

# Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial

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## Summary

**Background** Renal transplant recipients are at increased risk of premature cardiovascular disease. Although statins reduce cardiovascular risk in the general population, their efficacy and safety in renal transplant recipients have not been established. We investigated the effects of fluvastatin on cardiac and renal endpoints in this population.

**Methods** We did a multicentre, randomised, double-blind, placebo-controlled trial in 2102 renal transplant recipients with total cholesterol 4.0–9.0 mmol/L. We randomly assigned patients fluvastatin (n=1050) or placebo (n=1052) and follow up was for 5–6 years. The primary endpoint was the occurrence of a major adverse cardiac event, defined as cardiac death, non-fatal myocardial infarction (MI), or coronary intervention procedure. Secondary endpoints were individual cardiac events, combined cardiac death or non-fatal MI, cerebrovascular events, non-cardiovascular death, all-cause mortality, and graft loss or doubling of serum creatinine. Analysis was by intention to treat.

**Findings** After a mean follow-up of 5.1 years, fluvastatin lowered LDL cholesterol concentrations by 32%. Risk reduction with fluvastatin for the primary endpoint (risk ratio 0.83 [95% CI 0.64–1.06],  $p=0.139$ ) was not significant, although there were fewer cardiac deaths or non-fatal MI (70 vs 104, 0.65 [0.48–0.88]  $p=0.005$ ) in the fluvastatin group than in the placebo group. Coronary intervention procedures and other secondary endpoints did not differ significantly between groups.

**Interpretation** Although cardiac deaths and non-fatal MI seemed to be reduced, fluvastatin did not generally reduce rates of coronary intervention procedures or mortality. Overall effects of fluvastatin were similar to those of statins in other populations.

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## Introduction

Despite advances in immunosuppressive therapy and long-term graft survival, renal transplant recipients have a notably shortened life expectancy.<sup>1</sup> This effect is due largely to premature cardiovascular disease, which is the leading cause of death in patients with a functioning renal graft.<sup>1,2</sup> Many transplant recipients have pre-existing cardiovascular disease at the time of transplantation.<sup>1–3</sup> and immunosuppressive therapy may aggravate existing risk factors or promote development of new risk factors, notably hyperlipidaemia and hypertension.<sup>1,3</sup>

Lipid-lowering treatment with statins reduces cardiovascular events in a wide range of patients at increased risk of cardiovascular disease, including those with normal cholesterol concentrations.<sup>4–12</sup> In renal transplant recipients the relation between lipid concentrations and cardiovascular events is less clear than in other populations.<sup>1,3,13</sup> Although findings from observational studies suggest a potential benefit of statin therapy,<sup>14</sup> this benefit has not been shown in prospective controlled trials.

The Assessment of LEscol in Renal Transplantation (ALERT) trial is an investigator-initiated and investigator-led study designed to investigate the effects of fluvastatin on cardiac and renal endpoints in renal transplant recipients. We believed a large-scale interventional trial was necessary before recommending the widespread use of statins in transplant recipients, who require lifelong therapy with immunosuppressive and other drugs, and are at increased risk of drug interactions, malignant diseases, and infections.<sup>15,16</sup>

## Methods

The ALERT study design and baseline data have been previously described.<sup>17</sup> Briefly, we recruited 2102 renal transplant recipients from nephrology and transplant clinics in Belgium, Denmark, Finland, Germany, Norway, Sweden, Switzerland, the UK, and Canada.

## Participants

We recruited men and women aged 30–75 years who had received renal or combined renal and pancreas transplants more than 6 months before randomisation and who had stable graft function. All patients were receiving immunosuppressive therapy with ciclosporin and had total serum cholesterol concentrations of 4.0–9.0 mmol/L, to exclude recent myocardial infarction (MI). Patients who had had MI more than 6 months before randomisation could be enrolled if total cholesterol concentration was 4.0–7.0 mmol/L. We excluded patients who were already taking statins, who had familial hypercholesterolaemia, had experienced acute rejection episodes in the previous 3 months, or who had a predicted life expectancy of less than 1 year.

The study adhered to the International Conference on Harmonisation guidelines for good clinical practice and was done in accordance with the Declaration of Helsinki. All participants provided written informed consent, and

the ethics committee at each participating centre approved the trial.

