Management of Patients with Chronic Kidney Disease
Hint: Its all about the heart!
Case Authors

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Sunnybrook Health Sciences Centre, University of Toronto

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Editorial Project Manager: Diane Hua, MPH
Which of the following is most correct

a) Chronic kidney disease and albuminuria increase the risk of progressing to dialysis more than the risk of developing cardiovascular diseases

b) The CCS Lipid Guidelines recognize CKD as a high CV risk category

c) Only very low dose statins should be used in CKD
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Faculty/Presenter Disclosure
Slide 1

• Presenter:
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  Northern Ontario School of Medicine

• Relationships with commercial interests:
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  – **Consulting Fees:** None
Disclosure of Commercial Support
Slide 2

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• Potential for conflict(s) of interest:
  – None to declare
Case 4: Cardiovascular Management of Patients with Chronic Kidney Disease

Donald

A 55 year old man with a previous left nephrectomy and hypertension comes to your office after moving into the neighbourhood
Learning Objectives

Upon completion of this activity, participants should be able to:

1. Identify a patient with chronic kidney disease.
2. Formulate a treatment plan for cardiovascular risk reduction using the C-CHANGE guidelines including BP control and lipid management.
3. Communicate and initiate the treatment plan to reduce cardiovascular risk in patients with chronic kidney disease.
Donald is a 55 year old man with a remote history of a nephrectomy for renal cell carcinoma and a 10 year history of hypertension. He presents to your office for routine review after moving into your neighbourhood.
Past History

• Donald was recruited into the Study of Heart and Renal Protection (SHARP) study in 2005 and remained in the study on therapy until 2010
• He wants to know if the study results apply to him and if he should now be on therapy
• His blood pressure has been controlled on a CCB and an ACEi for 10 years
• He is a non-smoker, with social alcohol use
• Separated with 2 adult children.
Family History

• Father
  – Died at age 58 from a stroke

• Mother
  – Remains well, but is hypertensive

• Three older brothers have all had hypertension and non-fatal cardiovascular disease
Current Medications

- amlodipine 10 mg/d
- perindopril 8 mg/d
- ECASA 81 mg/d
Physical Examination

- Height: 178 cm
- Weight: 75 kg
- BMI: 24 kg/m²
- BP (left arm, seated): 148/92 mmHg using an automated device while the patient is unattended
- Funduscopic: normal
- Neck-Thyroid palpable, no nodule
- Heart: Normal
- Lungs: Normal
- Abdomen: no murmurs
- Arteries: Normal
- Ankle edema: nil
- Neuro: normal
# Lab Tests in 2010

<table>
<thead>
<tr>
<th></th>
<th>Current</th>
<th>One year ago</th>
<th>Two years ago</th>
<th>Three years ago</th>
<th>Four years ago</th>
<th>Five years ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>10.5</td>
<td>10</td>
<td>12.6</td>
<td>10.7</td>
<td>8.4</td>
<td>10.4</td>
</tr>
<tr>
<td>Creat</td>
<td>157</td>
<td>151</td>
<td>190</td>
<td>170</td>
<td>165</td>
<td>186</td>
</tr>
<tr>
<td>Hb</td>
<td>155</td>
<td>149</td>
<td>166</td>
<td>153</td>
<td>152</td>
<td>152</td>
</tr>
</tbody>
</table>
Question 1

After completing your introduction and orientation to your office and your initial evaluation, you turn to Donald’s blood pressure.

Donald’s current blood pressure is 148/92 mmHg. What is the target BP?
Question 1. This patient has CKD and no diabetes, what is his target BP?

a) $<140/90$ mmHg
b) $<135/85$ mmHg
c) $<130/80$ mmHg
d) $<120$ mmHg
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Question 1. This patient has hypertension CKD with no diabetes, what is his target BP?

a) < 140/90 Incorrect since 2016
Question 1. This patient has hypertension CKD with no diabetes, what is his target BP?

c) < 130/80 Incorrect

• CHEP had this as a target in the past.
• However, data from the AASK study and the REIN2 study did not demonstrate that lower BP targets improved renal outcomes in patients with CKD
• These studies were not powered for CV outcomes
Competing Risk

Vs
Competing Risk

Vs
Question 1. This patient has hypertension CKD with no diabetes, what is his target BP?

d) <120 mmHg

Correct

Treatment Targets: Hypertension and CKD
• The SPRINT study included a renal subgroup demonstrating that the lower BP target resulted in improved CV outcomes
• Renal outcomes were not improved and there were more people with rises in creatinine and in acute kidney injury
New thresholds/targets for the high risk patient post-SPRINT: who does this apply to??

