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Effect of HMG-CoA-Reductase Inhibitors on Survival in Type 2 Diabetes Patients with End Stage Diabetic Nephropathy*

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Abstract
Introduction: We studied the effect of HMG-CoA-reductase inhibitor (= CSE-I) treatment on mortality in a population of hemodialysis patients with diabetic nephropathy due to type 2 diabetes. Since the efficacy of CSE-I in dialysis patients is discussed controversially, we tested the hypothesis that only patients with LDL-cholesterol > 100mg/dl benefit from CSE-I.
Methods: We enrolled all 445 prevalent chronic hemodialysis patients with end-stage diabetic nephropathy from 30 centres in Southern Germany from August 1999 to January 2000 for prospective study until December 2003. Fasting lipid profiles prior to dialysis session and a complete clinical phenotype were determined at inclusion. We formed 2 patient groups (serum LDL > vs. ≤ 100 mg/dl). Only CSE-I were used as lipid lowering therapy in our cohort. 122 Patients were on CSE-I therapy during the study. All cause mortality (ACM) was the primary end point. Survival analysis was performed by Kaplan Meier and multivariate Cox regression analysis.
Results: Multivariate regression analysis and Kaplan Meier survival analysis showed a decrease in risk for ACM for patients on CSE-I therapy, irrespective of lipid status (multivariate hazard ratio (= HR) 0.58; p = 0.049; ACM 72.1% (no CSE-I) vs. 59.7% (+ CSE-I); mean survival 2.37 ± 0.08 years (no CSE-I) vs. 2.77 ± 0.12 years (+ CSE-I), p = 0.003). In patients with LDL > 100mg/dl, statin treatment was also associated with reduced ACM: 48.0% (+ CSE-I) vs. 70.1% (no CSE-I), (multivariate HR 0.28, CI 95% 0.11 – 0.75, p = 0.01), but not in patients with LDL ≤ 100mg/dl (HR 0.84, CI 95% 0.41 – 1.72 p = 0.63).
Conclusion: Our data indicates that hemodialysis patients with type 2 diabetic nephropathy may benefit from statin therapy irrespective of baseline LDL-cholesterol level. Patients with LDL>100mg/dl benefit most when treated with CSE-I.

Key words: diabetic nephropathy; HMG-CoA-Reductase-Inhibitors; survival; dialysis; nephropharmacology

Abbreviations: HMG-CoA-Reductase Inhibitor = CSE-I; All cause mortality = ACM; Body mass index = BMI; Coronary artery disease = CAD; C-reactive protein = CRP; End Stage Renal Disease = ESRD; Hazard Ratio = HR; Hemodialysis = HD; Peripheral arterial occlusive disease = PAD

Introduction

There is no population showing higher cardiovascular event rates and mortality than diabetic patients with end stage renal disease. The United States Renal Data System (USRDS) registry reports a rate of 7% cardiovascular events per year and about 20% annual mortality. In addition to optimal antidiabetic and antihypertensive therapy cholesterol lowering therapy may help reduce cardiovascular risk to improve survival. Data on efficacy of CSE-I in dialysis populations is sparse [1]. To date, there is no prospective, randomised controlled trial evaluating the effect of CSE-I in a hemodialysis population, let alone diabetic patients [2]. The therapeutic goal of CSE-I therapy in dialysis patients in terms of LDL-level is different to the population without renal insufficiency, since LDL levels may be pathologically reduced due to malnutrition, inflammation and other factors [3, 4]. Data about studies examining the safety of CSE-I in dialysis patients are limited [1]. Accordingly, dialysis physicians have previously been reluctant in prescription of CSE-I (US dialysis population: 9% and 16% [5, 6], UK population: 16% [7]). Internationally accepted treatment aims for diabetic patients suggest an LDL target for the diabetic population of ≤100mg/dL [8, 9]. We thus investigated the effect of CSE-I use on survival in a large cohort of type 2 diabetes ESRD patients. Specifically, we tested the hypothesis that only patients with an LDL>100mg/dl benefit from CSE-I use by a subgroup analysis.