### Trial procedure

Patients were randomly assigned fluvastatin 40 mg daily or matching placebo (figure 1). Treatment was assigned at each centre separately, according to medication-pack numbers, with use of fixed-block randomisation. After around 2 years, the dose of study drug was doubled in both groups after obtaining written informed consent from patients. The dose increase was implemented on the recommendation of the independent data safety monitoring board on the basis of emerging safety data and clinical outcome trials, published after ALERT was designed, that reported on the relation between achieved LDL-cholesterol concentrations and reduction of cardiovascular events.<sup>7,8</sup>

We followed up patients for a minimum of 5 and a maximum of 6 years. Patients were seen at 1·5 months after randomisation, and every 6 months thereafter. At each visit, laboratory measures, including fasting lipids (serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), serum creatinine, creatine kinase, and hepatic enzymes were assessed at a central laboratory (Medinet, Breda, Netherlands). No additional local lipid analyses were permitted. Labels on the front of patients' hospital records stated that they were participants in the study and that lipid measurements were proscribed. Investigators were unaware of patients' lipid concentrations unless informed by the central laboratory of predefined high values (total cholesterol 8·0 mmol/L in patients with previous MI or 10·0 mmol/L in all other patients on two consecutive visits). In the event of unacceptably high concentrations or after a cardiac event, investigators were permitted and encouraged to prescribe open-label fluvastatin 40 mg daily in addition to masked study medication. We did additional measurements of creatine kinase and hepatic enzymes 4 weeks after doubling the dose of study medication, and 12-lead electrocardiography was done annually.

The primary endpoint was the first occurrence of a major adverse cardiac event, defined as cardiac death, non-fatal MI verified by hospital records, or coronary revascularisation procedure, including coronary-artery bypass graft or percutaneous coronary intervention. We included definite and probable MI, since occurrence is difficult to establish in this population because of a high prevalence of resting echocardiographic abnormalities<sup>18</sup> and possible spurious increases in creatine kinase concentrations. We classified electrocardiographic changes according to the Minnesota code. An adjudicated MI was classified as definite if a new Q-wave developed in the presence of abnormal cardiac markers or symptoms, or pathological ST elevations and T-wave changes developed in the presence of abnormal cardiac markers plus symptoms. An MI was classified as probable if pathological ST elevations and T-wave changes developed in the presence of abnormal cardiac markers or symptoms.

Predefined secondary endpoints were: individual cardiac events; combined cardiac death or non-fatal MI; combined cerebrovascular events; non-cardiovascular death; all-cause mortality; and the composite renal endpoint of graft loss or doubling of serum creatinine. In addition, we assessed treatment effects on lipid concentrations and safety and tolerability of the study medication.

An independent critical events committee of two nephrologists and two cardiologists who were unaware of

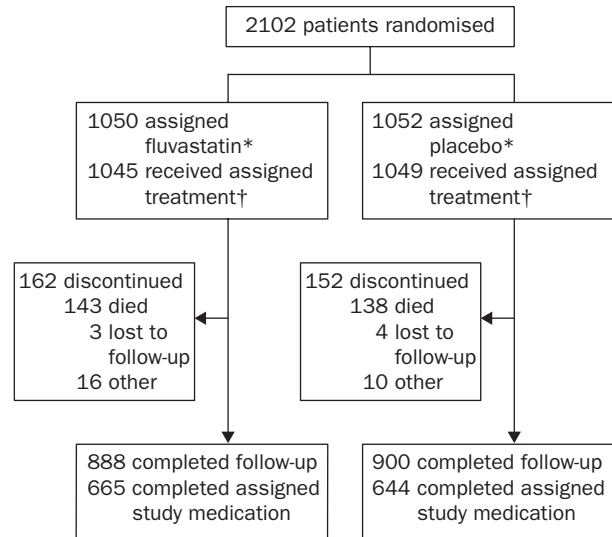


Figure 1: Trial profile

\*Included in intention-to-treat analysis. †Included in safety population.

treatment assignment, reviewed all primary and secondary endpoints for adjudication. All analyses were based on the committee's classification of endpoints, which were agreed by consensus or majority vote.

### Statistical analysis

In the original sample-size calculation we assumed a 25% placebo event rate after 5 years of follow-up, based on a survey of the renal transplant population in the participating countries<sup>19</sup> and a 25% size effect. By use of the  $\chi^2$  test statistic for a difference between two proportions, we calculated that a sample size of 1476 patients (738 per group) would give 80% power to detect a difference between groups for the primary endpoint ( $\alpha=0\cdot05$ , two-tailed). We increased this number to 1800 patients to allow for drop outs and treatment crossovers, giving a power estimate of 83%. A lower-than-predicted event rate in year 1 of follow-up prompted a reassessment of the sample size. A placebo event rate of 22·5% after 5 years was deemed a more realistic assumption, and an additional 250 patients were required, and recruited, to maintain the original power. To enable the maximum potential success of the study, we doubled study-medication dose after around 2 years. This rise in dose of fluvastatin from 40 to 80 mg daily was predicted to reduce LDL-cholesterol concentrations by an additional 6%.<sup>20</sup> In addition, only the first of three planned interim analyses were done after 149 patients had reached a primary endpoint, thus limiting the impact of repeated interim analyses on significance levels.

