Breadth of Care: Heart Health after Organ Transplantation

Stacy A. Crow; Pharm.D., BCPS
Solid Organ Transplant Pharmacist
Rejection  Net State of Immunosuppression  Infection
Cardiovascular disease

KIDNEY
#1 cause of death

LIVER
#3 cause of death

HEART
>50% CAV at 10 years

CAV: cardiac allograft vasculopathy
Objectives

1. Review anti-hypertensive agents and their use in the longitudinal care of a solid organ transplant patient

2. Relate drug-drug interactions between statins and immunosuppressive therapies to dyslipidemia treatment decisions in a solid organ transplant patient

3. Discuss short- and long-term considerations when selecting an anticoagulation regimen for a solid organ transplant patient
Agenda of Presentation

Hypertension  Hyperlipidemia  Anticoagulation
Hypertension
Hypertension in SOT

- 70-98% incidence\(^1\)
- Substantial non-immunologic risk factor directly related to patient survival\(^2,3\)
- Contributing factors\(^4\)
  - Organ specific, native, or transplanted
  - Medication related
- Major guidelines/studies excluding SOT patients
Hypertension after Kidney Transplant

• Native kidneys
  • Via renin secretion or sympathetic hyperactivity

• Allograft-related:
  • Donor age
  • Donor family history of HTN
  • Allograft dysfunction
  • Transplant renal artery stenosis
  • Post-transplant glomerulonephritis

• Medication-related
  • Calcineurin inhibitors
  • Steroids
Immunosuppression-related HTN

• Calcineurin inhibitors
  • Acute:
    • Arteriolar vasospasm
    • Hypoperfusion due to increased SVR or cardiac output
  • Chronic:
    • Enhanced sodium resorption in renal tubules leading to sodium sensitivity
    • Sympathetic over activity leading to vasoconstriction
    • Calcineurin-inhibitor nephrotoxicity

• Steroids
  • Via sodium and water retention + activation of glucocorticoid receptors on vascular smooth muscle
  • Pre-existing HTN more susceptible
Hypertension after Liver Transplant

- 50-99% of patients in some series

- Etiology
  
  Early
  
  - Pre-transplant vasodilation reduces arterial pressures, leading to hyper-dynamic cardiac output
  - Post-transplant portal vasculature decompression reverses vasodilatory state
    - Increased systemic vascular resistance, elevated plasma endothelin-1, increased arterial stiffness
Hypertension after Liver Transplant

- Etiology
  - Late
    - Abnormalities in renin-angiotensin-aldosterone system (RAAS)
      - Stimulation of renin release and upregulation angiotensin II receptors
    - Loss or reversal of normal nocturnal decrease in blood pressure
Hypertension after Heart Transplant

• 70-98% of patients among survivors at 10 years
  • Older recipients > younger counterparts
  • More prevalent in those with renal dysfunction

• Etiology
  • Early post-transplant related to intravascular volume & persistently increased systemic vascular resistance
  • Later post-transplant related to medications
    • Calcineurin inhibitors
      • Cyclosporine > Tacrolimus
    • mTORs
      • With tacrolimus > without tacrolimus
Immunosuppression-related HTN

- Mammalian Target of Rapamycin

Everolimus

Drug Classes: Antineoplastic Agent | Immune Suppressant | All
Routes: Oral

**Dosing/Administration**
- Adult Dosing
- Pediatric Dosing
- FDA Uses
- Non-FDA Uses
- Dose Adjustments
- Administration

**Medication Safety**

**Adverse Effects**

See 'In-Depth Answers' for detailed results.

**Common**
- **Cardiovascular:** Hypertension (Tumors, 4% to 13%; kidney transplant, 30%; liver transplant, 17%), Peripheral edema (Tumors, 13% to 30%; kidney transplant, 45%; liver transplant, 18%)
Immunosuppression-related HTN

• Mammalian Target of Rapamycin\textsuperscript{12}

Hypertension

1) Incidence: Tumors, 4% to 13% \textsuperscript{[43]}; kidney transplant, 30% \textsuperscript{[44]}; liver transplant, 17% \textsuperscript{[32]}

2) Combined Adult and Pediatric Clinical Trials
   a) Subependymal giant cell astrocytoma and tuberous sclerosis complex (oral route): All Grades, 11% with everolimus \textsuperscript{[15]}\textsuperscript{[45]}

