Secondary Prevention of Cardiovascular Events With Long-Term Pravastatin in Patients With Diabetes or Impaired Fasting Glucose

Results from the LIPID trial

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OBJECTIVE — Diabetes, a major health problem worldwide, increases the risk of cardiovascular disease and its associated mortality. Evidence of the overall benefits of lipid modification in this area is needed.

RESEARCH DESIGN AND METHODS — The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial showed that cholesterol-lowering treatment with pravastatin reduced mortality and coronary heart disease (CHD) events in 9,014 patients aged 31–75 years with CHD and total cholesterol 4.0–7.0 mmol/l. We measured the effects of pravastatin therapy, 40 mg/day over 6.0 years, on the risk of CHD death or nonfatal myocardial infarction and other cardiovascular outcomes in 1,077 LIPID patients with diabetes and 940 patients with impaired fasting glucose (IFG).

RESULTS — In patients allocated to placebo, the risk of a major CHD event was 61% higher in patients with diabetes and 23% higher in the IFG group than in patients with normal fasting glucose, and the risk of any cardiovascular event was 37% higher in the diabetic group and 19% higher in the IFG group. Pravastatin therapy reduced the risk of a major CHD event overall from 15.9 to 12.3% (relative risk reduction [RRR] 24%, $P < 0.001$) and from 23.4 to 19.6% in the diabetic group (19%, $P = 0.11$); in the diabetic group, the reduction was not significantly different from the reductions in the other groups. Pravastatin reduced the risk of any cardiovascular event from 52.7 to 45.2% (21%, $P < 0.008$) in patients with diabetes and from 45.7 to 37.1% (26%, $P = 0.003$) in the IFG group. Pravastatin reduced the risk of stroke from 9.9 to 6.3% in the diabetic group (RRR 39%, CI 7–61%, $P = 0.02$) and from 5.4 to 3.4% in the IFG group (RRR 42%, CI −9 to 69%, $P = 0.09$). Pravastatin did not reduce the incidence of diabetes. Over 6 years, pravastatin therapy prevented one major CHD event (CHD death or nonfatal myocardial infarction) in 23 patients with IFG and 18 patients with diabetes. A meta-analysis of other major trials confirmed the high absolute risks of diabetes and IFG and the absolute benefits of statin therapy in these patients.

CONCLUSIONS — Cholesterol-lowering treatment with pravastatin therapy prevents cardiovascular events, including stroke, in patients with diabetes or IFG and established CHD.

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Diabetes is the most common endocrine disorder worldwide, with an estimated prevalence of 140 million adults in 1997 (1). As many adults have an elevated fasting glucose level, or impaired fasting glucose (IFG) (2,3), which is not a clinical entity but a risk factor for future development of diabetes and macrovascular disease. Cardiovascular disease complications are now the leading causes of morbidity and mortality in people with diabetes (4). Diabetes increases the risk of developing cardiovascular disease up to fivefold, and as many as 80% of patients with type 2 diabetes die from cardiovascular complications. This high risk is not completely explained by traditional risk factors (5,6). IFG is also associated with cardiovascular disease (7,8), but it is unclear whether it is an independent risk factor because it commonly coexists with other cardiovascular risk factors present in the metabolic syndrome.

The hope that controlling blood glucose will substantially reduce the macrovascular complications of diabetes has not been realized in clinical trials (9,10), although rates of microvascular complications have been significantly reduced (9). Patients with diabetes also have poorer outcomes after an acute macrovascular event (11,12), so the role of other therapies, such as lipid lowering, in preventing further vascular disease in diabetes needs to be defined.

Two recent trials of cholesterol-lowering therapy, using hydroxymethylglutaryl (HMG)-CoA reductase

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Abbreviations: 4S, Scandinavian Simvastatin Survival Study; AFG, abnormal fasting glucose; CARE, Cholesterol and Recurrent Events trial; CHD, coronary heart disease; HMG, hydroxymethylglutaryl; HPS, Heart Protection Study; IFG, impaired fasting glucose; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease; NFG, normal fasting glucose; RRR, relative risk reduction; WOSCOPS, West of Scotland Coronary Prevention Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

