Hypertension, Hyperlipidemia, and GLP-1 agonists After Transplantation

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Objectives

Discuss risks, contributing factors, transplantconsiderations, and treatment options for hypertension and hyperlipidemia post-transplant

Analyze new treatment modalities for hyperlipidemia and their place in post-transplant care

Review

Analyze

Review literature assessing GLP-1 agonists in the post-transplant setting

Hypertension

Ris ks







Renovascular hypertension \rightarrow CKD



Non-alcoholic fatty liver disease (NAFLD)

Post-Transplant Hypertension Pathophysiology

Calcineurin Inhibitors (CNI)

- Cyclosporine > tacrolimus
- Independent of nephrotoxicity
- Potential mechanisms
 - Increase activity of vasoconstrictors
 - Stimulate renin angiotensin aldosterone system (RAAS)
 - Inhibit production of vasodilator substances

Prednisone

• Salt retention

Essential Hypertension

Other Contributing Factors

Fluid volume overload (FVO)

Pain

Obstructive sleep apnea (OSA)

Other medications:

- Serotonin and norepinephrine reuptake inhibitors (SNRI)
- Oral contraceptives

Blood Pressure Goals

		BP Categories ^a		
	BP Targets		SBP (mm Hg)	DBP (mm Hg)
JNC 7, 2003	< 140/90 mm Hg	Normal	< 120	< 80
	< 130/80 mm Hg for those with diabetes or chronic kidney disease	Prehypertension	120-139	80-89
		Stage 1 hypertension	140-159	90-99
		Stage 2 hypertension	≥ 160	≥ 100
JNC 8, 2014	< 150/90 mm Hg for patients ≥ 60 < 140/90 mm Hg for patients < 60, diabetes, and chronic kidney disease	Was not a comprehensive set of not discuss hypertension diagn	recommendation ostic thresholds	is, and did
ACP/AAFP, 2017	< 150/90 mm Hg for patients ≥ 60 < 140/90 mm Hg for patients at higher CV risk, or with a history of stroke or TIA	Was not a comprehensive set of not discuss hypertension diagn Did not address recommendation	recommendation ostic thresholds ns in patients < 60	is and did 0
ACC/AHA, 2017	≤ 130/80 mm Hg	Normal	< 120	< 80
		Elevated	120-129	< 80
		Stage 1 hypertension ^b	130-139	80-89
		Stage 2 hypertension	≥ 140	≥ 90

Hypertension Treatment

Lifestyle Modifications – 1st line for ALL



DIET

EXERCISE

STRESS REDUCTION

Non-Pharmacologic Treatment

	Nonpharmacological		Approximate Impact on SBP			
	Intervention	Dose	Hypertension	Normotension	Reference	
Weight loss	Weight/body fat	Best goal is ideal body weight, but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight.	–5 mm Hg	-2/3 mm Hg	(56.2-1)	
Healthy diet	DASH dietary pattern	Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.	—11 mm Hg	–3 mm Hg	(\$6.2-6,\$6.2-7)	
Reduced intake of dietary sodium	Dietary sodium	Optimal goal is <1500 mg/d, but aim for at least a 1000-mg/d reduction in most adults.	-5/6 mm Hg	-2/3 mm Hg	(\$6.2-9,\$6.2-10)	
Enhanced intake of dietary potassium	Dietary potassium	Aim for 3500-5000 mg/d, preferably by consumption of a diet rich in potassium.	-4/5 mm Hg	-2 mm Hg	(S6.2-13)	
Physical activity	Aerobic	90-150 min/wk65%-75% heart rate reserve	-5/8 mm Hg	-2/4 mm Hg	(\$6.2-18,\$6.2-22)	
	Dynamic resistance	 90-150 min/wk 50%-80% 1 rep maximum 6 exercises, 3 sets/exercise, 10 repetitions/set 	–4 mm Hg	–2 mm Hg	(\$6.2-18)	
	Isometric resistance	 4 × 2 min (hand grip), 1 min rest between exercises, 30%-40% maximum voluntary contraction, 3 sessions/wk 8-10 wk 	–5 mm Hg	-4 mm Hg	(\$6.2-19,\$6.2-31)	
Moderation in alcohol intake	Alcohol consumption	 In individuals who drink alcohol, reduce alcohol† to: Men: ≤2 drinks daily Women: ≤1 drink daily 	-4 mm Hg	–3 mm Hg	(56.2-22-56.2-24)	

Approximate Impact on SBP

Pharmacologic Therapy



Diuretics

- Thiazide diuretics
 - Hydrochlorothiazide
 - Chlorthalidone
- Clinical Pearls:
 - Longer half-life than loop diuretics
 - furosemide, torsemide, bumetanide
 - Worsen gout
 - Lower magnesium, potassium, sodium, and calcium



Calcium Channel Blockers

Dihydropyridine (DHP)

- Amlodipine, nifedipine, felodipine
 - Potential benefit with CNI toxicity
 - Peripheral edema

Non-dihydropyridine (non-DHP)

- Diltiazem, verapamil
 - Potential drug interactions due to moderate CYP3A4 inhibition
 - Bradycardia



Calcium influx into heart and vascular smooth muscles leads to vasoconstriction and contraction of these muscles.



