Metabolic syndrome and cardiovascular risk in renal transplant recipients: effects of statin treatment


Abstract: Background: Renal transplant recipients (RTR) have high risk for cardiovascular disease (CVD). They also have high prevalence of insulin resistance and metabolic syndrome (MS). Statin treatment reduces CVD risk in RTR. The aim was to study MS as CVD risk factor in RTR, and to investigate the effect of statin treatment in RTR with MS.

Methods: In total, 1706 non-diabetic RTR from the Assessment of Lescol in Renal Transplantation trial were followed for 7–8 yr. The captured endpoints included major adverse cardiac events [MACE, defined as cardiac death (CD), non-fatal myocardial infarction or coronary revascularization procedure], and CD. MS was defined at baseline according to Adult Treatment Panel III definition with waist girth replaced by body mass index ≥30 kg/m².

Results: MS was diagnosed in 32% of the patients. During the follow-up, MACE incidence was 16% in those with MS and 11% in those without MS (p < 0.001). Statin treatment reduced MACE risk by 53% in the group with MS. CD risk was 74% higher in RTR with MS (p = 0.012), and statin treatment reduced CD risk in those with MS (p = 0.03).

Conclusions: RTR with MS have increased risk for CVD. RTR with MS are an easily identifiable group of patients who benefit from statin treatment.

Inga Soveri, Sadollah Abedini, Hallvard Holdaas, Alan Jardine, Niclas Eriksson and Bengt Fellström

Department of Medical Sciences, Uppsala University, Acute Internal Medicine, Uppsala University Hospital, Uppsala, Sweden, Rikshospitalet, Oslo, Norway, Nephrology, General Infirmary, Glasgow, UK and Uppsala Clinical Research Center, Uppsala, Sweden

Key words: cardiovascular disease – insulin resistance – metabolic syndrome – renal transplantation – statin treatment

Corresponding author: Inga Soveri, MD, PhD, Department of Medical Sciences, Uppsala University Hospital, entr 40, 5th floor, 75185 Uppsala, Sweden. Tel.: +4618610000; fax: +4618509297; e-mail: inga.soveri@medsci.uu.se

Accepted for publication 11 May 2009

Metabolic abnormalities such as glucose intolerance, insulin resistance, central obesity, dyslipidemia and hypertension co-occur in an individual more often than might be expected by chance. The phenomenon is known as metabolic syndrome (MS) and insulin resistance has been implicated as the unifying pathology behind the syndrome.

The prevalence of MS in the general population is dependent on age, ethnicity, and geographic region varying in the Western population from 7% in French women to 24% in US men (1, 2). MS is known to contribute to the development of type 2 diabetes and cardiovascular disease (CVD) (2–4). MS has also shown to play a role in the development of kidney disease (5). The prevalence and thereby the consequences of MS are increasing.

Renal transplant recipients (RTR) are at increased risk for CVD and statin treatment reduces CVD risk in RTR (6–8). In addition to the unfavorable metabolic and hemodynamic conditions the patients have been exposed to prior to the transplantation, the onset or aggravation of diabetes mellitus, dyslipidemia or hypertension often occurs, and can be partly associated to the immunosuppressive regimen (9–13). RTR are insulin resistant when compared to age- and sex-matched controls (14). In addition, MS has been associated with increased risk for CVD and death in RTR (15–17).

The purpose of the current retrospective study was to investigate MS as CVD risk factor in a large population of RTR with 7–8 yr of follow up. In
addition, statin treatment effect in RTR with MS was studied.

**Methods**

The ALERT trial (Assessment of LEscol in Renal Transplantation) was an investigator-initiated and investigator-led, randomized, double-blind, parallel group study designed to investigate the effects of fluvastatin on cardiac and renal endpoints in RTR. The ALERT core study and the ALERT extension study design, baseline data and outcomes have been previously published (7, 8, 18).

