

Incidence and predictors of silent myocardial infarction in type 2 diabetes and the effect of fenofibrate: an analysis from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study

David C. Burgess^{1*}, David Hunt², LiPing Li¹, Diana Zannino¹, Elizabeth Williamson¹, Timothy M.E. Davis³, Markku Laakso⁴, Y. Antero Kesäniemi⁵, Jun Zhang¹, Raymond W. Sy⁶, Seppo Lehto⁴, Stewart Mann⁷, and Anthony C. Keech^{1*}

¹NHMRC Clinical Trials Centre, University of Sydney, Locked Bag 77, Camperdown, NSW 1450, Australia; ²Department of Cardiology, Royal Melbourne Hospital, Victoria, Australia; ³School of Medicine and Pharmacology, Fremantle Hospital, University of Western Australia, Fremantle, WA, Australia; ⁴Department of Medicine, University of Kuopio, Kuopio, Finland; ⁵Department of Internal Medicine, Oulu University Hospital, Oulu, Finland; ⁶University of Sydney, NSW, Australia; and ⁷Department of Medicine, University of Otago Wellington, Wellington, New Zealand

Received 18 February 2009; revised 27 July 2009; accepted 20 August 2009; online publish-ahead-of-print 29 September 2009

Aims

To determine the incidence and predictors of, and effects of fenofibrate on silent myocardial infarction (MI) in a large contemporary cohort of patients with type 2 diabetes in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study.

Methods and results

Routine electrocardiograms taken throughout the study were assessed by Minnesota-code criteria for the presence of new Q-waves without clinical presentation and analysed with blinding to treatment allocation and clinical outcome. Of all MIs, 36.8% were silent. Being male, older age, longer diabetes duration, prior cardiovascular disease (CVD), neuropathy, higher HbA_{1c}, albuminuria, high serum creatinine, and insulin use all significantly predicted risk of clinical or silent MI. Fenofibrate reduced MI (clinical or silent) by 19% [hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.69–0.94; $P = 0.006$], non-fatal clinical MI by 24% ($P = 0.01$), and silent MI by 16% ($P = 0.16$). Among those having silent MI, fenofibrate reduced subsequent clinical CVD events by 78% (HR 0.22, 95% CI 0.08–0.65; $P = 0.003$).

Conclusion

Silent and clinical MI have similar risk factors and increase the risk of future CVD events. Fenofibrate reduces the risk of a first MI and substantially reduces the risk of further clinical CVD events after silent MI, supporting its use in type 2 diabetes.

Keywords

Silent myocardial infarction • Type 2 diabetes • Fenofibrate

Introduction

Most patients with a myocardial infarction (MI) have significant symptoms and present to hospital for treatment. Some, however, have an asymptomatic MI that is identified later when an electrocardiogram (ECG) shows the presence of Q waves. The reported proportion of silent MIs ranges from 22 to 40%.¹

Although patients with diabetes are at greater risk of MI, the proportion of silent MIs may be similar to that in the general population.² One community-based observational study reported that the risk of cardiac death in type 2 diabetes was lower with silent MI than overt coronary heart disease,³ but active screening studies have shown that unrecognized myocardial ischaemia has a relatively poor prognosis.^{4,5}

* Corresponding authors. Tel: +61 2 9562 5000, Fax: +61 2 9562 5304, Email: fieldtrial@ctc.usyd.edu.au

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2009. For permissions please email: journals.permissions@oxfordjournals.org.

Estimates of prevalence of silent MI in type 2 diabetes vary, depending on the source populations and inclusion criteria such as sex, age, diabetes duration, and the presence of diabetic, cardiovascular, or renal complications. Also, there is no standard definition for the diagnosis of silent MI. Various methods of testing for silent MI, such as resting electrocardiography, thallium scintigraphy, and coronary angiography,^{2,3,5–15} have been used, complicating direct comparisons between studies.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was the largest clinical-endpoint trial of lipid-modifying therapy in type 2 diabetes.¹⁶ We reported that fenofibrate significantly reduced non-fatal clinical MI events (which by definition excluded silent MI) by 24% [fenofibrate 158 (3%) vs. placebo group 207 (4%); hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.62–0.94; $P = 0.01$].

We have now determined the proportion of silent first MIs on the basis of resting ECG readings taken routinely throughout the study and assessed their relationships with potential baseline risk factors and subsequent clinical cardiovascular disease (CVD) events. We also investigated whether fenofibrate prevented silent MI.

Methods

Patients

A total of 9795 patients with type 2 diabetes, aged 50–75 years, were recruited to the FIELD study and randomized to fenofibrate 200 mg daily or matching placebo.¹⁶ Patients had total cholesterol 3.0–6.5 mmol/L plus total-to-HDL cholesterol ratio over 4.0 or triglyceride 1.0–5.0 mmol/L. Patients were excluded if they had had a clinical MI within 3 months before study entry or if their physician felt that there was a clear indication for cholesterol-lowering medication. Clinical events and safety outcomes were monitored every 4–6 months over an average of 5 years of follow-up.

