Diabetes and Kidney Disease
Exciting Times

Louise Moist MSc.MD
Professor of Medicine and Epidemiology/Biostatistics
London CANADA
Louise.Moist@lhsc.on.ca

Objectives

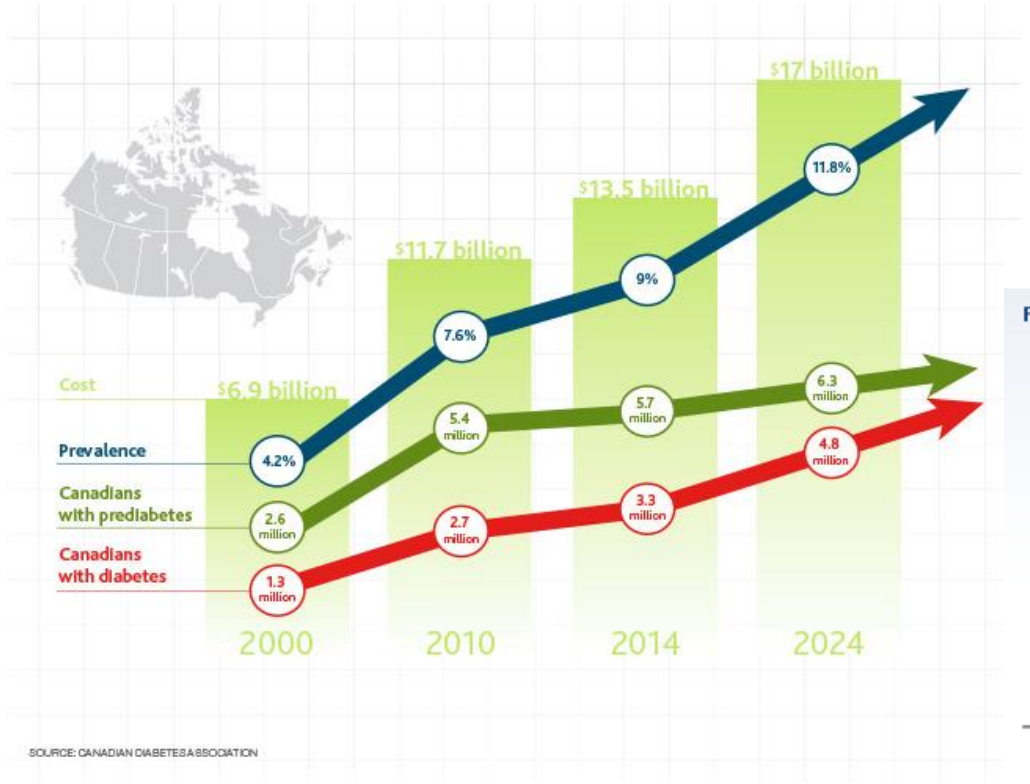
1. To understand the evidence supporting the use of SGLT2 I in patients with CKD

2. To identify the patient population best suited for use of SCLT2 I, weighing the risks and benefits

3. To promote safe and effective prescribing of SCLT2 I, including follow up

4. To provide tips on educating the patient and care giver when prescribing SCLT2 I

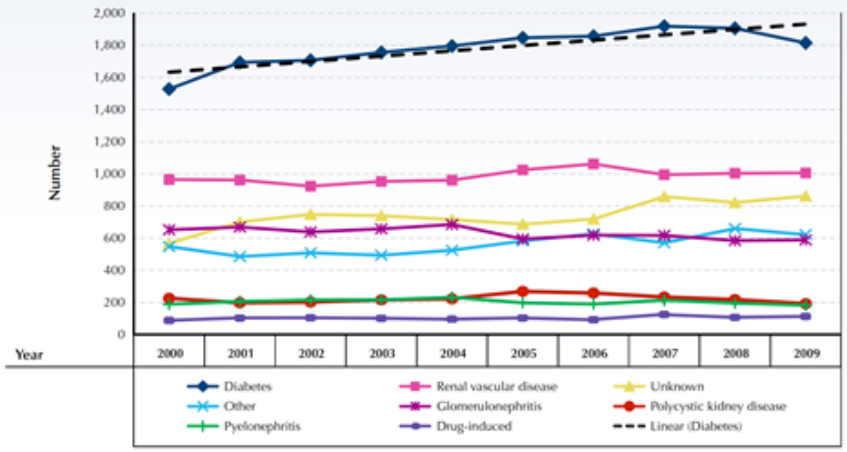
Diabetes Trends and Costs in Canada



Diabetes is the ***LEADING*** cause of kidney disease in Canada[1,2]

Diabetes is #1 Cause of New Cases of ESRD

Figure 2-3. Number of incident cases of end-stage renal disease, by primary diagnosis, Canada, 2000 to 2009

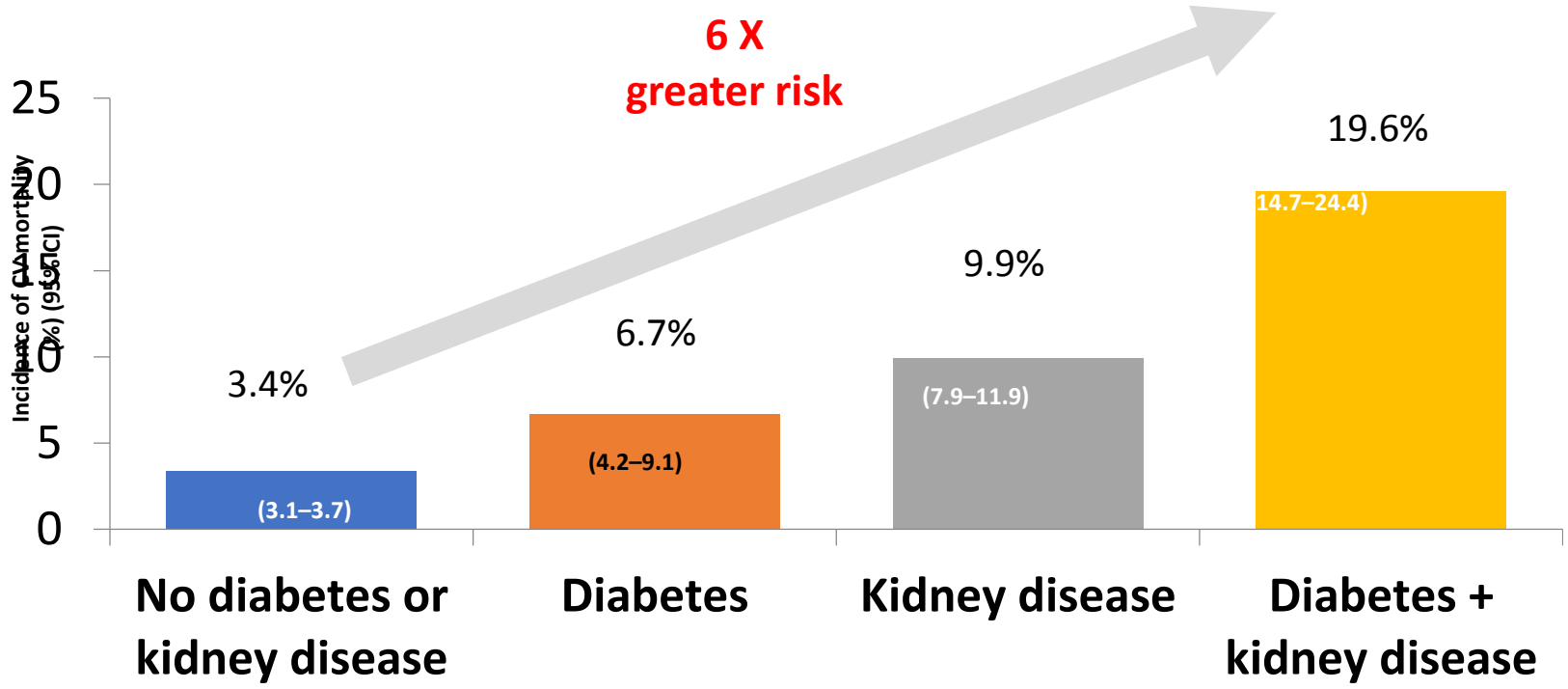


Source: Public Health Agency of Canada (2011); adapted from Canadian Institute for Health Information. Canadian Organ Replacement Register Annual Report: Treatment of End-Stage Organ Failure in Canada, 2000 to 2009. 2011. Ottawa.

Public Health Agency of Canada (August 2011); using 2008/09 data from the Canadian Chronic Disease Surveillance System (Public Health Agency of Canada)

Excess CV Risk Attributable to Kidney Disease

Ten-year standardized CV mortality by diabetes and kidney disease status (data from US NHANES III)

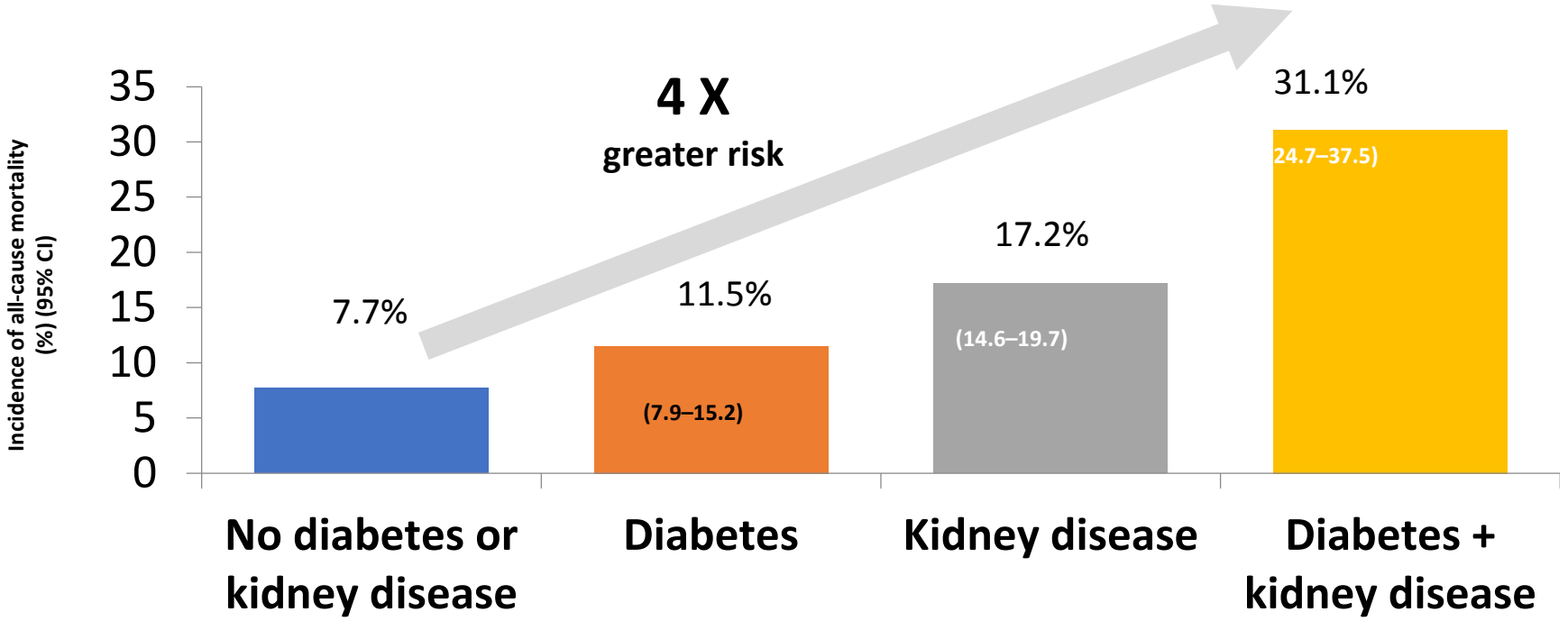


US, United States; NHANES III: Third National Health and Nutrition Examination Survey; eGFR, estimated glomerular filtration rate; ACR, albumin to creatinine ratio; Cr, creatinine.
Study included 15,046 participants aged ≥20 years who participated in a health examination and had available data on medications used, serum Cr and urine albumin and Cr concentrations and follow-up mortality data through 2006. Kidney disease was defined as urinary ACR ≥30 mg/g and/or eGFR ≤60 mL/min/1.73 m^2

Adapted from: Afkarian M, et al. *J Am Soc Nephrol* 2013;24:302-8.

DKD is Associated with Substantial Excess Risks of All-Cause Mortality

Ten-year standardized all-cause mortality by diabetes and kidney disease status (data from US NHANES III)



US, United States; NHANES III: Third National Health and Nutrition Examination Survey; eGFR, estimated glomerular filtration rate; ACR, albumin to creatinine ratio; Cr, creatinine.
Study included 15,046 participants aged ≥20 years who participated in a health examination and had available data on medications used, serum Cr and urine albumin and Cr concentrations and follow-up mortality data through 2006. Kidney disease was defined as urinary ACR ≥30 mg/g (≥3.4 mg/mmol) and/or eGFR ≤60 mL/min/1.73 m^2

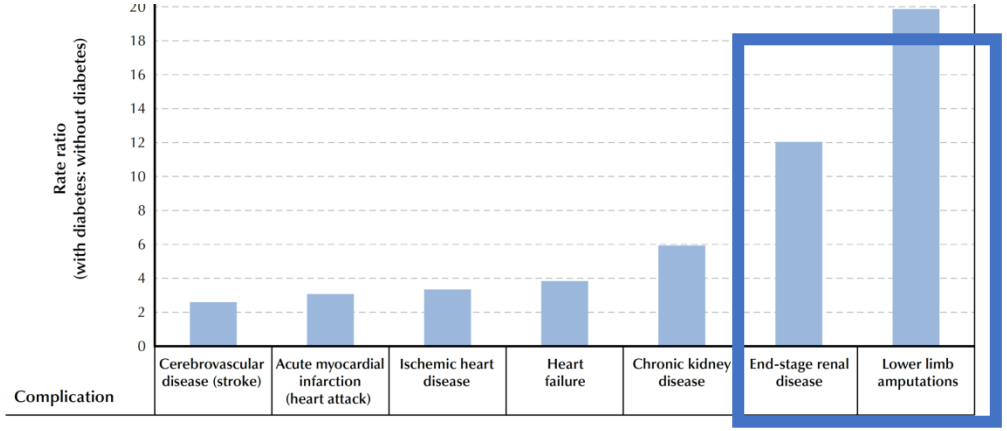
Adapted from: Afkarian M, et al. *J Am Soc Nephrol* 2013;24:302-8.

