Diuretics 2026

Peter Magner

Conflicts of interest

- I prescribe lots of diuretics

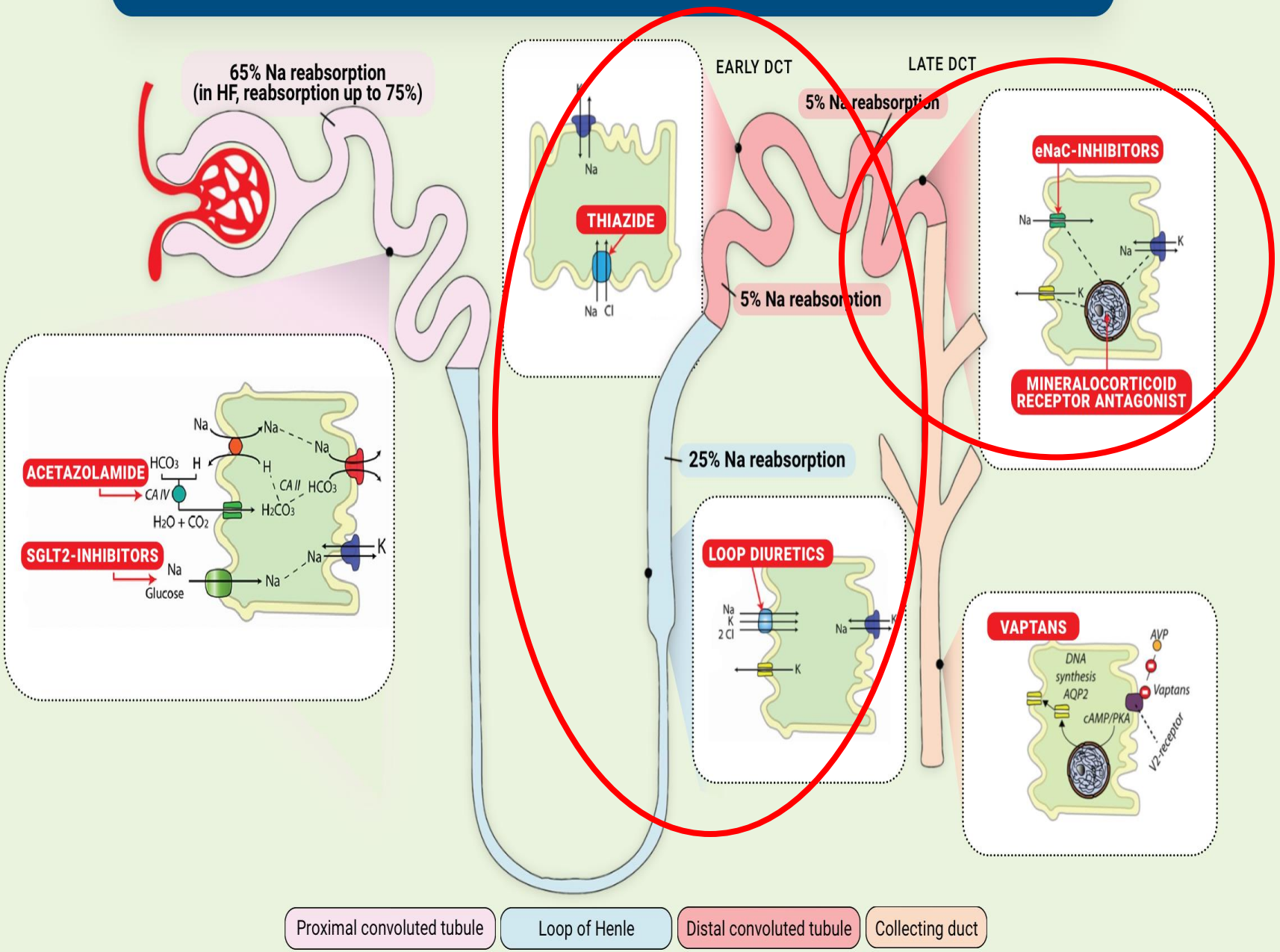
Diuretics = increase urine output

Natriuretics

- Increase urine sodium excretion
  → decrease body Na content
  = lower ECF Volume
  &/or lower BP

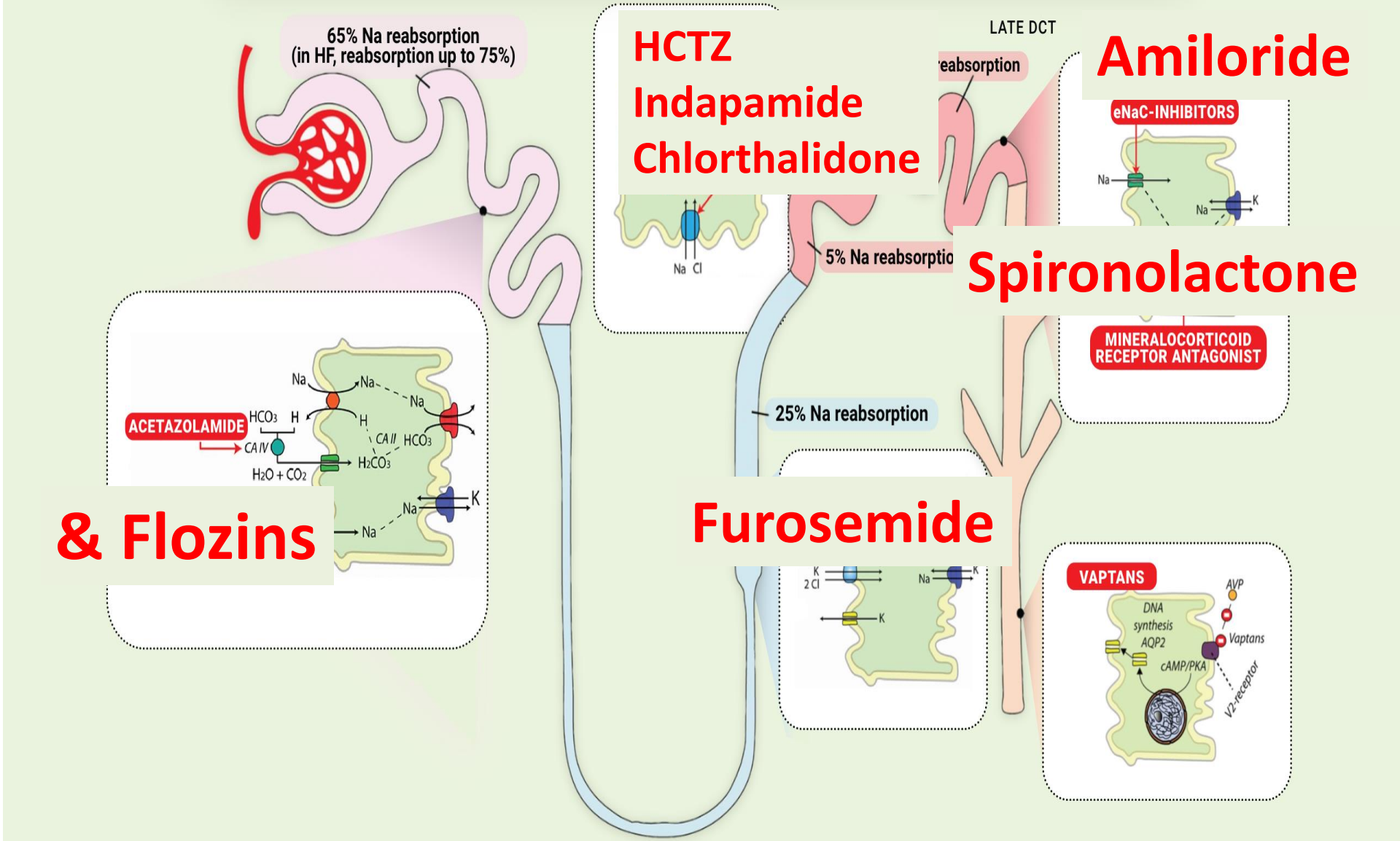
- Kaliuretics = most natriuretics that work upstream of collecting duct
- (Aquaretics = Vaptans that block ADH action & increase water excretion)

