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Analysis of risk factors in patients with severe chronic kidney disease. The role of atorvastatin.

Akademisk avhandling

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av

Benny Holmberg

Umeå University
SE- 901 87 Umeå
www.umu.se

Fakultetsopponent:
Peter M. Nilsson

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Abstract

Background and aim: There had been no randomized end-point studies with statins for patients with severe renal failure. The purpose of this prospective, open, randomized, controlled study was to investigate whether atorvastatin (10 mg/day) would alter cardiovascular end-points and the overall mortality rate of patients with chronic kidney disease stage 4 or 5 (creatinine clearance< 30 ml/min) and to influence risk factors.

Material & Methods: This was an open, prospective, randomized study. A total of 143 patients were included: 73 were controls and 70 were prescribed 10 mg/day of atorvastatin. As efficacy variables, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride levels were determined at the start of the study and at 1, 3, 6, 12, 18, 24, 30 and 36 months. The primary end-points were all cause of mortality, non-lethal acute myocardial infarction, and coronary artery intervention. Various risk factors were studied. In the 97 patients on haemodialysis inter dialysis weight gain (IDWG) was calculated as ultrafiltration in kg/body weight in kg given in percentage of the weight. The burden of IDWG was analyzed.

Results: In the atorvastatin group, total cholesterol and low-density lipoprotein cholesterol were significantly reduced, the latter by 35% at 1 month and then sustained. Atorvastatin was withdrawn in 23% of patients due to unacceptable side effects, most frequent complaints being gastrointestinal discomfort and headache.

Primary end-points occurred in 74% of the subjects. There was no difference in cardiovascular endpoint and survival between the control and atorvastatin groups. The 5-year end-point-free survival rate from study entry was 20%. There was no evidence of more benefit of atorvastatin for patients with diabetes mellitus and chronic kidney disease versus the other patients; instead plasma fibrinogen increased.

The IDWG was significantly larger in patients who suffered from end-points due to cardiovascular reasons, cardiac reasons, congestive heart failure, aortic aneurysm, and intracerebral bleeding.

Conclusion: These data showed that in contrast to other patient groups, patients with severe chronic kidney disease 4 and 5, including those with diabetes mellitus, seem to have no benefit from 10mg/day of atorvastatin. Instead we found a high IDWG to be an important risk factor that should be prevented. There was no evident connection between atorvastatin medication and IDWG.

Key Words: Atorvastatin, cholesterol, chronic kidney disease, haemodialysis, cholesterol, lipids, peritoneal dialysis, risk factors, statins, inter dialysis weight gain.

Sammanfattning på svenska

Denna studie var en öppen prospektiv randomiserad multicentrestudie av totalt 143 patienter. Av dessa var 97 i hemodialys (HD) respektive 13 i peritonealdialys (PD). Övriga 33 var njursjuka i stadium 4 (clearance <30ml/min o 1.73 kvm kroppsyta) (n=33). Randomisering har skett till behandling med atorvastatin 10 mg/d (n=70) respektive till en kontrollgrupp utan behandling (n=73). Utfall i form av död, hjärtinfarkt eller coronarintervention studerades. Analys har skett med avseende på atorvastatinets effekter och bieffekter samt utfall av kardiovaskulära tillstånd och död. Vidare har i huvudsak analys av lipider och metabola faktorer samt av viktuppgång mellan dialyserna, mätt som ultrafiltrationsbehov, utförts.

Studien består av fem delarbeten:

Delarbete **1** analyserade biverkan och säkerhetsaspekter av behandling med atorvastatin. 16 patienter (23%) avbröt studien pga biverkningar. Total kolesterol och LDL kolesterol reducerades signifikant, det senare med 35% efter en månads behandling.

Delarbete **2** var en studie av kardiovaskulära händelser och död, där 106 utfall inträffade (74%). Atorvastatinbehandling påverkade ej utfallet.

Delarbete **3** undersökte ultrafiltrationsbehov och viktuppgång mellan dialyserna hos 88 HD-patienter och om detta var av betydelse för utfall av kardiovaskulära tillstånd och död. Man fann att viktuppgång på mer än 3.5% av kroppsvikten mellan dialyserna medförde en minskad överlevnad.

Delarbete **4** inkluderade 97 HD-patienter och var en fortsättning av delstudie 3. Där utvärderades betydelsen av viktuppgången mellan dialyserna relaterad till incidens av olika orsaker till död och specifika orsaker till kardiovaskulära tillstånd. En för hög viktuppgång pga vätskeöverskott ökade risken för kardiovaskulär sjuklighet.

Det femte (**5**) och delarbetet utvärderade om 44 patienter med diabetes mellitus hade nytta av atorvastatinbehandling jämfört med övriga. Diabetespatienter hade ingen nytta av atorvastatinbehandling med avseende metabola markörerna lipider, HbA1c, fibrinogen, CRP, njurfunktion och proteinuri. Någon trend till överlevnadsvinst av atorvastatin kunde ej ses.

Konklusion: Våra data har visat att atorvastatin ej är till fördel för njursjuka CKD 4 och 5 inklusive de med diabetes mellitus. Viktuppgång mellan dialyserna utgör en signifikant riskfaktor som måste förebyggas.

Manuscripts as part of the thesis:

1. Holmberg B, Brannstrom M, Bucht B, Crougneau V, Dimeny E, Ekspong A, Granroth B, Grontoft KC, Hadimeri H, Ingman B *et al*: **Safety and efficacy of atorvastatin in patients with severe renal dysfunction**. *Scand J Urol Nephrol* 2005, **39**(6):503-510.

2. Stegmayr BG, Brannstrom M, Bucht S, Crougneau V, Dimeny E, Ekspong A, Eriksson M, Granroth B, Grontoft KC, Hadimeri H, Holmberg B *et al*: **Low-dose atorvastatin in severe chronic kidney disease patients: a randomized, controlled end-point study**. *Scand J Urol Nephrol* 2005, **39**(6):489-497.

3. Stegmayr BG, Brannstrom M, Bucht S, Dimeny E, Ekspong A, Granroth B, Grontoft KC, Hadimeri H, Holmberg B, Ingman B *et al*: **Minimized weight gain between hemodialysis contributes to a reduced risk of death**. *Int J Artif Organs* 2006, **29**(7):675-680.

4. Holmberg B, Stegmayr BG: **Cardiovascular conditions in hemodialysis patients may be worsened by extensive interdialysis weight gain**. *Hemodial Int* 2009, 13(1):27-31.

5. Holmberg B, Andersson C, Stegmayr BG: **There is no benefit of atorvastatin for patients with severe renal impairment independent if they have DM or not.** *Sent for publication*.

Overview of studies

Paper 1	**Safety and efficacy of atorvastatin in patients with severe renal dysfunction.**
AIM	To investigate the efficacy and safety of a daily dose of 10 mg of atorvastatin in patients with CKD 4 and 5.
Data source	All 143 patients. 70 cases with atorvastatin, 73 controls.
Measure	AE: Side-effects, ASAT, ALAT, GGT, CK; Efficacy: Total cholesterol(TC), LDL, HDL, TG
Results	Atorvastatin effectively lowered LDL and TC but 21% of the patients could not tolerate the side effects and stopped medication.
Paper 2	**Low-dose atorvastatin in severe chronic kidney disease patients: a randomized, controlled end-point study.**
AIM	To investigate whether atorvastatin 10 mg/day would alter cardiovascular end-points and the overall mortality rate of patients with CKD 4 and 5.
Data source	All 143 patients: 70 cases with atorvastatin, 73 controls
Measure	Primary endpoints: All-cause mortality, non-lethal AMI, CABG, PTCA.
Results	Primary end-points occurred in 74% of the subjects with no difference between the control groups and the atorvastatin group. Atorvastatin was not beneficial regarding long-term outcomes of cardiovascular endpoints and survival.
Paper 3	**Minimized weight gain between HD contributes to a reduced risk of death.**
AIM	To investigate if other risk factors such as the extent of inter dialytic weight gain (IDWG) was of importance for the survival.
Data source	88 haemodialysis (HD) patients.
Measure	The extent of ultrafiltration (UF) necessary to achieve dry weight. The IDWG was considered as the extent of fluid that retained in the body between two dialysis sessions. Endpoints: AMI, coronary by pass intervention, death.
Results	The extent of HD patients reaching endpoints was high, 40% . HD patients with higher need of UF had worse prognosis.
Paper 4	**Cardiovascular conditions in haemodialysis patients may be worsened by extensive interdialytic weight gain.**
AIM	Investigate whether the burden of interdialytic weight gain was of importance especially for cardiovascular end-points and survival.
Data source	97 HD patients.
Measure	IDWG and end-points: AMI, coronary vascular intervention, death any various reasons.
Results	End points occurred in 79% of the patients during the 5-year study period. Patients who had cardiovascular end-points had a higher IDWG than the others.
Paper 5	**There is no benefit of atorvastatin for patients with severe renal impairment independent if they have DM or not.**
AIM	To investigate if atorvastatin 10 mg/d would alter metabolic variables differently in patients with DM versus non-DM.
Sources	All 143 patients, among them 44 DM patients. Randomized to achieve either atorvastatin or to be a control group.
Measure	HbA1C, lipids, CRP, fibrinogen.
Results	Reduction in TC and LDL in both groups who received atorvastatin; No benefit of ator-vastatin for those with DM nor for non-DM patients; instead plasma fibrinogen increased

ABBREVIATIONS

AE	adverse events
AKI	acute kidney injury
ALAT	alanine aminotransferase
ALP	alkaline phosphatase
ANCA	anti-neutrophil cytoplasmic antibody
anti-GBM	anti-glomerular basement membrane antibody
APD	automated peritoneal dialysis
Apo	apo lipoprotein
ASAT	aspartate aminotransferase
AV-fistula	arterio-venous fistula
BMI	body mass index
CABG	coronary artery bypassgraft
CAPD	continuous ambulatory peritoneal dialysis
CDC	central dialysis catheter
CK	creatine kinase
CKD	chronic kidney disease
CRP	C-reactive protein
CVD	cardiovascular disease
CVL	cardiovascular lesion
DM	diabetes mellitus
ESRD	end-stage renal disease
FFA	free fatty acids
GFR	glomerulus filtration rate
eGFR	estimated glomerulus filtration rate
GT	glutamyl transferase
HD	haemodialysis
HDL	high density lipoprotein cholesterol
HTGL	hepatic triglyceride lipase
Ca	calcium
IDWG	interdialytic weight gain
IT	intention-to-threat
K	potassium
LD	lactate dehydrogenase
LDL	low density lipoprotein cholesterol

LPL	lipoprotein lipase
Na	sodium
MPA	medical product agency
PD	peritoneal dialysis
PP	per-protocol
PTH	parathyroid hormone
PTCA	percutaneous transluminal coronary angioplasty
SAE	severe adverse events
SR	sedimentation rate
TG	triglyceride
UF	ultrafiltrate
VAS	visual analogue scale
VLDL	very low density lipoproteins

INTRODUCTION

The kidneys are important for maintaining the body's internal balance of, especially, water and minerals (sodium, potassium, chloride, calcium, phosphorus, magnesium, sulphate). The kidneys also function as a part of the endocrine system and produce erythropoietin and 1,25-dihydroxycholecalciferol (calcitriol). Erythropoietin is involved in the production of red blood cells and calcitriol plays a role in bone formation. Besides hypertension various medical conditions can affect the kidneys, and renal function deterioration can occur acutely or chronically over several years. In such cases it is important to find out what the reasons for renal failure are (Jefferson and Schrier 2007). Thereby primary investigation should focus to exclude post-renal reasons. Those include abnormalities in the kidney pelvis, ureters, bladder and urethra. Disturbances in these areas are usually handled by the urologist. A prerenal reason for kidney injury is due to i.e., severe septic shock, bleeding, extensive surgery including aortic aneurysm, and obstruction of renal arteries. Here cooperation with specialists from various selected areas is important. A primary renal disease as a reason for kidney injury is, i.e., glomerulonephritis, interstitial nephritis due to local side effects of pharmacological drugs or toxins. If such reason (See Table 1) is suspected an early contact with nephrologists is important, in order not to delay treatment options.

Acute renal failure is divided in a) prerenal: usually due to hypoperfusion, b) renal: for example, acute tubular necrosis, primary and secondary nephritis, cardiovascular disease, infections, tumours, drug / intoxications, tubular obstruction and c) post-renal: for example, different types of congestion. In acute renal failure haemoglobin is often normal, and the kidneys may be normal or large or swollen. Urinary output may be reduced to so-called oliguria (<500 ml / day) or anuria (<100 mL / d). Despite severe kidney damage, urine output could be higher than normal (i.e. non-oliguric acute renal failure). Classifications according to the so-called Rifle stages are presented in Table 2.

Common reasons for acute kidney injury are seen in Table 1.

Table 1: Examples of various reasons for acute kidney injury.

Postrenal reasons	Prerenal reasons	Renal reasons
● Prostatic obstruction ● Urinary tract obstruction (i.e., tumour, blood clots or stones) ● Urinary retention due to dysfunction in detrusor by drugs and denervation ● Pyelonephritis and urosepsis	● Hypovolemia lead to diarrhoea, fever and bleeding ● Cardiac Failure ● Hepatorenal syndrome ● Renal artery occlusion ● Rhabdomyolysis ● Haemolysis ● Various severe infections and parasites such as Severe sepsis	● Glomerulonephritis including vasculitis ● Interstitial nephritis due to infections, drugs, intoxications ● Hereditary disturbances such as Polycystic kidney disease (acute bleeding) ● Transplant kidney rejection

Staging of acute kidney injury is based on a measurement or estimate of the glomerular filtration rate (see Table 2) and the extent of urinary output.

Table 2: The RIFLE criteria for staging of acute kidney injury are abbreviated after Risk, Injury, Failure, Loss and End-stage renal disease. Glomerular filtration (GFR), serum creatinine (s-creatine in μmol/l) and, the urine output (UO) criteria. UO criteria request adequate hydration and are given in ml/kg body weight and hour for a defined number of hours (Bellomo 2005).