**Participants**

To the ALERT core trial, 2102 adult RTR were recruited from nephrology and transplant clinics in Belgium, Denmark, Finland, Norway, Sweden, Switzerland, the UK, and Canada between June 1996 and October 1997. The patients had received renal or combined renal and pancreas transplants > 6 months prior to randomization. All patients were on cyclosporine-based immunosuppression, but no one received statins prior to inclusion. Total fasting cholesterol ranged from 4–9 mmol/L (4–7 mmol/L for those with previous cardiac event). Patients who had had an acute rejection episode in the last three months, or who had a predicted life expectancy of less than one yr were excluded. The recorded endpoints included cardiac death (CD) and MACE (defined as CD, non-fatal myocardial infarction or coronary revascularization procedure). Single event per patient was accounted for. The critical events committee (CEC) consisted of two nephrologists and two cardiologists who were unaware of treatment assignment. All endpoints were adjudicated by the CEC and classified after agreement by consensus majority vote (7). The study adhered to the International Conference on Harmonization Guidelines and for good clinical practice and was carried out in accordance with the declaration of Helsinki. All participants provided written informed consent, and the ethics committee at each participating center approved the trial.

Metabolic syndrome and cardiovascular risk in RTR

MS was defined at baseline using an adapted version of the National Cholesterol Education Expert Panel (Adult Treatment Panel III) definition. Because waist circumference was not recorded in the ALERT study patients, the measure was substituted by body mass index (BMI) as per Meigs et al., who showed that this change had little effect on the applicability of the MS definition (19). In the current study, MS was defined as three or more of the following: (i) BMI ≥30 kg/m², (ii) serum triglycerides ≥1.7 mmol/L, (iii) blood pressure (BP) > 130/85 mmHg, (iv) fasting plasma glucose ≥110 mg/dL, and (v) high density lipoprotein (HDL) < 1.03 mmol/L if male and HDL < 1.29 mmol/L if female (20). Patients with diabetes mellitus were excluded from the analyses because diabetes was considered an outcome of the syndrome and we have previously shown that RTR with diabetes mellitus have higher CVD risk (21, 22). The patients were followed to the end of the ALERT extension trial. Treatment allocation (statin or placebo) refers to core trial treatment allocation.

**Statistical analysis**

The statistical analysis plan of the study has been described previously (7, 8). Both treatment arms were analyzed separately for MS and non-MS patients to show comparability between the placebo and fluvastatin arm with regard to patient demographics, primary cause of renal failure, transplant characteristics, immunosuppressive, and cardiovascular medication, baseline cardiovascular risk factors and occurrence of clinical endpoints. SPSS version 15.0 (© 2007 SPSS Inc.) was used for statistical analysis. Independent-samples t-test was used for normally distributed variables and mean and SD is presented. Chi-square test was used for categorical variables. Cox proportional hazard model was the model of choice for the statistical analysis because covariates and events were well defined and precise time to event was available for the studied endpoints. All covariates were assessed to fulfill the assumptions for Cox proportional hazard models. Cox proportional hazard models were carried out to analyze univariate and multivariate risk factors associated with the risk of predefined clinical endpoints between MS and non-MS patients. All significant univariate and non-significant but potentially important covariates were included in the multivariate model. Corresponding hazard ratios (HR) for group comparisons were calculated with 95% confidence limits.

**Results**

**Patient characteristics**

In total, 1706 non-diabetic RTR were included in the analyses. Of the studied patients, 550 (32%) had MS at inclusion: 439 patients fulfilled three MS criteria, 105 patients fulfilled four MS criteria and six patients presented all five MS criteria. The individual criteria prevalence in the population
n = 1706) was following: 15% had BMI ≥30 kg/m², 64% had triglyceride levels ≥1.7 mmol/L, 34% had low HDL, 70% had BP >130/85 mmHg, and 5% had fasting plasma glucose above 110 mg/dL. The baseline characteristics of the RTR with and without MS are presented in Table 1. Median follow-up time was 7.4 yr (range: 0.002–8.389).

