Effect of Statins on Patients and Graft Survival in Kidney Transplant Recipients
A Survival Meta-analysis

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Introduction. Modifying cardiovascular risk factors is very important for the patients after kidney transplantation. Statins are a potentially beneficial intervention for kidney transplant patients, and the effect of statins on cardiovascular outcomes in patients with chronic kidney disease varies according to the stages. This systematic review summarizes the potential beneficial effects of statins on kidney allograft outcome.

Materials and Methods. A systematic review and meta-analysis was conducted by literature search using the PubMed, Science Direct, Scopus, ISI Web of Knowledge, and Google Scholar. Articles published after 2000 reporting hazard ratios (HRs) for the effect of statins on patient and graft survival of kidney transplant patients were included.

Results. Seven articles were included in the systematic review, involving 1870 kidney transplant patients that received statins and 3339 kidney transplant patients as the control group. Statins has no protective effect on transplant rejection, graft survival or patient survival after kidney transplantation. The effect of statins on graft survival, however, was significant when adjusted for factors such as age, sex, and serum creatinine level (HR, 0.80; 95% CI, 0.69 to 0.92; P = .003). Similarly, patient survival was significantly better with statin use (adjusted HR, 0.75; 95% CI, 0.63 to 0.88; P = .003).

Conclusions. The present study may provide valuable information on the potential beneficial effects of statins in kidney allograft recipients. Meta-analysis showed that the use of statins correlated independently with improved patient and graft survival after kidney transplantation.

INTRODUCTION

A protective effect of statin treatment on cardiac endpoints has consistently been confirmed in different populations.[1] The effect of statins on cardiovascular outcomes in patients with chronic kidney disease (CKD) varies according to the stage of CKD, since the relative benefit decreases as the severity of CKD worsens. There is also evidence suggesting that statins essentially not only preserve, but also improve kidney function in CKD patients.[2] However, although cardioprotective and renoprotective effects of statins have been well documented, the effects of statins on cardiovascular and renal outcomes have been less studied in kidney transplant recipients.[2]

The Assessment of LEscol in Renal Transplantation

(ALERT) multicenter randomized placebo-controlled trial designed in 2003 to investigates the effects of fluvastatin on cardiac and renal endpoints in renal transplant recipients.[3] They assess risk reduction and compare the frequency of endpoints. This study found no significant benefit of fluvastatin regarding cardiac and renal endpoints, graft survival, or overall mortality.[3] In addition, a recent Cochrane meta-analysis on the effect of statins in renal transplant recipients included 22 studies; however, approximately 2 out of 3 of the patients were from the ALERT.[4] This study concluded that statins may reduce the relative risk of cardiovascular events in these patients. However, the researchers pointed out that the findings should be interpreted cautiously because of the lack of data. Moreover, no effect was observed on all-cause mortality and stroke, and the effects of statins on kidney function were subtle.[2]

Kidney transplant recipients are a unique population with lifelong need for immunosuppressive drugs and other medications. They clearly differ from the general population and from other patients with CKD, especially with respect to cardiovascular risk and graft loss. This meta-analysis aimed to describe the relationship between use of statins and the time to death or graft loss in kidney transplant recipients.

MATERIALS AND METHODS
Types of Studies and Participants

Randomized control trials, cohort studies, and historical cohort studies that evaluated patients and allograft outcomes in kidney transplant recipients treated with statins were included. We excluded duplicate records, reviews, irrelevant articles, case series, and case reports.

Outcome Measures

Outcomes collected for this study were kidney transplant recipient survival and kidney allograft survival.

Search Methods for Identification of Studies

We made an electronic literature search using different combinations of key words including 'HMG-CoA reductase inhibitor,' 'statin,' 'atorvastatin,' 'simvastatin,' 'fluvastatin,' 'pravastatin,' 'rosuvastatin,' 'renal transplant,' 'renal transplantation,' 'kidney transplant,' 'kidney transplantation,' 'renal graft,' 'renal allograft,' 'kidney graft,' 'kidney allograft,' 'survival,' 'outcome,' 'efficacy,' 'safety', and 'mortality.' Electronic searches of the following databases were conducted from January 1990 to February 2016: PubMed (www.ncbi.nlm.nih.gov./entrez/query.fcgi), Science Direct (www.sciencedirect.com), Scopus (www.elsevier.com/solutions/scopus), ISI Web of Knowledge (http://www.isiwebofknowledge.com), Google Scholar (www.scholar.google.com), and CENTRAL (Cochrane Central Register of Controlled Trials (www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.htm). For unpublished trials, we searched the clinical trials registries, conference proceedings, and graduate dissertations. Also we communicated through emails with some authors.

Data Collection and Analysis

The review process was initially commenced by 4 authors. The search strategy described was used to obtain titles and abstracts of studies of potential relevance for this meta-analysis. The titles and abstracts were screened independently by 2 authors using data extraction forms for extraction of appropriate articles. They assessed selected abstracts, and if necessary, the full text of these articles, to define which studies fulfilled the inclusion criteria. When they found more than one publication of one study, the article with the most complete data was included. Finally, 2 experts performed the quality assessment for each study, independently. Then, the excluded and included studies were confirmed in a discussion meeting. The interrater agreement between the two reviewers was 80%.