Methods

Subjects

445 Caucasian patients with ESRD due to diabetic nephropathy were recruited from 30 dialysis centres in Southern Germany from August 1999 to January 2000

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[10]. Diagnostic criteria for diabetic nephropathy were: confirmation by biopsy or assumption by a typical clinical course (longstanding diabetes mellitus successively followed by microalbuminuria, proteinuria and renal insufficiency in the absence of other causes of proteinuria). Patients were recruited only if age was >35 years at diagnosis of diabetes mellitus. Medication was determined at baseline and at the final follow-up on December 4th, 2003, or at the time of death or loss to follow up.

The study was approved by the Ethics Committee of the Medical Faculty of the University of Regensburg (Study Nr. 97/38 GENDIAN: Genetic and clinical predictors of morbidity, mortality and diabetic nephropathy with end stage renal disease in diabetes mellitus type 2 – a prospective cohort study). All patients gave informed consent to participation in the study.

Clinical Parameters

Cardiovascular risk profile and morbidity, medication history and laboratory parameters established as predictors for survival in dialysis patients were determined by questionnaire and reviewing the patients´ charts. We determined date of birth, diagnosis of diabetes mellitus, of nephropathy and of begin of dialysis therapy, respectively.

Dialysis Parameters

For analysis of the effect of dialysis membrane type on inflammation, high flux dialysis was defined as an ultrafiltration coefficient > 20ml/h/mmHg and low flux dialysis was defined as an ultrafiltration coefficient < 20ml/h/mmHg. Biocompatibility of filters was differentiated based on data from Hoenich and Katopodis [11].

Specimen Collection

After enrolment of the patient 10ml whole blood samples were drawn prior to hemodialysis sessions in the fasting patient, and centrifuged within 6h.

Laboratory Parameters

Cholesterol measurements were undertaken while the patient was on CSE-I or not – but not before CSE-I. For cholesterol-measurements we used Cholesterol Reagents (BAYER: Prod. No.: B01-4124-01). For determination of HDL-Cholesterol, we used Direct HDL Cholesterol II Reagents (BAYER :Prod. No.: B01-4757-01).

The following formula was used for calculation of serum LDL cholesterol:

[total serum cholesterol] – [1/5 serum triglyceride] – [HDL-cholesterol in serum]

Statistical Analysis

This was a prospective uncontrolled study. All cause mortality served as endpoint. Results are expressed as mean (± 1 standard deviation), unless stated otherwise. Comparison of continuous variables between groups were performed by Student´s t-test, ANOVA and of categorical variables by χ^2 or Fisher´s exact test. Differences with $p < 0.05$ were considered as significant.

Survival analysis was performed by the Kaplan Meier method, comparing groups using the log-rank test. To correct for covariates, a Cox proportional hazard ratio model was applied. Censoring occurred for lost-to-follow-up, renal transplantation and if alive at the final examination. Duration of dialysis therapy from study inclusion onwards was the time variable if not indicated otherwise. Covariates used for survival analysis and explorative statistics for comparison of patient groups were age at start of dialysis therapy (years), duration of previous dialysis therapy and of diabetes at study inclusion (years), body mass index, systolic and diastolic blood pressure prior to dialysis session at inclusion (mmHg), serum albumin (g/L), log CRP (mg/l) and HbA1c (%), gender (reference: male), smoking history (reference: never smoker), medication with ACE-inhibitors or AT II receptor 1 antagonists, platelet inhibitors (ASS, clopidogrel, ticlopidin), beta-blockers (reference: no such therapy), presence of coronary heart disease (reference: no CAD), history of coronary intervention including bypass surgery and PTCA (reference: no intervention), history of myocardial infarction, peripheral artery occlusive disease stage IV (PAD) and stroke (reference: no such history). Covariates were included in the final model if they had a significant effect on survival in univariate Cox analysis (CSE-I therapy, age at start of dialysis, history of myocardial infarction, Stage IV PAD, log CRP). In addition, gender was included into the final model by a priori considerations. Also, the interaction [CSE-I therapy]*[log CRP] was included in the final model since this term was found to show a significant effect on survival in univariate analysis.

The interaction between LDL group status and therapy with CSE-I was found to be highly significant in the cohort (HR for [LDL group status]*[therapy with CSE-I] = 0.52, 95% CI 0.45-0.78, p = 0.002). Also, the likelihood ratio (LR) test for comparison of the log-likelihood statistics for the interaction model and the no-interaction model was highly significant ($p < 0.001$). Thus, the interaction model is acceptable, allowing separate analysis of patients in the two LDL subgroups.

