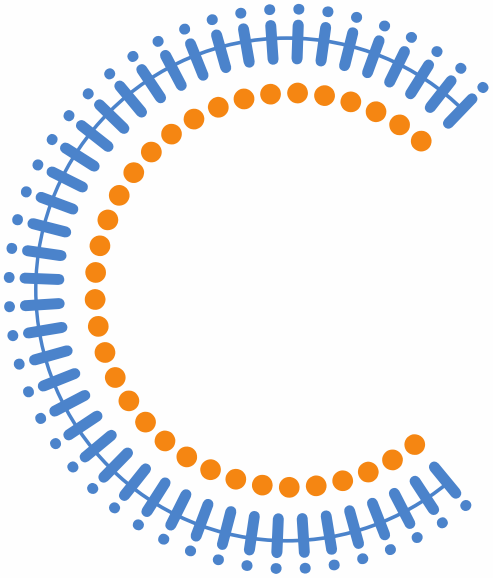

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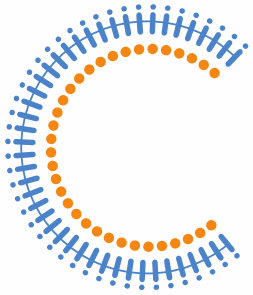

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The Patient with CKD
Case Module 4:
Cardiovascular Management of Patients with Chronic Kidney Disease

Case Development & Disclosures

C•CHANGE

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- Karen Mann, BN, MSc, PhD

Outline of Today's Activity

C•CHANGE

- Introduction
- Case Presentation
- Key Learnings & Questions
- Wrap Up

Northern Ontario School of Medicine

École de médecine du Nord de l'Ontario

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CEPD
continuing education and professional development

Faculty/Presenter Disclosure Slide 1

- **Presenter:**

- **Relationships with commercial interests:**
  - **Grants/Research Support:**
  - **Speakers Bureau/Honoraria:**
  - **Consulting Fees:**

Northern Ontario School of Medicine

École de médecine du Nord de l'Ontario

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CEPD
continuing education and professional development

Disclosure of Commercial Support Slide 2

- **This program has received financial support from** Public Health Agency of Canada, Ontario Ministry of Health and Long-Term Care **in the form of** educational grants.
- **This program has received in-kind support from** C-CHANGE **in the form of** content management, logistical and project support.

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- Altering control over content: information and recommendations given in the program are evidence based and sourced from multiple clinical practice guidelines/scientific professional associations.
- Program material is peer reviewed by a committee with members representative of the target audience.

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Case 5:
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

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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

Statement of Need

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"My greatest challenge as a health care professional in the cardiovascular management of patients with ***Chronic Kidney Disease*** *is _____"*

History of Present Illness

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- 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

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- 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

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- 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/m^2
- 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

	Current	One year ago	Two years ago	Three years ago	Four years ago	Five years ago
Urea	10.5	10	12.6	10.7	8.4	10.4
Creat	157	151	190	170	165	186
Hb	155	149	166	153	152	152

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 for Tom?

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

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a) <140/90 mmHg

b) <135/85 mmHg

c) <130/80 mmHg

d) <120/80 mmHg

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

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a) < 140/90 Incorrect since 2016

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

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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

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

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d) <120/80 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/1.73m^2**)

