



Association of Statin Use and Reduced Risk of Lower-Extremity Amputation Among Patients With Diabetes: A Nationwide Population-Based Cohort Observation

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Diabetes mellitus (DM) is a disease entity associated with metabolic abnormality and systemic vascular inflammation, causing microvascular as well as macrovascular organ damage. Statins are widely used for the management of dyslipidemia. Beyond the lipid-lowering effect, statins were found to have many pleiotropic effects, such as anti-inflammatory and antiatherogenic effects. We conducted a nationwide population-based cohort study to investigate the relationship between statin use and the risk of lower-extremity amputation in patients with DM. A database from the Taiwan National Health Research Institutes was used, and subjects with DM were identified using ICD-9 coding. The study cohort was separated to statin group and control groups. The observation end point was any lower-extremity amputation.

Out of a total of 38,973 patients with DM, 20,254 (51.97%) patients taking statins were compared with those not taking statins. During a mean follow-up of 5.2 years, the statin group had significantly lower risk of lower-extremity amputation compared with the control group (0.6% vs. 1.1%, log-rank $P < 0.001$) (Fig. 1A). After adjusting for comorbidities, statin use was independently associated with 52.0% risk reduction of amputation (odds

ratio 0.48 [95% CI 0.38–0.61], $P < 0.001$). Furthermore, the amputation risk gradually increased with hypoglycemic agents from metformin to insulin, indicating the amputation risk correlated with disease severity. Interestingly, statins effectively reduced the risk of amputation in patients with DM with variable treatment (Fig. 1B)—even insulin therapy—suggesting the consistent benefit of statins in reducing amputation risk even in these patients with higher DM severity. Subgroup analysis also revealed the consistent advantages of statin therapy but a less significant benefit among those patients with underlying coronary artery disease, chronic kidney disease, and peripheral artery disease.

It has been reported that statins may have beneficial effect with reduced risk of lower-extremity amputation among non-elderly patients with DM (1). Our observation expands the spectrum of benefit to all adult patients with DM and stratified DM groups with variable hypoglycemic treatments. Amelioration of inflammation, improved endothelial function, prevention of infection, and augmented wound healing may be possible explanations of the limb-preserving effect of statins. It has long been observed that statins have anti-inflammatory effects in

various settings via decreasing proinflammatory cytokine (2). As DM is associated with systemic microangiopathy and local inflammation, it is reasonable that statins may have a limb-preserving effect by mitigating systemic inflammation and improving local microangiopathy. Improved endothelial functions, in terms of the flow-mediated dilatation model or nitric oxide release, are enhanced with statins in type 2 DM (3). A meta-analysis concluded that statin use is associated with a beneficial effect in treating and preventing different infections (4). As patients with DM were prone to get mixed infections if DM foot ulcers developed, the anti-infection profiles of statins may exert a favorably protective effect for recovery. Also, statins were shown to improve wound healing by enhancing vascular endothelial growth factor production in animal models (5). Large, long-term, prospective, randomized clinical studies are needed to confirm whether statins provide preventive advantages among individuals with DM.

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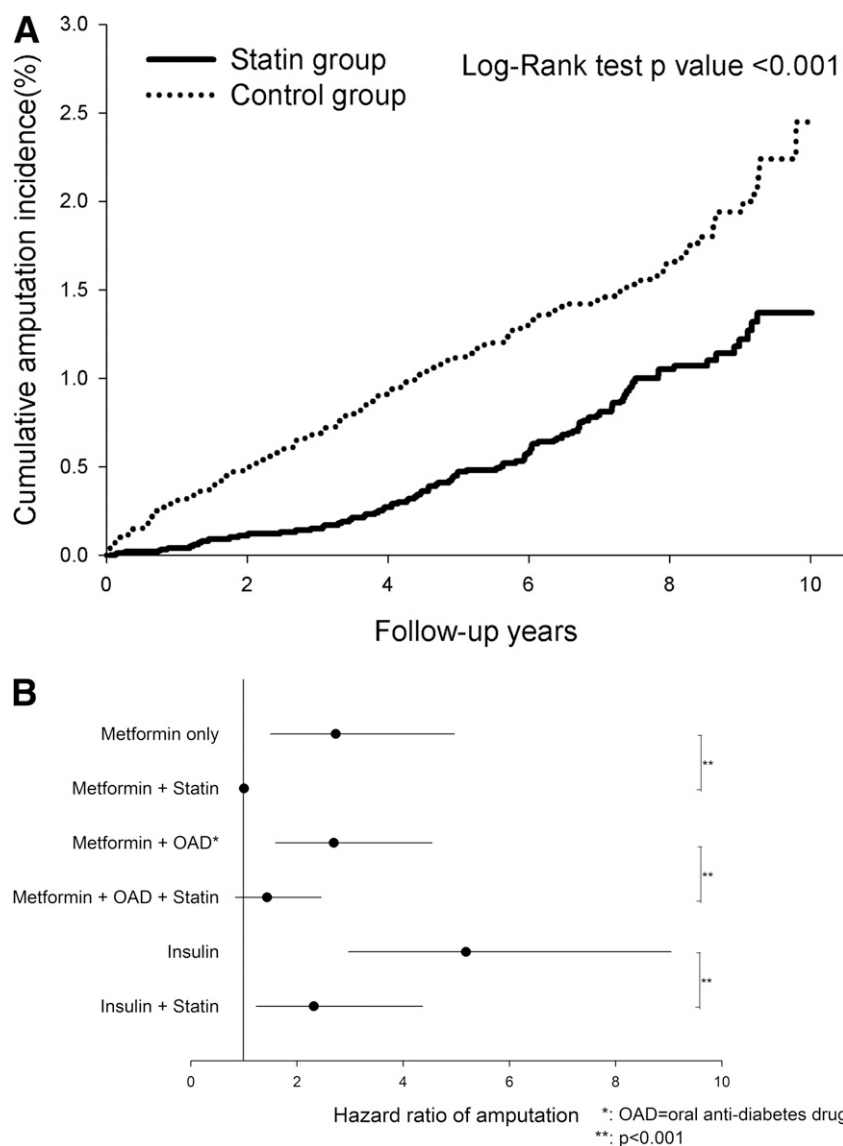


Figure 1—A: Cumulative incidence of amputation between statin and control groups. B: Relative hazard ratio of amputation stratified according to DM medications and statin use.

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