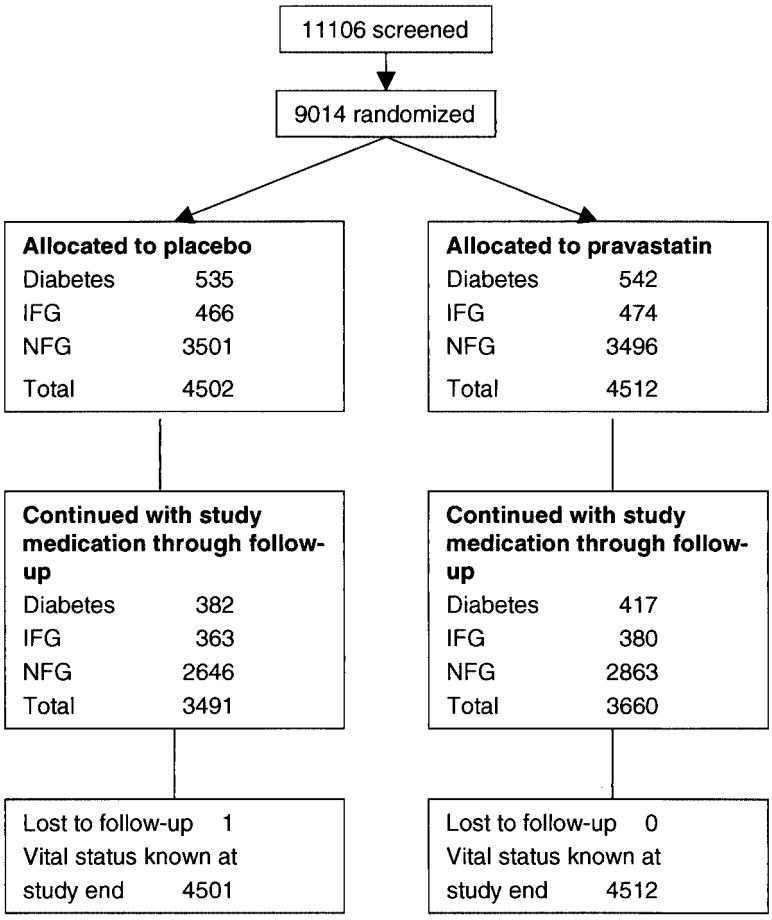

Figure 1—*Numbers of patients in the LIPID study by baseline glucose status. During the trial, 23.8% of patients on placebo commenced cholesterol-lowering therapy.*

inhibitors, in people with established coronary heart disease (CHD) have reported clinically important treatment benefits in patients with diabetes. The Scandinavian Simvastatin Survival Study (4S) reported a 42% lower rate of major CHD events (CHD death or nonfatal myocardial infarction) among patients with diabetes randomized to 20–40 mg simvastatin daily than in those on matching placebo (12). The 483 patients with clinical diabetes all had elevated total cholesterol levels (mean 6.7 mmol/l), which is well above average population levels. In the Cholesterol and Recurrent Events trial (CARE), which included 586 patients with diabetes, treatment with pravastatin reduced the relative risk of coronary events (CHD death, nonfatal myocardial infarction, and revascularization) by 25% (13). The mean cholesterol level of 5.3 mmol/l in this group was closer to the average level of the general population.

The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial showed that coronary and total mortality were significantly reduced by long-term pravastatin therapy among 9,014 patients with prior myocardial infarction or unstable angina when compared with placebo (14). The LIPID study included more patients with diabetes and more patients with IFG than the previous studies of HMG-CoA reductase inhibitors, providing an opportunity to study their response to treatment. The results from the three major trials (LIPID, 4S, and CARE) provided an opportunity to also explore the results from a larger number of patients with diabetes by meta-analysis. In CARE, the same dose of pravastatin was used and patients were similar; in 4S, 20–40 mg/day of simvastatin was used in patients with prior CHD but above-average cholesterol levels (5.5–8.0 mmol/l).

In this LIPID substudy, we aimed to measure the effects of pravastatin therapy on major CHD events (CHD death or nonfatal myocardial infarction) in patients with diabetes or IFG. Secondary outcomes for this substudy were cardiovascular death, death from any cause, CHD death, revascularization, stroke, and an expanded end point: CHD death, nonfatal myocardial infarction, hospitalization for unstable angina, stroke, or revascularization by coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty.

RESEARCH DESIGN AND METHODS

— The study design has been described previously (14,15). People who were 31–75 years of age and had suffered a myocardial infarction or hospital admission for unstable angina 3–36 months before registration were eligible for the LIPID trial if plasma total cholesterol was 4.0–7.0 mmol/l and fasting triglycerides <5.0 mmol/l. Patients were screened in 87 centers in Australia and New Zealand. After an 8-week placebo run-in phase, 9,014 patients were randomly allocated to receive pravastatin 40 mg daily or matching placebo. Analysis of the results in the subgroup of patients with diabetes was prespecified in the protocol. It was later decided to also present the results of the treatment effects in the diabetic and IFG groups combined because both conditions represent different stages of the same disease process and the larger number of events allowed more reliable comparisons. The prespecified primary outcome for all LIPID trial subgroup analyses was death from CHD or nonfatal myocardial infarction (combined).

Patients with abnormal glucose levels

All patients were asked at the first screening whether they had ever been diagnosed with diabetes. The present American Diabetes Association cut points for the diagnosis of diabetes and for IFG were used to classify the subgroups according to a single fasting venous plasma glucose level measured at baseline (Fig. 1) (3). The availability of a single glucose measurement was considered adequate for epidemiological purposes at the time the study commenced, although not for the clinical diagnosis of diabetes. This may have resulted in some misclassification between groups, but this would have been nondifferential, resulting in more conservative estimates of differences between groups in risks and effects of treatment.

Table 1—*Baseline characteristics of 9,014 patients in the LIPID study by glucose status*

Characteristic	Diabetes	IFG	NFG
n	1,077	940	6,997
Age (years)	64 (57–68)	63 (55–67.5)	62 (55–67)
Age-group (years)			
≥65	45	40	38
Sex			
Female	19	15	17
Qualifying event			
Myocardial infarction	63	62	64
Unstable angina	37	38	36
Coronary risk factors			
Current smoker	9	11	9
History of hypertension	52	46	39
Obesity	32	25	15
Other vascular disease			
Claudication	15	10	9
History of stroke	6	6	3
Drug use			
Insulin	10	0	0
Oral hypoglycemic	38	0	0

Data are percent of median (interquartile range). *The differences in the proportions among the three groups were significant (χ^2 test for heterogeneity $P < 0.05$) for all baseline characteristics.