Data Synthesis

We first sorted the included studies according to publication year and then ran a cumulative meta-analysis. A random-effects model was used in order to assess variation in effect sizes from one study to the next. Heterogeneity between trials was tested by means of the Cochrane Q (chi-square, n - 1 degrees of freedom) and the I^2 statistic using a P value less than .05. According to the result of heterogeneity tests, we used random model for our meta-analysis by means of the 'metan' command

in the Stata (version 11.0, StataCorp LP, College Station, TX, USA). The pooled hazard ratios (HR) and its 95% confidence interval (CI) were calculated to determine the statin effects according to the DerSimonian and Laird approach.

RESULTS
Search Results

Among 793 potentially relevant publications, 214 articles from PubMed, 137 from Scopus, 95 from Science Direct, and 347 from Web of Science were considered of interest and reviewed in full text. Of those, 144 articles were repeated and 649 articles were entered in the literature review. As seen in Figure 1, after removal of duplicate articles and reviews of titles and abstracts, full texts of 25 articles were reviewed. Finally, on the basis of input factors, 7 articles entered into our systematic review. All articles had been published after 2000. Three studies were from the United States and there was 4 studies from Poland, the United Kingdom, Spain, and Australia (Table).[3,5-10]

Statins and Graft Survival

Crude analysis. Five studies included 1870 kidney transplant patients in the treatment group and 3283 kidney transplant patients were enrolled in the control group. Based on the random effect modeling (chi-square = 64.17, df = 4, $P < .10$; $I^2 = 93.8\%$; $t^2 = 0.1606$), the crude pooled HR for the effect of statins on graft survival was 0.62 (95% CI, 0.38 to 1.02; $P = .06$; Figure 2).

Adjusted analyses. Five studies reported adjusted HRs, including 6539 kidney transplant patients in
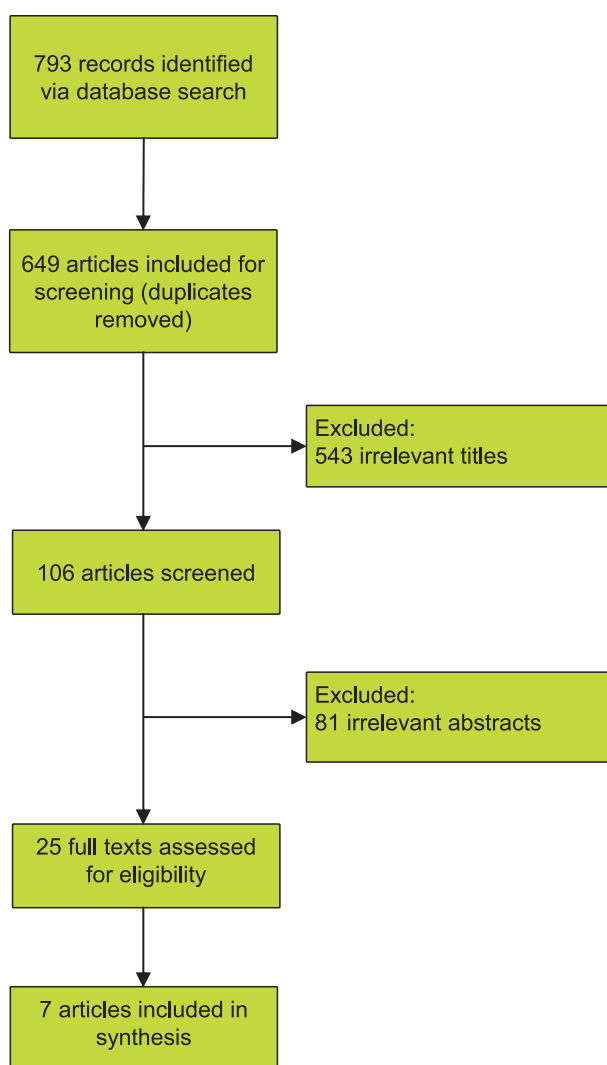

Figure 1. Review of articles according the PRISMA statement

Characteristics of Included Studies

Study	Year	Country	Study Type	Participants, n		Participants Age, y		Male Participants, %		Follow-up, mo
				Statin	Control	Statin	Control	Statin	Control	
Cosio et al[3]	2002	United States	Cohort	434	1140	44.9 ± 13	41.4 ± 14.0	55	60	98.4 ± 55.2
Fellstrom et al[7]	2004	United Kingdom	Randomized Controlled Trial	1050	1052	49.5 ± 10.9	50.0 ± 11.0	66.8	65.2	61.2
Lisik et al[8]	2007	United States	Cohort	258	67	45.0 ± 12.7	44.3 ± 14.6	57.9	69.7	75 ± 26
Pazik et al[10]	2008	Poland	Historical Cohort	20	31	42 ± 11.1	…	…	…	50.2
Wiesbauer et al[6]	2008	Austria	Randomized Controlled Trial	302	1739	54.0 ± 11.8	47.0 ± 15.8	56.6	60.6	144
Moreso et al[5]	2010	Spain	Cohort	2879	1803	49.2 ± 12.2	44.8 ± 13.5	60.7	64.6	12 to 24
Younas et al[9]	2010	United States	Historical Cohort	221	394	51 ± 12	48 ± 15	62.4	63.3	12

