The 44th Annual International Congress of the
EGYPTIAN SOCIETY OF CARDIOLOGY
CardioEgypt2017

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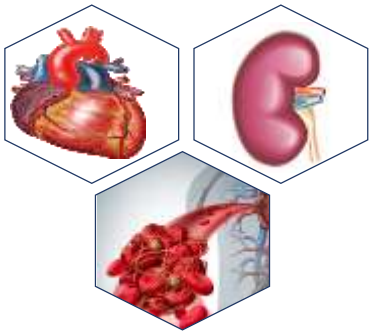

Approach to dyslipidemia in Chronic Renal Insufficiency

Prepared by: Noha Kamal Morsy Ibraheem

Board Certified Pharmacotherapy Specialist (BCPS)

Clinical Pharmacy diploma ASU

Clinical Pharmacist at Nephrology department Nasser Institute Hospital

Outline

Does dyslipidemia in renal impairment increase CVD risk ?

Evaluation & monitoring of lipid profile in patients with chronic renal insufficiency

Dyslipidemia in:

- Chronic kidney disease (CKD) in adults
- Dialysis
- Nephrotic syndrome
- Kidney transplantation
- Pediatric population with chronic renal insufficiency

Does dyslipidemia in renal impairment increase CVD risk ?

It is well known that **dyslipidemia** maybe the most important **risk factor** for the development of **cardiovascular disease (CVD)** in the **general population.**

On the other hand, the role of **dyslipidemia** in the pathophysiology of atherosclerotic disease in **patients with impaired renal function** remains **controversial.**

Some studies suggested an **inverse relationship between** serum cholesterol values and mortality in **ESRD individuals**, a phenomenon also known as **"reverse epidemiology"**

Tsimihodimos, Vasilis, Zoi Mitrogianni, and Moses Elisaf. "**Dyslipidemia Associated with Chronic Kidney Disease.**" *The Open Cardiovascular Medicine Journal* 5 (2011): 41–48. *PMC*. Web. 12 Feb. 2017.

Lipid profile in patients with chronic renal insufficiency

	CKD	Nephrotic syndrome	Hemodialysis	Peritoneal dialysis
Total cholesterol	↔	↑↑	↓ ,↔	↔ ,↑
LDL cholesterol	↔	↑↑	↓ ,↔	↔ ,↑
HDL cholesterol	↓	↓	↓	↓
Triglycerides	↑	↑↑	↑	↑
Lp(a)	↑	↑↑	↑	↑↑

Normal (↔), increased (↑), markedly increased (↑↑), and decreased (↓) plasma levels compared with non-uremic individuals. LDL: low density lipoproteins; HDL: high density lipoproteins; Lp(a): lipoprotein (a); CKD: chronic kidney disease.

Mesquita, J., Varela, A. & Medina, J.L. **Dyslipidemia in renal disease: Causes, consequences and treatment.** *Endocrinología y Nutrición* 57, 440-448 **(2010).**

Lipid profile evaluation & monitoring

In adults with **newly identified CKD** (including **chronic dialysis** or **kidney transplantation**)

→ **Baseline evaluation** with a complete lipid profile. (1C)

In adults with **CKD** (including those treated with **chronic dialysis**)

→ **Follow-up measurement** is not required for the majority of patients. (Not Graded)

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

AHA 2013 Four Statin Benefit Groups

ASCVD

LDL-C ≥190 mg/dL

DM 40-75 years & LDL 70-189 mg/dL (without ASCVD)

40 to 75 years, LDL-C 70- 189 mg/dL and an estimated 10-year **ASCVD risk of ≥7.5%** (without ASCVD or diabetes)

Stone, N.J., *et al*. **2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.** *A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines* **129**, S1-S45 (2014).