Patients who identified themselves as having diabetes (782 patients [8.7%]) and the 295 (3.3%) patients with probable undiagnosed diabetes (fasting plasma glucose ≥7.0 mmol/l) constituted the diabetic group (1,077 patients [11.9%]). Of the patients without diabetes, 940 (10.4%) were classified as having probable IFG (fasting plasma glucose 6.1–6.9 mmol/l) and 6,997 (77.6%) as having normal fasting glucose (NFG; fasting plasma glucose ≤6.0 mmol/l). Of those classified as having diabetes, 28 of 1,077 (2.6%) had type 1 diabetes. Metformin treatment was being taken by 136 patients and sulfonylureas by 358, of whom 84 were receiving both. Patients with no history of diabetes and who provided no baseline plasma glucose measurement (23 [0.3%]) were considered to have NFG to ensure conservative estimates in the analyses. In total, 2,017 patients (22.4%) showed glucose metabolism abnormalities at entry to the study; 1,001 were assigned to placebo and 1,016 to active treatment (Fig. 1).

Lipid measurements and management

Plasma cholesterol levels were measured by the core laboratory at baseline, 6 months later, yearly from baseline, and at study end. Fasting HDL cholesterol and triglyceride levels were measured at baseline, 1, 3, and 5 years later, and at study end. LDL cholesterol was estimated indirectly using the Friedewald formula (16). Apolipoprotein B levels were also measured at baseline and after 1, 3, and 5 years.

The study personnel and the patients remained blinded to the on-trial lipid results. The patients' usual care, including other cholesterol-lowering treatment, continued to be under the direction of their own doctors. The results of the other large-scale trials of HMG-CoA reductase inhibitors (17–19) were communicated to the patients and their doctors, with further clarification that open-label cholesterol-lowering therapy could be commenced if this was found necessary. Compliance with study medication, any hospital admissions, serious adverse events, and study outcomes were monitored at routine 6-month clinic visits.

Classification and review of outcomes

The Outcomes Assessment Committee or the Stroke Adjudication Committee, which was blinded to each patient's study treatment, reviewed all deaths, myocardial infarctions, and strokes. An independent safety and data monitoring committee monitored progress. The trial was planned to continue until 700 CHD deaths had occurred, unless the trial was stopped early following an interim analysis showing a difference of at least 3 SDs in all-cause mortality or serious adverse events associated with pravastatin treatment (15). The trial was conceived, managed, and analyzed independently of the sponsor. All patients gave written informed consent, and the ethics committee for each participating center approved the trial.

Statistical analysis

All analyses were performed on an intention-to-treat basis. All *P* values were unadjusted for multiple comparisons. Statistical significance was determined at $P < 0.05$ (two tailed). Time-to-event analyses used the log-rank test stratified by qualifying event (20). Estimates of relative risk reduction (RRR) and 95% CIs were derived from the Cox proportional hazards model (21). In analyses, patients with diabetes or IFG were considered as separate groups and also as a single group with abnormal fasting glucose (AFG). The variation in the effect of pravastatin among the fasting glucose subgroups was evaluated using the interaction in a Cox model. The number needed to treat was calculated in all cases using the common RRR for the whole cohort and may be unreliable for some individual groups. The meta-analysis used published data with odds ratios and a fixed-effects model (22).

RESULTS

Clinical characteristics and lipid levels

Patients with diabetes were older and more often obese than patients with NFG, and the diabetic group included more women and more patients with a history of hypertension, claudication, stroke, and transient ischemic attack (Table 1). Therapy with calcium-channel antagonists, ACE inhibitors, nitrates, and diuretics were all more common in the diabetic group. In the IFG group, these characteristics and the levels of drug use were intermediate. Balance in important prognostic variables between those allocated to pravastatin and those allocated to placebo was excellent (14).

The three groups differed in baseline lipid levels (all $P < 0.001$). Fasting levels of total cholesterol, and HDL and LDL cholesterol were lower in the diabetic

Table 2—*Baseline serum lipid and glucose levels (mmol/l) by glucose status*

Lipid	Diabetes	IFG	NFG
n	1,077	940	6,997
Total cholesterol	5.56 (4.98–6.10)	5.62 (5.09–6.27)	5.67 (5.09–6.22)
LDL cholesterol	3.70 (3.16–4.20)	3.80 (3.33–4.38)	3.91 (3.42–4.43)
HDL cholesterol	0.86 (0.75–1.01)	0.90 (0.78–1.04)	0.93 (0.80–1.09)
Triglycerides	1.90 (1.36–2.69)	1.72 (1.26–2.40)	1.53 (1.14–2.08)
Total/HDL cholesterol ratio	6.41 (5.38–7.53)	6.26 (5.21–7.36)	6.03 (5.09–7.05)
Apolipoprotein B	1.35 (1.19–1.53)	1.34 (1.18–1.52)	1.32 (1.16–1.49)
Fasting glucose	7.7 (6.9–9.4)	6.3 (6.2–6.6)	5.2 (4.9–5.5)

Data are median (interquartile range).

group, whereas triglyceride levels were higher (Table 2). Lipid levels of those with IFG were intermediate.

Effect of pravastatin treatment on blood lipids

The responses of blood lipids to pravastatin were very similar in all three groups with the exception of triglycerides, for which levels fell most in the diabetic group (Fig. 2). Apolipoprotein B levels, which reflect the total number of atherogenic lipoprotein particles and predict the risk of fatal myocardial infarction (23,24), fell by a similar proportion in the three groups.

The percentages of patients who permanently discontinued the study medication were significantly different in the three groups: 18% for NFG, 20% for IFG, and 23% for the diabetic group ($P = 0.006$). Prescription of active lipid-lowering therapy for those allocated to placebo increased progressively over time, which contributed to a 5% fall from baseline in mean blood cholesterol by study end. In the placebo group, 23% with diabetes, 22% with IFG, and 24% with NFG, respectively, dropped in to cholesterol-lowering medication. Patients withdrew from study medication over a similar time course; the observed difference in total cholesterol with pravastatin treatment fell from 21% at 1 year to 18% at 5 years.