Stages	**Glomerular filtration criteria / serum creatinine**	**Urine output criteria**
Risk	Increased s-creatinine x 1.5 or GFR decrease >25%	UO < 0.5 ml/kg/h for 6 hours
Injury	Increased s-creatinine x 2 or GFR decreased >50%	UO < 0.5 ml/kg/h for 12 hours
Failure	Increased s-creatinine x 3 or GFR decrease >75% or s-creatinine ≥320 μmol/l Acute rise ≥40 μmol/d	UO < 0.3 ml/kg/h for 24 hours (Oliguria) or Anuria x 12 hrs
	Dialysis dependence	
Loss	Persistent Acute Kidney Injury = complete loss of kidney function/dialysis dependent > 4 weeks	
End-stage renal disease	End-stage renal disease/ dialysis dependent for >3 months	

When acute kidney injury progresses retention of various uremic metabolites and water occurs. In addition drugs (or their metabolites) that normally are excreted by the kidneys will accumulate in the body and give more or less important side effects. A key metabolite that must be regarded is potassium that may cause acute cardiac arrhythmia. Another factor is retention of fluid that may cause i.e., acute pulmonary oedema. These patients should be submitted urgently, by the general practitioner, to the hospitals where they can be cared for by multidisciplinary teams. This thesis will focus further only on chronic kidney injury and its processes.

Chronic kidney disease

Aging, in addition to impaired function of organs such as the heart, also causes a gradually declining renal function. Impaired renal function is in itself linked to increased morbidity and mortality. This is especially true for cardiovascular diseases (CVD) – which are increased several-fold in patients whose renal function has started to deteriorate especially to the point when dialysis is needed (Foley, et al. 1998; Vanholder, et al. 2005). If the patient is also suffering from diabetes mellitus (DM), the risk for death due to CVD is considered to be further increased (Stenvinkel, et al. 2007). The causes of CVD have been connected with abnormal blood lipids, malnutrition, inflammation and atherosclerosis (MIA syndrome) (Stenvinkel 2001; Stenvinkel, et al. 2007). Up to 56% of the cases that start dialysis have shown the presence of cardiac events such as heart failure (Harnett, et al. 1995). When renal function is strongly impaired, urine output is reduced, thereby leading to an increased amount of fluid in the body which can contribute to heart failure.

At an early stage, many chronic kidney diseases are asymptomatic but need assessment and on-going monitoring and treatment since hypertension is a very common comorbidity (Haddad, et al. 2007). The aim of treatment is to reduce the risk of progression of kidney disease.

The most common causes of chronic renal failure that require dialysis are diabetic nephropathy, chronic glomerulonephritis, nephrosclerosis and polycystic kidney disease. Chronic renal failure is, by rule, discrete in its onset, exhibiting anaemia, normal urination, and small kidneys (with the exception of patients with amyloidosis, diabetic nephropathy and polycystic kidney disease).

For patients with diabetes mellitus, in addition to the classic progressive diabetic nephropathy, other conditions often worsen renal function. Such is pyelonephritis (acute or chronic inflammation of the kidney parenchyma as a result of bacterial infections), which is much more common in diabetics than in the general population. Other conditions include urinary disorders due to diabetic neuropathy. Because patients with diabetes mellitus often have high blood pressure, this contributes to an increased risk of atherosclerosis and secondary renal injury. Common causes of chronic renal impairment are seen in Table 3.

The progress of chronic kidney disease (CKD) is defined in 5 stages (Table 4). When the more severe kidney disturbances (CKD 4 and 5) are present various clinical symptoms develop due to retention of metabolic products in the body. If this stage of azotaemia / uraemia/ progresses it results in the death of the patient if no active measures are taken such as dialysis or transplantation. To decide about these stages various laboratory measures may be used.

Table 3: Examples of various reasons for chronic kidney injury.

Postrenal	Prerenal	Renal
● Prostatic obstruction ● Urinary tract obstruction (i.e., tumour, blood clots or stones) ● Urinary retention due to dysfunction in detrusor by drugs and denervation ● Intermittent pyelonephritis and urosepsis	● Myeloma ● Chronic cardiac failure ● Renal artery stenosis/ occlusion ● Chronic haemolysis ● Metabolic disorders such as Diabetes Mellitus ● Diseases with secondary deposits such as amyloidosis ● Various chronic infections and parasites such as HIV, hepatitis B or C, malaria	● Glomerulonephritis including Vasculitis ● Interstitial nephritis due to infections, drugs, intoxications ● Hereditary disturbances such as Polycystic kidney disease ● Hypertension ● Nephrosclerosis and arteriolosclerosis ● Deposits and ageing due to i.e., diabetes mellitus ● Transplant kidney rejection/ nephropathy

Estimation of kidney function

A rough estimate of kidney function may be made using laboratory variables such as serum- creatinine, urea and cystatin C, these are the most common analyses performed in daily clinical praxis. These variables do not by themself give a precise measure of the clearance capacity of the kidney measured as glomerular filtration rate (GFR).

To get a more accurate assessment of kidney function you need to determine GFR, which should be corrected to body weight. The methods for determining this do so by measuring the clearance of a substance from plasma (plasma clearance). Such methods are Cr-EDTA

clearance and iohexol-clearance. The latter is based on calculating the plasma clearance of the X-ray contrast agent iohexol. These methods are often expensive and time consuming. Another option is to measure the excretion of waste products in the urine (renal clearance). This is a cheap but more difficult approach for the patient, as it requires the patient to be thorough with urine collection, i.e. over an entire day. Another way to estimate GFR is to use blood samples of creatinine or cystatin C. These values can be inserted in formulas that include factors such as age, gender and body weight. In this way, a relatively good estimate of renal function is often provided.

The following formula demonstrates how this can be done by use of serum creatinine:

Cockcroft-Gault formula:

e GFR (men) = (1,23x (140-age) x weight)/ Serum -creatinine (μmol/l)

e GFR (women) = (1.04x (140-age) x weight) / Serum-creatinine (μmol/l)

CKD stages

When the analysis of GFR has been performed it allows the physician to clarify the extent of kidney disease that is present in the patient. A classification of CKD was proposed by the Kidney Disease Outcome Quality Initiative guidelines in 2002 (2002) and is used by most since then (Table 4).

Table 4: Various stages of chronic kidney disease (CKD)(Levey, et al. 2005).

CKD stage	GFR, ml/min/1.73 sqm	Other findings
1	≥ 90	Evidence for kidney damage: haematuria and/or proteinuria or histological changes
2	60-89	
3	30-59	
4	15-29	
5	<15	
5d	Dialysis treatment	

Investigation of renal disease begins, in rule, in primary care. As a start, post renal obstruction and pre renal causes of dehydration are ruled out. The clinical picture of renal failure is highly variable. For example, a rapidly progressing glomerulonephritis with risk of terminal renal failure can be gradual in onset with weak symptoms, whereas a moderate acute exacerbation of a chronic renal failure can cause severe symptoms including macroscopic haematuria which should always be further investigated. For progressive disease that include declining renal function and increasing creatinine levels it is recommended to contact a nephrologist, unless post renal causes exist that require urological operation or pre renal causes that require contact with another specialist. Renal medical investigation generally requires extensive sampling to evaluate renal function such as the following: blood count, C-reactive protein, sedimentation rate, plasma-glucose, potassium, sodium, creatinine, cystatin C and estimated GFR, liver function tests (ASAT, ALAT, LD, Bilirubin, GT, ALP), parathyroid hormone levels, lipids (cholesterol, LDL, HDL, TG), albumin, urea, uric acid, calcium and phosphate, urine dip sticks, diurnal U-

protein/albumin, Urine-electrophoresis, antibody titres evaluation for antinuclear antibody, anti-neutrophil cytoplasmic antibody , anti-glomerular basement membrane antibody. Chronic severe renal insufficiency is characterized by anaemia, metabolic acidosis, hypercalcaemia, increased serum creatinine, urea, urate and hyperphosphataemia, and sometimes hypocalcaemia and hypo-albuminaemia and albuminuria.

Assessment and management of CKD stages 1 + 2.

It does not seem to be cost beneficial to make population screenings to find these patients. Anamnesis including hereditary history helps to select younger patients at risk and those with hypertension, diabetes mellitus and concomitant chronic disease should be investigated. If no history exists, screening of patients above 60 years may not be cost beneficial (El Kossi and El Nahas 2007). Urinary tests with dipsticks and laboratory samples mentioned above help to early detect and manage most patients, and not to neglect those with post renal problems. If a progressive renal disease is present (decreasing GFR, increasing proteinuria and/or haematuria) it has to be considered to admit the patient for an evaluation by a nephrologist. Such evaluation has to decide if a more selective follow up and diagnostics is necessary. If the condition is stable the patient may be referred back to the general practitioner for follow up.

Assessment and management of CKD Stage 3

When the patient is presented to the general practitioner with a stage 3 kidney function it has to be decided if the change is acute or chronic, i.e., similar to the investigation mentioned above. If a progressive renal disease is present (decreasing GFR, increasing proteinuria and/or haematuria) it has to be considered to admit the patient for an evaluation by a nephrologist. The nephrological evaluation has to decide if a more thorough follow up and diagnostic evaluation has to be performed. If the condition is stable the patient may be referred back to the general practitioner for follow up. At this stage the patient has an increased risk for secondary cardiovascular complications (Vanholder, et al. 2005). A risk for retention of metabolic breakdown products of pharmaceutical drugs may occur. This has to be considered, and doses adjusted if recommended.

Assessment and management of CKD stage 4

If the patient for the first time meets the general practitioner in this stage of kidney function the patient should be further referred to a nephrologist for diagnostic and therapeutic workup. In addition, at this stage usually additional complications have developed in most patients, such as a more extensive hypertension, secondary hyperparathyroidism and anaemia. Kidney biopsy may reveal if specific treatment is useful. In patients with a chronic and quite stable situation intermediate visits may be performed with the help of a general practitioner. In this stage caution has to be taken for retention of metabolic breakdown products of pharmaceutical drugs. This has to be considered when prescribing a new drug and doses may have to be adjusted or in some drugs even avoided (see page 31). The risk for bleeding is increased in these patients due to disturbance of platelet function. Therefore, intramuscular injections should be avoided.

If an arterio-venous fistula or central dialysis catheter has been placed on the arm or

jugular vein these should not be used to take blood samples. Haematoma or contamination with infections may cause obstruction, stop and sepsis and thereby worsen conditions for later dialysis.

Assessment and management of CKD Stage 5

Up to 30 % of patients who start chronic kidney replacement treatment such as dialysis had not been in contact with a physician before initiation of dialysis. Once they are detected patients will be followed up by nephrologists. At this stage the kidney have severely impaired clearance that results in retention of metabolic waste products including potassium, phosphate, uric acid and urea and also a lot of uraemic retention products that usual are not measured (Vanholder, et al. 2003). When the CKD has progressed to this stage one has not to overlook the impaired function of the kidney to also remove water, resulting in retention of water. From the general practitioner's point of view the patient may presents for the first time with a congestive heart failure that is unresponsive to conventional diuretic treatment. The notion has to be taken to check for kidney failure. The progress of fluid retention may end up in a pulmonary oedema that is unresponsive to pharmaceutical treatment. The acute option may be to admit the patient to a dialysis unit to remove the excess of water. Before this thesis was initiated there were no data on whether there was a negative effect of fluid retention between haemodialysis.

Since many of the patients with CKD 5 also have an increased inflammation a question arises if the statins may reduce inflammation similarly to data from studies of patients without severe kidney disease (Albert, et al. 2001; Blake, et al. 2002; Ridker, et al. 2005) and thereby improve diagnoses. A particularly vulnerable group for cardiovascular morbidity are patients with diabetes mellitus and diabetics with renal/kidney disease (Ritz 2007; Stenvinkel, et al. 2007). At the start of this dissertation project, there were no studies on the benefits of the LDL-lowering effect for these patients in regard to cardiovascular

end-points, and metabolic, inflammatory, nutritional and renal variables.

In kidney failure there accumulates more than 90 substances in the body that normally are removed by healthy kidneys (Vanholder, et al. 2003). Many of these substances are not removed by dialysis, and most have not been investigated with respect to their side effects in the body. When renal failure has progressed too far dialysis (haemodialysis – HD, or peritoneal dialysis – PD) is required. Neither HD nor PD is optimal, and the 5-year survival rate for those who remain on dialysis (not transplanted) is only about 20% (Schon, et al. 2004). For HD, patients are subjected to blood-membrane interactions causing increased inflammation (Lundberg, et al. 1994; Stegmayr, et al. 1992).

For CKD stage 5d (dialysis) patients, the incidence of diabetic nephropathy is one of the most frequent diagnoses (25%). In addition, 10% of patients with other reasons for CKD 5 also suffer from diabetes mellitus. In these patients the additive of diabetes mellitus may then also contribute to further the deterioration of renal function and overall morbidity. Overall about 1/3 of the patients in Sweden who currently need dialysis or a kidney transplant have diabetes as a root cause to their kidney damage; thus this constitutes the largest group in need of an active treatment for uraemia with dialysis or transplantation (Svensson and Haraldsson 2012). Also considered to result in end stage renal disease (ESRD) are various forms of chronic glomerulonephritis that account for over 20% of cases, and nephrosclerosis, especially related to elderly, that has a similar incidence. Patients with a hereditary polycystic kidney disease constitute 5-10%, and those with chronic pyelonephritis represent 5% of the ESRD patients (Rippe 2011). From an international perspective, the Swedish proportion of ESRD with pyelonephritis/interstitial nephritis is quite low (Rippe 2011).

With regard to the prevalence of kidney disease, 28% of those with active treatment due to uraemia have glomerulonephritis as the underlying disease, 20% have diabetic

nephropathy, 12% cystic kidney disease, 10% have pyelonephritis, and a similar proportion has nephrosclerosis. The incidence of an unspecified cause to uraemia is about 20%. The difference between incidence and prevalence, i.e. new cases and presence, reflects the increased cardiovascular mortality in the diabetic group; however, patients with cystic kidney disease and glomerulonephritis have a relatively good survival rate.

Heart failure is common in patients with advanced renal failure with about 56% of patients starting dialysis having heart failure with hypertensive and/or ischemic heart disease as a cause (Harnett, et al. 1995). However, left ventricular hypertrophy is present in as much as 70% of the dialysis population (Levin, et al. 1996) and age-related cardiovascular reasons for mortality are increased in patients with dialysis compared to the general population (de Jager, et al. 2009).

The best option for a patient in this stage is to receive a kidney transplant from a living related donor. However, this option is only possible for a limited number of patients. For the other patients the option is either to decide not to accept dialysis therapy, usually an option when many complications are present in late life, or to decide for dialysis therapy. A person can undergo dialysis for a limited period before a kidney transplant is possible; for example, when a dialysis patient is to receive a kidney from a deceased person. Not all patients, however, are suitable for transplantation, which means that the dialysis treatment can be life-long.

