



MEDIA RELEASE

Fenofibrate reduces the risk of amputations in patients with type 2 diabetes

Exciting new data from the FIELD study show additional microvascular-associated benefits of fenofibrate

*The **first time** in a large-scale prospective study that any lipid-modifying therapy has been shown to significantly reduce the risk of lower-limb amputation in patients with type 2 diabetes*

FENOFIBRATE treatment in people with type 2 diabetes mellitus reduces the risk of amputations, including those associated with microvascular disease, according to new data from the FIELD study presented for the first time at the European Association for the Study of Diabetes, Rome, September 2008. ¹These findings add to other microvascular benefits demonstrated with fenofibrate in diabetic retinopathy, published in *The Lancet* 2007², and diabetic nephropathy, published in *The Lancet* 2005³.

The FIELD study researchers showed that, over an average follow-up of 5 years, treatment with fenofibrate reduced the risk of non-traumatic amputation by 38% ($p=0.011$), mainly due to a reduction in amputation considered related to microvascular disease by 47% ($p=0.025$). Patients who had an amputation associated with microvascular disease were slightly younger and heavier and were more likely to have other microvascular disease, including diabetic eye and kidney disease.

According to Professor Keech, lead investigator of the FIELD study: *'The effects of fenofibrate in reducing the risk of amputations in patients with established microvascular complications were particularly striking, and further support the important clinical benefits of fenofibrate on microvascular associated events in type 2 diabetes.'*

The FIELD analysis on amputations

All non-traumatic amputations that occurred during the FIELD study were reviewed by 2 clinicians blinded to study treatment. Reasons for amputation were recorded as presumed microvascular (amputations of toes or forefoot [called "minor" amputations], without embolism or existing large artery disease in the limb) or macrovascular (all other "minor" and all below-knee and above-knee ["major"] amputations).

The profile of patients more likely to require amputation was:

- Male

- Longer duration of diabetes
- Higher systolic blood pressure
- Current smoker
- Previous vascular disease
- More microvascular complications
- More insulin use at baseline

All these characteristics were considerably more common than in patients who did not undergo amputation.

Among all patients with an amputation, the profile of patients with a microvascular-associated complication was:

- Slightly younger ($p=0.03$)
- Heavier ($p<0.001$)
- Slightly higher HbA1c ($p=0.07$)
- More other microvascular complications ($p=0.002$)

Significance for millions of type 2 diabetes patients

Peripheral neuropathy (nerve damage) is a serious complication of diabetes. Recent data indicate that one in 5 people with diabetes (20%) have peripheral neuropathy, irrespective of whether diabetes has been clinically diagnosed. The risk for peripheral neuropathy is about 2-fold higher than in people without diabetes⁴. The combination of peripheral neuropathy with problems associated with the blood supply to the feet can lead to foot ulcers and slow-healing wounds. Infection of these wounds can result in amputation. Every 30 seconds a limb is lost to diabetes and 40–70% of all lower extremity amputations are related to diabetes.⁵

Evidence indicates that improvements in management, specifically drug therapy, have contributed to a decline in cardiovascular mortality in patients with diabetes.⁶ As people with diabetes live longer, they are more likely to experience microvascular complications of diabetes. Together with the increasing prevalence of type 2 diabetes among an ageing population,⁷ the burden of microvascular complications, including diabetic neuropathy and amputation, is expected to increase substantially in the future.

Even when treated in accordance with current standards for diabetes care, patients remain at high residual risk of vascular complications. This is highlighted by evidence from the STENO-2 trial in patients with type 2 diabetes. Despite optimal control of LDL-cholesterol and diastolic blood pressure and fair glycaemic and systolic blood pressure control, microvascular disease such as diabetic retinopathy, nephropathy or neuropathy developed or progressed in up to 50% of these patients within 8 years⁸.

Fenofibrate reduces the total cardiovascular risk in patients with type 2 diabetes and atherogenic dyslipidaemia (elevated triglycerides and low HDL-cholesterol)

While current management strategies aimed at lowering LDL cholesterol with statin therapy are effective in reducing cardiovascular risk in patients with diabetes, supported by extensive evidence from a large number of well-controlled studies⁹, there are also clear limitations to statin treatment. Even at optimal statin doses, extensive evidence from large clinical trials show that 65-90% of CVD events in diabetes patients are not prevented with statin therapy⁹. This is largely because statins only partly address the abnormalities of low HDL-cholesterol and elevated triglycerides which are common in patients with type 2 diabetes. It is important to note that triglyceride and HDL-cholesterol levels are strong predictors of cardiovascular events, even in patients achieving LDL-cholesterol levels below 1.8mmol/L (70mg/dL)