Calcium channel blockers inhibit L type calcium channels leading to vasodilation, decreased contractility, and a reduction in heart rate.

Beta Blockers

Selective Beta1 blockers

• Metoprolol, atenolol, nebivolol, esmolol

Non-selective

• Carvedilol, labetalol, propranolol

Clinical pearls:

- Caution in heart transplant
- Caution with airway disease (non-selective)
- Can be used for atrial fibrillation prophylaxis
- May improve tremors
- Fatigue
- ED



Beta blockers dilate arteries, lowering blood pressure





Renin-Angiotensin-Aldosterone System Blockade

Angiotensin-converting enzyme inhibitors (ACEi)

• Lisinopril, captopril, enalapril, ramipril

Angiotensin II receptor blockers (ARB)

• Losartan, candesartan, irbesartan, olmesartan, telmisartan, valsartan

Clinical Pearls:

- Improves proteinuria
- ACEi interaction with sirolimus
- Losartan reduces uric acid levels
- Acute kidney injury (AKI) caution with CNI use
- Angioedema
- Hyperkalemia

Renin-Angiotensin-Aldosterone System Blockade



Other Agents

Alpha1 antagonists

- Prazosin, doxazosin, tamsulosin, terazosin
- Orthostatic hypotension
- Treat benign prostatic hyperplasia (BPH), nightmares/post-traumatic stress disorder (PTSD)

Alpha2 adrenergic agonist

- Clonidine
- Rebound hypertension!

Vasodilators

- Hydralazine
- Can cause a lupus-like syndrome at high doses
- Short half-life requires frequent dosing
- Minoxidil
- Can treat alopecia
- Should be used with diuretic and beta blockade

Organ-Specific Blood Pressure Considerations

Kidney

KDIGO 2009

- BP Goal <130/80 mmHg in adults
- Use any class of antihypertensive agent
- Monitor closely for adverse effects and drugdrug interactions
- When urine protein excretion is >1g/day for adults, consider an ACE-I or ARB for first-line therapy

ACC/AHA2017

- BP Goal <130/80 mmHg
- It is reasonable to treat with calcium antagonist based on improved GFR and kidney survival

Procedural or Surgical Interventions in Kidney Transplant

Transplant renal artery angioplasty/stenting

Treatment of obstructive sleep apnea with continuous positive airway pressure (CPAP)

Bilateral native nephrectomy (failed native kidneys) Native renal denervation (sympathetic overactivity)

Liver

American Association for the Study of Liver Diseases (AASLD) 2012 Guidelines

- Goal BP 130/80 mmHg
- Combination of lifestyle modifications and pharmacological agents
- ACEi, ARBs and direct renin inhibitors should be used as first-line therapy in liver transplant recipients with DM, CKD, and or significant proteinuria

Heart

ISHLT2023

- BP Goal same as recommended for the general population
- Treatment should include recommendations for lifestyle modification in addition to drug therapy
- ACEi and CCB may be preferred as first-line therapy in patients with DM and as a cardiac allograft vasculopathy (CAV) prevention strategy
- HCTZ could be considered to specifically counteract CNI-induced hypertension
- CCBs should be considered the antihypertensive drug of choice when optimal blood pressure control cannot be achieved with ACEi/ARB, or when these drugs are contraindicated in HTrecipients

Lung



Hyperlipidemia (HLD)

Risks

High risk for the development of post-transplant cardiovascular disease (CVD)

Atherosclerosis is accelerated after transplantation

• Can be linked to cardiovascular events

Current Age 🚯 *	Sex *			Race *		
		Male	Female	White	African American	Other
ge must be between 20-79						
Systolic Blood Pressure (mm Hg) *		Diastolic Blo	od Pressure (mm Hg) *			
lalue must be between 90-200		Value must be bet	veen 60-130			
Total Cholesterol (mg/dL) *		HDL Cholest	erol (mg/dL) *	LDL Cholesterol (mg/dL) 🛛 ^O		
/alue must be between 130 - 320		Value must be bet	veen 20 - 100	Valu	e must be between 30-300	
History of Diabetes? *		Smoker? \end{split}	k			
Yes	No		Current 🚯	Former 🕄	Nev	er ()
On Hypertension Treatment? *		On a Statin?	0 0	On	Aspirin Therapy? 🔀 ^O	
Ves	No	Y	es	No	Yes	No