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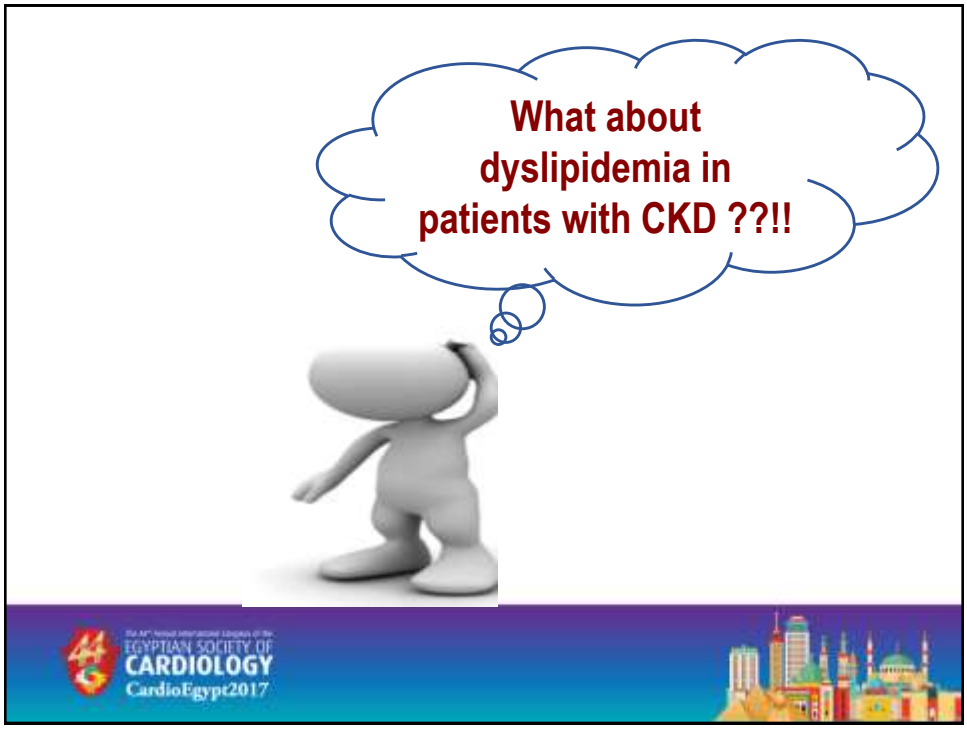

Pharmacological cholesterol-lowering treatment in adults with CKD

In adults aged ≥ 50 years with

- **eGFR < 60 ml/min/1.73 m²**
  - we recommend treatment with a **statin** or **statin/ezetimibe** combination. (1A)
- **CKD and eGFR ≥ 60 ml/min/1.73 m²**
  - we recommend treatment with a **statin.** (1B)

In adults aged 18–49 years with CKD

- **Statin treatment** in people with one or more of the following (2A):
  - Known coronary disease (myocardial infarction or coronary revascularization)
  - Diabetes mellitus
  - Prior ischemic stroke
  - Estimated 10-year incidence of coronary death or non-fatal myocardial infarction **> 10%**

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

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Dyslipidemia management in adults with CKD

KDIGO recommends **against** **"treat-to target"** strategy because it has never been proven beneficial in any clinical trial. In addition, **higher doses of statins have not been proven to be safe** in the setting of **CKD.**

KDIGO recommends a **"fire-and-forget"** strategy. Physicians may choose to perform **follow-up** in patients whom are judged to favorably **influence adherence** to treatment or **other processes of care.**

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

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Recommended doses (mg/d) of statins in adults with CKD

Statin	eGFR < 60, including patients on dialysis or with a kidney transplant
Lovastatin	nd
Fluvastatin	80
Atorvastatin	**20**
Rosuvastatin	**10**
Simvastatin/Ezetmibe	20/10
Pravastatin	40
Simvastatin	40

Rosuvastatin 40 mg daily is not recommended for use in CKD 1-2 non-transplant patients, nd, not done or not studied.

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

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Triglyceride-lowering treatment in adults with CKD

Fibrates not to be used concomitantly with statins in patients with CKD due to increased risk of adverse events.

