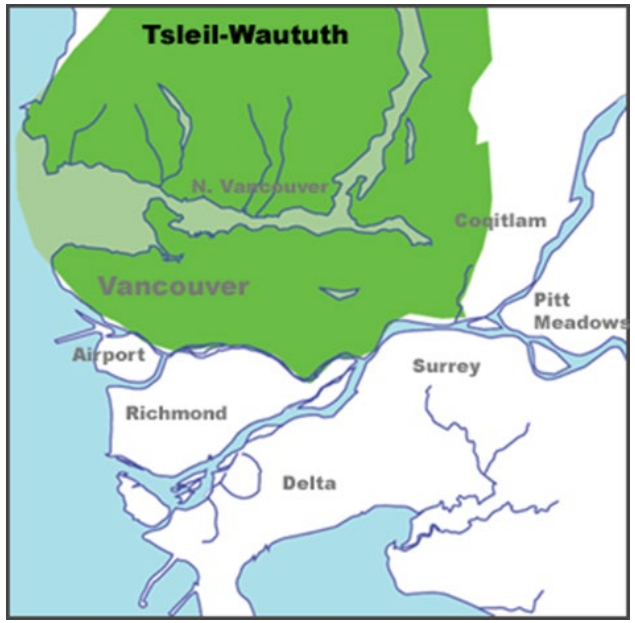
We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html



Care of the patient with advanced chronic kidney disease

Dr. Nadia Zalunardo

November 23, 2021

Disclosures

- None

Objectives

- Appreciate the variability in the risk progression to ESKD, and the increased risk of cardiovascular disease in CKD
- Recognize the value of a collaborative approach between Family Practice and Nephrology to optimize care, including delaying CKD progression, and supporting ESKD care
- Be aware of the increased risk of medication side effects, and be able to adjust medications used for common comorbid conditions in people with advanced CKD

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Risks associated with chronic kidney disease

- Increased risk of end stage kidney failure
- Increased risk of cardiovascular disease and mortality
- Increased risk of acute kidney injury and medication side effects
- Impaired immune response

CKD is classified based on CAUSE, GFR, Albuminuria
All 3 factors influence the future risk of kidney failure

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	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30–300 mg/g 3–30 mg/mmol	> 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			

Advanced CKD

Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk.
GFR, glomerular filtration rate.

Higher level of albuminuria associated with higher risk of ESKD, independent of eGFR level

Kidney International (2021) **99,** S1–S87

Cause of CKD is an important determinant of the risk of progression to kidney failure

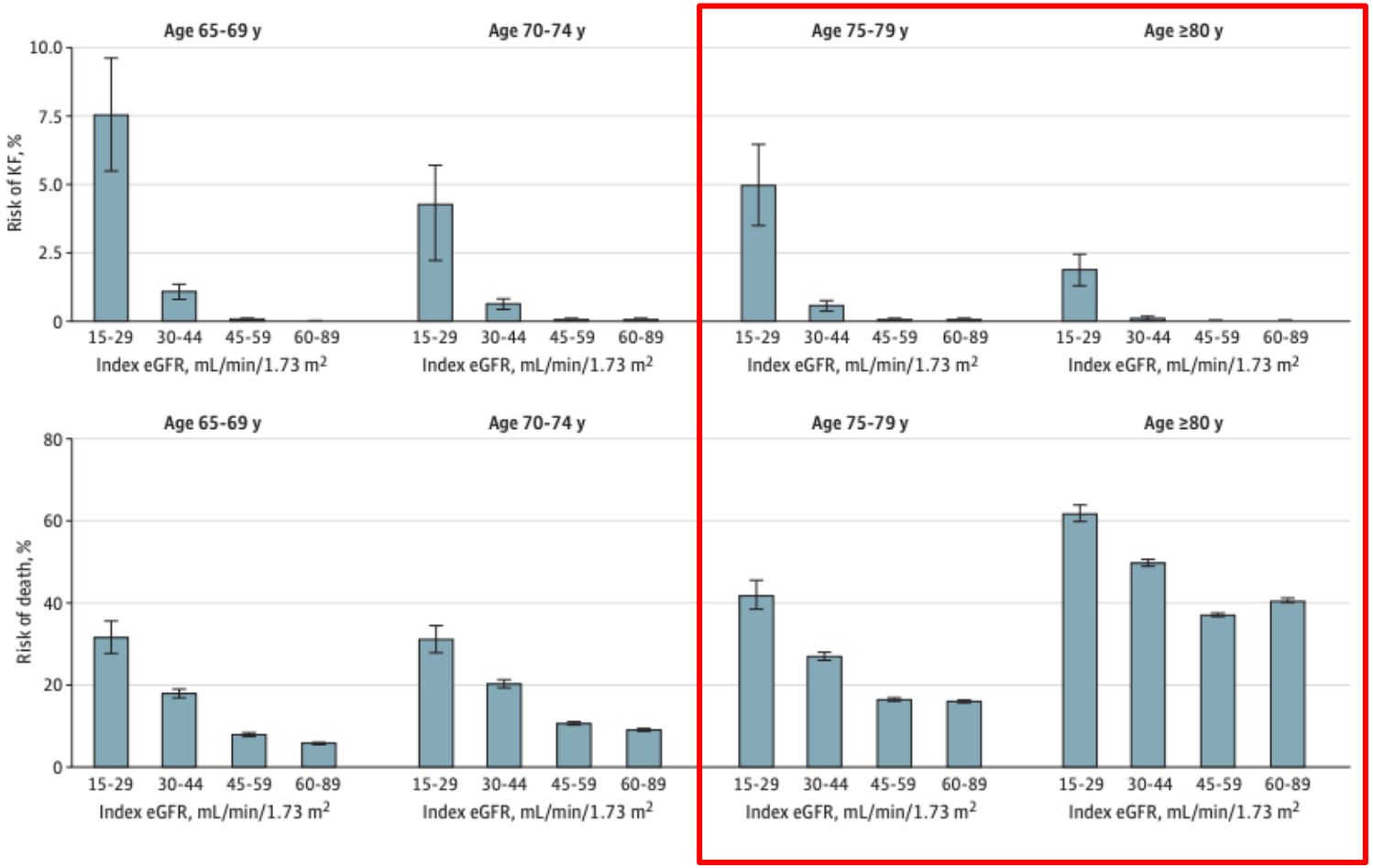
- Initial evaluation should focus on identifying the cause – determine reversibility, whether specific treatments may be indicated, and prognosis

