Supportive Evidence Document:
LIPID-LOWERING THERAPY IN ADPKD

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Statin Therapy for Renoprotection in ADPKD

Background

Statins have been of interest in ADPKD because of their pleotropic effects, which include reduction in inflammation, improvement in endothelial dysfunction, and increase in renal blood flow (1). These effects may be beneficial in reducing progression of ADPKD, as endothelial dysfunction and oxidative stress are important features of this condition (2). Furthermore, statin therapy has been shown to reduce kidney size, volume density of cysts, and serum urea nitrogen in heterozygous male Han:SPRD rats with ADPKD (3).

Evidence for Statin Therapy

A summary of the evidence regarding statin therapy for renoprotection in ADPKD is presented in Table 2.

Currently, the best evidence favoring statin therapy for renoprotection in ADPKD is a double blind, placebo-controlled trial of 91 patients aged 8-22 years with Schwartz CrCl > 80 mL/min/1.73 m^2 who were randomized to pravastatin [20 mg daily (8-12 years old) or 40 mg daily (13-22 years old)] or placebo for 3 years (4). In the pravastatin group, a lower proportion reached ≥ 20% change in height-adjusted total kidney volume (4). However, a 2-year randomized trial in 49 ADPKD adult patients with all levels of kidney function failed to show any difference in eGFR, CrCl, or urinary protein excretion when comparing pravastatin 20 mg daily to no treatment (5). A post-hoc analysis of 931 patients in the HALT-PKD studies also did not show any differences in renal outcomes when comparing patients who did not use statins to those who used statins for at least 3 years; however, statins were not randomly allocated in the HALT-PKD studies (1).

Due to the paucity of evidence in this area, as well as conflicting results in available studies, further data is required to confirm whether lipid-lowering therapy is renoprotective in ADPKD. A randomized, double-blind, placebo-controlled, parallel study (ClinicalTrials.gov Identifier: NCT03273413) is currently underway and will provide additional data about the utility of pravastatin therapy for delaying renal progression in early-stage ADPKD (6).

Recommendations

Until further evidence is available, we do not recommend statin therapy in ADPKD patients for the purpose of renoprotection. This recommendation is in line with those of several published ADPKD reviews/ guidelines (Table 1).

However, statin or statin/ezetimibe therapy may be recommended to select ADPKD patients for prevention of cardiovascular disease (See “Lipid-Lowering Therapy for Prevention of Cardiovascular Disease in ADPKD”).

References

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Lipid-Lowering Therapy for Prevention of Cardiovascular Disease in ADPKD

Background

The most common cause of morbidity and mortality in ADPKD patients is cardiovascular complications (1). A retrospective frequency-matched cohort showed that, compared to patients without ADPKD, ADPKD patients had a 1.40-fold, 1.41-fold, 1.40-fold, 1.20-fold, and 1.49-fold higher incidence of acute coronary syndrome, unstable angina, stroke, hemorrhagic stroke, and heart failure, respectively (2). The higher risk of cardiovascular disease observed was evident even in patients 20-49 years of age (2).

Therefore, it is very important to target all cardiovascular risk factors as early as possible in ADPKD patients. A multidisciplinary approach should be used when targeting cardiovascular risk factors, and measures to be addressed include blood pressure control (See the "Blood Pressure Monitoring and Targets in ADPKD" Supporting Document), smoking cessation, weight loss in overweight/obese patients, and lipid-lowering therapy.

Evidence for Lipid-Lowering Therapy

A summary of the evidence regarding lipid-lowering therapy for prevention of cardiovascular disease in ADPKD patients is presented in Table 4. The only lipid-lowering agent that has been studied prospectively for this purpose is statins.

There is currently no high-quality evidence evaluating the utility of lipid-lowering therapy for prevention of cardiovascular disease specifically in ADPKD patients.

Recommendations

Until higher-quality evidence is available to guide the use of lipid-lowering therapy in ADPKD for prevention of cardiovascular disease, we recommend that the KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease recommendations be applied to ADPKD patients. This recommendation is in line with those of several published ADPKD reviews/ guidelines (Table 3).