- Clinical or sub-clinical cardiovascular disease
  OR
- **Chronic kidney disease** (non-diabetic nephropathy, proteinuria <1 g/d, *estimated glomerular filtration rate 20-59 mL/min/1.73m²*)
  OR
- †Estimated 10-year global cardiovascular risk ≥15%
  OR
- Age ≥ 75 years

Patients with one or more clinical indications should consent to intensive management.

* Four variable MDRD equation
† Framingham Risk Score, D’Agostino, Circulation 2008

Sprint Study, NEJM, November 9 2015
Recommended Office BP Treatment Targets

Treatment consists of health behaviour ± pharmacological management

<table>
<thead>
<tr>
<th>Population</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>≤120</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes</td>
<td>&lt; 130</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>All others*</td>
<td>&lt; 140</td>
<td>&lt; 90</td>
</tr>
</tbody>
</table>

* Target BP with AOBP < 135/85
Maintenance of GFR with changes in BP

Palmer BF, NEJM, 347(16), 1256
Maintenance of GFR with changes in BP

Palmer BF, NEJM, 347(16), 1256
Question 2
This patient asked about whether he should be on lipid lowering therapy after the SHARP study had completed. What do you tell him?
Question 2) This patient asked about whether he should be on lipid lowering therapy after the SHARP study had completed. What do you tell him?

a) Tell the patient he is only intermediate risk and doesn’t need to worry

b) Tell the patient that because of his kidney disease he is at high CV risk and needs to lower his LDL < 2.0 mmol/L or ≥ 50% reduction

c) Tell the patient that he is at high CV risk and needs to lower his LDL < 3.0 mmol/L or ≥ 25% reduction
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Question 2) This patient asked about whether he should be on lipid lowering therapy after the SHARP study had completed. What do you tell him?

a) Tell the patient he is only intermediate risk and doesn’t need to worry
We recommend a statin or a statin/ezetimibe combination in adults 50 years of age and older with CKD not treated with dialysis or a kidney transplant:

- an eGFR < 60 ml/min/1.73 m²
- or

- In those with preserved eGFR urinary albumin:creatinine ratio (≥ 3 mg/mmol) for at least 3 months duration

Anderson TJ, CJC, 2016 Nov 32 1263-82
## Distribution of Albuminuria and Low eGFR in the US

<table>
<thead>
<tr>
<th>US Population</th>
<th>Normal Albuminuria</th>
<th>Abnormal albuminuria (ACR &gt; 3)</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR 60+</td>
<td>86%</td>
<td>7%</td>
<td>93%</td>
</tr>
<tr>
<td>eGFR &lt; 60</td>
<td>5%</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>All</td>
<td>91%</td>
<td>9%</td>
<td>100%</td>
</tr>
</tbody>
</table>

What is Don’s eGFR

Creatinine recently 155
Weight 78 kg
Race: African American
Age 55
eGFR = 50 by CKD Epi

https://www.kidney.org/professionals/kdoqi/gfr_calculator
Question 2) This patient asked about whether he should be on lipid lowering therapy after the SHARP study had completed. What do you tell him?

a) Tell the patient he is only intermediate risk and doesn’t need to worry

Incorrect: This patient meets the criteria for high CV risk and statin therapy (eGFR < 60 ml/min)
Question 2) This patient asked about whether he should be on lipid lowering therapy after the SHARP study had completed. What do you tell him?

b) Tell the patient that because of his kidney disease he is at high CV risk and needs to lower his LDL < 2.0 mmol/L or > 50% reduction
1,120,295 Ambulatory Adults