- "Minimum" initial work up for CKD in an adult:
  - Creatinine
  - Urinalysis
  - Urine ACR
  - Electrolytes
  - Calcium
  - SPEP, UPEP
  - CBC
  - Ultrasound

AGE and Risk of KIDNEY FAILURE:
In the elderly, the risk of death > risk of kidney failure

5 yr Risk of Kidney Failure

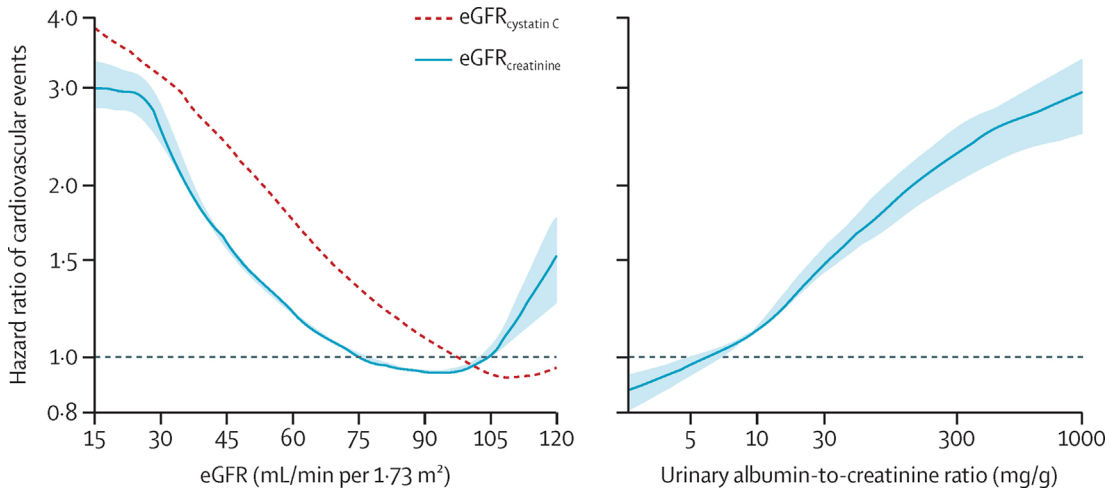
5 yr Risk of Death



People with no or minimal albuminuria (ACR < 3 mg/mmol)

JAMA Intern Med. 2021;181(10):1359-1366.

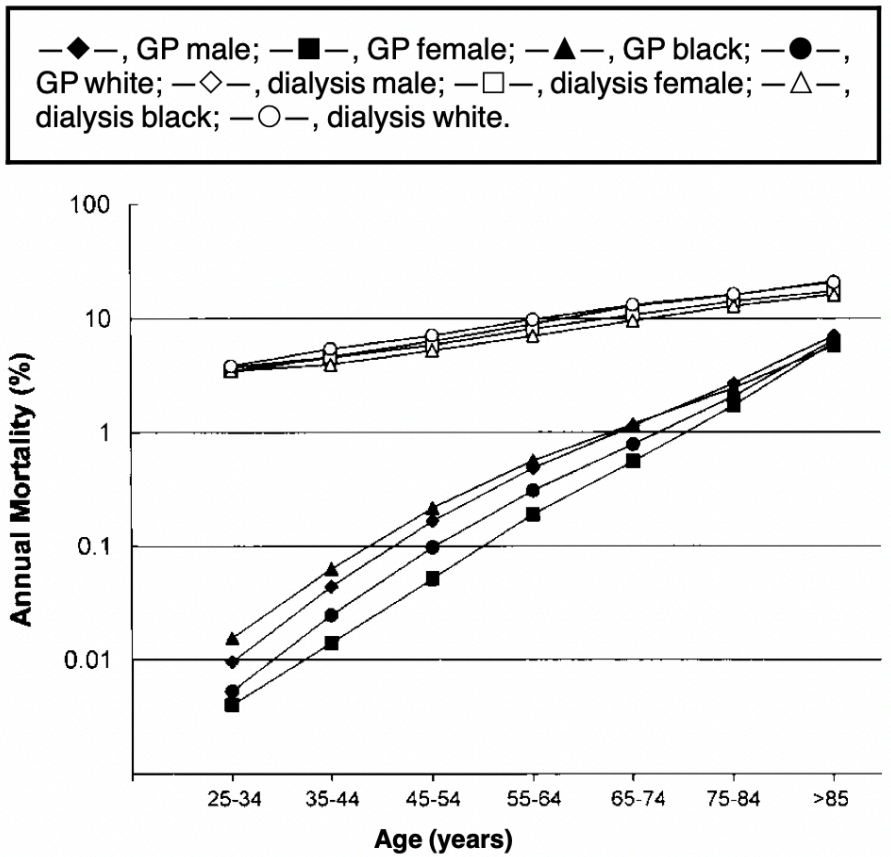
CKD is a risk factor for cardiovascular disease, which is a leading cause of death in CKD



Low eGFR and higher albuminuria are independently associated with a higher risk of cardiovascular events (in addition to risk conferred by traditional CV risk factors)