Chronic Kidney Disease and Diabetes Mellitus

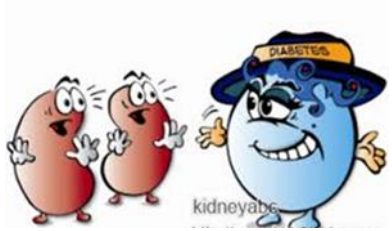
Individuals with diabetes are

6X more likely to be

hospitalized with kidney disease[3]



Key Point



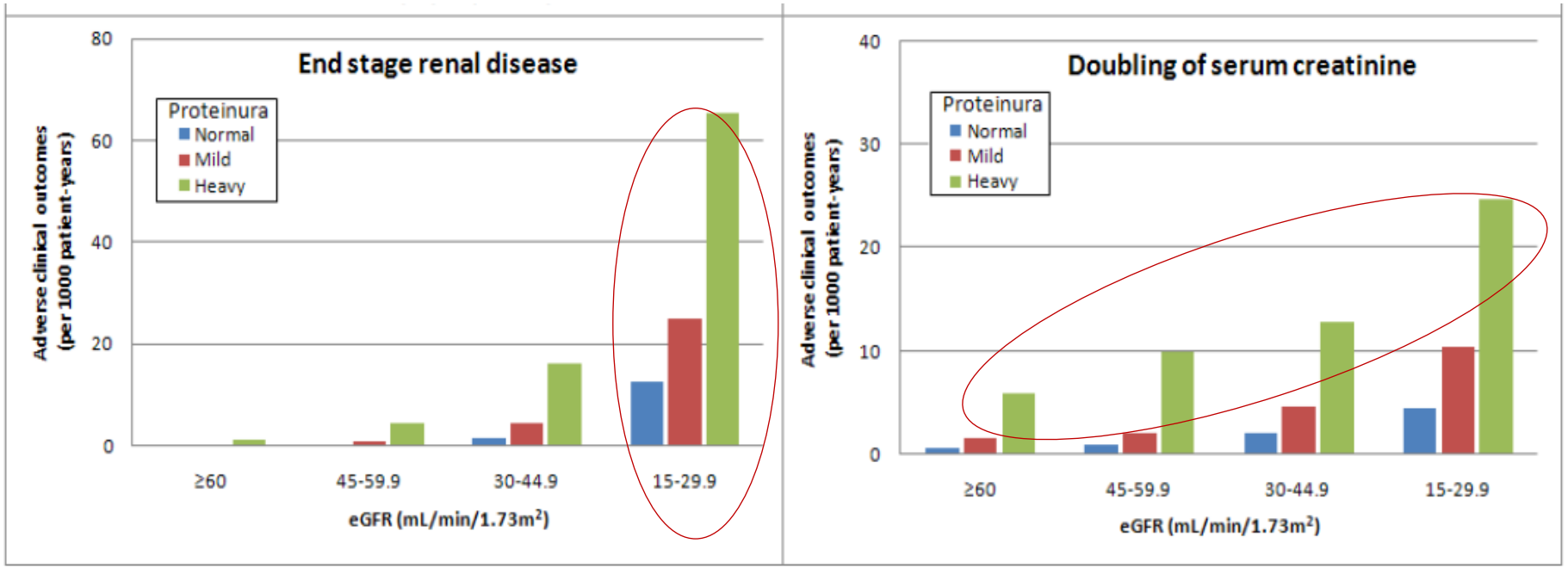
CKD is an independent cardiac risk factor

Diabetes and CKD

=

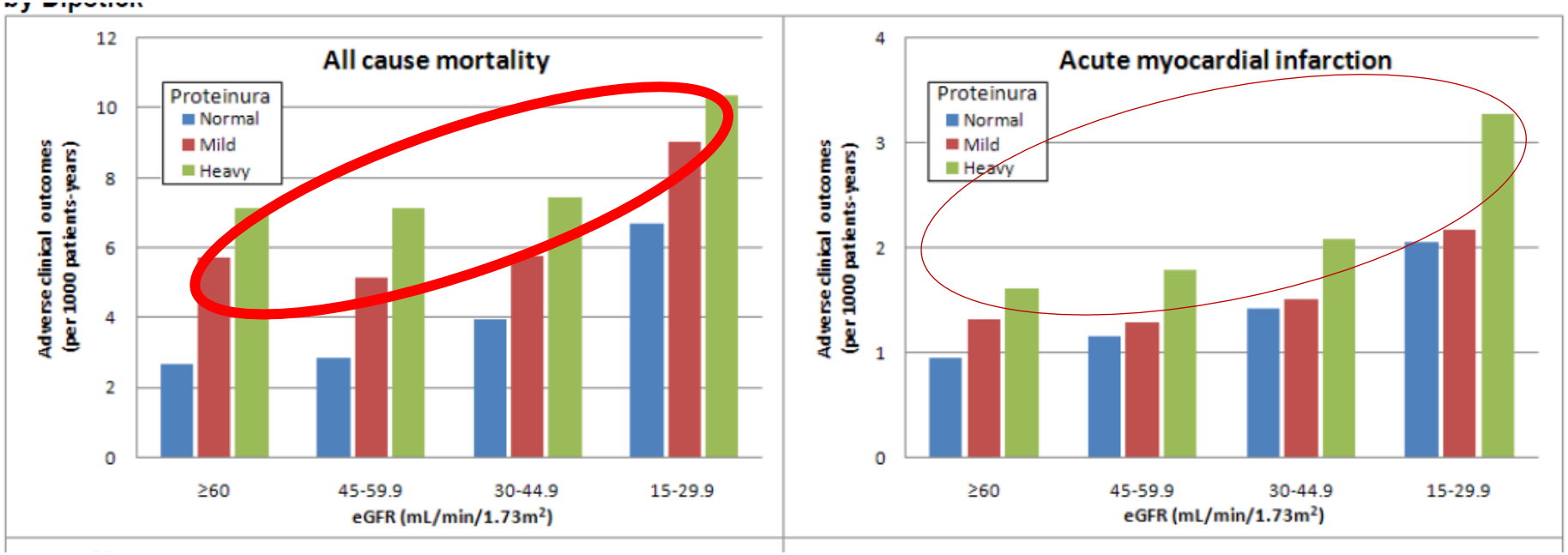
HIGH RISK CVD

Creatinine and Proteinuria Contribute to increased Kidney Risk

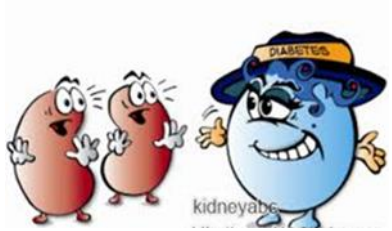


JAMA. 2010;303(5):423-429

Creatinine and Proteinuria Contribute to increased Cardiac Risk



Key Point



Proteinuria is a significant risk Factor for **CVD and CKD progression**

Three-pillared approach to treat patients with CKD

(Grade A)

Target < 7.0%

(Grade A)

Target < 130/80 mmHg

(Grade A)

1. Meltzer S, et al. *CMAJ* 1998;159(Suppl 8):S1-29. 2. CDA Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2008;32(Suppl 1):S1-S201.

3. CDA Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2013;37: S129-136.

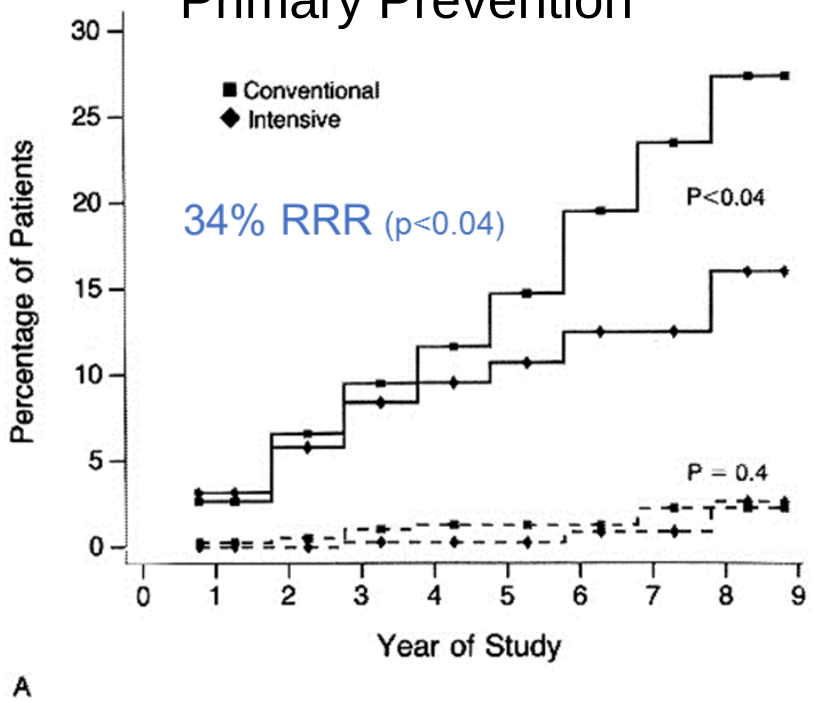
4. Diabetes Canada Clinical Practice Guidelines Expert Committee. *Can J Diabetes* 2018;42 :S201–209.

CDA: Canadian Diabetes Association; T2D: type 2 diabetes; A1C: glycated hemoglobin; BP: blood pressure; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker

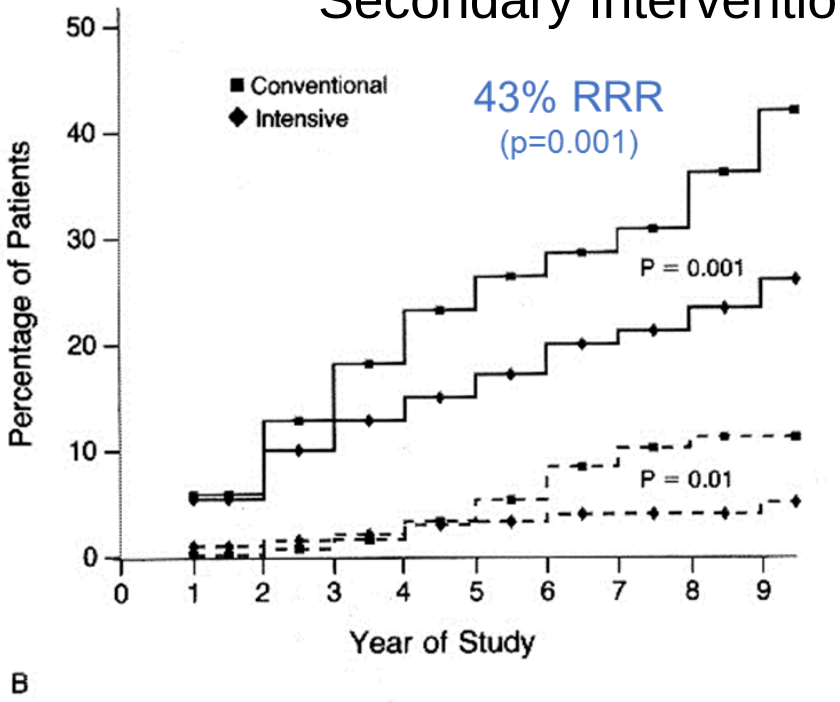
Reducing Progression of Diabetic Nephropathy

✓Optimal glycemic control

Primary Prevention



Secondary Intervention



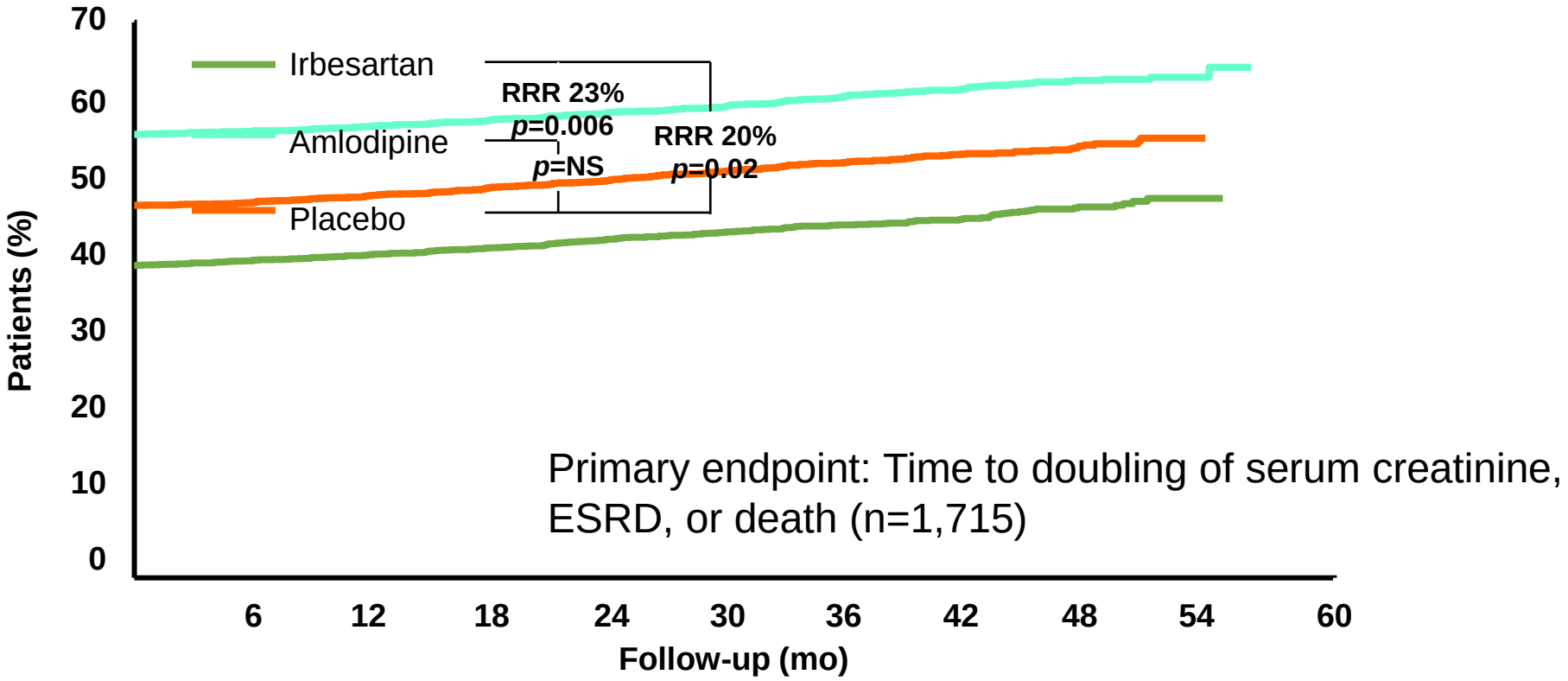
The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977-986