Additional FIELD data presented at this year's EASD highlight that cardiovascular risk reduction with fenofibrate treatment is greatest in patients with type 2 diabetes with atherogenic dyslipidaemia (the combination of elevated triglycerides (>2.3mmol/L) plus low high-density lipoprotein [HDL] cholesterol (<1.0mmol/L for men and <1.3mmol/L for women); fenofibrate treatment showed a 27% reduction in CVD risk in these patients¹⁰. The FIELD study investigators showed that in patients with marked diabetic dyslipidemia, 23 patients have to be treated with fenofibrate for 5 years to avoid one CV event (NNT = 23), which is comparable with the benefits of statin therapy already shown in landmark trials.

These new data highlight the benefits of fenofibrate on amputations, including microvascular-associated amputations. Together, with previously published data showing benefits for the eye and the kidney, these results support important microvascular effects of treatment. They highlight the urgent need to address residual vascular risk in patients with type 2 diabetes.

For more information, or to arrange an interview, please contact:

Australia:

Michael d'Emden, Diabetologist
James Best, Diabetologist
Russell Scott, Diabetologist

Via:

Beth Quinlivan, University of Sydney
Ph: +61 2 9036 6528
Mob: +61 0 419 229 134

At EASD, Rome, Italy

Peter Colman, Diabetologist
Richard O'Brien, Diabetologist
Anthony Keech, Study Chairman

Via:

Wendy Gerber, MS&L
Ph: +44 20 7878 3259
Mob: +44 7840 058 082

Notes to editors

About the study

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study is the largest study of lipid modifying therapy ever conducted in diabetic patients with and without dyslipidaemia. It randomised 9795 patients aged 50-75 years from Australia, New Zealand and Finland with type 2 diabetes. The subjects were treated with either fenofibrate or placebo for five years.

FIELD is the first study to show that a lipid modifying agent, fenofibrate, reduces the risk of macrovascular and microvascular events in a large prospective clinical trial in patients with type 2 diabetes³.

In addition a sub-study was conducted in order to evaluate the development of diabetic retinopathy and the symptoms of eye disease².

About diabetic amputations

Diabetes is the most common reason for lower-limb amputation that is not the result of accident, responsible for 40% to 70% of all lower-limb amputations⁵. This means that every 30 seconds a limb is lost to diabetes⁵. People with diabetes are at least 25 times more likely to suffer a lower-limb amputation than those without diabetes¹¹.

The combination of diabetic neuropathy (nerve damage) and problems with blood supply to the feet predispose to the development of ulcers and slow-healing wounds, which if infected may lead to amputation. Studies suggest that up to 70% of people with diabetes have evidence of diabetic neuropathy, and about 30% of people with diabetes aged 40 years or more have impaired feeling in the feet, indicative of peripheral neuropathy¹². The risk for peripheral neuropathy is about 2-fold higher in people with diabetes than in those without.⁷ Pathological changes associated with the development of diabetic neuropathy and risk for amputation are related to poor glycaemic control and microvascular changes in the diabetic foot¹³.

Within 3 years, 30% of people with diabetes who undergo lower-limb amputation will go on to have a second amputation¹⁴. About 70% of people with diabetes die within 5 years of amputation¹⁵. Lower limb amputation is also costly, both in terms of the acute cost related to the amputation, as well as ongoing management^{16, 17}, and impacts substantially on quality of life¹⁸.

About diabetes/metabolic syndrome and the associated risks

Patients with diabetes and/or metabolic syndrome are known to be at higher cardiovascular risk, as recognised by current treatment guidelines.¹⁹⁻²¹ Notably, diabetes is recognised as a 'coronary risk equivalent', by the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)²², based on evidence from a number of well-designed observational studies that people with diabetes are at about 2–4-fold higher risk of premature cardiovascular mortality compared with those without diabetes²³⁻²⁵.

These patients typically have an abnormal lipid profile characterised by low high-density lipoprotein (HDL) cholesterol and elevated triglycerides, often with elevated levels of small, dense low-density lipoprotein particles, although levels of low-density lipoprotein (LDL) cholesterol are often normal. Extensive epidemiological evidence shows that elevated triglycerides²⁶ and low HDL cholesterol²⁷ are each independent predictors of cardiovascular risk.

About fenofibrate

Fenofibrate is marketed widely by Solvay Pharmaceuticals as LIPANTHYL[®] and LIPIDIL[®], and marketed by Abbott Laboratories in the USA as TRICOR[®].

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