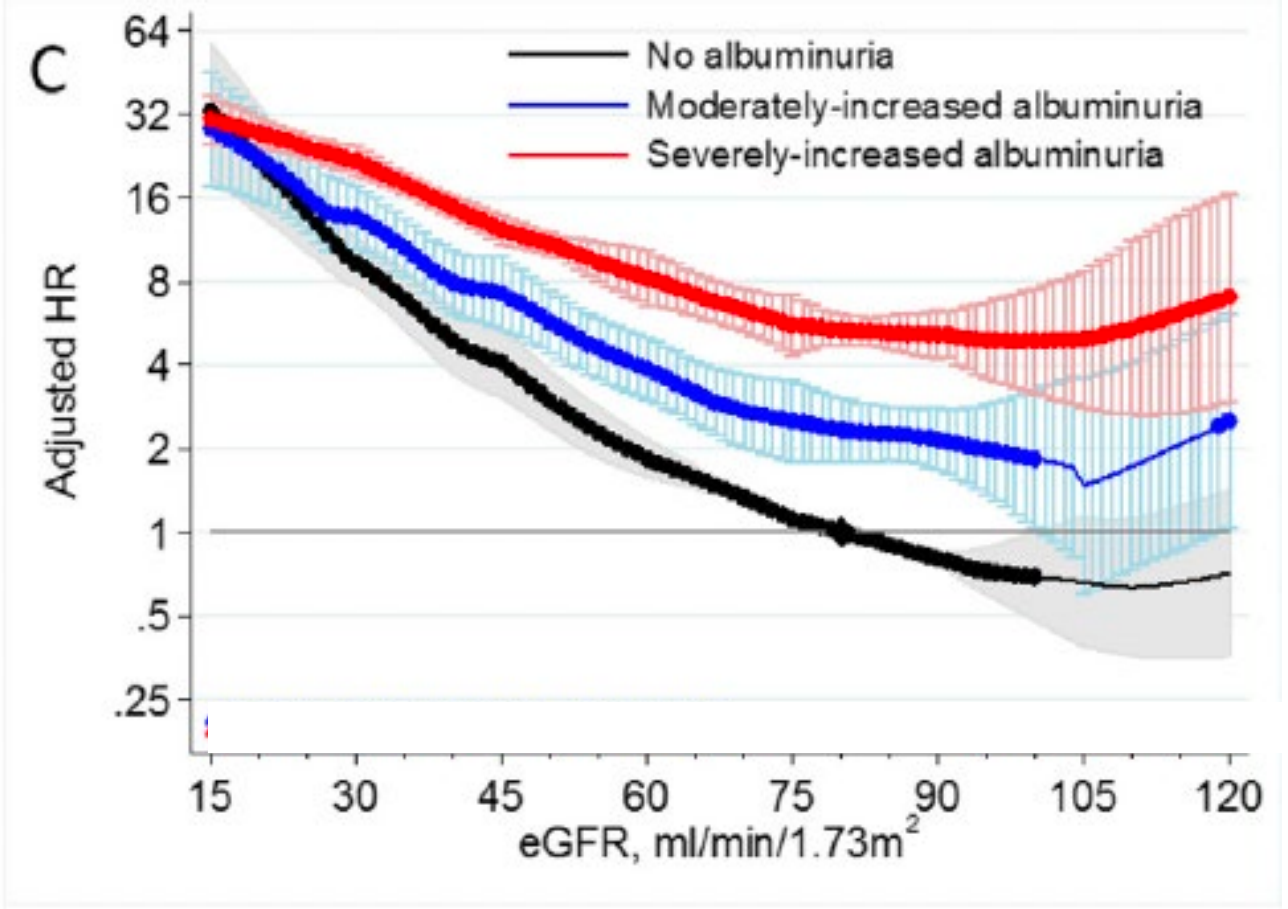
Data from CKD Prognosis Consortium, Figure from *Lancet* 2021; 398: 786–802

Risk of cardiovascular death in dialysis vs. general population



Foley et al, AJKD 32(5);1998:S112-9

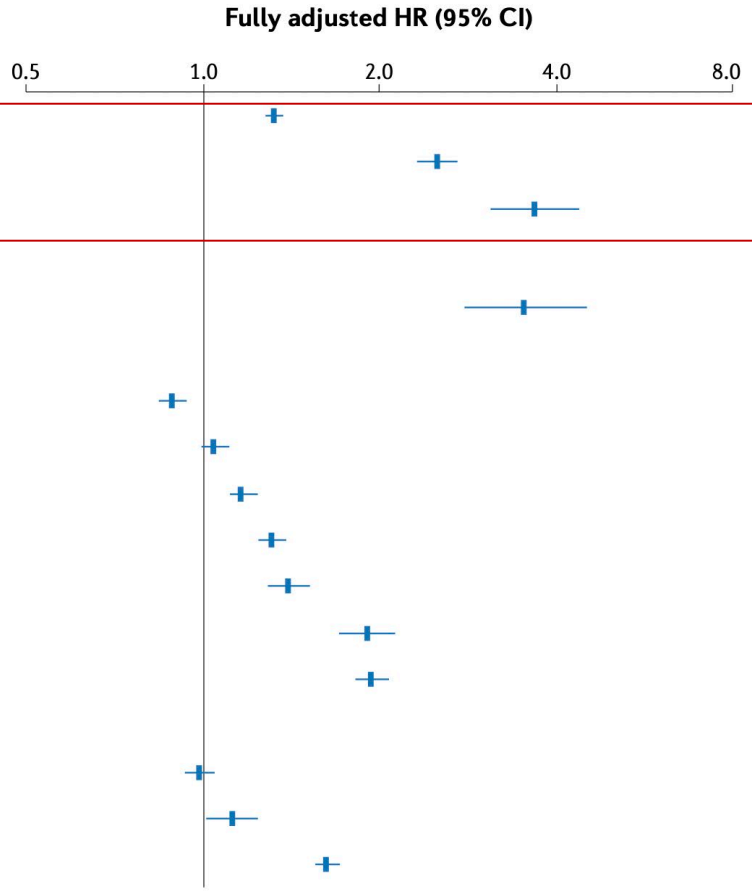
Risk of AKI increases as GFR declines, and as albuminuria increases



Am J Kidney Dis. 2015;66(4):591-601

CKD is a risk factor for mortality from COVID-19

Condition		Population (*n*)	Deaths (*n*)
CKD	eGFR 30–60 ml/min/1.73 m²	1,007,383	3,987
	eGFR <30 ml/min/1.73 m²	78,093	864
	Dialysis	23,978	192
Transplantation	Solid organ	20,001	69
CVD or CVD risk factor	Hypertension	5,925,492	8,049
	Moderate obesity	2,384,406	1,813
	Chronic heart disease	1,167,455	3,811
	Diabetes (well controlled)	1,038,082	2,391
	Severe obesity	922,398	762
	Morbid obesity	463,042	379
	Diabetes (not well controlled)	486,491	1,254
Lung disease	Asthma (no recent OCS use)	2,454,403	1,211
	Asthma (recent OCS use)	291,670	335
	Other respiratory disease	703,917	2,240