Study
Crude HR (95% CI) Weight

Fellstrom (2004)   1.05 (0.83, 1.33)   19.90

Lisik (2007)   0.26 (0.18, 0.37)   21.59

Pazik (2008)   0.37 (0.15, 0.88)   18.02

Wiesbauer (2008)   0.76 (0.58, 1.00)   20.45

Younas (2010)   0.97 (0.76, 1.24)   20.04

Overall (I-squared = 93.8%, p = 0.000)   0.62 (0.38, 1.02)   100.00

NOTE: Weights are from random effects analysis
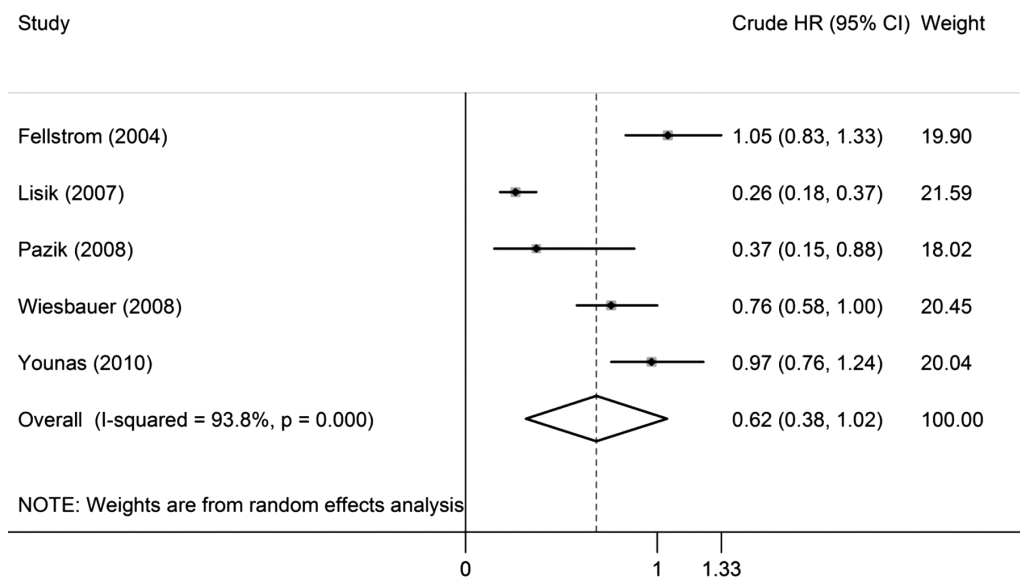
0   1   1.33

Figure 2. Pooled effect of statins on graft survival of kidney transplant recipients, based on the reported crude hazard ratios (HRs) and 95 % confidence intervals (CIs).

treatment group and 5806 in the control group. In these studies the covariates such as age, sex, and serum creatinine had been adjusted for in multiple cox regression models. We found heterogeneity among the studies (chi-square = 8.29, df = 4, $P < .10$; $I^2 = 51.8\%$; $t^2 = 0.0100$), and consequently, a random effect model was selected to calculate the pooled adjusted HR. Overall effect of statins on graft survival was significant (HR, 0.80; 95% CI, 0.69 to 0.92; $P = .003$; Figure 3).

Publication bias. There was no strong evidence of publication bias in the pooled report (crude and adjusted HRs) of the effect of statins on graft survival (Begg test with adjusted Kendall score = -8, $P = .09$, and Egger regression test with slope = -1.33, $P = .28$, for crude HR; Begg test with adjusted Kendall score = - 4, $P = .46$, and Egger regression test with slope = -0.76, $P = .50$, for adjusted HR).

Cumulative meta-analysis. Figures 4 and 5 show the cumulative meta-analysis for evolution