Power calculations for survival analysis were performed separately for each patient subgroup with the "PS Power and Sample Size Calculations" software package, Version 2.1.30 [11]. For patients with LDL > 100mg/dl, the study of the analysis of effect of CSE-I therapy on survival was powered with 0.8 to detect a hazard ratio of 0.54 with a 0.05 Type I error probability, given a 29.9% cumulative control survival rate at the end of the study, an accrual period of 6 months, and a follow up of 52 months. For the group with LDL ≤ 100mg/dL, the study's power was 0.8 to detect a hazard ratio (= HR) of 0.58 given a cumulative control survival rate of 25.2% at the end of the study.

Statistical analysis was performed with the SPSS® Version 11.5 software package (Chicago, USA).

Results

Patient Characteristics

54 of 222 patients with serum LDL-cholesterol levels > 100mg/dl and 68 of 223 patients with serum LDL ≤ 100mg/dl were taking CSE-I from baseline until death or last follow up. The baseline characteristics of the total collective (n = 445) revealed following differences: Participants taking CSE-I more frequently had a history of coronary intervention and were more frequently taking beta-blockers and anti-platelet-agents ($p<0.05$). Patients treated with CSE-I were more frequently using biocompatible and high flux dialysis membrane (+ CSE-I vs. no CSE-I: High Flux Dialysis membrane: p = 0.015, biocompatible dialysis membrane: p = 0.002).

Baseline characteristics between the subgroups as defined by serum LDL level are outlined in Table 1. Patients with lower serum LDL-cholesterol levels at baseline were more frequently male, more frequently taking calcium-antagonists and less frequently taking anti-platelet-agents. They had higher CRP values, lower serum albumin, lower BMI and had less frequently PAD stage IV. All other variables showed no significant difference between the subgroups. Mean LDL-cholesterol was similar irrespective of CSE-I treatment within both subgroups (low LDL + CSE-I: 68.0 ± 2.4mg/dl and low LDL, no CSE-I: 71.4 ± 1.6mg/dl, $p>0.05$; high LDL + CSE-I: 139.2 ± 4.7mg/dl and high LDL, no CSE-I: 136.0 ± 2.1mg/dl, $p>0.05$).

Survival Analysis

Mean survival in the high LDL-cholesterol subgroup was found to be significantly higher than in the low LDL-cholesterol group independent of statin use (2.7 ± 1.4 years for LDL > 100 mg/dl vs. 2.3 ± 1.4 years for LDL ≤ 100 mg/dl, $p<0.05$). CSE-I use in our total collective (n = 445) was associated with a significant 42% reduction in the end point all cause mortality (multivariate HR 0.58; Cl 0.34 – 0.99, p = 0.049, Fig. 1). Accordingly, all cause mortality was more frequent in patients not treated with CSE-I (72.1%) than in those with CSE-I (59.7%). Mean survival of patients with CSE-I therapy was significantly higher [2.77 ± 0.1 years (+ CSE-I) vs. 2.37 ± 0.1 years (no CSE-I), p = 0.003].

Similar results were obtained in the separate analysis of patients with LDL > 100mg/dl [ACM 48.0% (+ CSE-I) vs. 70.1% (no CSE-I); HR for therapy with CSE-I 0.28 (0.11-0.75); $p<0.01$; Fig. 2]. In contrast, there was an insignificant trend for improved survival under CSE-I therapy in the subgroup of patients with

Table 1. Baseline characteristics of study subgroups.

