been studied less extensively than that with arterial thrombosis. Some causes are responsible for this, such as Endothelial Dysfunction (ED). Several mechanisms have been suggested explaining HHcy-induced ED. Among these are included: nitric oxide (NO) inhibition due to the suppression of NO. The inhibition is caused by Asymmetric-D-Methyl-Arginine (ADMA), an endogenous inhibitor of nitric oxide synthase (NOS). ED is also dependent on the endothelin-1 induction, angiotensin II activation and oxidative stress [6]. Other factors involved in the induction of arterial thrombosis are impaired DNA methylation, vascular smooth muscle cells proliferation, and platelet activation [7]. On the contrary, a direct correlation between HHcy and venous thrombosis is substantially less known [8]. In this context, some AA show that HHcy promotes venous thrombosis by disturbing the procoagulant-anticoagulant balance [9]. But, a significant increase of VTE risk also happens in patients' contemporary suffering of inherited HHcy and factor V Leiden gene mutation. In addition, venous thrombosis can be evident when HHcy is present in association with other thrombophilic factors, such as prothrombin G 20210A, protein C deficiency, protein S deficiency or antithrombin deficiency [10].

On the view of these pieces of evidence, to prevent both arterial and venous thrombosis in HHcy-patients, an antiplatelet drug should be added to an anticoagulant compound. The combination of two antithrombotics seems to be effective to antagonize the risk of arterial and venous thrombi formation, even if this treatment increases the risk of major bleeding [11]. Antiplatelet therapy should consist of Aspirin or Clopidogrel, whereas anticoagulant treatment will require an acecumarol. But, conventional anticoagulants, such as acecumarol, also called Vitamin K Antagonists (VKAs), have multiple negative effects as: delayed onset of action, need to coagulation monitoring performed through the evaluation of International Normalized Ratio (INR), frequent dosage adjustments and numerous drugs and foods interaction [12]. Thus, a combination of an antiplatelet drug with a DOAC should be used in HHcy-patients. Specifically, likewise to the Cardiovascular OutcoMes for People using Anticoagulation Strategies (COMPASS) Study [13], Aspirin or Clopidogrel at full dosage + half dose of a DOAC could be administered. The choice of DOACs, as above referred, added to an antiplatelet treatment can be associated with risk of major bleeding. For this reason, DOAC should be given at a reduced dose.

Conclusively, HHcy is certainly associated with atherosclerosis, while its association with venous thrombosis is controversial. On the contrary, its presence in association with factor V Leiden and/or other coagulative factors could likely increase VTE [14]. In that case, the association of an antiplatelet drug with reduced doses of DOAC seems to be an attractive and rational treatment to antagonize both arterial and venous thromboembolism induced by HHcy. Interestingly, the supplementation with water soluble vitamins (folate, Vit. B₉, Vit. B₁₂) reducing the high Hcy levels can also decrease the severity of HHcyrelated thrombophilia [4, 15].

LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ADMA</td>
<td>Asymmetric-D-Methyl-Arginine</td>
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<td>COMPASS</td>
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<td>Nitric Oxide</td>
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NOS = Nitric Oxide Synthase
VKA = Vitamin Kappa Antagonists
VTE = Venous Thrombo-Embolism

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REFERENCES