Nature https:// doi.org/10.1038/s41586-020-2521-4 (2020)

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Goals of chronic kidney disease management: Opportunities for collaboration

- Slow CKD progression → Prepare for ESKD care → Transplant
  Dialysis
  Conservative care
  } Support, and end of life care

BP control
ACEi/ARB/SGLT2i
Disease specific agents

- Manage cardiovascular risk factors
- Manage CKD related complications and symptoms
- Safe medication prescribing: reduce AKI risk, dose adjustment for low eGFR
- Vaccination for respiratory diseases (pneumococcus, influenza, COVID-19)

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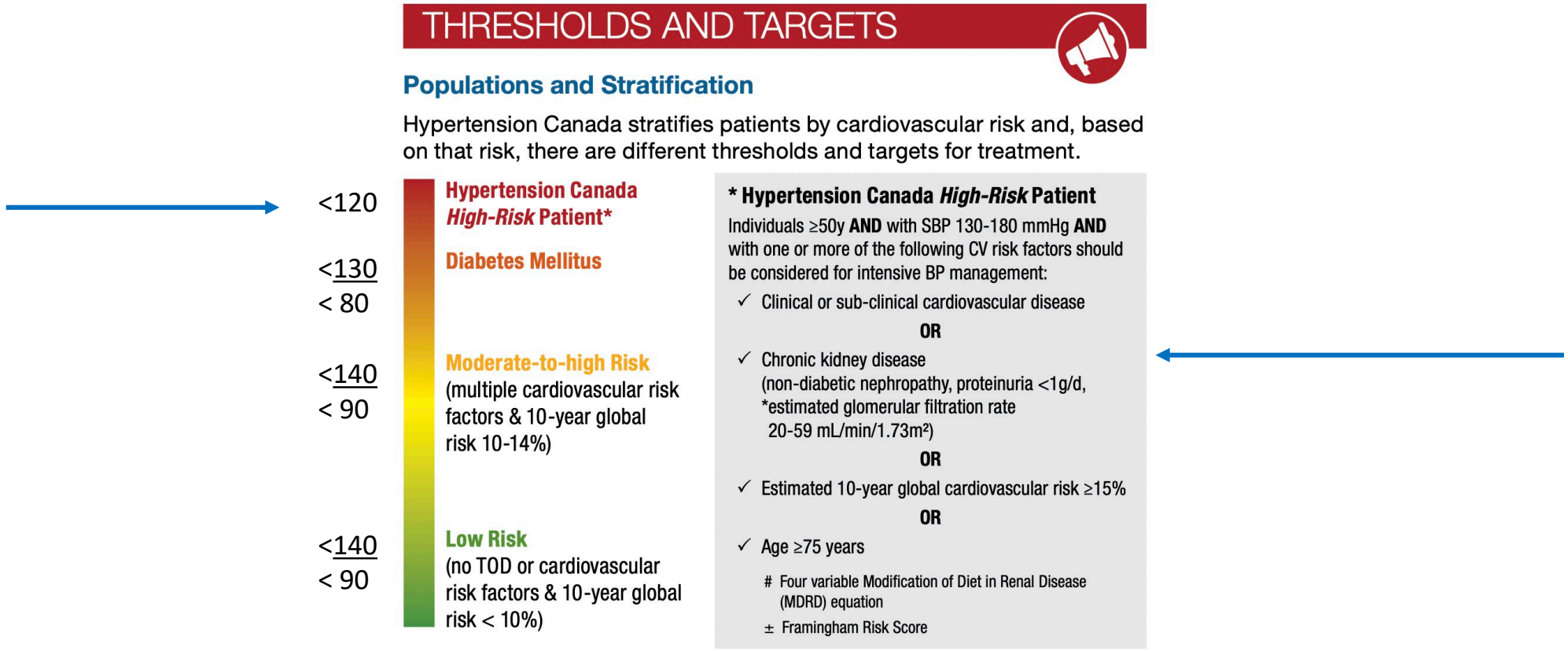
BP Targets: Hypertension Canada 2020
How does target BP <120 mmHg apply in CKD?



Canadian Journal of Cardiology 36 (2020) 596–624

Intensive (<120 mmHg) BP lowering is cardiovascular protective **not** renoprotective

- Recommendation for <120 mmHg is based on cardiovascular protective and survival benefit shown in SPRINT trial
- Evidence suggests that there is probably **no renoprotective effect** at SBP target <120 mmHg
- SPRINT trial **excluded people with advanced CKD** (most had eGFR > 45)

N Engl J Med 2015;373:2103-16.
J Am Soc Nephrol **28:** 2812–2823, 2017
Kidney International (2021) **99,** 559–569

Hypertension treatment in advanced CKD
Hypertension Canada 2020

- **Diabetes** <130/80 mmHg (if tolerated)

- **No diabetes** < 140 mmHg (if tolerated)
  - Nephrologists may recommend lower targets in some people, e.g. glomerulonephritis with higher degrees of proteinuria

- **Dialysis** No guidelines
  - Generally target < 140/90 mmHg
  - Achievable BP often limited by tolerability of dialysis and other comorbidities

Delaying CKD progression: ACEi/ARBs in advanced CKD

- In CKD **with** albuminuria: ACEi/ARB indicated to slow CKD progression
  - Evidence suggests that treatment is renoprotective even in advanced CKD
- In CKD **without** albuminuria: evidence that ACEi/ARB slows CKD progression is limited**,** regardless of CKD stage
- People with CKD often have other indications for ACEi/ARBs, and they are good antihypertensive agents
- Discontinue if complications e.g. AKI, hyperkalemia

SGLT2 inhibitors in CKD*:*

Game Changer

- "Thanks for all you're doing. I hope this brightens the place up a bit, even if its only black and white." –Banksy-

SGLT2 inhibitors in CKD:

Game Changer

- "Thanks for all you're doing. I hope this brightens the place up a bit, even if its only black and white." –Banksy-

BUT

SGLT2 inhibitors: In RCTs published to date the **lower limit eGFR for initiation = eGFR 25 mL/min/1.73 m^2**