Death

CV Events

Hospitalization

Mortality and End Stage Renal Disease by baseline GFR x Albuminuria data from ONTARGET study

1. Dialysis << death for all but macroalbuminuria
2. Both low GFR and albuminuria significantly increase the risk of death

Tobe, SW, Circulation 2011: 123:1098-1107
CKD and AF: Outcomes

- Retrospective cohort from Alberta Health administrative database
- All adult Albertans with new Afib from 2002 to 2013
- Excluded valvular AF or ESRD
- Anticoagulant naïve on diagnosis
- 58,451 in cohort
- Mean age 66, 47% female

McAlister F, CJC, 2016
Hazard Ratio by eGFR for Outcome in Albertans with non-Valvular AFib

McAlister F, CJC, 2016
Summary of CV Risk in CKD

• Patients with CKD are at higher risk of CV events
• Their risk of CV events is much higher than their risk of renal events
Question 2) This patient asked about whether he should be on lipid lowering therapy after the SHARP study had completed. What do you tell him?

b) Tell the patient that because of his kidney disease he is at high CV risk and needs to lower his LDL < 2.0 mmol/L or > 50% reduction

Correct
Question 3

What Therapy should the patient be started on for lipid management?
Question 3) What therapy should the patient be started on for lipid management?

a) Sufficient therapy to achieve targets
b) Only low dose statin or fibric acid derivative
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Question 3) What therapy should the patient be started on for lipid management?

a) Sufficient therapy to achieve targets
Study of Heart and Renal Protection (SHARP)

• Largest study of lipid-lowering therapy in CKD patients
• 9,438 CKD patients without overt CVD
  – 6,382 patients with stage 3-5 CKD not on dialysis
  – 3,056 patients on dialysis
• Ezetimibe 10 mg/simvastatin 20 mg vs. placebo
SHARP: Study of Heart and Renal Protection Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with Chronic Kidney Disease

SHARP Collaborative Group

- Key outcome
  - Major atherosclerotic events (coronary death, MI, non-haemorrhagic stroke, or any revascularization)

- Subsidiary outcomes
  - Major vascular events (cardiac death, MI, any stroke, or any revascularization)
  - Components of major atherosclerotic events

- Main renal outcome
  - End stage renal disease (dialysis or transplant)
Kaplan-Meier of protocol-specified Primary Endpoint (Major Atherosclerotic Events)

### SHARP:
**Major Atherosclerotic Coronary Events and Major Vascular Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>eze/simva (n=4650)</th>
<th>placebo (n=4620)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event</td>
<td>213 (4.6%)</td>
<td>230 (5.0%)</td>
<td>0.83 (0.74-0.94)</td>
</tr>
<tr>
<td>Non-hemorrhagic stroke</td>
<td>131 (2.8%)</td>
<td>174 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Any revascularization procedure</td>
<td>284 (6.1%)</td>
<td>352 (7.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Major Atherosclerotic Event</strong></td>
<td>526 (11.3%)</td>
<td>619 (13.4%)</td>
<td>0.85 (0.77-0.94)</td>
</tr>
<tr>
<td>Other cardiac death</td>
<td>162 (3.5%)</td>
<td>182 (3.9%)</td>
<td>0.94 (0.78-1.14)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>45 (1.0%)</td>
<td>37 (0.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Other Major Vascular Events</strong></td>
<td>207 (4.5%)</td>
<td>218 (4.7%)</td>
<td></td>
</tr>
<tr>
<td>Major Vascular Event</td>
<td>701 (15.1%)</td>
<td>814 (17.6%)</td>
<td></td>
</tr>
</tbody>
</table>

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>
</tr>
</thead>
<tbody>
<tr>
<td>Non-dialysis (n=6247)</td>
<td>296 (9.5%)</td>
<td>373 (11.9%)</td>
</tr>
<tr>
<td>Dialysis (n=3023)</td>
<td>230 (15.0%)</td>
<td>246 (16.5%)</td>
</tr>
<tr>
<td>Major atherosclerotic event</td>
<td>526 (11.3%)</td>
<td>619 (13.4%)</td>
</tr>
</tbody>
</table>