Fibric acid derivatives could be considered if serum **TG (> 1000 mg/dl)**. If such therapy is prescribed, fibric acid derivatives must be **dose-adjusted for kidney function.**

- **Fenofibrate :**
  - Contraindicated if **GFR <20 ml/min**
- **Gemfibrozil :**
  - **GFR 10 to 50 mL/min:** Administer 75% of dose,
  - **GFR <10 mL/min:** Administer 50% of dose

Nicotinic acid has not been well studied in advanced CKD and **not recommended,** given the risk of toxicity (especially flushing and hyperglycemia).

- Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. **KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease.** *Kidney inter., Suppl.***2013**;3: 259–305
- www.lexi.com accessed 12/2/2017

2016 ESC/EAS Guidelines for the Management of Dyslipidemias

For cardiovascular risk estimation	• Categorize **kidney disease patient** as **high risk** or **very high risk**. (IC)
Very high risk	• Severe CKD with **GFR< 30 ml/min**
High risk	• Moderate CKD with **GFR 30-60 ml/min**

Catapano AL, Graham I, De Backer G, et al. **2016 ESC/EAS Guidelines for the Management of Dyslipidaemias.** *European Heart Journal.* **2016 Oct** 14;37(39):2999-3058.

European Heart Journal

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Still what about dyslipidemia in CKD patients on regular dialysis??

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Pharmacological cholesterol-lowering treatment in dialysis

In adults with dialysis-dependent CKD:

Do not start

Statins or statin/ezetimibe combination **not to be initiated**. (2A)

To be continued

In patients already **receiving** statins or statin/ezetimibe combination **at the time of dialysis initiation**, these **agents to be continued**. (2C)

Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. **KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease.** *Kidney inter., Suppl.***2013**;3: 259–305 & **2016 ESC/EAS Guidelines for the Management of Dyslipidaemias**

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The 4D Study (RCT on the Efficacy and Safety of Atorvastatin in Patients with Type 2 Diabetes on Hemodialysis)

The 4D, a multicenter, double blind, randomized trial

Atorvastatin reduced the median LDL-C level by 42%, and placebo by 1.3%.

1255 HD patients with type 2 diabetes

Atorvastatin 20 mg | **Placebo**

median follow-up of 4 years

No significant difference in the **primary endpoint** (a composite of cardiac death, nonfatal MI, and fatal and nonfatal stroke (RR 0.92; 95% CI 0.77–1.10; **P- 0.37**) or total **mortality** (RR 0.93; 95% CI 0.79–1.08; **P- 0.33**).

Wanner, C., *et al.* **Randomized Controlled Trial on the Efficacy and Safety of Atorvastatin in Patients with Type 2 Diabetes on Hemodialysis (4D Study): Demographic and Baseline Characteristics**. *Kidney and Blood Pressure Research* **27**, 259-266 **(2004).**

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AURORA Study (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Dialysis: an Assessment of Survival and Cardiovascular Events)

International double-blind randomized trial

mean reduction in LDL-C of 43% in the intervention group

2776 HD patients

Rosuvastatin 10mg daily | **Placebo**

median follow-up of 3.8 years

Combined primary endpoint of death from cardiovascular causes, nonfatal MI, or nonfatal stroke **was not reduced** (HR 0.96; 95% CI 0.84–1.11; **P 0.59**) nor of all-cause **mortality** (HR 0.96; 95% CI 0.86- 1.07; **P 0.51**).

Fellström B, Holdaas H, Jardine AG, et al. **Effect of Rosuvastatin on Outcomes in Chronic Haemodialysis Patients: Baseline Data from the AURORA Study.** *Kidney & blood pressure research*. **2007**;30(5):314-322.