  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'Agastino, Circulation 2008

Sprint Study, NEJM, November 9 2015

Recommended Office BP Treatment Targets

Treatment consists of health behaviour ± pharmacological management

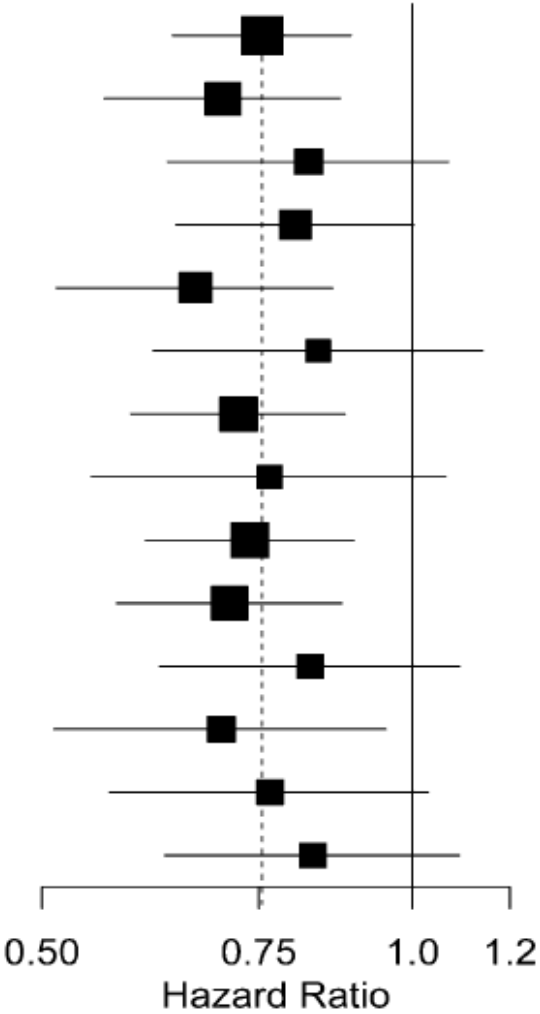
Population	SBP	DBP
High Risk	≤120	NA
Diabetes	< 130	< 80
All others*	< 140	< 90

* Target BP with AOBP < 135/85

SPRINT Primary outcomes in pre-specified subgroups of interest

Subgroup	HR	P*
Overall	0.75 (0.64,0.89)	
No Prior CKD	0.70 (0.56,0.87)	0.36
Prior CKD	0.82 (0.63,1.07)	
Age < 75	0.80 (0.64,1.00)	0.32
Age ≥ 75	0.67 (0.51,0.86)	
Female	0.84 (0.62,1.14)	0.45
Male	0.72 (0.59,0.88)	
African−American	0.77 (0.55,1.06)	0.83
Non African−American	0.74 (0.61,0.90)	
No Prior CVD	0.71 (0.57,0.88)	0.39
Prior CVD	0.83 (0.62,1.09)	
SBP ≤ 132	0.70 (0.51,0.95)	0.77
132 < SBP < 145	0.77 (0.57,1.03)	
SBP ≥ 145	0.83 (0.63,1.09)	

*Treatment by subgroup interaction
*Unadjusted for multiplicity



SPRINT
Systolic Blood Pressure Intervention Trial

The SPRINT Research Group, NEJM, Nov 9th, 2015

SPRINT Primary outcomes in pre-specified subgroups of interest

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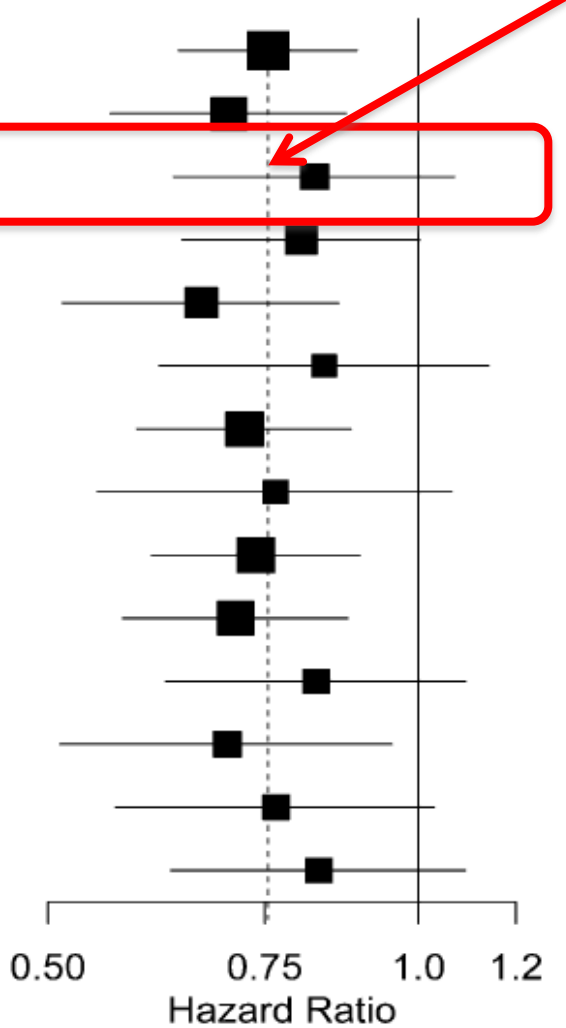
*Treatment by subgroup interaction
*Unadjusted for multiplicity



SPRINT
Systolic Blood Pressure Intervention Trial

The SPRINT Research Group, NEJM, Nov 9th, 2015

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?