As such, statin or statin/ezetimibe therapy should be considered for primary prevention in all ADPKD patients ≥ 50 years of age who do not have contraindications, regardless of serum lipid levels (3). We do not recommend the use of lipid targets to guide treatment because this approach has not been shown to be beneficial in any clinical trial, and the safety of higher statin doses has not been established in patients with reduced renal function (3).

The doses of statin or statin/ezetimibe recommended in accordance with KDIGO are listed in Table 5.

References

1. Helal I, Reed B, Mettler P, Fann KM, Tkachenko O, Yan X-D, et al. Prevalence of Cardiovascular Event in Patients with Autosomal Dominant Polycystic Kidney Disease. *Am J Nephrol.* 2012;36(4):362-70.

2. Chaung Y-W, Yu T-M, Huang S-T, Sun K-T, Lo Y-C, Fu P-K, et al. Young-Adult Polycystic Kidney Disease is Associated with Major Cardiovascular Complications. *Int J Environ Res Public Health*. 2018;15(5):903.

3. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. *Kidney Int Suppl*. 2013; 3: 259–305.

Table 1: Statements/Recommendations Regarding the Use of Statin Therapy for Renoprotection in ADPKD

PUBLICATION TYPE	PUBLICATION	YEAR OF PUBLICATION	STATEMENT/RECOMMENDATION
Guideline	Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes Controversies Conference (1)	2015	• "…a RCT of HMG-CoA reductase inhibition with pravastatin in ADPKD children showed slower kidney volume growth and reduced loss of kidney function." • "These data need confirmation, especially because a two-year RCT in the adult ADPKD population showed no effect of pravastatin treatment versus placebo."
	Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease: A Canadian Expert Consensus (2)	2017	• "The efficacy of pravastatin in the treatment of ADPKD has been demonstrated in pediatric patients. • "Further studies are required to assess efficacy in adults."
	Updated Canadian Expert Consensus on Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease (3)	2018	• "Further studies are required to evaluate the benefits of statin therapy in patients with ADPKD."
Review Article	Riella et al. (4)	2014	• "…more research will be necessary to investigate the effects of statin therapy in the adult ADPKD population." • "Although not FDA approved for ADPKD treatment, the good tolerability of pravastatin and the potentially favorable risk-benefit ratio may justify its off-label use, if individual patients and physicians desire."
	Potts et al. (5)	2017	• "Pravastatin use should not be ruled out in younger patients who are free of statin contraindications."

References

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4. Riella C, Czarnecki PG, Steinman TI. Therapeutic advances in the treatment of polycystic kidney disease. *Nephron Clin Pract.* 2014;128(3–4):297–302.
5. Potts JW, Mousa SA. Recent advances in management of autosomal-dominant polycystic kidney disease. *Am J Health Syst Pharm*. 2017;74:1959-68.

Table 2: Evidence Summary for the Use of Statin Therapy for Renoprotection in ADPKD

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	LIMITATIONS
van Dijk et al. 2001 (1)	• Double-blind, randomized, placebo- • controlled, crossover study with evaluations at the end of each 4-week treatment period	• 10 ADPKD patients with CrCl > 50 mL/min • Mean age 35 years	Simvastatin 40 mg daily	Placebo (crossover)	• GFR (inulin clearance) • Effective renal plasma flow (PAH clearance) • Vasodilator response to acetylcholine in forearm	• GFR increased from 124 ± 4 mL/min to 132 ± 6 mL/min ($p<0.05$) • Effective renal plasma flow increased from 494 ± 30 mL/min to 619 ± 67 mL/min ($p<0.05$) • Acetylcholine-induced forearm vasodilatation was significantly enhanced ($p<0.05$)	• Very small and heterogeneous study group • Short follow-up period • No safety data reported
Fassett et al. 2010 (2)	2-year randomized, open label clinical trial	• 49 ADPKD patients with all levels of kidney function and serum cholesterol • Mean age ~51 years	Pravastatin 20 mg daily (n=29)	No treatment (n=20)	Primary: • eGFR (MDRD equation) Secondary: • CrCl (24h urine collection) • UPE (24h urine collection)	• No statistically significant differences in rate of change of eGFR, CrCl, or UPE	• Small sample size • Low dose of pravastatin studied • No safety data reported