Site and Mechanism of Action of Diuretics



Adapted from Mullens, W., et al. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the ESC. European Journal of Heart Failure. 2018; Volume: 21, Issue: 2, Pages: 137-155.

Site and Mechanism of Action of Diuretics



Adapted from Mullens, W., et al. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the ESC. European Journal of Heart Failure. 2018; Volume: 21, Issue: 2, Pages: 137-155.

How to choose a diuretic?

Indication :

- ECFV overload
  - Pulmonary edema
  - Leg edema
  - Ascites
- High BP
- Kidney stones?
- High K

Potassium

- High K
- Low K

Tubular site of action?

Potency

What diuretic for ECFV overload?

Pulmonary edema/CHF

→Furosemide (no advantage of bumetanide or torsemide) .

rarely ethacrynic acid (non-sulphonamide)

&

→**Spironolactone** (or amiloride)

(unless K is high)

Synergistic diuresis

- Imroved outcomes
- Much better than KCl supplements!

CHF resistant to diuretics?

→Furosemide BID

- Double dose
- Usual max ~ 160 BID

&

→Spironolactone or amiloride (unless K is high)

» Synergistic diuresis

» Much better than KCl supplements!

→Thiazide-like :

- Metolazone is just a **very** potent thiazide

➢ Sliding scale, according to weight

Flexible Diuretic Regimen for Patients with Kidney Disease

Date _____

- Weigh yourself every morning, undressed, before breakfast and record your weight on the weight record sheet

Your target weight is: _____

- If your weight is **less** than _____ do not take **Furosemide** (Lasix)
- If your weight is _____ to _____ take **Furosemide** _____ (__ tabs) once daily in AM
- If your weight is _____ to _____ take **Furosemide** _____ (__ tabs) AM **&** _____ (__ tabs) PM
- If your weight is _____ to _____ take **Furosemide** _____ (__ tabs) AM **&** _____ (__ tabs) PM
- If weight is **greater** than _____ take **Furosemide** _____ (__ tabs) AM **&** _____ (__ tabs) PM

Metolazone (Zaroxolyn) to your diuretic regimen.

- If your weight is greater than _____ take Metolazone ___ mg (__tabs) **once** daily

at the same time as AM dose of Furosemide

Spironolactone not usually adjusted daily: it is long acting

Other causes of ECFV overload?

Ascites due to cirrhosis

- RAS very activated in cirrhosis
  - Spironolactone; often need very high dose

& sometimes

- Furosemide (particularly if K is high)

What diuretic for ECFV overload?

Leg edema

Think about cause

- CHF?
  - LV failure with pulmonary congestion?
  - RV failure/pulmonary HTN?
- Venous stasis
  - Venous occlusion
  - Obesity
- Inflammation
- **Amlodipine & Nifedipine**

- ➢ Furosemide if BP not high
- ➢ Maybe Thiazide-like if BP high
- ➢ If intravascular depletion, low BP, low Lt heart filling: may have to reduce or avoid diuretics

What diuretic for Hypertension?

What diuretic for Hypertension?

→Thiazide-like or HCTZ

- More BP lowering than Furosemide

Thiazide-like diuretics

Indapamide & Chlorthalidone are:

- Longer acting & more potent than HCTZ
- More effective for BP reduction ?
- More potent: for BP lowering & *side effects*
- Chlorthalidone 25 ~ Indapamide 5 ~ HCTZ 50-75 mg

- So don't start a diuretic-naïve patient on chlorthalidone 50 mg (the smallest size tablet in Canada)!!
- Maybe start with Indapamide 1.25 mg or HCTZ 12.5

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 29, 2022 VOL. 387 NO. 26

94% pts **HCTZ 25 mg vs Chlorthalidone 12.5 mg**

5 % pts HCTZ 50 mg → Chlorthalidone 25 mg

Chlorthalidone vs. Hydrochlorothiazide for Hypertension–Cardiovascular Events

Areef Ishani, M.D., William C. Cushman, M.D., Sarah M. Leatherman, Ph.D., Robert A. Lew, Ph.D.,

Characteristic	Chlorthalidone (N=6756)	Hydrochlorothiazide (N=6767)
Age — yr	72.4±5.4	72.5±5.3
Male sex — no. (%)	6536 (96.7)	6556 (96.9)
Body-mass index§	31.7±5.8	31.8±5.9
Diabetes	2967 (43.9)	3062 (45.2)
Receiving hydrochlorothiazide at a daily dose of 25 mg — no. (%)	6379 (94.4)	6402 (94.6)
Systolic blood pressure — mm Hg	139±14	139±14
No. of antihypertensive drugs prescribed	2.6±1.0	2.6±1.1

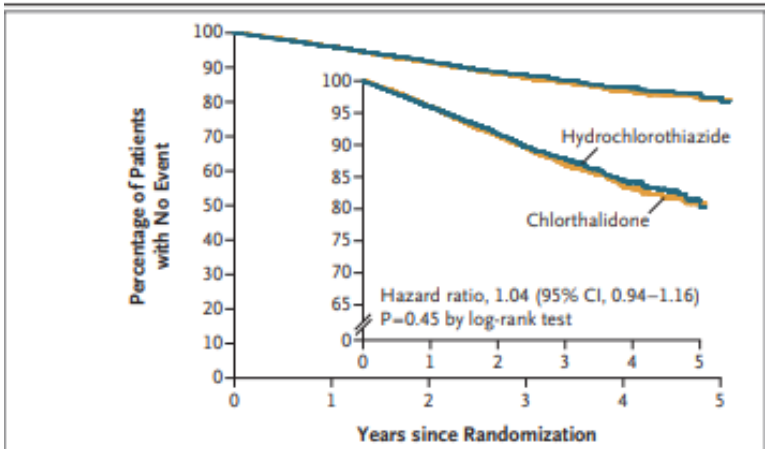


Figure 2. Kaplan–Meier Survival Curve for the Primary Outcome.
A primary composite outcome event (a composite of nonfatal myocardial infarction, stroke, heart failure that resulted in hospitalization, urgent coronary revascularization for unstable angina, and non–cancer-related death)