Study
Adj HR (95% CI)   Weight

Lisik (2007)   0.49 (0.28, 0.85)   13.29

Wiesbauer (2008)   0.76 (0.55, 1.04)   15.92

Moreso1 (2010)   0.90 (0.76, 1.06)   25.31

Moreso2 (2010)   0.74 (0.63, 0.87)   30.32

Younas (2010)   0.93 (0.71, 1.22)   15.15

Overall (I-squared = 51.8%, p = 0.081)   0.80 (0.69, 0.92)   100.00

NOTE: Weights are from random effects analysis
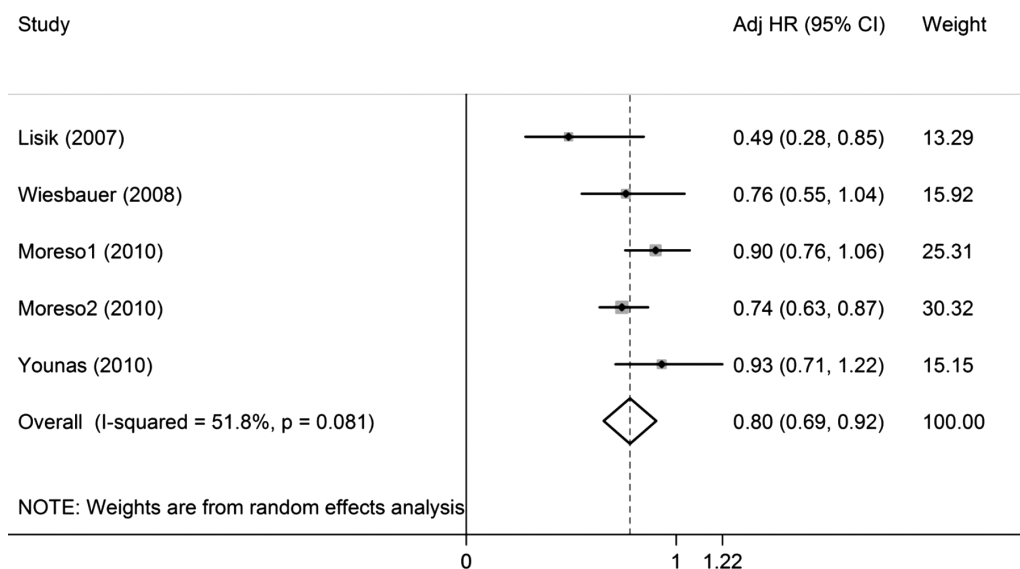
0   1   1.22

Figure 3. Pooled effect of statins on graft survival of kidney transplant recipients, based on the reported adjusted hazard ratios (HRs) and 95 % confidence intervals (CIs).

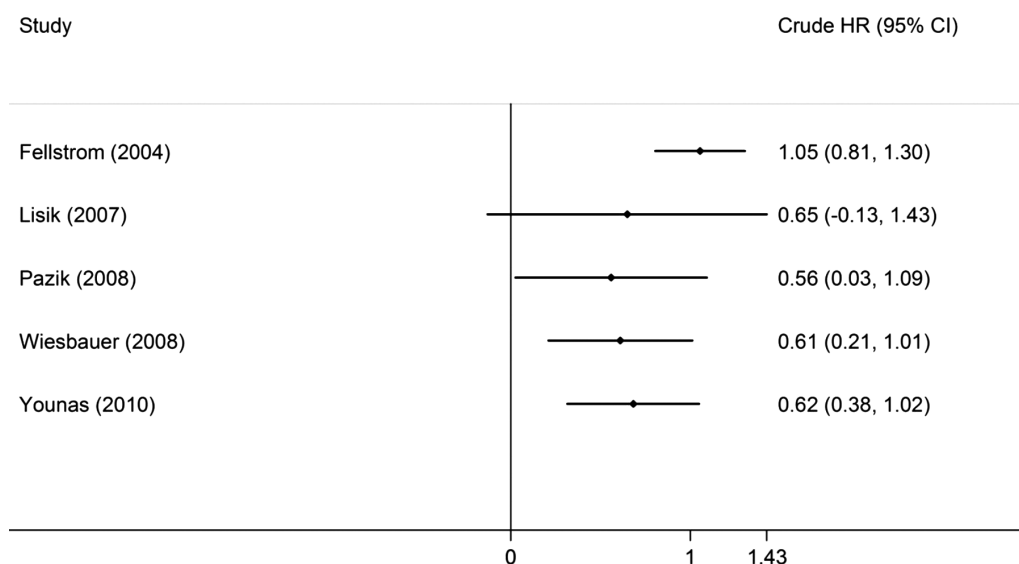| Study		Crude HR (95% CI)
Fellstrom (2004)		1.05 (0.81, 1.30)
Lisik (2007)		0.65 (-0.13, 1.43)
Pazik (2008)		0.56 (0.03, 1.09)
Wiesbauer (2008)		0.61 (0.21, 1.01)
Younas (2010)		0.62 (0.38, 1.02)

0   1   1.43

Figure 4. Cumulative meta-analysis of the effect of statins on graft survival of kidney transplant recipients, based on the reported crude hazard ratios (HRs) and 95 % confidence intervals (CIs).