	LDL > 100mg/dl mean ± SD or % (n = 222)	**LDL ≤ 100mg/dl** mean ± SD or % (n = 223)	**p**
LDL	138.5 ± 41.2	70.4 ± 19.7	<0.001
CSE-I	24.3%	30.5%	0.204
Male gender	47%	62.8%	0.001
Age at Begin of Dialysis (years)	65.4 ± 8.4	64.4 ± 8.9	0.409
Duration HD at inclusion (years)	2.6 ± 2.3	2.5 ± 2.0	0.266
Duration Diabetes at Begin of HD (years)	15.8 ± 9.6	14.9 ± 9.6	0.311
CAD	61.1%	53.9%	0.066
Coronary intervention	19.7%	16.7%	0.456
PAD stage IV	47.3%	37.6%	0.035
History of Stroke	31.0%	31.1%	0.917
History of Smoking	41.5%	46.9%	0.292
Anti-Platelet-Agents	62.4%	48.7%	0.004
Beta-Blocker	26.6%	24.8%	0.666
ACE-Inhibitors / AT II-Receptor-Antagonists	51.4%	54.9%	0.506
Calcium-Antagonists	41.7%	51.8%	0.035
CRP (mg/l)	11.75 ± 13.83	14.70 ± 17.19	0.046
Albumin (g/L)	43.46 ± 4.70	41.54 ± 5.53	<0.001
HbA1c (%)	6.90 ± 1.17	6.86 ±1.08	0.748
BMI	27.1 ± 4.34	26.06 ± 4.63	0.016
High Flux Dialysis membrane	42.8%	46.2%	0.620
Biocompatible Dialysis membrane	71.1%	78.0%	0.260
Total dialysis time (h/week)	12.41 ± 1.23	12.85 ± 1.26	0.086

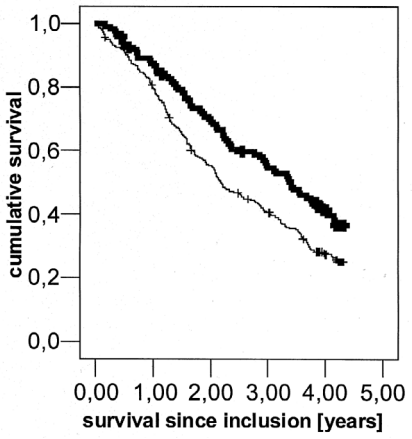

Fig. 1. Kaplan-Meier-Analysis: Effect of therapy with CSE-I on survival in the total collective. Primary endpoint is all cause mortality.
Bold line:+ CSE-I. Thin line: no CSE-I. Univariate log rank statistic = 6.35; p = 0.012.

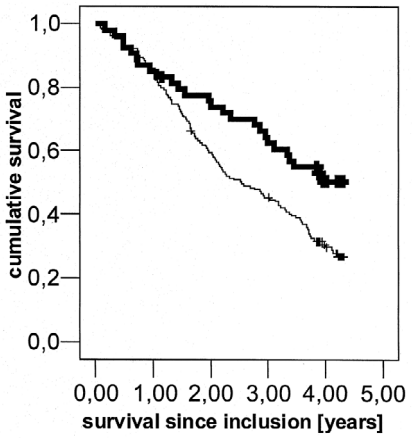

Fig. 2. Kaplan-Meier-Analysis: Effect of therapy with CSE-I on survival in patients with LDL > 100mg/dl. Primary endpoint is all cause mortality.
Bold line:+ CSE-I. Thin line: no CSE-I. Univariate Log rank: 7.0; p = 0.0082.

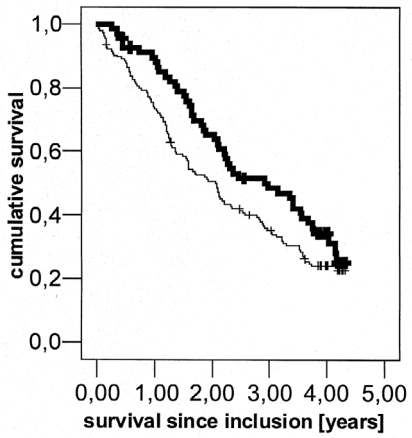

Fig. 3. Kaplan-Meier-Analysis: Effect of therapy with CSE-I on survival in patients with LDL ≤ 100mg/dl. Primary endpoint is all cause mortality.
Bold line: + CSE-I. Thin line: no CSE-I. Univariate Log rank: 3.49; p = 0.062.

LDL ≤ 100mg/dl [ACM 76.6% (+ CSE-I) vs. 74.8% (no CSE-I); HR for therapy with CSE-I = 0.84 (0.41-0.72); p = 0.63, Fig. 3].

Discussion

National and international guidelines claim a serum LDL-cholesterol level less 100mg/dl as therapeutic goal in any diabetic patient [8, 9]. It is unknown if the guidelines, based on populations without renal insufficiency and with a different cardiac risk profile, can be extrapolated to diabetic dialysis patients [1, 13, 14]. An important difference between patients with and without renal insufficiency is the observation that high not low total serum cholesterol is a favourable prognostic survival marker in hemodialysis patients (reverse epidemiology) [14].