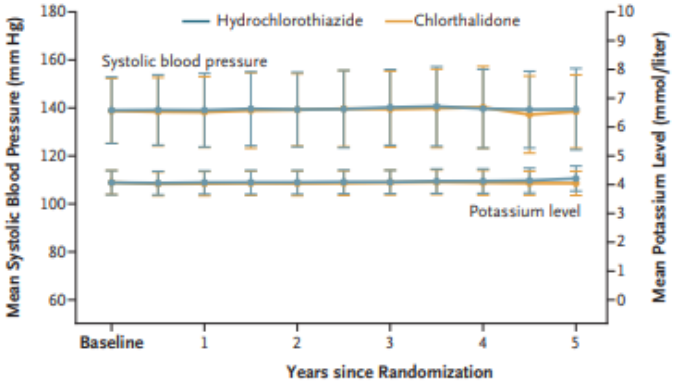
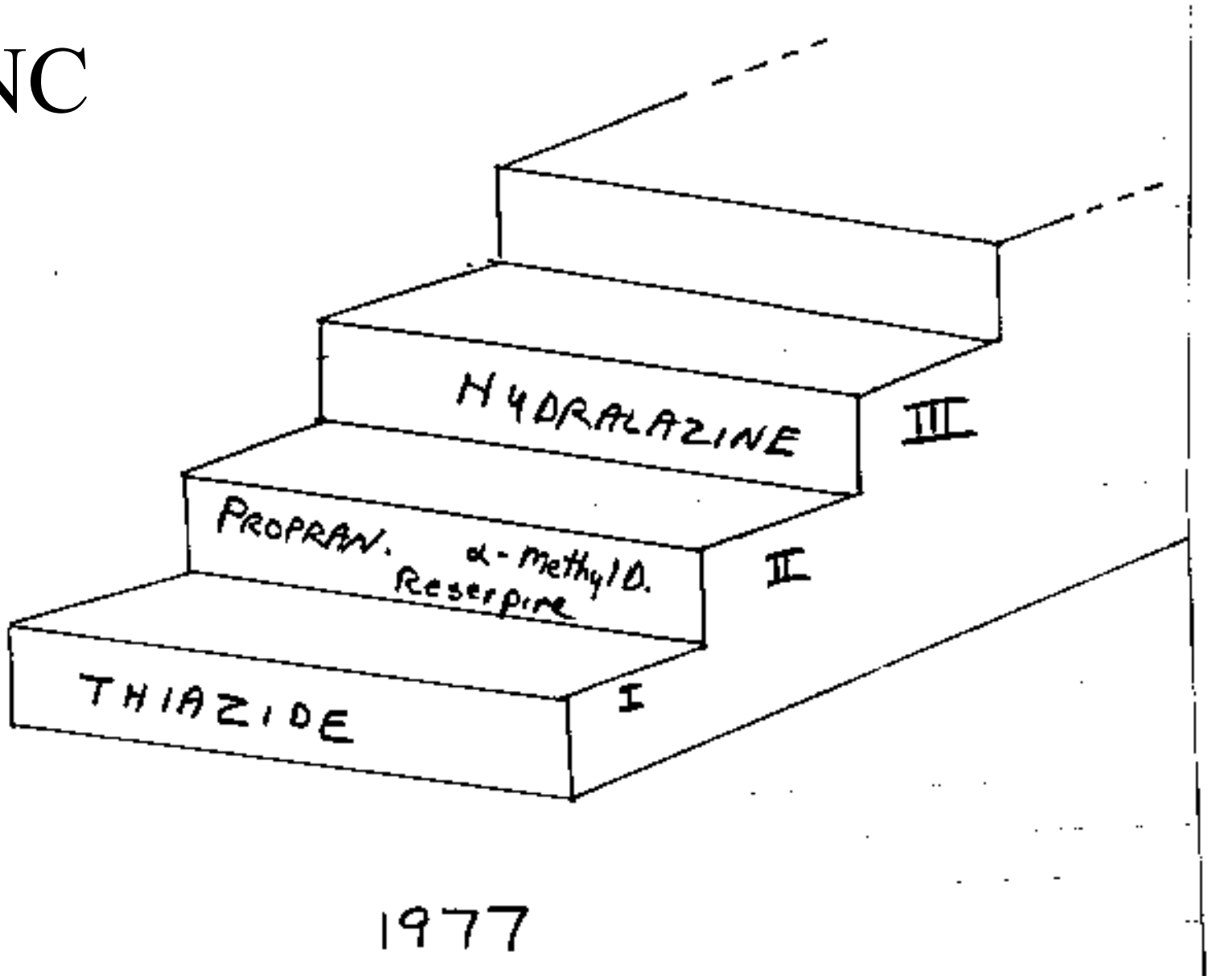


Figure 1. Systolic Blood Pressure, Potassium Level, and Potassium Supplementation over Time.
Laboratory values for potassium include both serum and plasma measurements. I bars indicate confidence intervals.

JNC


HYDRALAZINE
III
PROPRAN.
α-methyl D.
Reserpine
II
THIAZIDE
I
1977

LATE 20th CENTURY MOSES

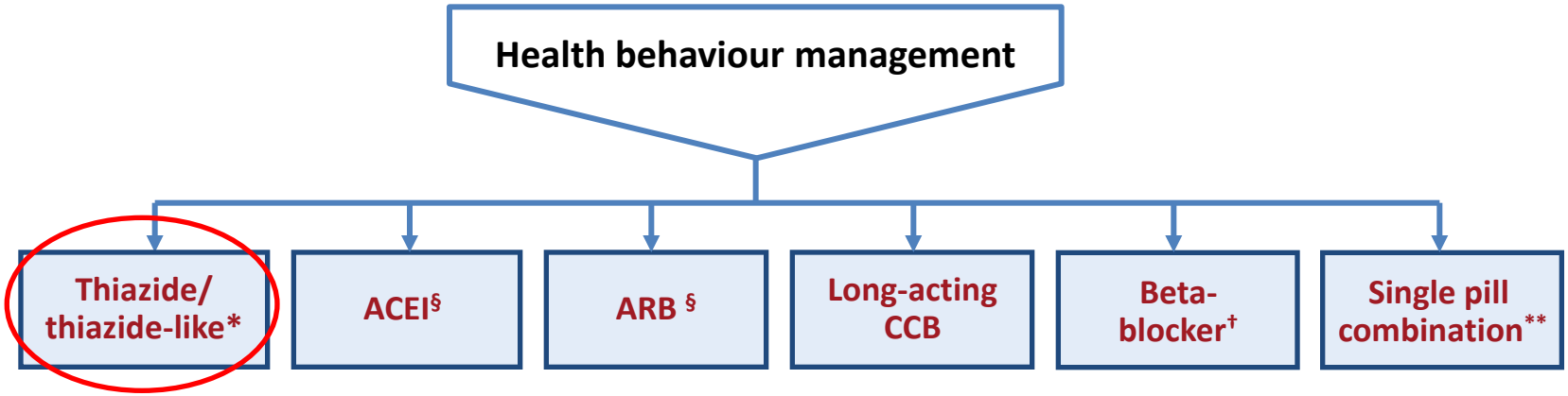
Hypertension CANADA

2020

First Line Treatment of Adults with Systolic/Diastolic Hypertension Without Other Compelling Indications

TARGET <135/85 mmHg (automated measurement method)