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SHARP (Study of Heart and Renal Protection)

International double-blind randomized trial

9270 participants ≥ 40 years old with CKD with **3023 HD**

Mean reduction in LDL-C among the treatment group was 32 mg/dl

Simvastatin 20mg plus ezetimibe 10 mg daily

Placebo

median follow-up of 4.9 years

Combination treatment did **not significantly reduce** the risk of the **primary outcome** of major atherosclerotic events in the subgroup of HD patients (RR 0.90, 95% CI, 0.75- 1.08), nor **all cause mortality** (RR,1.01, 95% CI, 0.94-1.11)

Group, S.C. Study of Heart and Renal Protection (SHARP): **Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease**. *American Heart Journal* **160**, 785-794.e710.

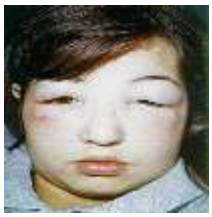
Dialyzability & doses of lipid lowering agents on regular hemodialysis

Non- dialyzable	Dose
Atorvastatin	**Use with caution**; these patients are predisposed to myopathy.
Fluvastatin (unlikely)	**Use with caution**, doses >40 mg/day (has not been studied).
Pravastatin	**Use with caution**, Initial: 10 mg once daily
Rosuvastatin	Initial: 5 mg once daily **(maximum: 10 mg/day).**
Simvastatin (unlikely)	5 –20 mg daily, doses > **10 mg should be used with caution** (doses up to 40 mg have been used)
Cholestyramine	**Use with caution**; may cause hyperchloremic acidosis.
Colestipol	Dosage adjustment is unlikely because not absorbed from the gastrointestinal tract.
Fenofibrate	**Use is contraindicated.**
Gemfibrozil	Initially 900 mg daily. Monitor carefully
Ezetimibe (unlikely)	Dose as in normal renal function

Caroline Ashley and Aileen Currie , **The Renal Drug Handbook ,**Third Edition @2009 & www.lexi.com accessed 17/2/2017

Dyslipidemia in Nephrotic syndrome

Before nephrotic syndrome episode



After nephrotic syndrome episode

Cholesterol lowering therapy in nephrotic syndrome

Do not use!

For the **initial episode** of nephrotic syndrome associated with **MCD**, **statins not be used** to treat hyperlipidemia. (2D)

Statins are **well tolerated** and **effective** in correcting the lipid profile, although **not proven to reduce cardiovascular events** in nephrotic syndrome.

It may also be that **statin** therapy **protects from a decline in GFR**, although this is not established.

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. **KDIGO Clinical Practice Guideline for Glomerulonephritis.** *Kidney inter., Suppl.* **2012**; 2: 139–274

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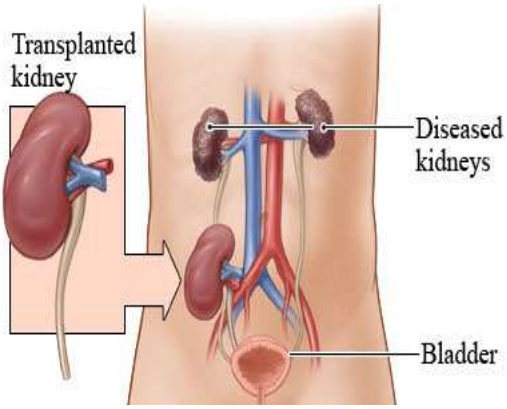
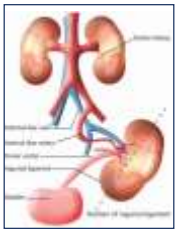
Dyslipidemia in Kidney transplantation

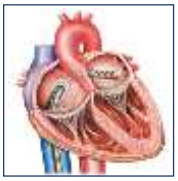


Does dyslipidemia in kidney transplantation increase CVD risk ?



Prevalence of dyslipidemia during the **first year after transplantation** is **> 50%,** although greatly influenced by the type of **immunosuppression** used and the **presence of other factors**, such as **proteinuria**, **acute rejection** and **graft dysfunction**.