We did the primary efficacy analysis by intention to treat—all randomised patients were analysed according to their original treatment assignment. The number of randomised patients was previously given as 2100.<sup>17</sup> In the final analysis, one additional patient in each group had been randomised but received no study medication; these two patients were included in the intention-to-treat population for the current analysis. We analysed comparability of demographic and clinical baseline characteristics with Fisher's exact test, the Mann-Whitney test, or the paired *t* test, dependent on the variable. The primary efficacy analysis is based on a log-rank test stratified by country and coronary-heart-disease

	Fluvastatin (n=1050)	Placebo (n=1052)
<b>Demographic and clinical characteristics</b>		
Mean (SD) age (years)	49.5 (10.9)	50.0 (11.0)
Male	701 (66.8%)	686 (65.2%)
Mean (SD) diastolic blood pressure (mm Hg)	85.6 (10.1)	85.6 (10.0)
Mean (SD) systolic blood pressure (mm Hg)	143.8 (18.7)	144.0 (19.1)
Mean (SD) BMI (kg/m <sup>2</sup> )	25.8 (4.4)	25.8 (4.6)
Mean (SD) total cholesterol (mmol/L)	6.4 (1.1)	6.5 (1.1)
Mean (SD) LDL cholesterol (mmol/L)	4.1 (1.0)	4.1 (1.0)
Mean (SD) HDL cholesterol (mmol/L)	1.3 (0.5)	1.4 (0.4)
Mean (SD) triglycerides (mmol/L)	2.2 (1.2)	2.2 (1.5)
<b>Primary cause of renal failure</b>		
Glomerulonephritis	387 (36.9%)	364 (34.6%)
Polycystic disease	138 (13.1%)	183 (17.4%)
Diabetic nephropathy	135 (12.9%)	138 (13.1%)
Pyelonephritis or interstitial nephritis	124 (11.8%)	135 (12.8%)
Hypertensive nephrosclerosis	59 (5.6%)	46 (4.4%)
Systemic lupus erythematosus or vasculitis	30 (2.9%)	22 (2.2%)
Unknown	58 (5.5%)	53 (5.0%)
Other	157 (15.0%)	134 (12.7%)
<b>Transplant characteristics</b>		
First transplantation	894 (85.1%)	900 (85.6%)
Mean (SD) time taking renal replacement therapy (months)	88.5 (56.5)	88.8 (58.3)
Type of last transplant		
Live donor	240 (22.9%)	229 (21.8%)
Cadaveric donor	809 (77.0%)	822 (78.1%)
Mean (SD) serum creatinine (μmol/L)	147 (54.4)	143 (51.0)
<b>Concomitant immunosuppressive therapy*</b>		
Azathioprine	684 (65.1%)	680 (64.6%)
Prednisolone	851 (81.0%)	848 (80.6%)
Cyclophosphamide	9 (0.9%)	10 (1.0%)
Mycophenolate mofetil	167 (15.9%)	159 (15.1%)
Other	198 (18.9%)	224 (21.3%)
<b>Cardiovascular risk factors</b>		
History of angina pectoris	71 (6.8%)	77 (7.3%)
Previous MI	32 (3.0%)	34 (3.2%)
Diabetes	197 (18.8%)	199 (18.9%)
Hypertension	798 (76.0%)	777 (73.9%)
History of cerebrovascular disease	62 (5.9%)	60 (5.7%)
History of PVD	80 (7.6%)	78 (7.4%)
Current smoker	204 (19.4%)	185 (17.6%)
Known family history of CHD	91 (8.7%)	124 (11.8%)
<b>Concomitant cardiovascular medications*</b>		
Any cardiovascular drug	1001 (95.3%)	999 (95.0%)
Aspirin	371 (35.3%)	353 (33.6%)
Dipyridamole	21 (2.0%)	26 (2.5%)
Coumarin or warfarin	90 (8.6%)	94 (8.9%)
β blockers	649 (61.8%)	627 (59.6%)
Calcium antagonists	728 (69.3%)	738 (70.2%)
ACE inhibitor or AIIA	520 (49.5%)	529 (50.3%)
Diuretics	590 (56.2%)	573 (54.5%)
α blockers	176 (16.8%)	170 (16.2%)
Other	316 (30.1%)	373 (35.5%)

BMI=body-mass index. PVD=peripheral vascular disease. CHD=coronary heart disease. ACE=angiotensin-converting enzyme. AIIA=angiotensin-II-receptor blocker. \*Taken at least once during study. Data are n (%) unless stated otherwise.

