ADMA is a useful marker, but many confounding factors should be considered!

To the Editor,

We read the article entitled "Could plasma asymmetric dimethylarginine level be a novel predictor beyond the classic predictors of stent restenosis?" by Bal et al. (1) published in Anatolian J Cardiol 2014; 14: 491-7. The authors assessed the factors associated with coronary stent restenosis and if there is an association between plasma asymmetric dimethylarginine (ADMA) levels and stent restenosis. They concluded that plasma ADMA levels may be used as a novel marker for stent restenosis beyond the classic stent restenosis markers.

Novel inflammatory markers have been identified in recent years for stent restenosis. One of the major endothelium-derived vasoactive mediators is nitric oxide (NO). A growing body of data indicates that endogenous NO synthase inhibitors, like asymmetric dimethylarginine (ADMA), may be responsible for endothelial vasodilator dysfunction in many individuals with coronary and peripheral arterial diseases and in those with their risk factors, particularly hypertension, diabetes mellitus, hypercholesterolemia, hyperhomocysteinemia, smoking, and aging (2).

First, we have some comments on the present study. Renal failure is one of the most important prognostic variables in patients with cardiovascular disease (3). ADMA is eliminated from the body via renal excretion. The glomerular filtration rate (GFR) provides more accurate knowledge about renal function than the serum creatinine level. A mild reduction in GFR is associated with an increased plasma level of ADMA. The Cockcroft-Gault equation (CGE) and the modification of diet in renal disease (MDRD) are methods for calculating the GFR. However, the CGE and MDRD may estimate different values of GFR according to age (4). Instead of using these methods, the Berlin Initiative Study (BIS) equation (which estimates the GFR more precisely) or Chronic Kidney Disease-Epidemiology Collaboration (CKDEPI) are more useful methods in recent studies (5).

Second, the authors said that plasma ADMA levels were analyzed by using high-performance liquid chromatography (HPLC). This novel assay allows the rapid, reproducible, and available sensitive determination of ADMA compared with ELISA method (2), but many assays are time-consuming and costly and deliver quite unstable results, which are not suitable to differentiate ADMA from SDMA, NMMA, and other methylated arginine analogs. They did not determine other arginine derivatives, such as symmetric dimethylarginine and L-arginine, or assess endothelial function. For this reason, HPLC coupled to mass spectrometric detection (LC-MS/MS) has the clear advantage to be the current gold standard for the differentiation between ADMA and the other methylated arginine derivatives; however, this method is not widely available, and the equipment is comparatively expensive (6).

Furthermore, they used coronary angiography to assess coronary artery stenosis; however, intravascular ultrasonography is the best method to demonstrate neointimal tissue burden completely. They also did not measure other relevant biomarkers, such as homocysteine, lipoprotein (a), and lipoprotein-associated phospholipase A2.

As a conclusion, ADMA is clearly tightly related to oxidative-inflammatory mechanisms of atherosclerosis, and it would have been very helpful to have measured other relevant biomarkers, such as C-reactive protein, homocysteine, lipoprotein (a), and lipoprotein-associated phospholipase A2, to help define that the 2 groups were adequately matched, whether ADMA tracks simply as a covariate with these other biomarkers, and whether differences in ADMA survive and remain statistically significant after adjusting for them (7).

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Author`s Reply

To the Editor,

We would like to thank the authors of the letter for their interest and criticism about our study entitled "Could plasma asymmetric dimethylarginine level be a novel predictor beyond the classic predictors of stent restenosis?" published in September issue of The Anatolian Journal of Cardiology 2014; 14: 491-7. (1). We agree with the authors that the glomerular filtration rate (GFR) provides more accurate knowledge about renal function than the serum creatinine level (2). But, we excluded the patients with chronic renal disease, and also, the average age of the study population was 59 years, and creatinine levels were in the normal range. So, we thought that the difference between the groups would be small and could be neglected and that serum creatinine might be enough to assess the renal functions of both groups.

Comparative studies revealed that the ELISA method produces considerably higher asymmetric dimethylarginine concentrations in plasma or serum in healthy humans in the basal state than mass spec-

trometry and high-performance liquid chromatography methods and runs varyingly in different laboratories (3). As stated by the authors, HPLC coupled to mass spectrometric detection (LC-MS/MS) is not widely available, and the equipment is comparatively expensive (4). So, HPLC was the preferable method for us to detect ADMA.

Intravascular ultrasonography is a validated and superior method when compared with coronary angiography to determine neointimal tissue burden, assessment of lesion significance, and stent restenosis (5). But, in our country conditions, it is not feasible to evaluate stent restenosis for every patient because of its cost and low availability.

There are so many relevant biomarkers known for stent restenosis (6), but it is not feasible to evaluate all of them in one study protocol. Our aim was to evaluate if ADMA predicts stent restenosis beyond classic predictors or not. In our study, we concluded that plasma ADMA level may be used as a novel marker for stent restenosis beyond the classic stent restenosis markers. However, as we stated in our study, this result should be confirmed by larger, prospective, and controlled studies.

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Should systemic thrombolytic therapy be considered a first-line treatment in acute pulmonary embolism?

To the Editor,

We read the article, entitled "Successful treatment of a pulmonary embolism with low-dose prolonged infusion of tissue-type plasminogen activator in a 37-year-old female in the early postoperative period," by Aykan et al. (1) in Anatolian J Cardiol 2014; 14: 400-2. We believe that it can be a really good idea to administer low-dose thrombolytic agents in pulmonary embolism to minimize possible complications. Of course, randomized controlled trials should be performed to test the reliability of this low-dose regimen. We are curious as to why the authors did not consider using well-proven modalities, like percutaneous ultrasound-accelerated thrombolysis (PUAT) and directed thrombolysis (CDT) (2-4). There is no clinical study available so far comparing systemic thrombolytic therapy and endovascular thrombolytic therapy, but this kind of study can take considerable time and can also yield major hemorrhagic complications up to 20%; so, it is preferable to go for an endovascular approach, where direct administration of a thrombolytic agent into the thrombus is possible (4, 5). In PUAT therapy, the dose of tissue plasminogen activator (tPA) is 0.5 mg/kg. Engelhardt et al. (4) even showed the efficacy of doses as low as 20 mg tPA for treatment of pulmonary embolism. In our institution, 4 patients with massive/sub-massive pulmonary embolism received PUAT with 0.5 mg/kg tPA infusion for 6 hours. We did not experience any complications or mortality. Remarkable improvement in right ventricular functions was shown in all patients with echocardiography and computed tomography.

Measurements of right ventricle and left ventricle diameters could also be a very useful tool in assessing the efficacy of treatment in massive pulmonary embolism. We would like to hear the authors' opinions regarding the concerns mentioned above.

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