Elevation of triglycerides, VLDL-cholesterol and HDL-cholesterol accompanied by a reduction of Apo-Lipoprotein a and LDL-cholesterol in dialysis patients are common and possibly due to toxic uremic effects and influences of the dialysis procedure itself [3, 6, 15, 16]. These typical changes of the lipid profile suggest an even higher atherogenic potency, which might be reduced by CSE-I treatment [17]. Complicating matters, there is a subgroup in the dialysis population showing reduced total and LDL-cholesterol serum levels irrespective of lipid lowering treatment [5]. Thus the application of targets for lipid lowering therapy in a general population to the dialysis population may be questionable.

The efficacy of CSE-I in lowering total cholesterol, LDL-cholesterol and triglyceride levels in dialysis patients has been demonstrated before without side effects specific to dialysis patients [18]. In contrast, others assume more side effects of CSE-I in patients with renal impairment [19, 20]. A meta-analysis of prospective trials in patients with ESRD with CSE-I compared to placebo and other lipid lowering substances showed a cholesterol lowering effect of CSE-I in dialysis patients that was equivalent to that observed in the general non-renal population [21]. None of these studies investigated the effect of statin therapy on mortality.

The only large prospective interventional trial investigating mortality and cardiovascular end points in diabetic dialysis patients is the German 4D-study which did not stratify patients for nutritional or LDL status in the randomisation procedure and excluded patients with LDL cholesterol < 80mg/dl [2]. Interestingly, therapy with atorvastatin had no effect on mortality in the complete collective in that study (Christoph Wanner, personal communication).

Nonetheless, the reduction of all-cause-mortality by CSE-I therapy seen in our prospective cohort analysis is comparable to findings in observational studies on general dialysis collectives such as the USRDS, with a reduction in mortality risk of 32% under statin use (USRDS-analysis: multivariate HR 0.68, CI 0.54-0.87) [22].

However, we found a significant survival benefit for CSE-I use only in patients with LDL > 100mg/dL and only a trend for risk reduction in patients with LDL ≤ 100mg/dL. The former was observed in spite of baseline mean LDL under CSE-I therapy (139.2 mg/dl)

being significantly above the target of 100mg/dL. In contrast, the effect on survival in the low-LDL group may have been too small to be detected by the power of our study.

There are several limitations to our study, which had a non-interventional, uncontrolled design. First, the use of cohort data to determine an association between medication use and outcomes must be regarded as exploratory since the non-randomised prescription of CSE-I's may confound the observed association. Also, in a subgroup analysis we found an insignificant trend for increased CRP and lower albumin values in patients dialysed with bioincompatible or low flux filter membranes (data not shown). The type of dialysis filter might influence survival per se [23]. Thus, a prospective, randomised controlled trial would optimally take into account subgroups with differing LDL-status, comorbidity, chronic inflammatory activity, nutritional status and dialysis modality profiles.

Also, we cannot exclude that patients treated with CSE-I had a different quality of general medical care than those without a CSE-I [24, 25].

A further limitation is the lack of follow-up lipid values. We cannot exclude that LDL values differed significantly over the course of the study, thus confounding the cardiovascular risk profile determined by lipid status at baseline.

In spite of the stated limitations, our data may enable the development of a dialysis specific approach to lipid lowering therapy. Hereby, patients with LDL > 100mg/dL benefit from CSE-I therapy. This has been previously shown in patients with total cholesterol >220mg/dL [25]. Considering the BMI, CRP and albumin levels observed in our cohort, it is likely that patients with LDL > 100mg/dL represent a subgroup with better general health that are comparable to a general non-renal population [10, 26-31]. It is highly likely that these patients would benefit from CSE-I therapy with a target LDL < 100mg/dL. However, the number needed to treat to prevent one cardiovascular death may be significantly higher in the low-LDL group. Our study suggests that cardiovascular comorbidity, inflammation and malnutrition in this group may be so advanced that LDL lowering therapy may come too late and be only marginally effective. Developing an effective therapeutic strategy for improving survival in these patients remains a challenge to dialysis physicians, thus emphasising the need for effective primary prophylaxis.

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