C•CHANGE

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 $\leq$ 2.0 mmol/L or $\geq$ 50% reduction

c) Tell the patient that he is at high CV risk and needs to lower his LDL $\leq$ 3.0 mmol/L or $\geq$ 25% reduction

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?

C•CHANGE

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

CCS Lipid Guidelines 2016 Statin-Indicated Conditions

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- We recommend management that includes statin therapy in high-risk conditions to decrease the risk of CVD events and mortality including:
  - clinical atherosclerosis,
  - abdominal aortic aneurysm,
  - most DM,
  - CKD (age older than 50 years),
  - LDL-C 5.0 mmol/L
- 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
  - an eGFR <60 ml/min/1.73 m^2
  - In those with preserved eGFR urinary albumin:creatinine ratio (≥ 3 mg/mmol) for at least 3 months duration

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Conditions for which pharmacotherapy with statins is indicated

CLINICAL ATHEROSCLEROSIS

Myocardial infarction, acute coronary syndromes
Stable angina, documented coronary disease by angiography (>10% stenoses)
Stroke, TIA, documented carotid disease
Peripheral artery disease, claudication and/or ABI < 0.9

ABDOMINAL AORTIC ANEURYSM

Abdominal aorta > 3.0 cm or
Previous aneurysm surgery

DIABETES MELLITUS

≥ 40 years of age or
> 15 years duration and age ≥ 30 years or
Microvascular complications

CHRONIC KIDNEY DISEASE

> 3 months duration and
ACR > 3.0 mg/mmol or
eGFR < 60 ml/min/1.73m^2

LDL-C ≥ 5.0 MMOL/L

LDL-C ≥ 5.0 mmol/L or
Document familial hypercholesterolemia
Excluded 2nd causes

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Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30-300 mg/g 3-30 mg/mmol	A3 Severely increased >300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

KDIGO CKD management KI 2013 3(1)

Distribution of Albuminuria and Low eGFR in the US

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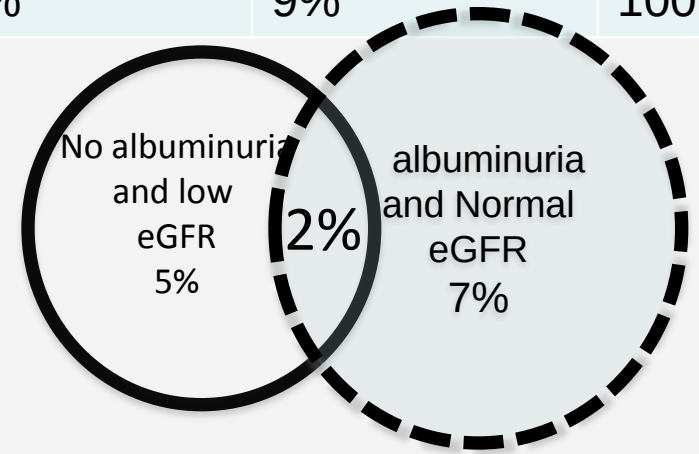
US Population	Normal Albuminuria	Abnormal albuminuria (ACR > 3)	All
eGFR 60+	86%	**7%**	93%
eGFR < 60	5%	2%	**7%**
All	91%	9%	100%

Low eGFR<60 7%



Total Albuminuria 9%

Data from NHANESIII: Adapted from
Levey A and Coresh J, Lancet 2012, vol 379. 165-180 and Garg AX KI 2002, vol 61. 2165-2175

What is Don's eGFR

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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?

C•CHANGE

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?

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

Relationship Between eGFR and Clinical and Cardiovascular Outcomes

Age-Adjusted Death, Cardiovascular Events Hospitalization in Chronic Kidney Disease