Cardiovascular event rates by glucose status

In patients allocated to placebo, event rates were higher in those with diabetes than in the other groups (Figs. 3 and 4). For patients with diabetes compared with patients with NFG, the absolute excess risks were 8.9% for CHD death or nonfatal myocardial infarction and 6.3% for stroke, although their baseline cholesterol levels were similar. The risk of any cardiovascular event was 1.4 times (95% CI 1.3–1.5) the risk for those with NFG.

In placebo patients with IFG, the absolute excess risks were 3.3% for CHD death or nonfatal myocardial infarction and 1.8% for stroke. The risk of any cardiovascular event was 1.2 times (95% CI 1.1–1.3) the risk for those with NFG.

Cardiovascular event rates and pravastatin

Allocation to pravastatin was associated with lower observed risks of all major cardiovascular end points for all three patient groups (Figs. 3 and 4). For most end points, RRRs were similar, but the measured reductions in absolute risk associated with pravastatin treatment were greater among those with diabetes and IFG than in those with NFG. Despite pravastatin treatment, the event rates for these outcomes among patients with diabetes were mostly higher than among those with NFG allocated to placebo. In contrast, for all end points, those with IFG allocated to pravastatin had lower event rates than patients with NFG allocated to placebo.

For the primary combined outcome of CHD death or nonfatal myocardial infarction, pravastatin therapy reduced the risk among all patients from 15.9 to 12.3% (RRR 24%, $P < 0.001$). In patients with diabetes, the RRR was 19% (23.4 vs. 19.6%, $P = 0.11$) compared with 23% (14.5 vs. 11.3%, $P < 0.001$) in the NFG group. The RRR in the IFG group was 36% (17.8 vs. 11.8%, $P = 0.009$); these treatment effects were not significantly different from one another (test for interaction, $P = 0.53$) (Fig. 3). The absolute risk was larger in the diabetic group (23.4%) than in the NFG group (14.5%), so the estimated number needed to treat to prevent one event, based on the common risk reduction, was lower in the diabetic group ($n = 18$) than in the NFG group ($n = 29$).

Pravastatin reduced the risk of stroke from 9.9 to 6.3% in the diabetic group (RRR 39%, CI 7–61%, $P = 0.02$) and from 5.4 to 3.4% in the IFG group (42%, CI −9 to 69%, $P = 0.09$). Pravastatin therapy thus reduced the absolute risk of stroke by 3.6% in the diabetic group and by 2.0% in the IFG group, compared with only 0.2% in the NFG group. A similar trend was seen for the expanded end point (any major cardiovascular event) and for coronary revascularization procedures.

Among all patients with AFG (diabetes and IFG combined), the increased numbers of events resulted in statistically significant

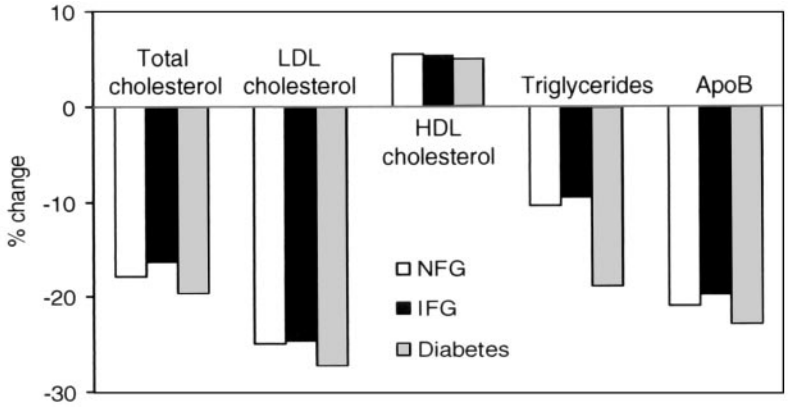

Figure 2—*Changes in blood lipid levels with pravastatin therapy compared with placebo over 5 years in subgroups by glucose status in the LIPID study. ApoB, apolipoprotein B.*

