Dyslipidemia in Transplantation

Istvan Mucsi

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Objectives

• To understand the causes of dyslipidemia after organ transplantation
• Describe the conventional treatments in transplanted patients with dyslipidemia
• Describe the changes in immunosuppressive therapy in transplanted patients with dyslipidemia
55 yr old male, 2 yrs after kidney transplant for ESKD secondary to IgA nephropathy. No Hx of rejection. immunosuppression: tacrolimus 6 mg/day, trough tacrolimus level 4-5; mycophenolate mofetil 2 g/day (trough level above 1.6); prednisone 5 mg/day. Exercising 3-4 times/week, received dietary advice with no change in lipids. Serum creatinine 140, blood pressure is 120-130/80 Hgmm on average (both home and office). Lipid profile: LDL-cholesterol 2.9, triglycerides 2.1.

What would you suggest to do:

• A) do nothing, continue current treatment
• B) start a statin
• C) stop prednisone
• D) start a fibrate
The ESRD cycle
Cardiovascular mortality in kidney transplant recipients

cardiovascular disease management after renal transplantation

Epidemiology and etiology
What proportion of kidney transplant recipients has suboptimal control of LDL cholesterol?

A. 10%
B. 20%
C. 30%
D. 50% or more
Epidemiology of dyslipidemia in solid organ recipients

- 93% following heart transplant
- 52% following lung transplant
- 66% following liver transplant
- 60% following renal transplant
Majority of transplant recipients have kidney function equivalent to stage 3 CKD or worse (UK data)

19,074 adult patients with a functioning kidney transplant at the end of 2005
Dyslipidemia Following Kidney Transplantation: Diagnosis and Treatment

Stéphanie Badiou, PhD, PharmD, Jean-Paul Cristol, MD, PhD, and Georges Mourad, MD
### Metabolic effects of common immuno-suppressive agents

<table>
<thead>
<tr>
<th></th>
<th>CSA</th>
<th>TAC</th>
<th>SRL</th>
<th>MMF</th>
<th>AZA</th>
<th>Steroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidaemia</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Hypertension</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>NODAT</td>
<td>+</td>
<td>+ (+)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
</tbody>
</table>

Impact of dyslipidemia
Cholesterol level as an independent predictor of mortality

N = 676 RTRs alive with functioning grafts at 1 year posttransplant
Hypercholesterolemia: Relative Risk for Ischemic Heart Disease in Patients More Than One Year After Renal Transplantation

Relative Risk of IHD in Males From the Framingham Heart Study (FHS) or Transplant Patients

- **Cholesterol (mg/dL)**
  - ≥280: Transplant patients = 2.25, FHS = 1.93
  - 240-279: Transplant patients = 2.02, FHS = 1.66
  - 200-239: Transplant patients = 2.39, FHS = 1.66
  - 160-199: Transplant patients = 1.19, FHS = 1.66
  - <160: Transplant patients = 1.00, FHS = 1.00

Low levels of high-density lipoprotein cholesterol: an independent risk factor for late adverse cardiovascular events in renal transplant recipients

Kulpreet Barn, Mark Laftavi, Drew Pierce, Chin Ying, William E. Boden and Oleh Pankewycz

1 Department of Medicine, State University of New York, University at Buffalo, Buffalo General Hospital, Kaleida Health, Buffalo, NY, USA
2 Department of Surgery, State University of New York, University at Buffalo, Buffalo General Hospital, Kaleida Health, Buffalo, NY, USA
3 Department of Biostatistics, Social and Preventive Medicine, State University of New York, University at Buffalo, Buffalo, NY, USA
Lipid lowering treatment
Lipid lowering strategies in transplant patients

- statins,
- fibrates,
- bile acid binding resins,
- cholesterol absorption inhibitors,
- nicotinic acid

- Tx patients will have the same cardiovascular benefits from lipid lowering therapy achieving target or very low LDL-c levels (eg < 70 mg/dl) as non-transplant subjects
<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL &lt;160mg</td>
<td>LDL &lt;130mg</td>
<td>LDL &lt;100mg</td>
</tr>
<tr>
<td>non-HDL &lt;190mg</td>
<td>non-HDL &lt;160mg</td>
<td>non-HDL &lt;130mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HDL ♂ &gt;40mg - ♂ &gt;50mg</td>
</tr>
</tbody>
</table>

♀ ♂ ≥20 years old. Framingham General 2008

After first classification and integrated reclassification

Enrique C. Morales Villegas*

Current Hypertension Reviews, 2011, 7,
Harmonization of guidelines for the prevention and treatment of cardiovascular disease: the C-CHANGE Initiative

Sheldon W. Tobe MD, James A. Stone MD PhD, Melissa Brouwers PhD, Onil Bhattacharyya MD PhD, Kimberly M. Walker BA, Martin Dawes MD PhD, Jacques Genest Jr MD, Steven Grover MD MPA, Gordon Gubitz MD, David Lau MD PhD, Andrew Pipe MD, Peter Selby MBBS, Mark S. Tremblay MD MSc, Darren E.R. Warburton PhD, Richard Ward MD, Vincent Woo MD, Lawrence A. Leiter MD, Peter P. Liu MD

Dyslipidemia

Treatment target is based on the person’s risk level.