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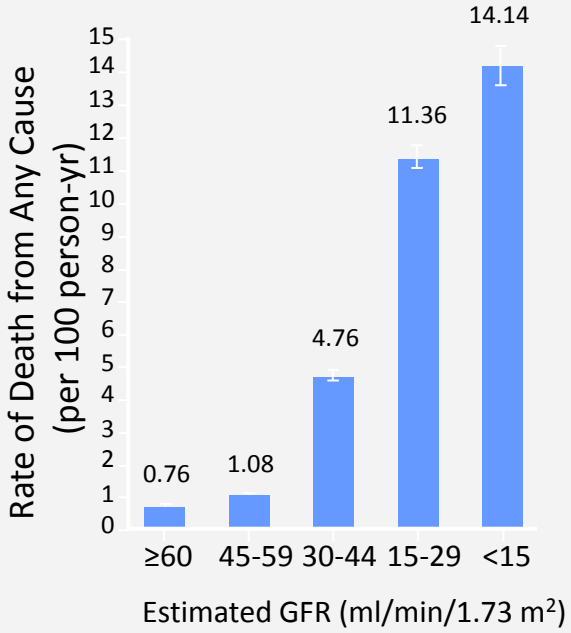
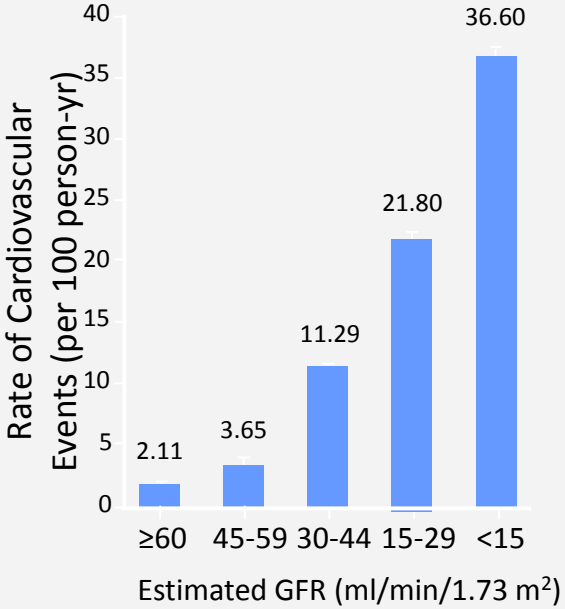
1,120,295 Ambulatory Adults

Death



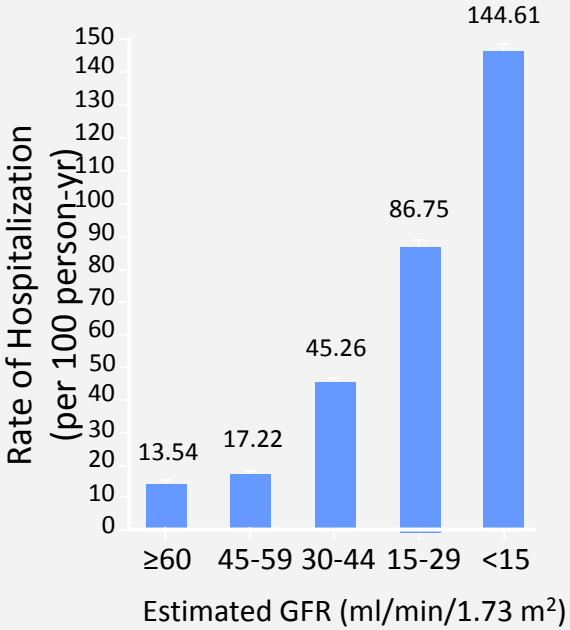
	≥60	45-59	30-44	15-29	<15
No. of Events	25,803	11,569	7802	4408	1842