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	LIMITATIONS

Patch et al. 2011 (3)	Purpose was to determine association between 5 antihypertensive classes and death or new RRT. Only data pertaining to lipid-lowering therapy are presented in this table
	• Retrospective cohort study using the UK General Practice Research
	• Patient data collected using diagnostic codes from medical records and prescription data
		• 1877 ADPKD patients aged > 15 years in UK General Practice Research Database between 1991 and 2008	• Regression model to determine association between various factors and:
			  • Death
			  • Composite of death or RRT
			
			• Factors included in regression model:
			  • Age
			  • Sex
			  • Year of entry to cohort
			  • Calendar year of study
			  • Coronary heart disease
			  • Stroke
			  • Diabetes
			  • Hyperlipidemia
			  • Prescription of lipid lower drugs including statins and others
						All incident rate ratios below are using "not prescribed lipid-lowering therapy" as the reference
						
						Death:
						• Lower mortality in patients who were prescribed lipid-lowering
						• Adjusted incident rate ratio 0.18 (95% CI 0.11-0.32), p<0.001
						
						Death or RRT:
						• Adjusted incident rate ratio 0.61 (95% CI 0.44-0.84), p = 0.003
							• Major limitation is retrospective design
							• Reliance on medical codes and prescription data, which may not be accurate
							• Large sample size
							• Although data was available, did not adjust for antihypertensives when determining association between lipid-lowering therapy and outcomes
							• Specific lipid-lowering therapies not specified

Cadnapaphorn-chai et al. 2014 (4)	3-year randomized, double blind, place-bo-controlled phase III trial	• 91 ADPKD patients aged 8-22 years with Schwartz CrCl > 80 mL/min/1.73 m^2 • Mean age 16 years	Pravastatin 20 mg daily (8-12 years old) or 40 mg daily (13-22 years old) (n=49)	Placebo (n=42)	Primary: • ≥20% increase in HtTKV, LVMI, or UAE	• Lower proportion had a ≥20% increase in HtTKV, LVMI, or UAE (88% vs. 69%; p=0.03)	• Limited to a young population

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	LIMITATIONS
					Secondary: • ≥20% increase in each component of the primary outcome • Percent change in each component of the primary outcome	• Above result was driven by a lower percent change in HtTKV (23% ± 3% vs. 31% ± 3%; p=0.02, after adjusting for baseline age, sex, and hypertension status) • No statistically significant differences between groups for LVMI and UAE • Exploratory analysis: No significant difference in LDL-C between participants who had ≥20% increase in HtTKV compared to those who had <20% increase	
Zand et al. 2016 (5)	4-week prospective study with 11 healthy volunteers as comparator	• 11 ADPKD patients with mild renal dysfunction (SCr ≤1.6 mg/dL and iothalamate clearance ≥65 mL/min/1.73 m^2) • 10 patients with moderate renal dysfunction (SCr 1.4-2.0 mg/dL and iothalamate clearance 30-64 mL/min/ 1.73 m^2)	Simvastatin 40 mg daily	Baseline	• GFR (iothalamate clearance) • Estimated renal plasma flow (PAH clearance) • Renal blood flow (based on PAH or MRI)	• No statistically significant changes in GFR, estimated renal plasma flow, or renal blood flow after statin therapy in any groups (including healthy volunteers, ADPKD patients with mild renal dysfunction, and ADPKD patients with mild renal dysfunction, and ADPKD patients with moderate dysfunction)	• Small sample size • Short follow-up period • Repeat MRI measurements to determine renal blood flow were not performed on all patients (only on 2 of 11 healthy volunteers, 2 of 11 ADPKD patients with mild renal dysfunction, and 3 of 10 ADPKD

