Guideline on Lipid Management
Treat patients & stop measuring

but .......

April 23-26, 2014 | Manila, Philippines
PSN 34th Annual Convention
Trials in non-CKD-specific population identified by domain expert and other sources
\( n = 38 \)

Trials in CKD population identified in MEDLINE and Cochrane databases (January 2000–November 2011)
\( n = 13,055 \)

Excluded after abstract review
\( n = 12,986 \)

Articles retrieved for full-text review
\( n = 107 \)

Excluded for not meeting eligibility criteria
(\( \leq 50 \) per group, follow-up <6 mo, no intervention of interest, or no outcome of interest)
\( n = 87 \)

Studies that met eligibility criteria
\( n = 18 \) RCTs in 20 articles
A 58-y old non-smoking male (Mr N) is referred with a serum creatinine concentration of 1.8 mg/dl (160 umol/l).

The history, classification and prognosis evaluation identifies a chronic kidney disease CGA categories G3bA3:
A 58-y old non-smoking male (Mr S) is referred with a serum creatinine concentration of 1.8 mg/dl (160 umol/l).

The history, classification and prognosis evaluation identifies a chronic kidney disease CGA categories G3bA3:

C) 10-years ago: biopsy profen IgA-nephropathy
G) CKD-EPI eGFR 43 (GFR category G3b 30-44 ml/min/1.73m²)
A) UACR 1.1 g/g creatinine (Category A3). Measurement in a 24h urine specimen: protein 2.45 g and albumin 1.8 g)
### Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

<table>
<thead>
<tr>
<th>GFR categories (ml/min/1.73 m²)</th>
<th>Description and range</th>
<th>A1: Normal to mildly increased</th>
<th>A2: Moderately increased</th>
<th>A3: Severely increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or high</td>
<td>≥90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>Mildly decreased</td>
<td>60-89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3a</td>
<td>Mildly to moderately decreased</td>
<td>45-59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3b</td>
<td>Moderately to severely decreased</td>
<td>30-44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>Severely decreased</td>
<td>15-29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
<td>&lt;15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Persistent albuminuria categories

- **A1**: Normal to mildly increased
- **A2**: Moderately increased
- **A3**: Severely increased
- Albuminuria levels:
  - <30 mg/g
  - <3 mg/mmol
  - 30-300 mg/g
  - 3-30 mg/mmol
  - >300 mg/g
  - >30 mg/mmol
At presentation no serum lipid profile is available. A fasting profile is ordered (guideline 1.1).

Why should we measure cholesterol?

Total cholesterol 236 mg/dl, HDL-C 39 mg/dl, Triglyceride 165 mg/dl
LDL-C 142 mg/dl
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Secondary causes of dyslipidemias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Conditions</strong></td>
<td><strong>Excessive alcohol consumption</strong></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
</tbody>
</table>

**Medications**
- 13-cis-retinoic acid
- Anticonvulsants
- Highly active anti-retroviral therapy
- Diuretics
- Beta-blockers
- Androgens
- Oral contraceptives
- Corticosteroids
- Cyclosporine
- Sirolimus

At presentation no serum lipid profile is available. A fasting profile is ordered (guideline 1.1).

1.1: In adults with newly identified CKD (including those treated with chronic dialysis or kidney transplantation), we recommend evaluation with a lipid profile (TC, LDL-C, HDL-C, triglycerides)

1 = we recommend. Most patients should receive the recommended course of action.
C = low quality of evidence. The true effect may be substantially different from the estimate of the effect.
Can I ask you:

“Who wants to treat this patient?“

A) Yes, I treat with a statin

B) I wait and treat at a later timepoint

C) No, I do not treat
   I invest energies and resources into other treatments
Based on large observational studies (posthoc analysis of CKD patients included in RCTs) and on the SHARP study, the responsible physician is in favor of treatment (guideline 2.1.1).

2.1.1: In adults aged ≥50 years with eGFR <60 ml/min/1.73 m² but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), we recommend treatment with a statin or statin/ezetimibe combination.