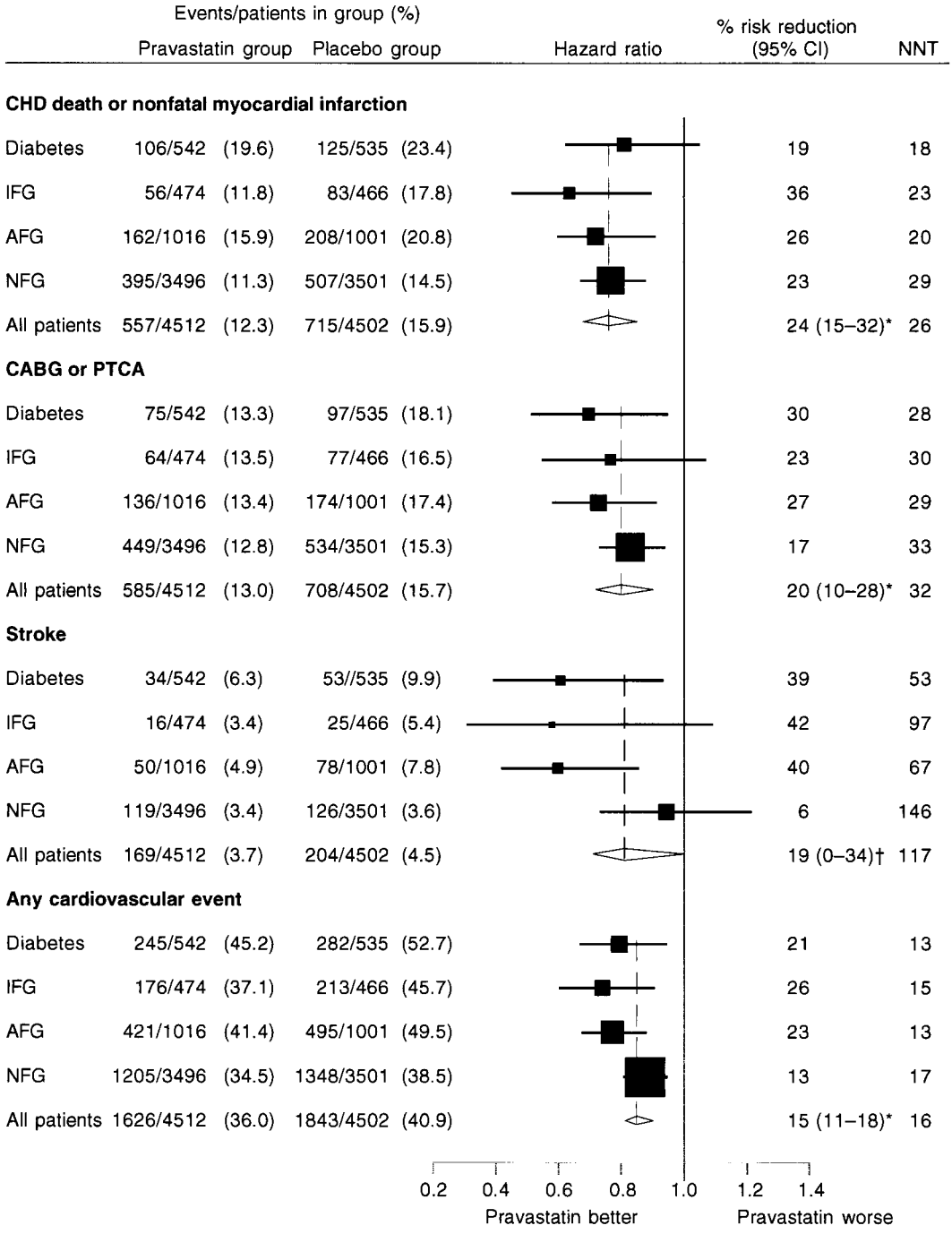

Figure 3—*Effects of pravastatin on cardiovascular end points over a median of 6 years by glucose status. RRRs were derived from the Cox proportional hazards model.* P *for heterogeneity between end points = 0.7, within end points = 0.4. The lines show 95% CIs for each glucose group and the diamonds show 95% CIs for all patients. CABG, coronary artery bypass grafting; NNT, number needed to treat (based on the common RRR for the whole cohort); PTCA, percutaneous transluminal coronary angioplasty.* *P $<$ *0.001;* †P = *0.048.*

reductions in major coronary events, stroke, and cardiovascular events, suggesting that separately nonsignificant results for these outcomes for the diabetic and IFG groups related to statistical power rather than an absence of benefit (Fig. 3).

Development of new diabetes during follow-up

Of the 6,997 patients with NFG at study entry, over the mean 6.0 years of follow-up, 264 patients (3.8%) developed diabetes, as evidenced by a fasting blood glucose level of ≥7 mmol/l or reported use of oral hypoglycemic medication or insulin. There was no apparent effect of pravastatin on the development of new diabetes: 138 (4.5%) of the survivors among those allocated to placebo and