Outcomes and treatment effect

Major adverse cardiac event. During the follow-up time, 87 (16%) patients with MS experienced MACE, compared to 124 (11%) patients without MS (p = 0.001). The 550 RTR with MS had increased risk for MACE [HR 1.57 (95% confi-

Table 1. Patient demographic and prevalence of traditional and non-traditional risk factors for non-diabetic patients with and without metabolic syndrome (MS) in the ALERT study

<table>
<thead>
<tr>
<th>Placebo arm</th>
<th>Fluvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS Patients N = 271</td>
<td>Non-MS Patients N = 582</td>
</tr>
</tbody>
</table>

Patients demographics
- Age at baseline (yr): 50.4 (10.9) vs. 49.6 (11.3), p = 0.316
- Male N (%): 159 (59.0) vs. 398 (68.0), p = 0.007
- Systolic BP (mmHg): 145.0 (18.0) vs. 142.0 (18.0), p = 0.009
- Diastolic BP (mmHg): 87.0 (9.0) vs. 86.0 (9.0), p = 0.009
- Total cholesterol (mmol/L): 6.6 (1.1) vs. 6.4 (1.1), p = 0.112
- HDL cholesterol (mmol/L): 1.0 (0.3) vs. 1.5 (0.4), p = 0.112
- LDL cholesterol (mmol/L): 4.2 (1.0) vs. 4.2 (1.0), p = 0.112
- Triglycerides (mmol/L): 3.0 (1.6) vs. 1.8 (0.7), p = 0.112
- Apolipoprotein B (mg/dL): 126.0 (25.0) vs. 113.4 (25.0), p = 0.112

Primary cause of renal failure N (%):
- Glomerulonephritis: 106 (39.1) vs. 240 (41.2), p = 0.608
- Polycystic kidney disease: 54 (20.1) vs. 107 (18.4), p = 0.659
- Pyelo- or interstitial nephritis: 45 (16.6) vs. 83 (14.3), p = 0.430
- Hypertensive nephrosclerosis: 15 (5.5) vs. 27 (4.6), p = 0.430

Transplant characteristics
- Time on RRT (months): 91.0 (66.0) vs. 91.0 (57.0), p = 0.964
- Living donor N (%): 53 (19.6) vs. 139 (23.8), p = 0.187
- Cadaveric donor N (%): 218 (80.4) vs. 443 (76.1), p = 0.187
- Serum creatinine (umol/L): 151.0 (61.0) vs. 141.0 (45.0), p = 0.013
- Estimated GFR (MDRD*): 46.0 (15.0) vs. 50.0 (15.0), p = 0.001

Immunosuppressive medication** N (%):
- Prednisolone: 216 (79.7) vs. 475 (81.6), p = 0.570
- Cyclosporine: 265 (97.7) vs. 572 (98.2), p = 0.821
- Azathioprine: 164 (60.5) vs. 379 (65.1), p = 0.221
- Mycophenolate mofetil: 43 (15.9) vs. 94 (16.2), p = 0.996

Cardiovascular risk factors N (%):
- Left ventricular hypertrophy: 31 (11.4) vs. 98 (16.8), p = 0.051
- Smoking (current): 60 (22.1) vs. 94 (16.1), p = 0.044
- Hypertension: 220 (81.0) vs. 139 (23.8), p = 0.187
- Previous MACE: 32 (11.8) vs. 58 (10.1), p = 0.487
- Previous CHD: 25 (9.2) vs. 44 (7.6), p = 0.487