Table 1: Characteristics of study population

status at time of randomisation. Cumulative incidence curves were generated by the Kaplan-Meier method; we used Cox's proportional hazards model and the Cochran-Mantel-Haenszel test to assess risk reduction and to compare the frequency of endpoints, respectively. The final  $\alpha$  level for testing significance was adjusted to 0.04965 after one interim analysis; all secondary endpoints were tested with a 0.05 significance level. No correction was made for multiple comparisons and, in the absence of a significant primary endpoint, the p values for secondary endpoints are exploratory and should be interpreted with caution.

The safety population consisted of all randomised patients who received at least one dose of study

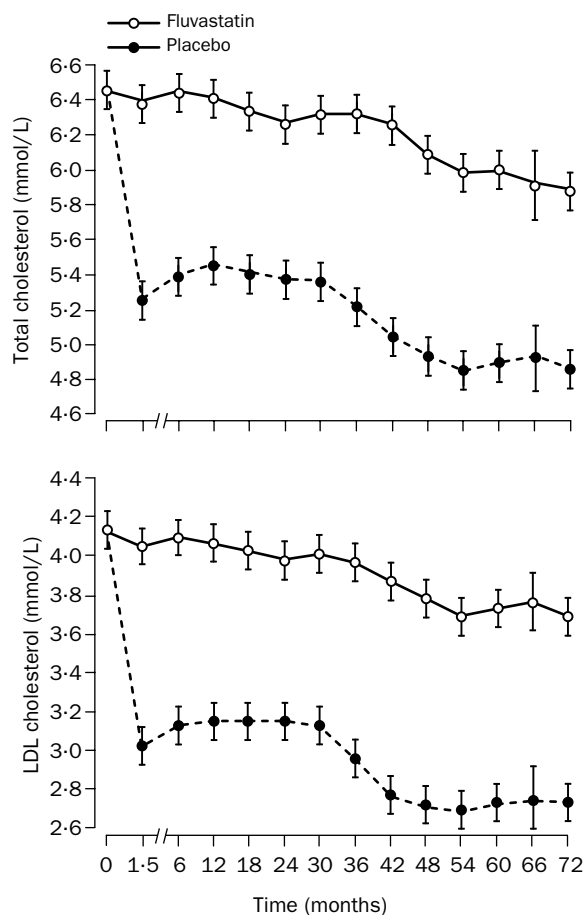


Figure 2: Mean (SD) change from baseline to end of study in total cholesterol and LDL-cholesterol concentrations

medication. We calculated the frequencies of adverse events, deaths, and discontinuations from the study because of clinical or laboratory adverse events for the total safety population. A safety analysis was done with the  $\chi^2$  or Cochran-Mantel-Haenszel test to assess between-group differences.

#### Role of the funding source

The study sponsor, Novartis Pharma AG, which had one non-voting representative on the steering committee, had no role in the study design, data analysis, data interpretation, writing of the paper, or the decision to submit the paper for publication. The sponsor did collect the data.

#### Results

Between June, 1996, and October, 1997, 2102 patients were recruited; 1050 were randomly assigned fluvastatin and 1052 placebo (figure 1). The number of patients screened and recruitment strategy in individual centres were not recorded. All eligible patients were randomised. Follow-up was sought for all patients who discontinued treatment early and was achieved for all except seven.

Overall, 66% of patients were male, and the mean age was 50 years. The major causes of renal failure among all patients were glomerulonephritis and polycystic kidney disease. 1575 (75%) of patients had hypertension, 396 (19%) had diabetes, and 15% in each group had experienced a cardiac, cerebrovascular, or other vascular event. The groups were well balanced for baseline demographic and clinical characteristics (table 1).