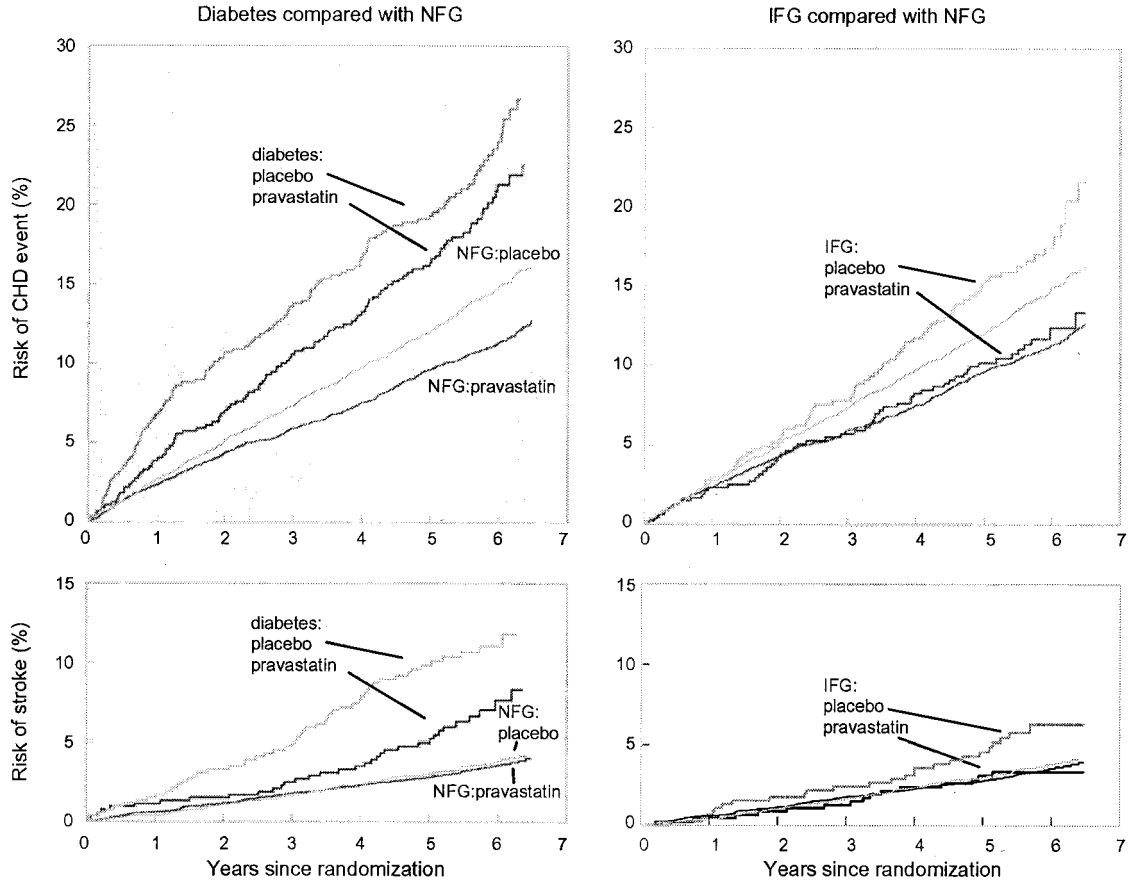

Figure 4—*Kaplan-Meier plots showing the effects of pravastatin on CHD events (CHD death or nonfatal myocardial infarction) and stroke by glucose status.*

126 (4.0%) of the survivors allocated to pravastatin developed diabetes (P = 0.32). In the IFG group, 9.2% of the placebo group survivors and 9.7% of the pravastatin group survivors developed diabetes.

Meta-analysis of secondary prevention trials

A total of 2,782 major coronary events (coronary death or nonfatal myocardial infarction) occurred among 17,445 individuals with recorded glucose status during scheduled follow-up in LIPID, CARE, and 4S combined, and 499 strokes among 13,046 individuals with recorded glucose status in LIPID and CARE combined (stroke results for 4S by glucose status were not found in the published literature). Large, clinically important reductions were seen in major coronary events in all glucose groups. Long-term allocation to statin therapy reduced coronary events by 28% overall in diabetes (P = 0.001), 39% in IFG ($P < 0.0001$), and 29% in NFG ($P < 0.0001$) without evidence of statistical heterogeneity ($P > 0.15$) between individual study results within any category of glucose status (Fig. 5).

Statin therapy reduced stroke events by 32% (P = 0.04) overall in diabetes, 39% in IFG (P = 0.08), and 15% in NFG (P = 0.1) without evidence of statistical heterogeneity ($P > 0.4$) between study results. For both outcomes, the absolute event rate in the placebo groups was substantially higher among those with diabetes than those with IFG, with the lowest rate observed in those with NFG, which is consistent with the results of the LIPID study.

CONCLUSIONS — The LIPID study confirms that patients with a history of myocardial infarction or unstable angina and diabetes or IFG have a substantially higher risk of cardiovascular events. The risk of a major coronary event (CHD death or nonfatal myocardial infarction) for placebo patients with clinically diagnosed diabetes in the LIPID study was 1.6 times that of patients with NFG, compared with ~1.8 times in CARE or 4S (12,13). For patients with IFG on placebo in the LIPID study, the risk of a major coronary event was 1.2 times that of patients with NFG (a significant difference) compared with nearly 1.2 times in 4S and nearly 1.3 times in CARE.

Treatment with pravastatin conferred clinical benefits across all groups, but in those with IFG or diabetes, the absolute risk reductions were greater. For example, over 6 years, preventing a single death from any cause would require treating 39 patients with NFG but only 23 patients with IFG or diabetes. Preventing one CHD death or myocardial infarction would require treating 29 patients with NFG compared with 20 patients with IFG or diabetes. Treating 33 patients with NFG or 29 patients with IFG or diabetes would prevent one revascularization procedure.