Reducing Progression of Diabetic Nephropathy

✓Optimal BP control

✓ACE-inhibitor or ARB **BUT not both**

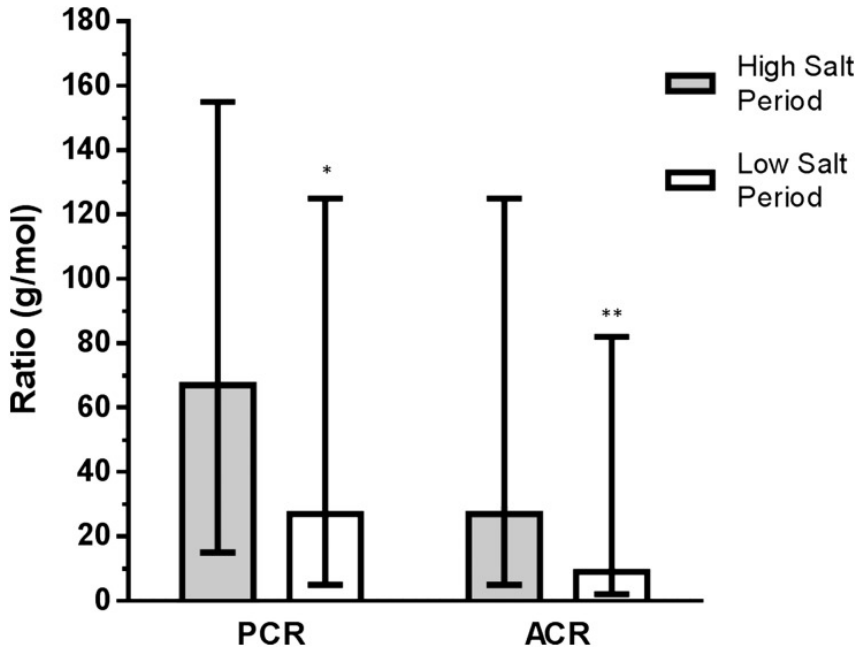
✓**Target Proteinuria 120-130/70-80**



Lewis et al. *N Engl J Med* 2001;345:851-60

ESRD, end stage renal disease

Salt Restrictions Lowers BP and Proteinuria



- Can reduce proteinuria by 30%

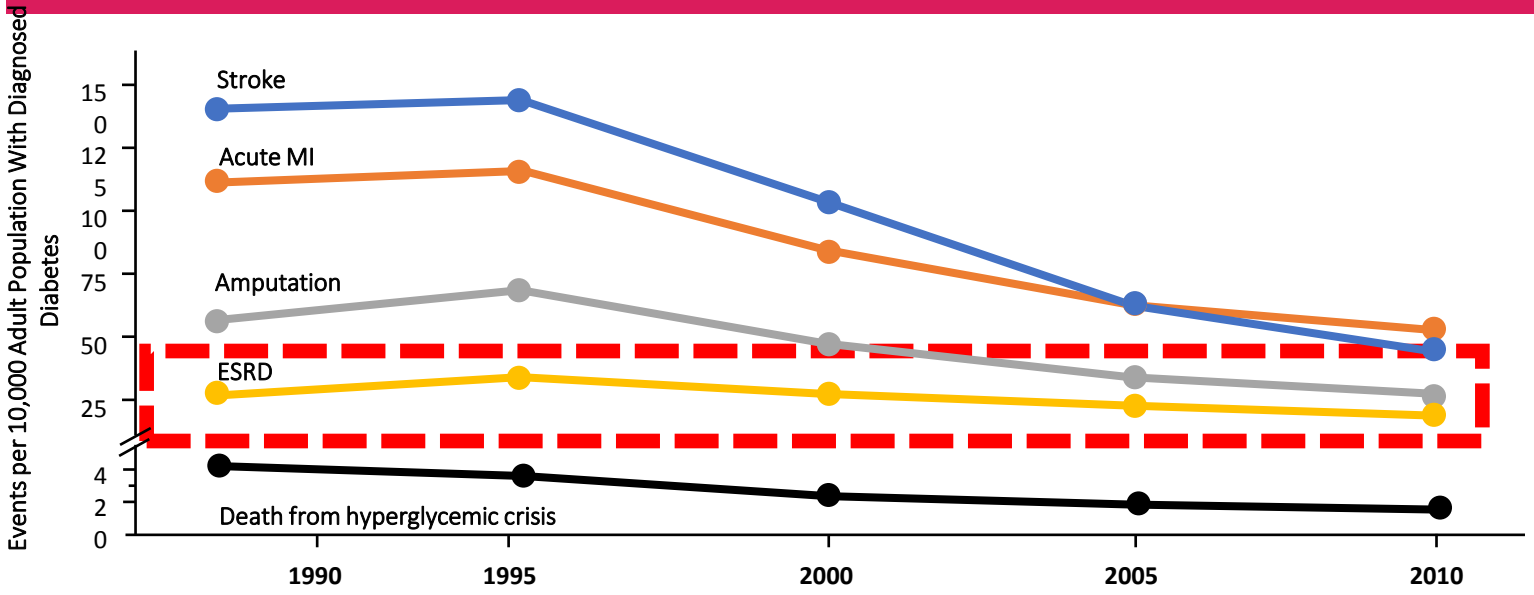
JASN December 2013 vol. 24 no. 12 2096-2103

Reducing Progression of Diabetic Nephropathy

- ✓Optimal glycemic control (as shown)
- ✓Optimal BP control
- ✓ACE-inhibitor or ARB **BUT not both**
  - ✓**Target Proteinuria 120-130/70-80**
- ✓**? SGLT2 Inhibitors**

Rates of ESRD have increased

- Rates of the other major complications in diabetes have declined
- Rates of ESRD have actually increased among older adults



ESRD, end-stage renal disease; MI: myocardial infarction

Adapted from: Gregg EW, et al. *N Engl J Med* 2014;370:1514-23.

CKD/CVD Reduced Risk with SGLT2 I/ GLP1 in DM

Meet Our Patient – Kevin

- 57 years old with type 2 diabetes for 12 years, HT, dyslipidemia, gout,, No hx of CAD or CHF
- Current meds: DPP-4 inhibitor/metformin 1 gm bid, ACE inhibitor, statin, allopurinol, ASA
- Current labs:
  - A1C = 7.9%
  - BP = 143/82 mmHg
  - eGFR = 63 mL/min
  - ALB/Cr 3
  - BMI = 27 kg/m^2
- On today's visit the patient asks about the new SGLT2 inhibitors
- Should I start one of these new drugs ?
- What are the benefits and risks
- Will it help my heart , kidneys, diabetes
- What are the risks
- What do you suggest

Thought Process ??

Physician

- Not at target A1C
- BP above target
- Proteinuria increased
- CKD
- History of CAD

Patient:

- ❑ Staying healthy
- ❑ Preventing emerg/hospitalization
- ❑ Fewer meds
- ❑ Avoidance of complications of DM

Management Of Diabetes

First-line metformin treatment for type 2 diabetes

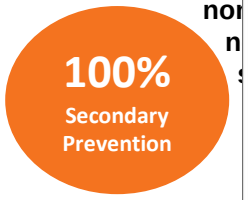
Begin treatment	Optional approach
Start with initial dose of 500 mg daily	• Consider extended-release form to minimize risk of gastrointestinal (GI) adverse effects
Adjust dose	**Approach for GI side effects**
Increase dose gradually to 2000 mg daily if tolerated	• Try extended-release form and consider using highest dose tolerable rather than stopping medication

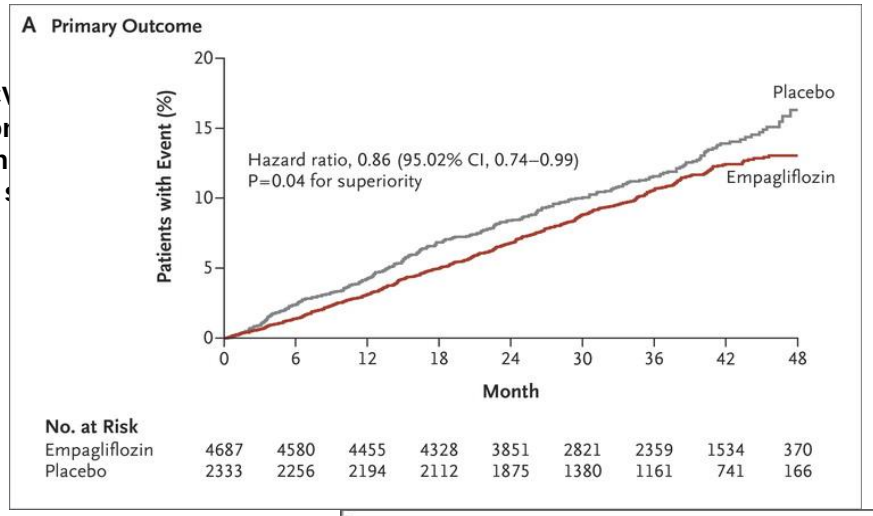
Common obstacles to using metformin

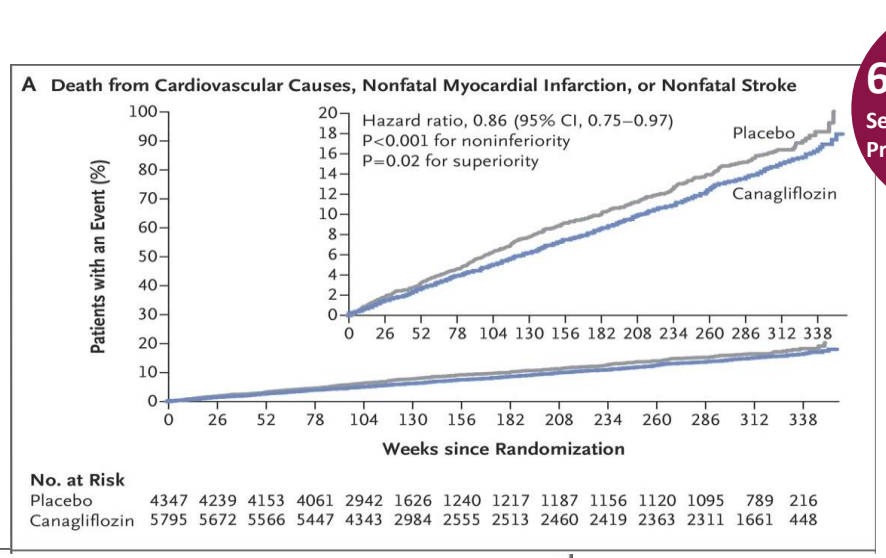
Condition	Suggested approach
GI intolerance	• Reduce dose until adverse effects resolve • Consider use of extended-release form
Impaired kidney function	• Use freely if eGFR ≥45 mL/min • Use with caution if eGFR 30-45 mL/min • Do not use if eGFR <30 mL/min
Heart failure	• Acceptable to use with stable, chronic heart failure • Do not use with acute heart failure and evidence of end-organ hypoperfusion
Liver disease	• Acceptable to use with chronic liver disease (including mildly elevated liver enzymes, but intact liver function) • Do not use with functional hepatic failure or acute liver injury

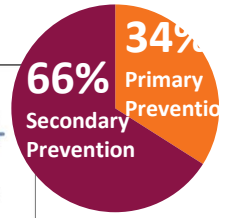
Sodium-glucose cotransporter 2 (SGLT-2) inhibitors	• Cardiovascular (CV) benefit • Weight loss	• High cost • Genitourinary infections	• Amputation [redacted]ic diabetic ketoacidosis
Glucagon-like peptide 1 (GLP-1) receptor agonists	• CV benefit • Weight loss	• High cost • Requires injections • GI adverse effects	• Pancreatitis
Dipeptidyl peptidase 4 (DDP-4) inhibitors	• Few side effects	• High cost • Modest effect on glucose levels • No CV benefit	• Pancreatitis • Heart failure (alogliptin, saxagliptin)
Sulfonylureas	• Low cost	• Weight gain • Hypoglycemia • No CV benefit	
Thiazolidinediones	• Low cost • Possible CV benefit after stroke	• Weight gain • Edema • Heart failure • Fractures	• Bladder can