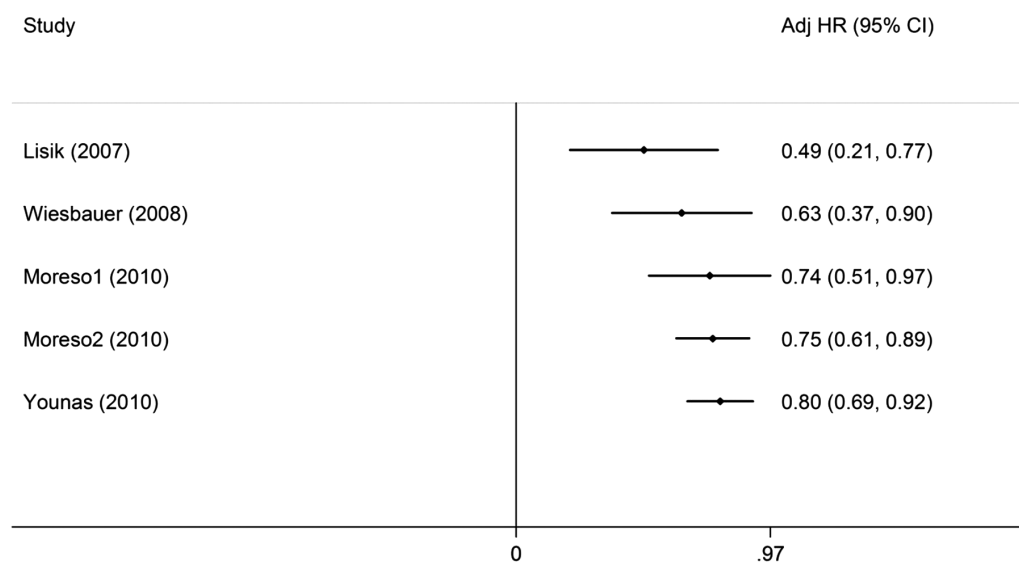| Study		Adj HR (95% CI)
Lisik (2007)		0.49 (0.21, 0.77)
Wiesbauer (2008)		0.63 (0.37, 0.90)
Moreso1 (2010)		0.74 (0.51, 0.97)
Moreso2 (2010)		0.75 (0.61, 0.89)
Younas (2010)		0.80 (0.69, 0.92)

0   .97

Figure 5. Cumulative meta-analysis of the effect of statins on graft survival of kidney transplant recipients, based on the reported adjusted hazard ratios (HRs) and 95 % confidence intervals (CIs).

of treatment effects over time. This chronological combining of the experiments shows a consistency in the results of consecutive experiments after 2007 in crude analysis and after 2008 in adjusted analysis. After those points, addition of new studies could not significantly change overall results.

Statins and Patient Survival

Crude analysis. Three studies involving 781 kidney transplant patients in the treatment group and 2200 in the control group were enrolled for meta-analysis of unadjusted HRs. To estimate the combined HR, a random effect modeling was used due to heterogeneity between studies (chi-square = 36.58, df = 2, $P < .10$; $I^2 = 94.5\%$; $t^2 = 0.1754$). Overall, patient survival was not affected by statin use in crude analysis (HR, 0.55; 95% CI, 0.26 to 1.17; $P = .13$; Figure 6).

Adjusted analysis. The included studies evaluated associations between treatment effect of statin and study characteristics such as age, sex, and serum creatinine in a cox regression model. These
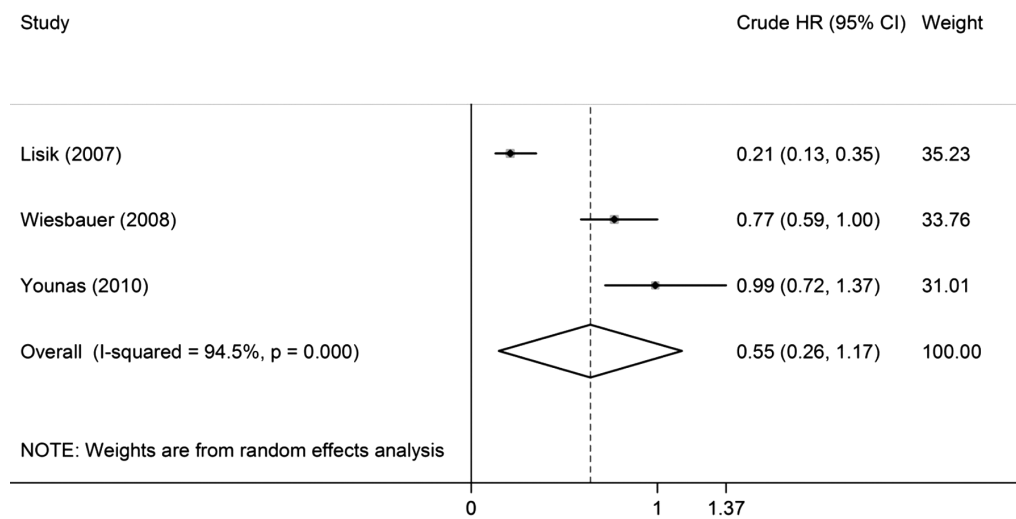
Study   Crude HR (95% CI)   Weight

Lisik (2007)   0.21 (0.13, 0.35)   35.23

Wiesbauer (2008)   0.77 (0.59, 1.00)   33.76

Younas (2010)   0.99 (0.72, 1.37)   31.01

Overall (I-squared = 94.5%, p = 0.000)   0.55 (0.26, 1.17)   100.00

NOTE: Weights are from random effects analysis

        0   1   1.37

Figure 6. Pooled effect of statins on patient survival of kidney transplant recipients, based on the reported crude hazard ratios (HRs) and 95 % confidence intervals (CIs).

5 studies, including 6973 kidney transplant patients in the treatment group and 6943 in the control group, were entered into the analysis. We found heterogeneity among the studies (chi-square = 18.94, df = 5, P < .10; I^2 = 73.6%; t^2 = 0.0302), and a random effect model was selected to calculate the pooled adjusted HR. Patient survival was significantly influenced by statin use (HR, 0.75; 95% CI, 0.63 to 0.88; P = .003; Figure 7).