Contributing Factors to HLD Post-transplant



Goals – Primary Prevention

Benefit Group	First Line Therapy Based on 10-year ASCVD Risk	Goal	
Baseline LDL <u>≥</u> 190 mg/dL	Any Risk High Intensity statin	>50% reduction and LDL<100 mg/dL or non-HDL <130 mg/dL	
	< 7.5%: Moderate intensity statin	≥30-49% LDL reduction and LDL <100 or non-HDL <130 mg/dL	
Age 40-75 years old with DM, baseline LDL <190mg/dL	>7.5%: risk enhancers, or subclinical atherosclerosis: high intensity statin	>50% reduction and LDL<100 mg/dL or non-HDL <130 mg/dL	
	>20%: High intensity statin	>50% LDL reduction and LDL <70 or non- HDL <100	
	<5%: Risk discussion	Lifestyle Modification	
Age 40-75 years old without DM or ASCVD	5-7.4%: Consider moderate intensity statin	30-49% LDL reduction and LDL <100 mg/dL	
with LDL 70-189 mg/dL	7.5 – 19.9%: Moderate intensity statin	30-49% LDL reduction and LDL <100 mg/dL	
	≥ 20%: High intensity statin	>50% LDL reduction and LDL <70	

Lloyd-Jones D, et al. JACC. 2022

Goals - Secondary Prevention

Benefit Group	First Line Therapy	Goal
ASCVD at high risk	High intensity statin	≥50% reduction in LDL and LDL <55 mg/dL or non–HDL <85 mg/dL
ASCVD not at very risk	High intensity statin	≥50% reduction in LDL and LDL <70 mg/dL or non–HDL <100 mg/dL
ASCVD and LDL ≥190 mg/dL	High intensity statin	≥50% reduction in LDL and LDL <70 mg/dL or non–HDL <100 mg/dL

Hyperlipidemia Treatment

Lifestyle Modification



Giles L. J Midw and Wom Hlth 2024

Pharmacologic Therapy

First-line

• Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors

If Goals not met:

- Ezetimibe
- Bile acid sequestrants
- Niacin
- Fibrates
- Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors
- Microsomal triglyceride transfer protein (MTP) inhibitors
- Angiopoietin-like protein 3 (ANGPTL3)
- Antilipemic Small Interfering Ribonucleic Acid (siRNA) Agent



HMG CoAReductase Inhibitors

- Lovastatin, simvastatin, and atorvastatin are metabolized via CYP3A4
- All statins are substrates of OATP1B1 transporter
 - Using them with CNIs increases statin concentrations
 - Increased risk of myalgias / rhabdomyolysis
- Cholesterol synthesis occurs at night, so statins should be administered in the evening



HMG CoAReductase Inhibitors

Drug	Low Intensity 20-25%↓	Moderate Intensity 30-49%↓	High Intensity ≥50%↓	Clinical Pearls
Lovastatin	10-20 mg	40-80 mg		Metabolized via CYP3A4 Short half-life
Pravastatin	10-20 mg	40-80 mg		
Simvastatin	10 mg	20-40 mg		Metabolized via CYP3A4 Can cause kidney injury Short half-life
Fluvastatin	20-40 mg	80 mg		Short half-life
Pitavastatin		1-4 mg		
Atorvastatin	5 mg	10-20 mg	40-80 mg	Metabolized via CYP3A4
Rosuvastatin		5-10 mg	20-40 mg	Can cause kidney injury

Non-statin therapies

Drug Class	Mechanism of Action	LDL-C Lowering	Side Effects
Ezetimibe	 Reduces cholesterol absorption in the small intestine Raise LDL receptor activity 	15-25%	GI
Bile acid sequestrants	- Impairs absorption of cholesterol - Raise LDL receptor activity	15-25% depending on dose	Constipation GI Increases TG *Contraindicated with MMF *Decreases statin concentration
Niacin	- Reduces hepatic secretion of VLDL	5-20%	Flushing Rash Increased plasma glucose Hepatic dysfunction
Fibrates	 Reduces secretion of VLDL Enhances degradation of VLDL 	5-15%	Myopathy (in combination with statins)