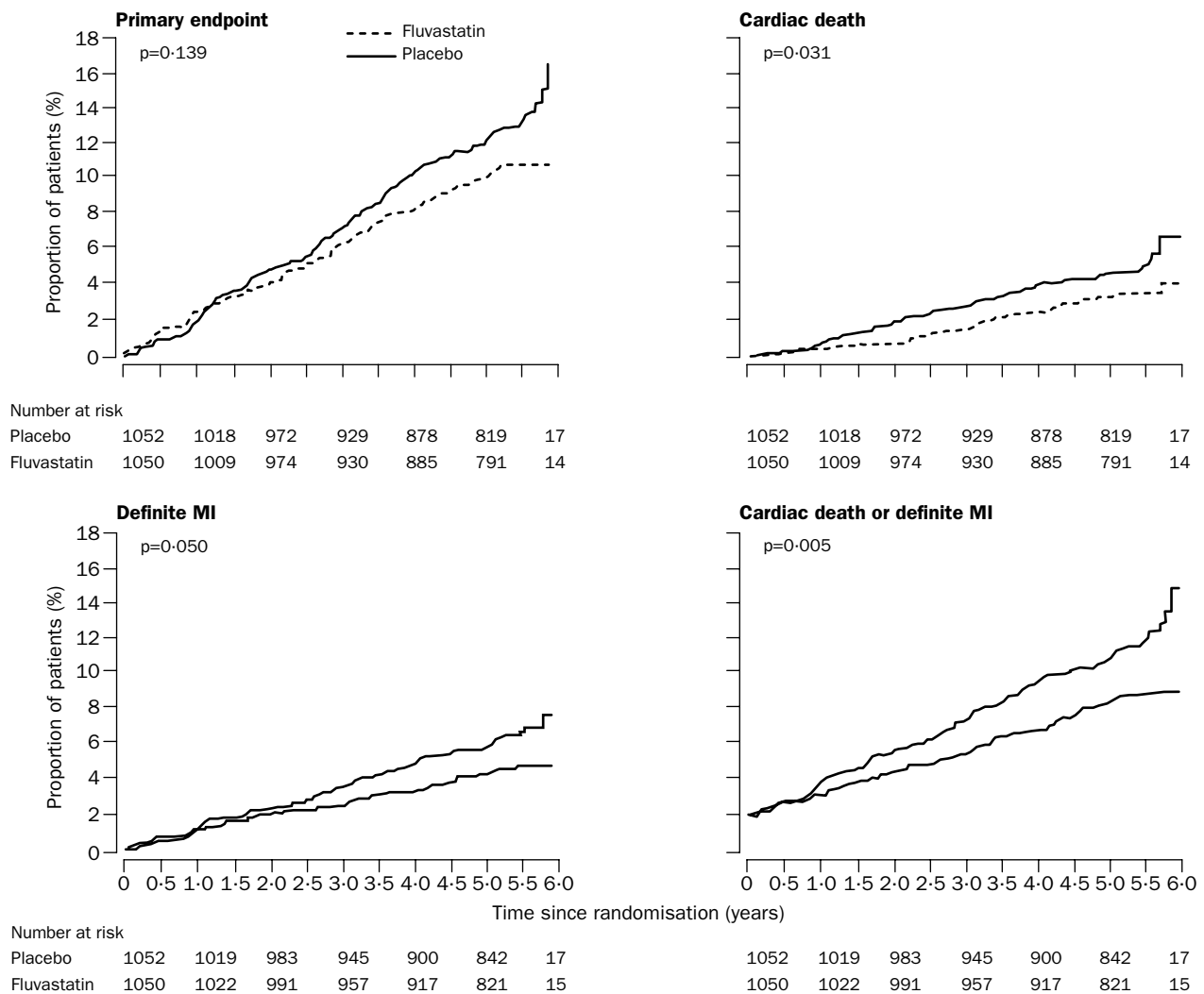


Figure 3: Cumulative rates for primary composite endpoints

Analyses by intention-to-treat and stratified by country and coronary heart disease status at baseline.

The mean duration of follow-up was 5.1 (SD 1.1) years; the median follow-up was 5.4 years (IQR 5.2–5.6). The dose of study medication was doubled in 65% of patients in both groups after a mean follow-up duration of 2.8 years. Over the duration of the study, 77 (7%) patients in the fluvastatin and 145 (14%) in the placebo group took other lipid-lowering treatments, mainly statins. Concurrent medications taken by patients during the study were similar in both groups (table 1). All recruited patients received ciclosporin and 1699 (81%) received steroids.  $\beta$  blockers and calcium antagonists were the most frequently used cardiovascular drugs and 724 (34%) received aspirin; 2000 (95%) received cardiovascular drugs during the study.

By 6 weeks, fluvastatin had significantly lowered LDL cholesterol concentrations by a mean of 25% (95% CI –26 to –24) compared with placebo (0.4% [–0.9 to 1.8]), and these effects continued throughout the study (figure 2). At the end of the study, fluvastatin had significantly lowered mean LDL cholesterol by 32% (–33, to –30) compared with placebo (mean reduction 7.9 mmol/L [–10.0 to –5.7]). On average, there was a net difference of 1.0 mmol/L between groups throughout the study. Mean total cholesterol and mean triglycerides decreased significantly in the fluvastatin group compared with placebo, whereas mean HDL cholesterol

concentrations did not differ significantly between groups. During the course of the study, 696 (66.3%) of the patients in the fluvastatin group achieved total cholesterol concentrations lower than 5.0 mmol/L, and 779 (74.2%) achieved an LDL cholesterol concentrations lower than 3.0 mmol/L, meeting recommended values for prevention of CHD.<sup>20,21</sup>