Today it is estimated that about 3,800 people in Sweden need dialysis and approximately 4,900 have a kidney transplant. This results in about 8,700 patients in Sweden that require active treatment for end stage renal disease. Of these 3000 have haemodialysis and 800 peritoneal dialysis. This compares to approximately 1 million patients that require dialysis in the world (Rippe 2011)(www.njur.se). The number of patients undergoing active treatment for uraemia in Sweden has grown steadily since documentation was started by the Swedish Registry for Active Uraemic treatment in 1991. For the whole country, this gives a prevalence rate of 900 per million inhabitants. The previously forecasted growth in

the number of patients was exceeded. The annual growth average was 4.2%. In recent years, it is mostly the number of patients with functional kidney transplant that have increased, but in 2011 even the number of haemodialysis patients increased significantly. Approximately 2/3 of the patients are men and 1/3 are women (Rippe 2011).

Dialysis therapy

There are two types of dialysis – haemodialysis (HD) and peritoneal dialysis (PD).

Peritoneal dialysis (PD).

Peritoneal dialysis (PD), also called abdominal dialysis, is used in Sweden for about 20% of all dialysis cases. PD means that dialysis fluid is infused into the abdominal cavity via a catheter that is permanently placed (Stegmayr 2002; Stegmayr 2006; Stegmayr 2008; Stegmayr 1994; Stegmayr 2003; Stegmayr, et al. 1996; Stegmayr, et al. 2005a; Stegmayr, et al. 1993; Stegmayr, et al. 2005b; Stegmayr, et al. 1990). The peritoneum acts as a membrane over which waste is transported by osmosis. Having a high concentration of glucose in the dialysis fluid also drives the water out from the body into the retained fluid intra abdominally by an osmotic effect. Dialysis fluid is then drained from the body. Emptying and filling takes 20-30 minutes, and the dialysis phase takes 3-8 hours. The procedure is usually repeated 4-5 times daily. PD can be done completely manually; but, there is also Automated Peritoneal Dialysis (APD). APD is done by a programmed machine, APD machine, that works while the patient sleeps. The most common form of PD is called Continuous Ambulatory Peritoneal Dialysis (CAPD) and managed by the patient itself at home (Rippe 2007).

The advantage of PD over HD is that the patient will not have to go to the hospital several times a week and be bound by the dialysis machine for several hours at each session. Moreover, with PD one can eliminate excess fluid from the body regularly throughout the

day, and on every day. This reduces the risk of pulmonary oedema. PD can be done both at home and at work. PD is not appropriate for patients with inflammatory bowel disease where there is a risk of peritonitis caused by intestinal bacteria, which penetrate through the intestine to the abdominal cavity. The catheter for PD is fixed firmly and exits the skin with an outer part. This part has an opening outside the body that is to be sealed securely after each dialysis exchange. If this seal is improperly done this allows an opportunity for bacteria to follow the inside of the tube of the catheter directly into the abdominal cavity of the body, which presents a risk of peritonitis. To avoid this, hand hygiene is of great importance for bag changing. For more reading see Rippe (Rippe 2007).

Haemodialysis (HD)

Haemodialysis (HD) is the most common dialysis treatment (about 80%). To dialyze effectively requires a large blood flow and a blood vessel that can withstand being punctured with a thick needle as often as the patient needs dialysis (typically 3 days/week). Therefore, as part of the preparations for dialysis a surgical procedure in which an artery is joined to a vein in the forearm to create an arteriovenous fistula, i.e. AV fistula, is done. When the vein is exposed to the arterial blood pressure it grows, while the blood flow is increased to 1000-1500 ml / min. A month later it can be used as a puncture site to deliver blood to the dialysis machine as well as a puncture site to allow for returning blood from the machine to the patient. If a patient does not have a fistula, haemodialysis can be done through a central dialysis catheter (CDC) which has two ports. The purification process is carried out in the dialyzer in which the blood and the dialysis liquid flow in the opposite direction and on opposite sides of a semipermeable membrane. Toxic waste products pass through the dialyzer membrane by diffusion and are carried away by the dialysis fluid. Following the same principle, but in the opposite direction, bicarbonate and electrolytes pass through the dialyzer membrane from the dialysis fluid to the blood. In addition, the excess fluid that has accumulated between treatments is removed through the membrane.

Some patients go up 4-5 kg in weight between dialysis sessions, due to their intake of liquid by drinking and eating, and since they cannot produce urine volumes effectively because of the damaged renal function. This fluid elimination can be a set function of the dialysis machine and is called ‘ultrafiltration’. The dialysis machine can be set so that it only eliminates the fluid (ultrafiltration) without concomitant dialysis. The entire dialysis process is monitored and controlled by the dialysis machine and a specially trained nurse. Dialysis can be done either at the dialysis clinic or in the home. Those who dialyze at home are called home dialysers and have learned to dialyze themselves. There are also those who are called self-dialysis patients that dialyze at the hospital but perform all or part of the treatment themselves; they only need the normal security associated with being in the hospital and to have knowledgeable staff on hand during dialysis. For more on this topic see (Kotanka, et al. 2007).

Diabetes mellitus and kidney diseases

Diabetic nephropathy is the kidney damage that develops as a complication to diabetes mellitus, and is due to that the capillaries in the glomeruli of the kidney are damaged. There are a number of different types of kidney damage such as papillary necrosis, glomerulosclerosis and interstitial nephritis that can cause the nephropathy. There are two types of diabetes: type 1 – diabetes (formerly called juvenile diabetes), and type 2 – diabetes (formerly called adult-onset diabetes). Type 1 diabetics are approximately 0.5% of the population. These patients are more likely to have kidney complications due to having had the disease for a longer period than that for type 2 diabetics. Approximately 20% of type 2 diabetics and 75% of type 1 diabetes develop severe kidney failure within 20 years after diagnosis, and thus require dialysis or transplantation. Renal failure starts out as microalbuminuria (30-300mg/d) and evolves over time to macroalbuminuria (> 300mg/d) in 80% of type 1 diabetics and 20-40% of type 2 diabetics. Screening control using a dip stick test for albuminuria is used for early detection of diabetic nephropathy.

Risk factors for diabetes for the development of renal damage are hyperglycaemia, hypertension, and hyperlipidaemia, i.e., a deficient metabolic control (Tanaka, et al. 2001). Good blood sugar control, and an effective blood pressure treatment and medication with an ACE inhibitor or ARB counteract the risk of progression of kidney damage (Nyström and Nilsson 2012; Östgren 2012). Another risk factor for the patient at risk for cardiovascular disease is tobacco usage (Agewall, et al. 2012) including patients with DM and severe renal kidney disease (Stegmayr 1990; Stegmayr and Lithner 1987).

If a thorough dipstick urine control is not performed routinely, symptoms develop late in progressive diabetic nephropathy, and side effects due to hypertension may be the first findings of severe kidney damage. When uraemia has developed weight loss, itching, nausea and oedema may develop. Besides the diabetes angiopathy, there is an increased risk for inflammation in the kidneys in these patients. Thereby a direct toxicity due to hyperglycaemia may develop in the endothelial cells and mesangial cells of the kidneys.

Pyelonephritis, acute or chronic inflammation of the kidney parenchyma, is much more common in diabetics than in the general population. Infections begin in the parenchyma and then spread to the tubules. Necrotizing papillitis is a form of pyelonephritis that is very common in diabetics. Ischaemic injury is also a common cause of kidney damage; a hyaline arteriolosclerosis with thickening of both afferent and efferent arterioles and atherosclerosis of renal arteries, so-called macro angiopathy, contribute to ischemic kidney parenchyma and exacerbate kidney damage. Diabetics often have hypertension that in itself is a major risk factor for progression of renal failure (Colhoun, et al. 2004). In all prospective studies diabetics with coronary artery disease have a strongly elevated risk of re-infarction and death (Wanner, et al. 2005). In type 2 diabetes and metabolic syndrome hyperlipidaemia is very common, and often manifested as combined hyperlipidaemia with a high VLDL and low HDL (Nyström and Nilsson 2012; Östgren 2012).

The basis for treatment of a metabolic disorder, as always, is having a good control over the diabetes with a lifestyle change of exercise, proper diet and medication.

Guidelines recommend (Bozentowicz-Wikarek, et al. 2012) that these patients should also be treated with a statin, which is a first-line pharmaceutical treatment of hyperlipidaemia. This approach is strongly supported in the subgroup analyses done in large statin trials. For example, in the 4S study simvastatin showed a significantly protective cardiovascular effect even among diabetics (1994; Pyorala, et al. 1997). To further reduce triglycerides, a combination with fibrates may be an attractive option. When this work began, it was considered that the beneficial effects of statins seen in patients in previous studies (where kidney patients were excluded) could also apply to groups of kidney patients despite the lack of scientific documentation for the benefit of statin therapy.

Lipid disorders in renal disease

Lipid disorders can be found in kidney disease and can vary depending on the type of kidney disease. A consistent pattern emerges in renal impairment and in conjunction with dialysis treatment. It is characterized by elevated VLDL triglycerides, Lipoprotein(a) and reduced or unchanged levels of ApoA-containing lipoproteins in the HDL fraction. Apo B-content ratio lipids increase in extent with the degree of renal damage (Attman, et al. 2011). The causes of dyslipidaemia in renal impairment include reduced activity of lipoprotein lipases (LPL) and hepatic triglyceride lipase (HTGL), but as well reduced LDL receptor activity and increased expression of scavenger receptors in uraemia. The re-transport of cholesterol is also affected in uraemia (Attman, et al. 1993). A lack of balance between the different types of blood fats increases the risk for patients with cardiovascular disease. Therefore, a high proportion of LDL cholesterol is considered to increase the risk for developing cardiovascular disease. A way to reduce LDL cholesterol is by treatment with statins. Statins are used for the treatment of hypercholesterolemia in patients who had not had a beneficial effect of exercise and changing diet, and are at risk of getting cardio-vascular disease. At the start of the study only a few statins were approved for use in renal failure. One of these was atorvastatin.

Atorvastatin

Atorvastatin is a lipid-regulating drug that belongs to the statins. The drug was provided initially under the brand name Lipitor®. There are five different types of statins in Sweden; they have different potency reflected in their LDL-reduction per mg. Atorvastatin is number 2 on the list in efficacy after rosuvastatin (Olsson 2006; Östgren 2012). Treatment with atorvastatin reduces the body's amount of LDL cholesterol, and in some cases also of triglycerides. For some cases the content of the favourable HDL cholesterol increases. The result is that the blood lipids change in a direction toward normal (Shepherd, et al. 2008a;

Shepherd, et al. 2008b).

Atorvastatin is metabolized in the liver by inhibiting the enzyme HMG-CoA reductase. This enzyme is needed to build cholesterol, thereby leading to an increased uptake and degradation of LDL cholesterol. Reducing the level of LDL cholesterol in the blood reduces the risk of cardiovascular disease (Baigent, et al. 2005).

In rare cases, atorvastatin can cause liver damage and muscle pain side effects; these are dose dependent and can be avoided by a dose reduction or a change in prescription. Rhabdomyolysis is considered the most serious muscle side effect. In this case the muscle is more or less dissolved and the myoglobin precipitates out off the cells and into the blood, which can lead to an acute renal failure. It is therefore very important to stop treatment and consult a doctor if side effects such as muscle pain, tenderness, or weakness continue without a known cause. Upon prescription, liver samples are taken before treatment and are monitored usually after 1-2 months (FASS 2013).

Medical Product Agency recommendations of treatment of hyperlipidaemia

Dyslipidaemia in renal disease has increasingly come to attention because of its presumed significance for cardiovascular complications encountered in renal disease and in renal impairment, and because of its importance to the progression of renal impairment. This thesis complies with the use of statins for patients with severe kidney disease. The work aimed to clarify i.e., the recommendations made by the Swedish Medical Products Agency using statins on a wide indication in patients at risk for cardiovascular disease, including those with CKD 4 and 5 (Läkemedelsverket 2005; Läkemedelsverket. 2003).

Drugs and severe kidney disease

Thiazides are ineffective in glomerular filtration rate < 25 mL/min, with the exception of metazolon (Zaroxolyn, license preparation). Potassium-sparing drugs should be avoided with glomerular filtration rate below 25 mL/min, due to risk for high potassium concentrations in blood. Oral antidiabetics are unsuitable for kidney failure, as increased risk for hypoglycaemia and lactacidosis exists. Metformin is contraindicated when renal impairment is below 60 ml/min because it can cause lactic acidosis (FASS 2013). One should switch to insulin instead, which is more easily controlled. Insulin dosages often must be reduced due to the decreased metabolism of insulin in the kidneys. Non-steroid anti-inflammatory drugs (NSAID) decrease renal blood flow and can further affect kidney function as well as ACE inhibitors and angiotensin receptor blockers.

Basic principles for therapeutic measures are to correct acidosis, lower phosphate and uric acid levels, adjust anaemia, using iron and erythropoietin administration, to be at a level of 110-120 mg/l, and adjust blood pressure to a level of ≤ 130/80. If the patient suffers from diabetes nephropathy the blood pressure is suggested to be reduced even further (< 125/80 mm Hg)(Nilsson 2006). Patients should be informed to control protein and fluid intake and diet in regard to lipid as well as recommended to stop smoking and to reduce obesity (Haddad, et al. 2007).

With a progressive impairment of kidney function the risk for morbidity due to cardiovascular disease increases further (Vanholder, et al. 2005), and dyslipidaemia occurs (Attman, et al. 1993; Attman, et al. 2011). The interactive processes that emerge when either the heart or the kidneys are impaired may occur acute and chronic. In addition, both organs may deteriorate when a metabolic disorder is present such as diabetes mellitus or vasculitis such as lupus erythematosis (SLE). These interactions between heart and kidneys are defined as cardiorenal syndromes (Ronco, et al. 2010). These processes may also interfere and favour development of mediasclerosis. The latter is present in these patients in addition to conventional atherosclerosis (Stenvinkel, et al. 2007). The presence of intima

and media sclerosis in combination has urged clinician to add statins to the other medications mentioned above. At initiation of this thesis, statins were recommended by the Medical Product Agency in Sweden and prescription was generally recommended to patients with various levels of CKD despite the lack of controlled studies for these groups of patients. Still it is recommended for patients at risk for cardiovascular diseases and those with diabetic nephropathy (Läkemedelsverket 2005).

