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Albumin as a Pharmacokinetic Confound and the Temporal Validity of the MAPH Score in Atrial Fibrillation

Atriyal Fibrilasyonda Farmakokinetik Bir Karıştırıcı Faktör Olarak Albümin ve MAPH Skorunun Zamansal Geçerliliği

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

I read with great interest the article by Konte et al.,[1] which evaluated the MAPH score (Mean platelet volume–Age–total Protein–Hematocrit) as a predictor of left atrial appendage thrombus (LAAT) in patients with atrial fibrillation (AF) scheduled for ablation. The authors demonstrated that the MAPH score outperformed the CHA_2DS_2-VASc score (Congestive heart failure–Hypertension–Age ≥ 75 (2 points)–Diabetes mellitus–Stroke/TIA/thromboembolism (2 points)–Vascular disease–Age 65–74–Sex category (female)) in discriminating LAAT presence on transesophageal echocardiography (TEE), and they appropriately flagged the extreme odds ratio (OR) observed for serum albumin (OR: 1328.5) as a likely statistical artifact. I wish to expand on two points that I believe merit further discussion: the pharmacokinetic interpretation of the albumin finding and the temporal validity of MAPH score components in chronically anticoagulated patients.

The multivariable model revealed that higher albumin was independently associated with LAAT presence. This association warrants pharmacokinetic scrutiny, particularly given the overwhelming predominance of warfarin use in the thrombus group. Warfarin circulates approximately 97–99% protein-bound, primarily to human serum albumin (HSA).[2] Well-established pharmacokinetic literature consistently demonstrates that it is hypoalbuminemia—not hyperalbuminemia—that increases the free, pharmacologically active fraction of warfarin, thereby enhancing its anticoagulant effect and elevating bleeding risk.[3,4] Conversely, higher serum albumin is associated with greater warfarin protein binding, which increases the dose requirement needed to maintain the same anticoagulant effect and, under conditions of fixed dosing, may result in a reduced free drug concentration.[2] In the context of the present cohort, patients with LAAT who had higher albumin levels and were predominantly anticoagulated with warfarin may therefore have been receiving relatively insufficient anticoagulant exposure for their protein-binding capacity—a pharmacokinetic mechanism distinct from, and perhaps complementary to, the inadequate time-in-therapeutic-range (TTR) explanation the authors correctly raise as a limitation. The absence of TTR data precludes definitive conclusions, but this mechanistic pathway reinforces the call for prospective studies incorporating detailed anticoagulation quality metrics.

A second consideration concerns the temporal stability of MAPH score components in a chronically anticoagulated AF population. The MAPH score was originally validated in patients with ST-segment elevation myocardial infarction (STEMI), where laboratory values reflect an acute thromboinflammatory state at a clearly defined moment.[1] In contrast, hematocrit and mean platelet volume (MPV) are dynamic biomarkers subject to chronic modification in AF patients receiving long-term oral anticoagulation. Occult gastrointestinal blood loss—a well-recognized complication of anticoagulant therapy—progressively lowers hematocrit over time, independently of the thrombogenic milieu the score was designed to capture.[5] Similarly, MPV is influenced by antiplatelet co-medication, inflammatory comorbidities, and renal function—all prevalent in the AF population. Because blood sampling in the present study was performed 24–48 hours prior to TEE as a single time point, a chronically depressed hematocrit resulting from subclinical bleeding, rather than a genuinely elevated thrombogenic viscosity, could

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artificially elevate the MAPH score. This raises the possibility that the score is partly capturing anticoagulation-related hematological side effects rather than intrinsic thrombus-promoting physiology in this population. Longitudinal MAPH assessment, or at minimum correction for chronic anemia at baseline, would strengthen the mechanistic inference.

In conclusion, the albumin-LAAT association in this cohort likely reflects a pharmacokinetic disadvantage of warfarin under conditions of higher protein-binding capacity rather than a direct prothrombotic effect of albumin itself. Furthermore, the dynamic nature of hematocrit and MPV under chronic anticoagulation warrants careful consideration before the MAPH score is applied as a cross-sectional screening tool in this population. I concur with the authors that prospective validation studies are warranted, and I particularly emphasize that such studies should include TTR data for warfarin users, parallel direct oral anticoagulant (DOAC) subgroups with their more predictable pharmacokinetic profiles, and longitudinal MAPH assessments to disentangle the thrombogenic signal from anticoagulation-related hematological noise.

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