3) Adult Clinical Trials
   a) Advanced renal cell cancer (oral route): All Grades, 4% with everolimus and more frequent vs placebo \textsuperscript{[43]}

b) Pancreatic neuroendocrine tumors (oral route): All Grades, 13% vs 6% with placebo \textsuperscript{[43]}

c) Kidney transplant (oral route): All Grades, 30% with everolimus plus \textbf{cyclosporine} vs 30% with mycophenolic acid and \textbf{cyclosporine} \textsuperscript{[44]}

d) Liver transplant (oral route): All Grades, 17% with everolimus, \textbf{corticosteroids} and \textbf{tacrolimus} vs 16% with corticosteroids and \textbf{tacrolimus} \textsuperscript{[32]}
Treatment of HTN in SOT

Definition of HTN\textsuperscript{13}: $\geq 130/80$ mmHg

- Low CV Risk: Lifestyle changes advised
- High CV Risk: Lifestyle changes + medication
Treatment of HTN in SOT

Not a one-size-fits-all model

CKD  Hepatic dysfunction

Considerations with HTN

Allograft dysfunction  CAV
Figure 1. Cumulative Incidence of Chronic Renal Failure among 69,321 Persons Who Received Nonrenal Organ Transplants in the United States between January 1, 1990, and December 31, 2000.

The risk of chronic renal failure was estimated with a noncompeting-risk model. Measurements of renal function were obtained at six-month intervals during the first year and annually thereafter.
Treatment of HTN in SOT

Allograft Abnormalities

- Kidney\textsuperscript{14,17}
  - Autoregulation between heart and kidney abnormal but can improve over time
Treatment of HTN in SOT

Allograft Abnormalities

• Kidney\textsuperscript{14}
  • Allograft and native dysfunction
  • CKD historically excluded from clinical trials and CV risk calculations

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Consideration for Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid status positive</td>
<td>Diuretic therapy consideration</td>
</tr>
<tr>
<td>Fluid status neutral</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>Proteinuria ≥ 300mg/day</td>
<td>ACE inhibitor or ARB (IIa/b)</td>
</tr>
<tr>
<td>Persistent proteinuria</td>
<td>Consider mineralocorticoid receptor antagonist</td>
</tr>
</tbody>
</table>

• Removal of native kidneys may be an option
Treatment of HTN in SOT

Allograft Abnormalities

• Liver\textsuperscript{15,16}
  • Hepatic failure #1 cause death leading to recurring liver disease management

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Consideration for Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varices history</td>
<td>Propranolol, nadolol, carvedilol</td>
</tr>
<tr>
<td>+ Hepatorenal</td>
<td>Propranolol, carvedilol</td>
</tr>
<tr>
<td>Indication for ACEi/ARB: diabetes, proteinuria, etc.</td>
<td>Preference non-prodrugs (e.g. lisinopril)</td>
</tr>
</tbody>
</table>
Treatment of HTN in SOT

Allograft Abnormalities

- Heart (OHT)$^{12}$
  - Pre-OHT parasympathetic and sympathetic fibers regulate autonomic nervous system
  - Post-OHT sympathetic re-innervation 40-70% patients
    - ↑ sympathetic activity
    - +
    - ↑ adrenergic activation
    - +
    - ↓ parasympathetic activity

- Long-term result:
  - Myocyte apoptosis, remodeling, myocardial ischemia, impaired contraction, and increased risk of cardiac death
Treatment of HTN in SOT

**Heart:** CAV, CAD, allograft dysfunction

- Heart rate a predictor of coronary artery atherosclerosis and overall cardiac mortality
  - No clear consensus in heart transplant

**Issues:**
- Atherogenesis promoted via injury to arterial wall & endothelial dysfunction
- Eventual facilitation of plaque rupture
- Frequency of asymptomatic presentation

**Oxygen delivery < oxygen consumption**
Treatment of HTN in SOT

Allograft Abnormalities

• Heart
  • Hepatic and renal considerations may apply
  • Beta blockers immediately post-transplant - helpful or harmful?