- High risk: LDL-C < 2.0 mmol/L or 50% in LDL-C; alternate target: apoB < 0.80 g/L.

- Moderate risk: LDL-C < 2.0 mmol/L or 50% reduction in LDL-C; alternate target: apoB < 0.80 g/L.

- Low risk: if LDL-C ≥ 5.0 mmol/L, reduce LDL-C ≥ 50%; apoB < 0.90 g/L.
Statins

• Statins decrease cholesterol synthesis and increase the expression of LDL receptors which improves LDL-c clearance

• Fluvastatin, pravastatin and rosuvastatin are metabolized through different cytochrome P450 enzymes than the others

• Cyclosporine increases the blood levels of all statins

• statins may also have immunosuppressant effects (inhibit natural killer cell function and inhibition of major histocompatibility complex class II mediated T cell activation) and anti-fibrotic effects

• all statins except atorvastatin and fluvastatin require dose reductions in patients with impaired renal function

• Monitor lfts, CK – patients may need dose reduction, drug holiday in case of side effects
Cholesterol absorption inhibitors: ezetimibe

- Monotherapy with ezetimibe reduces LDL-c by approximately 18%; in combination with statins ezetimibe can add an additional 25% LDL-c lowering.

- Ezetimibe is not approved for use in subjects with moderate or severe hepatic insufficiency, and no data is available regarding its use in hepatic transplant subjects at this time.

- In subjects with other solid organ transplants the addition of ezetimibe to statin therapy, or substitution in statin intolerant subjects, is a safe and efficacious option.

- Cyclosporine can induce a 2 to 12 fold increase in ezetimibe levels.
ALERT: Assessment of Lescol in Renal Transplantation

- Randomized, double blind, placebo controlled multicentric study, 2102 Tx patients

- Fluvastatin (40 mg/d - 80 mg/d) or placebo

- Outcome: cardiac mortality, AMI, coronary intervention
The ALERT trial: effect of fluvastatin on cardiac death or nonfatal MI

Holdaas H. Lancet 2003;361:2024

N = 2,102 RTRs receiving either fluvastatin or placebo; follow-up 5-6 years
SHARP: Randomisation structure

Randomised (9438)

Simva/Eze (4193)
Simvastatin (1054)
Placebo (4191)

Randomised (886)

Not re-randomised (168)

Simv/Eze (4650)
Placebo (4620)

Median follow-up 4.9 years
Lost to mortality follow-up 1.5%
SHARP: Main outcomes

• **Key outcome**
  • Major atherosclerotic events (coronary death, MI, non-haemorrhagic stroke, or any revascularisation)

• **Subsidiary outcomes**
  • Major vascular events (cardiac death, MI, any stroke, or any revascularisation)
  • Components of major atherosclerotic events

• **Main renal outcome**
  • End stage renal disease (dialysis or transplant)
SHARP: Major Atherosclerotic Events

Risk ratio 0.83 (0.74 – 0.94)
Logrank 2P=0.0022

Proportion suffering event (%)

Years of follow-up

Placebo
Eze/simv
Comparison of SHARP with other trials: Vascular Death

<table>
<thead>
<tr>
<th>Trial</th>
<th>Allocated LDL-C reduction</th>
<th>Allocated control</th>
<th>Risk ratio (RR) per mmol/L LDL-C reduction</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>4D</td>
<td>151 (8.52)</td>
<td>167 (9.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALERT</td>
<td>66 (1.23)</td>
<td>73 (1.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AURORA</td>
<td>324 (6.87)</td>
<td>324 (6.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHARP</td>
<td>361 (1.82)</td>
<td>388 (1.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal: 4 renal trials</td>
<td>902 (2.85)</td>
<td>952 (3.01)</td>
<td>0.94 (0.85 - 1.04)</td>
<td>0.27</td>
</tr>
<tr>
<td>23 other trials</td>
<td>3679 (1.05)</td>
<td>4230 (1.21)</td>
<td>0.85 (0.81 - 0.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All trials</td>
<td>4581 (1.20)</td>
<td>5182 (1.36)</td>
<td>0.86 (0.83 - 0.90)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Difference between renal and non-renal trials: $\chi^2 = 3.8$ (p = 0.05)
What Should LDL Target Be?