INITIAL TREATMENT



*** Longer-acting (thiazide-like) diuretics are preferred over shorter-acting (thiazide) diuretics**

† BBs are not indicated as first line therapy for age 60 and above

§Renin angiotensin system (RAS) inhibitors are contraindicated in pregnancy and caution is required in prescribing to women of child bearing potential

****Recommended SPC choices are those in which an ACE-I is combined with a CCB, an ARB with a CCB, or an ACE-I or ARB with a diuretic**

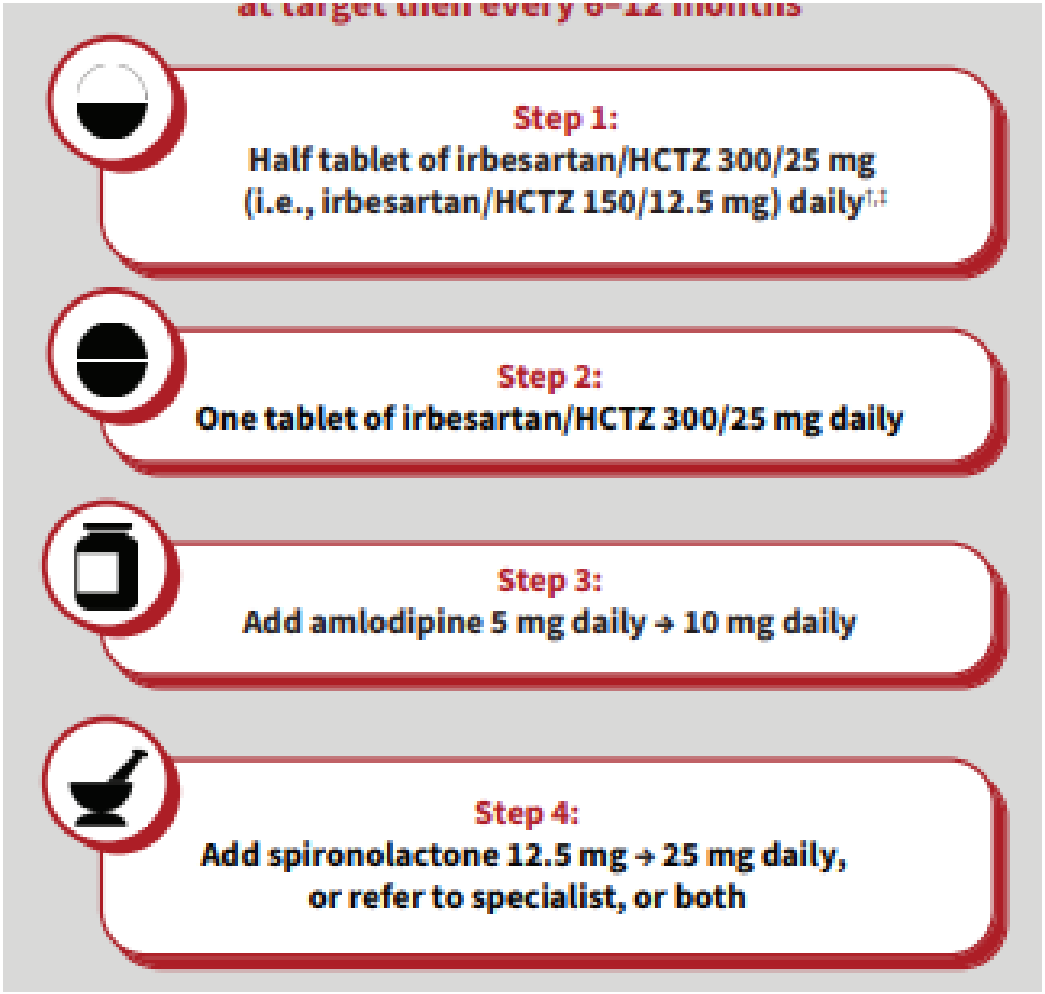
Useful Dual Combinations

For additive or synergistic **BP lowering** in dual therapy
combine an agent from
Column 1 one from Column 2

Column 1	Column 2
• Thiazide diuretic (or thiazide-like?) • Long-acting dihydropyridine calcium channel blocker	• Beta-blocker • ACE Inhibitor • ARB

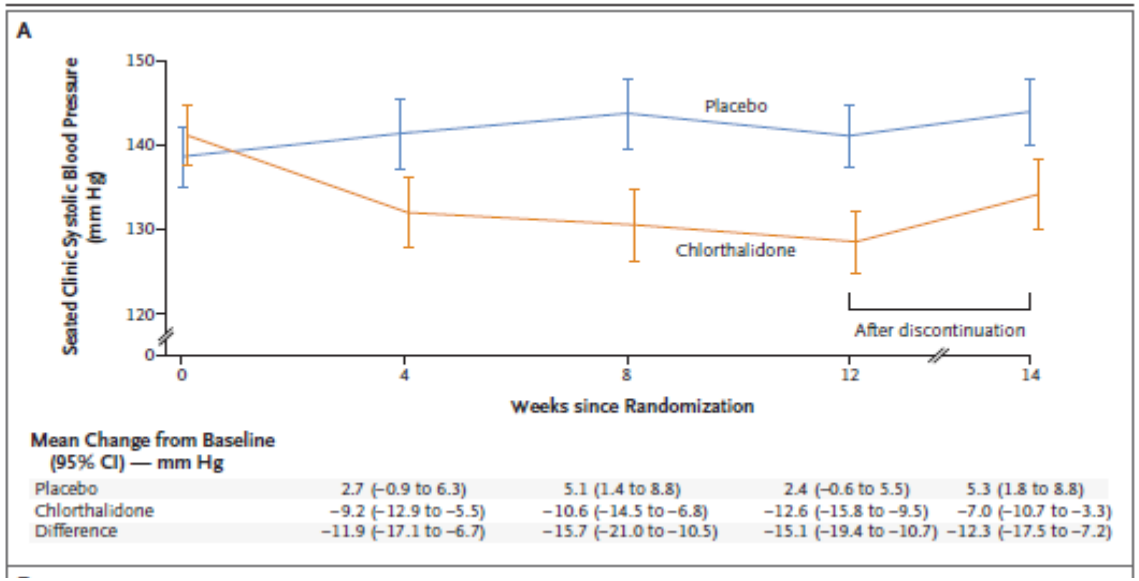
Hypertension Canada guideline for the diagnosis and treatment of hypertension in adults in primary care

2025



Myth: Thiazides don't work in advanced CKD

RCT of Chlorthalidone



Mean Change from Baseline (95% CI) — mm Hg				
Placebo	2.7 (−0.9 to 6.3)	5.1 (1.4 to 8.8)	2.4 (−0.6 to 5.5)	5.3 (1.8 to 8.8)
Chlorthalidone	−9.2 (−12.9 to −5.5)	−10.6 (−14.5 to −6.8)	−12.6 (−15.8 to −9.5)	−7.0 (−10.7 to −3.3)
Difference	−11.9 (−17.1 to −6.7)	−15.7 (−21.0 to −10.5)	−15.1 (−19.4 to −10.7)	−12.3 (−17.5 to −7.2)

Agarwal NEJM 2021

- mean Age 66
- Mean Wt 97 kg
- 77 % diabetics
- eGFR 24
- Most ACR >30
- All on ACE/ARB

Many of these patients were on furosemide
- many of whom had a jump in creatine due to overdiuresis!