Diabetic Kidney Disease

- ↓ risk of all cause death, nonfatal MI, hospitalization heart failure, and ESKD

Nondiabetic CKD **with** Albuminuria

- ↓ risk of combined outcome of 50% ↓ eGFR, ESKD, death
- Ongoing RCT (EMPA Kidney) in CKD with or without albuminuria, enrolling eGFR as low as 20

N Engl J Med 2019; 380:2295-2306
N Engl J Med 2021; 384:388-390

Treatment of CKD related complications

- Anemia
  - Rule out causes other than CKD e.g. Fe deficiency, hypothyroid, myeloma
  - ESAs rarely needed until eGFR < 30, and not initiated until hb $\lesssim$ 95 g/L
- Hyperkalemia
  - Consider chronic K binder use if diet and medication adjustments not sufficient
- Acidosis
  - Target bicarbonate in the normal range
- Mineral and bone disease

Preparing for ESKD care: it takes time!
Ideally followed for at least 2 years before ESKD is anticipated

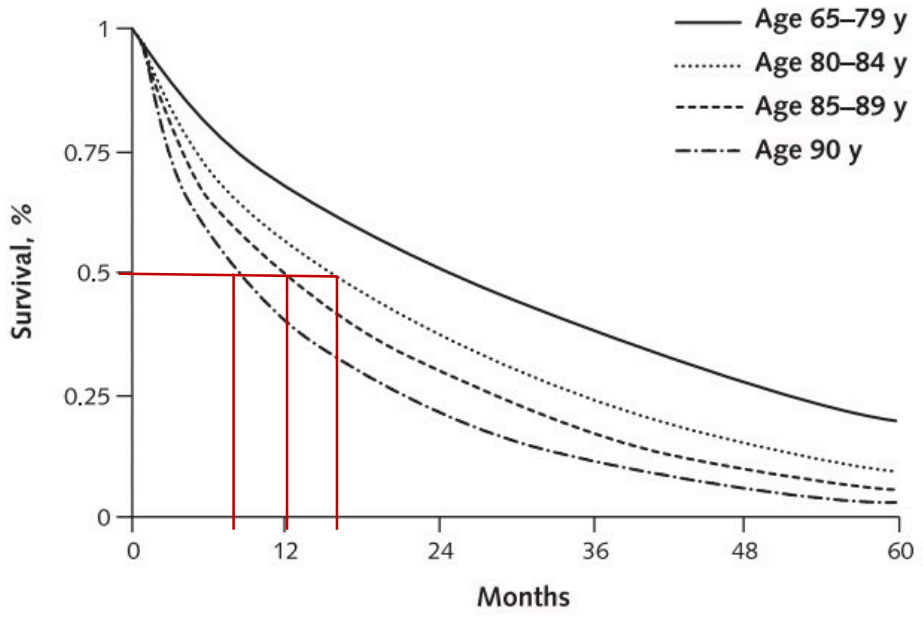
- Understand patient preferences and goals of care
- Education regarding kidney disease, complications, and treatment options
- Referral for kidney transplant assessment if appropriate
- Preferences of dialysis modality (PD or HD) or conservative care
  - Strongly encourage independent dialysis: PD or Home HD

Preparing for ESKD care: it takes time!
Ideally followed for at least 2 years before ESKD is anticipated

- For those who choose hemodialysis: timely placement of vascular access
  - Refer for AVF creation 9 – 12 months before anticipated HD start
- For those who choose peritoneal dialysis: timely placement of PD catheter
  - Insert PD catheter at least 2 weeks before anticipated PD start
- For those who choose conservative treatment or are not candidates for dialysis
  - Focus on symptom management
  - Ensure strong connections to community care providers and supports

Predictors of mortality on dialysis

- Age…but it's more than that…
- Functional status
- Frailty
- Cognitive impairment
- Comorbidities
  - Diabetes
  - Cardiovascular disease



Ann Intern Med. 2007;146:177-183.

Dialysis vs Conservative Management: What's the difference in survival?

Table 3. Estimated survival for patients who initiate dialysis compared with patients who receive medical management, by age group and eGFR

Age, yr	eGFR (ml/min per 1.73 m^2)	Median Survival in Months (25th, 75th percentile)		Difference in Median Survival (mo)
		Dialysis	Medical Management	
60	<6	71 (28, NE)	17 (5, 39)	54
	6–<9	67 (26, NE)	45 (16, 90)	22
	9–<12	54 (20, NE)	52 (19, NE)	2
65	<6	37 (13, 75)	11 (3, 26)	26
	6–<9	36 (12, 74)	30 (10, 64)	6
	9–<12	42 (15, 85)	36 (12, 76)	6
75	<6	34 (11, 70)	9 (3, 22)	25
	6–<9	29 (10, 62)	8 (2, 20)	21
	9–<12	26 (9, 57)	21 (7, 46)	5
85	<6	24 (8, 52)	7 (2, 16)	17
	6–<9	21 (7, 46)	6 (2, 15)	15
	9–<12	21 (7, 47)	11 (3, 27)	10

NE values correspond to times which extend beyond the maximum follow-up time. eGFR values >12 ml/min per 1.73 m^2 are not presented because they were not associated with higher dialysis survival in any age group.

J Am Soc Nephrol **29:** 2169–2177, 2018

Disparities in kidney disease care in Canada

- CKD is more common and earlier onset in Indigenous communities
- Association between remote location and ↑ rates of CKD and mortality, regardless of race and ethnicity
- Indigenous and remote communities face a disproportionate burden of CKD due to many factors: ↓ access to care, long travel distances, SE disparity, and lack of culturally safe health care infrastructure
- Kidney transplant is less likely in African, East and South Asian, and Indigenous Canadians compared to white and non-Indigenous patients
  - Lower likelihood of completing the kidney transplant evaluation
  - Contributing factors: SE disparities, knowledge gaps about organ donation/transplant, religious/spiritual and cultural beliefs, systemic concerns regarding pain and disrespect during surgery, concerns that doctors would not do everything possible to preserve a life of a potential donor, and experiences of racism within the health care system

Canadian Journal of Kidney Health and Disease: (6) 2019
Canadian Journal of Kidney Health and Disease: (8) 2021