Together with the other major stud-

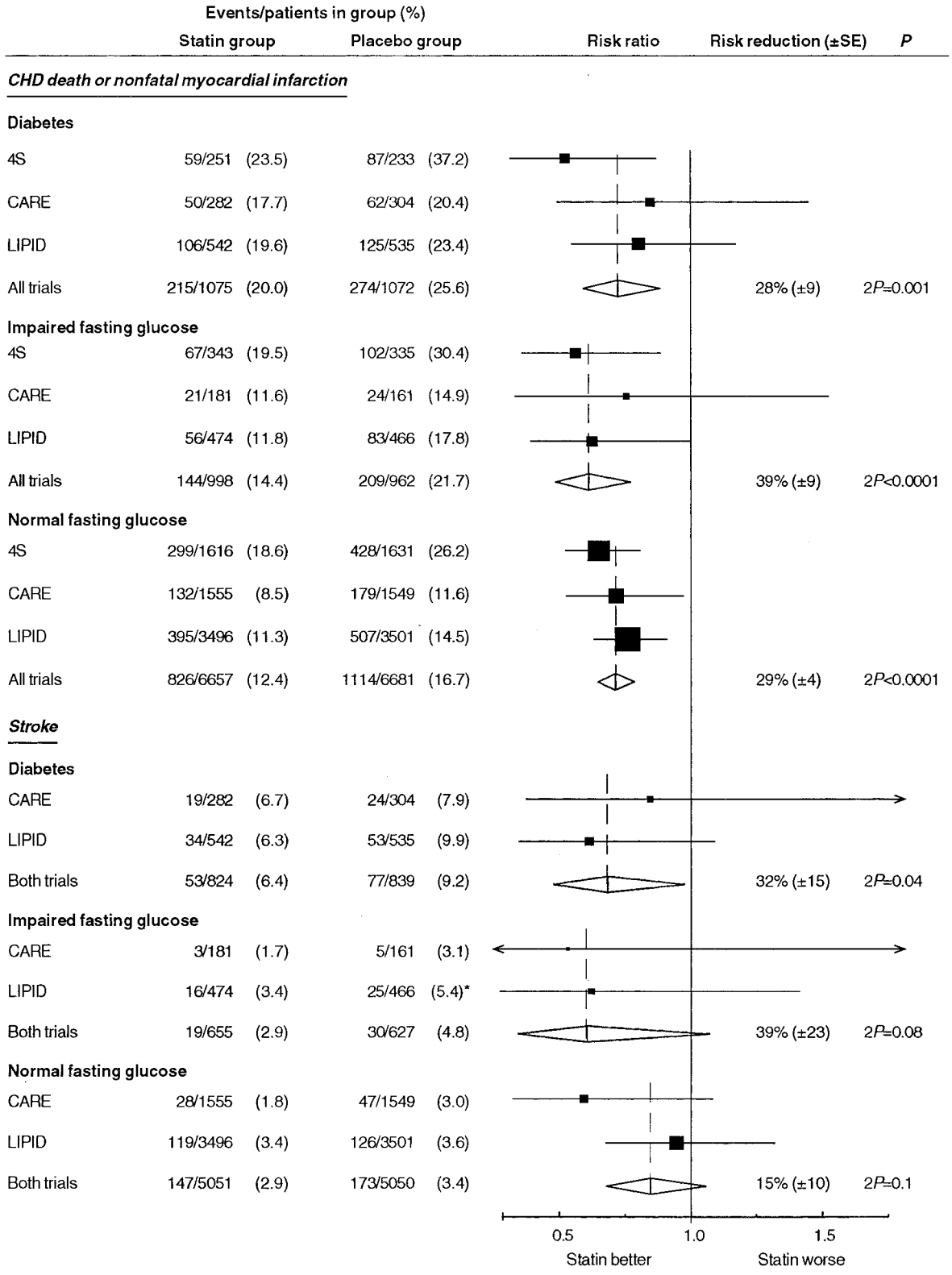

Figure 5—*Meta-analysis of CHD secondary-prevention trials of effects of statin therapy in patients with a history of diabetes and patients with IFG or NFG: effects of statin drugs on CHD end points. Risk reductions and SEs were calculated using a fixed-effects model.*

ies, LIPID provides clear evidence for the benefits of treatment with an HMG-CoA reductase inhibitor for secondary prevention of CHD in patients with diabetes or IFG. Meta-analysis of data from 4S, CARE, and LIPID supports the findings of LIPID alone with regard to coronary events and stroke. The baseline levels of plasma cholesterol were 4.0–7.0 mmol/l in LIPID (14), very similar in CARE (13), and 5.5–8.0 mmol/l in 4S (17), so the findings are applicable across a wide range of cholesterol levels, covering nearly all patients with diabetes and CHD seen in clinical practice.

The effects of pravastatin therapy in reducing stroke in diabetes are also especially important. The rates of stroke were substantially higher among those with diabetes and IFG, and treatment was more effective in these groups than in the group with NFG.

An unexpected outcome of the West of Scotland Coronary Prevention Study (WOSCOPS), a study of primary prevention with pravastatin, was a 30% reduction with pravastatin in the risk of developing diabetes during the study (25). Triglyceride-lowering or anti-inflammatory properties of pravastatin were postulated as a possible mechanism. In LIPID, the pravastatin and placebo groups did not differ in the rates at which they developed diabetes. The studies were of similar size, but LIPID had an older cohort with a median age of 62 years (14); the mean age in WOSCOPS was 55 years (18). In LIPID, 17% of the patients were women, whereas WOSCOPS only studied men. Finally, subjects in LIPID had clinical evidence of prior CHD, but those in WOSCOPS did not. However, the recently completed U.K. Heart Protection Study (HPS) (26) also reported no effect of statin therapy on the development of diabetes in a wide range of patients. Only 139 patients developed diabetes in WOSCOPS, suggesting that this finding could be plausibly related to random imbalances at baseline.

The worldwide prevalence of diabetes is expected to double between 1997 and 2010 (27). This prediction has led the World Health Organization to identify diabetes as one of the three largest health problems to be tackled globally at the start of this millennium. The meta-analysis (Fig. 5) presents strong evidence of the benefit of cholesterol-lowering therapy with statins for patients with prior CHD and diabetes or IFG. The HPS findings of a 17% reduction in major CHD events and a 27% reduction in major cardiovascular events with simvastatin in patients with prior CHD and diabetes support our results (26). The HPS further extends the findings to people with diabetes without prior cardiovascular disease, showing a similar proportional risk reduction in people at lower absolute risk. In the HPS, however, fasting blood glucose was not measured at baseline, so this study offers no additional information about patients with IFG, with or without vascular disease.