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Consideration for Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard presentation</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>Time since transplant</td>
<td>Beta blocks and ACEi/ARB increasingly feasible with time from transplant</td>
</tr>
<tr>
<td>Pill burden/regimen complexity</td>
<td>Patch if available</td>
</tr>
</tbody>
</table>
Treatment of HTN in SOT
Not a one-size-fits-all model

- Considerations with concurrent medications:

<table>
<thead>
<tr>
<th>Class</th>
<th>CNIs</th>
<th>mTOR</th>
<th>Azoles</th>
<th>Azoles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent(s)</td>
<td>Tacrolimus, cyclosporine</td>
<td>Sirolimus, everolimus</td>
<td>Class effect</td>
<td>Ketoconazole, voriconazole</td>
</tr>
<tr>
<td>Issue</td>
<td>Hyperkalemia</td>
<td>Edema</td>
<td>CYP3A4 / PgP inhibition</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Potentially Avoid</td>
<td>ACEi, ARB, mineralocorticoid receptor antag.</td>
<td>CCB</td>
<td>Nifedipine, felodipine</td>
<td>Losartan, irbesartan</td>
</tr>
<tr>
<td>Consider</td>
<td>CCB</td>
<td>ACEi/ARB</td>
<td>Amlodipine</td>
<td>Valsartan, candesartan</td>
</tr>
</tbody>
</table>
Question 1:

Hyperkalemia is common among transplant patients. Which of the following medications commonly used in this patient population does NOT contribute to this issue:
Question 1:

Hyperkalemia is common among transplant patients. Which of the following medications commonly used in this patient population does NOT contribute to this issue:

A) Cyclosporine modified
B) Tacrolimus extended-release
C) Everolimus
D) Bactrim
Hyperlipidemia
History of Hyperlipidemia in SOT

• 1973 first reports of high prevalence of dyslipidemia at 50-80% among kidney patients\textsuperscript{19}
  • Azathioprine + corticosteroid era

• 1980s cyclosporine introduced
  • Hypercholesterolemia > Hypertriglycerideridemia

• After 2000 mTORs introduced
  • Hypertriglycerideridemia > Hypercholesterolemia
Prevalence of Hyperlipidemia in SOT

Kidney
- Yes 80%
- No 20%

Liver
- Yes 42%
- No 58%

Heart
- Yes 60%
- No 40%
### Causes of Hyperlipidemia in SOT

**Table 1** Factors associated with lipid abnormalities after transplantation

<table>
<thead>
<tr>
<th>Hypercholesterolemia</th>
<th>Hypertriglyceridemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic predisposition</td>
<td>Genetic predisposition</td>
</tr>
<tr>
<td>Age</td>
<td>Excessive dietary intake of carbohydrates, cholesterol, and saturated fat</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
</tr>
<tr>
<td>Excessive dietary intake of cholesterol and saturated fats</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Obesity</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Anti-hypertensive agents, e.g., diuretics, beta-blockers</td>
<td>Mammalian target-of-rapamycin inhibitors (sirolimus)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Calcineurin-inhibitors (cyclosporine, possibly tacrolimus)</td>
<td></td>
</tr>
<tr>
<td>Mammalian target-of-rapamycin inhibitors (sirolimus, everolimus)</td>
<td></td>
</tr>
</tbody>
</table>

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Mechanisms of Dyslipidemia

• Corticosteroids
  1. Increased VLDL
     • Induction of insulin resistance
     • Uptake of free fatty acids (FFA)
     • FFA main substrate for VLDL synthesis
  2. Increased triglycerides
     • Reduction in lipoprotein lipase
     • Reduced triglyceride clearance
  3. Altered LDL production
     • Increased conversion VLDL → LDL
  4. Increased activity of HMG-CoA reductase
     • Increased cholesterol synthesis
Mechanisms of Dyslipidemia

• Calcineurin Inhibitors
  1. Interference between LDL cholesterol and receptor and a reduced number of LDL receptors
     • Reduced LDL clearance
  2. Lipophilicity of cyclosporine and tacrolimus
     • Transported within the core of LDL cholesterol
       • Potentially changes molecular configuration of LDL
       • Alters feedback regulation of cholesterol synthesis

Cyclosporine > Tacrolimus
Mechanisms of Dyslipidemia

- mTORs
  1. Inhibit lipoprotein lipase
     - Reduced lipolysis
  2. Increases secretion of VLDL cholesterol
     - Reduction in LDL receptors
  3. Synergistic lipid-based alterations
     - Almost never used as monotherapy
     - Issues with concomitant immunosuppression
Consequences of Dyslipidemia