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	LIMITATIONS
		• Mean age ~48 years					patients with with moderate renal dysfunction) • No safety data reported
Brosnahan et al. 2017 (6)	Post-hoc analysis of HALT PKD trials (randomized, double-blind, multicenter trials with 5-8 year follow-up)	Study A: • ADPKD patients aged 15-49 years with eGFR > 60 mL/min/1.73 m^2 Study B: • ADPKD patients aged 18-64 years with eGFR 25-60 mL/min/1.73 m^2	Statin x ≥ 3 years Study A: n = 59 Study B: n = 118	No statin Study A: n = 462 Study B: n = 292	Study A: • Percent change in TKV • Percent change in height-adjusted liver volume • Rate of eGFR decline Study B: • Time to composite of death, ESRD, or 50% decline in eGFR	Study A: • No statistically significant differences in percent change of TKV, percent change in height-adjusted liver volume, or rate of eGFR decline Study B: • No statistically significant difference in time to composite of death, ESRD, or 50% decline in eGFR	• Non-randomized allocation to statin therapy • Small number of patients who were on statin therapy for ≥ 3 years in Study A • Statin drugs used and their doses were not recorded • No safety data available

ADPKD = autosomal dominant polycystic kidney disease; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GFR = glomerular filtration rate; HtTKV = height-adjusted total kidney volume; LDL-C = low-density lipoprotein cholesterol; LVMI = left ventricular mass index; MDRD = Modification of Diet in Renal Disease; PAH = para-aminohippurate; RRT= renal replacement therapy; TKV = total kidney volume; UAE = urinary albumin excretion; UPE = urinary protein excretion

References

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Table 3: Statements/Recommendations Regarding the Use of Lipid-Lowering Therapy for Prevention of Cardiovascular Disease in ADPKD

PUBLICATION TYPE	PUBLICATION	YEAR OF PUBLICATION	STATEMENT/RECOMMENDATION
Guideline	Spanish guidelines for the management of autosomal dominant polycystic kidney disease (1)	2014	• "Guidelines for the management of cardiovascular risk in CKD, including… lipids (http://kdigo.org/home/guidelines/lipids/)… should be applied until ADPKD-specific evidence becomes available."
	KHA-CARI Autosomal Dominant Polycystic Kidney Disease Guideline: Pharmacological Management (2)	2015	• "We recommend the use of lipid-lowering therapies such as 3-hydroxy-methyl-glutaryl-CoA reductase inhibitors, as recommended for those with chronic kidney disease (1B)."
	KHA-CARI guideline recommendations for the diagnosis and management of autosomal dominant polycystic kidney disease (3)	2016	• "Reducing overall mortality: lipid lowering agent (LLA) therapies are indicated for mortality prevention via minimization of cardiovascular risk, amongst those with CKD regardless of aetiology"
	European ADPKD Forum multidisciplinary position statement on autosomal dominant polycystic kidney disease care (4)	2018	• ADPKD patients should be provided with comprehensive, up-to-date written information on self care aspects, which include cardiovascular risk management with cholesterol-lowering therapy
	Updated Canadian Expert Consensus on Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease (5)	2018	• Statin therapy may be considered in cases whether there are indications for chronic kidney disease other than for renoprotection in ADPKD

Review Article/ Practical Guide	Chebib et al. (6)	2018	• Grade 2B evidence for the following:
			  • Aim for serum LDL ≤ 100 mg/dL (2.6 mmol/L)
			  • Methods to achieve LDL goal include dietitian follow-up, regular exercise and statin if needed (ezetimibe if intolerant)
			• Low threshold to start statin therapy for lipid control

	Chebib et al. (7)	2018	• Target LDL < 100 mg/dL (2.6 mmol/L) and HDL > 50 mg/dL (1.3 mmol/L) • Low threshold to start statin for lipid control
	Perrone et al. (8)	2018	• "The current evidence suggests that patients with chronic kidney disease and significant risk factors for coronary artery disease should be prescribed a lipid-lowering agent (2013 KDIGO). Given the paucity of data that can guide dyslipidemia treatment in patients with ADPKD, it is reasonable to extrapolate