Two further studies that included people with diabetes have recently been published, but so far neither has reported results for people with IFG. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA) was terminated early after 3.3 of 5 years' scheduled follow-up, reporting an overall 36% (CI 17–50%, $P < 0.001$) reduction in coronary events with 10 mg atorvastatin daily. There was, however, only a nonsignificant trend to fewer primary end point events among 2,532 people with diabetes (28). In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT), allocation to pravastatin 40 mg daily resulted in an average difference in cholesterol levels of only 9.6%, owing to free use of statins in the control (usual-care arm), and resulted in no significant reduction in events overall or separately in the 3,638 people in the diabetic group (29). A third study, the Collaborative Atorvastatin Diabetes Study (CARDS) (30), recently concluded early, apparently because of significant benefits of atorvastatin 10 mg daily on a composite cardiovascular end point in >2,800 people with diabetes at high risk for, but with no prior, clinical coronary disease (H.A.W. Neil, personal communication).

Because patients with diabetes and established CHD have a high absolute risk of further events, substantial and prolonged reductions in their blood cholesterol levels are imperative. With pravastatin therapy, their RRR is similar to that of patients without diabetes but their absolute risk reduction is greater, so the number needed to treat to reduce cardiovascular events is less and, therefore, the cost-effectiveness of therapy is greater (31). The LIPID study reliably confirms that for patients with established CHD, the absolute benefits of statin treatment are substantially greater for those with AFG. Therapy is clearly indicated in this group.

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References

1. King H, Aubert RE, Herman WH: Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *CVD Prev* 21:1414–1431, 1998
2. National Institute of Diabetes and Digestive and Kidney Diseases: *Diabetes Statistics: National Diabetes Information Clearinghouse*. Bethesda, MD, National Institute of Diabetes and Digestive and Kidney Diseases, 1999 (NIH publ. no. 99-3926)
3. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (Committee Report). *Diabetes Care* 20: 1183–1202, 1997
4. American Diabetes Association, National Heart, Lung and Blood Institute, Juvenile Diabetes Foundation International, National Institute of Diabetes and Digestive and Kidney Diseases, American Heart Association: Diabetes mellitus: a major risk factor for cardiovascular disease. *Circulation* 100:1132–1133, 1999
5. Kannel WB: Lipids, diabetes and coronary heart disease: insights from the Framingham study. *Am Heart J* 110:1100–1107, 1985
6. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
7. Barzilay JI, Spiekerman CF, Kuller LH, Burke GL, Bittner V, Gottdiener JS, Brancati FL, Orchard TJ, O'Leary DH, Savage PJ: Prevalence of clinical and isolated subclinical cardiovascular disease in older adults with glucose disorders: the Cardiovascular Health Study. *Diabetes Care* 24: 1233–1239, 2001
8. Fisman EZ, Motro M, Tenebaum A, Boyko V, Mandelzweig L, Behar S: Impaired fasting glucose concentrations in nondiabetic

patients with ischemic heart disease: a marker for a worse prognosis. *Am Heart J* 141:485–490, 2001
9. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
10. Duckworth WC, McCarren M, Abraira C: Glucose control and cardiovascular complications: the VA Diabetes Trial. *Diabetes Care* 24:942–945, 2001
11. Sprafka JM, Burke GL, Folsom AR, McGovern PG, Hahn LP: Trends in prevalence of diabetes mellitus in patients with myocardial infarction and effect of diabetes on survival: the Minnesota Heart Survey. *Diabetes Care* 14:537–543, 1991
12. Haffner SM, Alexander CM, Cook TJ, Boccuzzi SJ, Musliner TA, Pedersen TR, Kjekshus J, Pyorala K: Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 159:2661–2667, 1999
13. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E: Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analysis in the cholesterol and recurrent events (CARE) trial: the CARE Investigators. *Circulation* 98:2513–2519, 1998
14. Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group: Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 339:1349–1357, 1998
15. LIPID Study Group: Design features and baseline characteristics of the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) study: a randomized trial in patients with previous acute myocardial infarction and/or unstable angina pectoris. *Am J Cardiol* 76:474–479, 1995
16. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
17. Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 344:1383–1389, 1994
18. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia: the West of Scotland Coronary Prevention Study Group. *N Engl J Med* 333:1301–1307, 1995
19. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels: the Cholesterol and Recurrent Events Trial Investigators. *N Engl J Med* 335:1001–1009, 1996
20. Lee ET: *Statistical Methods for Survival Data Analysis*. 2nd ed. New York, Wiley, 1992
21. Cox DR: Regression models and life-tables. *J R Stat Soc [B]* 34:187–220, 1972
22. Yusuf S, Peto R, Lewis J, Collins R, Sleight P: Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 27:335–371, 1985
23. Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E: High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet* 358:2026–2033, 2001
24. Sniderman AD, Furberg CD, Keech A, Roeters van Lennep JE, Frohlich J, Jungner I, Walldins G: Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. *Lancet* 361: 777–780, 2003
25. Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, Shepherd J, Gaw A: Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* 103:357–362, 2001
26. Collins R, Armitage J, Parish S, Sleight P, Peto R, Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 361:2005–2016, 2003
27. Amos AF, McCarty DJ, Zimmet P: The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabet Med* 14 (Suppl. 5): S1–S85, 1997
28. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J, ASCOT Investigators: Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 361:1149–1158, 2003
29. ALLHAT Collaborative Research Group: Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 288:2998–3007, 2002
30. Colhoun HM, Thomason MJ, Mackness MI, Maton SM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Fuller JH, the Collaborative AtoRvastatin Diabetes Study (CARDS) Investigators: Design of the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes. *Diabet Med* 19:201–211, 2002
31. Jonsson B, Cook JR, Pedersen TR: The cost-effectiveness of lipid lowering in patients with diabetes: results from the 4S trial. *Diabetologia* 42:1293–1301, 1999