• Atherosclerosis, cerebrovascular disease, peripheral vascular disease in non-SOT
  • Kidney: hypertriglyceridemia associated with progression of coronary after calcification
  • Liver: hypertriglyceridemia and CVD linked
  • Heart: hypercholesterolemia associated with non-fatal major adverse cardiac events

• Contribution to atherosclerosis of allografts?
Goals of Therapy: Hyperlipidemia in SOT

1. Preserve or improve allograft function
2. Reduce cardiovascular risk

Interventions have an impact on reducing cardiac events in clinical trials within SOT.
Treatment of Hyperlipidemia in SOT

1. Consultation with dietician
   • American Heart Association Step I diet starting point for elevated LDL cholesterol

2. Weight loss & exercise

3. Most herbal medications (e.g. red yeast) should be avoided
   • Fish oil is acceptable

4. Statins considered safe if dosed and monitored appropriately
## Considerations of Statin Pharmacokinetics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Major Metabolism</th>
<th>Minor Metabolism</th>
<th>OAT Substrate</th>
<th>PgP Substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>----</td>
<td>CYP 2C9 / -19</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Sulfate conjugation &amp; acidic degradation</td>
<td>Non-P450</td>
<td>Minimal</td>
<td>Yes</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>CYP 2C9</td>
<td>CYP 3A4/2D6</td>
<td>Minimal</td>
<td>No</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>CYP 3A4</td>
<td>CYP 2C9</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lovastatin (P)</td>
<td>CYP 3A4 (bile metabolites)</td>
<td>Esterases (to active form)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Simvastatin (P)</td>
<td>CYP 3A4 (prior hydrolyzation)</td>
<td>CYP 3A5</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

OAT: organic anion transporting polypeptide; CYP: cytochrome; (P): prodrug; P-gp: P-glycoprotein
## Considerations with Statin Interactions

<table>
<thead>
<tr>
<th></th>
<th>Tacrolimus</th>
<th>Cyclosporine</th>
<th>mTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>20 mg</td>
<td>5 mg</td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40 mg</td>
<td>20 mg</td>
<td>-Reports unclear</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>80 mg</td>
<td>40 mg</td>
<td>-Start low, go slow</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40-80 mg</td>
<td>Avoid / 10 mg</td>
<td>-Monitor mTOR levels</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Avoid</td>
<td>Avoid / 20 mg</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Avoid / 40 mg</td>
<td>Ci</td>
<td>-Consider monitoring CK</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>20 mg</td>
<td>Start at 5</td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>900 mg</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

*Table based in part on interpretation of case reports, case series, pharmacokinetics, etc.*

- Adjustment for CKD: pravastatin, rosuvastatin, simvastatin
- Concomitant use: azoles, diltiazem, verapamil, etc.
Question 2:

Statins are a mainstay of cholesterol control in transplant patients. Multidisciplinary assessment of a patient 8 years status post kidney transplant indicates that she qualifies for a high-dose statin regimen. The physician asks for your recommendation.

Which of the following is/are also needed to best advise?
Question 2:

Statins are a mainstay of cholesterol control in transplant patients. Multidisciplinary assessment of a patient 8 years status post kidney transplant indicates that she qualifies for a high-dose statin regimen. The physician asks for your recommendation.

Which of the following is/are also needed to best advise?

A) Immunosuppression regimen
B) Distant historic infectious disease regimens
C) Renal function
D) A & C
E) All the above
Anticoagulation