Several questions arose and resulted in the present Thesis.

AIMS

The aims of this thesis were to clarify the presence of risk factors and to determine if medication with atorvastatin had preventive measures to improve health of patients with CKD 4 and 5.

The sub-aims were:

1. To investigate the efficacy and safety of a daily dose of 10 mg of atorvastatin in patients with CKD 4 and 5.

2. To investigate whether atorvastatin (10 mg/day) would alter cardiovascular endpoints and the overall mortality rate of patients with CKD 4 and 5.

3. To investigate if other factors could be risk factors, such as if the extent of interdialytic weight gain (IDWG) was of importance for the survival.

4. To investigate whether the burden of interdialytic weight gain was of importance for cardiovascular end-points and survival.

5. To investigated if atorvastatin 10 mg/d would alter metabolic variables differently in patients with diabetes mellitus compared to non-diabetic patients.

Development of study design

During a regional meeting a question arose if there was any evidence to motivate treatment with statins to patients with severe kidney damage. Based on studies on other patient groups, recommendations were to prescribe statins also to kidney patients although there was no knowledge of effects and side effects for this group. Since such evidence was not available it was decided to perform a study to address this. Patients elected for inclusion should belong to the group of more severely impaired in kidney function. There was no knowledge if there would be a difference in efficacy if patients were on dialysis or not. This resulted in a block randomisation to avoid interference of outcome from various groups. All Swedish larger centres that treated patients with uraemia and dialysis were asked to participate in the study. However, many of the Swedish nephrology physicians were convinced that statins should be given to all these patients and therefore many centres refused to participate. Atorvastatin had just been released and introduced in Sweden by Pfizer Inc. The study group considered this statin as the most appropriate compared to Pravastatin and Fluvastatin, that were also accepted for the patient group by the Medical Product Agency in Sweden.

Atorvastatin is metabolized by the liver and therefore not expected to cause much side effects. The company (Pfizer) who provided atorvastatin was not involved in the study and did not support the trial with placebo tablets. The study group investigated the possibility to have a pharmacy produce placebo tablets. However, this was not possible, and the placebo tablets would not resemble the original drugs in any regard. It was then decided to perform an open trial. The Swedish Product Agency was informed and commented on the study such as the importance of large enough number of inclusions. It was decided to prolong the study beyond 3 years that was originally planned, if the number of end-points was too small to achieve a study power of at least 80%. The physicians involved in the planning of the study are listed below (Table 5). This became the Nediat study group.

Table 5: Centres and physicians involved in planning and study follow up (Centres in alphabetic order).

Bollnäs: Benny Persson
Eksjö: Henrik Hadimeri, Lars Svensson
Eskilstuna: Knut-Christian Gröntoft
Skellefteå: Mats Brännström, Bert Isaksson
Sollefteå: Lars Mikaelsson
Sunderbyn: Stig Bucht, Bo Ingman
Sundsvall: Erland Olausson, Barbara Granroth, Anders Ekspong
Umeå & Tärnaby: Ann-Marie Wikdahl, Emöke Dimeny, Lennart Lundberg, Ola Lundström, Monica Mörtzell, Benny Holmberg, Bernd Stegmayr
Örnsköldsvik: Gunnar Johansson
Östersund: Kerstin Lindberger

Study nurses for the project were appointed at each of the hospitals included in the study (Table 6). Study centre was the Research Department at the Division of Nephrology, Department of Internal Medicine, University Hospital in Umeå, Sweden.

Table 6: Nurses appointed for the study at the various centres are given below.

Bollnäs: Marie Blom
Eksjö: Anneli Johansson, Annette Ljunggren ,Ulf Tedeby
Eskilstuna: Anki Brkan and Ingela Almstam-Gustavsson
Skellefteå: Carina Johansson and Lena Rindegren
Sollefteå: Per Viklund
Sunderbyn: Lilian Sundqvist
Sundsvall: Eva Geijer, Carina Hedin, Gunnel Jonsson and Katrin Lindström
Umeå & : Ann Sofie Lindgren, Margareta Lundgren and Renström Lars **Tärnaby:** Kicki Mosesson
Örnsköldsvik: Eva Olsson
Östersund: Anita Olofsson

STUDY DESIGNS

The main study was designed as an open and prospective multicentre study. Patients were included for randomization to either treatment with a daily dose of 10 mg atorvastatin in addition to conventional therapy versus no addition to conventional therapy. Basic data was collected before start (Figure 2) and various plausible side effects and risk factors were registered and followed (Figures 3-5). End-point data was registered (Figure 3) and all data sent to the study centre. Collection and investigation of data of adverse events and efficacy was reported in study 1. Collected end-point data were used for analyses of study 2.

Collection of data for studies 1 and 2 also included data of various risk factors and laboratory variables that were considered as plausible risk factors (Figure 6 and 7). Such established risk factors were serum albumin and C-reactive protein. In addition, we collected data of other variables such as inter dialysis weight gain to evaluate additional effects or interactions with statin therapy (studies 3 and 4).

For study 5 data collected for studies 1 and 2 were specifically analysed in regard to patients with diabetes mellitus who are considered to be at a higher risk for cardiovascular disease than the general population of CKD 4 and 5 patients.

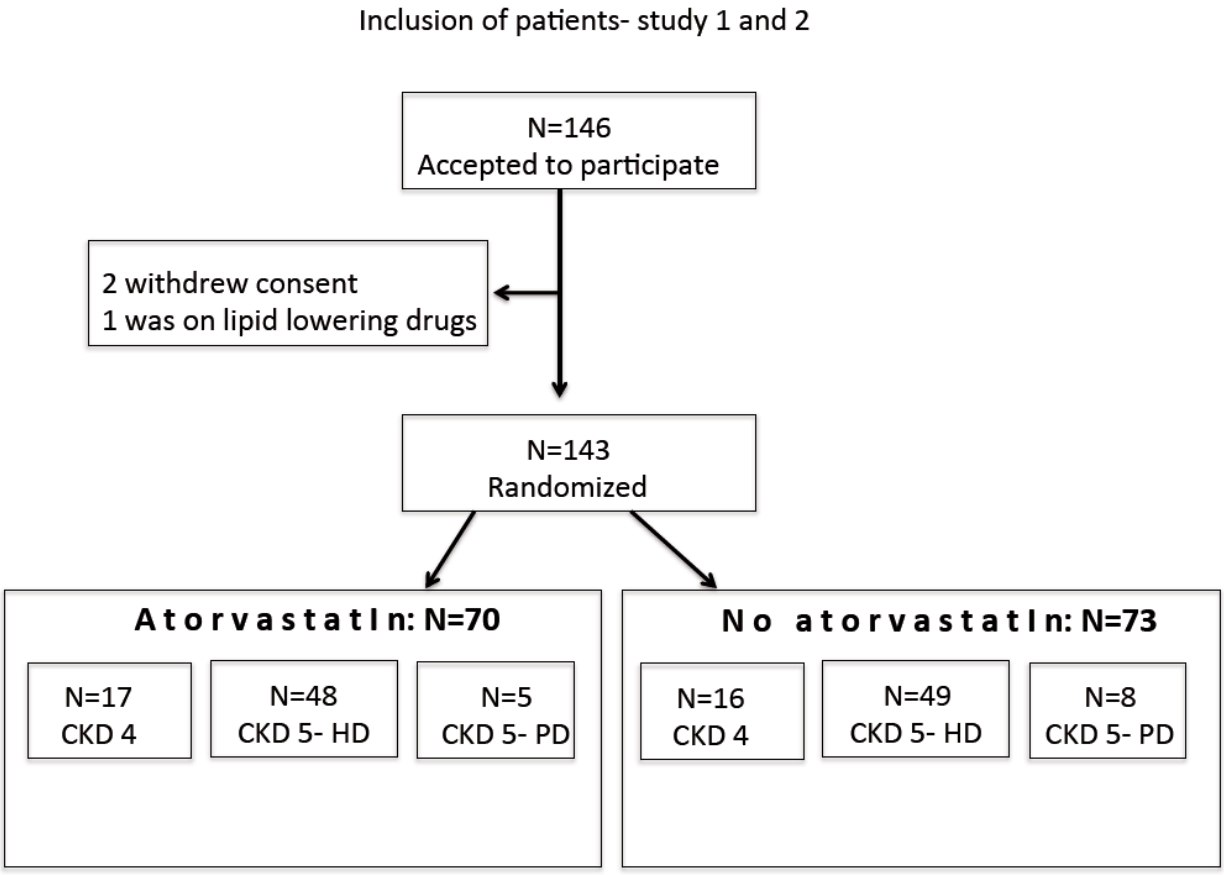
MATERIAL

A total of 143 patients were included in the study and were randomized to receive either medication with atorvastatin 10 mg/day (Group A; n= 70) or no statin medication [controls (Group C); n= 73]. The study was open and was not supported by Pfizer, the manufacturer of atorvastatin. The patients were followed up to 5 years for end-points. Blood samples were taken until 36 months. Patients were stratified (Group A versus Group C) with regard to gender (48 vs. 51 men), diabetes mellitus (22 vs. 22), other renal diagnoses (48 vs. 51), predialysis (17 vs. 16), haemodialysis (48 vs. 49) and peritoneal dialysis (5 vs 8). The mean ages of Groups A and C were 67.8 and 69.4 years, respectively. Patients were informed and consented to be included in this multicentre study, which was approved by the respective ethical committees. The Swedish Product Agency was informed about the study and comments on the design were considered.

Inclusion criteria were a glomerular filtration rate of less than 30 ml/min / area of 1.73 m^2 as measured by either creatinine clearance, Cr-EDTA or iohexol clearance.

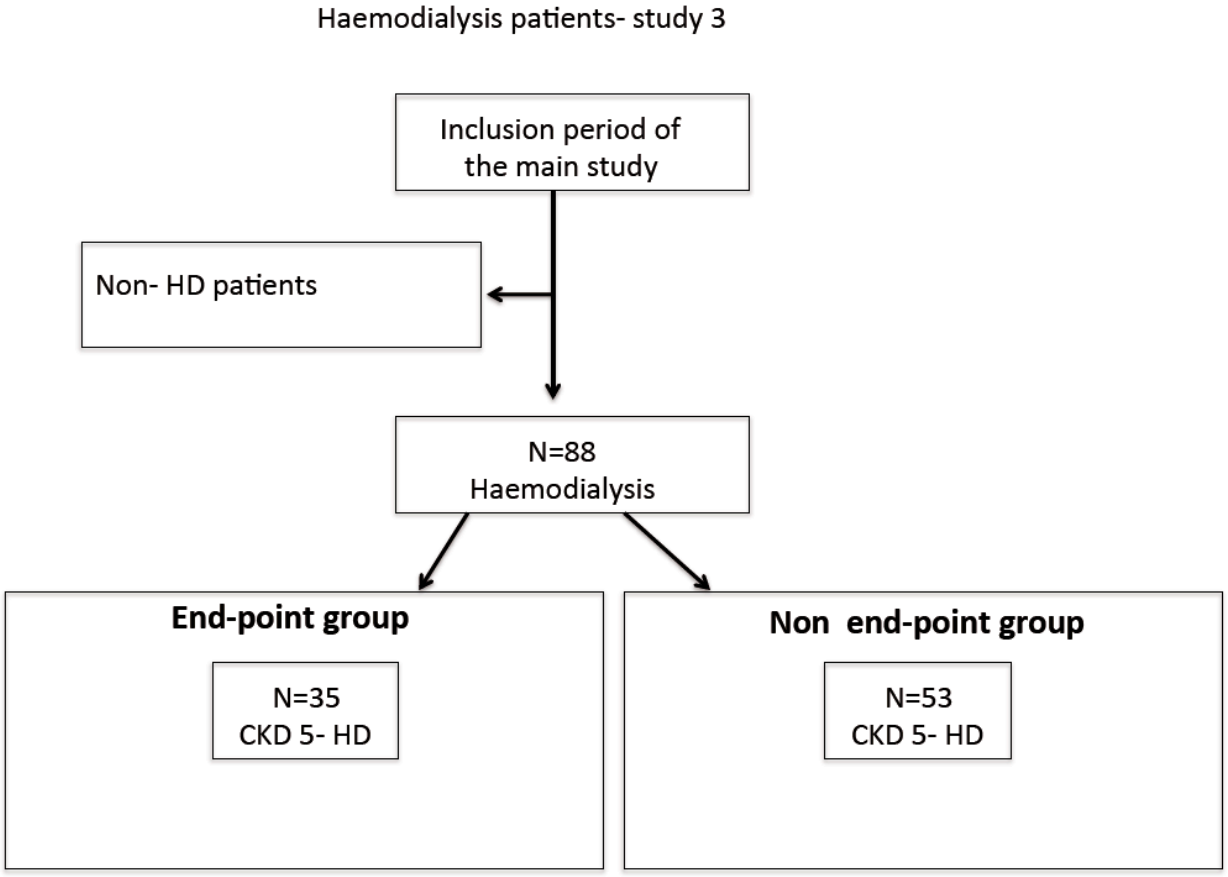
Exclusion criteria were as follows: age less than 18 years; fertile women who were not using contraception; pregnant or nursing women; patients with active liver disease, e.g. aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) levels three times the upper reference values; a history of adverse reactions to statins; patients with a functioning kidney transplant; patients who were on a waiting list for kidney transplantation; patients on a protein-restricted diet (less than 40 g/day); and patients with a history of bad compliance with medication or follow-up. Patients with a history of an active progressive neoplastic disease as well as those expected to live for less than 6 months were also excluded.

Study 1: Included data as described in the total study. This study included a total of 143 patients: 73 were controls and 70 were prescribed 10 mg/day of atorvastatin. Efficacy and safety variables are given below.