Electrocardiogram collection and reading

Electrocardiograms were routinely done at baseline, 2 years, 5 years, and study close. Standard 12-lead ECGs were obtained with the patient supine at rest and forwarded to the coordinating centre in Sydney for blinded adjudication. Electrocardiograms were recorded with a calibration mark in millivolts and paper speed was marked on each trace, against which standardized measurements could be made. All ECGs were read by medical practitioners who had received training in ECG reading according to the Minnesota ECG code¹⁷ and were unaware of patients' study treatment allocation or clinical outcome.

Definitions of Q waves and silent myocardial infarction

A diagnosis of clinical MI during the study required at least two of three criteria: ECG changes, ischaemic symptoms suggestive of myocardial ischaemic chest pain, and raised cardiac enzymes.¹⁶ Q waves were defined as present when duration exceeded 0.03 s and they were in at least two ECG leads in the same lead group and in the absence of left bundle branch block or ventricular pacing. They were defined as new if absent from baseline or previous ECGs and as diagnostic of silent MI in the absence of a preceding clinical history of MI or unstable angina during study follow-up. All ECGs were reviewed by one reporter, and those with possible Q waves plus a random 10% of all other ECGs were reviewed by a second reporter. In the absence of concordance, a third (cardiologist) reporter adjudicated.

Endpoints

The main aims of the study were to determine: (i) the proportion of new MIs that were silent; (ii) the prognostic significance of silent MI; (iii) the effects of fenofibrate on the occurrence of silent MI and subsequent clinical outcomes; and (iv) the baseline risk factors for silent compared with clinical MI.

Statistical analyses

Analysis of differences for baseline characteristics used χ^2 tests for binary variables and ANOVA for continuous variables. All continuous variables were tested for normality, and if the distribution of the data was not normal, the Kruskal–Wallis test was used. Cox proportional-hazards analysis was used to compute HRs to assess the effect of fenofibrate treatment on the time to first event. P -values were computed from the log-rank test for all non-MI outcomes. Cumulative incidence curves of the time to first event, and by treatment group, used the Kaplan–Meier method. Landmark analysis was used to analyse events after a silent MI,¹⁸ which could be detected only at 2 or 5 years after randomization or at study close, when routine ECGs were done; using the 2 year time point ensured an average of at least 3 years of follow-up thereafter. For outcomes measured at intervals (silent MI and all composite outcomes that included silent MI), interval-censored proportional-hazards methods were used.¹⁹ All statistical inferences used two-sided $P = 0.05$, with no adjustment for multiple comparisons.²⁰ All analyses were by intention-to-treat and used SAS (version 9.1) or ACCORD (Analysis of Censored and Correlated Data; version 1.6.3, 2008).

Results

Incidence of silent myocardial infarction

A total of 31 190 ECGs were retrieved and adjudicated, from over 92% of patients at each time point (Figures 1 and 2; Table 1). Concordance between two readers in reporting Q waves exceeded 92% (Cohen's kappa 0.74). New Q waves

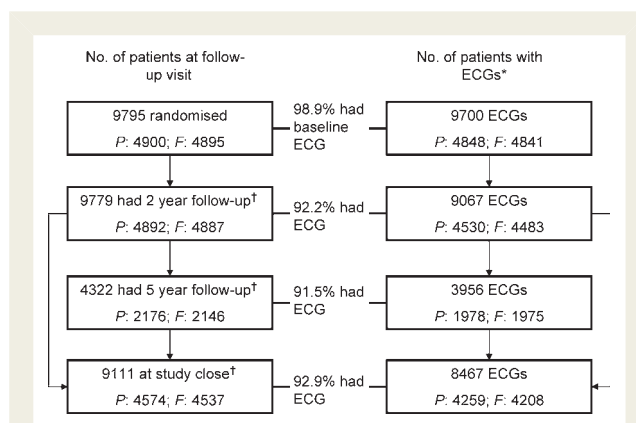


Figure 1 Electrocardiogram collection by treatment group.

* Numbers of ECGs are higher than the number of patients as more than one intervening ECG was recorded in some patients. For example, baseline ECGs included ECGs taken from visit 1 to visit 3 during run-in before randomization. †Reasons for no ECGs: patient deceased, withdrawn consent, lost to follow-up, permanent discontinuation, and other reasons for not attending for a clinic visit. P, placebo group; F, fenofibrate group.

reflecting silent MI were found in 265 patients (2.7% of all participants). In contrast, 406 patients developed clinical MI during follow-up (4.1%), 45 (11.1% fatal), and 94 (23.2%) developed new Q waves with their first clinical MI. Of all MIs, 36.8% were silent (Table 2). The distributions of territories for silent and clinical Q-wave MIs were not significantly different, with a slightly higher proportion of inferior (and fewer anterior) infarcts among silent events (Table 3).