Publication bias. There was no strong evidence of publication bias in the pooled report (crude and adjusted HRs) of the effect of statins on patient survival (Begg test with adjusted Kendall score = -1, P > .99, and Egger regression test with slope = -1.56, P = .36, for crude HR; Begg test with adjusted Kendall score = -7, P = .26, and Egger regression test with slope = -2.52, P = .07, for adjusted HR).

Cumulative meta-analysis. For cumulative meta-analysis of unadjusted HR, we could not judge the impact of years, due to the limited number of articles. In cumulative meta-analysis of adjusted HR, a significant association was first achieved in 2002 to 2008, and this result remained relatively unchanged thereafter (Figures 8 and 9).
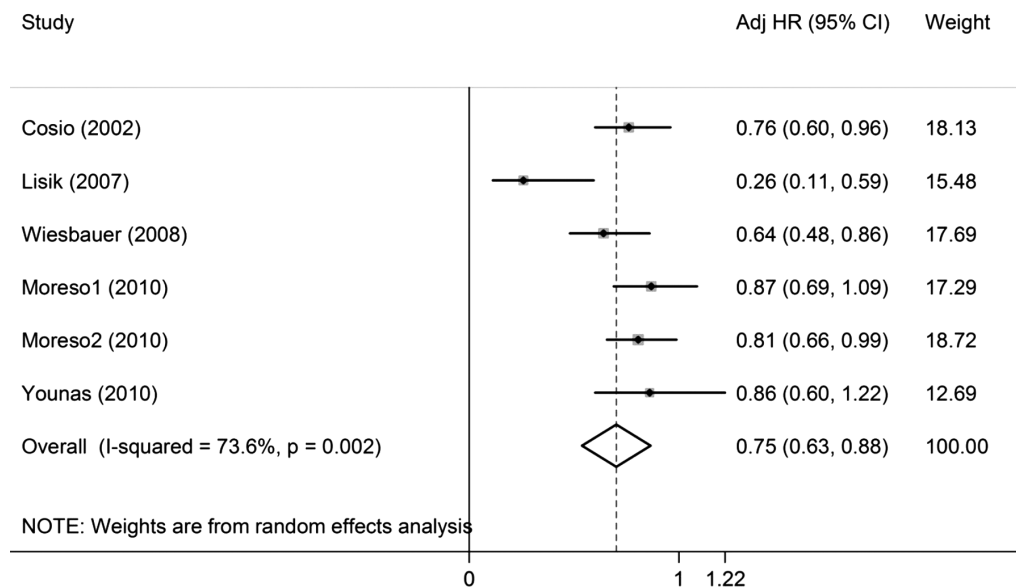
Study   Adj HR (95% CI)   Weight

