**Online-Only Supplemental Material**

**To Szili-Torok et al. “Statin use is prospectively associated with new onset diabetes after transplantation in renal transplant recipients”**

**Use of immunosuppressive medication over time at the University Medical Center Groningen**

Over time we applied different immunosuppressive therapy regimes in the Unversity Medical Center Groningen. Standard immunosuppression consisted of the following: azathioprine (100 mg/day) and prednisolone (starting with 20 mg/day and tapering to 10 mg/day) from 1968 to 1989; cyclosporine (target trough levels 175–200 mg/L in the first 3 months, 100 mg/L thereafter) and prednisolone (starting with 20 mg/day and tapering to 10 mg/day) from 1989 to 1996. In 1997 mycophenolate mofetil (2 g/day) was added to the standard immunosuppressive regimen, and for RTRs with no complications, cyclosporine was slowly withdrawn from 1 year after transplantation onward. In 2012 cyclosporine was replaced by tacrolimus, and RTRs continued triple-immunosuppressive therapy with prednisolone (20 mg/day, tapering to 5 mg/day), tacrolimus (target trough levels 8–12 mg/L in the first 3 months, 6–10 mg/L until month 6, and 4–6 mg/L from 6 months onward), and mycophenolate mofetil (starting with 2 g/day, tapering to 1 g/day).

**Supplemental table S1:** Clinical baseline characteristics of 95 statin using renal transplant recipients compared with age- and gender-matched controls stratified by statin use

|  |  |  |
| --- | --- | --- |
|  | **Use of Statins** |  |
| Variable | Yes | No | P value for trend |
| General characteristics |
| Age (years) | 51.4 [42.2-58.7] | 49.13 [40.8-58.4] | 0.361 |
| Male sex (%) | 49.5 | 50.9 | 0.839 |
| Smoking status |
| Never smoker (%) | 35.8 | 42.0 | 0.364 |
| Former smoker (%) | 50.5 | 29.5 | 0.002 |
| Current smoker (%) | 13.7 | 28.6 | 0.10 |
| Alcohol consumption |
| None (%) | 44.2 | 47.3 | 0.138 |
| >4 units/day (%) | 3.1 | 0 |
| 1-3 units/day (%) | 16.8 | 9.8 |
| 2-7 units/week (%) | 24.2 | 25.9 |
| 1-4 units/month (%) | 10.5 | 17.0 |
| Body composition |
| BMI (kg/m2) | 25.7 [23.6-27.9] | 24.0 [22.0-27.1] | 0.009 |
| Waist circumference (cm) | 97.0 ± 12.4 | 93.3 ± 14.7 | 0.069 |
| Transplant history |
| Time since renal transplantation (years) | 6.0 [3.4-11.7] | 7.0 [3.6-12.2] | 0.253 |
| Deceased donor (%) | 85.3 | 89.3 | 0.384 |
| Donor age (years) | 35 [21-48] | 32 [23-49] | 0.953 |
| Dialysis duration (months) | 27 [11-49] | 19 [9.3-43.8] | 0.162 |
| Acute rejection episodes (%) | 42.1 | 45.5 | 0.620 |
| Renal allograft function |
| Serum creatinine (µmol/L) | 125 [103-145] | 128 [109.5-149.5] | 0.479 |
| eGFR (mL/min/1,73 m2) | 50.8 ± 15.5 | 50.7 ± 15.2 | 0.925 |
| Proteinuria (>0,5 g/24h) (%) | 22.1 | 26.8 | 0.436 |
| Inflammatory markers |
| C-reactive protein (mg/l) | 1.7 [0.6-3.4] | 1.4 [0.7-3.9] | 0.422 |
| Blood pressure |
| Diastolic blood pressure (mmHg) | 88.2 ± 10.8 | 89.4 ± 9.7 | 0.354 |
| Systolic blood pressure (mmHg) | 150 [136-163] | 144 [131-162] | 0.179 |
| Glucose homeostasis |
| Fasted glucose (mmol/L) | 4.3 [3.9-4.7] | 4.4 [4.0-4.8] | 0.928 |
| Plasma insulin (µmol/L) | 10.3 [7.9-13.5] | 10.1 [7.3-14.1] | 0.724 |
| HbA1c (%) | 5.8 [5.6-6.2] | 5.8 [5.6-6.2] | 0.735 |
| HbA1c (mmol/mol) | 40 [38-44] | 40 [38-44] | 0.735 |
| HOMA-IR [mU X mol/(L2 X 22,5)] | 2.0 [1.5-2.7] | 1.9 [1.3-2.8] | 0.676 |
| Family history of diabetes: parent or sibling with diabetes, n (%) | 35.1 | 20.5 | 0.015 |
| Lipids and lipoproteins |
| Total cholesterol (mmol/L) | 5.4 ± 1.0 | 5.8 ± 0.9 | 0.321 |
| LDL cholesterol (mmol/L) | 3.1 [2.6-3.7] | 3.8 [3.3-4.3] | <0.001 |
| HDL cholesterol (mmol/L) | 1.1 [0.9-1.3] | 1.1 [0.9-1.4] | 0.662 |
| ApoA-I (g/l) | 1.6 [1.4-1.8] | 1.6 [1.3-1.8] | 0.133 |
| ApoB (g/l) | 1.0 ± 0.2 | 1.1 ± 0.2 | 0.196 |
| Triglycerides (mmol/L) | 2.0 [1.6-2.5] | 1.6 [1.1-2.4] | 0.002 |
| Medication use |
| Antihypertensives (%) | 86.3 | 77.7 | 0.125 |
| Proliferation inhibitor (%) | 76.8 | 82.1 | 0.345 |
| * Azathioprine (n)
 | 33 | 49 | 0.186 |
| * mycophenolic acid (n)
 | 40 | 43 | 0.587 |
| Calcineurin inhibitor (%) | 75.8 | 74.1 | 0.781 |
| Tacrolimus (%) | 7.4 | 8.9 | 0.684 |
| Concentration of tacrolimus (µg/L) | 8.7 [1.6-10.1] | 9.1 [5.9-10.3] | 0.364 |
| Cyclosporine (%) | 68.4 | 64.3 | 0.531 |
| Cyclosporine concentration (µg/L) | 105.0 [81.5-139.0] | 102.5 [70.8-138.8] | 0.619 |
| Prednisolone (mg/24 h) | 10.0 [7.5-10.0] | 10.0 [7.5-10.0] | 0.734 |