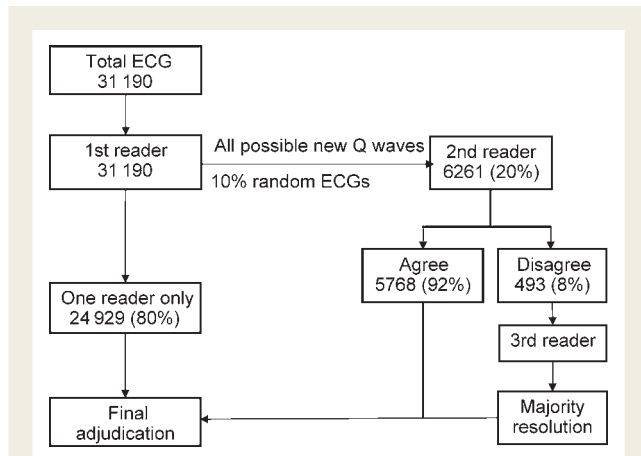


Figure 2 Electrocardiogram adjudication processing.

Table 1 Proportions of patients with an electrocardiogram reading and silent myocardial infarction (MI) detected between visits 1 and 3 (baseline) and study close in the FIELD study

Time	No. of visits	No. alive with ECG (%)	No. (%) of silent MIs (n = 269) ^a	Silent MIs as percent of those with ECG
Baseline	9795	9689 (98.9)	—	—
2 years	9779	9013 (92.2)	114	1.3
5 years	4322	3953 (91.5)	52	1.3
Close	9111	8467 (92.9)	103	1.2

^aFour patients had two silent MI events.

Characteristics of patients with silent and clinical myocardial infarction

The baseline characteristics of those who had an on-study MI differed strikingly from those with no MI (Table 4). The prevalence of standard coronary risk factors and indicators of diabetic microvascular disease were highest in those with clinical MI, intermediate with silent MI, and lowest among those without MI (Table 4). Thus, 30.6, 26.1, and 21.0%, respectively, of these groups had microalbuminuria. Similarly, 42.8, 32.2, and 20.6% of these groups, respectively, had prior clinical CVD.

Risk factors for silent and clinical myocardial infarction

No measured characteristics significantly predicted greater odds of having a silent rather than a clinical MI. In a multivariate analysis, microalbuminuria and macroalbuminuria were somewhat stronger baseline predictors for silent than for clinical MI, but this did not reach statistical significance (Table 5). The estimated likelihood of silent MI appeared to fall (about 3% per annum) with duration of diabetes, but there was no significant heterogeneity between silent and clinical MI. Predictors such as male sex, older age, prior CVD, higher haemoglobin A_{1c}, elevated serum creatinine, and insulin use showed a lower estimated strength of association for silent MI than for clinical MI when compared with no MI, but these differences between clinical and silent MI were not statistically significant.

Effects of fenofibrate on myocardial infarction and cardiovascular disease

Clinical non-fatal MIs were reduced by 24% in the group taking fenofibrate, and there was a non-significant reduction of 16% in silent MI (Figure 3). Non-fatal MIs were reduced significantly by 20%. Total MIs (including fatal) were also reduced by 19%. Therefore, the number of patients needed to be treated (NNT) with fenofibrate to avoid one or more MIs over 5 years of therapy was 70. Total clinical CVD events (the first of non-fatal MI, stroke, CVD death, or coronary or carotid revascularization) were reduced by 11%, and when combined with silent MI, by 10%, an NNT of 67. After a first clinical or silent MI by the end of year 2, fenofibrate reduced further clinical CVD events by 25%, and by 78% after a silent MI.

Table 2 Clinical and silent myocardial infarctions (MI) in patients with type 2 diabetes

	No. of patients			Total no. of events ^b
	First MI	After other MI	Total ^a	
Silent MI	245 (38.3%)	20 (64.5%) after clinical MI	265	269 (36.8%)
Clinical MI	395 (61.7%)	11 (35.5%) after silent MI	406	461 (63.2%)

^aOf the 640 patients, 31 had both silent and clinical MIs.

^bFour patients had two silent MI events; 44 patients had two or more clinical MI events.

Prognosis after a silent or a clinical myocardial infarction

When all survivors at 2 years were classified according to having had an on-study MI, or no MI, subjects without MI had the lowest risk of future clinical CVD events. In the placebo group, the risk of CVD events in patients with silent MI (HR 4.55, 95% CI 2.90–7.13, $P < 0.001$) was similar to the risk in

those with clinical MI (HR 4.51, 95% CI 3.08–6.61, $P < 0.001$), compared with those with no MI (Figure 4A). The absolute risks of further CVD events over 3 years among placebo patients were 33.7% for silent MI, 28.8% for clinical MI, and 8.3% for no MI.