Cosio (2002)   0.76 (0.60, 0.96)   18.13

Lisik (2007)   0.26 (0.11, 0.59)   15.48

Wiesbauer (2008)   0.64 (0.48, 0.86)   17.69

Moreso1 (2010)   0.87 (0.69, 1.09)   17.29

Moreso2 (2010)   0.81 (0.66, 0.99)   18.72

Younas (2010)   0.86 (0.60, 1.22)   12.69

Overall (I-squared = 73.6%, p = 0.002)   0.75 (0.63, 0.88)   100.00

NOTE: Weights are from random effects analysis

        0   1   1.22

Figure 7. Pooled effect of statins on patient survival of kidney transplant recipients, based on the reported adjusted hazard ratios (HRs) and 95 % confidence intervals (CIs).
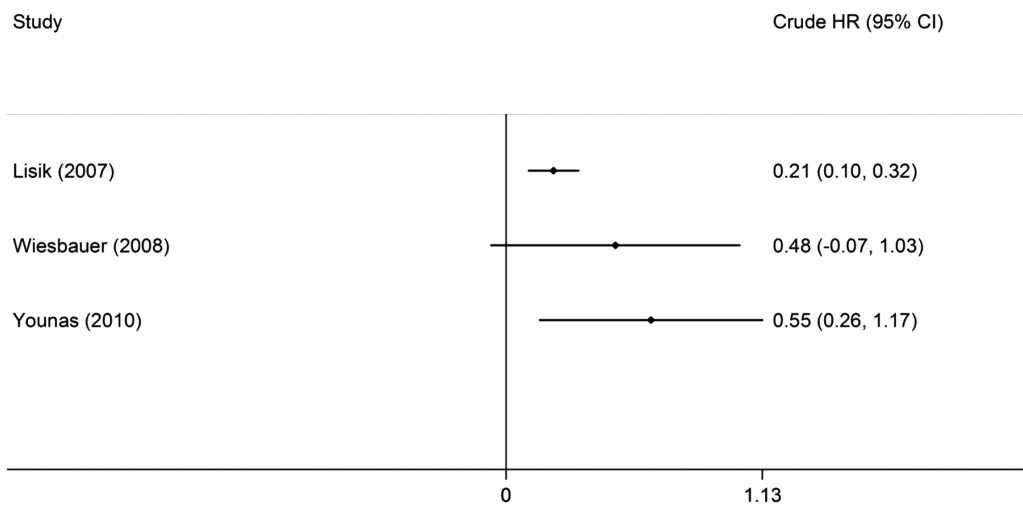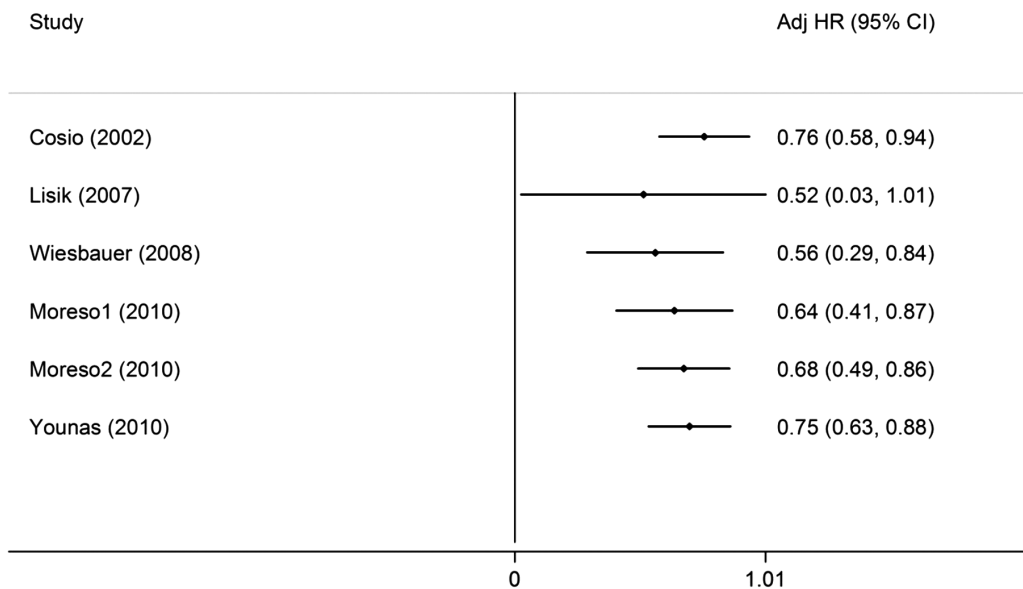
Study   Crude HR (95% CI)

Lisik (2007)   0.21 (0.10, 0.32)

Wiesbauer (2008)   0.48 (-0.07, 1.03)

Younas (2010)   0.55 (0.26, 1.17)

0   1.13

Figure 8. Cumulative meta-analysis of the effect of statins on patient survival of kidney transplant recipients, based on the reported crude hazard ratios (HRs) and 95 % confidence intervals (CIs).

Study   Adj HR (95% CI)

Cosio (2002)   0.76 (0.58, 0.94)

Lisik (2007)   0.52 (0.03, 1.01)

Wiesbauer (2008)   0.56 (0.29, 0.84)

Moreso1 (2010)   0.64 (0.41, 0.87)

Moreso2 (2010)   0.68 (0.49, 0.86)

Younas (2010)   0.75 (0.63, 0.88)

0   1.01

Figure 9. Cumulative meta-analysis of the effect of statins on patient survival of kidney transplant recipients, based on the reported adjusted hazard ratios (HRs) and 95 % confidence intervals (CIs).

DISCUSSION

Statins have indefinite effects on kidney function and mortality in kidney transplant recipients. The data are particularly deficient due to the lack of systematic reviews in this regard. Although the initial crude analysis (ie, without corrections for other variables) in our study showed no significant relationship between the use of statins and survival, the adjusted HRs were suggestive of possible beneficial effect of statin treatment after kidney transplantation, with narrow confidence intervals

for patient and graft survival resulted from the standard Cox regression analyses.

As dyslipidemia is known as a nonimmunologic risk factor associated with chronic allograft nephropathy following kidney transplantation, the ALERT trial enrolled 2102 kidney transplant recipients who were followed up for 5 to 6 years in a randomized double-blind placebo controlled study.[3] Renal end points included graft loss or doubling of serum creatinine or death. The results showed that fluvastatin treatment led to 35% risk reduction for cardiac death or definite nonfatal

myocardial infarction.[3] Nevertheless no difference was found between the fluvastatin and placebo groups for kidney outcomes, such as doubling of serum creatinine or graft loss.[4] Moreover, studies by Moreso and colleagues in 2010 and Wiesbauer and colleagues in 2008 are two other large studies that showed that benefits of statins in kidney transplant population were mainly dependent on an improvement in patient survival.[5,6] Similarly in our study, graft survival after kidney transplantation was not affected by statins crude results, but this analysis showed that the use of statins was correlated independently with improved graft survival after kidney transplantation, when confounding variables such as age, sex, and serum creatinine were controlled.