CV Events



	≥60	45-59	30-44	15-29	<15
No. of Events	73,108	34,690	18,580	8809	3824

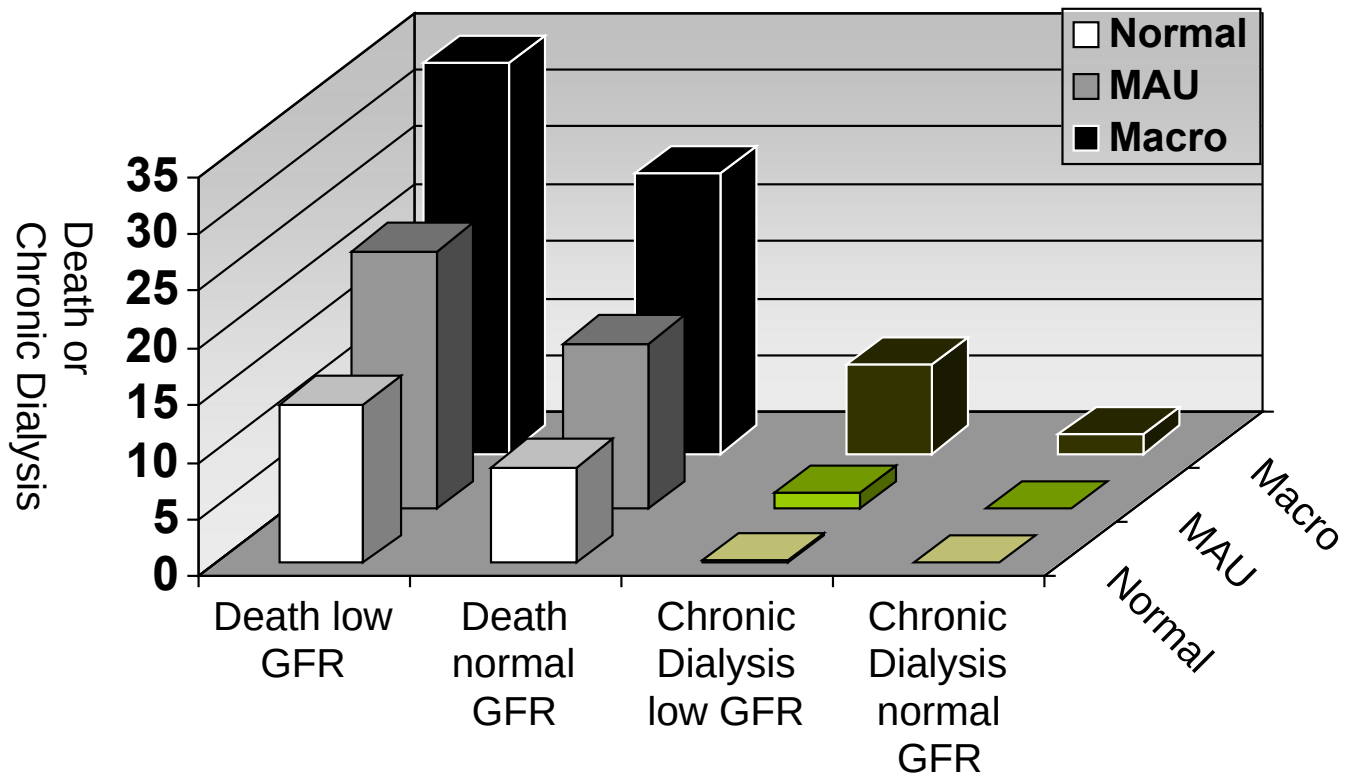
Hospitalization



	≥60	45-59	30-44	15-29	<15
No. of Events	366,757	106,543	49,177	20,581	11,593

Go et al. N. Engl. J. Med 351:1296, 2004

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

Online supplement: http://circ.ahajournals.org/content/suppl/2011/02/24/CIRCULATIONAHA.110.964171.DC1

Summary of CV Risk in CKD

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- Patients with CKD are at higher risk of CV events
- Their risk of CV events is much higher than their risk of renal events

CCS Lipid Guidelines for High CV Risk

- We recommend a target LDL-C $\leq$ 2.0 mmol/L or > 50% reduction of LDL-C for high risk individuals in whom treatment is initiated to decrease the risk of CVD events and mortality

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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?

C•CHANGE

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

Correct

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?

C•CHANGE

c) Tell the patient that he is at high CV risk and needs to lower his LDL $\leq$ 3.0 mmol/L or $\geq$ 25% reduction

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?

C•CHANGE

a) Sufficient therapy to achieve targets

b) Only low dose statin or fibric acid derivative

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

C•CHANGE

a) Sufficient therapy to achieve targets

Study of Heart and Renal Protection (SHARP)

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- 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