Concomitant medication N (%):
- Beta-blockers: 189 (69.7) vs. 319 (54.8), p = 0.000
- Calcium antagonists: 202 (74.5) vs. 396 (68.0), p = 0.009
- ACE inhibitor or AT1- blockers: 154 (56.8) vs. 273 (47.0), p = 0.013
- Alpha blockers: 49 (18.1) vs. 95 (16.3), p = 0.633
- Nitrate: 27 (10.0) vs. 40 (6.8), p = 0.167
- Aspirin: 88 (32.5) vs. 155 (26.6), p = 0.112
- Active vitamin-D: 55 (20.3) vs. 85 (14.6), p = 0.054

Clinical endpoint N (%):
- MACE: 55 (20.3) vs. 70 (12), p = 0.002
- Cardiac death: 25 (9.2) vs. 25 (4.3), p = 0.007

Data are expressed as mean (SD) unless otherwise indicated.
*Modification of Diet in Renal Disease (MDRD) simplified.
**Taken at least once during study.
The association remained significant after adjustment for age, gender, previous coronary heart disease, current smoking, low density lipoprotein (LDL) cholesterol, and serum creatinine [HR 1.47 (1.11–1.94), \( p = 0.007 \) (Table 2)]. Risk factors for MACE differed in the placebo and statin arms when adjustment for MS was made (Table 2). Patients with MS randomized to treatment (fluvastatin) arm, had reduced risk for MACE compared to the placebo arm (Table 3). No significant effect of statin treatment was found in RTR without MS (Table 3).

\[ p = \text{NS} \]

\[ p = 0.015 \]

\[ p = 0.03 \]

\[ p = 0.03 \]

**Cardiac death.** In total, 37 (7%) patients with MS died of cardiac causes, compared to 46 (4%) patients without MS (\( p = 0.012 \)). RTR with MS had increased risk for CD [HR 1.74 (1.13–2.68)] (Fig. 1C, D). The association remained significant after adjustment for age, gender, previous coronary heart disease, current smoking, LDL cholesterol and serum creatinine [HR 1.67 (1.05–2.64)], \( p = 0.03 \) (Table 2). Patients with MS randomized to treatment arm had reduced risk for CD when compared with the placebo arm (Table 3). No significant effect of statin treatment was found in RTR without MS (Table 3).

### Discussion

This longitudinal study in 1706 non-diabetic RTR showed that MS was associated with increased CVD risk. In addition, statin treatment reduced CVD risk in RTR with MS. To our knowledge, this is the largest study on MS as CVD risk factor in RTR. Also, this is the first study on statin treatment effect in CVD prevention in RTR with MS.

The prevalence of MS in the ALERT trial was 32%. The discrepancies in the prevalence of MS (17–63%) in RTR in different studies can largely be explained by the syndrome definition used and time elapsed since transplantation (15–17, 23, 24). We chose the definition proposed by ATP III because of practical need to maintain simplicity.
contrast to some previous studies, no gender predisposition to MS was found in the current trial (15, 23, 25).

The etiology of MS in RTR is likely to be multifactorial, but the most common predisposing factors are obesity preceding transplantation and the metabolic consequences of immunosuppressive therapy (12, 26). In addition to abdominal obesity, atherogenic lipoprotein phenotype (high triglyceride, increased small, dense LDL, and reduced HDL concentrations), insulin resistance, and raised BP, also proteinuria, prothrombotic, and proinflammatory state have been associated with MS (27).

Surprisingly, the CVD risk factors in non-diabetic RTR differed in the placebo and statin arms. In the placebo arm, smoking and previous coronary heart disease had no independent association to MACE risk when MS was in the model. The explanation to the finding may be that the hazard by MS in the placebo arm outweighed the hazard by other risk factors.