Steps to address disparities in kidney disease care

- **Nationally**: Can-SOLVE CKD, a pan-Canadian patient-oriented research network
  - Indigenous Peoples' Engagement and Research Council created to guide national activities
  - **Goal**: increase the proportion of Indigenous people screened for CKD and diabetes, ensure access to treatment in a culturally sensitive manner

- **BC Renal**
  - Senior Medical Lead for Diversity & Inclusion recently appointed to lead the diversity/inclusion strategic priorities within the organization
  - **Short term goals**:
    - Enhance cultural competency
    - Strengthen connections with Indigenous organizations and communities
    - Increase Indigenous representation
    - Support specific initiatives in kidney care to positively impact the health and wellness of Indigenous peoples

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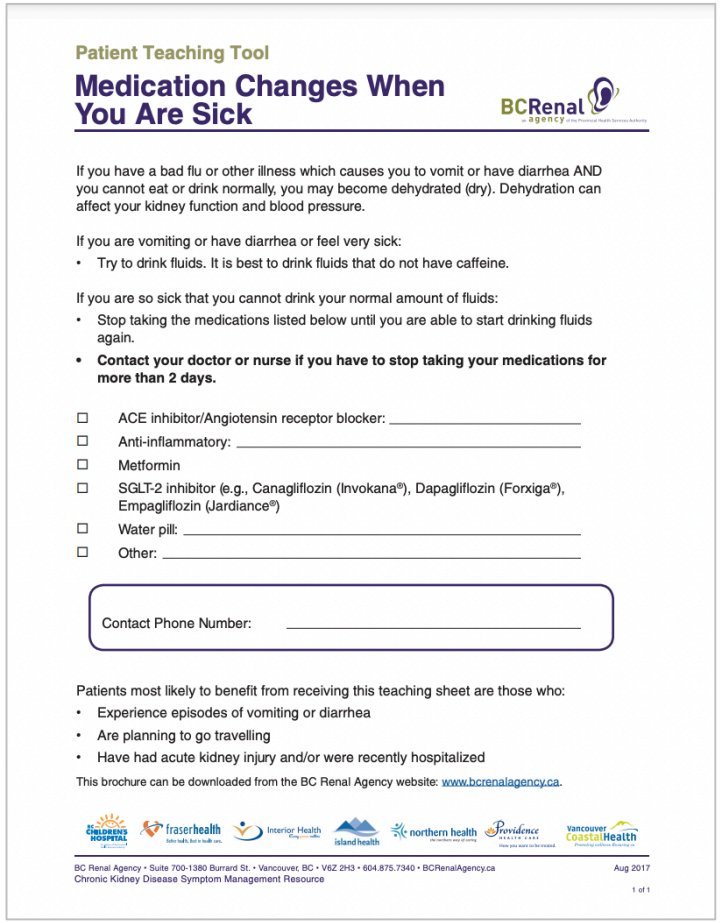
Anticipate situations that increase risk of medication toxicity: provide “sick day advice”

Withhold medications that increase risk for AKI or have reduced clearance in AKI and can cause complications:

- Sulfonylureas
  - Avoid glyburide in eGFR <30
- ACE inhibitors
- Diuretics
- Metformin
  - Avoid metformin in eGFR <30
- ARBs
- NSAIDS
- SGLT2 inhibitors



Patient Teaching Tool

Medication Changes When You Are Sick

BCRenal agency

If you have a bad flu or other illness which causes you to vomit or have diarrhea AND you cannot eat or drink normally, you may become dehydrated (dry). Dehydration can affect your kidney function and blood pressure.

If you are vomiting or have diarrhea or feel very sick:

- Try to drink fluids. It is best to drink fluids that do not have caffeine.

If you are so sick that you cannot drink your normal amount of fluids:

- Stop taking the medications listed below until you are able to start drinking fluids again.
- **Contact your doctor or nurse if you have to stop taking your medications for more than 2 days.**

- ☐ ACE inhibitor/Angiotensin receptor blocker: _____
- ☐ Anti-inflammatory: _____
- ☐ Metformin
- ☐ SGLT-2 inhibitor (e.g., Canagliflozin (Invokana®), Dapagliflozin (Forxiga®), Empagliflozin (Jardiance®)
- ☐ Water pill: _____
- ☐ Other: _____

Contact Phone Number: _____

Patients most likely to benefit from receiving this teaching sheet are those who:

- Experience episodes of vomiting or diarrhea
- Are planning to go travelling
- Have had acute kidney injury and/or were recently hospitalized

This brochure can be downloaded from the BC Renal Agency website: www.bcrenalagency.ca.

BC Renal Agency • Suite 700-1380 Burrard St. • Vancouver, BC • V6Z 2H3 • 604.875.7340 • BCRenalAgency.ca
Chronic Kidney Disease Symptom Management Resource