Among patients allocated to fenofibrate, those who had a clinical MI were at the highest risk of further CVD events (Figure 4B). In contrast, the risks of those who had a silent MI and those who had no MI were not statistically different (HR 1.08, 95% CI 0.40–2.89; $P = 0.88$). Those who had a clinical MI were at a significantly higher risk of CVD events than those who had a silent MI (HR 5.76, 95% CI 2.01–16.50; $P = 0.001$). The absolute risks of further CVD events over 3 years were 9.1% for silent MI, 39.4% for clinical MI, and 7.6% for no MI (with fewer fenofibrate-allocated subjects having had either a silent or clinical MI at 2 years Figure 4B).

Mortality also differed significantly by MI status: coronary heart disease mortality (placebo group) was 8.6% for those with silent MI, 10.1% for clinical MI, and 1.2% for no MI ($P < 0.001$). Among placebo-treated subjects, all-cause mortality was 13.8% for those with silent MI, 15.2% for clinical MI, and 4.8% for no MI ($P < 0.001$). The same mortality patterns according to MI status were seen among the fenofibrate subjects, though there were no statistical differences in mortality between treatment arms overall or by MI status.

Table 3 The number and percentage of all clinical and silent myocardial infarctions according to site*

Site of MI	No. (%) of clinical Q-wave MIs ($n = 97^a$)	No. (%) of silent MIs ($n = 269^b$)
Anterior	40 (41.2)	83 (30.9)
Anterior and inferior	2 (2.1)	5 (1.9)
Inferior	53 (54.6)	164 (61.0)
Lateral	2 (2.1)	17 (6.3)

* $P = 0.15$ for χ^2 test for association of site with MI type.

^aTwo patients had two clinical Q-wave MI and one patient had both a clinical Q-wave MI and a silent MI.

^bFour patients had two silent MIs.

Table 4 Baseline characteristics of patients with no myocardial infarction (MI), or silent MI or clinical MI as a first event*

Characteristic	No MI ($n = 9155$)	Silent MI ($n = 245$)	Clinical MI ($n = 395$)
Male, n (%)	5679 (62.0)	166 (67.8)	293 (74.2)
Age in years, mean (SD)	62.1 (6.9)	63.6 (7.3)	64.4 (6.6)
Diabetes duration in years, median (IQR) ^a	5 (2–10)	5 (2–9)	7 (3–12)
Systolic blood pressure, median (IQR) ^a	140 (130–150)	140 (133–152)	142 (132–153)
Clinical history, n (%)			
Previous cardiovascular disease	1883 (20.6)	79 (32.2)	169 (42.8)
Microvascular disease	1852 (20.2)	48 (19.6)	125 (31.6)
Diabetic retinopathy	739 (8.1)	20 (8.2)	55 (13.9)
Diabetic neuropathy	1261 (13.8)	40 (16.3)	94 (23.8)
Laboratory data			
Haemoglobin A _{1c} in %, median (IQR) ^a	6.85 (6.05–7.75)	6.95 (6.15–7.80)	7.25 (6.45–8.30)
Plasma creatinine in $\mu\text{mol/L}$, mean (SD)	77.3 (15.7)	80.0 (16.9)	83.4 (16.9)
Homocysteine in $\mu\text{mol/L}$, median (IQR) ^a	9.5 (7.9–11.4)	9.9 (8.0–12.4)	10.0 (8.4–12.5)
Microalbuminuria, n (%) ^b	1919 (21.0)	64 (26.1)	121 (30.6)
Macroalbuminuria, n (%) ^b	341 (3.7)	22 (9.0)	41 (10.4)
Monofilament test, n (%)	512 (5.6)	17 (6.9)	35 (8.9)
Baseline medication			
Insulin use, n (%)	1220 (13.3)	34 (13.9)	92 (23.3)

SD, standard deviation; IQR, interquartile range.

* $P < 0.001$ for comparisons of proportions (or mean or median) with each characteristic across three groups, except for systolic blood pressure ($P = 0.002$) and monofilament test ($P = 0.02$).

^aCompared by Kruskal–Wallis test.

^bNormal albumin/creatinine ratio was < 2.5 for men and < 3.5 for women; microalbuminuria was ≥ 2.5 for men and ≥ 3.5 for women, and macroalbuminuria was > 25.0 for men and > 35.0 for women.

Table 5 Multivariate odds ratios for myocardial infarction (MI) compared with no MI for general characteristics, clinical history, laboratory data, and baseline medication among those having a first clinical or silent MI