• transplant recipients should be treated as high CV risk

• Studies suggest higher dose statin better than less intensive therapy

• Some have suggested LDL of 1.81 mM (70 mg%) for high risk patients

• No study has yet shown significant reduction of mortality based on specific target

• While % reduction in risk may be the same with same % LDL reduction the absolute benefit is less at lower LDL

• For high risk e.g. diabetics, CAD consider very low LDL target
Should Triglycerides Be Treated in Transplant Recipients?

- Less data for benefit than for LDL in general population and no data in transplant recipients
- Fibrates increase risk of rhabdomyolysis if used with statin
- Some experts suggest to treat only if > 10mM (885 mg%) (prevention of pancreatitis)
- Current guidelines say treat if >3.4 - 5.6mM (3-500 mg%)
- Niacin (prolonged acting) may be best choice but still not tolerated by all because of flushing
All statements are true, except:

A. The risk carried by elevated total cholesterol is similar in transplant recipients than in the general population.
B. Low HDL cholesterol is a cardiovascular risk factor in kidney transplant recipients independent of total cholesterol.
C. Statin treatment reduces all cause mortality in kidney transplant recipients.
D. Statin treatment reduces cardiovascular events in kidney transplant recipients.
Immunosuppressive protocols and dyslipidemia
MINIMIZING GLUCOCORTICOID USE

• Lower doses administered earlier after transplantation

• Complete withdrawal, which can either be performed early after transplantation (approximately three to six months post-surgery) or at a later time (after one year)

• Complete avoidance, which most frequently has been utilized with a calcineurin inhibitor-based immunosuppressive regimen and polyclonal antibody induction therapy
Steroid Avoidance or Withdrawal After Renal Transplantation Increases the Risk of Acute Rejection but Decreases Cardiovascular Risk. A Meta-Analysis

Simon R. Knight\textsuperscript{1,2} and Peter J. Morris\textsuperscript{1,3}

<table>
<thead>
<tr>
<th>Table 2. Meta-analysis of cardiovascular risk factors in all studies and studies reporting intention-to-treat analysis only</th>
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<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>-------------</td>
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<tr>
<td></td>
</tr>
<tr>
<td>All studies</td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Hypercholesterolemia</td>
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<tr>
<td>New-onset diabetes</td>
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<tr>
<td>Intention-to-treat analysis only</td>
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</tr>
</tbody>
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CI, confidence interval; Random, random-effects analysis; Fixed, fixed-effects analysis; I^2, I-squared statistic (measure of heterogeneity, see text).

(Transplantation 2010;89: 1–14)
Steroid Avoidance or Withdrawal After Renal Transplantation Increases the Risk of Acute Rejection but Decreases Cardiovascular Risk. A Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Avoidance/withdrawal Mean ± sd (N)</th>
<th>Maintenance Mean ± sd (N)</th>
<th>WMD [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincenti 2008</td>
<td>55.54±23.25 (226)</td>
<td>58.8±20.5 (109)</td>
<td>-3.26 [-8.16, 1.64]</td>
</tr>
<tr>
<td>Laftavi 2005</td>
<td>81.5±36.4 (39)</td>
<td>78.6±32.2 (39)</td>
<td>2.90 [-12.35, 18.15]</td>
</tr>
<tr>
<td>Ponticelli 1997</td>
<td>57.3±16.3 (76)</td>
<td>61.2±20.3 (77)</td>
<td>-3.90 [-9.73, 1.93]</td>
</tr>
<tr>
<td>Montagnino 2005</td>
<td>52.3±17.08 (65)</td>
<td>52.2±21.52 (68)</td>
<td>0.10 [-6.49, 6.69]</td>
</tr>
<tr>
<td>Vitko 2005</td>
<td>59.4±21.31 (151)</td>
<td>65.3±21.12 (147)</td>
<td>-5.90 [-10.72, -1.08]</td>
</tr>
<tr>
<td>Woodie 2008</td>
<td>58.6±19.7 (191)</td>
<td>59.8±20.5 (195)</td>
<td>-1.20 [-5.21, 2.81]</td>
</tr>
<tr>
<td>Nematall 2007</td>
<td>74.9±23.1 (50)</td>
<td>71.3±10.9 (50)</td>
<td>3.60 [-3.48, 10.68]</td>
</tr>
<tr>
<td>Vanrenterghem 2005</td>
<td>65.6±26.2 (137)</td>
<td>66.1±29.62 (194)</td>
<td>-0.50 [-6.55, 5.55]</td>
</tr>
<tr>
<td>Park 1994</td>
<td>54.4±19.9 (141)</td>
<td>59.9±27.5 (153)</td>
<td>-5.50 [-10.96, -0.04]</td>
</tr>
<tr>
<td>Sinclair 1992</td>
<td>52.87±32.76 (210)</td>
<td>55.54±34.65 (225)</td>
<td>-2.67 [-9.00, 3.66]</td>
</tr>
<tr>
<td>Smak Gregoor 2002</td>
<td>58±15.57 (76)</td>
<td>65±17.13 (73)</td>
<td>-7.00 [-12.26, -1.74]</td>
</tr>
<tr>
<td>Isoniemi 1990</td>
<td>57±20 (25)</td>
<td>62±19 (24)</td>
<td>-5.00 [-15.92, 5.92]</td>
</tr>
<tr>
<td>Hollander 1997</td>
<td>66±33 (42)</td>
<td>63±20 (41)</td>
<td>3.00 [-8.71, 14.71]</td>
</tr>
<tr>
<td>Ratcliffe 1996</td>
<td>47±17 (49)</td>
<td>56±18 (51)</td>
<td>-9.00 [-15.86, -2.14]</td>
</tr>
</tbody>
</table>