The reduction in the primary endpoint, total major adverse cardiac events, of 17% was not significant despite a slightly favourable result for the fluvastatin group (risk ratio 0.83 [95% CI 0.64–1.06],  $p=0.139$ ; figure 3, figure 4). Analyses of the predefined secondary endpoints (figure 3, figure 4) are limited by the absence of a significant reduction in the primary endpoint and should be interpreted cautiously. However, treatment with fluvastatin reduced the risk of cardiac death by 38% (0.62 [0.40–0.96]) and of definite non-fatal MI by 32% (0.68 [0.47–1.00]; figure 3, figure 4). There was a 35% risk reduction in the combined endpoint of cardiac death or definite non-fatal MI in the fluvastatin group (0.65 [0.48–0.88]). Rates of probable non-fatal MI or coronary interventions did not differ significantly between groups. Cardiac deaths accounted for 90 (32%) of 281 deaths (table 2). The rates of cerebrovascular events, non-cardiovascular deaths, all-cause mortality, and the renal composite endpoint of graft loss or

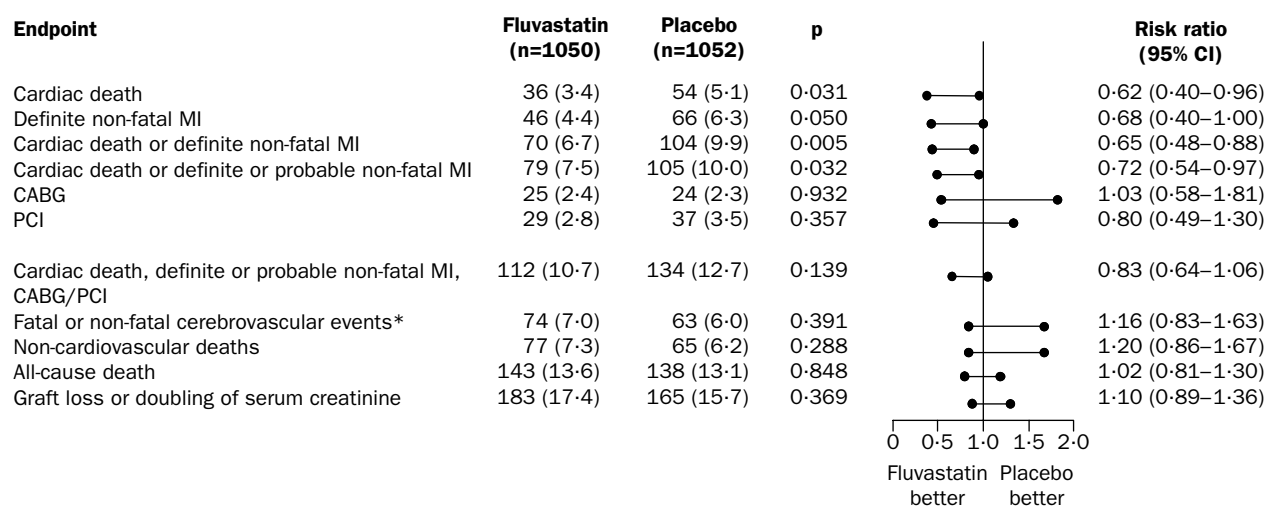


Figure 4: **Study endpoints in intention-to-treat population**

CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention. \*Fatal or non-fatal stroke, transient ischaemic attack, reversible ischaemic neurological deficit, subarachnoid haemorrhage.

doubling of serum creatinine were similar in the two groups (figure 4). In the fluvastatin and placebo groups there were 146 graft losses compared with 137, and 183 instances of doubling of serum creatinine compared with 165, respectively.

A risk-factor analysis of baseline LDL cholesterol concentrations among placebo-treated patients revealed that each 1.0 mmol/L increase was associated with a 41% increase in risk of the primary endpoint and the composite endpoint of cardiac death or non-fatal MI (table 3). No significant association was noted between LDL cholesterol concentrations and non-cardiovascular death or renal endpoints.

The safety population included 1045 patients in the fluvastatin group and 1049 in the placebo group. Rates of adverse events for fluvastatin at 40 mg and 80 mg daily were similar to those in the placebo group (table 4). 155 (15%) patients in the fluvastatin group and 172 (16%) controls permanently discontinued study medication because of clinical or laboratory adverse events. The frequency of critical rises in alanine aminotransferase (three-fold) or creatine kinase concentrations (five-fold) did not differ significantly between groups, and no rise was accompanied by musculoskeletal symptoms. Two patients developed non-fatal rhabdomyolysis, one in each group; both occurrences were due to severe trauma and, after resolution, both patients re-started study medication and completed the trial. The observed rates of infection and malignant disease did not differ between treatment groups.