PUBLICATION TYPE	PUBLICATION	YEAR OF PUBLICATION	STATEMENT/RECOMMENDATION
			our management approach based on the data for chronic kidney disease in general." • "… we favor starting lipid-lowering agents in all patients with ADPKD with any risk factor for coronary artery disease as this population is clearly at high risk to develop cardiovascular disease." • "Statins are the drug of choice as they may have other potential favorable outcomes in patients with ADPKD."
	Torra (9)	2019	• **"**…evidence in ADPKD, and in CKD in general, indicates that it is appropriate to keep the low-density lipoprotein (LDL) cholesterol at not more than 100 mg/dL [2.6 mmol/L].

References

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Table 4: Evidence Summary for the Use of Lipid-Lowering Therapy for Prevention of Cardiovascular Disease in ADPKD

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	LIMITATIONS
Namli et al. 2009 (1)	6-month single-cohort prospective study	• 16 ADPKD patients having well-preserved renal function; excluded patients with diabetes mellitus, established cardiovascular disease, other chronic diseases that could affect endothelial function, or family history of hyperlipidemia or of premature atherosclerosis • Mean age 39.4 ± 10.6 years	Simvastatin 40 mg daily	Baseline	• Endothelial function (evaluated from endothelial-dependent dilatation, expressed as percentage change in brachial artery diameter from baseline to reactive hyperemia) • IL-6 level • hs-CRP level	• Endothelial-dependent dilatation increased from 11.3 ± 6.9% to 14.6 ± 4.6% (p-=0.016) • IL-6 decreased from 21.6 ± 21.7 pg/mL to 9.1 ± 3.5 pg/mL (p=0.002) • No significant change in hs-CRP	• Use of surrogate outcomes • Small sample size • Short follow-up period • No safety data reported

Sung et al. 2017 (2)	Population-based cohort study with mean follow-up duration of 9 years
	
	Multiple analyses done; only data from comparisons
		• 2647 ADPKD patients in the Taiwan National Health Insurance Research Database
		• Median age 46 years (IQR 37-55 years)
			• Multivariable Cox proportional hazard regression analysis of factors associated with cerebrovascular accident (defined as ischemic or hemorrhagic stroke)
			• Factors included in multivariable analysis ("exposure" defined as regimen duration >3 months based on prescription data):
			  • Gender
			  • Age
			  • Hypertension
						Compared to patients with no exposure to RAAS blockade or statin:
						• Lower risk of cerebrovascular accident with statin exposure alone (adjusted HR 0.44; 95% CI 0.24-0.79
							• Reliance on ICD-9-CM codes and prescription data, which may not be accurate
							• Some patient data were not available (eg. laboratory values, lifestyle

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	LIMITATIONS
	pertaining to statin exposure in ADPKD are presented in this table		• Diabetes mellitus • Dyslipidemia • Statin exposure (n = 702; 26.5% of patients) • RAAS blockade exposure (n = 1595; 60.3% of patients)			• Even lower risk of cerebrovascular accident with combined statin + RAAS blockade exposure (adjusted HR 0.19; 95% CI 0.11-0.31)	factors, body mass index, functional capacity) • Only collected prescription data on statins and RAAS blockade; therefore, did not adjust for any other potential medication-related confounders • No safety data available

HR = hazards ratio; hs-CRP = high-sensitivity C-reactive protein; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; IQR = interquartile range; IL-6 = interleukin 6; RAAS = renin-angiotensin-aldosterone system

References

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Table 5: Recommended Statin Doses for Primary Prevention of Cardiovascular Disease in ADPKD Patients (mg/day) (1)

STATIN	eGFR 60-90 mL/min/1.73 m^2	eGFR < 60 mL/min/1.73 m^2
Lovastatin	General population	Not studied
Fluvastatin	General population	80
Atorvastatin	General population	20
Rosuvastatin	General population	10
Simvastatin/Ezetimibe	General population	20/10
Pravastatin	General population	40
Simvastatin	General population	40

General population = Any dose approved for use in the general population

References

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