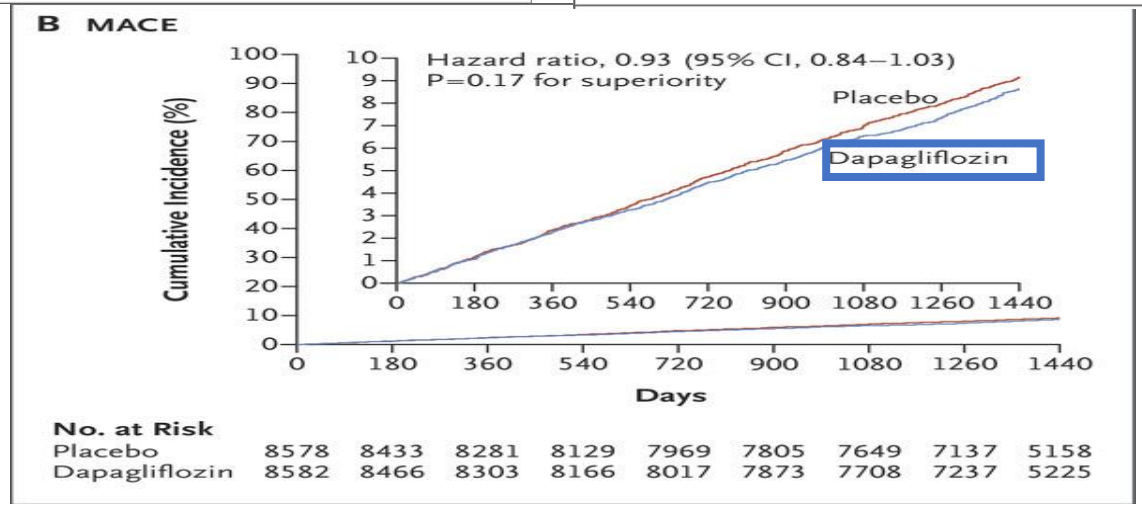
SGLT2 Inhibitors CVS Outcomes and Mortality in Type 2 DM









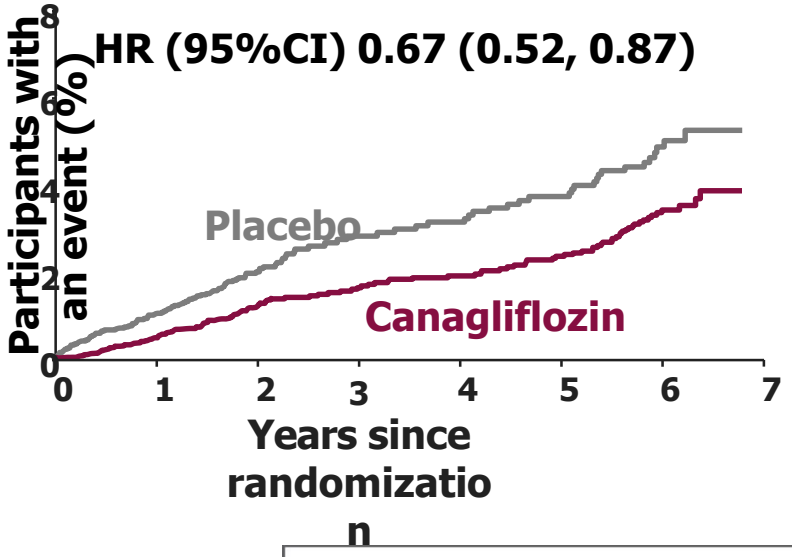


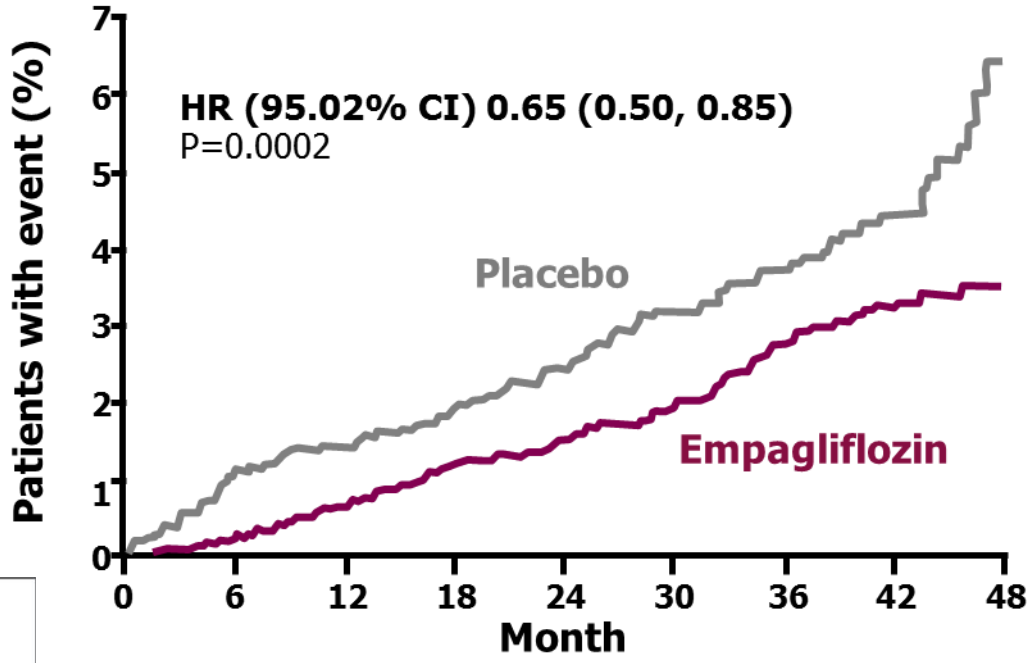
Zinman B et al. N Engl J Med. 2015;373:2117-28; Wanner C et al. N Engl J Med. 2016;375:323-34

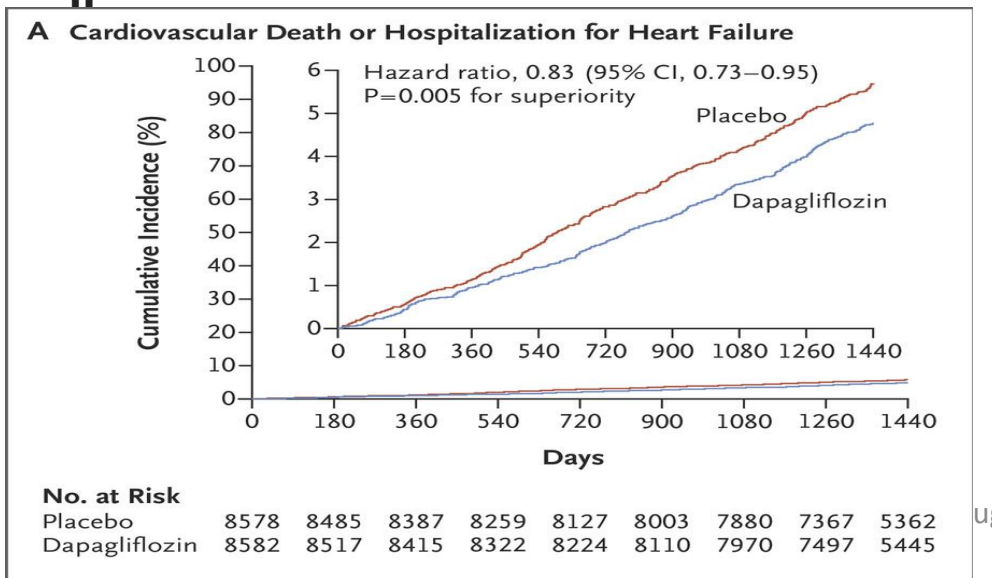
Neal B et al. N Engl J Med ;377:644-657

Stephen D. Wiviott, M.D., et al for the DECLARE–TIMI November 10, 2018DOI: 10.1056/NEJMoa1812389

SGLT2 I and Reduction in Heart Failure

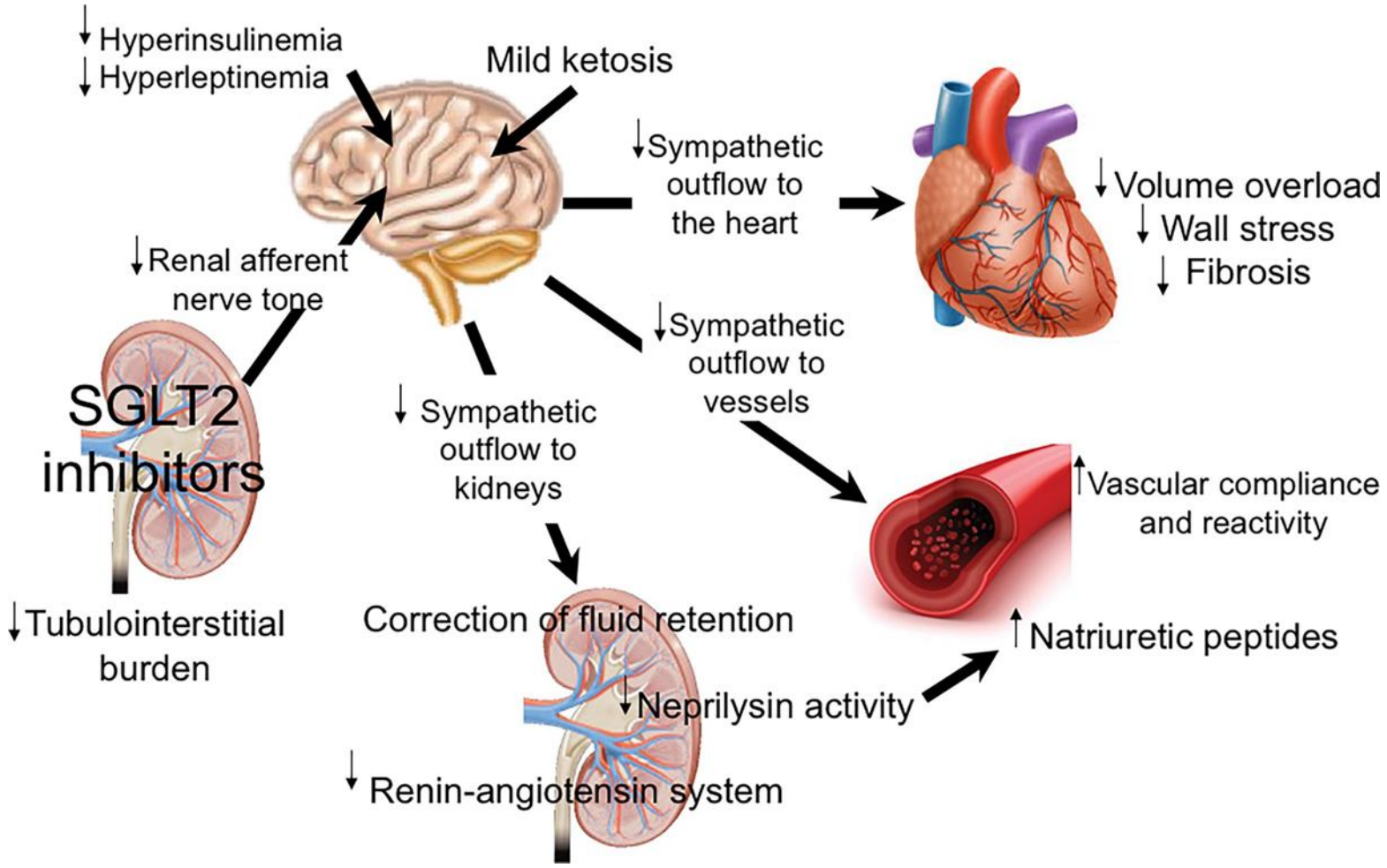






ug 17;377(7):644-657.

SGLT2 inhibitors Modulate CV risk



Inzucchi et al. Diab Vasc Dis Res 2015;12:90–100

Journal of Cardiology Volume 71, Issue 5, Pages 471–476, 2018

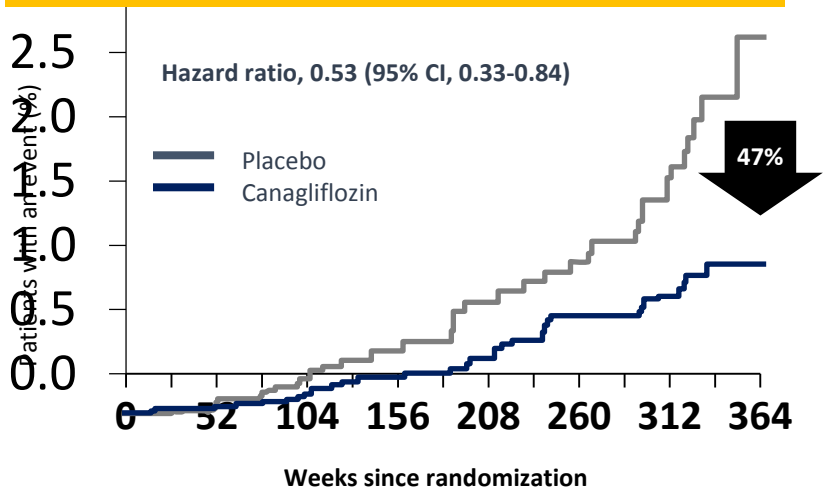
Meet Our Patient – Kevin

- 57 years old with type 2 diabetes for 12 years, HT, dyslipidemia, gout, **Stable Angina, NO MI Angio neg for intervention**
- Current meds: DPP-4 inhibitor/metformin 1 gm bid, ACE inhibitor, Hct 25, statin, allopurinol, ASA
- Current labs:
  - A1C = 7.9%
  - BP = 143/82 mmHg
  - eGFR = 63 mL/min
  - ALB/Cr 89
  - A1C=7.9
  - BMI = 27 kg/m^2
- On today's visit the patient asks about the new SGLT2 inhibitors
- Should I start one of these new drugs ?
- What are the benefits and risks
- Will it help my heart , YES
- Will it help my Kidneys