Risk ratio & 95% CI

0.6 0.8 1.0 1.2 1.4

Eze/simv better
Placebo better

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

16.5% SE 5.4 reduction (p=0.0022)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Eze/simv (n=4650)</th>
<th>Placebo (n=4620)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK &gt;10 x but ≤40 x ULN</td>
<td>17 (0.4%)</td>
<td>16 (0.3%)</td>
</tr>
<tr>
<td>CK &gt;40 x ULN</td>
<td>4 (0.1%)</td>
<td>5 (0.1%)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>21 (0.5%)</td>
<td>18 (0.4%)</td>
</tr>
<tr>
<td>Persistently elevated ALT/AST &gt;3x ULN</td>
<td>30 (0.6%)</td>
<td>26 (0.6%)</td>
</tr>
<tr>
<td>Complications of gallstones</td>
<td>85 (1.8%)</td>
<td>76 (1.6%)</td>
</tr>
<tr>
<td>Other hospitalization for gallstones</td>
<td>21 (0.5%)</td>
<td>30 (0.6%)</td>
</tr>
<tr>
<td>Pancreatitis without gallstones</td>
<td>12 (0.3%)</td>
<td>17 (0.4%)</td>
</tr>
</tbody>
</table>

• We recommend treatment with a statin or a statin/ezetimibe combination to reduce CVD events in adults 50 years of age and older with CKD not treated with dialysis or a kidney transplant.
Case progression

• Donald is pleased to know the results of the SHARP study and the resulting new lipid guidelines.

• He is started on a statin (atrovastatin 10 mg/d) and ezetrol 10 mg/d and achieves an LDL < 2.0 mmol/L. He tolerates the therapy with no increase in muscle aches and cramping from his usual baseline and no GI upset from ezetrol.
Kidney disease is prevalent
- 7% with abnormal albuminuria and normal eGFR
- Another 7% with eGFR < 60 ml/min
- Albuminuria and low eGFR are both markers of renal and CVD risk
- CV risk in CKD
Learning Objectives

Upon completion of this activity, participants should be able to:

- 1. Identify a patient with chronic kidney disease.
- 2. Formulate a treatment plan for cardiovascular risk reduction using the C-CHANGE guidelines including BP control and lipid management.
- 3. Communicate and initiate the treatment plan to reduce cardiovascular risk in patients with chronic kidney disease.
Which of the following is most correct

a) Chronic kidney disease and albuminuria increase the risk of progressing to dialysis more than the risk of developing cardiovascular diseases

b) The CCS Lipid Guidelines recognize CKD as a high CV risk category

c) Only very low dose statins should be used in CKD
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SHARP: Major Atherosclerotic Events by CKD

<table>
<thead>
<tr>
<th>MDRD estimated GFR (mL/min/1.73m²)</th>
<th>eze/simva (n=4650)</th>
<th>placebo (n=4620)</th>
<th>Risk ratio &amp; 95% CI</th>
<th>P value for Het/Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60 (stage 2)</td>
<td>3 (6.8%)</td>
<td>3 (6.8%)</td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>≥ 45&lt; 60 (stage 3a)</td>
<td>6 (4.2%)</td>
<td>17 (10.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30 &lt;45 (stage 3b)</td>
<td>81 (8.5%)</td>
<td>93 (10.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 15 &lt;30 (stage 4)</td>
<td>127 (10.2%)</td>
<td>168 (12.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15 (stage 5)</td>
<td>67 (10.9%)</td>
<td>81 (13.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Subtotal: Not on dialysis 296 (9.5%) 373 (11.9%) 0.78 (0.67-0.91) p=0.0016

Dialysis
- Hemodialysis 194 (15.2%) 199 (15.9%) 0.21
- Peritoneal dialysis 36 (14.0%) 47 (19.7%) 0.90 (0.75-1.08) p=0.25

Subtotal: On dialysis 230 (15.0%) 246 (16.5%) 0.83 (0.74-0.94) p=0.0021

Major atherosclerotic event 526 (11.3%) 619 (13.4%)