What diuretic for Hypertension?

→Thiazide-like

(often in combination pill with ACE or ARB)

If K low, or need another agent

→Spironolactone (or amiloride)

(unless K is high)

- » Synergistic diuresis
- » Imroved outcomes
- » Much better than KCl supplements!

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

Lancet 2015; 386: 2059–68

Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon McInnes, Ian Ford, J Kennedy Cruickshank,

Table 1: baseline

	Mean (SD) or N (%)
Age (years)	61·4 (9·6)
Sex	
Male	230 (69%)
Female	105 (31%)
Weight (kg)	93·5 (18·1)
Smoker	26 (7·8%)
Home	
Systolic blood pressure (mm Hg)	147·6 (13·2)
Diastolic blood pressure (mm Hg)	84·2 (10·9)
Heart rate (beats per min)	73·3 (9·9)
Clinic	
Systolic blood pressure (mm Hg)	157·0 (14·3)
Diastolic blood pressure (mm Hg)	90·0 (1·5)
Heart rate (beats per min)	77·2 (12·2)
24 h urine (mmol/24 h)	
Sodium	137·1 (71·8)
Potassium	70·5 (29·5)
Blood electrolytes (mmol/L)	
Sodium	139·6 (3·0)
Potassium	4·1 (0·5)
eGFR (mL/min)	91·1 (26·8)
Diabetic	46 (14%)

eGFR=estimated glomerular filtration rate.

Table 1: Baseline characteristics of the patients randomised into the PATHWAY-2 study (n=335)

- Resistant hypertension:

  Clinic BP > 140 systolic

  or home BP > 130

  despite ACE/ARB, CCB and diuretic

- Each patient went through 4periods of 12 weeks each:
  - Spironolactone 25 → 50 mg
  - Doxazosin 4 → 8 mg
  - Bisoprolol 5 → 10 mg
  - Placebo

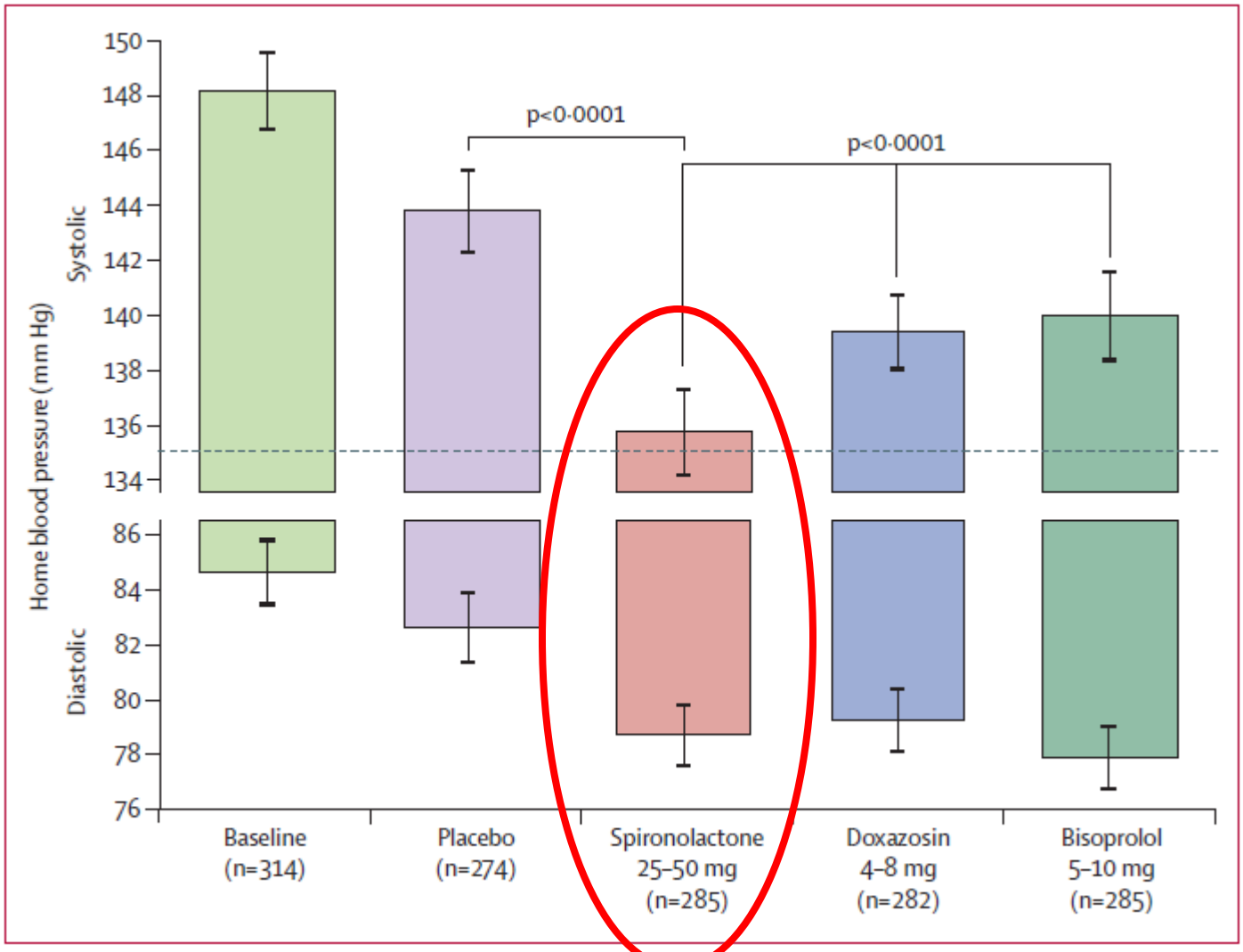
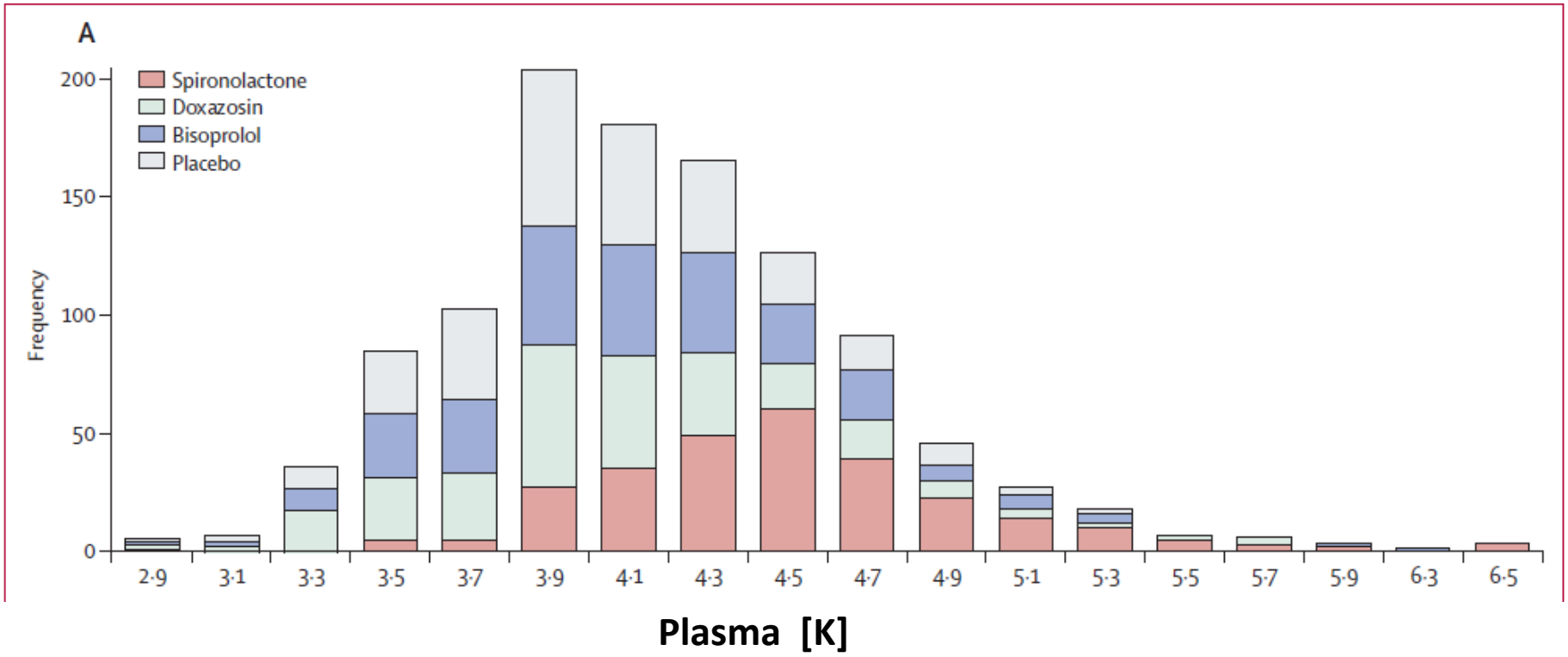


