

Fenofibrate may decrease the risk of amputation in type 2 diabetes mellitus

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In patients with type 2 diabetes mellitus amputations substantially impair the quality of life and impose high costs on health-care systems. Therefore, reduce the risk of amputations represents a major task for clinicians. Fibrates have been shown to induce keratinocyte differentiation and improve the epidermal barrier in vivo suggest that some of the benefits of fenofibrate may relate to improved wound healing. This effect — more so than anti-inflammatory, antioxidant, or endothelium-mediated effects — could put fibrates apart from the many agents, like statins, that have so far been unable to reduce amputations in people with diabetes.

In order to evaluate the effect of fenofibrate on amputation events, 9795 patients aged 50 to 75 years with type 2 diabetes were randomly assigned to receive fenofibrate 200 mg per day ($n = 4895$) or matching placebo ($n = 4900$) for 5 years. A prespecified, tertiary endpoint of the study was nontraumatic amputation, about which information was gathered routinely. The amputations were classified according to the presence or absence of large-vessel disease, and were defined as minor (below the ankle) or major (above the ankle).

From all patients, 115 had at least 1 nontraumatic, diabetes-related lower-limb amputation. Compared with patients who had other cardiovascular events or those who had no cardiovascular events, those who had amputations during the trial had higher rates of previous cardiovascular disease, microvascular disease, previous nontraumatic amputation or skin ulcer, and smoking, as well as longer duration of diabetes (all $P < .001$ for 3-way comparison).

Differences in mean lipid concentrations between patients who had limb amputations during the study and those who had other cardiovascular events or neither event did not exceed 0.2 mmol/L. Compared with patients receiving placebo, those receiving fenofibrate had lower risks for first amputation (45 vs 70 events; hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.44 – 0.94; $P = .02$) and for minor amputations without known large-vessel disease (18 vs 34 events; HR, 0.53; 95% CI, 0.30 – 0.94; $P = .027$). However, the risk for major amputations was not significantly different between groups (24 vs 26 events; HR, 0.93; 95% CI, 0.53 – 1.62; $P = .79$).

Limitations of this study include lack of standardized routine testing, such as angiography or ankle-brachial index, at baseline.

In conclusions, this study support the treatment with fenofibrate, irrespective of the presence of dyslipidaemia, in patients with type 2 diabetes who are at high risk for amputation (including those with peripheral vascular disease, existing microvascular complications, and a long

duration of diabetes). In this category of patients, use of fenofibrate is associated with a lower risk of amputations, particularly minor amputations without known large-vessel disease, probably through non-lipid mechanisms. Therefore, this approach could reduce the substantial morbidity, mortality, and economic burden associated with amputation due to diabetes. ▣



Comment on the paper:

Fazio S, Linton MF – Fenofibrate and risk of minor amputations in diabetes. *Lancet* 2009; 373:1740-1741