Direct Oral Anticoagulants (DOACs) and Enoxaparin
Anti-Coagulation in SOT

Warfarin vs. DOACS
### DOACs in SOT^{25,27}

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolism</strong></td>
<td>Dabigatran etexilate rapidly converted to</td>
<td>Oxidative degradation catalyzed by</td>
<td>CYP3A4, 1A2, 2C8, 2C9, 2C19, and 2J2</td>
<td>Minimal metabolism via hydrolysis, conjugation, and oxidation by CYP3A4</td>
</tr>
<tr>
<td></td>
<td>dabigatran by esterase catalyzed hydrolysis</td>
<td>CYP 3A4/-5, 2J2, hydrolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic Adjustment</strong></td>
<td>Not listed</td>
<td>Child-Pugh B or C: Avoid</td>
<td>Child-Pugh C: Avoid</td>
<td>Child-Pugh B or C: Avoid</td>
</tr>
<tr>
<td><strong>Renal Adjustment</strong></td>
<td>CrCl &lt;30-50 ml/min: 150 mg/day</td>
<td>&lt;50ml/min: 15 mg/day</td>
<td>2/3: SCr ≥1.5, age ≥80yrs, wt ≤60kg</td>
<td>&lt;50ml/min: 15-30 mg/day</td>
</tr>
<tr>
<td><strong>Dialysis</strong></td>
<td>Bleed RR 1.48; CI 1.21-1.81; <em>p</em>=0.001</td>
<td>Bleed RR 1.38; CI 1.03-1.83; <em>p</em>=0.04</td>
<td>DVT or PE: no Δ Stroke prevention: 2.5mg BID</td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>DDI</strong></td>
<td>Avoid use if CrCl &lt;30-50 ml/min &amp; P-gp inhibitor</td>
<td>Avoid use if CrCl &lt; 80 ml/min &amp; on P-gp &amp; strong 3A4 inhibitor</td>
<td>Decrease by 50% if &gt;2.5mg BID if on P-gp &amp; strong 3A4 inhibitor. Avoid if already on 2.5mg BID</td>
<td>Decrease by 50% if DVT/PE &amp; on P-gp &amp; 3A4 inhibitor</td>
</tr>
</tbody>
</table>
Enoxaparin in SOT\textsuperscript{29-31}

- Publications in SOT demonstrate prudence in 20-25\% dose reduction
  - Singer et al: 67\% supratherapeutic Anti-Xa with 1mg/kg BID in lung transplants
  - Moten et al: 44\% supratherapeutic despite nearly 20\% decrease in initial dosing of BID regimen for lung, kidney, liver, heart transplants
  - Sofjan et al: 14.9\% (33/222) had bleeding event, 17/33 classified as major
Recommendations for Enoxaparin in SOT

• Consider empirically reducing dose
  • Enoxaparin 0.8mg/kg SQ q12h
  OR
  • Enoxaparin 1mg/kg SQ q24h
• Check 4 hour post-dose Anti-Xa peak at steady stat, after at least two days’ therapy
  • Renal function – current and trends
  • Linear kinetics - adjust dose to mid-goal range
• Syringe availability: 30 MG/0.3 ML, 40 MG/0.4 ML, 60 MG/0.6 ML, 80 MG/0.8 ML, 100 MG/1 ML, 120 MG/0.8 ML, 150 MG/1 ML
• Dexterity of patient / caregiver if between doses
Conclusions

1. Hypertension: Prudent to factor in comorbidities, drug interactions, type of transplant, time since transplant, risk/benefit when choosing anti-hypertensive approach

2. Hyperlipidemia: No robust dyslipidemia guideline exists for SOT. Consider desired statin intensity, drug interactions [many as case series or reports]. If between doses, start low and go slow. Monitor immunosuppression.

3. DOACs still new in SOT. Additional studies, kinetic and clinical data are needed. Apixaban potentially most favorable at present?
Question 3:

- You are consulted to start warfarin and dose bridging enoxaparin for a 39-year-old male liver transplant patient 4 years out from transplant.
  - Indication: DVT  
  - Patient Weight: 100 kg  
  - Baseline SCr 1.2, current SCr 1.4 = CrCl 46 ml/min  
  - All other labs within normal limits
Question 3:

- You are consulted to start warfarin and dose bridging enoxaparin for a 39-year-old male liver transplant patient 4 years out from transplant.
  - Indication: DVT       Patient Weight: 100 kg
  - Baseline SCr 1.2, current SCr 1.4 = CrCl 46 ml/min
  - All other labs within normal limits

- True or false: A transplant-literature-based dosing of this patient would be enoxaparin 100mg SQ BID as dose adjustment occurs at CrCl < 30 ml/min


18. Ojo, et al. NEJM. 2003;349(10)


Questions or discussion?
mTORs: a kidney/HTN-friendly substitution?
Table 1. Studies Correlating Heart Rate and Clinical Outcomes After Cardiac Transplantation