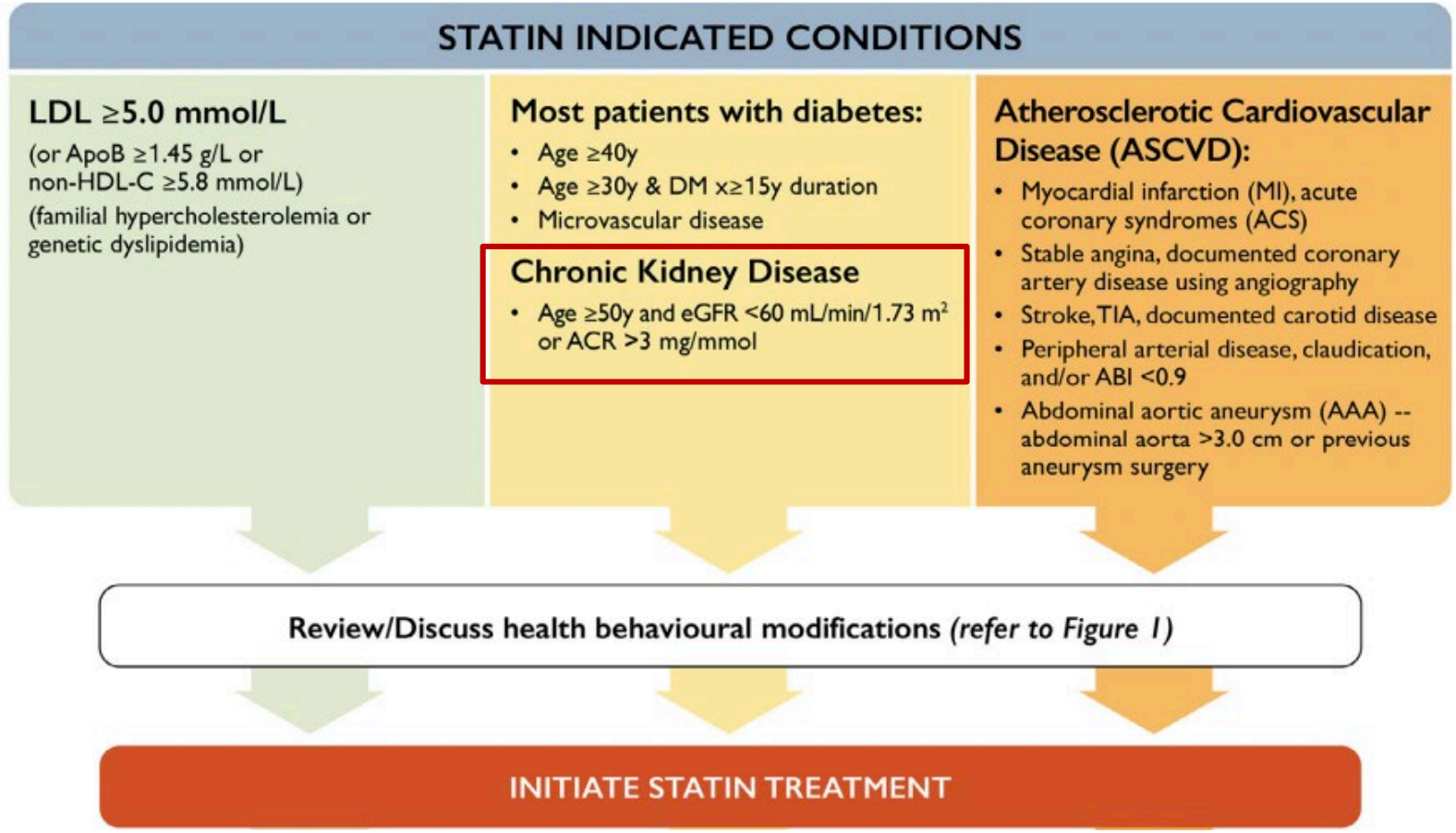
Aug 2017

1 of 1

Management of common comorbidities in people with advanced CKD

- Cardiovascular disease
  - Primary prevention, Heart failure, OACs for AF
- Type 2 diabetes
- Gout

Primary prevention for CVD: statin is indicated in CKD **not** on dialysis



eGFR <30

Atorva – no Δ
Rosuva – start 5 mg, max 10 mg/d

Canadian Journal of Cardiology 37 (2021) 1129–1150

HFrEF: LVEF ≤ 40% and Symptoms

Diuretics to Relieve Congestion (titrated to minimum effective dose to maintain euvolemia)

Initiate Standard Therapies

- **ARNI** or **ACEi/ARB** then substitute **ARNI**
- **Beta blocker**
- **MRA**
- **SGLT2 Inhibitor**

Some need renal dose adjustment

Assess Clinical Criteria for Individualized Therapies

- **HR >70 bpm and sinus rhythm**
  - Consider ivabradine*
- **Recent HF hospitalization**
  - Consider vericiguat**
- **Black patients on optimal GDMT, or patients unable to tolerate ARNI/ACEi/ARB**
  - Consider H-ISDN
- **Suboptimal rate control for AF, or persistent symptoms despite optimized GDMT**
  - Consider digoxin

Treating HFrEF in advanced CKD, not on dialysis

- General strategies are the same as in non CKD, but:
  - Advanced CKD (eGFR < 30) mostly excluded from clinical trials
  - Increased risk of medication toxicity: AKI and electrolyte disturbances
  - MRAs generally **not** recommended for eGFR < 30 (including dialysis) due to high risk of hyperkalemia

- Close monitoring of hemodynamic status, kidney function, and electrolytes is recommended
  - Start with low dose of ACEi/ARB/ARNI
  - Labs within 2 weeks of uptitrating therapies that can affect GFR, electrolytes
  - Routine labs at a frequency dictated by stability of heart and kidney function (q 1 – 3 months)

Managing common complications of medications for HF in advanced CKD, not on dialysis: Hyperkalemia

Initial management:

Mild (<5.6 mmol/L):	diet
Mod (5.6 – 5.9 mmol/L):	diet + ↓ dose / stop K sparing meds (if on MRA – stop)
Severe (≥ 6.0 mmol/L):	diet + stop K sparing meds + binder (e.g. Kayexalate 30 gm daily X 2- 3 d) +/- treatment in ER
Repeat lab tests	mild – w/in 4 weeks, mod – w/in 2 weeks, severe – w/in days, or ER

Chronic management:

Moderate – severe hyperkalemia:	recommend against restarting MRA
If use of ACEi/ARB/ARNI desired:	restart at lower dose → repeat labs if mod-severe hyperkalemia recurs → stop or consider chronic K binder use
Some people can't tolerate ACEi/ARB:	consider hydralazine + nitrate

Medications provided at no charge by the BC Renal Formulary (if ordered by Nephrologist)

ACIDOSIS
sodium Bicarbonate

ANEMIA

Iron Bivalent
darbepoetin (Aranesp) (restricted)*✦
erythropoetin (Eprex) (restricted)*✦
ferrous fumarate
ferrous gluconate ferrous sulfate
iron gluconate ✦
iron sucrose (restricted)✦

HYPERKALEMIA

Exchange Resins
sodium polystyrene sulfonate
calcium polystyrene sulfonate

MINERAL METABOLISM

alfacalcidol
aluminum hydroxide
calcitriol
calcium acetate
calcium carbonate (not Calsan brand) lanthanum (restricted)**
sevelamer carbonate(restricted)**