1 = *we recommend*. Most patients should receive the recommended course of action. 
A = *high quality of evidence*. We are confident that the true effect lies close to that of the estimate of the effect.
SHARP
STUDY OF HEART AND RENAL PROTECTION

Am Heart J 2010;0:1-10.e10.
Lancet 2011;377:2181-2192

Hemodialysis 2.527
Peritonealdialysis 496
CKD 6.029
CKD3b 1.853
CKD4 2.565
CKD5 1.221

20 mg Simvastatin / 10 mg Ezetimibe

n=9.052

versus placebo, median follow-up 4.9 years

Patients: 62 years, 37% women, 23% diabetics,
eGFR 27 ml/min/1.73m² in CKD stages 3-5
SHARP: Major Atherosclerotic Events

Risk ratio 0.83 (0.74 – 0.94)
Logrank 2P=0.0022
(16.5% reduction)

Proportion suffering event (%)

Years of follow-up

Placebo
Eze/simv

Other actions:

Blood pressure lowering medication is intensified.

A control visit is appointed in 3 month for monitoring of albumin excretion and specific serum parameter.
Implementation of the guideline in the Philippines?

Treatment:

What statin or statin/ezitimibe combination is available?

What dose of statin do you select for the patient?
Table 4 | Recommended doses (mg/d) of statins in adults with CKD

<table>
<thead>
<tr>
<th>Statin</th>
<th>eGFR G1-G2</th>
<th>eGFR G3a-G5, including patients on dialysis or with a kidney transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>GP</td>
<td>nd</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>GP</td>
<td>80&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>GP</td>
<td>20&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>GP</td>
<td>10&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Simvastatin/Ezetmibe</td>
<td>GP</td>
<td>20/10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>GP</td>
<td>40</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>GP</td>
<td>40</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>GP</td>
<td>2</td>
</tr>
</tbody>
</table>

Lower doses than those used in major trials of statins in CKD populations may be appropriate in Asian countries.  

1 ALERT, 2 4D, 3 AURORA, 4 SHARP

3 months later the patient is well and has tolerated the medication without adverse effects. He is reassuring that he has taken the lipid lowering medication on most days of the week. Thus we can assume that LDL-C has dropped by about 35% to below 100 mg/dl and we do not order another lipid profile (guideline 1.2).

1.2: In adults with CKD (including those treated with chronic dialysis or kidney transplantation), follow-up measurement of lipid levels is not required for the majority of patients.

Not graded was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence.
Can I ask you:

Are you in agreement with this guideline?

A) Yes, I am happy with this guideline
B) No, I am unhappy and want to remeasure
Why do other guidelines emphasize regular monitoring of LDL-cholesterol?
Why do other guidelines emphasize regular monitoring of LDL-cholesterol?

**ACC/AHA workgroup:**
- (1) A lipid panel should be done 4-12 weeks after initiation of statin therapy to determine a patient’s adherence.
- (2) Down titrating statin dose due to unacceptable adverse effects when taking the recommended intensity of statin therapy (decide on new prescriptions and intensity of therapy).

**KDIGO work group:**
- Random variation in TC on a single measurement is -0.8 to +0.8 mmol/l (-30 to +30 mg/dl)
Use moderate intensity statin therapy  
Avoid high intensity statin therapy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>NHLBI Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Targets</strong></td>
<td></td>
</tr>
<tr>
<td>1. The panel makes no recommendations for or against specific LDL–C or non-HDL–C targets for the primary or secondary prevention of ASCVD.</td>
<td>N (No recommendation)</td>
</tr>
<tr>
<td><strong>Heart Failure and Hemodialysis</strong></td>
<td></td>
</tr>
<tr>
<td>1. The Expert Panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA class II–IV ischemic systolic heart failure or in patients on maintenance hemodialysis.</td>
<td>N (No Recommendation)</td>
</tr>
</tbody>
</table>
Further result of this visit:

Albuminuria decreased to < 0.5 g/g
Blood pressure is well controlled (130/80 mmHg).
S-creatinine increased by 0.2 mg/dl (eGFR 39 ml/min/1.73m²).

Another visit was appointed 6 months later.
6 month later: Mr N. meanwhile has seen his GP, but „he has forgotten to measure cholesterol.“

We declare that a repeated measurement of 'cholesterol' is not necessary, because no further consequences arise (an increase in dose should not be done due to safety concerns). We are certain that the prescribed medication is effective.

Mr N. declares that he does not experience any effect and insists in knowing his cholesterol level, because otherwise he would not take a drug for nothing!

(Rationale of guideline 1.2): "Physicians may choose to perform follow-up measurement of lipid levels in patients for whom these measurements are judged to favorably influence processes of care".
The measurement resulted in:

- TC: 165 mg/dl
- HDL-C: 35
- Triglyceride: 189
- LDL-C: 92
**Case 2:** A 78 year old female patient has acute on chronic kidney failure and remains with ESRD. She did not take a statin in the past. Should we start statin therapy?