Characteristic	Individual effect			P for heterogeneity
	MI type	Odds ratio (95% CI)	P-value	
Male	Clinical	1.38 (1.07–1.78)	0.01	0.37
	Silent	1.15 (0.85–1.57)	0.37	
Age (years)	Clinical	1.03 (1.02–1.05)	<0.001	0.60
	Silent	1.03 (1.01–1.05)	0.008	
Diabetes duration (years)	Clinical	0.99 (0.98–1.01)	0.48	0.12
	Silent	0.97 (0.95–0.99)	0.02	
Clinical history				
Prior CVD	Clinical	2.12 (1.71–2.64)	<0.001	0.14
	Silent	1.62 (1.22–2.17)	<0.001	
Diabetic neuropathy	Clinical	1.34 (1.04–1.73)	0.02	0.30
	Silent	1.07 (0.75–1.52)	0.72	
Laboratory data				
Haemoglobin A _{1c} (%)	Clinical	1.14 (1.06–1.23)	<0.001	0.17
	Silent	1.04 (0.94–1.16)	0.41	
Creatinine (μmol/L)	Clinical	1.01 (1.00–1.02)	0.009	0.25
	Silent	1.00 (0.99–1.01)	0.55	
Microalbuminuria ^a	Clinical	1.42 (1.12–1.80)	0.003	0.79
	Silent	1.35 (1.00–1.83)	0.05	
Macroalbuminuria ^a	Clinical	2.21 (1.53–3.20)	<0.001	0.68
	Silent	2.51 (1.56–4.03)	<0.001	
Baseline medication				
Insulin use vs. none	Clinical	1.42 (1.08–1.88)	0.01	0.23
	Silent	1.05 (0.70–1.59)	0.80	

^aNormal albumin/creatinine ratio was <2.5 for men and <3.5 for women; microalbuminuria was ≥2.5 for men and ≥3.5 for women, and macroalbuminuria was >25.0 for men and >35.0 for women.

Discussion

There was a low incidence of silent (2.7%) and clinical (4.1%) MI in this cohort over 5 years (with silent MIs making up 36.8% of all MIs), reflecting the low risk of the population recruited into the FIELD study. The Fremantle Diabetes Study of 1269 patients detected silent MI in 3.9% of patients, 43.9% of all MIs.³ The lower rates in the FIELD study may be due to a lower baseline risk profile or greater use of cardiovascular therapies, but the proportion of MIs that were silent remained high.

Most predictors of clinical MI also predicted silent MI, although the associations appeared more modest for silent events. Overall, the silent MI group had an intermediate risk profile between the no MI and clinical MI groups. Microalbuminuria is associated with silent coronary artery disease in people with type 1²¹ and type 2²² diabetes. It has been suggested that in patients over 60 years of age with type 1 or type 2 diabetes, autonomic neuropathy and other cardiovascular risk factors, such as development of microalbuminuria, should be screened for silent myocardial ischaemia.²³ The combination of microalbuminuria and silent ischaemia in patients with asymptomatic diabetes identifies a high-risk subgroup²⁴ who are likely to benefit from further investigation.²⁵

No risk factors, including neuropathy, preferentially predicted silent MI (compared with clinical MI). However, the causal association between diabetic autonomic neuropathy and silent MI has been challenged by some authors.² Furthermore, the Fremantle Diabetes Study showed no correlation between peripheral sensory neuropathy or other microvascular complications and silent MI.³ Peripheral neuropathy was also not implicated when type 2 diabetic patients were screened for silent myocardial ischaemia in two other studies.^{13,26}

All studies of silent MI have an inherent survival bias, in that to have a detectable silent MI the patient must survive the index event until the time of the surveillance ECG. This may partly explain the intermediate baseline risk profile of those experiencing silent MI and the lower rate of anterior silent MI, as patients at higher risk and those with large anterior MIs may be more likely to present clinically or not survive the event. Despite this potential bias, the risk of future CVD events in the FIELD study was very similar for those experiencing a silent MI and those with a clinical MI.

The high mortality rate after a clinical MI^{27,28} and after revascularization^{29,30} is well documented in patients with type 2 diabetes, but less well after a silent MI. This study shows that total mortality and cardiovascular mortality after silent MI is significantly higher