	Fluvastatin (n=1050)	Placebo (n=1052)
<b>Cause of death</b>		
Cardiac	36 (3.4%)	54 (5.1%)
Cerebrovascular	17 (1.5%)	14 (1.3%)
Other vascular	13 (1.2%)	5 (0.5%)
Peripheral gangrene	2 (0.2%)	2 (0.2%)
Aortic aneurysm	6 (0.6%)	2 (0.2%)
Intra-abdominal infarction	1 (0.1%)	0
Pulmonary embolism	4 (0.4%)	1 (0.1%)
Malignant disease	37 (3.5%)	33 (3.1%)
Infections	25 (2.4%)	26 (2.5%)
Violence	1 (0.1%)	1 (0.1%)
Suicide	1 (0.1%)	0
Withdrawal from dialysis	3 (0.3%)	2 (0.2%)
Other	7 (0.7%)	2 (0.2%)
Unknown	3 (0.3%)	1 (0.1%)

Table 2: **Causes of death among fluvastatin-treated and placebo-treated patients**

## Discussion

In the ALERT study the net reduction of LDL-cholesterol was generally 1.0 mmol/L lower in the fluvastatin group than in the placebo group and was associated with a lower cardiac event rate than placebo. However, the observed cardiac event rate was lower than predicted at the outset, and the trial had insufficient power to detect a significant reduction in the chosen primary endpoint. The 35% reduction in the secondary endpoint of cardiac death and non-fatal MI, with fluvastatin use are consistent with the beneficial effects of statins in other populations. These findings have implications for the management of cardiovascular risk<sup>22</sup> and for future cardiovascular intervention trials in renal transplantation.

Most patients were able to achieve recommended target LDL cholesterol concentrations for the prevention of CHD.<sup>22,23</sup> The absolute net reduction in LDL cholesterol in the fluvastatin group and the percentage reduction in cardiac events are similar to those reported in other major statin outcome trials.<sup>4-12,24</sup> We did not permit local lipid measurement in any patient and, although not formally monitored, we believe that this policy was strictly adhered to. However, when patients were admitted to other hospitals or visited other non-participating specialists, some lipid measurements were made. Increasingly, towards the end of the study and with the emergence of data supporting statin use in other groups, patients received statins from non-participating physicians. This observation, together with treatment of high values reported by the central laboratory, account for the higher rate of open-label statin use in the placebo group than in the fluvastatin group. This factor might have limited the apparent benefits of fluvastatin in our study.

We recruited renal transplant recipients with stable graft function and low rates of previous cardiovascular disease. The recruitment strategy and proportion of patients

	Risk ratio per unit increase in LDL cholesterol (95% CI)	p
<b>Clinical event</b>		
Primary outcome	1.41 (1.20–1.66)	<0.0001
Cardiac death or non-fatal MI	1.41 (1.18–1.69)	0.002
Non-cardiovascular death	0.99 (0.77–1.27)	0.912
Graft loss or doubling of serum creatinine	0.99 (0.84–1.16)	0.871

Table 3: **Relation between baseline LDL cholesterol concentration and risk of clinical events in placebo-treated patients**

	Fluvastatin (n=1045; n [%])	Placebo (n=1049; n [%])
Total adverse events	1029 (98.5)	1034 (98.6)
Infections	678 (64.9)	671 (64.0)
Gastrointestinal	562 (53.8)	541 (51.6)
Malignancies	296 (28.3)	316 (30.1)
Skin papilloma	138 (13.2)	115 (11.0)
Non-melanoma skin cancer	116 (11.1)	137 (13.1)
Melanoma	2 (0.2)	5 (0.5)
Haematological	11 (1.1)	18 (1.7)
Solid-organ	57 (5.5)	52 (5.0)
Other	38 (3.6)	52 (5.0)
Musculoskeletal	526 (50.3)	531 (50.6)
Hepatobiliary	38 (3.6)	57 (5.4)
Alanine transaminase		
>3× upper limit of normal*		
Once	11 (1.1)	12 (1.1)
Twice, non-consecutive	1 (0.1)	3 (0.3)
Twice, consecutive	0	2 (0.2)
Creatine kinase		
≥5 to <10× upper limit of normal†	3 (0.3)	4 (0.4)
≥10× upper limit of normal†	3 (0.3)	1 (0.1)

\*Normal range 0–45 IU/L. †Normal range 35–232 IU/L.