Figure 2: Home systolic and diastolic blood pressures comparing spironolactone with each of the



Distribution of plasma potassium at the end of each phase

- 6 patients (2 %) developed potassium greater than 6 on 1 occasion

Effect of amiloride, or amiloride plus hydrochlorothiazide, versus hydrochlorothiazide on glucose tolerance and blood pressure (PATHWAY-3): a parallel-group, double-blind randomised phase 4 trial

Lancet Diabetes Endocrinol 2016; 4: 136–47

Morris J Brown, Bryan Williams, Steve V Morant, David J Webb, Mark J Caulfield, J Kennedy Cruickshank, Ian Ford, Gordon McInnes, Peter Sever,

Table 1: baseline

	Amiloride (n=132)	Amiloride plus hydrochlorothiazide (n=133)	Hydrochlorothiazide (n=134)
Age (years)	62·1 (10·4)	61·5 (10·2)	62·8 (9·9)
Female sex	52 (39·4%)	63 (47·4%)	47 (35·1%)
Weight (kg)	89·3 (16·7)	88·8 (16·7)	88·2 (17·1)
BMI (kg/m²)	31·4 (7·6)	31·0 (4·7)	30·6 (5·1)
Number of current smokers	10 (7·6%)	12 (9·0%)	15 (11·2%)
Blood pressure (mm Hg)			
Clinic systolic	153·8 (11·4)	156·2 (12·4)	154·4 (11·7)
Clinic diastolic	91·3 (9·7)	91·2 (9·4)	90·0 (10·2)
Home systolic	149·3 (12·4)	150·6 (11·4)	148·8 (10·9)
Home diastolic	86·9 (9·8)	86·6 (8·9)	85·1 (9·6)
Previously untreated	7 (5·3%)	12 (9·0%)	11 (8·2%)
Receiving ACE inhibitor or ARB	119 (90·2%)	115 (86·5%)	117(87·3%)
Receiving β blocker	18 (13·6%)	24 (18·0%)	23 (17·2%)
Receiving calcium-channel blocker	56 (42·4%)	57 (42·9%)	56 (41·8%)
Number of drugs (if treated)	1·5 (0·7)	1·5 (0·7)	1·6 (0·7)
Central obesity*	129 (97·7%)	133 (100·0%)	132 (98·5%)
Serum potassium (mmol/L)	4·1 (0·4)	4·2 (0·3)	4·2 (0·4)
2 hour glucose during OGTT (mmol/L)	7·2 (2·3)	7·2 (2·1)	6·9 (2·4)
Impaired glucose tolerance†	44 (33·3%)	45 (33·8%)	42 (31·3%)

- Clinic BP > 140 systolic or home BP > 130 systolic on 0-3 drugs, but no diuretic
- Randomly assigned to one of 3 groups with doubling of dose after 12 weeks
  - Amiloride 10 → 20 mg
  - HCTZ 25 → 50 mg
  - Amiloride 5 mg/HCTZ 12.5 mg → amiloride 10 mg/HCTZ 25 mg