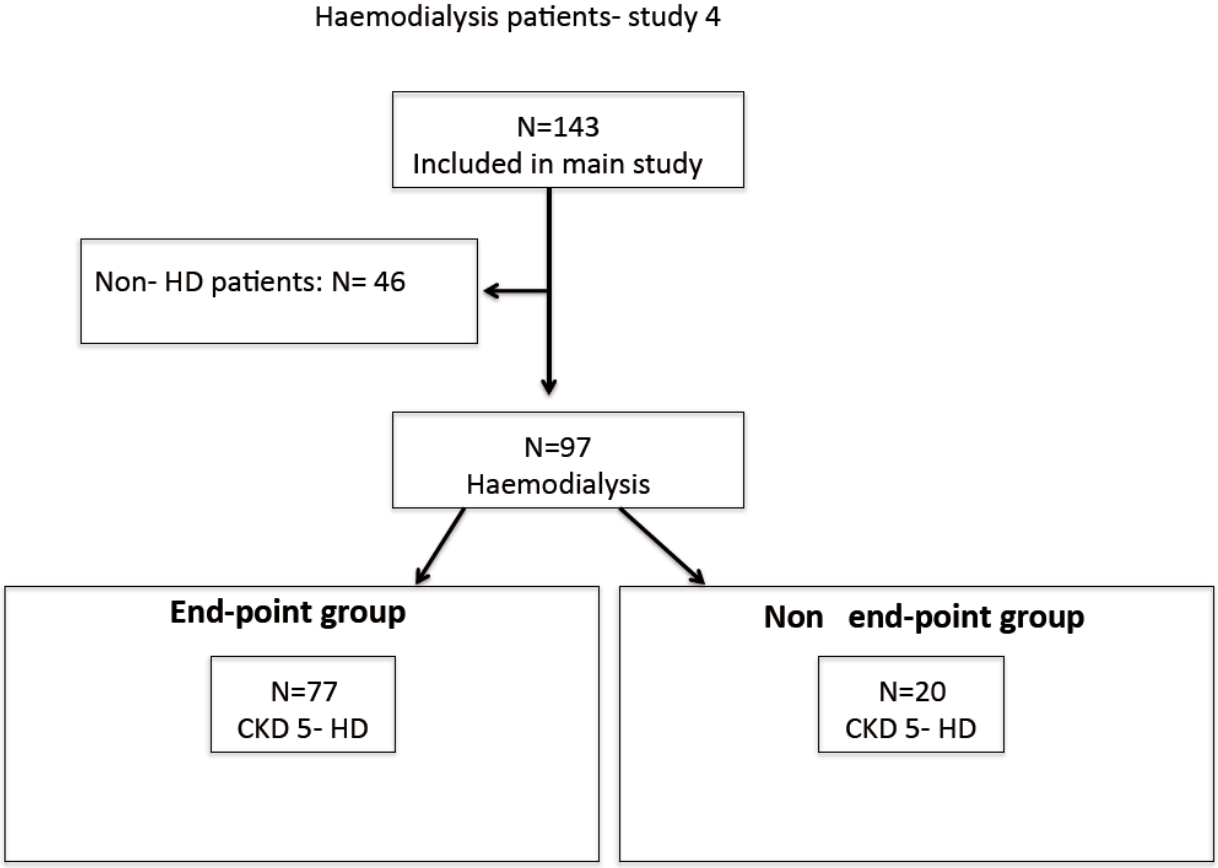


Study 2: The study subjects were the same as described above. The mean age of the controls was 69.4 years (n=73) and of those randomized to treatment with atorvastatin was 67.8 years (n=70).

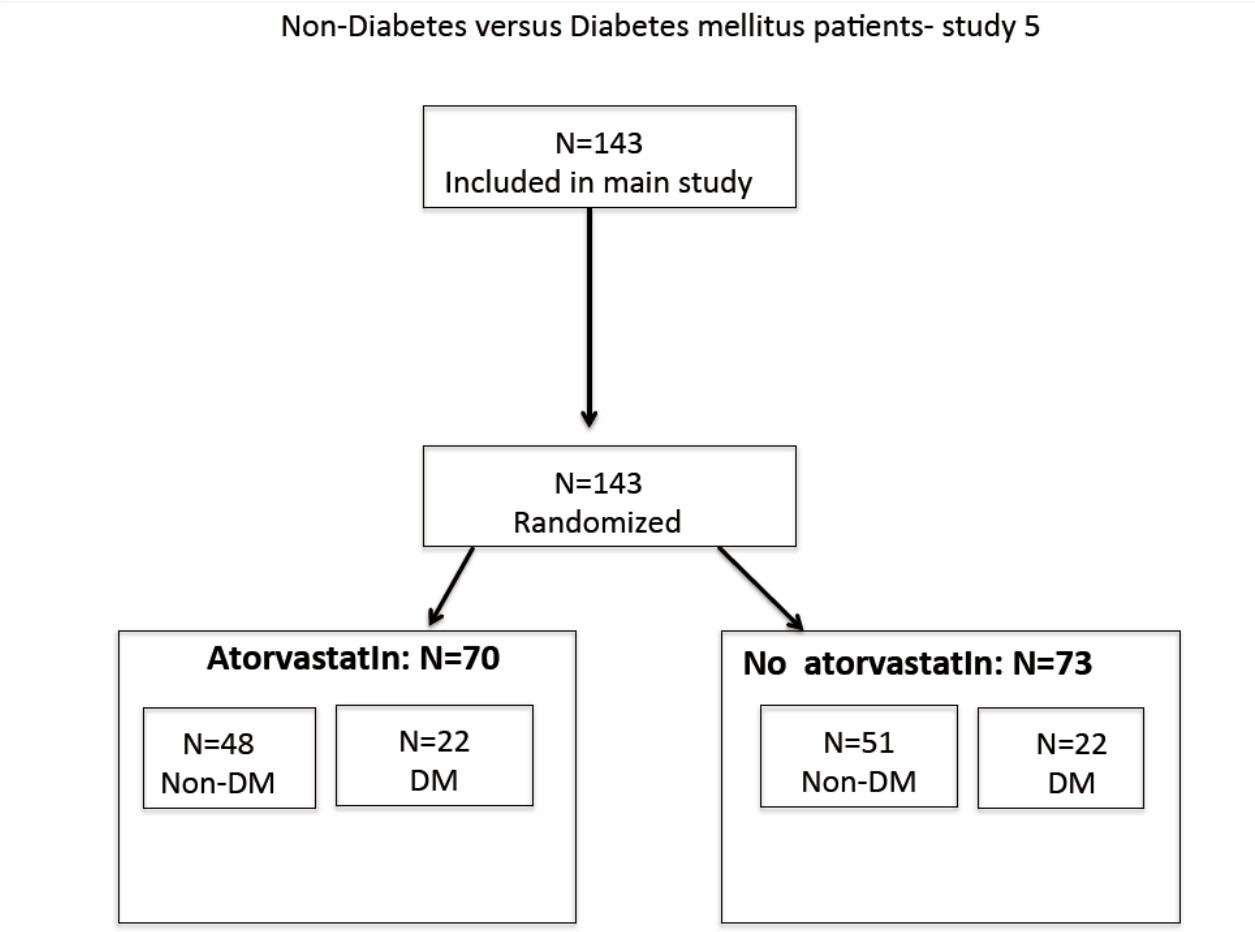
Study 3: The present study 3 was performed before all patients in studies 1 and 2 had been included. This resulted in inclusion of 88 HD patients that had been followed prospectively. The mean extent of fluid retention between dialyses measured as estimated ultrafiltration volume in relation to body weight was compared for patients who did not suffer from and end-point (group 1, n=53) versus those who suffered from an end-point during the period (group 2, n=35).



Study 4: A total of 97 HD patients were studied. These represented all patients and the whole observation period that also was included in the main material.



Study 5: This part of the prospective study focused to compare those 44 patients with diabetes mellitus versus those 99 patients without diabetes mellitus within the 143 patients with CKD studied. Inclusion and exclusion criteria were the same as in studies 1 and 2.



METHODS

Main study procedures (used for study 1-5)

Randomisation of patients was centralised in Umeå, where the study was co-ordinated.

Block randomisation was done according to the Figure below (Fig 1).

After informed consent was obtained from the patients, randomization was performed by contact between the local nurse and the research nurse at the study centre in Umeå. The randomization procedure was blinded, using closed envelopes for each block.

Patients were coded, with a parallel list for identification only at each study centre at the individual hospital. Protocols for inclusion, adverse events and end-point or withdrawal from study were constructed (Figures 2 and 3).

Questionnaires for various side effects were performed and a list of laboratory measures, based on routine samples, was arranged. Visual analogue scale (VAS) was used if possible to allow statistical analyses (Figure 4 and 5).

Venous samples were taken from outpatients planned in conjunction with a clinical visit, for HD patients samples were taken from the AV-fistula or central dialysis catheter and urea was also taken 5 minutes after HD. Analyses were performed by the local laboratory that was certified by the Swedish authorities. Data were registered (Figure 6 and 7) and data files faxed to the study centre in Umeå. Coordination of sampling was performed with local routine sampling to allow laboratory samples without extra costs for the study.

The proceeding months (month 6, 12, 18, 24, 30, 36) further data were collected according to the figure 7.

Figure 1: Randomization procedure was performed in blocks shown below.

BLOCK 1: MEN

1a) preuraemic patients

1 a1) diabetes mellitus

1 a2) others

1 b) haemodialysis patients

1b1) diabetes mellitus

1b2) others

1 c) peritoneal dialysis patients

1 c1) diabetes mellitus

1 c2) others

BLOCK 2: WOMEN

2a) preuraemic patients

2 a1) diabetes mellitus

2 a2) others

2 b) haemodialysis patients

2b1) diabetes mellitus

2b2) others

2 c) peritoneal dialysis patients

2 c1) diabetes mellitus

2 c2) others

Figure 2: The start report was designed to be filled in by the patient partly by circling and partly by inserting numeric value.

Start report- History of patient-code: .....

Born year:.....

Hospital: .....

Start date:.....

Use of tobacco? never / regularly from year ..... to ....

How many cig/day at a mean: .....

How many gram tobacco/d at a mean:.....

Currently: Smoking :...../d, Snuff:.....g/d, Never smoked/snuff

---

Diabetes mellitus since ..... juvenile/age:

Myocardial infarction: .....

CABG/PTCA op. : .....

Angina pectoris since .....

Cerebral Stroke: TIA/ Infarction/haemorrhagia/ UNS : .....

Claudicatio intermittens: left/right leg debut/in hospital due to: /op./angio/ : .....

Amputation due to vessel disease left/right limb / upper/lower/toe :.....

when: ..... left/right hand/finger nr: .....

Wound on extremity, due to vessel disease left/right limb / upper/lower/toe :.....

Since when: ..... left/right hand/finger nr: .....

Tumor: .....
Liver disease: .....
Myeloma since :.....
Amyloidosis since: .....
Vasculitis /SLE/Wegener/ RA: since ..... Other:.....
Other diseases: .....

Information was sent to research nurse at study centre Umea by mail or fax

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Figure 3. Events were reported by sending the questionnaire to study center.

Report of EVENTS patient-code: .....

Event: date: .....

1. Died autopsy/ no autopsy : Reason for death: .....

2. Myocardial infarction enzyme- positive/negative date:.....
EKG - positive/negative

3. CABG/PTCA op. date: .....

Angina pectoris Newly developed/in hospital due to / angio due to: .....

Cerebral Stroke: TIA/ Infarct/haemorrhagic/ UNS
without/with residing sequelae >24 hours

Claudicatio intermittens: left/right leg debut/in hospital/op for/angio for/

Amputation due to vessel disease left/right limb /upper/lower/toe :.....
left/right hand/finger nr: .....

Wound on extremity due to vessel- left/right limb /upper/lower/toe nr .....
dysfunction left/right hand/finger nr: .....

Stop participation in the study due to:
Criteria 1-3
Refuse to proceed within study
Adverse events of study drug:
Increase of CK > 10 times the reference value or
Increase of ASAT, ALAT > 3 times the reference value.
Other reasons: give adverse event/reason: .....
Information was sent to research nurse at study centre Umea by mail or fax

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Figure 4: Questionnaire to evaluate the general health condition

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Questionnaire 1: To evaluate the general health condition

patient-code: ..... date:.....Hospital: .....

Visit: Start, Months: 1, 3, 6, 12, 18, 24, 30, 36

Mark appropriate with –X-, i.e., if your appetite is relatively good :

Very bad _____X_____ Excellent

How is your appetite?

Very bad _____ Excellent

How much do you eat in a week?

Nothing _____ Extremely much

How was your wellbeing the latest 4 weeks ?

Miserable _____ Excellent

How is your endurance?

Very poor _____ Excellent

How often do you experience angina pectoris?

Never _____ several times/day

How often do you get pain in your legs?

Never _____ several times/day

How many full stairs do you climb without a break? .....number

If you suffer from other discomfort note here:.....
How often/frequent?

Never _____ several times/day

Thanks for your important contribution. Give the questionnaire to your nurse or doctor.

Figure 5: Questionnaire to evaluate the general health condition

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Questionnaire 2: To evaluate the general health condition

patient-code: ..... Hospital: ..... date:.....

Visit: Start, Month: 1, 3, 6, 12, 18, 24, 30, 36

Nausea
Never _____ extremely frequent

Vomit
Never _____ extremely frequent

Muscle ache
None _____ Extremely much

Muscle fatigue
None _____ Extremely much

How is your satisfaction with your life?
Suicidal _____ Extremely happy

.....
Never _____ Extremely much

.....
Never _____ Extremely much

.....
Never _____ Extremely much

Thanks for your important contribution.
Give the questionnaire to your nurse or doctor.

Fig 6: Data collection at first 3 sampling periods of study (LR: local routine; S: s variable)

Data collection - 1 Date:.....Pat code nr :.....

Inclusion data:

Treatment A ; Control C , Height of patient: .....cm,

	start	Sample month 1	Sample month 3
Date			
S-creatinine,		LR	LR
S-Urea, before HD		LR	LR
S-Urea, 5 min after HD		LR	LR
S-K		LR	LR
S-albumin		LR	LR
S-Ca corr f alb		LR	LR
S-phosphate		LR	LR
S-carbonate		LR	LR
S-iron		LR	LR
S-ferritin		LR	LR
S-CRP		LR	LR
pat.-weight		LR	LR
Cholesterol, fasting		S	S
Triglyceride, fasting		S	S
HDL-cholest, fasting		S	S
LDL-cholest, fasting		S	S
HbA1c/glyc Hb, diab.		LR	LR
S-fibrinogen	LR	LR	LR
S-ASAT		S	S
S-ALAT		S	S
S-GT		S	S
S-CK		S	S
S-amylase		LR	LR
Creatinine clearance		LR	LR
dU-protein		LR	LR
Kt/V		LR	LR
PCR		LR	LR
Blood pressure, l/r arm		LR	LR
Inter dialysis Weight gain		LR	LR
.....		LR	LR

LR= according to local routine, S=to decide efficacy or adverse events acc. to FASS

Figure 7: Variables measured at month 6, 12, 18, 24, 30, 36.