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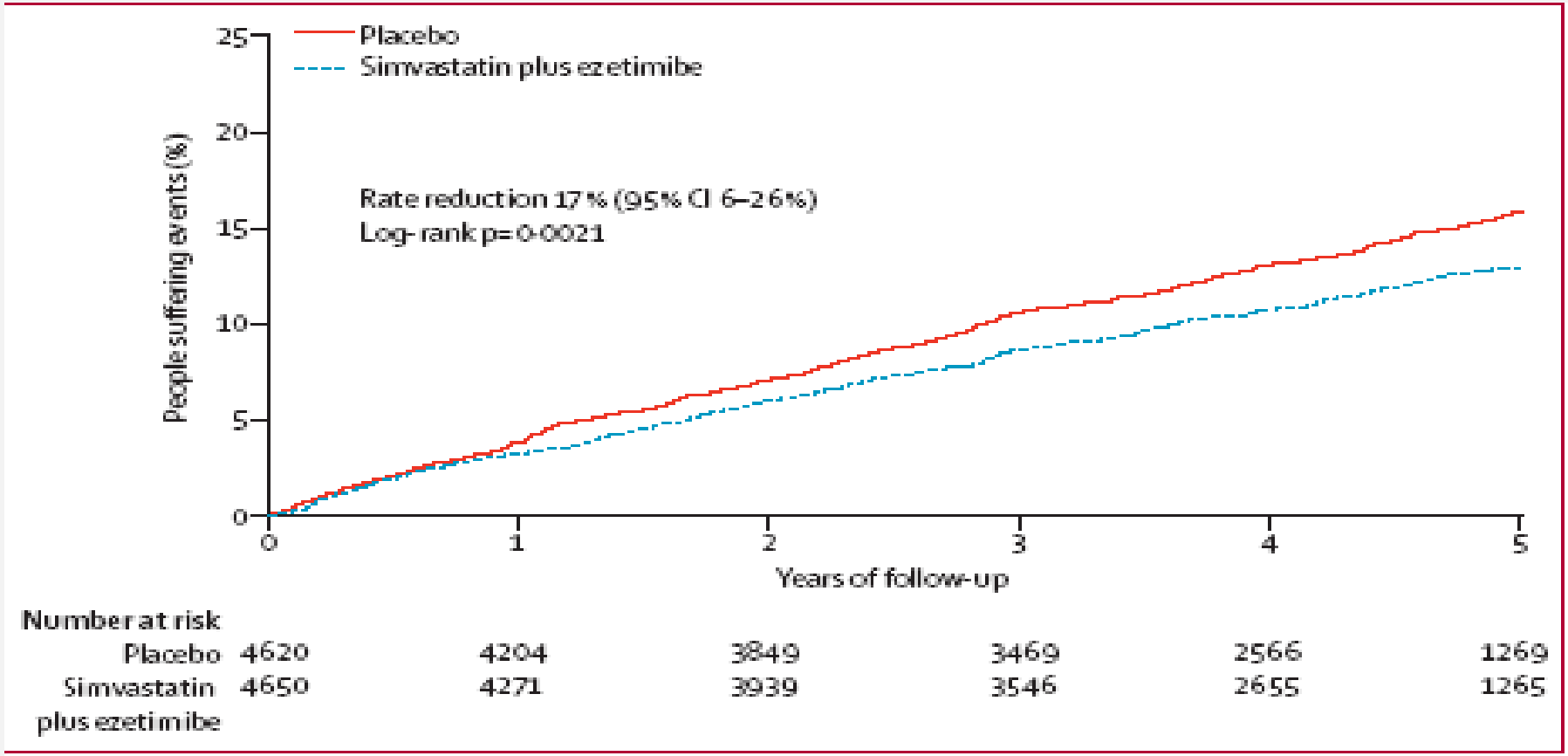
SHARP Collaborative Group

- 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)

Baigent et al. Lancet 2011; 377(11):2181-92

Kaplan-Meier of protocol-specified Primary Endpoint (Major Atherosclerotic Events)



