LETTER TO THE EDITOR

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

Federico Cacciapuoti[1,*]

[1]*Department of Internal Medicine, "L. Vanvitelli" Campania University-Naples, Italy*

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. Interestedly, the supplementation with water soluble vitamins (folate, Vit. $B_{6,}$ Vit. B_{12}) reducing the high Hcy levels can also decrease the severity of HHcyrelated thrombophilia [4, 15].

LIST OF ABBREVIATIONS

ADMA	=	Asymmetric-D-Methyl-Arginine
COMPASS	=	Cardiovascular OutcoMes for People using Anticoagulation Strategies
CV	=	CardioVascular
DOACs	=	Direct Oral Anti-Coagulants
HHcy	=	HyperHomocysteinemia
NO	=	Nitric Oxide

*Address correspondence to this author at the Department of Internal Medicine, "L. Vanvitelli", Campania University, Piazza Miraglia, 2 Naples-80131, Italy; Tel: 081/5665022; E-mail: fulvio.cacciapuoti@gmail.com

1573-403X/21 $65.00+.00

NOS = Nitric Oxide Synthase

VKA = Vitamin Kappa Antagonists

VTE = Venous Thrombo-Embolism

CONSENT FOR PUBLICATION

None.

FUNDING

None.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Mitchell RS, Kumar B, Abbas K, Fausto N. Robbins Basic Pathology. 8th ed. Philadelphia: Saunders 2007.
[2] Key NS, McGlennen RC. Hyperhomocyst(e)inemia and Thrombophilia. Arch Pathol Lab Med 2002; 126(11): 1367-75. PMID: 12421143
[3] Sharma V, Agarwal MP, Giri S, Sahu SK, Roy U. Thrombophilia in hyperhomocysteinemia. Int J Emerg Med 2010; 3(4): 495-6. http://dx.doi.org/10.1007/s12245-010-0199-3 PMID: 21373340
[4] Božič-Mijovski M. Hyperhomocysteinemia and thrombophilia. Clin Chem Lab Med 2010; 48(Suppl. 1): S89-95. http://dx.doi.org/10.1515/CCLM.2010.365 PMID: 21105837
[5] Wuillemin WA, Solenthaler M. Hyperhomocysteinemia: a risk factor for arterial and venous thrombosis. Vasa 1999; 28(3): 151-5. http://dx.doi.org/10.1024/0301-1526.28.3.151 PMID: 10483317
[6] Cheng Z, Yang X, Wang H. Hyperhomocysteinemia and endothelial dysfunction. Curr Hypertens Rev 2009; 5(2): 158-65. http://dx.doi.org/10.2174/157340209788166940 PMID: 20495681
[7] Di Minno MN, Tremoli E, Coppola A, Lupoli R, Di Minno G. Homocysteine and arterial thrombosis: Challenge and opportunity. Thromb Haemost 2010; 103(5): 942-61. http://dx.doi.org/10.1160/TH09-06-0393 PMID: 20352150
[8] Hirmerova J. Homocysteine and venous thromboembolism- is there any link. Cor Vasa 2013; 55: E248-58. http://dx.doi.org/10.1016/j.crvasa.2013.01.007
[9] Cattaneo M. Hyperhomocysteinemia and venous thromboembolism. Semin Thromb Hemost 2006; 32(7): 716-23. http://dx.doi.org/10.1055/s-2006-951456 PMID: 17024599
[10] Ventura P, Cobelli M, Marietta M, Panini R, Rosa MC, Salvioli G. Hyperhomocysteinemia and other newly recognized inherited coagulation disorders (factor V Leiden and prothrombin gene mutation) in patients with idiopathic cerebral vein thrombosis. Cerebrovasc Dis 2004; 17(2-3): 153-9. http://dx.doi.org/10.1159/000075784 PMID: 14707415
[11] Eikelboom JW, Hirsh J. Combined antiplatelet and anticoagulant therapy: clinical benefits and risks. J Thromb Haemost 2007; 5(Suppl. 1): 255-63. http://dx.doi.org/10.1111/j.1538-7836.2007.02499.x PMID: 17635734
[12] Mekaj YH, Mekaj AY, Duci SB, Miftari E. New oral anticoagulants: their antagonists in the prevention and treatment of patients with thromboembolic events. Ther Clin Risk Manag 2015; 11: 967-77. http://dx.doi.org/10.2147/TCRM.S84210 PMID: 26150723
[13] Eikelboom JW, Connolly SJ, Bosch J, *et al.* COMPASS Investigators. For COMPASS Investigators: Rivaroxaban with or without Aspirin in stable cardiovascular disease. N Engl J Med 2017; 377(14): 1319-30. http://dx.doi.org/10.1056/NEJMoa1709118 PMID: 28844192
[14] Eldibany MM, Caprini JA. Hyperhomocysteinemia and thrombosis: an overview. Arch Pathol Lab Med 2007; 131(6): 872-84. PMID: 17550314
[15] Tinelli C, Di Pino A, Ficulle E, Marcelli S, Feligioni M. Hyperhomocysteinemia as a risk factor and potential nutracetic target for certain pathologies. Front Nutr 2019; 6: 49. http://dx.doi.org/10.3389/frnt. 2019.00049