Data collection - continued

Data - month 6, 12, 18, 24, 30 or 36 Date:..... Pat-Code:.....

Treatment A ; Control C , Mark sample month 6, 12, 18, 24, 30, 36 Date

S-creatinine,	
S-Urea, before HD	
S-Urea, 5 min after HD	
S-K	
S-albumin	
S-Ca corr f alb	
S-phosphate	
S-carbonate	
S-iron	LR
S-ferritin	LR
S-CRP	LR
pat.-weight	
Cholesterol, fasting	S
Triglyceride, fasting	S
HDL-cholest, fasting	S
LDL-cholest, fasting	S
HbA1c, diab.	LR
S-fibrinogen	LR
S-ASAT	S
S-ALAT	S
S-GT	S
S-CK	S
S-amylase	LR
Creatinine clearance	LR
dU-protein	LR
Kt/V	LR
PCR	LR
BPressure, l/r arm	
Inter dialysis Weight gain	LR
.....	LR

LR= according to local routine, S=to decide efficacy or adverse events acc. to FASS

VAS results were measured on a line in cm with a ruler. Information about adverse event was faxed directly to Umeå to enable dissemination of experience to all centres.

A safety committee was performed in Umeå. Its purpose was to perform intermediate analyses and alarm if deviating data occurred after each 50 included patients. Each year all study centres were invited to be informed of safety and progress of study in regard to lipid lowering effect. End-point data were not given until the termination of the study. An intermediate discussion was performed in the study group after 6 months. Since approximately 23% of patients had withdrawn from the study, to experienced side effects and due to their own request, the daily dose of atorvastatin of 10 mg/d was not increased.

Efficacy and safety variables were measured at the start of the study (Group C, n= 73; Group A, n= 70) and after 1 month (70 vs. 67), 3 (66 vs. 59), 6 (63 vs. 49), 12 (52 vs. 41), 18 (41 vs. 33), 24 (28 vs 32), 30 (23 vs 25) and 36 months (18 vs 17).

Since patients with uraemia suffer from various symptoms that are similar to the side-effects of atorvastatin therapy, and as this was an open study, it was considered difficult to accurately interpret side-effects caused by the medication. Thus, there was a risk of overestimating side-effects. Therefore, side-effects were only registered if the patient experienced a persistent subjective adverse event (AE) that caused them to stop taking their medication or if laboratory safety parameters indicated an AE.

Provocation test: Patients who refused to continue with their medication were asked to stop taking it for up to 2 weeks (washout) and were then asked to resume taking it (provocation test). If symptoms reoccurred the medication was considered to cause the AE and was stopped again.

Symptoms or side-effects that were tolerated by the patients were not registered and such patients continued to take their medication.

Safety variables such as ASAT, ALAT, gamma glutamyl transferase (GGT) and creatine kinase (CK) were analyzed before the initiation of therapy, and after 1, 3, 6, 12, 18, 24, 30 and 36 months of treatment.

Efficacy variables: Serum total cholesterol (TC), HDL-cholesterol (HDL-c) and triglycerides (TG) were determined by means of routine methods using a VITROS 950 IRC multianalyzer (Ortho-Clinical Diagnostics Inc., Rochester, NY). LDL-cholesterol (LDL-c) levels were calculated using the Friedewald formula. Laboratory parameters were analysed at the local hospital.

Study 2

Analysis focused on the primary endpoints of all-cause mortality, non-lethal acute myocardial infarction, coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty. Analysis of endpoint data was by intention-to-treat. Baseline data for both groups are seen in Table 7.

Table 7: Baseline characteristics for both groups, mean and 1SD.

	Controls Mean (n=73)	1SD	Atorvastatin Mean (n=70)	1SD	p=
Continuous variables (Mean, SD)					
Age (years)	69.4	(10.2)	67.8	(12.4)	ns
Systolic blood pressure (mmHg)	147.2	(23.2)	150.3	(26.2)	ns
Diastolic blood pressure (mm Hg)	80.9	12.8	81.4	(13.7)	ns
Height (m)	1.70	(0.09)	1.70	(0.087)	ns
Weight (kg)	75.0	(15.5)	77.0	(16.5)	ns
Body-mass index (kg/m^2)	26.3	(4.6)	26.4	(5.1)	ns
Total cholesterol (mmol/L)	5.76	(1.57)	5.79	(1.52)	ns
LDL cholesterol (mmol/L)	3.46	(1.24)	3.56	(1.19)	ns
HDL cholesterol (mmol/L)	1.15	(0.46)	1.13	(0.40)	ns
Triglycerides (mmol/L)	2.57	(2.11)	2.47	(1.31)	ns
Categorical variables (N, %)	**Controls N**	**%**	**Atorvastatin N**	**%**	**p=**
Men	51	(69.9)	48	(68.6)	ns
History of diabetes	22	(29.7)	22	(31.9)	ns
History of angina	18	(24.3)	19	(27.5)	ns
History of claudicatio	10	(13.5)	2	(2.9)	0.031
History of myocardial infarction	14	(18.9)	21	(30.4)	ns
History of stroke or transient ischaemic attack	8	(10.8)	10	(14.5)	ns
History of percutaneous transluminal coronary angioplasty and coronary artery bypass graft	5	(6.8)	6	(8.7)	ns
History of amput. of leg due to peripheral arterial disease surgery	2	(2.7)	1	(1.4)	ns
History of leg ulcers	2	(2.7)	5	(7.2)	ns
History of tumours	7	(9.5)	10	(14.5)	ns
History of liver disease	0	(0.0)	4	(5.8)	0.055
History of myeloma	0	(0.0)	1	(1.4)	ns
History of amyloidosis	2	(2.7)	2	(2.9)	ns
History of vasculitis (e.g., SLE, Wegeners')	3	(4.1)	2	(2.9)	ns

Study 3

The Inter Dialysis Weight Gain (IDWG) was considered as the extent of fluid that retained in the body between two dialysis sessions. If the patient still had normal urine output this change was 0 kg. In those who had reduced elimination of water, in addition to uraemic waste products from the kidneys, IDWG increased above 0 kg. The extent of ultrafiltration

necessary to achieve dry weight was registered at start, after 1 month, 3 months and thereafter every 6 months until 36 months.

Group 1 consisted of patients that survived the observation period without end-points. Group 2 included patients that during the observation period suffered from the end-points that were acute myocardial infarction and had to perform coronary bypass interventions or died.

The mean extent of ultrafiltration (IDWG) was registered at each period given above according to the protocol. Thereby the extent of ultrafiltration was calculated from the increase in the estimated dry weight until the next dialysis. This weight was also related to the dry weight of the patient and given as increase in percentage of body weight. For example, an increase in weight of 2.5 kg in a patient with a dry weight of 100 kg corresponded to an increase of 2.5% of body weight (given as %bow). In contrast a weight gain of 2.5 kg in a 50 kg patient corresponds to 5% of the body weight.

Study 4

The end-points included death (reasons given), acute myocardial infarction, or coronary vascular intervention. The extent of ultrafiltration was measured at predefined follow-up points.

The IDWG was calculated as ultrafiltration/body weight given in weight%. The burden of IDWG was analysed as in study 3. Patients were followed prospectively and data were collected in the same way as for study 3. In study 4 the patients had been followed for the whole study period; an additional 9 patients were included compared to study 3. A total of 97 HD patients were studied. Midweek samples were obtained. Predialysis values were used and blood pressure was measured and recorded before the start of dialysis. Mostly, a

diffusive technique with a low-flux dialyzer was used. End-points in the prospective trial were the same as in studies 1-3 including myocardial infarction, CABG operation or coronary artery dilatation and death. The end-points in this study were further divided into those with (1) various cardiovascular lesions including aortic aneurysms and stroke (subgrouped as those with congestive heart failure, cardiac reason, aortic aneurysm, and intracerebral bleeding); (2) cancer; (3) cachexia; (4) infectious reasons for death; and (5) other reasons.

Study 5

This study was performed to investigated whether atorvastatin, given at a dose of 10 mg/day, has a survival benefit and improves the metabolic variables or cardiovascular end-points and death of patients with chronic kidney disease (CKD) Stages 4 and 5, and if so, whether it does so differently in patients with diabetes mellitus than in patients without it.

Here comparisons were made in efficacy variables but also possible side effects on laboratory data. Data collection and analysis was similar to studies 1 and 2 but focused to compare those with diabetes mellitus with the other patients. The primary end-points were myocardial infarction, performance of coronary artery bypass surgery or dilatation, and death from any cause.

STATISTICS

Studies 1 through 5

In general statistical analyses was performed using Student's t-test for paired samples when data of the patient were compared with new data of him/herself over time. If the numbers were few and a skewed distribution could be suspected non-parametric analyses of paired samples were performed using Wilcoxon's test. If data from different groups were compared with each other Student t-test for unpaired samples or the non-parametric analysis Mann Whitney test was used. Pearson's test for univariate correlation was used. If outliers were present data were checked with the Spearman test. Multivariate regression analyses were performed. The two tailed significance level of a p-value less than 0.05 was considered significant. For small samples with a skewed distribution, additional non-parametric analyses were done. For parametric data, mean values and SDs were given. The median value and range (lowest – highest value) were given when non parametric statistics were performed. SPSS software was used in all studies.

Studies 2 through 5

In study 2 additional analyses of differences in outcome of categorical variables were performed using the Chi-2 test with Yates correction or Fisher's exact test. The time to the primary end-point was analysed by means of Kaplan Meier survival curves, including treatment group as a factor. In addition, Cox regression survival analysis was performed adjusting for age and gender. The analyses were performed according to intention to treat (IT) and also according to per-protocol (PP) for ''all primary end-points''. Ninety-five % confidence intervals (CI) are given.

Study 4

The burden of exposure may vary. Thus, extensive exposure for a short period of time may be as harmful as long-term exposure to a moderate risk factor (i.e., one high potassium value may cause death while many slightly elevated do not). Using the area under the curve may not be suitable to calculate this risk factor because a low exposure for a long period would accumulate more area under the curve than a short, intensive period (i.e., smoking few cigarettes for many years may result in a high total consumption in contrast to a few years with 40 cig/day). A mean value would not be representative of this factor because a certain duration of time is needed to develop a risk for a moderate risk factor level (i.e., one episode of increased lipids versus many years of increased values). In addition, the extent may vary over the period of time. Because all patients, entered in this study, were subjected to sampling of data at the same intervals, we decided to include all individual values in the statistical analyses. Each value obtained was considered independent of the others regarding the burden of the risk factor. If there was a deviation in one or another group from the others, this would be shown in the statistical analyses. Fisher's test was used to assess whether the proportion of patients with more or less IDWG% differed in terms of the end-points. Mann-Whitney comparisons were made between groups with a larger variation in data such as IDWG%. Thus, all data from all measured points were entered in some of the analyses.

ETHICAL CONSIDERATIONS

The Swedish Medical Product Agency (MPA) had approved the use of atorvastatin for this type of patient before the study was initiated. The drug was extensively used in various dialysis units.

This study was reviewed and approved prior to its start by the ethics committee for each respective centre. The Swedish Medical Product Agency was informed. The design of the study was adjusted according to the comments of the Swedish Medical Product Agency. To fulfil criteria of adequate power of the study this resulted in a prolongation of the observation period from 3 to 5 years, due to a lower inclusion of patients than expected.

Patients were thoroughly informed in writing about the purpose of study, but as well verbally by the research nurse and doctor at the respective centres. The patients were allowed to terminate the study at any time. Side effects were reported regularly on a special form, and samples were taken continuously. A safety committee consisting of an independent doctor at Norrland University Hospital was included in the study. No severe adverse events were reported during the study. A question of increasing the dosage was discussed, but since already several of the patients in the atorvastatin group did not accept to proceed with atorvastatin medication, it was considered unethical to increase the dose and to risk aide effects in a larger extent of patients in the study.

The study was proceeded since other studies of this type for patients with severe renal disease (CKD 4-5) were lacking and medication was already used for these patients in general. It was important to clarify the role of lipid-reducing treatment for kidney disease since it had appeared data in other studies that atorvastatin had a beneficial effect on reducing the risk of cardiovascular complications in non-renal patients (Baigent, et al. 2005). The benefit for the patients by fulfilling this study would be an increased evidence based knowledge how to treat and what the benefit and risks would be for the patients prescribed atorvastatin. In addition the study would clarify if other important risk factors should be considered.

RESULTS

Study 1

Analysis of efficacy of atorvastatin

The follow-up period was similar for both groups with a mean of 20 ± 14 months for those on atorvastatin versus 22 ± 13 months for the controls. Compared with baseline values, patients treated with atorvastatin had a significant reduction of total cholesterol at the 1st month of treatment through month 36 (mean value 5.8 mmol/l at start versus 4.4 mmol/l at 1 month;i.e. - 23%; $p < 0.001$). LDL -cholesterol was also reduced within the first months of atorvastatin medication throughout month 36 (3.6 at start versus 2.2 mmol/l; i.e. -35%; $p < 0.001$). A reduction was also found of triglycerides from the start through month 24 (2.5 versus 1.9 mmol/l) and 36 (2.5 versus 1.8 mmol/l).

Notably, the controls had significantly reduced levels of total cholesterol already from the 1st month through month 36 ($p < 0.021$) and also of LDL cholesterol that became significant at months 30 and 36 ($p < 0.020$).

Compared with the controls, the atorvastatin group had significant lower levels of total cholesterol and LDL cholesterol at month 1 through 30.

Analysis of safety

Sixteen patients (23%) stopped taking their medication since they did not tolerate the side-effects, the most frequent complaints being gastrointestinal discomfort and headache. No serious adverse events due to atorvastatin could be verified.

Study 2

The results of analyses of primary end-points (all-cause mortality, non-lethal acute myocardial infarction, coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty) occurred in 74% of the subjects (Table 8). There was no difference in outcome between the control and the atorvastatin (10 mg/day) groups. The 5-year end-point-free survival rate from study entry was 20%. Subgroup analyses revealed no significant difference in end-points neither in those on dialysis nor those being predialysis.

Table 8: End-points of study according to intention to treat analyses.