NUTRITIONAL DISORDERS

Replavite/Renavite
zinc gluconate

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

Tolvaptan***

BCRenal
Provincial Health Services Authority

www.bcrenal.ca

Managing common complications of medications for HF in advanced CKD, not on dialysis: AKI

Drop in eGFR >25-30% from baseline

- Assess AKI: intercurrent illness, nephrotoxic med use (e.g. NSAIDs)….
- If not hypervolemic – reduce/stop diuretic
  - if diuretic is reduced/stopped, monitor weight
- +/- Reduce / stop ACEi/ARB/ARNI
- Repeat labs 1 - 2 weeks later
- Rechallenge with lower dose ACEi/ARB/ARNI – if AKI recurs, switch to hydralazine/nitrate
- If AKI is progressive or severe, associated with superimposed illness or hemodynamic concerns → ER visit

Using OACs for AF in CKD

Stage 1 – 4 CKD: apply CCS guidelines as usual
Stage 5 CKD: benefit of OACs is unclear – no RCTs, have ↑ risk of major bleeding → assess on case by case basis

CrCl	Warfarin	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
CrCl >50 mL/min	Dose adjusted for INR 2.0-3.0	5 mg BID†	150 mg BID*	60 mg daily∞	20 mg daily
CrCl 30-49 mL/min	Dose adjusted for INR 2.0-3.0	5 mg BID†	Consider 110 mg BID	30 mg daily	15 mg daily
CrCl 15-29 mL/min	No RCT Data**	Very limited RCT Data§	No RCT Data¶	Very limited RCT Data¶	No RCT Data
CrCl <15 mL/min (or on dialysis)	No RCT Data‡	Very limited RCT Data¶	No RCT Data¶	No RCT Data¶	Very limited RCT Data¶

BID, twice daily; CrCl, creatinine clearance, INR, international normalized ratio; RCT, randomized clinical trial.
*Dabigatran 110 mg po BID is recommended if age ≥80 years, or ≥75 years with other bleeding risk factors including CrCl 30-50mL/min
†Apixaban 2.5 mg po BID is recommended if 2 of the 3 following criteria are present: 1) age ≥80 years, 2) body weight ≤60 kg, or 3) serum creatinine ≥133 μmol/L
∞Consider Edoxaban 30mg daily if weight ≤60 kg or concomitant potent P-Gp inhibitor therapy EXCEPT amiodarone or verapamil
**Dose adjusted warfarin has been used, but data regarding safety and efficacy is conflicting
‡Dose adjusted warfarin has been used, but observational data regarding safety and efficacy is conflicting and suggests harm.
§The ARISTOTLE trial included a small number of patients with a CrCl as low as 25 mL/min
¶Product monographs suggest the drug is contraindicated for this level of renal function.

Canadian Journal of Cardiology 2020 361847-1948DOI: (10.1016/j.cjca.2020.09.001)

Management of diabetes in advanced CKD

- Not all people with diabetes + CKD have CKD due to diabetes
- HbA1c can be falsely low due to shortened RBC survival
- RCTs of glycemic targets do not include people with advanced CKD
- For most adults, target HbA1c < 7% is recommended
- In the elderly and in CKD, the risk of hypoglycemia is increased
  - Diabetes Canada guidelines for individualization of HbA1c targets based on degree of frailty and presence of dementia
  - Online tool: https://guidelines.diabetes.ca/reduce-complications/a1ctarget

Diabetes Canada 2020

Pharmacologic considerations for glycemic control in advanced CKD

Medication	Stage 4 CKD	Stage 5 CKD/Dialysis	Comments
Metformin	Use alternative due to risk of accumulation and lactic acidosis		
SGLT2 inhibitors	Limited glycemic efficacy Limited RCT data for CV and renal benefits for eGFR < 25		
GLP-1 receptor agonist	Preferred treatment RCTs support CV, renal benefit	No safety or outcome data	Dulaglutide and liraglutide: RCTs included stage 4 CKD
DPP-4 inhibitor	Okay, but no RCTs support CV benefits Ltd glycemic benefit in combo w GLP-1	Preferred treatment Low risk of hypoglycemia	Linagliptin – no dose adjust Saxagliptin ↓ 2.5 mg/day
Insulin	Better choice than SU unless desire to avoid injections Beware of extended duration of action		
Sulfonylurea	Increased risk of hypoglycemia Beware of extended duration of action – start low dose		Gliclazide preferred if SU used

Diabetes Canada 2020

Kidney International (2020) **98**, S1–S115

Gout prevention in advanced CKD

- **Hyperuricemia and gout are common in CKD**
  - Treatment for asymptomatic hyperuricemia is **not** indicated

- **Gout prevention:**
  - **Allopurinol** is first line treatment
    - Hypersensitivity syndrome associated with higher starting dose and presence of HLA-B*5801 allele
    - **HLA-B*5801 genotype testing** indicated in some Asian populations (Han Chinese, Korean, Thai) prior to treatment
    - Starting dose **50 mg q 2 days** and uptitrate by 50 mg q 2 – 5 weeks to target uric acid <350
  - Concomitant anti-inflammatory therapy for first 3 – 6 mo
    - Colchicine 0.3 mg/day, **caution** in Stage 5 CKD not on dialysis, generally avoid in dialysis

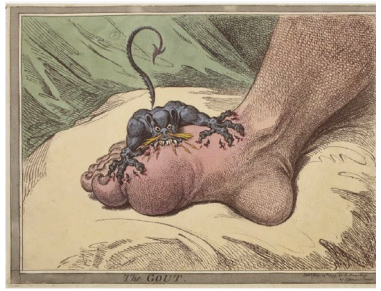
ACR Guidelines 2020
AJKD 2017:70,422-39
FDA colchicine prescribing information

Gout flare management in advanced CKD

- **Colchicine: increased risk of toxicity in advanced CKD**
  - Low dose colchicine 1.2 mg at first sign of flare, then 0.6 mg 1 hour later
  - If on dialysis: 0.6 mg X 1 dose only
  - Do not repeat more than once course in 14 days
  - Beware of drug interactions

- **Prednisone**
  - If on dialysis, or if other contraindication to/alternative to colchicine
  - 30 mg daily X 5 days (or similar)

- **NSAIDs**
  - Short term use (days) acceptable in dialysis



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Thank you