COMMENT ON YANG ET AL.

Association of Statin Use and Reduced Risk of Lower-Extremity Amputation Among Patients With Diabetes: A Nationwide Population-Based Cohort Observation. Diabetes Care 2016;39:e54–e55

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It is estimated that 2 million Americans, two-thirds of whom have diabetes mellitus (DM), are currently living with a limb amputation (1). Patients with DM are at significant risk for limb amputation, as one in four will develop a diabetic foot ulcer (DFU) over their lifetime and nearly one in six will require amputation (2). In 2009, U.S. hospital costs due to amputation exceeded $8.3 billion, and annual U.S. DFU treatment costs are approaching $13 billion (1–3).

With this in mind, we were pleased to read the study by Yang et al. (4) investigating the association between statin use and reduced risk of lower-limb amputation (LLA) in patients with DM. Yang et al. studied a population-based cohort comprising 38,973 patients with just over half of the patients taking statins. The authors reported that, during a mean follow-up of 5.2 years, those taking statins had a relative risk reduction for lower-extremity amputation of 46% (0.006 vs. 0.011, log-rank $P < 0.001$). Amputation risk correlated with the severity of DM assessed by the hypoglycemic agents prescribed.

Yang et al. (4) hypothesize that statins may facilitate limb salvage partly because of their ability to augment wound healing. One mechanism by which statins may improve wound healing is by antagonizing hydroxymethylglutaryl-CoA reductase to inhibit farnesyl pyrophosphate formation, an intermediate in the cholesterol synthesis pathway whose effects reduced epithelialization following binding to keratinocyte glucocorticoid receptors (5). Recently, we reported (5) a secondary finding of a large prospective cohort study assessing DFU healing after 6 weeks of standardized care and use of statins among other medications. Most medications (α-blockers, β-blockers, ACE inhibitors, angiotensin receptor blockers, or calcium channel blockers) were not associated with improved healing among the 139 enrolled subjects. However, among the 91 patients taking statins (simvastatin [54], rosuvastatin [11], atorvastatin [22], pravastatin [3], unknown [1]), we found a trend associating their use with DFU healing (regression coefficient −0.148, $P = 0.057$).

Our results are consistent with several diabetic animal model studies associating statins with improved wound healing (5). One small (13 subjects) randomized clinical pilot trial assessing the effect of statins on patients' DFU healing, recurrence, and prevention found that subjects taking 80 mg atorvastatin had significantly lower rates of DFU recurrence and neoulcerogenesis compared with those administered 10 mg atorvastatin (5).

Interestingly, recent evidence suggests an association between the use of statins and new-onset DM, hyperglycemia, reduced insulin sensitivity and reduced insulin secretion, and peripheral neuropathy (6). These later observations require further exploration as does research into elucidating and confirming mechanisms by which statins improve DFU healing and reduce the risk of LLA in patients with DM (5). Other possible mechanisms by which statins improve healing include upregulation of vascular endothelial growth factor and endothelial nitric oxide synthase (5).

We agree with Yang et al. (4) that larger prospective clinical trials are crucial to further investigate the use of statins in the prevention of both LLA and healing and prevention of DFUs, although the large sample sizes needed might suggest that logistically a pragmatic trial design might be most feasible.

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References

1. Varma P, Stineman MG, Dillingham TR. Epidemiology of limb loss. Phys Med Rehabil Clin N Am 2014;25:1–8
2. Fox JD, Baquerizo-Nole KL, Berriman SJ, Kirsner RS. Chronic wounds: the need for greater emphasis in medical schools, post-graduate training and public health discussions. Ann Surg. 13 January 2016 [Epub ahead of print]
3. Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for medicare and private insurers. Diabetes Care 2014;37:651–658
4. Yang T-L, Lin L-Y, Huang C-C, et al. Association of statin use and reduced risk of lower-extremity amputation among patients with diabetes: a nationwide population-based cohort observation. Diabetes Care 2016;39:e54–e55
5. Fox JD, Baquerizo-Nole KL, Macquhae F, et al. Statins may be associated with six-week diabetic foot ulcer healing. Wound Repair Regen 2016;24:454–457
6. Cederberg H, Stančáková A, Yaluri N, Modi S, Kuusisto J, Laakso M. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. Diabetologia 2015;58:1109–1117