**2A**

**2.3.1:** In adults with dialysis-dependent CKD we suggest that statins or statin/ezetimibe combination **not** be initiated.

2 = we suggest. Different choices will be appropriate for different patients. Each patients needs help to arrive at a management decision consistent with her or his values and preferences.

A = *high quality of evidence*. We are confident that the true effect lies close to that of the estimate of the effect.
Case 2: A 78 year old female patient has acute on chronic kidney failure and remains with ESRD. She did not take a statin in the past. Should we start statin therapy?

Can I ask you:

Do you want to treat this patient with a statin?

A) Yes I will treat her with a statin
B) No I do not treat her
Case 2: A 78 year old female patient has acute on chronic kidney failure and remains with ESRD. She did not take a statin in the past. Should we start statin therapy?

2A

2.3.1: In adults with dialysis-dependent CKD we suggest that statins or statin/ezetimibe combination not be initiated.

2 = we suggest. Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.

A = high quality of evidence. We are confident that the true effect lies close to that of the estimate of the effect.
RCTs in hemodialysis patients have shown no benefits of statins

Wanner et al, NEJM 2005; Fellström B et al, NEJM 2009
# SHARP: Major Atherosclerotic Events by renal status at randomization

<table>
<thead>
<tr>
<th></th>
<th>Eze/simv (n=4650)</th>
<th>Placebo (n=4620)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-dialysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=6247)</td>
<td>296 (9.5%)</td>
<td>373 (11.9%)</td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=3023)</td>
<td>230 (15.0%)</td>
<td>246 (16.5%)</td>
<td></td>
</tr>
<tr>
<td>Major atherosclerotic event</td>
<td>526 (11.3%)</td>
<td>619 (13.4%)</td>
<td>16.5% SE 5.4 reduction (p=0.0022)</td>
</tr>
</tbody>
</table>

No significant heterogeneity between non-dialysis and dialysis patients (p=0.25)

* LDL-Reduction: 37 mg/dl (0.96 mmol/l)

** LDL-Reduction: 23 mg/dl (0.60 mmol/l)

Baigent et al, Lancet 2011
Mr. N will one day, most likely, progress to end-stage renal disease and will require renal replacement therapy.

2.3.2: In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, we suggest that these agents be continued.

2 = we suggest. Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.

C = low quality of evidence. The true effect may be substantially different from the estimate of the effect.
2.3.2: Rationale

- SHARP, 4D and AURORA don’t address this issue

- 2141 (34%) of SHARP participants in non-dialysis group initiated dialysis during follow-up
  - benefit observed in non-dialysis group for SHARP

- Reasonable to continue statins
  - recognize that benefits may be lower than in ND pts
  - could discontinue if patient preferences warrant it
2.1.2: In adults aged ≥50 years with CKD and eGFR ≥60 ml/min/1.73 m² (GFR categories G1-G2) we recommend treatment with a statin.

2.2: In adults aged 18-49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest statin treatment in people with one or more of the following:
- 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%
Alberta Kidney Disease Kohorte (n=1,268,029)

CKD: eGFR 15-59,9 ml/min/1,73m²
2.4: In adult kidney transplant recipients, we suggest treatment with a statin.

5.1: In adults with CKD (including those treated with chronic dialysis or kidney transplantation) and hypertriglyceridemia, we suggest that therapeutic lifestyle changes be advised.
Contributors

Guideline Chairs
Marcello Tonelli (Canada)
Christoph Wanner (Germany)

Work Group
- Alan Cass (Australia)
- Amit Garg (Canada)
- Hallvard Holdaas (Norway)
- Alan Jardine (UK)
- Lixin Xiang (China)
- Florian Kronenberg (Austria)
- Rulan Parekh (Canada)
- Tetsuo Shoji (Japan)
- Robert Walker (New Zealand)

Evidence Review Team
- Ashish Upadhyay
- Ethan Balk
- Amy Earley
- Shana Haynes

KDIGO Staff
- Michael Cheung

KDIGO Chairs
- Bertram Kasiske (USA)
- David Wheeler (UK)
KDIGO is the world’s only organization developing and implementing global guidelines in kidney disease. It was founded on the principle that science is not regional or country specific. Rather it is global in nature; only implementation should be locally designed to take into account variations in practice and medication availability.
😊 Thank you for your attention!