Editorial

Underestimation of Risk of Carotid Subclinical Atherosclerosis by Cardiovascular Risk Scores in Patients with Psoriatic Arthritis: How Far Are We from the Truth?

Inflammatory disease states are associated with early cardiovascular (CV) events and are increasingly being recognized as a risk factor for developing atherosclerosis[1,2]. Several autoimmune conditions such as psoriasis[1,3,4], systemic lupus erythematosus[5], and rheumatoid arthritis (RA)[6,7,8] accelerate atherosclerosis through an increase in inflammatory signaling, thus predisposing to increased CV risk. Traditional CV risk scoring systems and risk score calculation are a cornerstone in the prediction of adverse CV events[9]. Further, risk score calculation plays an important role in shaping treatment guidelines that are tailored to fit each patient's individual risk factors[10,11], emphasizing the need to accurately predict and stratify a patient's CV risk. Assessment of absolute CV risk is also integral to assess major prevention and treatment targets[10,11].

While current scoring systems provide a modestly accurate prediction for the general population[11], each scoring system has certain inherent limitations. For example, the Framingham risk score (FRS) does not incorporate socioeconomic and genetic factors (e.g., family history)[12]. Further, FRS does not account for systemic inflammation and, therefore, has not performed well in inflammatory diseases such as psoriasis[13] and RA[14]. Thus, almost all the risk scoring systems do not account for systemic inflammation except the Reynold's Risk Score, which incorporates high-sensitivity C-reactive protein[12]. Recognizing the burden of increased CV risk in RA, the European League Against Rheumatism (EULAR) had recommended multiplying traditional risk scores such as FRS by 1.5 in RA[14]. Additionally, they extended these recommendations to inflammatory disease states such as ankylosing spondylitis and psoriatic arthritis (PsA) in their recent update while maintaining the multiplication factor of 1.5 for RA[15].

In the current issue of *The Journal*, Shen and colleagues[16] used carotid intima-media thickness (CIMT), a reliable surrogate marker of subclinical atherosclerosis, as an outcome to test the validity of standard CV risk algorithms in patients with PsA. They also assessed whether applying the EULAR recommended multiplication factor of 1.5 significantly improved the sensitivity of traditional risk estimates in patients with PsA.

The study was performed in a total of 162 patients, 93 of whom had participated in a prior cohort study and 69 of whom were enrolled in an ongoing prospective study to assess the effect of treat-to-target to prevent the progression of atherosclerosis. Sixteen participants were excluded because of the inability to calculate at least 1 CV risk score. Depending on their eligibility, the remaining participants underwent CV risk score assessment by FRS, QRISK2, Systematic Coronary Risk Evaluation (SCORE), and the American College of Cardiology and the American Heart Association 10-year atherosclerotic CV disease risk (ASCVD). All participants also underwent thorough estimation of severity of PsA and a carotid ultrasound to determine intima-media wall thickness, with a thickness of > 0.9 mm and/or carotid plaques serving as a cutoff for presence of subclinical atherosclerosis.

On stratifying participants by presence of subclinical atherosclerosis, subjects with carotid artery disease were older and had higher total cholesterol than those without. However, there was no significant difference between the 2 groups in terms of other traditional CV risk factors. Additionally, there was no statistically significant difference in psoriasis severity, PsA severity, inflammatory biomarker levels, or PsA treatment (nonsteroidal antiinflammatory drugs, systemic steroids, and synthetic or biologic disease-modifying antirheumatic drugs) between the groups.

Patients with subclinical atherosclerosis had significantly higher CV risk calculated by all 4 CV risk scoring systems. However, using standard cutoff values that are used for the general population, the study found that only 44.1%, 1.8%, 10.9%, and 43.6% of the subjects with subclinical atherosclerosis were at "high risk" of CV disease, defined as FRS > 10%, QRISK2 > 20%, SCORE > 5%, and ASCVD > 7.5%,

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respectively. After applying the EULAR multiplication factor of 1.5, the investigators found that 50.8%, 14.3%, 14.5%, and 54.5% of the participants with subclinical atherosclerosis were at high risk of CV disease. Thus, the study concluded that all routinely used CV risk scores underestimated the risk of "CV disease" in patients with PsA, and this underestimation persisted (albeit not as grossly) even after adjustment for the presence of inflammatory joint disease by EULAR criteria[14,15].