	Controls (n)	**Atorvastatin (n)**
Primary end-point- all	45	40
Death by any reason	38	34
of these death due heart disease	(15)	(19)
Non-fatal myocardial infarction	7	5
PTCA or CABG	0	1
Secondary endpoints		
Non-fatal stroke (died 6 months later, incl. above)	1	0
Deaths	38	34
Acute myocardial infarction	7	9
Congestive heart failure or other cardiac death	8	10
Infections	6	3
Cancer	4	3
Cachexia	6	5
Cerebral (infarction, bleeding)	2	2
Other reasons	5	2

PTCA= Percutaneous transluminal coronary angioplasty
CABG= coronary artery bypass graft

Study 5 - Since patients with diabetes mellitus (DM) are considered to have a higher risk to suffer from cardiovascular disease than the other patients with kidney disease study 5 was performed. Therefore further subanalysis of data was performed comparing those suffering diabetes mellitus with those without such disease, and those with or without additional atorvastatin medication. There were no significant differences at baseline between those with DM and those without DM with respect to age, weight, and levels of

serum albumin, fibrinogen, total cholesterol, LDL-cholesterol, HDL-cholesterol, or triglycerides. As expected, HbA1c was higher in those with DM. A significant but similar reduction in total cholesterol and LDL-cholesterol occurred in both groups who received atorvastatin. Plasma fibrinogen increased significantly over time in these groups (See Figure 8 below), while there were no changes in serum albumin, CRP, HbA1c, residual renal function or proteinuria. A Cox regression analysis did not show a survival benefit for patients who received atorvastatin with or without DM compared with controls. There was no evidence of benefit for atorvastatin medication.

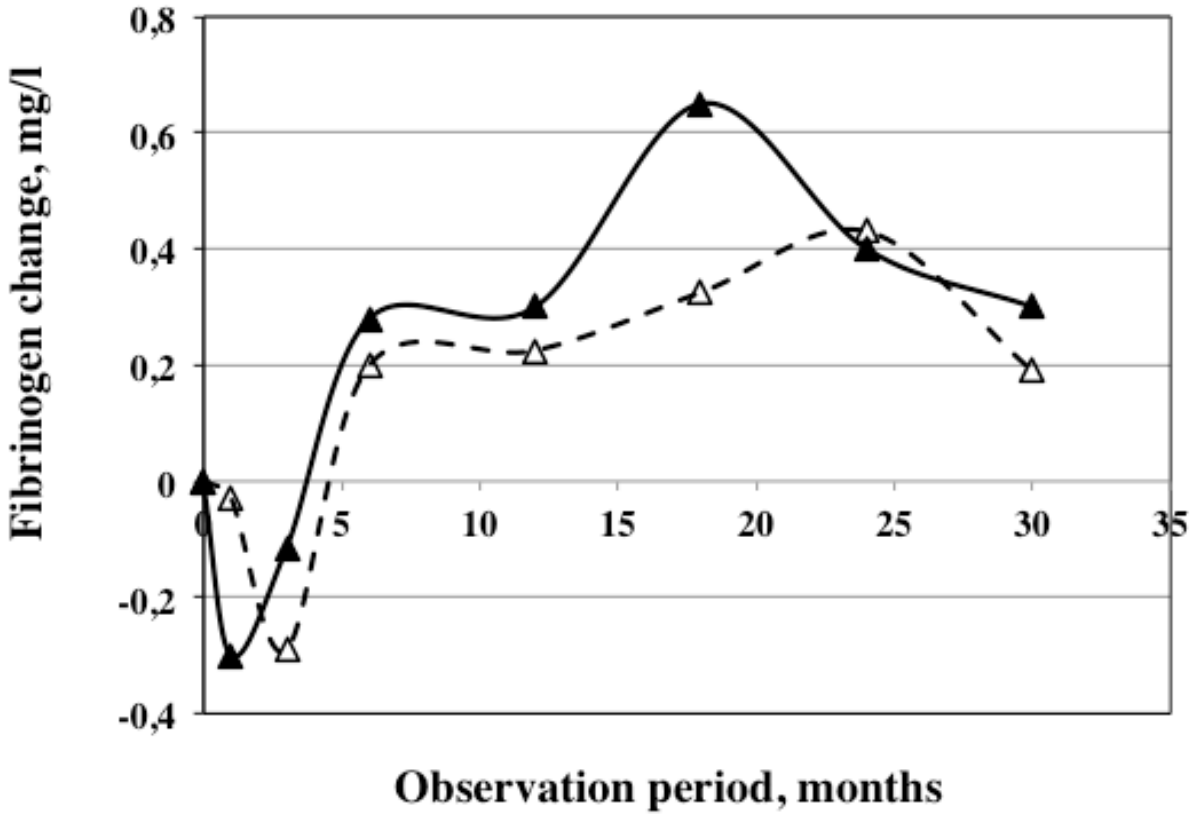

Figure 8 : Change in median fibrinogen concentration (mg/l) over time in patients with DM. Patients taking atorvastatin (filled triangle) and those not taking atorvastatin (open triangles).

Study 3

Haemodialysis patients are at a special risk for CVD. Risk factors mostly found in retrospective studies have been related to the extent of dialysis (Kt/V), serum values of albumin, phosphate and CRP and blood haemoglobin. In parallel to the question of whether atorvastatin would have a beneficial impact on the outcome of the patients in the main study (study 2), the question arose if there were any other risk factors that could be identified especially for haemodialysis patients, in this prospective study. Since this study was performed before the main study was finished it included only 88 of the haemodialysis patients. Patients with an end-point (group 2: death, acute myocardial infarction or coronary vascular intervention) were compared to those without end-points (group 1). At this point of the main study, still ongoing, 40% of the haemodialysis patients had reached an end-point. There was no difference at baseline between the groups in regard to age, prevalence of diabetes mellitus or history of previous cardiovascular disease, KT/V, residual renal function, ultrafiltration need, C-reactive protein, s-albumin, cholesterol, LDL-cholesterol, HDL-cholesterol, appetite or wellbeing, while triglyceride was lower in group 2 ($p = 0.035$). The observation period for group 1 was at a mean 24.7 months (SD ±13.1) and for those in group 2 at a mean 13.8 months (±11.7)($p < 0.001$). After a follow up of 24 and 30 months patients in group 1 had less inter dialysis weight gain than those in group 2. The need of ultrafiltration was about 27% lower at 24 months (n= 29) in group 1 (3.63 ± 1.93 weight% versus 4.97 ± 1.70 weight%, n=9) than in group 2 ($p = 0.046$) and 46% lower at 30 months (for 18 from group 1: 3.48 ± 1.95 versus 6.45 ± 1.55 for 3 from group 2, $p = 0.030$). Thus Group 2, who reached end-point, had greater need for ultrafiltration. C-reactive protein did not differ significantly between the groups during the period.

Study 4

A total of 97 HD patients with a mean age of 70 years (±10 years) were studied. The end-points included death (specific reasons given), acute myocardial infarction, or coronary vascular intervention. The burden of inter dialysis weight gain (IDWG) was analysed. End-points occurred in 77 (79%) of the patients during the 5-year study period. The extent of IDWG was higher in those with end-points due to cardiovascular reasons (3.77 vs. 3.19 weight%, $p<0.001$), cardiac reasons ($p<0.001$), congestive heart failure ($p<0.01$), aortic aneurysm, and intracerebral bleeding ($p<0.024$). Those with cancer as a cause of death did not differ in IDWG% from the control group, while patients who died due to cachexia more frequently had IDWG% below 2.5% than the controls (OR 0.45, CI 0.24–0.86, P=0.018). Patients who died due to infectious reasons had a lower weight gain between dialysis than controls (OR 0.37, CI 0.18–0.77, P=0.010). Atorvastatin medication did not influence the extent of IDWG.

DISCUSSION

Studies 1, 2 and 5

Safety and efficacy study (study 1)

When this study was initiated we had no data on the efficacy of atorvastatin in patients with CKD 4 and 5. This resulted in a start with the lowest recommended daily dose of 10mg/d. This dose resulted in a 35% reduction of LDL-cholesterol and a 23% reduction of total cholesterol. Triglycerides were also lowered significantly. These data were similar to reports, that came up during our study, on non-uremic patients (Davidson, et al. 1997; Tanaka, et al. 2001) and short-term studies of patients on dialysis (Harris, et al. 2002; Hufnagel, et al. 2000; Lins, et al. 2003). In a peritoneal dialysis population the effect of atorvastatin seemed to be somewhat greater in lipid reduction, especially regarding triglycerides (Hufnagel, et al. 2000). In our study we were not prepared to increase the dose due to the number of patients who withdrew due to experienced side effects. Our long-term data showed that the values remained stable during the whole period. Notable was that the control group also showed significant reductions in LDL-c and total cholesterol over time, and that the differences between the groups were lost at 36 months. The control patients might have been motivated to be stricter with their diets to achieve the lower cholesterol levels. However, triglycerides were not lowered in the control group, which would have been expected if diet changes had occurred. A plausible explanation for the reduction of the lipid values over time for the control group could be that those control patients had survived for a longer period and therefore they might have been able to change their living to be more "cardioprotective".

Our study also showed that atorvastatin reduced LDL-cholesterol by the same percent in patients with higher vs. lower baseline levels. Therefore, the same atorvastatin dose can be used for patients with higher or lower baseline levels.

Adverse effects

Since the reduction of lipids was acceptable and the extent of withdrawals, with given reason, from the study was quite extensive (approximately 20%) we did not increase the atorvastatin dose further.

If the patient felt that the symptom was related to the medication and wanted to stop medication the symptom was registered as a significant side-effect. The same occurred when safety laboratory parameters were impaired (in one patient). Before stopping treatment definitely patients were asked to perform a provocation test after a medication-free period of about 2 weeks. However, only few patients accepted to do this provocation test since their adverse events were described as very distinct and strongly related to medication. Poor compliance may be a reason to stop medication. However, we think that the compliance of our patients to take atorvastatin was good. Only two of the atorvastatin-group patients did not show reduced LDL concentrations at 1 and at 3 months, which might indicate that they had not taken their medication. In general these patients are very compliant, since they are followed up over a long period, and usually by the same staff. Medication can be checked by the number of prescriptions required. However, this requires a lot of resources. The motivation to prolong life and avoid cardiovascular complications is generally strong, even in elderly patients. This probably motivated the patients to remain on atorvastatin since they were aware of the cardiovascular benefit in non renal patients by information before entry into the study. Only few patients showed impairment in laboratory safety variables, while some other signs of interaction may be suspected by results from the questionnaire from time to time. Changes in laboratory parameters developed after more than 1 year on atorvastatin in some patients. Therefore, continuous laboratory follow up seems necessary. One reason for the high incidence of adverse events might be due to metabolites, usually excreted by the kidneys but eventually to a greater extent retained in these patients. Notable is that in another study analysing safety of atorvastatin in haemodialysis patients they noted that some metabolites were not eliminated by dialysis. Adverse events were present in 27-45% of those patients (Lins, et

al. 2003).

After this study was finished a study on atorvastatin in patients with diabetes mellitus and on haemodialysis was published. Notable was that in that study only few side effects were reported by atorvastatin medication (Wanner, et al. 2005).

End-point and efficacy study (study 2)

When this study was initiated there had been no end-point studies using statins for patients with severe chronic kidney disease (CKD) stage 4 and 5. Therefore guidelines recommending statins for lipid lowering also for these patients (Läkemedelsverket 2005; Läkemedelsverket. 2003) were based on studies of other populations. The present study focused to include patients at risk for cardiovascular disease having severe CKD. With a daily dose of 10 mg atorvastatin that patient group reached considerable reduction in their LDL-cholesterol levels. Despite this effect the atorvastatin medication had no apparent benefit with regard to primary end-points. Thereby the overall mortality was not different, nor were cardiovascular endpoints. Notable is that the ALERT study (patients with kidney grafts) neither had a significant difference in survival (Holdaas, et al. 2003). This might indicate that patients with severely impaired renal function will have less benefit by statin medication than is found in other studies. Notable was that the subanalysis of pre-dialysis patients tended to have a slight trend towards benefit by atorvastatin. A larger study focused merely on inclusion of such patients is worthwhile to perform. In contrast when the dialysis patients were analysed separately, without including predialysis patients, the differences in the end-point curve was even further lost.

When planning this study there were no data on what the upper or lower limits of cholesterol for inclusion should be in this type of patients. Data from studies of other groups of patients existed and indicated that lowering total- and LDL-C even below recommended guidelines (5 and 3 mmol/l, respectively) could be useful (Verschuren, et al. 1995). We therefore decided not to have thresholds for inclusion of these variables for

entry into the study, as was also decided by the ethical committee. In addition, we avoided to have strict primary or secondary prevention criteria for inclusion since data indicated that this group of patients overall had a high risk for cardiovascular diseases (EDTA-ERA. 1988; Schon, et al. 2004). We did not include patients with a functioning kidney graft since the ALERT-trial, mentioned above, was planned and later ongoing in parallel (Holdaas, et al. 2003). In addition, that group is usually selected to have less cardiovascular problems before acceptance for the waiting list for transplantation. Many of those patients also have a renal function of a level of CKD 2 and 3. We also excluded patients who were in a poor clinical condition and were not expected to survive the first 6 months. Therefore, in general we feel that the patients selected for inclusion into the study would be the group that could be expected to benefit from statin therapy.

Notable is that the overall survival in our study is very low, especially in the dialysis group. However, the outcome data are in line with outcome data from the Swedish registry of uraemia where patients have a survival of approximately 16% at 5 years follow up (Schon, et al. 2004).

However, the lack of efficacy in outcome, in any of the groups in this study, indicate that other factors than statins are more important to counteract to the poor survival in these patients. Such factors might be to prevent inflammatory processes in these patients (Pecoits-Filho, et al. 2002a; Pecoits-Filho, et al. 2002b), and/or or to remove specific uraemic toxins interfering with mechanisms responsible for the immune system and cardiovascular conditions (Vanholder, et al. 2001).

The lack of efficacy of atorvastatin to reduce end-points may correspond with data from the ASCOT study including more than 10000 patients (without severe kidney disease). Although there was a benefit in primary cardiovascular end-point criteria there was no significant difference in the all-cause mortality in the ASCOT study using atorvastatin with a 36% LDL-C lowering at 6 months (Sever, et al. 2003). A lack of efficacy may also exist, since in CKD patients, in contrast to the general population, atherosclerosis is more

focused in the media of the than the intima of the vessels (London, et al. 2003).

Translation of the results from that study into daily clinical practise provides no evidence to support a benefit of atorvastatin medication in these patients. To focus especially on patients with an expected higher risk for cardiovascular diseases patients with diabetes mellitus would be such a group.