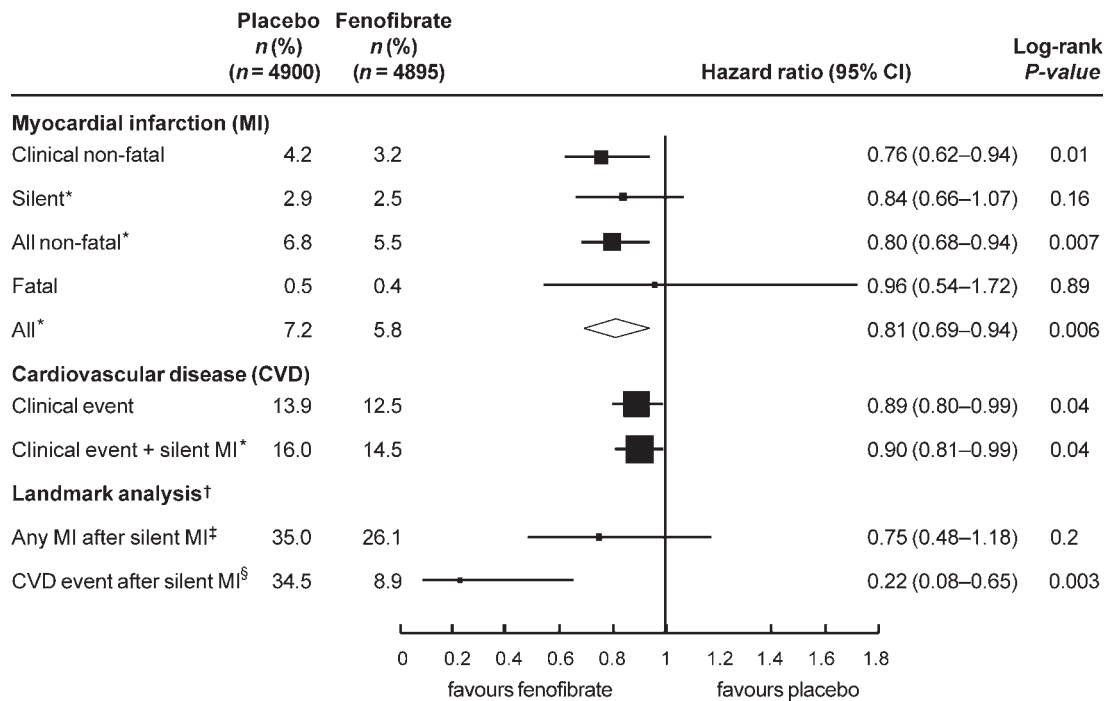


Figure 3 Effects of fenofibrate treatment on myocardial infarction and cardiovascular events. *Interval-censored proportional-hazards methods were used. †Analyses were landmarked at 2 years (see methods for details). ‡Placebo group, 48 events, $n = 137$; fenofibrate group, 30 events, $n = 115$. §Placebo group, 20 events, $n = 58$; fenofibrate group, 4 events, $n = 45$.

than for those who have not had an MI. Total mortality and cardiovascular mortality are not significantly different between those surviving a silent MI and those surviving a clinical MI. This confirms the findings of several large cohort studies, including the Framingham³¹ and Reykjavik studies,³² that silent and clinical MIs have a similar long-term prognosis.¹ This further emphasizes the importance of detection.

This study did not count non-Q wave infarctions. Criteria for retrospective diagnosis of non-Q wave MI are problematic, with ECG changes that are much less specific. As their MIs were silent, these patients would not have ECGs available from the period of such an event. In contrast, a Q wave infarction is regarded as a more important clinical event and can be adjudicated reliably. The low frequency of surveillance ECGs meant that the exact dates of silent MIs could not be identified, affecting our ability to definitively describe prognosis. There is evidence that Q waves can resolve with time,^{33,34} which could explain why the prevalence of silent MI was lower than in the Fremantle Diabetes Study, which employed yearly ECG screening.³ Many fatal FIELD cases lacked autopsy, precluding a diagnosis of fatal silent MI. Autonomic neuropathy was not formally tested and as such cannot be excluded as an important risk factor for silent MI.

In summary, in this large cohort of 9795 patients with type 2 diabetes, silent MI defined on a resting 12-lead ECG was an important clinical endpoint, identifying a group with intermediate baseline risk and high risk of future CVD events. Treatment with fenofibrate reduced not only the risk of a first MI but also the risk of

further CVD events after a silent MI. This study suggests that consideration of ECG screening for silent MI may be warranted in asymptomatic patients with type 2 diabetes to predict future cardiovascular events and to better identify those who might benefit from more aggressive risk screening and management, including fenofibrate therapy.