Non-statin therapies

Drug Class	Mechanism of Action	LDL-C Lowering	Side Effects
PCSK9 inhibitors (alirocumab, evolocumab, lerodalcibep)	Inhibits PCSK9 to increase the number of LDL receptors available to clear circulating LDL-C	45%-60%	Headache, injection- site reaction
MTP inhibitors (lomitapide)	Reduces hepatic secretion of VLDL	50%+	Fatty liver, hepatotoxicity
Evinacumab	Blocks angiopoietin-like protein 3 (ANGPTL3)	~50%	Infusion reactions
Inclisiran	Antilipemic Small Interfering Ribonucleic Acid (siRNA) Agent Inhibits PCSK9 production in the liver	48% - 52%	Injection site reactions

PCSK9 Inhibitors

Agent	Dosing	Adverse Effects	Other Considerations
Evolocumab (Rep <u>a</u> tha®)	140mg SQ every 2 weeks	Injection site reactions Angioedema (rare) Potential for	Avoid with latex allergy
Alirocumab (Praluent®)	75mg SQ every 2 weeks	immunogenicity Flu-like illness	May cause LFT elevation
Lerodalcibep	300mg SQ monthly		Third generation



Warden B, et al. J Am Coll Cardiol Case Rep 2020

CASE REPORT: CLINICAL CASE SERIES

Use of PCSK9 Inhibitors in Solid Organ Transplantation Recipients

Bruce A. Warden, РнакмD,^a Tina Kaufman, РнD, PA-C,^a Jessica Minnier, РнD,^{a,b} P. Barton Duell, MD,^a Sergio Fazio, MD, РнD,^a Michael D. Shapiro, DO, MCR^{a,c}

Results

- Case series of 12 SOT recipients with inadequately treated HLD with standard lipid lowering therapy
 - 75% heart transplant
 - Kidney, liver, and lung also represented
- Indications were familial HLD (50%), ASCVD risk (75%) and CAV(18%)
- Median LDL-C levels decreased 60%
- Median CSA levels decreased (37%), tacrolimus increased (6%)
 - Proportion of time within therapeutic range did not change
- 25% of patients experienced mild, self-limiting adverse reactions
 - Rhinorrhea, injection site reactions, nausea
 - No discontinuation

Organ Specific Considerations

Kidney

• KDIGO 2013

• Statin treatment for all adult kidney transplant recipients (KTRs), except those aged <30 years of age and without prior cardiovascular risk factors (CVRF)

Heart

• ISHLT2023

- In adults, the use of statins after HTis recommended regardless of cholesterol levels. Due to pharmacologic interactions with CNI and risk for toxicity, statin doses should generally be lower than those recommended for hyperlipidemia.
- Although there is no evidence for a target LDL concentration in these patients, it is reasonable to aim for level below 100 mg/dL (or 2.5 mmol/L) for most patients, with more aggressive targets reserved for those with evidence of CAV
- PCSK9 inhibitors are reasonable adjuncts to statins in adult heart transplant patients with uncontrolled hyperlipidemia or as alternative agents in the setting of statin intolerance

Glucagon-Like Peptide-1 Agonists

Talk of the Town



Cardiovascular Benefits of GLP1-A

- Improvement in multiple cardiovascular risk factors:
 - Reduction in systolic blood pressure (2-6 mmHg)
 - Reduction in total cholesterol, LDL and triglycerides
 - Hemoglobin Alc reduction from 0.8 1.5%
 - Weight reduction (2.5 4kg)
- 15% reduction in major adverse cardiovascular events (MACE)

Post-Transplant Concerns

Safety

Tolerability

- GIadverse effects
 - Delayed gastric emptying
 - Medication absorption

Efficacy

• How can these agents benefit transplant patients?

Kidney Transplantation



OPEN

The Use of GLP1R Agonists for the Treatment of Type 2 Diabetes in Kidney Transplant Recipients

Aleksandra Kukla, MD,¹ Jennifer Hill, DNP,¹ Massini Merzkani, MD,¹ Andrew Bentall, MD,¹ Elizabeth C. Lorenz, MD,¹ Walter D. Park, BS,² Matthew D'Costa, MD,² Yogish C. Kudva, MD,³ Mark D. Stegall, MD,² and Pankaj Shah, MD³

Results

- 14 kidney transplant patients
 - 12-month outcomes:
 - No change in weight
 - Decrease in total daily insulin dose
 - No change in renal function
 - No significant change in tacrolimus dose
 - Tolerability
 - 5 patients discontinued (29%)
 - Pancreatitis
 - Nausea
 - Diarrhea
 - Fatigue
 - Uncontrolled DM

Kidney Meta-Analysis



Embase®

Safety and efficacy of glucagon-like peptide-1 receptor agonists among kidney transplant recipients: a systematic review and meta-analysis

Evidence supporting glucagon-like peptide-1 receptor agonists (GLP-1RAs) in kidney transplant recipients (KTRs) remains scarce. This systematic review and meta-analysis aims to evaluate the safety and efficacy of GLP-1RAs in this population.