SGLT2I and Kidney Outcomes

SGLT2 inhibitors reduced the exploratory composite renal endpoint by >45%

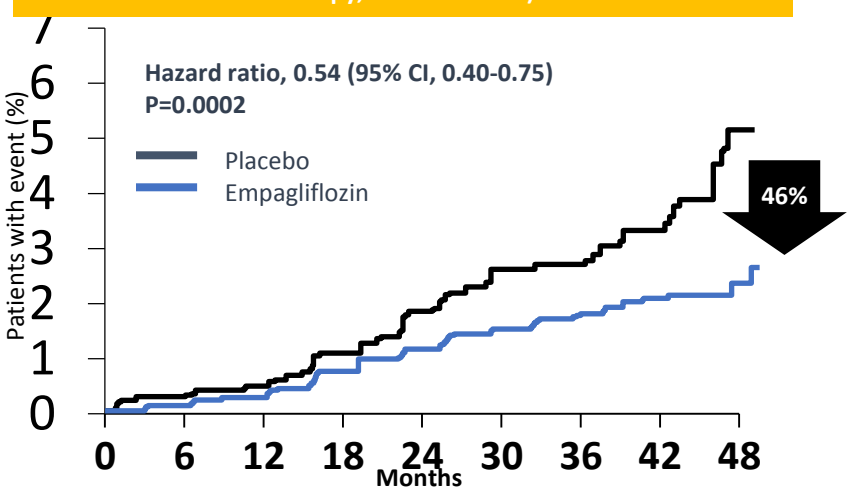
CANVAS Program[1]
(composite of doubling of SCr, ESRD, or renal death)



No. at risk

PBO	4347	4291	4235	4170	3050	1693	1294	1276	1253	1229	1200	1181	844	237
CANA	5795	5741	5677	5599	4476	3089	2670	2641	2597	2564	2520	2481	1809	501

EMPA-REG OUTCOME[2]:
(composite of doubling of SCr*, initiation of renal replacement therapy, or renal death)



No. of patients

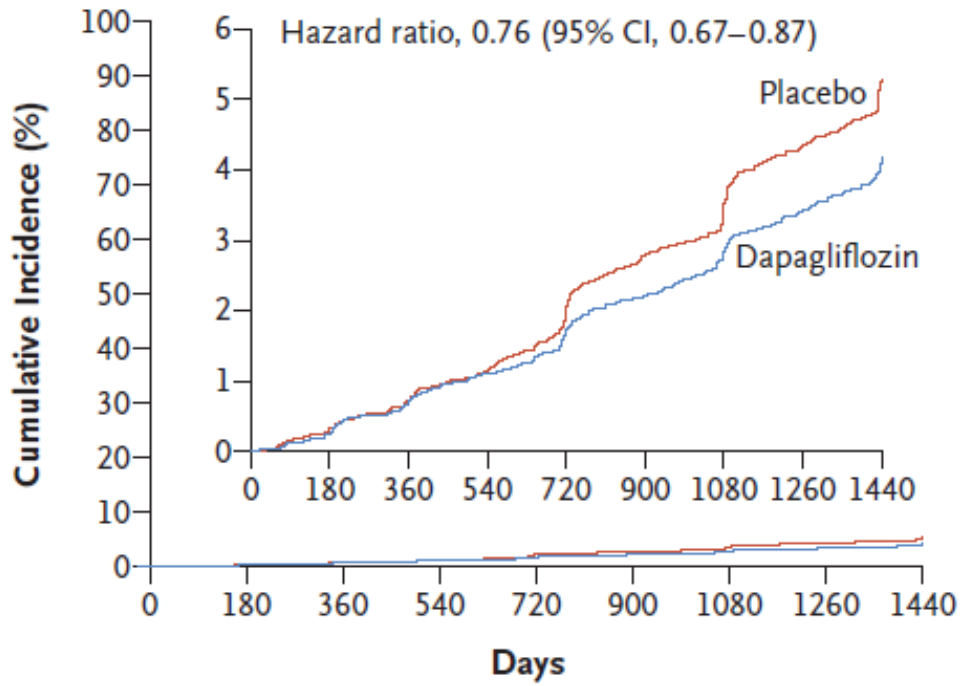
PBO	4645	4500	4377	4241	3729	2715	2280	1496	360
EMPA	2323	2229	2146	2047	1771	1289	1079	680	144

* Accompanied by eGFR ≤ 45 mL/min/1.73 m². Kaplan- Meier estimate. Treated set.

CANA: canagliflozin; SCr: serum creatinine; ESRD: end-stage kidney disease; PBO: placebo; HR: hazard ratio; CI: confidence interval

1. Perkovic V, et al. *Lancet Diabetes Endocrinol* 2018;6:691-704.
2. Wanner C, et al. *N Engl J Med* 2016;375:323-34.

C Renal Composite



No. at Risk

Placebo	8578	8508	8422	8326	8200	8056	7932	7409	5389
Dapagliflozin	8582	8533	8436	8347	8248	8136	8009	7534	5472

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy

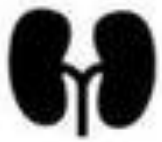
Perkovic et al. N Engl J Med DOI: 10.1056/NEJMoa1811744

The George Institute for Global Health

Study design and participants

4401 patients with T2DM & UACR >300 mg/g

62 years

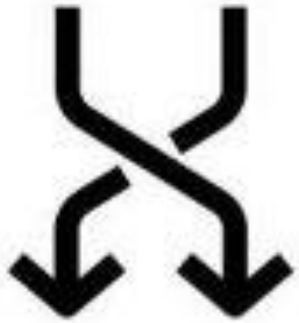


eGFR 57

UACR 927 mg/g

Intervention

Stable on maximum dose tolerated ACEi or ARB for 4 weeks

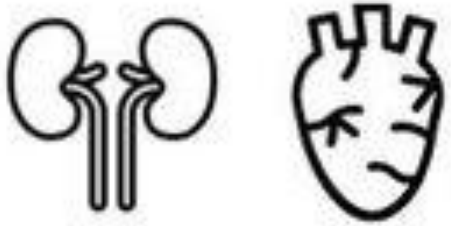


Canagliflozin **Placebo**

Outcomes

Primary outcome

(Doubling of serum creatinine, ESKD, death due to cardiovascular or kidney disease)



HR 0.70
(95% CI 0.59-0.82)

NNT 21

End-stage kidney disease

HR 0.68
(95% CI 0.54-0.86)

NNT 42

No increased risk of:

Amputations

HR 1.10
(95% CI 0.79-1.56)

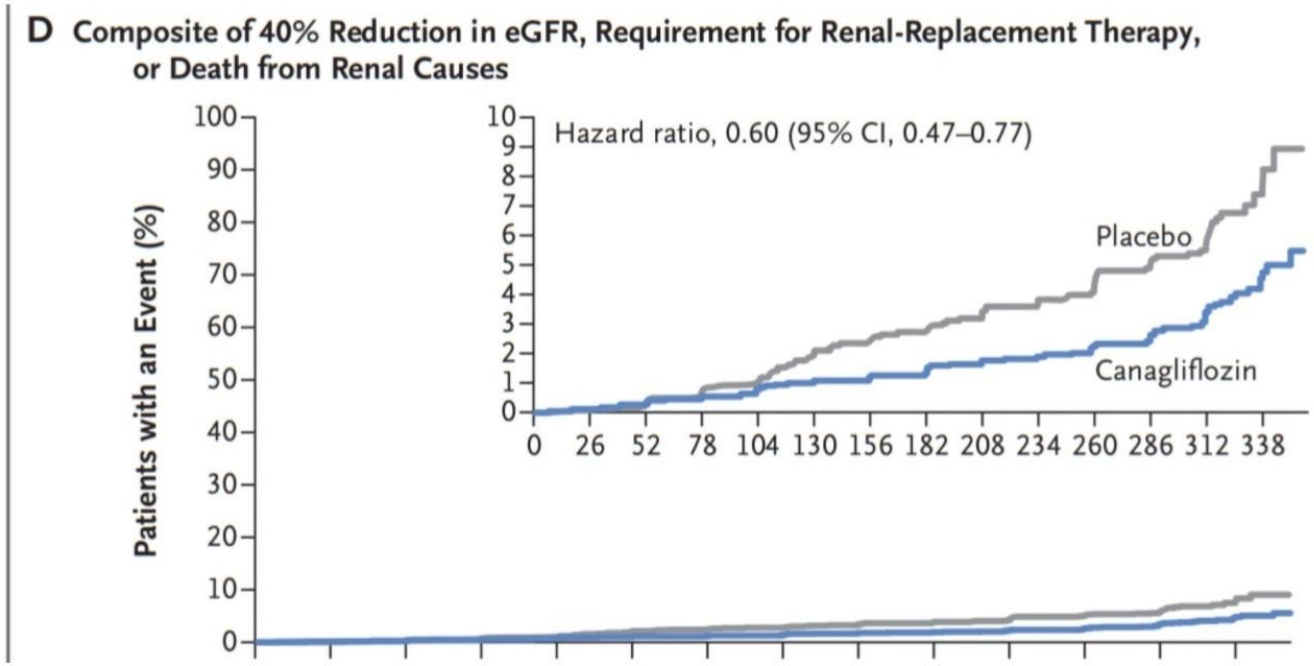
Fractures

HR 0.98
(95% CI 0.70-1.37)

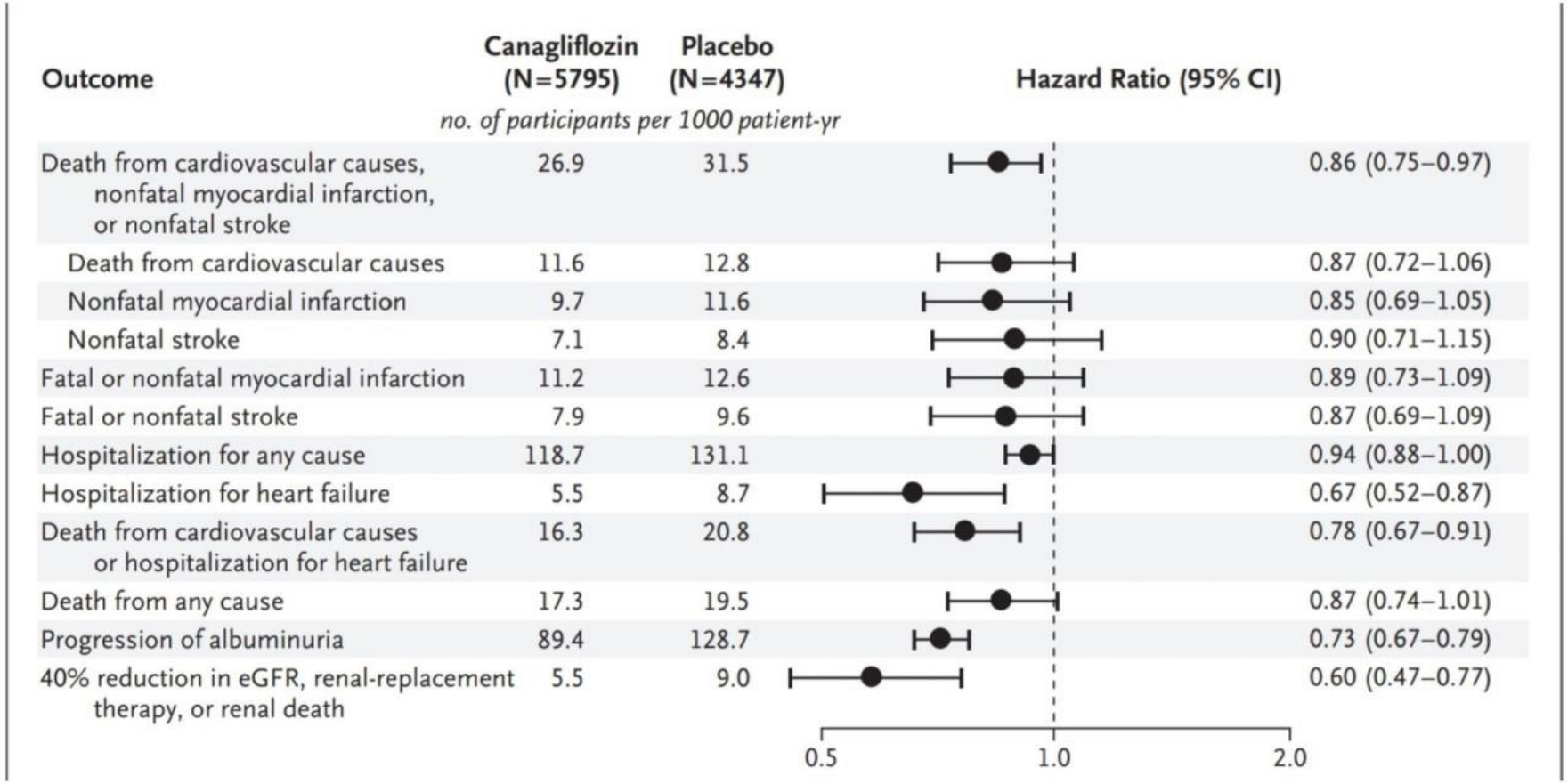
Conclusion

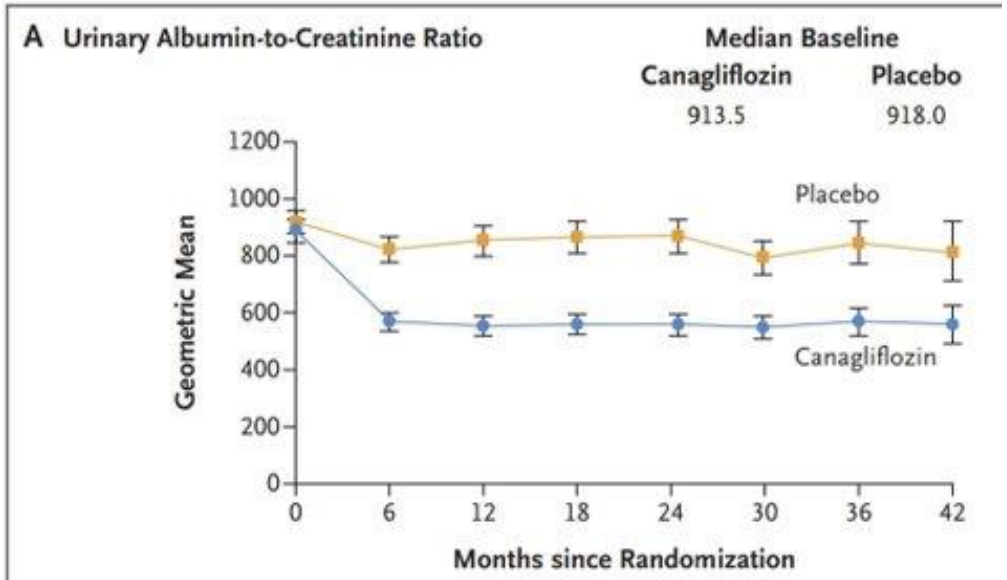
In patients with type 2 diabetes and kidney disease, canagliflozin reduces the risk of kidney failure and cardiovascular events