Baigent C et al *Lancet* 2011; 377: 2181–92

SHARP: Major Atherosclerotic Coronary Events and Major Vascular Events

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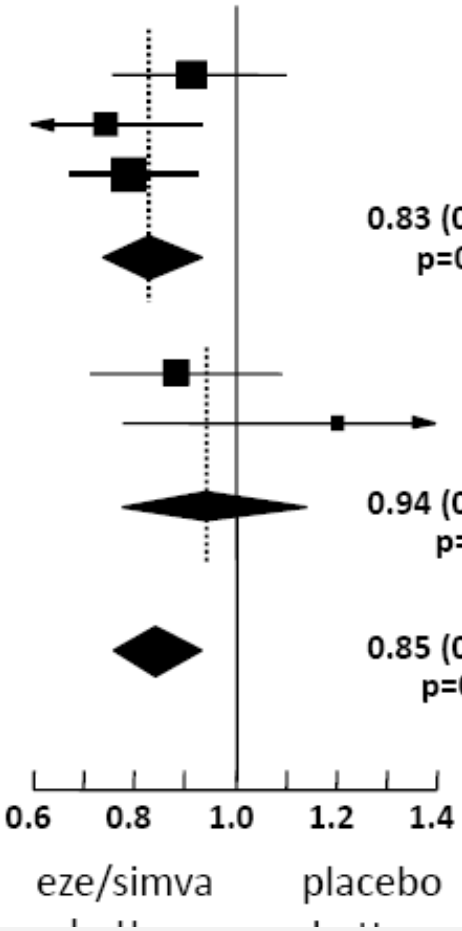
Event	eze/simva (n=4650)		placebo (n=4620)		Risk ratio & 95% CI
Major coronary event	213	(4.6%)	230	(5.0%)	
Non-hemorrhagic stroke	131	(2.8%)	174	(3.8%)	
Any revascularization procedure	284	(6.1%)	352	(7.6%)	
Major Atherosclerotic Event	**526**	**(11.3%)**	**619**	**(13.4%)**	**0.83 (0.74-0.94) p=0.0021**
Other cardiac death	162	(3.5%)	182	(3.9%)	
Hemorrhagic stroke	45	(1.0%)	37	(0.8%)	
Other Major Vascular Events	**207**	**(4.5%)**	**218**	**(4.7%)**	**0.94 (0.78-1.14) p=0.56**
Major Vascular Event	**701**	**(15.1%)**	**814**	**(17.6%)**	**0.85 (0.77-0.94) p=0.0012**

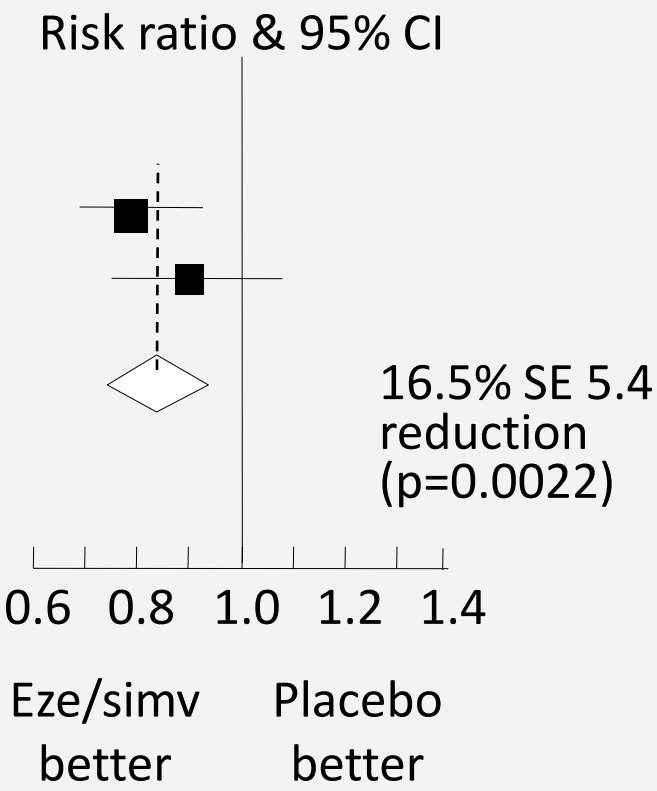


Baigent C et al *Lancet* 2011; 377: 2181–92

SHARP: Major Atherosclerotic Events by renal status at randomization

	Eze/simv (n=4650)	Placebo (n=4620)
Non-dialysis (n=6247)	296 (9.5%)	373(11.9%)
Dialysis (n=3023)	230(15.0%)	246(16.5%)
Major atherosclerotic event	526(11.3%)	619(13.4%)

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



Baigent et al. Lancet 2011; 377(11):2181-92

SHARP: Safety

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

Baigent et al. Lancet 2011; 377(11):2181-92

CCS Lipid Guidelines for High CV Risk

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

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

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b) Only low dose statin or fibric acid derivative

Safety Issues According to Product Monograph

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	GFR 60-90 (Mild)	GFR 30-60 (Moderate)	GFR 15-30 (Severe)	GFR <15 (ESRD)	NOTES
Atorvastatin	OK	10 mg	10 mg		
Rosuvastatin	OK	OK	10 mg		
Simvastatin	OK	OK	5mg		
Ezetimibe	OK	OK	OK		
Fibrate	↓ 50%	↓ 75%	AVOID	AVOID	Increases creatinine in CKD
Bile Acid Sequestrant	OK	OK	OK		

Atorvastatin Product Monograph Canada Feb 2016
Rosuvastatin Product Monograph Canada April 2015
Simvastatin Product Monograph Canada Dec 2014
Ezetimibe Product Monograph Canada March 2012

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.