Given that 1 of the 3 main recommendations of EULAR is that the rheumatologist is responsible for CVD risk management in patients with inflammatory joint disease[15], this study by Shen and colleagues is a unique approach to CV risk prediction in patients with PsA. It is known that inflammatory disease states add to the risk of CV disease; however, the extent to which such diseases contribute to CV burden is not well known. Shen, *et al* have made a commendable contribution to the growing body of literature that aims to shed light on the underestimation of CV risk in patients with inflammatory disease states.

One of the major concerns with this study is that simple atherosclerotic plaque presence by carotid ultrasound is not a putative outcome of defining CV risk compared to hard CV events. While the study did determine CV risk by routinely used CV risk score calculators, it used subclinical atherosclerosis defined by CIMT > 0.9 mm and/or presence of frank carotid plaques. Although CIMT is a reliable marker of atherosclerosis[17] that may predict future CV events[18], the investigators had no data that directly addressed CV events in their participants. Further, there is limited data on how CIMT precisely correlates with risk of CV events. Therefore, how risk scores designed to estimate future CV events perform on surrogate markers such as CIMT is unclear. Ideally, this study would have followed participants prospectively to ascertain true CV risk with CV outcomes and compare these events to calculated CV risk scores. However, such a study would require over a decade of followup in many hundreds to thousands of patients. For example, in our cohort of about 300 patients (NCT01778569), we have observed fewer than 10 incident CV events over 4 years of followup [Mehta Lab, US National Heart, Lung, and Blood Institute (NHLBI), unpublished data].

This study raises important questions about accurate CV risk prediction using routine traditional CV risk scores in patients with an inflammatory disease. Moreover, it also highlights that the commendable EULAR recommendations do not fully identify the lack of sensitivity of traditional CV risk score estimates. Until a large prospective outcomes study is undertaken, the major message of Shen, *et al* that CV risk scores underestimate risk in PsA should be echoed to providers caring for these patients.

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REFERENCES

1. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA 2006;296:1735-41.
2. Skeoch S, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? Nat Rev Rheumatol 2015;11:390-400.
3. Eder L, Gladman DD. Atherosclerosis in psoriatic disease: latest evidence and clinical implications. Ther Adv Musculoskelet Dis 2015;7:187-95.
4. Mehta NN, Yu Y, Pinnelas R, Krishnamoorthy P, Shin DB, Troxel AB, et al. Attributable risk estimate of severe psoriasis on major cardiovascular events. Am J Med 2011;124:775.e1-6.
5. Cacciapaglia F, Zardi EM, Coppolino G, Buzzulini F, Margiotta D, Arcarese L, et al. Stiffness parameters, intima-media thickness and early atherosclerosis in systemic lupus erythematosus patients. Lupus 2009;18:249-56.
6. Nagata-Sakurai M, Inaba M, Goto H, Kumeda Y, Furumitsu Y, Inui K, et al. Inflammation and bone resorption as independent factors of accelerated arterial wall thickening in patients with rheumatoid arthritis. Arthritis Rheum 2003;48:3061-7.
7. Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. J Rheumatol 2003;30:36-40.
8. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 2003;107:1303-7.
9. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-47.
10. Ozen G, Sunbul M, Atagunduz P, Direskeneli H, Tigen K, Inanc N. The 2013 ACC/AHA 10-year atherosclerotic cardiovascular disease risk index is better than SCORE and QRisk II in rheumatoid arthritis: is it enough? Rheumatology 2016;55:513-22.
11. Karmali KN, Goff DC, Jr., Ning H, Lloyd-Jones DM. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. J Am Coll Cardiol 2014;64:959-68.
12. Cook NR, Paynter NP, Eaton CB, Manson JE, Martin LW, Robinson JG, et al. Comparison of the Framingham and Reynolds Risk scores for global cardiovascular risk prediction in the multiethnic Women's Health Initiative. Circulation 2012;125:1748-56, S1-11.
13. Torres T, Sales R, Vasconcelos C, Martins da Silva B, Selores M. Framingham Risk Score underestimates cardiovascular disease risk in severe psoriatic patients: implications in cardiovascular risk factors management and primary prevention of cardiovascular disease. J Dermatol 2013;40:923-6.

14. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010;69:325-31.
15. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis 2017;76:17-28.
16. Shen J, Lam SH, Shang Q, Wong CK, Li EK, Wong P, et al. Underestimation of risk of carotid subclinical atherosclerosis by cardiovascular risk scores in patients with psoriatic arthritis. J Rheumatol 2018;45:218-26.
17. Hurst RT, Ng DW, Kendall C, Khandheria B. Clinical use of carotid intima-media thickness: review of the literature. J Am Soc Echocardiogr 2007;20:907-14.
18. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol 2010;55:1600-7.

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