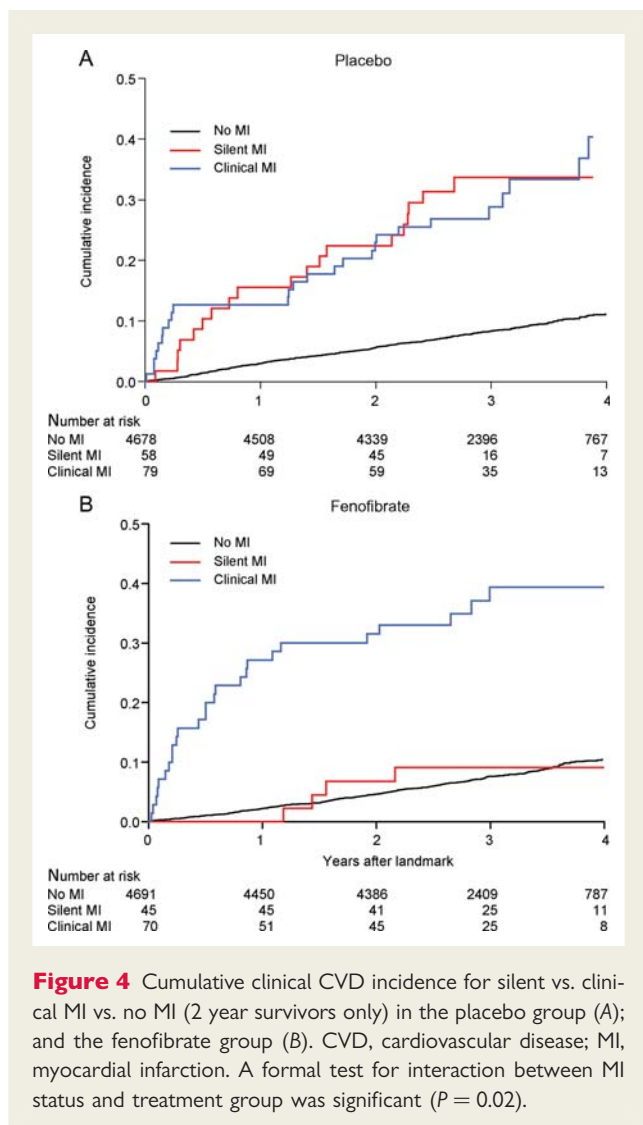
Acknowledgements

We thank the National Heart Foundation of Australia, Diabetes Australia, Diabetes New Zealand, and the Finnish Diabetes Association for endorsing the study. We thank W Liao and H Xu, who assisted in ECG reading. We also thank Dana Tse and Rhana Pike for assistance in preparing this manuscript and J.-C. Ansquer for comments; and the many patients, nurses, and contributors on whose behalf we present this paper.

Funding

This work was supported by Laboratoires Fournier SA, Dijon, France (main study sponsor) and the National Health and Medical Research Council (NHMRC) of Australia through grants to the NHMRC Clinical Trials Centre. The study was designed by an independent management committee, and was coordinated independently by the NHMRC Clinical Trials Centre, University of Sydney.

Conflict of interest: Some members of the writing committee (D.B., D.H., T.M.E.D., M.L., Y.A.K., S.L., S.M., and A.C.K.) have had the costs of participating in scientific meetings and/or contributing to advisory



boards or doing other research reimbursed by the pharmaceutical industry.

References

- Sheifer SE, Manollo TA, Gersh BJ. Unrecognized myocardial infarction. *Ann Intern Med* 2001;**135**:801–811.
- Airaksinen KE. Silent coronary artery disease in diabetes—a feature of autonomic neuropathy or accelerated atherosclerosis? *Diabetologia* 2001;**44**:259–266.
- Davis TM, Fortun P, Mulder J, Davis WA, Bruce DG, Fremantle Diabetes Study. Silent myocardial infarction and its prognosis in a community-based cohort of Type 2 diabetic patients: the Fremantle Diabetes Study. *Diabetologia* 2004;**47**:395–399.
- Valensi P, Paries J, Brulport-Cerisier V, Torremocha F, Sachs R, Vanzetto G, Cosson E, Lormeau B, Attali J, Marechaud R, Estour B, Halimi S. Predictive value of silent myocardial ischemia for cardiac events in diabetic patients: influence of age in a French multicenter study. *Diabetes Care* 2005;**28**:2722–2727.
- Sejil S, Janand-Delenne B, Avierinos J, Habib G, Labastie N, Raccach D, Vague P, Lassmann-Vague V. Six-year follow-up of a cohort of 203 patients with diabetes after screening for silent myocardial ischaemia. *Diabet Med* 2006;**23**:1186–1191.
- Aguilar D, Goldhaber SZ, Gans DJ, Levey AS, Porush JG, Lewis JB, Rouleau J, Berl T, Lewis EJ, Pfeffer MA, Collaborative Study Group. Clinically unrecognized Q-wave myocardial infarction in patients with diabetes mellitus, systemic hypertension, and nephropathy. *Am J Cardiol* 2004;**94**:337–339.