After our study was finished two other randomised studies on patients with CKD 5, in dialysis, have been finished (Fellstrom, et al. 2009; Wanner, et al. 2005). None of these studies could confirm any survival benefit using statins to this group of patients (atorvastatin versus rosuvastatin).

Atorvastatin and diabetes mellitus (DM) (study 5)

The benefit of lipid-lowering drugs in reducing cardiovascular end-points have been established for primary and secondary prevention both for non-DM and for those with DM, resulting in guidelines for statin use. The American Diabetes Association recommend that a large group of DM patients, considered to be at risk of developing cardiovascular disease, take statins (Eldor and Raz 2009). A consequence of this is that most patients with diabetic nephropathy receive statins. These statin prescriptions are maintained in most patients also when renal function deteriorates extensively and the patient enters a dialysis program. Based on those assumptions one would expect beneficial outcome in several variables in the present study. However, although atorvastatin reduced LDL-cholesterol and total cholesterol to similar extents in patients with DM and the non-DM group there was no beneficial effect on the end-points. Neither did the use of atorvastatin in this study improve the HbA1c in general nor specifically in the DM+A group. Similar results have been obtained in a Japanese study of type 2 diabetes patients without renal failure (Chu, et al. 2008; Tanaka, et al. 2001). Atorvastatin did not improve HbA1c levels in the DM+A group in the present study. However, there was no worsening in the HbA1c level in the non-DM+A group while such increase in HbA1c over time was seen in the non-DM-C group. Such haltering effect on HbA1c in the present study, would resemble outcome in another

study, where atorvastatin improved metabolic control in type 2 diabetic patients who were free from microangiopathic complications (Dalla Nora, et al. 2003). In contrast, others showed that the metabolic control worsened in those receiving atorvastatin (Her, et al. 2010; Tehrani, et al. 2010).

A lack of effect would be similar to medication with simvastatin that did not result in any difference in HbA1c levels in the HPS study (Collins, et al. 2003). Notable is that Shurraw et al. showed that higher HbA1c levels are not associated with increased mortality in HD patients with DM (Shurraw, et al.).

In the present study there was no reduction of CRP by atorvastatin; nor did it do so in another study (Krane, et al. 2008), where the dose was 20 mg/day. In contrast, rosuvastatin 10 mg/day caused a small reduction of CRP in the AURORA study (Fellstrom, et al. 2009), suggesting that different statins have different effects.

It is notable that in the present study plasma fibrinogen levels increased significantly in patients who received atorvastatin, both in those with diabetes and in those without. Previous short-term studies of various groups of patients have given conflicting results. Some studies showed that atorvastatin medication gave an increase in fibrinogen (Tehrani, et al. ; Walter, et al. ; Wierzbicki, et al. 2001). In HD patients some found no change when measured at 36 weeks (Joy, et al. 2008), and others noted a decrease of fibrinogen (Baldassarre, et al. 2009; Kinlay, et al. 2009; Krysiak, et al. ; Ukinc, et al. 2009). The different outcomes in those studies may be due to often short-term observation periods. An increase in fibrinogen is a disadvantage for the patient, since such an increase is coupled with increased vascular morbidity (Wierzbicki, et al. 2001). Fibrinogen is a marker of inflammation (Baldassarre, et al. 2009; Hamirani, et al. 2008), and thus an increased level of fibrinogen may indicate increased inflammation. However, CRP levels in our study were unchanged throughout the period, and we concluded that there was no general increase in inflammation. The increase in fibrinogen may indicate a more specific effect that may involve coagulation, arising from the atorvastatin medication.

In other studies atorvastatin was reported to reduce proteinuria and halt the decline in renal

function, such as in patients with nephrotic syndrome (Valdivielso, et al. 2003) or glomerulonephritis, (Ozsoy, et al. 2005) and in heterozygous hypercholesterolemic patients (Sinzinger, et al. 2003). Simvastatin also resulted in a retarded fall in the estimated glomerular filtration rate in patients with DM (Collins, et al. 2003). However, in our study, atorvastatin did not lead to improved renal function, nor a retardation in renal impairment or diurnal proteinuria in any of the groups. It is possible that this lack of effect is due to the fact that kidneys of patients with CKD Stage 4 or 5 are too extensively damaged. These data are congruent with others, showing that atorvastatin does not reduce renal impairment or diurnal proteinuria in transplant patients (Navarro-Munoz, et al. 2007).

Body weight increased in patients with DM+A. This may be due to loss of endurance and thereby less exercise. This may be undesired effects of atorvastatin. Atorvastatin induced side effects that differed between the groups. Patients in the non-DM+A group experienced a greater loss of appetite and a higher tendency to vomit than patients in the DM+A group. Muscle pain also increased in the non-DM+A group. This may explain a lower ability to walk up as many stairs as before. One should be cautious about signs of muscle pain and the impairment in the ability to walk up stairs, since in general, patients in the haemodialysis programme have only approximately 50% of physical strength of age-matched persons (Sterky and Stegmayr 2005). While the endurance of patients with DM-C improved over time in contrast, it was reduced for DM+A. Thus, one should take notice and ask patients with DM on atorvastatin about the change of their endurance.

After our main study was finished 3 other randomized trials have been concluded in this area.

The 4D study (published 2005) included 1.255 patients with type 2 diabetes mellitus. The primary end-point was a composite of death from cardiac causes, nonfatal myocardial infarction, and stroke. Secondary end-points included death from all causes and all cardiac and cerebrovascular events combined. Patients were randomised to either atorvastatin (20mg/d) versus controls. LDL-cholesterol was reduced by 42% (from 3.23 mmol/l). The significant effect of atorvastatin on the individual components of the primary end-point

was that the relative risk of fatal stroke among doubled while all cardiac events combined decreased but, not all cerebrovascular events combined and neither total mortality (Wanner, et al. 2005).

In the AURORA study (published 2009) 2776 haemodialysis patients were randomized to either placebo or rosuvastatin (10mg/d) that was used as statin. The combined primary end-point was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary end-points included death from all causes and individual cardiac and vascular events. The LDL-cholesterol fell by 43%. Rosuvastatin had no effect on individual components of the primary end-point. There was also no significant effect on all-cause mortality (Fellstrom, et al. 2009).

The SHARP study (published 2011) included 9,270 patients with chronic kidney disease (3,023 on dialysis and 6,247 non-HD patients. The patients had no known history of myocardial infarction or coronary revascularisation. Patients were randomly assigned to simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo. A total of 4,650 patients were assigned to receive simvastatin plus ezetimibe and 4,620 to placebo. LDL cholesterol was reduced by 23% versus 31% for HD versus non-HD patients. This resulted in a 17% proportional reduction in major atherosclerotic events (11.3%) simvastatin plus ezetimibe *vs* (13.4%) placebo (p=0.0021). After weighting for subgroup-specific reductions in LDL cholesterol, there was no good evidence that the proportional effects on major atherosclerotic events differed from the summary rate ratio in any subgroup examined, and, in particular, they were similar in patients on dialysis and those who were not. Death by any cause was present in 24.6% of the treated group and 24.1% of controls (not significant). Eighty per-cent of patients were suspected of not taking their medication (Baigent, et al. 2011).

Thus, neither the present nor other randomized studies thereafter could find any benefit for overall survival using lipid reducing approaches. Therefore, the lack of survival benefit should restrict prescription of statins to DM as well non-DM patients if they suffer from

CKD4 and CKD5. It seems as much earlier prevention measures are necessary, already during the first 5 years of DM, as proposed by Del Prato (Del Prato 2009). Notable is that although guidelines recommend the use of statins in a larger group of patients with DM (Eldor and Raz 2009) the studies they are based on mainly refer to improvement of cardiovascular composite end-points (Armani and Toth 2006; Colhoun, et al. 2004; Collins, et al. 2003; Goldberg, et al. 1998; Knopp, et al. 2006; Pyorala, et al. 1997; Sever, et al. 2005; Shepherd, et al. 2006). None of the studies concluded that there is an overall survival benefit in taking statins for patients with diabetes mellitus.

In conclusion, the present study has shown that patients with or without diabetes mellitus and CKD stage 4 or 5 have no benefit from taking atorvastatin (10 mg/day). Atorvastatin does neither have a beneficial effect on inflammatory variables. On the contrary, fibrinogen levels increased, raising the possibility that this drug is of detriment to patients. The lack of evident benefits of atorvastatin therapy for both the variables and the end-points we have examined motivate a restriction in prescription to patients with and without diabetes mellitus and CKD stage 4 or 5.

Studies 3 and 4

Inter Dialysis Weight Gain (IDWG; studies 3 and 4)

These studies showed that the extent of a haemodialysis patients with end-points (group 2) is high. The risk to develop an end-point based on entry variables was only significant for age in Cox analysis. However, only base line criteria at study entry were entered and not various follow up criteria. Notable is that there was no significant difference in weight gain at entry into the study between the groups. Significant differences came out first after an observation period of 18 months. Thereby patients who reached a primary end-point had significantly higher weight gain between dialysis (group 2) than those in group 1. The latter had at a mean less than 3.5% weight gain during the observation period while the others had more extensive weight gain. In group 1 those with the longest observation

period had a mean weight gain of 2.5 % at 36 months. This indicates that it might be important for the patient to have a limited weight gain between dialysis to improve long-term survival. Thereby the effect of such measures seems to become significant with time and in this study after about 18 months of observation. A reason to find differences first after 18 months of observation might be that several of the deaths are not due to cardiac reasons. In addition, the divergence of the weight lines between the group over time indicates that the difference in weight gain seems to be a process that develops in specific individuals over time, since there was no difference comparing base line data between the groups. The reason for this increased weight gain may be a change of compliance. However, a change in the experience of thirst may be another reason. Notable is that the lipids did not differ between the groups and probably are not of extensive importance in the prognosis of these patients. The albumin levels were quite normal in both groups as were scoring for appetite and values for KT/V. These factors indicate that there were no large adverse effects present due to malnutrition or too short dialysis treatments in group 2. Neither was there any significant difference in the CRP between the groups. The lack of difference may indicate that this group of patients are less influenced by an eventual inflammation per se, probably since patients with active malignant diseases were not included in the trial. Malnutrition and inflammation enhancing atherosclerosis (MIA) in dialysis patients are suggested as parts of a cardiovascular syndrome (Stenvinkel, et al. 2001). This, MIA syndrome is probably also implicated by other factors such as too much weight gain due to fluid intake between dialysis. The data in our study strengthen the importance of the variable volume overload as a risk factor for morbidity. In the present study, there was no difference in residual renal function between the groups, that otherwise would error the interpretation. Therefore, a larger intake of fluid is a plausible reason for worse outcome. The increase in fluid intake seems not to be due to increased thirst by e.g., hyperglycaemia, since the representation of patients with diabetes mellitus were quite similar in both groups even with a tendency to fewer patients with DM in the end-point group.

In addition, there was no difference in dialysis prescriptions that, for less well-dialyzed, could have resulted in a more hyperosmotic condition, caused by retention of uremic solutes, and thereby more extensive thirst. Instead this difference in IDWG might be due to a different drinking behaviour between the groups. This difference in drinking behaviour seems to have developed over time since the groups had the same extent of IDWG at baseline. Another study, congruent to the present study, showed that fluid overload of more than 5.7% contributed to increased risk of death (Leggat, et al. 1998). In contrast, a short-term study by Lopez-Gomez et al., showed that there was a better outcome if the IDWG was greater. It was interpreted being beneficial as an indicator of adequate nutrition (Lopez-Gomez, et al. 2005). Notable is, however, that in the latter study the IDWG was measured only as a mean of the first 12 dialysis sessions and not followed over time. Based on the present study, it seems that retention of more than 2.5% between dialysis seems to be a risk factor for increased morbidity.

Study 4

IDWG continues (study 4)

In this study we were able to further analyse the effect of IDWG on various end-point diagnoses. Thereby we found that patients who received an end-point due to cardiac reasons, congestive heart failure, aortic aneurysm and intracerebral bleeding, all as indicators for cardiovascular lesions had significantly higher IDWG. The outcome of these data seem reasonable since high IDWG will be strenuous for the heart due to increased intravascular volume. In addition the volume overload in the lungs will contribute to decreased saturation, especially in the presence of pulmonary oedema. This may lead to cardiomyopathy (Parfrey and Foley 2000). An intensified ultrafiltration during the dialysis procedure increases the risk for hypotensive episodes during dialysis (Saran, et al. 2006). In that study the importance of a longer HD duration/session was independently associated with a lower mortality risk. In contrast, ultrafiltration rates more extensive than 10ml/h/kg body weight were independently associated with higher risk of intradialysis hypotension

and mortality (Saran, et al. 2006).

In the present study the use of atorvastatin did not influence the outcome of IDWG, indicating that this medication has no favour in this regard. Notable was that overhydration caused complications related to cardiovascular diseases and in contrast a restricted extent of IDWG may indicate malnutrition and dehydration by, e.g. presence of fever or diarrhoea.

GENERAL CONCLUSION

Atorvastatin, 10 mg/day, significantly reduced LDL-cholesterol , total cholesterol and triglycerides.

Although no severe side-effects developed, about 23% of the patients refused to continue treatment due to their experienced side-effects. Notable was the significant improvement of the lipid profile over time also in the control group. Although the medication caused no severe side-effects we suggest continued caution when using atorvastatin for severe CKD patients until its long-term safety and efficacy have been repeatedly verified. The present study, as well as other studies, have not been able to confirm beneficial effects on long term survival in CKD 4 and 5 patients using statin therapy. If the expected length of survival is short, by various reasons, and the eventual benefit of statin therapy expected to be negligible or limited to prolong survival, the patient probably is favoured in quality of life, by less risk for adverse events, being off statin medication, even if diabetes mellitus is one of the diagnoses.

Other risk factors for cardiovascular disease in these patients have to be looked for. Our studies were able to confirm that increased inter dialyses weight gain above 3% is an important risk for the patient. Based on those data, therefore, the patients should be made aware of the importance to restrict fluid intake, but not starve, between dialysis. The restriction probably should be as extensive as possible and probably below 2.5% of the body weight aimed at after dialysis. This will also result in the need of less extensive ultrafiltration and allow a rate below 10 ml/h/kg. In contrast CRP by itself and lipid variables seemed to be of less importance. CRP could much more be expected as a marker for a severe disease, such as infection or tumour, that shortens the life span of the patient.

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