Canagliflozin and Renal Outcomes

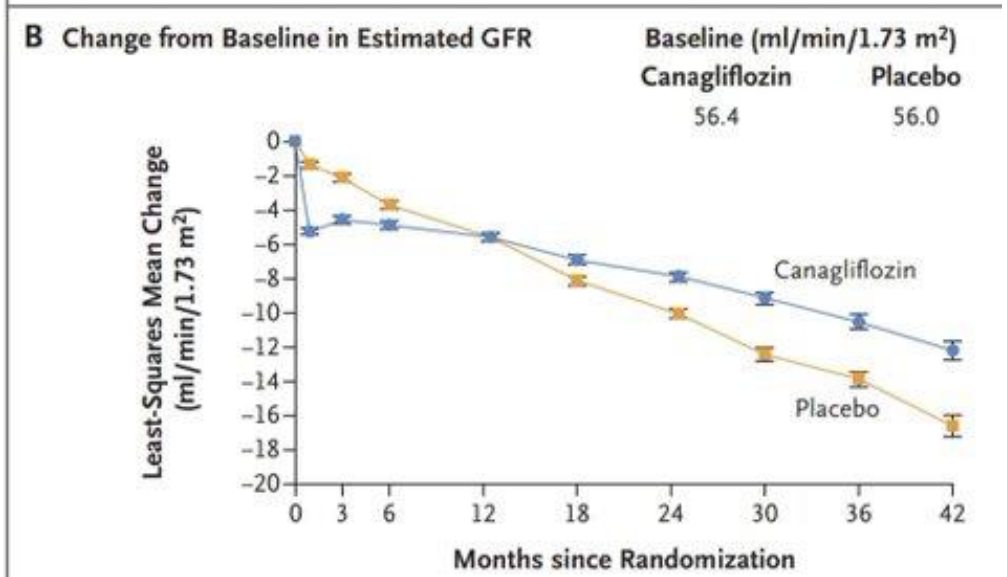


Canagliflozin and Renal Outcomes





No. of Patients								
Placebo	2113	2061	1986	1865	1714	1158	685	251
Canagliflozin	2114	2070	2019	1917	1819	1245	730	271



No. of Patients								
Placebo	2178	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2005	1919	1782	1648	1116	652	241

Putting evidence into perspective

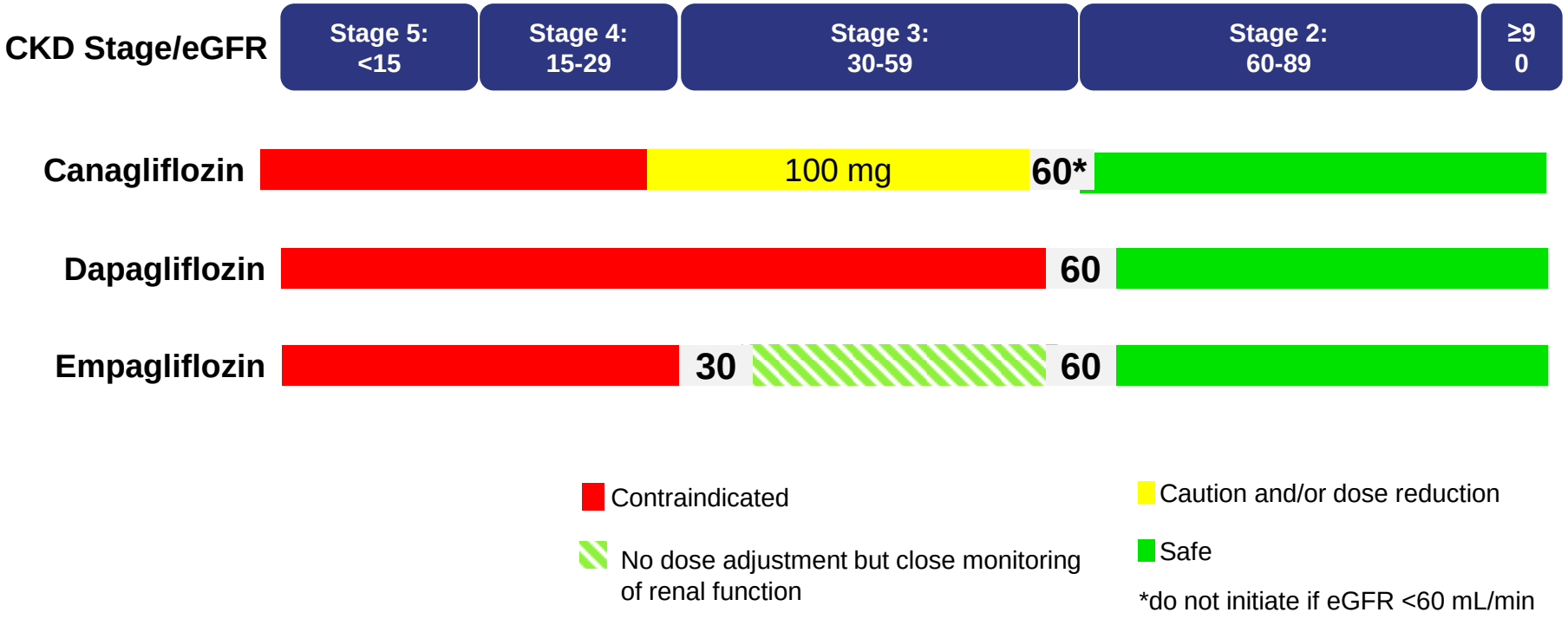
	Albuminuria	eGFR/Cr	2xCr, ESRD, Renal Death N=??	RRR
IDNT[1]	Median 1900 mg/d (1000 – 3800 mg/d)	Mean Cr: 148 µmol/L	644	20%
RENAAL[2]	Median ACR: ~1250	Mean Cr: 168 µmol/L	686	16%
CANVAS Program[3-5] (80% on RAASi)	Median UACR ~12 mg/g Normal: ~70% Micro: ~23% Macro: ~7.5%	Mean eGFR: 77 mL/min/1.73 m^2 eGFR <60: 20% eGFR<45: 6%	73	47%
EMPA-REG OUTCOME[6,7]* (81% on RAASi)	Micro: 29% Macro: 11%	Mean eGFR: 74 mL/min/1.73 m^2 eGFR<60=26% eGFR<45=8%	152	46%

- **Dedicated renal trials**
- **Patient population: advanced DKD**
- **Primary renal endpoints**
- **>1300 renal outcomes observed**
- **CVOTs not dedicated renal trials**
- **Patient population: mild or no DKD**
- **Renal outcomes were secondary endpoints and/or exploratory analyses**
- **Only ~230 renal outcomes observed**
- **But large magnitude of benefit noted**

***Kidney outcomes were not confirmed or adjudicated during the EMPA-REG OUTCOME trial[5]**

1. Lewis EJ, et al. *N Engl J Med* 2001;345:851-60. 2. Brenner BM et al *New Engl J Med* 2001;345:861-69. 3. Neal B, et al. *N Engl J Med*. 2017;377:644-57.
4. Perkovic V, et al. Presented at ASN Kidney Week 2017 Annual Meeting; October 31 – November 5, 2017; New Orleans, Louisiana.
5. Perkovic V, et al. *Lancet Diabetes Endocrinol* 2018;6:691-704. 6. Zinman B, et al. *N Engl J Med* 2015;373:2117-28. 7. Wanner C et al. *N Engl J Med* 2016;375:323-34.

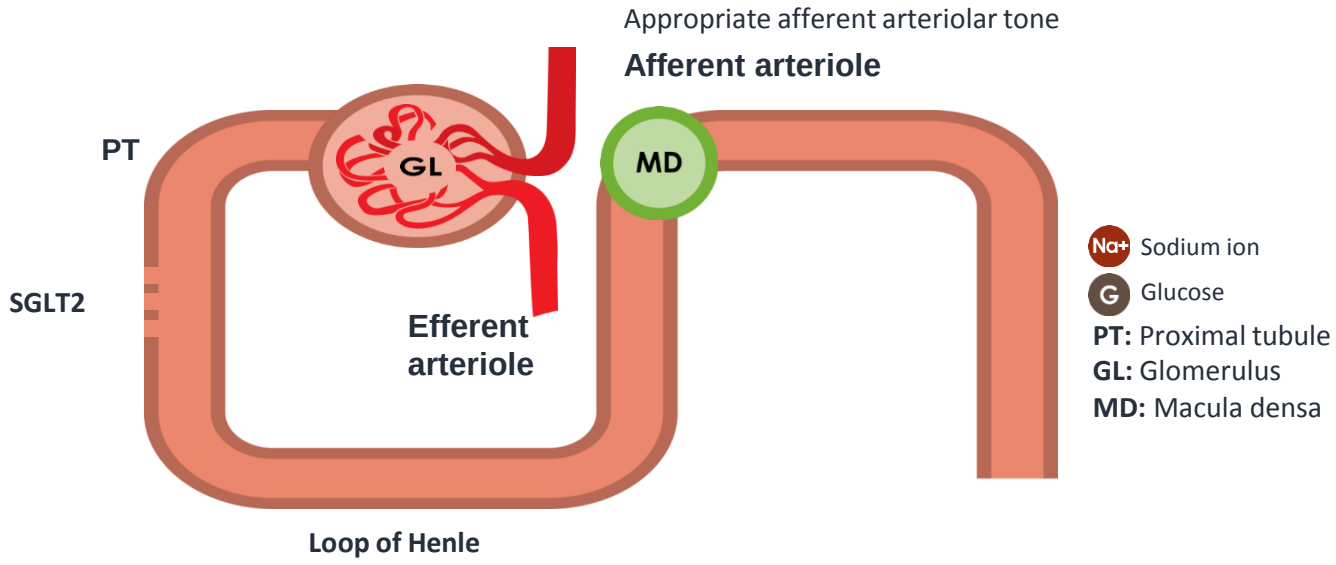
Prescribing SGLT2I According to Renal Function



Adapted from: INVOKANA® (Canagliflozin) Product Monograph, Janssen Inc, November 7, 2017, FORXIGA® (Dapagliflozin) Product Monograph, AstraZeneca Canada Inc, March 28, 2018, JARDIANCE® (Empagliflozin) Product Monograph, Boehringer Ingelheim (Canada) Ltd, April 16, 2018. Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes 42 (2018) S315.

Leading Hypothesis: Tubuloglomerular feedback (TGF)

The healthy kidney:



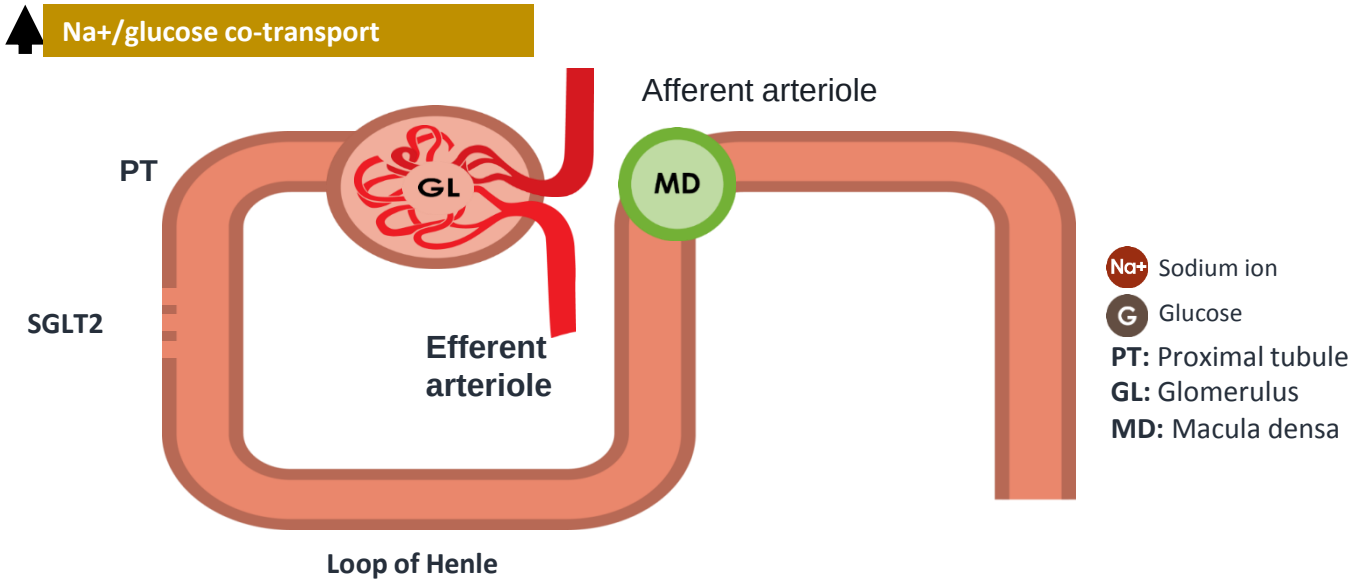
Renal hemodynamics under euglycemia

SGLT, sodium glucose cotransporter; GFR, glomerular filtration rate.

Adapted from: Cherney D, et al. *Circulation* 2014;129:587.