Summary

-3.05 [-4.66, -1.45]

(Transplantation 2010;89: 1–14)
Belatacept-Based Regimens Are Associated With Improved Cardiovascular and Metabolic Risk Factors Compared With Cyclosporine in Kidney Transplant Recipients (BENEFIT and BENEFIT-EXT Studies)

Yves Vanrenterghem,1,13 Barbara Bresnahan,2 Josep Campistol,3 Antoine Durrbach,4 Josep Grinyó,5 Hans-Hellmut Neumayer,6 Philippe Lang,7 Christian P. Larsen,8 Eduardo Mancilla-Urrea,9 José Medina Pestana,10 Alan Block,11 Tao Duan,11 Alan Glicklich,11 Sheila Gujrathi,11 and Flavio Vincenti12

(Transplantation 2011;91: 976–983)
Conclusions
All statements are true, except:

- Steroid minimization strategies (steroid withdrawal, steroid avoidance) will improve lipid profile after solid organ transplantation.
- The use of belatacept improves lipid profile compared to calcineurin inhibitors in kidney transplant recipients.
- Improving LDL cholesterol has been proven to improve all cause mortality.
- Rapamycin use is associated with more pronounced dyslipidemia compared to calcineurin inhibitors.
Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on kidney transplantation: a European Renal Best Practice (ERBP) position statement

Uwe Heemann¹, Daniel Abramowicz², Goce Spasovski³ and Raymond Vanholder⁴ for the European Renal Best Practice (ERBP) Work Group on kidney transplantation

16.2.1: Measure a complete lipid profile in all adult (≥18 years old) and adolescent (puberty to 18 years old) KTRs (based on KDOQI Dyslipidemia Recommendation 1):

• 2–3 months after transplantation;
• 2–3 months after a change in treatment or other conditions known to cause dyslipidaemias;
• at least annually, thereafter.

doi: 10.1093/ndt/gfr169
Advance Access publication 9 May 2011
Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on kidney transplantation: a European Renal Best Practice (ERBP) position statement

Uwe Heemann¹, Daniel Abramowicz², Goce Spasovski³ and Raymond Vanholder⁴ for the European Renal Best Practice (ERBP) Work Group on kidney transplantation

16.2.2.1: For KTRs with fasting triglycerides ≥500 mg/dL (≥5.65 mmol/L) that cannot be corrected by removing an underlying cause, treat with:

- Adults: therapeutic lifestyle changes and a triglyceride-lowering agent (based on KDOQI Recommendation 4.1);
- Adolescents: therapeutic lifestyle changes (based on KDOQI Recommendation 5.1).

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• Adults: If low density lipoprotein cholesterol (LDL)-C ≥100 mg/dL (≥2.59 mmol/L), treat to reduce LDL-C to <100 mg/dL (<2.59 mmol/L) (based on KDOQI Guideline 4.2);
• Adolescents: If LDL-C ≥130 mg/dL (≥3.36 mmol/L), treat to reduce LDL-C to <130 mg/dL (<3.36 mmol/L) (based on KDOQI Guideline 5.2).

doi: 10.1093/ndt/gfr169
Advance Access publication 9 May 2011
55 yr old male, 2 yrs after kidney transplant for ESKD secondary to IgA nephropathy. No Hx of rejection. immunosuppression: tacrolimus 6 mg/day, trough tacrolimus level 4-5; mycophenolate mofetil 2 g/day (trough level above 1.6); prednisone 5 mg/day. Exercising 3-4 times/week, received dietary advice with no change in lipids. Serum creatinine 140, blood pressure is 120-130/80 Hgmm on average (both home and office). Lipid profile: LDL-cholesterol 2.9, triglycerides 2.1.

What would you suggest to do:

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