In KTRs, there is **moderate evidence** that dyslipidemias contribute to CVD and that treatment of increased LDL-C with a **statin may reduce CVD events.**



Improving Global Outcomes (KDIGO) Transplant Work Group. **KDIGO clinical practice guideline for the care of kidney transplant recipients.** *American Journal of Transplantation* **2009**; 9 (Suppl 3): S1–S157.

Effect of immunosuppressive drugs on lipid parameters

	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides
Cyclosporine	↑↑	↑↑	↓	↑↑
Tacrolimus	↑	↑	↓	↑
Sirolimus	↑↑	↑↑	↓	↑↑↑
Everolimus	↑↑	↑↑	↓	↑↑↑
Mycophenolate mofetil	–	–	–	–
Azathioprine	–	–	–	–
Prednisone	↑	↑	↑	↑

Normal (↔), increased (↑), markedly increased (↑↑), and decreased (↓) plasma levels.
LDL: low density lipoproteins; HDL: high density lipoproteins.

Mesquita, J., Varela, A. & Medina, J.L. **Dyslipidemia in renal disease: Causes, consequences and treatment.** *Endocrinología y Nutrición* **57**, 440-448 **(2010).**

Screening & goals of therapy

Measure a complete lipid profile in KTRs:

- **2–3 months** after transplantation
- after change in treatment
- other conditions known to cause dyslipidemias
- **at least annually, thereafter**.

Treatment targets:

- **Adults :**
  - LDL <100mg/dL & non-HDL <130 mg/dL.
- **Adolescents:**
  - LDL <130 mg/dL & non-HDL <160 mg/dL

Improving Global Outcomes (KDIGO) Transplant Work Group. **KDIGO clinical practice guideline for the care of kidney transplant recipients.** *American Journal of Transplantation* **2009**; 9(Suppl 3): S1–S157.

Pharmacological cholesterol-lowering treatment in Kidney transplant recipients

KDIGO guidelines for Lipid Management in CKD 2013:

- In adult kidney transplant recipients, we suggest treatment **with a statin**. (2B)

ESC and EAS guidelines for dyslipidemias 2016:

- In adult kidney transplant recipients treatment with **statins may be considered**. (IIb- C)

Cyclosporin + **Atorvastatin**

Grade X: Avoid combination

Cyclosporine may increase the serum concentration of Atorvastatin. **Severity** Major **Reliability Rating** Good

Patient Management

- Concurrent use increases risk for atorvastatin-related toxicities such as ***myopathy*** and ***rhabdomyolysis***.
- Consider changing to a statin that is less sensitive to this interaction (e.g., ***pravastatin*** or ***fluvastatin***) or to an alternative type of LDL-lowering medication.

www.lexi.com last accessed 10/2/2017

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Cyclosporin

Fluvastatin

Pravastatin

MODIFY

Grade D: Consider therapy modification

Cyclosporine may increase the serum concentration of Fluvastatin or Pravastatin.
Severity: Major ,**Reliability Rating:** Good

Patient Management

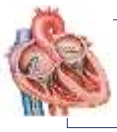
- Limit **Fluvastatin to 20 mg twice daily** or **Pravastatin to 20 mg/day** in patients who are also receiving cyclosporine.
- Monitor for toxic effects (e.g., myalgia, myopathy, rhabdomyolysis).

www.lexi.com last accessed 10/2/2017

Dyslipidemia Pediatric population with chronic renal insufficiency

Does dyslipidemia in pediatrics with CKD increase CVD ?

Young adults with eGFR < 15 ml/min/1.73m^2 have at least **10-folds higher risk for CVD** mortality compared to the general population.



Few studies demonstrate the **association of dyslipidemia with clinical CVD events** in **adolescents** or **young adults**, especially in the setting of CKD.

