Editorial

Symmetric dimethylarginine, high-density lipoproteins, and cardiovascular risk assessment: are we ready for clinical use?

Arduino A. Mangoni[1], Angelo Zinellu[2], Salvatore Sotgia[2], Ciriaco Carru[2,3]

[1]Department of Clinical Pharmacology, School of Medicine, Flinders University and Flinders Medical Centre, Adelaide, Australia; [2]Department of Biomedical Sciences, University of Sassari, Sassari, Italy; [3]Quality Control Unit, University Hospital (AOUSS), Sassari, Italy

Correspondence to: Professor Ciriaco Carru. Department of Biomedical Sciences, University of Sassari, Viale S. Pietro 43/B, Sassari 07100, Italy. Email: carru@uniss.it.

Comment on: Zewinger S, Kleber ME, Rohrer L, *et al.* Symmetric dimethylarginine, high-density lipoproteins and cardiovascular disease. Eur Heart J 2017;38:1597-607.

Received: 23 May 2017; Accepted: 05 June 2017; Published: 01 July 2017.

doi: 10.21037/jlpm.2017.06.11

View this article at: http://dx.doi.org/10.21037/jlpm.2017.06.11

There is very good evidence that patients with chronic kidney disease (CKD), particularly those with end-stage renal disease (ESRD), have an increased risk of cardiovascular morbidity and mortality when compared with the general population (1). The proposed mechanisms for the increased cardiovascular risk in CKD patients include the coexistence of major risk factors such as hypertension and diabetes, the main risk factors for CKD/ESRD in the first instance, the presence of significant functional and structural cardiovascular alterations, particularly arterial wall stiffening and left ventricular hypertrophy, that increase *per se* cardiovascular risk, and the high prevalence of previous cardiovascular events, e.g., myocardial infarction and stroke (1,2). Although there is a strong association between CKD and cardiovascular disease, research continues to focus on the identification of novel biomarkers, and the development of specific scoring systems, to further enhance cardiovascular risk stratification. This would assist with better identifying and monitoring patients benefiting from aggressive cardioprotective strategies, with or without the need for renal replacement therapy.

Over the last 25 years, *in vitro* and *in vivo* studies have investigated the pathophysiological role of two endogenous methylated arginine analogues, asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA), not only in CKD but also in other disease states characterized by high cardiovascular risk. Both ADMA and, particularly, SDMA undergo renal clearance. Not surprisingly, therefore, CKD/ESRD patients have higher ADMA and SDMA concentrations when compared with the general population (3). Prospective studies have provided good evidence that higher circulating ADMA concentrations significantly predict cardiovascular morbidity and mortality in CKD, particularly ESRD (4,5). The proposed mechanisms to explain the increased cardiovascular risk primarily involve the inhibitory effects of ADMA towards nitric oxide (NO) synthase *in vitro*, with a consequent reduction in NO synthesis, although this is controversial *in vivo* (3,6,7). A reduction in NO synthesis would lead to endothelial dysfunction, cardiovascular remodelling, and impaired vascular homeostasis, with a consequent increase in atherothrombotic risk (8). By contrast, the role of SDMA in cardiovascular risk prediction has not been thoroughly investigated, mainly because of the lack of knowledge regarding its biological effects in health and disease (9). Experimental work has shown that SDMA might inhibit L-arginine cell uptake, albeit at supraphysiological concentrations (10). This, in turn would reduce the amount of intracellular L-arginine available as a substrate for NO synthase. More recently, other *in vitro* studies have shed new light on the pathophysiological role of SDMA. Schepers *et al.* reported that SDMA triggers the intracellular production of reactive oxygen species, a well-known step in the pathophysiology of vascular disease and atherosclerosis (11,12). Furthermore, Speer et al demonstrated that SDMA accumulates in high-density lipoproteins (HDL) in patients with CKD (13). Notably, SDMA accumulation not only reduces the biological anti-atherosclerotic

effects of HDL, but also transforms this lipoprotein into a lipid fraction that is able to promote endothelial dysfunction, inflammation and vascular damage (13). The detrimental effects of SDMA-enriched HDL are thought to be mediated by the Toll-like receptor-2 (13). Therefore, the biological and pathophysiological effects of HDL on vascular homeostasis seem to be highly dependent on circulating SDMA concentrations, and the consequent degree of SDMA accumulation in this lipoprotein. This hypothesis, however, requires confirmation in longitudinal studies assessing SDMA, HDL-C and clinical outcomes in patients with CKD.