Tubuloglomerular feedback (TGF) hypothesis (cont'd)

Diabetes causes glomerular hypertension: LOSS of TGF



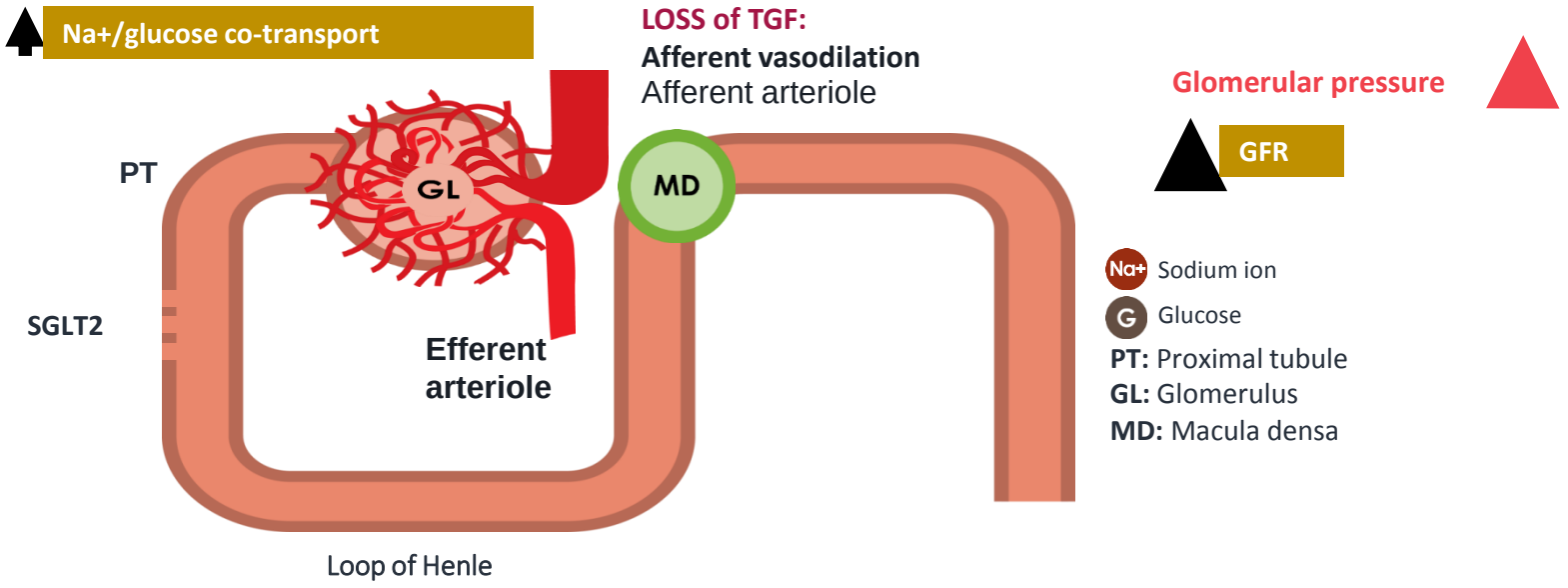
Renal hemodynamics under hyperglycemia

SGLT, sodium glucose cotransporter; GFR, glomerular filtration rate.

Adapted from: Cherney D, et al. *Circulation* 2014;129:587.

Tubuloglomerular feedback (TGF) hypothesis (cont'd)

Diabetes causes glomerular hypertension: LOSS of TGF



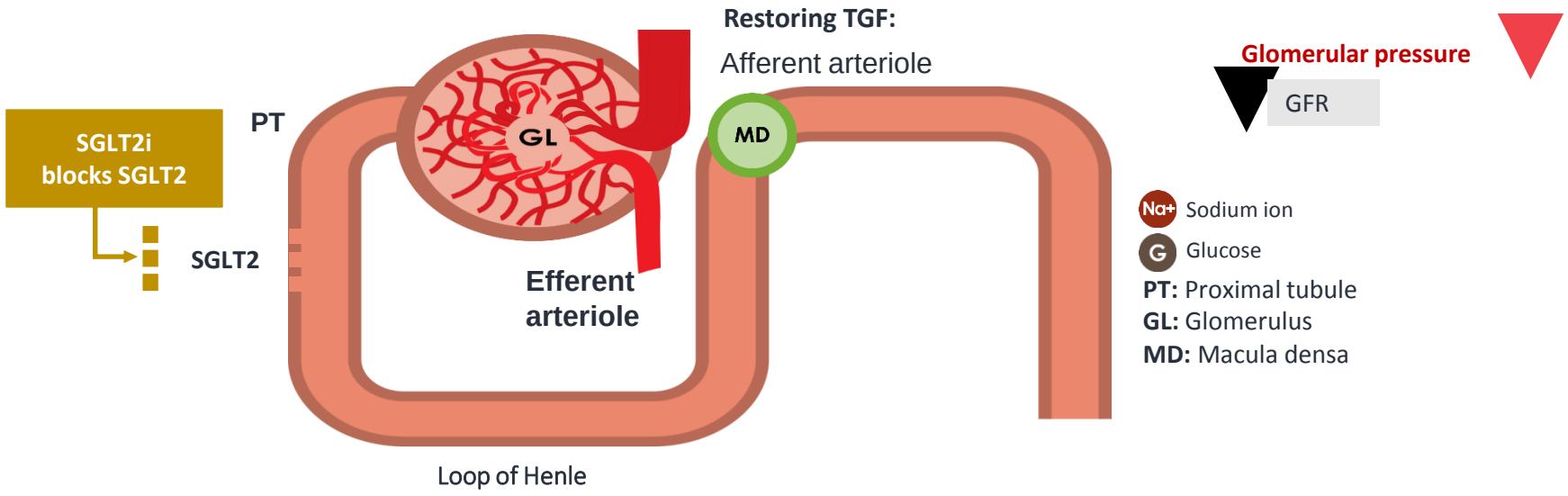
Renal hemodynamics under hyperglycemia

SGLT, sodium glucose cotransporter; GFR, glomerular filtration rate

Adapted from: Cherney D, et al. *Circulation* 2014;129:587.

Tubuloglomerular feedback (TGF) hypothesis (cont'd)

SGLT2i lowers intraglomerular pressure in DM



Renal hemodynamics with SGLT2i

SGLT, sodium glucose cotransporter; GFR, glomerular filtration rate

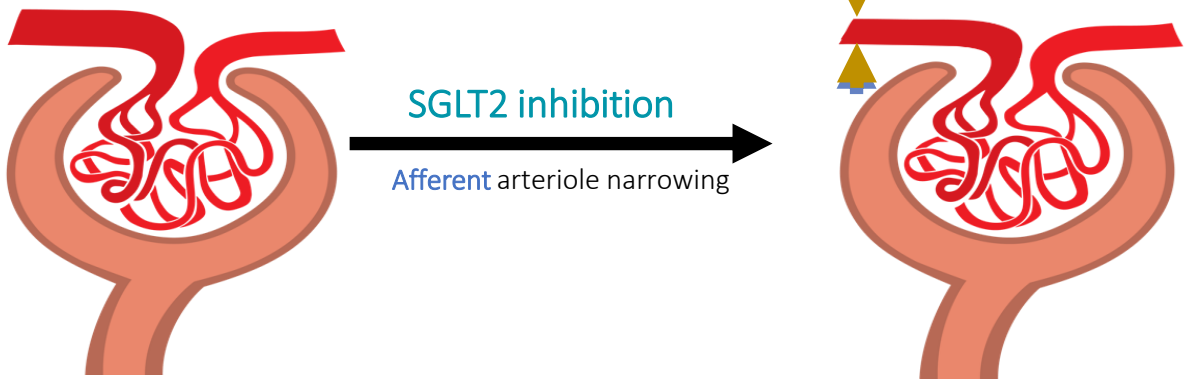
Adapted from: Cherney D, et al. *Circulation* 2014;129:587.

Tubuloglomerular feedback (TGF) hypothesis (cont'd)

SGLT2i exerts a hemodynamic effect within the kidney

- By restoring the tubuloglomerular feedback (TGF), SGLT2i increase the afferent arteriole tone, thereby lowering glomerular hypertension

Action:



Clinical implications:

- Glomerular pressure decreases
- Early clinical marker:
  - Initial dip in GFR
  - Reduction of albuminuria
- Long term:
  - Possible renal benefits?

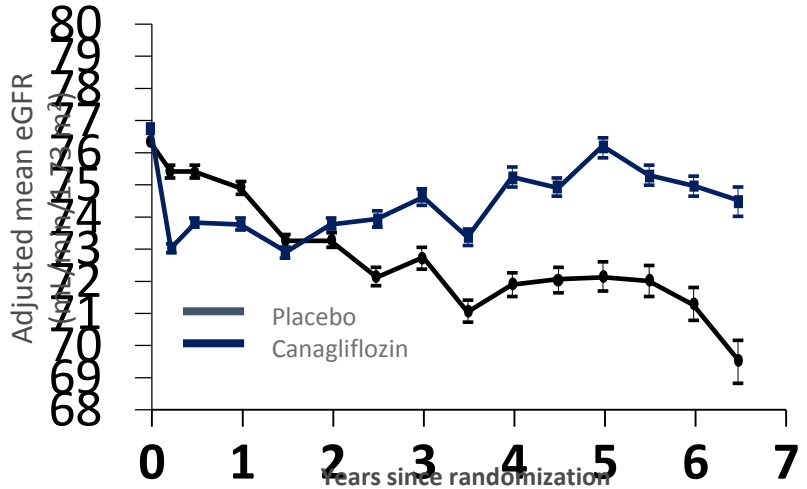
SGLT, sodium glucose cotransporter; GFR, glomerular filtration rate

Adapted from: Cherney D, et al. *Circulation* 2014;129:587; Skrtic M, et al. *Diabetologia* 2014;57:2599.

Why does the eGFR drop when initiating the SGLT2

In CVOTs, eGFR remained stable over time with SGLT2 inhibitors

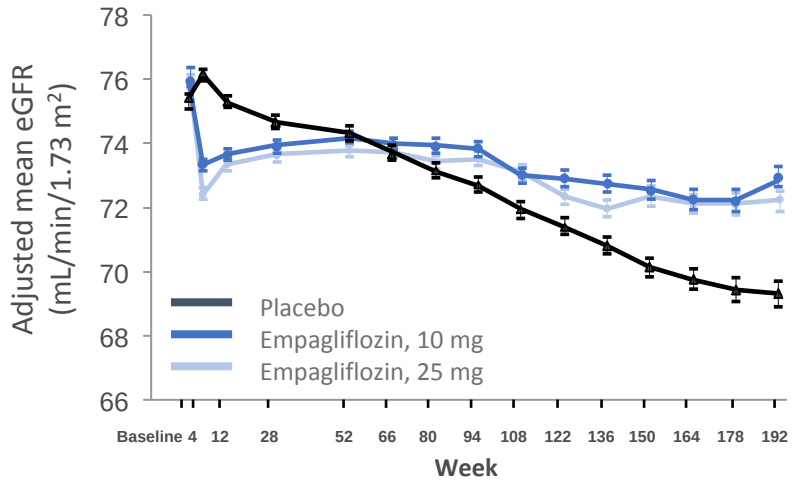
CANVAS Program:
Change in eGFR over 6.5 years[1]



No. of patients

PBO	4276	3867	3212	1030	899	809	694
CANA	5711	5212	4570	2230	2039	1895	1653

EMPA-REG OUTCOME:
Change in eGFR* over 192 weeks[2]



No. at risk

PBO	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
EMPA, 10 mg	2322	5590	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
EMPA, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524

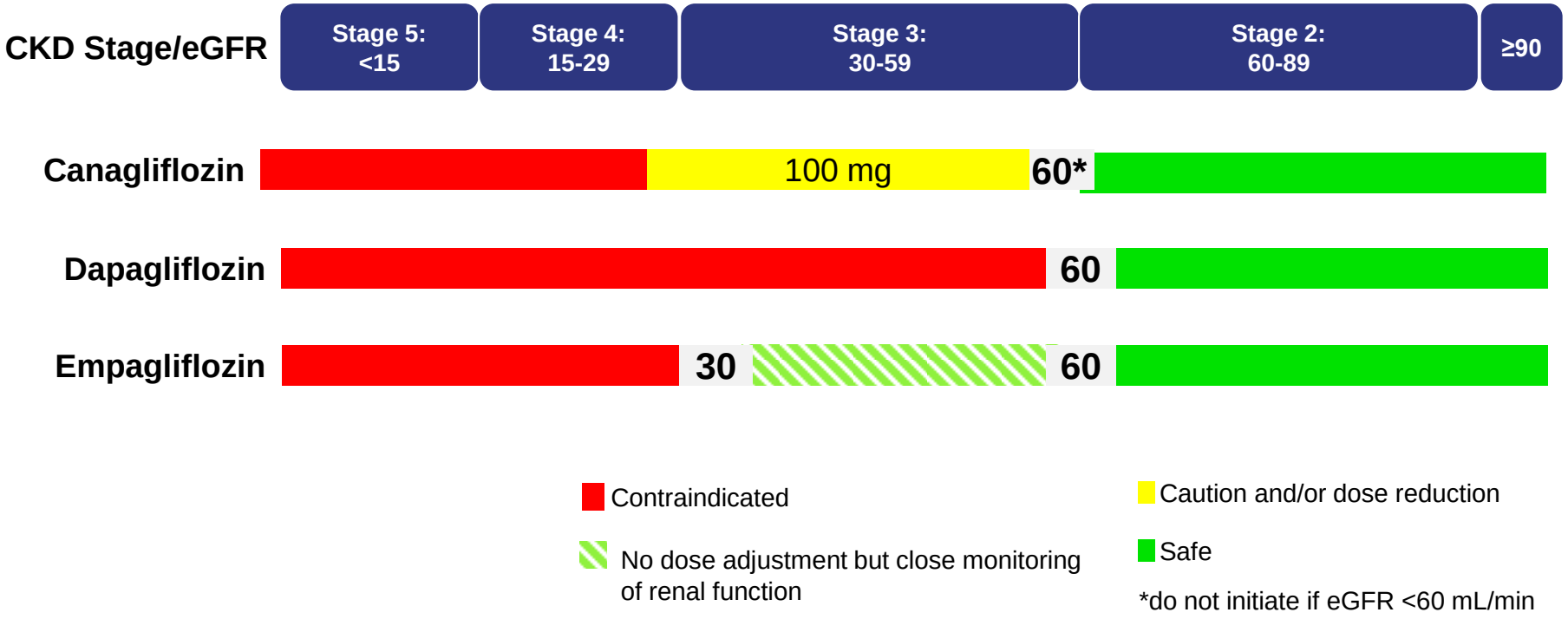
*CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; CVOTs: cardiovascular outcome trials

1. Perkovic V, et al. *Lancet Diabetes Endocrinol* 2018;6:691-704.
2. Wanner C, et al. *N Engl J Med* 2016;375:323-34.

Meet Our Patient – Kevin

- 57 years old with type 2 diabetes for 12 years, HT, dyslipidemia, gout, Stable Angina, NO MI Angio neg for intervention
- Current meds: DPP-4 inhibitor/metformin 1 gm bid, ACE inhibitor, Hct 25, statin, allopurinol, ASA
- Current labs:
  - A1C = 7.9%
  - BP = 143/82 mmHg
  - eGFR = 63 mL/min
  - ALB/Cr 89
  - A1C=7.9
  - BMI = 27 kg/m^2
- On today's visit the patient asks about the new SGLT2 inhibitors
- Should I start one of these new drugs ?
- Will it benefit my kidneys
- yes

Prescribing SGLT2I According to Renal Function



Adapted from: INVOKANA® (Canagliflozin) Product Monograph, Janssen Inc, November 7, 2017, FORXIGA® (Dapagliflozin) Product Monograph, AstraZeneca Canada Inc, March 28, 2018, JARDIANCE® (Empagliflozin) Product Monograph, Boehringer Ingelheim (Canada) Ltd, April 16, 2018. Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes 42 (2018) S315.