- Araz M, Celen Z, Akdemir I, Okan V. Frequency of silent myocardial ischemia in type 2 diabetic patients and the relation with poor glycemic control. *Acta Diabetol* 2004;**41**:38–43.
- Fornengo P, Bosio A, Epifani G, Pallisco O, Mancuso A, Pascale C. Prevalence of silent myocardial ischaemia in new-onset middle-aged Type 2 diabetic patients without other cardiovascular risk factors. *Diabetic Med* 2006;**23**:775–779.
- Gokcel A, Aydin M, Yalcin F, Yapar AF, Ertorer ME, Ozsahin AK, Muderrisoglu H, Aktas A, Guvener N, Akbaba M. Silent coronary artery disease in patients with type 2 diabetes mellitus. *Acta Diabetol* 2003;**40**:176–180.
- Kannel WB. Prevalence and clinical aspects of unrecognized myocardial infarction and sudden unexpected death. *Circulation* 1987;**75**:114–115.
- May O, Arildsen H, Damsgaard E, Mickley H. Prevalence and prediction of silent ischaemia in diabetes mellitus: a population-based study. *Cardiovasc Res* 1997;**34**:241–247.
- Moller CS, Byberg L, Sundstrom J, Lind L. T wave abnormalities, high body mass index, current smoking and high lipoprotein (a) levels predict the development of major abnormal Q/QS patterns 20 years later. A population-based study. *BMC Cardiovasc Disord* 2006;**6**:10.
- Naka M, Hiramatsu K, Aizawa T, Momose A, Yoshizawa K, Shigematsu S, Ishihara F, Niwa A, Yamada T. Silent myocardial ischemia in patients with non-insulin-dependent diabetes mellitus as judged by treadmill exercise testing and coronary angiography. *Am Heart J* 1992;**123**:46–53.
- Rosenman RH, Friedman M, Jenkins CD, Strus R, Wurm M, Kositchek R. Clinically Unrecognized Myocardial Infarction in the Western Collaborative Group Study. *Am J Cardiol* 1967;**19**:771–775.
- Tarkun I, Cetinarlan B, Canturk Z, Tarkun P, Agacdiken A, Komsuoglu B. Homocysteine concentrations in type 2 diabetic patients with silent myocardial ischemia A predictive marker. *J Diabetes Complicat* 2004;**18**:165–168.
- Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;**366**:1849–1861.
- Blackburn H, Keys A, Simonson E, Rautaharju PM, Punsar S. The electrocardiogram in population studies. A classification system. *Circulation* 1960;**21**:1160–1175.
- Marubini E, Valsecchi MG. *Analysing Survival Data from Clinical Trials and Observational Studies*. Chichester: Wiley; 1995.
- Hosmer D, Lemeshow S. *Applied Survival Analysis Regression Modelling of Time to Event Data*. New York: Wiley; 1999.
- Rothman KJ. No adjustments are needed for multiple testing. *Epidemiology* 1990;**1**:43–46.
- Earle KA, Mishra M, Morocutti A, Barnes D, Stephens E, Chambers J, Viberti GC. Microalbuminuria as a marker for silent myocardial ischemia in IDDM patients. *Diabetologia* 1996;**39**:854–856.
- Rutter MK, McComb JM, Brady S, Marshall SM. Silent myocardial ischemia and microalbuminuria in asymptomatic subjects with non-insulin-dependent diabetes mellitus. *Am J Cardiol* 1999;**83**:27–31.
- Chico A, Tomas A, Novials A. Silent myocardial ischemia is associated with autonomic neuropathy and other cardiovascular risk factors in type 1 and type 2 diabetic subjects, especially in those with microalbuminuria. *Endocrine* 2005;**27**:213–217.
- Rutter MK, Wahid ST, McComb JM, Marshall SM. Significance of silent ischemia and microalbuminuria in predicting coronary events in asymptomatic patients with type 2 diabetes. *J Am Coll Cardiol* 2002;**40**:56–61.
- Doubell AF. Managing the asymptomatic diabetic patient with silent myocardial ischaemia. *Cardiovasc J S Afr* 2002;**13**:189–193.
- Bacci S, Vilella M, Vilella A, Langialonga T, Grilli M, Rauseo A, Mastroianni S, De Cosmo S, Fanelli R, Trischitta V. Screening for silent myocardial ischaemia in type 2 diabetic patients with additional atherogenic risk factors: applicability and accuracy of the exercise stress test. *Eur J Endocrinol* 2002;**147**:649–654.
- Koek HL, Soedamah-Muthu SS, Kardaun JWPF, Gevers E, de Bruin A, Reitsma JB, Bots ML, Grobbee DE. Short- and long-term mortality after acute myocardial infarction: comparison of patients with and without diabetes mellitus. *Eur J Epidemiol* 2007;**22**:883–888.
- Norhammar A, Lindbäck J, Rydén L, Wallentin L, Steneström U, on behalf of the Register of Information Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA). Improved but still high short- and long-term mortality rates after myocardial infarction in patients with diabetes mellitus: a time-trend report from the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission. *Heart* 2007;**93**:1577–1583.
- Wilson SR, Sanborn TA, Vakili BA, Brown DL, Sherman W. Effect of diabetes on long-term mortality following contemporary percutaneous coronary intervention. *Diabetes Care* 2004;**27**:1137–1142.

30. Leavitt BJ, Sheppard L, Maloney C, Clough RA, Braxton JH, Charlesworth DC, Weintraub RM, Hernandez F, Olmstrad EM, Nugent WC, O'Connor GT, Ross CS, and for the Northern New England Cardiovascular Disease Study Group. Effect of diabetes and associated conditions on long-term survival after coronary artery bypass graft surgery. *Circulation* 2004;**110**:II-41–II-44.
31. Kannel WB, Sorlie P, McNamara PM. Prognosis after initial myocardial infarction: the Framingham study. *Am J Cardiol* 1979;**44**:53–59.
32. Sigurdsson E, Thorgeirsson G, Sigvaldason H, Sigfusson N. Unrecognized myocardial infarction: epidemiology, clinical characteristics, and the prognostic role of angina pectoris: the Reykjavik Study. *Ann Intern Med* 1995;**122**:96–102.
33. Marcus EB, Yano K, MacLean CJ. Regression of Q waves following acute myocardial infarction. *Am J Epidemiol* 1989;**129**:105–111.
34. Sztajzel J, Urban P. Early and late Q wave regression in the setting of acute myocardial infarction. *Heart* 2000;**83**:708–710.