EDITORIAL

True-resistant hypertension and serum fibrinogen; much more than a marriage of convenience?

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A recent meta-analysis of a pooled sample of 3.2 million patients with hypertension under antihypertensive therapy reported a global prevalence of true-resistant hypertension (tRH) of 10.3% with a higher burden in elderly patients or those with chronic kidney disease [1]. This condition is defined as an inadequate blood pressure (BP) control (systolic and diastolic BP values ≥ 140 and or ≥90 mmHg, respectively) despite the use of three or more antihypertensive drugs, including a diuretic, properly combined and at maximum doses [2]. Due to high prevalence of "pseudo-resistance", out-of-office BP measurements (Home or Ambulatory BP monitoring) is required to exclude white-coat phenomenon. Some other common causes of pseudo-resistant hypertension, such as non-adherence to treatment or secondary hypertension should be ruled out prior to confirm diagnosis [2, 3].

In addition to its high prevalence, tRH poses a unique challenge to both patients and healthcare providers, since it is a significant independent risk factor for hypertension-mediated organ damage, coronary heart disease, chronic kidney disease, stroke or heart failure [4, 5].

Fibrinogen is a key plasma component of the coagulation cascade and a well-known acute phase reactant that has been recognized as an independent risk factor for cardiovascular disease even in apparently healthy people, highlighting its value as a risk marker in primary and secondary prevention [6, 7]. Furthermore, recent studies suggest that fibrinogen plays a central role in the progression of atherosclerosis, promoting plaque adhesion, proliferation of smooth muscle cells and thickening of arterial walls, which facilitates the formation of vulnerable plaques [8].

It strongly associates with other markers of inflammation and thrombosis but the lack of studies determining causality between high serum levels of fibrinogen and cardiovascular disease together with lower predictive value beyond conventional risk markers such as LDL cholesterol or BP, leads to only advocate its use as a risk marker, or even not considered of interest its use in risk prediction [9].

Regarding BP control, higher levels of fibrinogen positively associate with 5-year incidence of hypertension among men and inversely correlated with nocturnal BP decline, increasing risk of non-dipper circadian BP profile [10, 11].

In a recent issue of the Journal of Human Hypertension, Köktürk U et al. investigated the long-term prognostic effects of fibrinogen levels in patients with resistant hypertension [12]. The authors stratified 266 hypertensive patients with tRH according to their serum fibrinogen levels and retrospectively assessed for major adverse cardiovascular events (MACE) after 5 years of follow-up. All patients underwent a 24-h ABPM and the validated Morisky-Green questionnaire was performed to measure medication adherence. The patients were divided into three tertiles based on the serum fibrinogen levels (tertile 1: <257.2 mg/dl, tertile 2: 257.2–326.4 mg/dl and tertile 3: 326.4 mg/dl) without significant difference observed in terms of the patient's baseline characteristics.

Perhaps, the study's most compelling finding was the prognostic value of serum fibrinogen levels for morbidity and mortality since MACE was approximately 2.5 times higher in tertile 2 and approximately 6.9 times higher in the highest tertile, compared to the lowest tertile. The rate of all-cause mortality and cardiovascular mortality was 13.5% and 7.9% respectively for the participants in the highest tertile (compared to 4.5% and 3.4% of those in tertile 2; *p*-value: 0.001 and 0% of individuals in the lowest tertile; *p*-value: 0.022). A significant increased rate was also observed for non-fatal MI (44.9% for T3 vs 15.9% for T1; *p*-value: <0.001), non-fatal stroke (13.5% for T3 vs 3.4% for T1; *p*-value: 0.047) and peripheral artery disease (11.2% for T3 vs 2.3% for T1; *p*-value: 0.033). No significant differences were observed between the two groups with respect to new diagnoses or hospitalization due to heart failure. The authors suggested a cut-off value 350.3 mg/dl of serum fibrinogen to predict MACE albeit limited discriminatory power (low AUC value in ROC analysis).

This study yields important findings with promising clinical translation. First, fibrinogen may contribute to identify those patients with tRH at high risk of MACE who would eventually benefit from intensive BP treatment. Secondly, these findings suggest an etiopathogenic relationship between elevated fibrinogen and tRH. It has been reported how fibrinogen binds to cellular receptors like intercellular adhesion molecule-1 and increases the expression of inflammatory cytokines such as interleukin-6 (IL-6), as well as the production of reactive oxygen species and nitric oxide, leading to oxidative stress and cell death [13]. On the other hand, higher levels of IL-6 and tumor necrosis factor-α (TNF-α) independently associate with odds of tRH [14]. We do also have some strong evidence pointing out mechanisms underlying inflammation in cardiovascular disease. Both trials with canakinumab (a human IgGκ monoclonal antibody targeting IL-1β) and very recent trials with ziltivekimab (a fully human monoclonal antibody targeting the interleukin-6 ligand), showed significantly reduction of fibrinogen levels together with some other inflammatory biomarkers compared with placebo in patients at high atherosclerotic risk [15, 16].

So far, current major clinical practice guidelines emphasize the use of traditional risk factors such as cholesterol and BP but do not recommend fibrinogen testing as a routine tool for risk stratification. Further research is needed to validate these findings with prospective studies examining whether this could offer better risk stratification and, thus, mitigation of cardiovascular complications in patients with tRH.

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AUTHOR CONTRIBUTIONS

Conceptualization, NV-A and AH-A; Data review, AH-A; Methodology, NV-A and AH-A; Project administration, AH-A and AP-R; Resources, AP-R; Supervision, AP-R; Validation, AP-R; Writing—original draft, AH-A; Writing—review and editing, NV-A; All authors have read and agreed to the published version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.