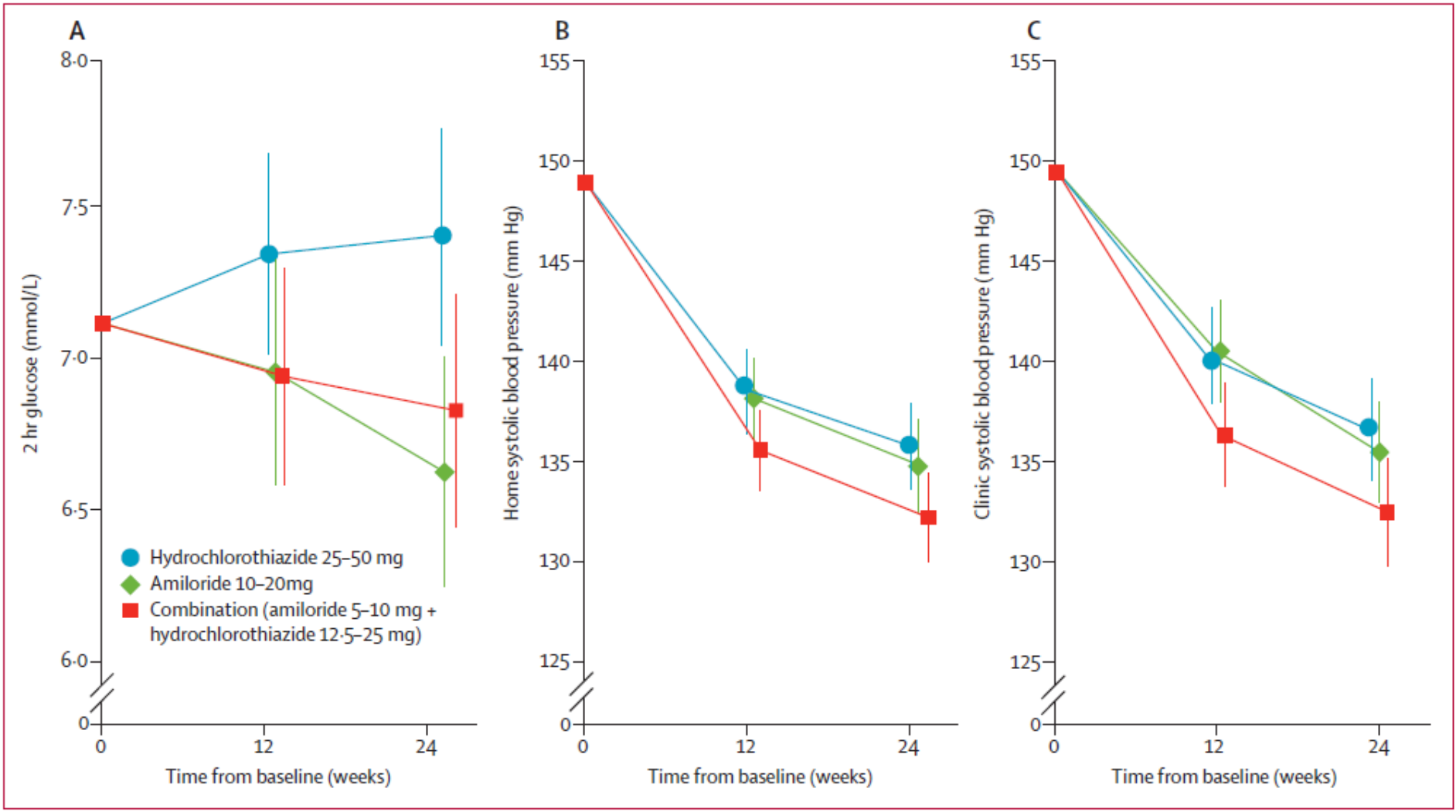


Figure 2: **Changes in 2 h blood glucose concentrations (A), home systolic blood pressure (B), and clinic systolic blood pressure (C)**

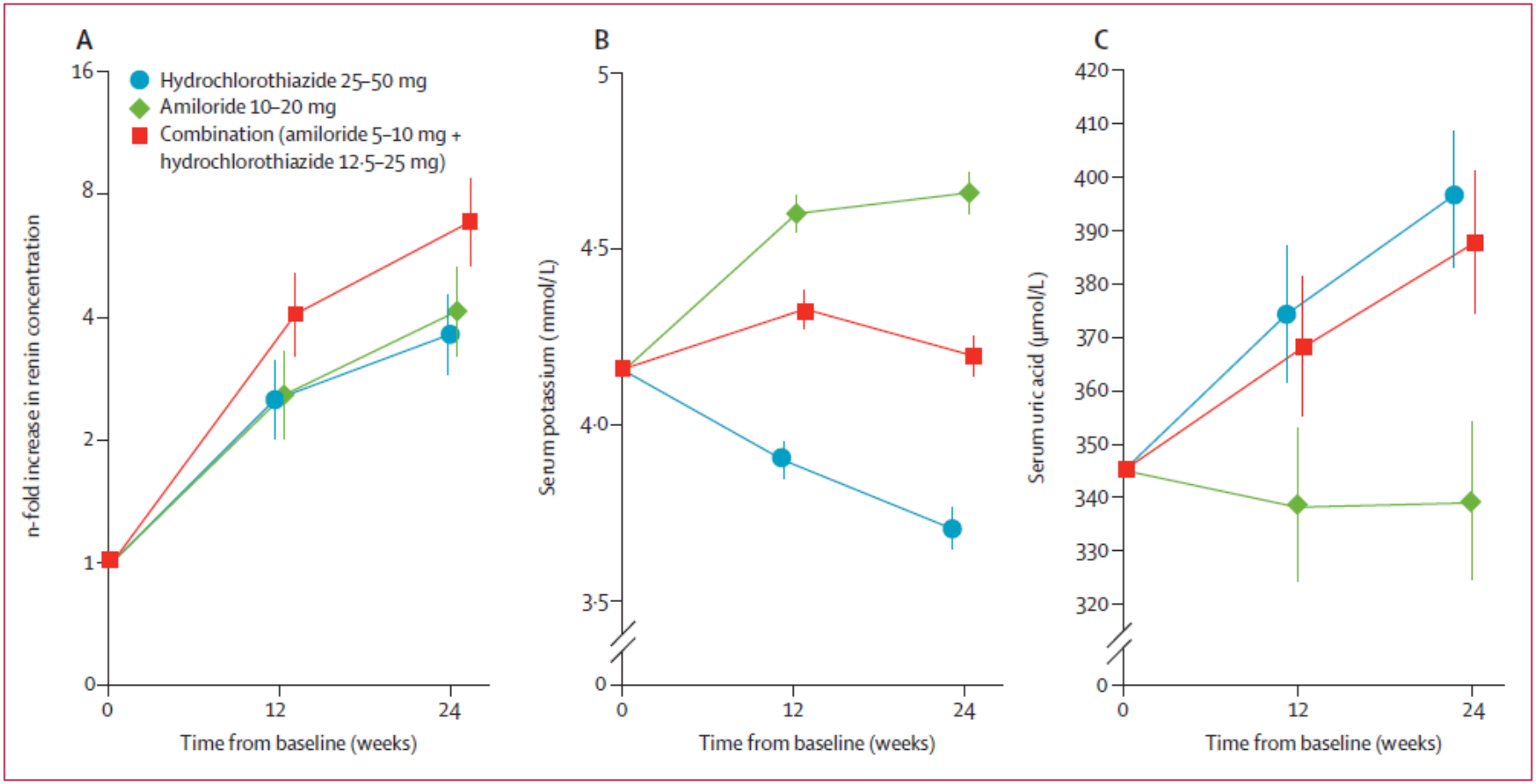


Figure 3: Changes in plasma renin (A), serum potassium (B), and serum uric acid (C) concentrations

- One Patient on amiloride had K 5.8

Side effects & Precautions

Consult for increased creatinine

- 83 F
- Previous edema, better with diuretic
- HTN: recent BP ~ 120/60
  - Amlodipine 10 mg daily
  - Chlorthalidone 25 mg
- Creatinine 130 , previously ~ 100;
  - no proteinuria
- Na 132, K 3.4, TCO2 31

- 50 kg, down 3 kg in last year
- Trace edema
- BP initially 120/66
- Resting automated BP avg 102/58
- Initial standing 96/60
- Mild postural lightheadedness, but is careful to get up slowly

Adverse effects of diuretics

1. Too much volume depletion +/- low BP +/- worsened GFR
   - May have peripheral edema but intravascular volume depletion
     - Venous stasis (obesity; venous occlusion)
     - CCB
   - Diuretic dose may be too high
     - Need to match to changes in Na intake
     - Patients who are losing weight usually need a reduction in diuretic dose

Diuretic potency: HCTZ & thiazide-like diuretics

- HCTZ 25 mg ~= Chlorthalidone 12.5 mg
  - But smallest tablet is 50 mg!
  - Indapamide 1.875 mg

(indapamide 1.25 < HCTZ 25mg < indapamide 2.5 mg)

- Indapamide and chlorthalidone are longer-acting than HCTZ

Adverse effects of diuretics

2. **HypoKalemia**
   - More K depletion with:
     - Higher dose/more potent diuretic
     - Higher salt diet
     - More revved up RAS:
       - Decompensated CHF, Cirrhosis
   - Much better to add K-sparing diuretic than KCl supplement!