**Table 4: Frequency of most relevant adverse events and abnormal laboratory values**

entered was different in each participating centre and the recruited population comprised long-term survivors with good graft function. Patients with pre-existing cardiac disease were probably excluded because of statin use for secondary prevention and the reluctance of investigators to enter patients who had complex therapeutic regimens, severe comorbidity or who were in the early post-transplant period. These factors may limit the generalisability of the study. Given the mean total cholesterol concentration, rates of diabetes and cigarette smoking, and average blood pressure, despite antihypertensive therapy, ALERT was essentially a primary prevention study in a population with a moderately high rate of cardiovascular risk factors. The annual rate of fatal or non-fatal cardiac events in the placebo group is within the range of annual rates reported in previous primary and secondary prevention studies with statins.<sup>4–12,24</sup> The cardiovascular event rate is lower, however, than those noted in the elderly<sup>11</sup> or in post-MI patients with very high cholesterol concentrations.<sup>4</sup>

There are two major differences between ALERT and previous statin studies. The first is ALERT's small size and the second is a high rate of non-cardiovascular deaths. The study population were most similar to that in the Heart Protection Study<sup>16</sup> for rates of cardiac and non-cardiac deaths, and the proportions of MI and cardiac deaths, although the average age is much lower in the ALERT study and the sample size ten times smaller. We based the size of ALERT on registry data from the Scandinavian countries, which estimated a primary endpoint rate of around 5% per year. We recognised early during the study that cardiovascular risk and cardiovascular event rate among the recruited study population was low, since 85% of patients did not have established cardiovascular disease, and, therefore, we increased recruitment, increased fluvastatin dose, and calculated the optimum duration of the study. Despite these efforts, the primary endpoint did not achieve significance. In retrospect, a larger study was required, although we recognise that to do a larger study would be difficult given the small numbers of renal transplant recipients and competition to do other clinical trials, such as of immunosuppressive therapy, in this population. A post-hoc analysis, based on a 17% reduction in the chosen primary endpoint, revealed that 6800 patients

followed up for 5 years would be required to provide 80% power,  $\alpha=0.05$ , two-tailed. However, had we chosen an alternative primary endpoint, such as cardiac death and definite non-fatal MI, as in the West of Scotland Coronary Prevention Study,<sup>5</sup> the result would have been significant. A preplanned 2-year extension of the ALERT study is now in progress, in which all patients receive active therapy, following the models established in, for example, the 4S study.<sup>25</sup>

Most of the major statin outcome studies have shown that survival curves diverge after roughly 1 year of follow-up. We noted a similar pattern in the primary endpoint and for combined cardiac death and non-fatal MI. There are alternative interpretations for the diverging curves, such as the reduction in cardiac endpoints is a consequence of an excess of early revascularisation in the fluvastatin group, since 11 of the 12 revascularisations that occurred in ALERT in year 1 were in the fluvastatin group. However, it is unclear whether coronary revascularisation prolongs survival among renal transplant patients, and the increased number of revascularisations in the fluvastatin limb was probably due to chance. Similar arguments can be made for other findings in the study, for example that fluvastatin increases non-cardiac death or non-fatal MI. We judge these effects to be unlikely and, since the lipid-lowering effects of fluvastatin and the survival curves are similar to those in other studies that show benefits of statin therapy, they are probably a consequence of limited statistical power.

We did not design ALERT to detect an effect on all-cause mortality, and, given its small size, the absence of an effect is not unexpected. Furthermore, although the age-adjusted cardiovascular risk of renal transplant recipients is increased, the overall proportion of cardiac deaths compared with total deaths (around 33%) is substantially lower than that seen in trials in which statin treatment reduced the overall death rate.<sup>4,8,10</sup> Moreover, although total and LDL-cholesterol concentrations were associated with cardiac events in placebo-treated patients, they were not associated with non-cardiac death or renal events. This may explain why lipid-lowering treatment with fluvastatin had no effect on the latter two endpoints. The absence of an effect on graft loss or doubling of serum creatinine was unexpected, since chronic allograft nephropathy, the most common cause of late graft failure, shares pathophysiological mechanisms with atherosclerosis and has been associated with hypercholesterolaemia.<sup>26</sup>

A major concern for long-term survivors of renal transplantation is an increased risk of malignant disease<sup>15</sup> and infectious disease.<sup>16</sup> In the PROSPER study<sup>11</sup> an increase in the rate of cancer was reported among elderly patients, raising possible concerns about an increased risk of malignant disease with statin use. As expected, the renal transplant recipients in the our study had a high frequency of malignant diseases, especially skin tumours. Reassuringly, the rate of cancer or infection was not increased in the fluvastatin group.

As many as 50% of renal transplant recipients are now treated with statins,<sup>14</sup> which reflects the widespread acceptance of data from other populations, particularly for the secondary prevention of cardiac disease and in diabetes. Subgroup analyses of the study populations in the Heart Protection Study,<sup>10</sup> and Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm,<sup>12</sup> and the Cholesterol and Recurrent Events study<sup>27</sup> have shown that statins are effective in patients with mild renal failure who are at increased cardiovascular risk, some of whom may ultimately require renal transplantation. The ALERT study shows a similar beneficial effect for fluvastatin, a statin

that has minimum interaction with immunosuppressive therapy<sup>28,29</sup> in patients at the opposite end of the spectrum of renal failure.

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