Methods Results Following treatment with GLP-1RAs: Cochrane MEDLINE eGFR and creatinine levels **3 databases searching from inception** through May 2023 UPCR SMD -0.47 g/g (95% CI -0.77, -0.18; I² = 74%) Clinical trials and observational studies that reported kidney graft function, HbA1c levels and total daily insulin doses glycemic and metabolic parameters, MD -0.85% (95% CI - 1.41, -0.28; I² = 77%) weight, cardiovascular outcomes, and and -7.62 unit (95% CI - 12.41, -2.82; I² = 0%) respectively adverse events were identified Weight Study characteristics: MD -4.03 kg (95% CI -5.30, -2.77; I2 = 0%) 9 cohort studies 338 kidney transplant Common adverse events: recipients (KTRs) Nausea and vomiting (17.6%) No significant alteration 4 GLP-1RAs: dulaglutide, • Diarrhea (7.6%) in tacrolimus trough levels iraglutide, semaglutide, Injection site pain (5.4%) when compared to baseline and exenatide UPCR, urine protein creatinine ratio; SMD, standard mean difference; MD, mean difference

Conclusion: While GLP-1RAs may lead to an elevated risk of GI side effects in KTRs, they demonstrate substantial benefits in reducing proteinuria, improving blood glucose control, and promoting weight loss, all without impacting tacrolimus levels.

Krisanapan, P., et al. Clinical Kidney Journal (2024) Pajaree_fai@hotmail.com @CKJsocial

Semaglutide is effective in achieving weight loss in liver transplant recipients

(b) Chow, Kenneth W.¹; (b) Ibrahim, Brittney^{2,3}; Rahal, Kabir²; (b) Hsu, Ryan H.⁴; (b) Tan, Teresa²; (b) Meneses, Katherine²; (b) Saab, Sammy^{2,3}

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Liver Transplantation 30(2):p 223-225, February 2024. | DOI: 10.1097/LVT.00000000000247

Results

- 23 OLT recipients
- Indication:
 - 70% T2DM
 - 26.1% Obesity
 - 4.3% NAFLD
- Statistically significant decrease in mean body weight (92kg → 87kg)
- Lower doses than package insert were used
- Adverse effects:
 - Nausea (30.4%)
 - Emesis (26.1%)
 - Diarrhea (30.4%)
 - Early satiety (8.7%)



NAFLD: nonalcoholic fatty liver disease



ORIGINAL ARTICLE

Cardio-Renal-Metabolic Outcomes Associated With the Use of GLP-1 Receptor Agonists After Heart Transplantation

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Results



- 74 HTrecipients
- Indications were T2DM and/or obesity
- 16% discontinued for adverse effects
- 6.8% required significant change in CNI dosage after initiation of GLP-1 agonist
 - 3 required CNI decrease
 - 2 required CNI increase

Results

Variable	Baseline	Most recent follow-up	Significance (p-value)
BMI (kg/m ²)	33.3 (6.9)	31.5 (6.5)	< 0.0001
HbA1C (%)	7.3 (1.6)	6.7 (1.4)	0.0005
LDL (mg/dL)	78.6 (36.7)	70.3 (32.5)	0.018
TG (mg/dL)	148.1 (75.4)	137.8 (64.9)	0.200
eGFR (mL/min/1.73m ²)	57.2 (19.7)	56.1 (20.1)	0.588
NT-proBNP (pg/mL)	435 [252, 1070]	317 [153, 787]	0.746
Urine protein (mg/dL)	28 [9.8, 57]	31 [18.5, 187]	0.442
Insulin dose (units)	32.6 (17.1)	24.8 (16.5)	0.0003
Prednisone dose (mg)	4.5 [2.5, 5.0]	2 [0, 3]	0.0006

TABLE 2Cardiometabolic profile before and after GLP1-RA Therapy.

Note: Values are mean (SD) or median [Q1, Q3].

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1C; HT, heart transplant; LDL, low density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TG, triglycerides.

Summary

Refer to organ specific guidance (where available) for hypertension and lipid management

Use medication clinical pearls to help guide difficult clinical decision making / agent selection

GLP1 agonists have been safely and effectively used in the post-transplant setting but require careful patient selection and monitoring

Hypertension, Hyperlipidemia, and GLP-1 agonists After Transplantation

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