Adverse effects of diuretics

3. **HypoNatremia**

   = water retention due to impaired kidney water excretion

   - Tubular diluting segments inhibited by diuretics
     - Thiazides > Furosemide
   - ADH stimulated by volume depletion (or low effective arterial volume)
     - Severe CHF & cirrhosis
     - Old, frail, poor intake: mostly women
       - Inadequate protein intake

Adverse effects of diuretics

4. **Gout**
   - High Uric acid in many patients taking diuretics
     - If asymptomatic: do not treat
   - Gout in a minority
     - Sometimes requires stopping diuretic
     - If diuretic needed, might have to delay a few months until Allopurinol has lowered uric acid

Adverse effects of diuretics

5. **HyperCalcemia**

- Thiazides reduce urine calcium excretion
  - Good for patients with Calcium stones
    - (may reduce osteoporotic fractures)
  - Bad for patients with hyperCalcemia

- Furosemide increases urinary Ca loss

Adverse effects of diuretics

6 Allergy (Rash; rarely interstitial nephritis)

- Thiazides and furosemide both have sulphur groups similar to sulphonamides
- But many patients who have sulfa allergy can take diuretics
- And those who develop rash with HCTZ may tolerate indapamide or furosemide

Skin

- Allergic rash: rare, but all diuretics contain a Sulphur group (except ethacrynic acid)
  - those who develop rash with HCTZ may tolerate indapamide or furosemide
- Sun sensitivity: rare with HCTZ; maybe less with chlorthalidone & indapamide

Table 5 Antihypertensive medications reported to cause photosensitive drug eruptions

From: Drug-Induced Photosensitivity—An Update: Culprit Drugs, Prevention and Management

Subclass	Drug	Evidence
Diuretics	Thiazides	PP [130], PT [4, 129]
	Furosemide	RC [133]
	Indapamide	–
	Triamterene	PP [135], RC [135]
ACE inhibitors	Ramipril	PP [138]
	Enalapril	–
	Quinapril	PT [137], RC [137]
Angiotensin receptor blockers	Valsartan	–
	Olmesartan	RC [141]
	Losartan	–
	Irbesartan	–
	Valsartan	–
	Candesartan	–
	Telmisartan	–
Calcium channel blockers	Amlodipine	PT [143]
	Nifedipine	RC [146]
	Diltiazem	PT [148], RC [149]

- Long-term users of photosensitizing drugs might be at increased skin cancer risk.

diuretics: photosensitivity & skin cancer

- 2019: "Health Canada has concluded that prolonged use of hydrochlorothiazide may be associated with a risk of non-melanoma skin cancer that is at least four times the risk of not using hydrochlorothiazide."

- "Thiazide-like diuretics are used much less frequently than HCTZ. Fewer data are therefore available, although one study found an association between indapamide and skin cancer"

HCTZ & Thiazide-like diuretics: other Side Effects

- Glucose intolerance: maybe less with Indapamide than HCTZ? Usually not a big issue
- (male) sexual dysfunction - probably more than with Beta Blockers!

Blakely; Drug Safety 2019

K sparing diuretics?

I always use these in preference to K supplement in diuretic-induced hypoKalemia

Spironolactone (if K not high)

- A great 2nd / 3rd / 4th line drug for lowering BP
- Mortality benefit in CHF
- Reduces proteinuria

- Dose-dependant antiandrogen effect
- Gynecocomastia in 5% of men on 25 mg/day
  - Reversible in a few weeks

Amiloride: also a pretty good BP drug

- GI disturbance at high doses

Acetazolamide

- Blocks bicarbonate reabsorption in proximal tubule
- If used by itself, not much diuresis because of increased downstream NaCl reabsorption
- If used with loop & thiazide diuretics can cause large diuresis
  - And large loss of bicarbonate
  - And large loss of K
- May have a role in rapid diuresis of decompensated CHF

Flozins

- If hyperglycemia, will lead to larger glucose loss in urine

➢ Glucose osmotic diuresis

  ➢ Polyuria

  ➢ Risk ov ECF volume depletion

Reducing risk in patients starting a Flozin

- Don’t start if glucose very high
- Don’t start when volume depleted
- If euvolemic & normal BP, consider reducing concomitant diuretic

Sick day rules

Counsel all Patients About

Sick Day Medication List

2013

Instructions for Healthcare Professionals:
If patients become ill and are unable to maintain adequate fluid intake, or have an acute decline in renal function (e.g. due to gastrointestinal upset or dehydration), they should be instructed to hold medications which will:

A) Increase risk for a decline in kidney function:
- Angiotensin-converting enzyme inhibitor
- Angiotensin receptor blockers
- Direct renin inhibitors
- Non-steroidal anti-inflammatory drugs
- Diuretics

B) Have reduced clearance and increase risk for adverse effects:
- Metformin
- Sulfonylureas (gliclazide, glimepiride, glyburide)

S sulfonylureas
A ACE-inhibitors
D diuretics, direct renin inhibitors

M metformin
A angiotensin receptor blockers
N non-steroidal anti-inflammatory
S SGLT2 inhibitors

Please complete the following card and give it to your patient.

Patients should be instructed that increased frequency of self blood glucose monitoring will be required and adjustments to their doses of insulin or oral antihyperglycemic agents may be necessary.

Instructions for Patients
When you are ill, particularly if you become dehydrated (e.g. vomiting or diarrhea), some medicines could cause your kidney function to worsen or result in side effects.

If you become sick and are unable to drink enough fluid to keep hydrated, you should **STOP** the following medications:

- Blood pressure pills
- Water pills
- Metformin
- Diabetes pills
- Pain medications
- Non-steroidal anti-inflammatory drugs (see below)

_____

_____

_____

_____

_____

Please be careful not to take non-steroidal anti-inflammatory drugs (which are commonly found in pain medications (e.g. Advil) and cold remedies).

Please check with your pharmacist before using over-the-counter medications and discuss all changes in medication with your healthcare professional.

Please increase the number of times you check your blood glucose levels. If they run too high or too low, contact your healthcare professional.

CDA 2013

A Better Sick Day handout?

"Sick Day" Medication List

When you are sick, particularly if you become dehydrated, some medications could cause your kidney function to worsen or result in side effects.

If you are sick, vomiting or not eating
SKIP the following medications until you are better:

Metformin	*Indapamide*
Perindopril	*Spironolactone*
Dapagliflozin	

Do not take non-steroidal anti-inflammatory drugs: Ibuprofen (Advil, Motrin),or Naproxen (Aleve)

If you are diabetic: increase the number of times you check your blood glucose levels.

If you have any problems, you can call your family doctor or the nephrology clinic

Liste de médicaments pour votre « Journée de maladie »

Lorsque vous êtes malade, en particulier si vous êtes déshydraté(e), certains médicaments peuvent aggraver la santé de vos reins.
Si vous êtes malade, que vous vomissez, ou que vous ne mangez pas, **ÉVITEZ** les médicaments suivants jusqu'à ce que vous vous sentiez mieux :

Ne prenez pas de: Ibuprofen (Advil, Motrin) ou Naproxen (Aleve)

Si vous êtes diabétique, vérifier votre sucre plus souvent.

Si vous avez d'autres problèmes, appelez votre médecin de famille ou la clinique de néphrologie