Discussion & Reflection

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1. Do you need to change your current practice to implement any of these recommendations?
2. How do you engage patients and their families in therapy and manage expectations?
3. What are some other adherence strategies that were discussed or not discussed that could work for your practice?
4. Who are some agents of change who can help you implement the recs?

Key Learnings:

- 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

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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

Additional Slides

The C-Change Collaborative

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Founding Partners

- Institute of Circulatory and Respiratory Health (ICRH) and the Public Health Agency of Canada (PHAC)

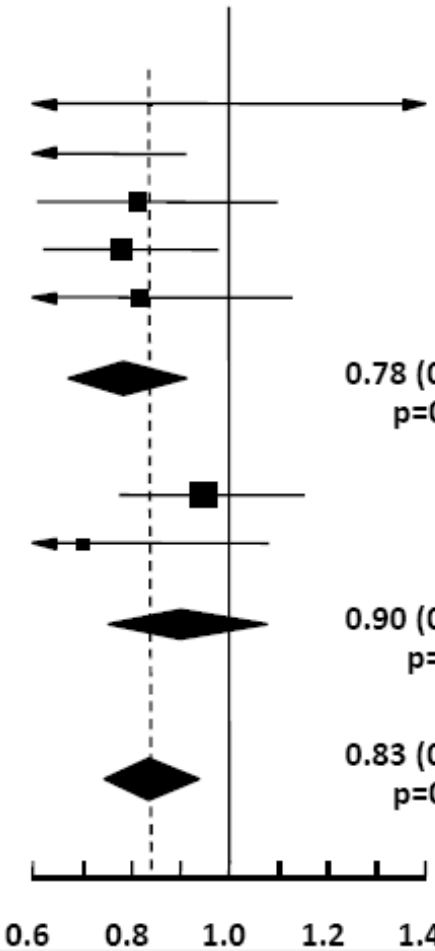
Partner Organizations

- **Canadian Association for Cardiac Rehabilitation (CACR)**
- **Canadian Action Network for the Advancement, Dissemination and Adoption of Practice-informed Tobacco Treatment (CAN ADAPTT)**
- **Canadian Cardiovascular Society (CCS) - Lipids**
- **Canadian Diabetes Association (CDA)**
- **Canadian Hypertension Education Program (CHEP)**
- **Canadian Society for Exercise Physiology (CSEP)**
- **Canadian Stroke Network (CSN)**
- Cardiac Care Network of Ontario (CCN)
- Centre for Effective Practice (CEP)
- Heart and Stroke Foundation of Canada
- Heart and Stroke Foundation of Ontario
- **Obesity Canada**
- KT Canada

SHARP: Major Atherosclerotic Events by CKD

C•CHANGE

	eze/simva (n=4650)	placebo (n=4620)	Risk ratio & 95% CI	P value for Het/Trend
MDRD estimated GFR (mL/min/1.73m²)				
≥ 60 (stage 2)	3 (6.8%)	3 (6.8%)		0.50
≥ 45< 60 (stage 3a)	6 (4.2%)	17 (10.8%)		
≥ 30 <45 (stage 3b)	81 (8.5%)	93 (10.4%)		
≥ 15 < 30 (stage 4)	127 (10.2%)	168 (12.7%)		
<15 (stage 5)	67 (10.9%)	81 (13.3%)		
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%)		
Subtotal: On dialysis	**230 (15.0%)**	**246 (16.5%)**	**0.90 (0.75-1.08) p=0.25**	
Major atherosclerotic event	**526 (11.3%)**	**619 (13.4%)**	**0.83 (0.74-0.94) p=0.0021**	



Baigent C et al *Lancet* 2011; 377: 2181–92 Webappendix page 1

Compliance – Dialysis vs Non-Dialysis

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	LDL-lowering Drug Use		LDL Difference (mmol/L)	
Baseline characteristic	EZ/Simva	Placebo	EZ/Simva	Placebo
GFR > 15	73%	8%	-1.11	-0.15
On Dialysis	65%	11%	-0.75	-0.16

Adapted from Baigent, et al. Lancet. 2011;377(9784):2181-92 (Webappendix)