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Cohort Size</th>
<th>Follow-up</th>
<th>Measure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anand et al, 2009²³</td>
<td>USA</td>
<td>78</td>
<td>10 years</td>
<td>HR and survival outcome</td>
<td>Patients with an HR &gt; 90 bpm within the first 3 months after HT were 2.8 times more likely to die than patients with an HR ≤ 90 bpm.</td>
</tr>
<tr>
<td>Scott et al, 1993²⁴</td>
<td>UK</td>
<td>104</td>
<td>NA</td>
<td>HR and late mortality</td>
<td>Patients with an inappropriately high resting HR in long-term survivors of cardiac transplantation is an adverse prognostic sign.</td>
</tr>
<tr>
<td>Ambrosi et al, 2010²⁶</td>
<td>UK</td>
<td>143</td>
<td>23 years</td>
<td>HR and CAV</td>
<td>No significant difference in mean basal HR was observed in patients who had coronary lesions and those who had normal coronaries. This series did not support a prognostic influence of HR for CAV.</td>
</tr>
<tr>
<td>Gullestad et al, 1997²⁸</td>
<td>USA</td>
<td>130</td>
<td>3.7 ± 3.0 years</td>
<td>HR and CAV</td>
<td>CAV is more prevalent in patient with lower rather than higher HR.</td>
</tr>
<tr>
<td>Olmetti et al, 2011²⁹</td>
<td>UK</td>
<td>244</td>
<td>96 months</td>
<td>HR and CAV</td>
<td>HR &lt; 90 but not ≥ 90 bpm was significantly associated with an increased CAV development. Sinus tachycardia in a denervated heart is not a risk factor for coronary atherosclerosis.</td>
</tr>
</tbody>
</table>

Abbreviations: CAV, cardiac allograft vasculopathy; HR, heart rate; NA, not available.
Figure 1. Overview of the effect of faster heart rate on endothelial function. Abbreviations: CAV, cardiac allograft vasculopathy; IL, interleukin; TNF, tumor necrosis factor.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>HR-Lowering Agent</th>
<th>Cohort Size</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verani et al, 1994</td>
<td>USA</td>
<td>β-Blocker</td>
<td>n = 40 (35 HTX recipients and 5 healthy subjects)</td>
<td>Acute β-adrenergic blockade accentuates impairment in ventricular performance and appears to be detrimental in HTX recipients.</td>
</tr>
<tr>
<td>Bexton et al, 1983</td>
<td>UK</td>
<td>β-Blocker</td>
<td>n = 6</td>
<td>β-Blockade reduces the exercise capability in HTX recipients.</td>
</tr>
<tr>
<td>Hall et al, 1995</td>
<td>USA</td>
<td>β-Blocker</td>
<td>n = 26</td>
<td>β-Blockade improves systolic performance in heart failure patients not until 1 month after therapy and may have mild systolic impairment initially.</td>
</tr>
<tr>
<td>Gardner et al, 2002</td>
<td>UK</td>
<td>β-Blocker</td>
<td>n = 1</td>
<td>β-Blockade improved symptoms and graft function in an HTX recipient with idiopathic left ventricular systolic dysfunction over an 8-month period.</td>
</tr>
<tr>
<td>Schroeder et al, 1993</td>
<td>USA</td>
<td>Diltiazem</td>
<td>n = 106 (52 received and 54 did not receive diltiazem)</td>
<td>Diltiazem prevents or slows decline in the coronary artery diameter during the first year after heart transplantation.</td>
</tr>
<tr>
<td>Delgado et al, 2003</td>
<td>UK</td>
<td>Diltiazem</td>
<td>n = 112</td>
<td>Diltiazem administration and cyclosporine level &gt;362 ng/mL in the first month after heart transplantation reduced acute rejection during the first year.</td>
</tr>
<tr>
<td>Doesch et al, 2009</td>
<td>UK</td>
<td>Ivabradine</td>
<td>n = 30</td>
<td>Ivabradine reduced HR effectively and caused significant reduction in left ventricular mass index.</td>
</tr>
<tr>
<td>Zwicker et al, 2010</td>
<td>UK</td>
<td>Ivabradine</td>
<td>n = 1</td>
<td>Increasing doses of ivabradine, in contrast to a short acting β-blocker, controlled heart rate and supported recovery from cardiogenic shock in a HTX recipient with tachycardia induced cardiomyopathy.</td>
</tr>
<tr>
<td>Doesch et al, 2007</td>
<td>UK</td>
<td>Ivabradine</td>
<td>n = 25</td>
<td>Ivabradine lowered heart rate effectively and is better tolerated than β-blocker therapy.</td>
</tr>
</tbody>
</table>

Abbreviations: HR, heart rate; HTX, heart transplant.