Zewinger *et al.* have recently sought to address this issue, by investigating the capacity of ADMA, SDMA and HDL cholesterol (HDL-C) concentrations to predict cardiovascular outcomes in two established epidemiological cohorts, LURIC (n=3,310) and MONICA/KORA S3 (n=1,424) (14). Both ADMA and SDMA concentrations at baseline, in separate analyses, significantly predicted the primary outcomes, all-cause mortality and cardiovascular mortality. Further analyses showed that, in the presence of relatively low SDMA concentrations, higher HDL-C concentrations predicted lower all-cause and cardiovascular mortality. By contrast, in the presence of high SDMA concentrations, higher HDL-C concentrations were associated with an increased risk of adverse outcomes (14). No effect on the predictive capacity of HDL-C concentrations was observed with different ADMA concentrations. Complementary *in vitro* studies confirmed the association between an impairment in renal function, with consequent increase in circulating SDMA concentrations, and accumulation of SDMA in HDL. The effects of different methylated arginine concentrations on cholesterol efflux capacity were also studied. Cholesterol efflux is an increasingly recognized protective mechanism by which key target cells, e.g., macrophages within the atherosclerotic vascular wall, are able to revert the LDL-induced intracellular cholesterol accumulation, therefore favouring its elimination through the liver and bile (15). CKD patients with higher SDMA concentrations had a significantly lower cholesterol efflux capacity when compared with patients with lower SDMA concentrations. By contrast, ADMA concentrations were not a significant effect modifier of cholesterol efflux capacity (14).

The results of the study by Zewinger *et al.* suggest a novel pathophysiological role of SDMA, whereby this methylated arginine analogue accumulates in HDL, inducing important structural and functional modifications of these lipid particles. This, in turn, leads to detrimental, rather than salutary, effects on vascular homeostasis and integrity (14). However, an important issue is whether the measurement of SDMA and HDL-C concentrations in patients with CKD can provide significant additional knowledge, in terms of risk stratification and treatment decisions, to that already provided by conventional risk factors. From a practical standpoint, the use of novel biomarkers in clinical practice is likely to be considered if they (I) are easily measurable; and (II) provide significant additional predictive capacity particularly in patients at moderate risk, who often present treatment challenges and require an individualized approach. By contrast patients with previous cardiovascular events are considered by definition at high-risk, and normally require aggressive pharmacological and non-pharmacological treatment for secondary prevention. Therefore, the identification of novel biomarkers in this group is unlikely to change treatment decisions. With this background in mind, several limitations curtail the data interpretation and the routine applicability of the results of the study by Zewinger *et al.*:

While the predictive capacity of ADMA in CKD/ESRD patients is well established, the role of SDMA as a biomarker is still under investigation. In a recent study by Shafi *et al.*, baseline SDMA concentrations in CKD patients were associated with a higher risk for cardiac death (HR 1.40, 95% CI: 1.03 to 1.92). However, this effect was no longer significant after adjusting for baseline ADMA concentrations (HR 1.20, 95% CI: 0.86 to 1.68) (16). The lack of adjustment for ADMA concentrations in the study by Zewinger *et al.* does not allow to establish whether SDMA and HDL-C concentrations provide predictive capacity that is independent of ADMA concentrations.

The relatively long duration of follow-up in the LURIC (9.9 years) and MONICA/KORA S3 (16.8 years), together with the lack of data during intermediate time points, does not rule out the possibility that subsequent changes in clinical status and/or prescribed medications might have affected *per se* the outcomes of interest.

Important confounders, such as presence/severity of hypertension and treatment with renin angiotensin system inhibitors or beta-blockers, were not accounted for in the regression models. Hypertension has been shown to be a major predictor of adverse cardiovascular outcomes in CKD patients (17). Furthermore, drugs used in cardiovascular risk management are likely to influence, by definition, all-cause and cardiovascular mortality, and affect methylated arginine concentrations (18-20).

A significant proportion of participants in the LURIC study had suffered a previous cardiovascular event, e.g. myocardial infarction or stroke, which by itself would increase their risk of subsequent cardiovascular events during the follow-up (21). The inclusion of a history of cardiovascular event in the regression models might have significantly diluted the predictive capacity of ADMA, SDMA and HDL-C.

The discriminatory superiority of the HDL-C/SDMA model over the HDL/serum amyloid model demonstrated by Zewinger *et al.*, albeit convincing, does not provide evidence of superiority over conventional risk factors or scoring systems, e.g. the Framingham score (22).

In conclusion, the recent study by Zewinger *et al.* provides significant insight into a novel biological and pathophysiological role of SDMA in the context of impaired renal function and cardiovascular risk (14). However, from an economic and public health perspective, the aforementioned issues do not currently support the routine assessment of SDMA and HDL-C concentrations in patients with CKD. Further studies, using more comprehensive statistical analyses, are required to demonstrate the independent effects of these parameters on hard cardiovascular end-points and their additional predictive capacity over established risk factors, before their routine measurement for clinical decisions and patient management can be justified.