SGLT2i-Associated Side Effects

Common
Genital infections

Less Common
Urinary tract infections
Osmotic diuresis, hypovolemia, hypotension
Mild LDL-C increase

Rare
Diabetic ketoacidosis*
Amputations†
Possible increase in fractures‡
Increase in bladder cancer§

*, observed with all SGLT2 inhibitors; †, avoid using canagliflozin in individuals with a history of lower extremity amputation(s); ‡, observed with canagliflozin; §, observed with dapagliflozin.
Adapted from Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2018 Apr;42 (Suppl 1):S88-103.

SGLT2 Inhibitors
Renal Adverse Effects

- Polyuria
- Volume Depletion
- AKI
- Hyperkalemia

- No significant differences but reported in mild renal dysfunction and effect cumulatively are 15-≅20% in both groups (so you will see it)

DKA with SGLT2 Inhibitors

- May occur in **≤ 0.1%** of SGLT2i- treated T2D
- Some are **euglycemic DKA**

Triggers Include:

- surgery, extensive exercise, MI
- stroke, infections, **prolonged fasting, keto diet**
- stressful physical and medical conditions

shift substrate metabolism from carbohydrate to fat oxidation, predisposing to ketonemia and DKA

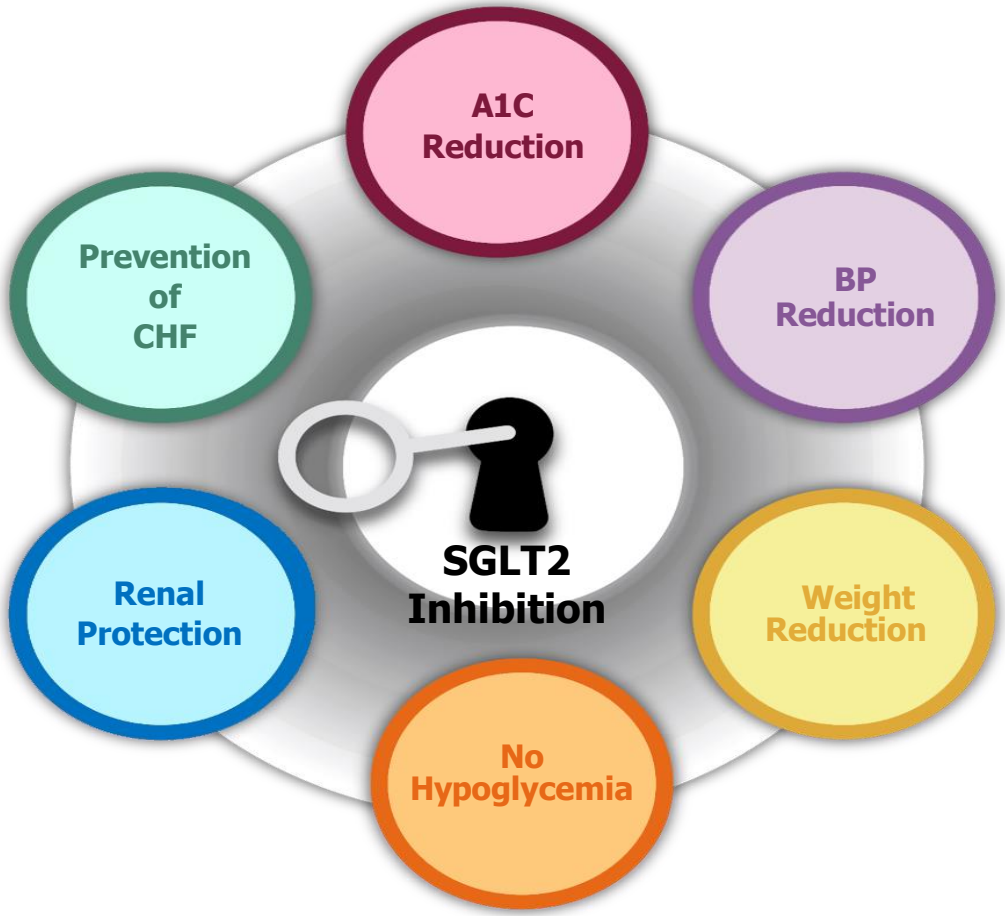
Risk Mitigation

- Stop SGLT-2 inhibitor 24-72 h before elective surgery, invasive procedures, or anticipated severe stressful physical activity
- Discourage fasting(Ramadan?),very low Carbs
- Urinary glucose loss due to SGLT-2 I may persist after the drug is stopped. Monitor if NPO
- Avoid stopping insulin or ↓ the dose excessively.
- Avoid excess alcohol intake

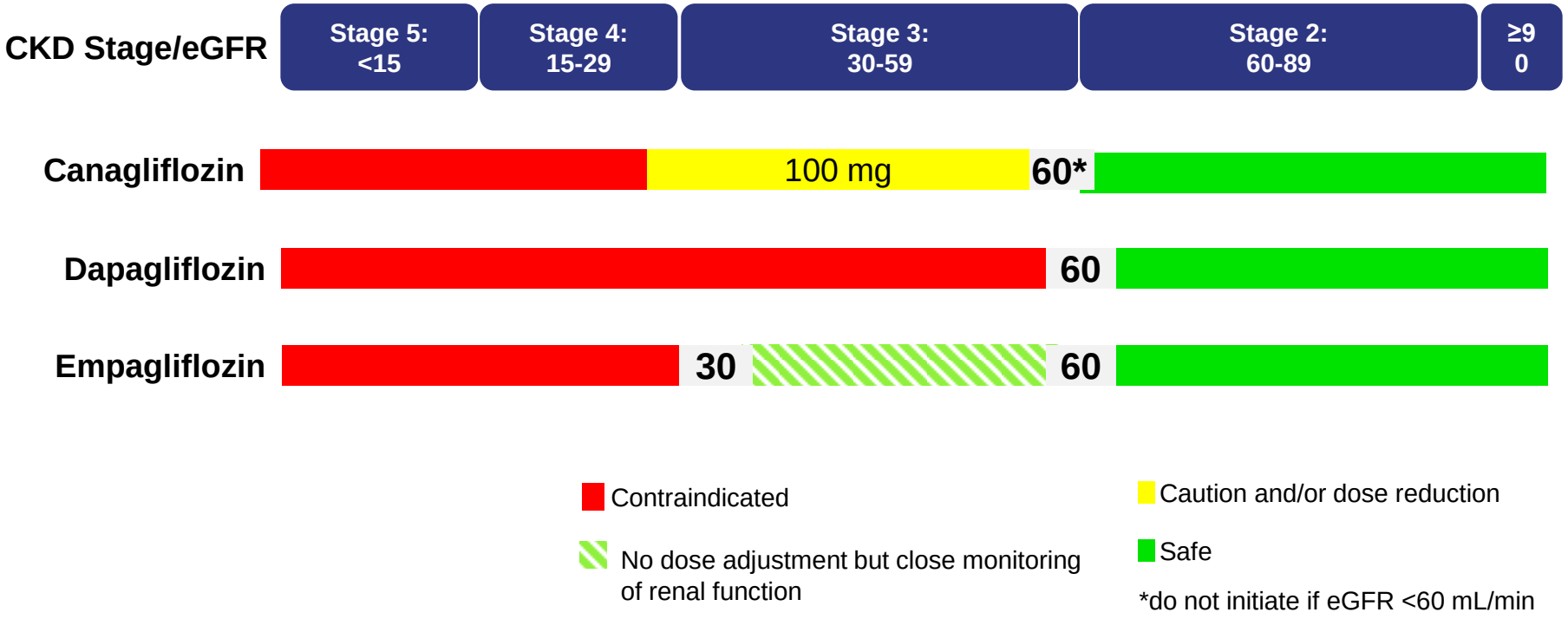
Meet Our Patient – Kevin

- 57 years old with type 2 diabetes for 12 years, HT, dyslipidemia, gout, Stable Angina, NO MI Angio neg for intervention
- Current meds: DPP-4 inhibitor/metformin 1 gm bid, ACE inhibitor, Hct 25, statin, allopurinol, ASA
- Current labs:
  - A1C = 7.9%
  - BP = 143/82 mmHg
  - eGFR = 63 mL/min
  - ALB/Cr 89
  - A1C=7.9
  - BMI = 27 kg/m^2
- On today's visit the patient asks about the new SGLT2 inhibitors
- Should I start one of these new drugs ?
- What are the benefits and risks

Benefits of SGLT 2 Inhibitors



Prescribing SGLT2I According to Renal Function



Adapted from: INVOKANA® (Canagliflozin) Product Monograph, Janssen Inc, November 7, 2017, FORXIGA® (Dapagliflozin) Product Monograph, AstraZeneca Canada Inc, March 28, 2018, JARDIANCE® (Empagliflozin) Product Monograph, Boehringer Ingelheim (Canada) Ltd, April 16, 2018. Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes 42 (2018) S315.

Patient Information

- Must drink water
  - Usually see increase in diuresis 500ml
  - Will depend on the glucose loads which acts as a diuretic
  - Avoid cramps, muscle spasm
- Also causes sodium loss (good for edema!)
- Patient must stop if not taking fluids or symptomatic low BP
- DO not use if fasting or on Keto diet
- Sick Day Drug along with Metformin, ACEI/ARB, diuretic

Key Points SGLT2 I Kidney Adverse Effects

- **What factors will influence this**
  - Kidney reserve /eGFR
  - Dehydration
  - Use of ACEI/ARB/DRI
  - Use of NSAIDs
- Suggested monitoring
  - Repeat K, Creat if volume status uncertain or ↓eGFR, ↑K
- Reassess BP in 1 mo
- Consider stopping diuretic if BP close to target
- Lower Insulin if sugars high
- Stop NSAIDs

Patient Information

SGLT2 Inhibitors

Type of drug	SGLT2 inhibitors
How does it work?	Reduces glucose (sugar) levels in your body by increasing the amount of sugar you pass in your urine
Typical names	Canagliflozin (Invokana®), Dapagliflozin (Forxiga™), Empagliflozin (Jardiance™)
Usual doses	• Canagliflozin 100 mg may be increased to 300 mg (Your dose may depend on your kidney function) • Dapagliflozin 5 mg may be increased to 10 mg • Empagliflozin 10 mg may be increased to 25 mg
Dosing instructions	Take once a day as directed by your healthcare provider
What if I forget a dose?	• Take it as soon as you remember • If more than 12 hours has passed since your missed dose, then skip the missed dose and take the next dose at the regularly prescribed time • Do not double your dose
A1C lowering (↓ = least, ↓↓↓ = most)	↓↓ to ↓↓↓
Effect on weight	↓↓
Risk of low blood sugar (hypoglycemia)	Rare
Medication considerations and/or side effects	• May cause yeast infections, urinary tract infections, low blood pressure and slight increase in cholesterol • If you take medication for blood pressure discuss this with your doctor • In rare cases, this medication may cause diabetic ketoacidosis (DKA), which is acid build up in the blood
When to call your doctor	• Call if you have signs of DKA, which may include nausea, vomiting, lack of appetite, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue, or sleepiness
When you are sick	• When you are sick, vomiting, have diarrhea, or cannot drink enough fluids, you should stop taking this medication until these symptoms go away
Cost ($ = lowest, $$$$ = highest)	$$$

diabetes.ca
1-800-BANTING (226-8464)
Canadian Diabetes Association

TABLE 11 **Patient and Clinician Preferences and Priorities for Considering SGLT2 Inhibitors with Demonstrated CV Benefit Versus GLP-1RAs With Demonstrated CV Benefit**

Consider Using an SGLT2 Inhibitor First When Patient and Clinician Priorities Include:	Consider Using a GLP-1RA First When Patient and Clinician Priorities Include:
Reducing MACE and CV death	Reducing MACE and CV death
Preventing heart failure hospitalization	Substantial weight loss
Reducing blood pressure	Once weekly (subcutaneous) dosing
Orally administered therapies	Therapy when eGFR consistently <45 ml/min/1.73 m^2*
Consider alternative agents if: ■ Significant CKD* ■ History of prior amputation, severe peripheral arterial disease, neuropathy, or diabetic foot ulcers (avoid canagliflozin) ■ History of recurrent genital candidiasis ■ History of diabetic ketoacidosis ■ History of osteoporosis (avoid canagliflozin)	Consider alternative agents if: ■ Persistent nausea, even at low doses ■ History of pancreatitis ■ History of gastroparesis ■ History of MEN2 or medullary thyroid cancer ■ History of proliferative retinopathy (semaglutide)

*eGFR <45 ml/min/1.73 m^2 is currently a caution due to a decrease in glycemic efficacy

Thank You