Table 2. Hazard ratios for risk factors by multivariate Cox regression for MACE and CD in non-diabetic patients in the ALERT study, placebo, and fluvastatin arm

<table>
<thead>
<tr>
<th></th>
<th>MACE (CI)</th>
<th>p-Value</th>
<th>CD (CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>The ALERT study (placebo + fluvastatin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>1.47 (1.11–1.94)</td>
<td>0.007</td>
<td>1.67 (1.05–2.64)</td>
<td>0.030</td>
</tr>
<tr>
<td>Age</td>
<td>1.05 (1.04–1.07)</td>
<td>0.000</td>
<td>1.10 (1.07–1.13)</td>
<td>0.000</td>
</tr>
<tr>
<td>Gender</td>
<td>0.71 (0.52–1.00)</td>
<td>0.03</td>
<td>0.96 (0.59–1.56)</td>
<td>0.881</td>
</tr>
<tr>
<td>CHD</td>
<td>1.77 (1.21–2.58)</td>
<td>0.004</td>
<td>1.87 (1.07–3.30)</td>
<td>0.029</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.45 (1.28–1.65)</td>
<td>0.000</td>
<td>1.25 (1.01–1.53)</td>
<td>0.036</td>
</tr>
<tr>
<td>Smoker (current)</td>
<td>1.36 (0.96–1.93)</td>
<td>0.085</td>
<td>1.63 (0.91–2.85)</td>
<td>0.123</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.01 (1.00–1.01)</td>
<td>0.000</td>
<td>1.01 (1.00–1.01)</td>
<td>0.008</td>
</tr>
<tr>
<td>Placebo arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>1.80 (1.24–2.58)</td>
<td>0.002</td>
<td>2.15 (1.19–3.87)</td>
<td>0.011</td>
</tr>
<tr>
<td>Age</td>
<td>1.04 (1.02–1.06)</td>
<td>0.000</td>
<td>1.10 (1.07–1.14)</td>
<td>0.000</td>
</tr>
<tr>
<td>Gender</td>
<td>0.74 (0.49–1.12)</td>
<td>0.151</td>
<td>0.86 (0.45–1.65)</td>
<td>0.644</td>
</tr>
<tr>
<td>CHD</td>
<td>1.44 (0.87–2.39)</td>
<td>0.162</td>
<td>1.67 (0.81–3.44)</td>
<td>0.163</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.46 (1.25–1.71)</td>
<td>0.000</td>
<td>1.26 (0.97–1.64)</td>
<td>0.085</td>
</tr>
<tr>
<td>Smoker (current)</td>
<td>1.02 (0.57–1.81)</td>
<td>0.951</td>
<td>1.95 (0.85–4.45)</td>
<td>0.286</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.01 (1.00–1.01)</td>
<td>0.002</td>
<td>1.01 (1.00–1.01)</td>
<td>0.526</td>
</tr>
<tr>
<td>Fluvastatin arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>1.23 (0.77–1.92)</td>
<td>0.364</td>
<td>1.09 (0.50–2.37)</td>
<td>0.823</td>
</tr>
<tr>
<td>Age</td>
<td>1.06 (1.03–1.08)</td>
<td>0.000</td>
<td>1.10 (1.05–1.14)</td>
<td>0.000</td>
</tr>
<tr>
<td>Gender</td>
<td>0.73 (0.44–1.20)</td>
<td>0.212</td>
<td>1.13 (0.51–2.54)</td>
<td>0.759</td>
</tr>
<tr>
<td>CHD</td>
<td>2.15 (1.21–3.85)</td>
<td>0.010</td>
<td>2.15 (0.84–5.47)</td>
<td>0.109</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.42 (1.14–1.75)</td>
<td>0.001</td>
<td>1.31 (0.92–1.85)</td>
<td>0.134</td>
</tr>
<tr>
<td>Smoker (current)</td>
<td>2.71 (1.51–4.87)</td>
<td>0.001</td>
<td>1.41 (0.53–3.76)</td>
<td>0.493</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.01 (1.00–1.01)</td>
<td>0.000</td>
<td>1.01 (1.00–1.01)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Table 3. MACE and cardiac death (CD) risk reduction in fluvastatin versus placebo group

<table>
<thead>
<tr>
<th></th>
<th>MACE HR (% risk reduction), p-value</th>
<th>CD HR (% risk reduction), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS (N = 550)</td>
<td>0.47 (53%), p = 0.015</td>
<td>0.48 (52%), p = 0.03</td>
</tr>
<tr>
<td>No MS (N = 1156)</td>
<td>0.87 (13%), p = 0.16</td>
<td>0.86 (14%), p = 0.61</td>
</tr>
</tbody>
</table>

Patients with metabolic syndrome (MS) and without MS (% risk reduction). Unadjusted analyses.