Though several studies confirmed the protective effect of statin on patient survival,[5-7] surprisingly, our crude analysis has not resulted the same effect in kidney transplant recipients. However, we showed statin therapy was independently associated with prolonged patient survival when some important confounding variables were controlled in adjusted analysis. Consistently, in a multivariable analysis, Cosio and colleagues in 2002 and Del Castillo and colleagues in 2004 showed that the use of statins correlated independently with improved patient survival and graft survival, respectively.[3,11] Ozieh and coworkers revealed high doses of statin reduced the risk of graft loss in kidney transplant recipients, with a mortality benefit in African Americans, despite similar low-density lipoprotein cholesterol levels.[12]

Several years after the ALERT study published in 2003, a Cochrane meta-analysis on the effect of statins in kidney transplant recipients was published in 2014, in which approximately 2 out of 3 patients were from the ALERT. Both studies reported no significant effect of statins on kidney function and all-cause mortality in kidney transplant recipients.[2] It is important to remark that in the ALERT trial, age-adjusted mortality from cardiovascular disease in kidney transplant recipients has increased over a mean follow up 5.1 years,[13] and some patients died with normal kidney function in this period and were excluded from the study. On the other hand, early statin therapy might be an independent predictor of long-term graft survival.[5] In the ALERT study, they included patients who had received a kidney (or combined kidney and pancreas) transplant at least 6 months prior to randomization, and had stable graft function.[7] Fluvastatin was not used from the beginning but was initiated only for hyperlipidemia patients or primary prevention. Then, it would be expected that renal lesions may be too advanced at that time and statin initiation was too late to preserve graft survival.

The ALERT study evaluated lipid-lowering effect of only fluvastatin on cardiac death and renal end points. Limited data are available comparing the renal effects of different statins head-to-head.[2] As potency, efficacy, nephrotoxicity, pharmacokinetics, and pharmacodynamics of different statins are not the same, ineffectiveness of fluvastatin cannot rule out the beneficial effect of other ones such as pravastatin and simvastatin.[7,14-16] In addition, the doses used in previous studies might be low, while pleiotropic property of statins are frequently more prominent with high doses of statins, and there may be particular differences between several kind of statins.[17] Nonetheless, the benefits and harms of more intensive treatments are less known.[4]

The ALERT study was designed to detect lipid-lowering effect of fluvastatin on cardiac outcomes and renal end points, while there are reasons to believe that statins may have other beneficial effects that are at least partially independent of lipid levels. For instance, statins are known to have pleiotropic effects such as anti-inflammatory, antiproliferative, and immunosuppressive effects,[3,18,19] which suggested their possible impact on acute allograft rejection.[20-22] The immunomodulatory and antiproliferative effects of statins on meningeal cells and myofibroblasts confirm the inhibitory effect of statin on the progression of chronic allograft vasculopathy in heart transplant recipients.[10] Regarding the vascular remodeling, interstitial fibrosis, and tubular atrophy, chronic allograft nephropathy as the most common cause of late kidney allograft rejection, CKD, and atherosclerosis exhibit many similarities.[13] Intensive statin treatment can halt the progression of atherosclerosis.[23] The beneficial effects of statins on coronary atherosclerosis progression have been attributed not only to lipid-lowering effects, but probably also to their anti-inflammatory aspects.[24] Also, nephroprotective properties of statins have been ascribed to regulate fibrogenic mechanisms and their effect on endothelial dysfunction.[25] Therefore, it could

be suggested that statin treatment might preserve kidney allograft function by decreasing the incidence of chronic graft loss.[2,26] Although the ALERT study showed no beneficial effect of fluvastatin on the kidney transplant function or on patient survival, recent studies suggest that statins inhibit interstitial fibrosis in kidney allografts and maintain or even ameliorate its function.[10,27] These findings seem to be independent of the lipid-lowering impact of statins and might explain why lipid-lowering treatment with fluvastatin did not affect the renal endpoints. Furthermore, many observational studies did not apply adequate statistical techniques to account for "confounding by indication" that is likely to occur in this type of study design. It is therefore possible that the reported results could be due to residual confounding rather than to statin treatment.[6]

In our study, both acute and chronic rejection were evaluated. Some of the clinical trials with small sample sizes and short periods of follow-up have suggested that statins may reduce the risk of acute rejection or kidney transplant vasculopathy, if they are introduced just after transplantation. However, information about the long-term evolution of kidney function or death-censored graft survival is lacking.[5]

The majority of eligible articles reported relative risk instead of HR. Although both are used to compare the chance of an event happening in two (or more) groups, HR is used often in the context of survival analysis, where two groups are followed over time. In our study, we designed a meta-analysis and we selected the articles that reported HR.

In the current study, cumulative analyses indicated that no further experiments are necessary, because articles published after the 2008 could not significantly change the overall results.

CONCLUSIONS

The present study may provide valuable information on the potential beneficial effects of statins graft outcome. This analysis showed that the use of statins independently correlated with improved patient and graft survivals after kidney transplantation, when the population was controlled for confounding variables. We conclude that kidney transplant patients benefit from statins, and that they decrease mortality and morbidity

of this group of patients. These results suggest a compelling reason to optimize statin therapy in kidney transplant recipients.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

None declared.

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