Baseline characteristics including laboratory values were determined at inclusion into the study, which was at least one year after transplantation. Normally distributed continuous variables are presented as mean ± standard deviation, differences were tested using independent samples T test. Continuous data with skewed distribution are presented as median [IQR], differences were assessed utilizing independent-samples Mann-Whitney U test. Categorical data are shown as n (%) and differences were analyzed using Pearson chi-square test.

**Supplemental table S2:** Univariate analysis of the association of different variables with NODAT in 95 statin using renal transplant recipients compared with age- and gender-matched controls. Significant values are indicated by bold font.

|  |  |
| --- | --- |
| Variable | P value for trend |
| Age (years) | 0.979 |
| **Male sex (%)** | **0.017** |
| Never smoker (%) | 0.085 |
| Former smoker (%) | 0.633 |
| Current smoker (%) | 0.142 |
| Alcohol use | 0.203 |
| **BMI (kg/m2)** | **0.002** |
| **Waist circumference (cm)** | **0.001** |
| **Time since renal transplantation (years)** | **0.016** |
| Deceased donor (%) | 0.925 |
| Donor age (years) | 0.312 |
| Dialysis duration (months) | 0.218 |
| Acute rejection episodes (%) | 0.448 |
| Serum creatinine (µmol/L) | 0.373 |
| eGFR (mL/min/1,73 m2) | 0.957 |
| Proteinuria (>0,5 g/24h) (%) | 0.665 |
| C-reactive protein (mg/l) | 0.648 |
| Diastolic blood pressure (mmHg) | 0.856 |
| Systolic blood pressure (mmHg) | 0.719 |
| **Fasted glucose (mmol/L)** | **0.003** |
| **Plasma insulin (µmol/L)** | **0.001** |
| **HbA1c (%)** | **0.033** |
| **HOMA-IR [mU X mol/(L2 X 22,5)]** | **0.001** |
| **Family history of diabetes: parent or sibling with diabetes, n (%)** | **0.008** |
| Total cholesterol (mmol/L) | 0.616 |
| **LDL cholesterol (mmol/L)** | **0.017** |
| HDL cholesterol (mmol/L) | 0.069 |
| ApoA-I (g/l) | 0.275 |
| ApoB (g/l) | 0.927 |
| **Triglycerides (mmol/L)** | **0.002** |
| Antihypertensives (%) | 0.661 |
| Proliferation inhibitor (%) | 0.487 |
| Calcineurin inhibitor (%) | 0.635 |
| Tacrolimus (%) | 0.453 |
| Cyclosporine (%) | 0.967 |
| Prednisolone (mg/24 h) | 0.100 |

**Supplemental table S3:** Hazard ratios for incident NODAT by statin use determined by COX regression analysis.

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| --- | --- | --- | --- |
| Model | Variables | HR [95% CI] | P value |
| 1 | **Statin use** | **3.70 [1.17-11.75]** | **0.026** |
| 2 | **Statin use** | **3.86 [1.21-12.27]** | **0.022** |
| Age | 1.00 [0.95-1.06] | 0.887 |
| Gender | 4.10 [1.15-14.62] | 0.030 |
| 3 | **Statin use** | **3.96 [1.19-13.19]** | **0.025** |
| BMI | 1.03 [0.84-1.25] | 0.800 |
| Waist circumference | 1.06 [0.99-1.13] | 0.121 |
| 4 | **Statin use** | **3.40 [1.06-10.89** | **0.039** |
| Time since renal transplantation | 0.88 [0.77-1.00] | 0.049 |
| 5 | **Statin use** | **3.65 [1.08-12.38]** | **0.038** |
| LDL cholesterol | 0.66 [0.33-1.31] | 0.231 |
| Triglycerides | 1.44 [1.11-1.86] | 0.006 |
| 6 | **Statin use** | **3.99 [1.25-12.74]** | **0.020** |
| HDL-C | 0.15 [0.02-1.21] | 0.075 |
| 7 | **Statin use** | **3.75 [1.18-11.97]** | **0.025** |
| Glucose concentration | 2.66 [1.32-5.38] | 0.006 |
| HbA1c | 5.31 [1.06-26.51] | 0.042 |
| 8 | **Statin use** | **5.20 [1.55-17.47]** | **0.008** |
| Plasma Insulin | 0.76 [0.59-0.97] | 0.030 |
| HOMA IR | 6.05 [1.96-18.70] | 0.002 |
| 9 | **Statin use** | **3.45 [1.09-10.95]** | **0.036** |
| Family history of diabetes | 2.84 [1.13-7.16] | 0.027 |