Statin treatment effect was more pronounced in RTR with MS compared to the entire ALERT cohort (53% vs. 21% MACE risk reduction) (8). In addition, MACE risk reduction in a pooled analysis of 30 clinical trials with fluvastatin remained lower (27%) when compared with the current study (28). A substudy of PREVEND-IT, however, reports MACE risk reduction in microalbuminuric subjects with MS in the same order of magnitude as the current study (29). Interestingly, pravastatin in PREVEND-IT had no effect on triglyceride levels, whereas fluvastatin treatment, in addition to LDL reduction, lowered the triglyceride levels significantly (8, 29). Therefore, lipid independent statin effects, such as nitric oxide mediated vasodilation, decrease in inflammation and improvement of fibrinolytic balance need to be considered as potential mechanisms lowering CVD risk in patients with MS.

We have previously shown in the ALERT trial, that renal transplant dysfunction and renal graft loss are associated with increased CVD risk (30). Different studies have associated MS with worse renal graft function and worse graft survival (16, 17, 23). Therefore, we cannot exclude the possibility that worsening of renal graft function was the true cause of increased CVD risk in RTR with MS. However, it needs to be considered that statin treatment did not alter renal risk in the ALERT trial (8, 31). The associations between MS and renal endpoints in the ALERT trial are going to be reported in the near future (data available upon
request from author). In addition, we cannot exclude the possibility that subsequent diabetes may explain some of the increased CVD risk, because incidence of diabetes was not recorded over the follow-up.

To appreciate the findings, some issues need to be critically addressed. The study is a subgroup analysis of the ALERT trial and was not designed to study treatment effects in RTR with or without MS. Therefore, negative results, such as lack of statin treatment effect in patients without MS, have to be interpreted cautiously. Low number of events and low overall power of the study may have contributed to negative results in the group without MS. In addition, disparity in elapsed time on renal replacement therapy, including transplantation, before baseline data collection needs to be acknowledged. It also needs to be considered that immunosuppressive therapy protocols have changed since 1996–1997 when the patients were included in the ALERT study. In addition, no center from the USA participated in the ALERT trial and this may limit the generalizability of the results to different ethnic groups and to patients with different causes of renal failure. Furthermore, the definition of MS used in this study, did not include insulin resistance as a definition component and therefore some patients with insulin resistance may have been missed. However, measurement of insulin resistance is impractical and there is a need to maintain simplicity in large trials and in clinical practice. Finally, anthropometric differences between the ethnic groups were not accounted for.

In conclusion, RTR with MS are at high risk for CVD. RTR with MS are easily identifiable group of patients who benefit from statin treatment.

Acknowledgements

The authors thank Novartis for access to ALERT trial data.

Disclosure

Alan Jardine has received consulting income, honoraria, and travel grants from Roche, Novartis, Astellas, Wyeth, MSD, AstraZeneca. Sadollah Abedini, Hallvard Holdaas, Niclas Eriksson, and Bengt Fellstroem declare no conflict of interest.

Inga Soveri has received research grants from Swedish Society of Nephrology, Selanders Foundation, CUWX Counties’ Renal Patients’ Foundation, Lilly and Ragnar Åkerhams Foundation, Stina and Bertil Engströms Foundation, and Astrid Karlssons Foundation. Inga Soveri has received travel grants from Swedish Society of Medicine, Bergmarks Foundation, Josephsons Foundation, Astellas, Roche, Novartis, Amgen and Swedish Orphan.

References