Levels of **total cholesterol < 170 mg/dL**, **LDL-C < 110 mg/dL** considered acceptable

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

Assessment of lipid status in children with CKD

In children with newly identified CKD (including chronic dialysis or kidney transplantation)

- **Baseline evaluation** with a complete lipid profile. (1C)

In children with CKD (including chronic dialysis or kidney transplantation)

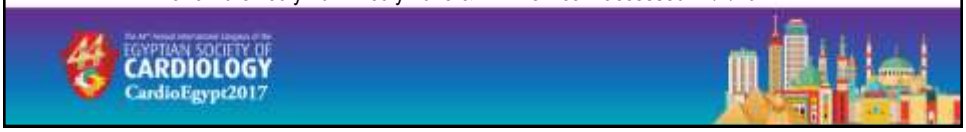
- **Annual follow-up** measurement of fasting lipid levels. (Not Graded)
- Unlike adults, growth and development in children have potential to influence lipid levels over time. Therefore, the **fasting lipid levels** be followed in children with CKD to screen for underlying secondary causes of dyslipidemia.

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

Medications for dyslipidemia in pediatrics

	Starting age	General population dose	Renal impairment
Atorvastatin	10 years	10 mg- **20 mg once daily**	Use with caution
Fluvastatin	9 years	20-80 mg dialy (40mg twice daily)	Use with caution, doses >40 mg/day (has not been studied).
Pravastatin sodium	8 years	10mg - max. 40mg once daily at night	Use with caution
Rosuvastatin	7 years	5 to max. **20 mg once daily**	CrCl <30 mL/min: Initial: 5 mg once daily; **maximum : 10 mg/day**
Simvastatin	5 years	10 to max. 40mg at night	eGFR < 30 mL/min : initial 5 mg, doses > 10mg daily used with caution
Colestyramine	6 years	4g - max. 8 g daily (1-4 doses)	Use with caution in renal impairment; may cause hyperchloremic acidosis.
Fenofibrate	4 years	1 capsule/20 kg body-weight (max. 4 capsules or max. 3 capsules with statin) daily	Reduce dose if eGFR < 60 mL/min; **avoid if eGFR< 20mL/min**

BNF for children July 2014 - July 2015 & www.lexi.com accessed 17/2/2017



Statins used in pediatric studies

Study	Statin dose	Population	Effect
Coleman , JE et al. 1996	**Simvastatin 5 - 40 mg/day**	children, **1.8–16.3 years** of age, who had dyslipidemia 2ry to nephrotic syndrome	There was a significant **reduction in TC & TG** but **two children suffered from transient elevation of CPK**
Sanjad ,SA et al. 1997	**Lovastatin maximum of 40 mg / day**	children, **8 months to 15** years of age, with nephrotic syndrome	There was a significant reduction in TC, LDL-C & TG ($p<0.004$). No change in HDL-C.
Song, M. et al. 2013	**Fluvastatin (5 mg/d if aged <5 years; 10 mg/d if aged ≥5 years),**	Pediatric patients (**4–12 years of age)** with minimal change nephropathy	TG, TC, and Upr were significantly decreased (all, $P < 0.01$)

Take home messages

Role of dyslipidemia in the development of atherosclerotic disease in patients with **impaired renal function** **remains controversial** & it may have **inverse relationship** in **dialysis patients**.

In **KTRs & pediatrics** there is **evidence** that dyslipidemias contribute to **CVD** and that treatment of increased LDL-C with a **statin** may reduce CVD events.

In patients with **nephrotic syndrome** **statins may protect from a decline in GFR**, but **not proven to reduce CV events**.

Use statins with **lower doses than general population** and monitor for **adverse effects** while considering **significant drug-drug interactions**.

Safety and **effectiveness** of lipid lowering therapy in patients with different categories of renal impairment **require more research.**

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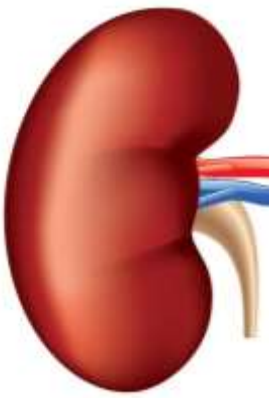
Thank you!



QUESTIONS?

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