



RESPONSE TO 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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We thank Fox et al. (1) for their noteworthy comments concerning the need for clinical trials regarding the role of statins in preserving the lower extremities of patients with diabetes mellitus (DM). Complications of the extremities, comprising peripheral artery disease, peripheral neuropathy, foot ulcer, critical limb ischemia, and ultimately limb loss, constitute a huge health burden for patients with DM. Our recent study (2) showed the beneficial effect of statins in patients with type 2 diabetes leading to a 52% reduction in risk for lower-limb amputation during a mean follow-up of 5.2 years. Additionally, amputation risk correlated with the severity of DM assessed by the hypoglycemic medication prescribed. We agree that statins may provide the benefit of enhanced wound healing, and other mechanisms have been proposed, including amelioration of inflammation, improved endothelial function, and prevention of infection (3). Statin therapy has been associated with 30% earlier wound epithelialization and 80% greater wound-breaking strength combined with faster wound healing rates in cardiac surgery patients (4). Evangelista et al. (5) reported

that administration of 40 mg simvastatin daily in addition to standard wound care and compression was associated with a significant improvement in healing rate and time, as well as improved patient quality of life, further demonstrating the beneficial effects of statins in wound healing.

Although guidance from the International Working Group on the Diabetic Foot (6) recommends aggressive cardiovascular risk management including cessation of smoking, treatment of hypertension, and prescription of an antiplatelet drug and a statin, the scientific evidence regarding statin use and lower-limb amputation is still limited. Therefore, further prospective, randomized, placebo-controlled clinical trials with adequate statistical power are probably needed to delineate the therapeutic contour of statins in the diabetic extremity. We appreciate that Fox et al. (1) share our opinions and have done great work in the pilot study on diabetic foot ulcer healing using statin therapy. We also agree with the authors that now is the time for clinical trials to determine whether statin treatment can provide a preventive benefit in patients with DM. Hopefully there will be multicenter trials

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on a multidisciplinary basis in the near future, encompassing cardiologists, dermatologists, endocrinologists, surgeons, and pharmacists, to address the issue.

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References

1. Fox JD, Baquerizo-Nole KL, Macquhae F, et al. 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 (Letter). *Diabetes Care* 2016;39:e159–e160. DOI: 10.2337/dci16-0415
2. 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
3. Wang CC, Yang PW, Yang SF, Hsieh KP, Tseng SP, Lin YC. Topical simvastatin promotes healing of *Staphylococcus aureus*-contaminated cutaneous wounds. *Int Wound J*. 8 March 2015 [Epub ahead of print]. DOI: 10.1111/iwj.12431
4. Fitzmaurice GJ, McWilliams B, Nölke L, Redmond JM, McGuinness JG, O'Donnell ME. Do statins have a role in the promotion of

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postoperative wound healing in cardiac surgical patients? *Ann Thorac Surg* 2014;98:756–764

5. Evangelista MT, Casintahan MF, Villafuerte LL. Simvastatin as a novel therapeutic agent

for venous ulcers: a randomized, double-blind, placebo-controlled trial. *Br J Dermatol* 2014;170:1151–1157

6. Hinchliffe RJ, Brownrigg JR, Apelqvist J, et al.; International Working Group on the Diabetic

Foot. IWGDF guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes. *Diabetes Metab Res Rev* 2016;32(Suppl. 1):37–44