Acknowledgments

AA Mangoni has participated in this work during a Visiting Professorship at the University of Sassari.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Chao Xuan (Department of Clinical Laboratory, the Affiliated Hospital of Qingdao University, Qingdao, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jlpm.2017.06.11). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet 2013;382:339-52.
2. London GM. Cardiovascular disease in chronic renal failure: pathophysiologic aspects. Semin Dial 2003;16:85-94.
3. Vallance P, Leiper J. Cardiovascular biology of the asymmetric dimethylarginine:dimethylarginine dimethylaminohydrolase pathway. Arterioscler Thromb Vasc Biol 2004;24:1023-30.
4. Lu TM, Chung MY, Lin CC, et al. Asymmetric dimethylarginine and clinical outcomes in chronic kidney disease. Clin J Am Soc Nephrol 2011;6:1566-72.
5. Zoccali C, Bode-Boger S, Mallamaci F, et al. Plasma concentration of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: a prospective study. Lancet 2001;358:2113-7.
6. Hewitson CL, Whiting MJ, Barbara JA, et al. Acute effects of haemodialysis on biochemical modulators of endothelial function. J Intern Med 2007;262:571-80.
7. Bouteldja N, Woodman RJ, Hewitson CL, et al. Methylated arginines and nitric oxide in end-stage renal disease: impact of inflammation, oxidative stress and haemodialysis. Biomarkers 2013;18:357-64.
8. Napoli C, de Nigris F, Williams-Ignarro S, et al. Nitric oxide and atherosclerosis: an update. Nitric Oxide 2006;15:265-79.
9. Mangoni AA. The emerging role of symmetric dimethylarginine in vascular disease. Adv Clin Chem 2009;48:73-94.
10. Closs EI, Basha FZ, Habermeier A, et al. Interference of L-arginine analogues with L-arginine transport

mediated by the y+ carrier hCAT-2B. Nitric Oxide 1997;1:65-73.
11. Schepers E, Glorieux G, Dhondt A, et al. Role of symmetric dimethylarginine in vascular damage by increasing ROS via store-operated calcium influx in monocytes. Nephrol Dial Transplant 2009;24:1429-35.
12. Nowak WN, Deng J, Ruan XZ, et al. Reactive Oxygen Species Generation and Atherosclerosis. Arterioscler Thromb Vasc Biol 2017;37:e41-52.
13. Speer T, Rohrer L, Blyszczuk P, et al. Abnormal high-density lipoprotein induces endothelial dysfunction via activation of Toll-like receptor-2. Immunity 2013;38:754-68.
14. Zewinger S, Kleber ME, Rohrer L, et al. Symmetric dimethylarginine, high-density lipoproteins and cardiovascular disease. Eur Heart J 2017;38:1597-607.
15. Rosenson RS, Brewer HB Jr, Davidson WS, et al. Cholesterol efflux and atheroprotection: advancing the concept of reverse cholesterol transport. Circulation 2012;125:1905-19.
16. Shafi T, Hostetter TH, Meyer TW, et al. Serum Asymmetric and Symmetric Dimethylarginine and Morbidity and Mortality in Hemodialysis Patients. Am J Kidney Dis 2017. [Epub ahead of print].
17. Shlipak MG, Fried LF, Cushman M, et al. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. JAMA 2005;293:1737-45.
18. Mangoni AA, Zinellu A, Carru C, et al. Transsulfuration pathway thiols and methylated arginines: the Hunter Community Study. PLoS One 2013;8:e54870.
19. Wadham C, Mangoni AA. Dimethylarginine dimethylaminohydrolase regulation: a novel therapeutic target in cardiovascular disease. Expert Opin Drug Metab Toxicol 2009;5:303-19.
20. Maas R. Pharmacotherapies and their influence on asymmetric dimethylargine (ADMA). Vasc Med 2005;10 Suppl 1:S49-57.
21. Winkelmann BR, Marz W, Boehm BO, et al. Rationale and design of the LURIC study--a resource for functional genomics, pharmacogenomics and long-term prognosis of cardiovascular disease. Pharmacogenomics 2001;2:S1-73.
22. Weiner DE, Tighiouart H, Elsayed EF, et al. The Framingham predictive instrument in chronic kidney disease. J Am Coll Cardiol 2007;50:217-24.

doi: 10.21037/jlpm.2017.06.11
Cite this article as: Mangoni AA, Zinellu A, Sotgia S, Carru C. Symmetric dimethylarginine, high-density lipoproteins, and cardiovascular risk assessment: are we ready for clinical use? J Lab Precis Med 2017;2:40.

