Mark Thomas, Dept of Nephrology, RPH

SGLT2 INHIBITORS:
CURRENT STATE OF PLAY

Declarations

Abbott
Amgen
Astra Zeneca
Bristol Myers Squibb
Boehringer Ingelheim
Fresenius
Genzyme
Glaxo Smith Klein
Lilly
MSD
Novartis
Otsuka
Pfizer
Roche
Sanofi
Servier
Shire
Solvay

… and RPH since ‘88

Medical miracle: discovery of insulin

1889 Pancreatectomy causes diabetes in dogs (Mering & Minkowski)

1910 Pancreatic islet (Latin = *insula*) cells proposed as source of peptide (Sharpey-Schafer)

1921 Banting & Best reverse canine diabetes with purified islet cell extract

1922 Bovine insulin purified and used in humans

Polonsky, The Past 200 Years in Diabetes
NEJM 2012;367:1332

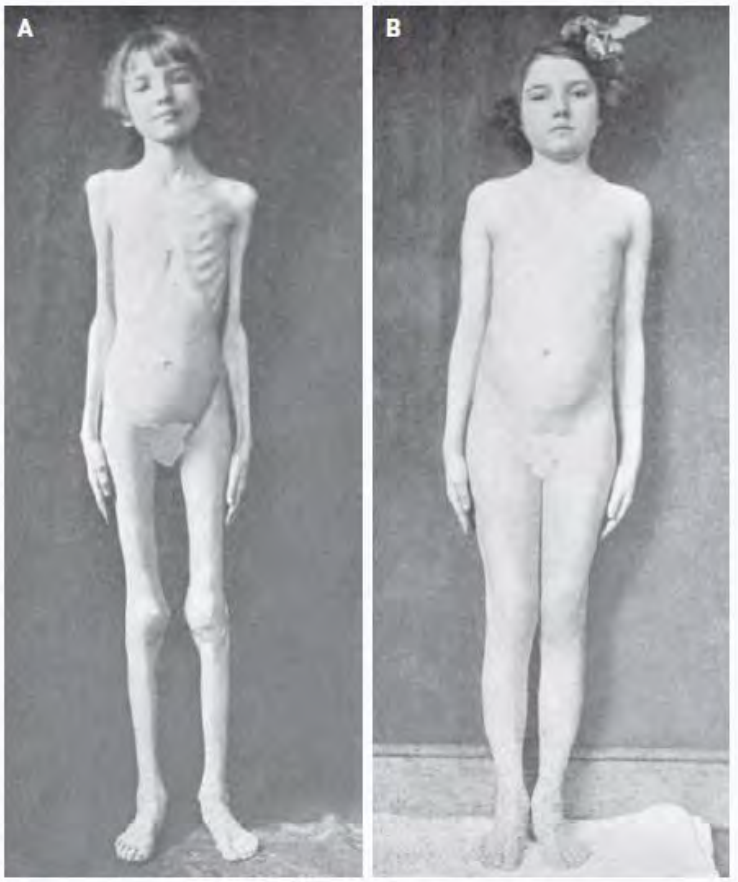
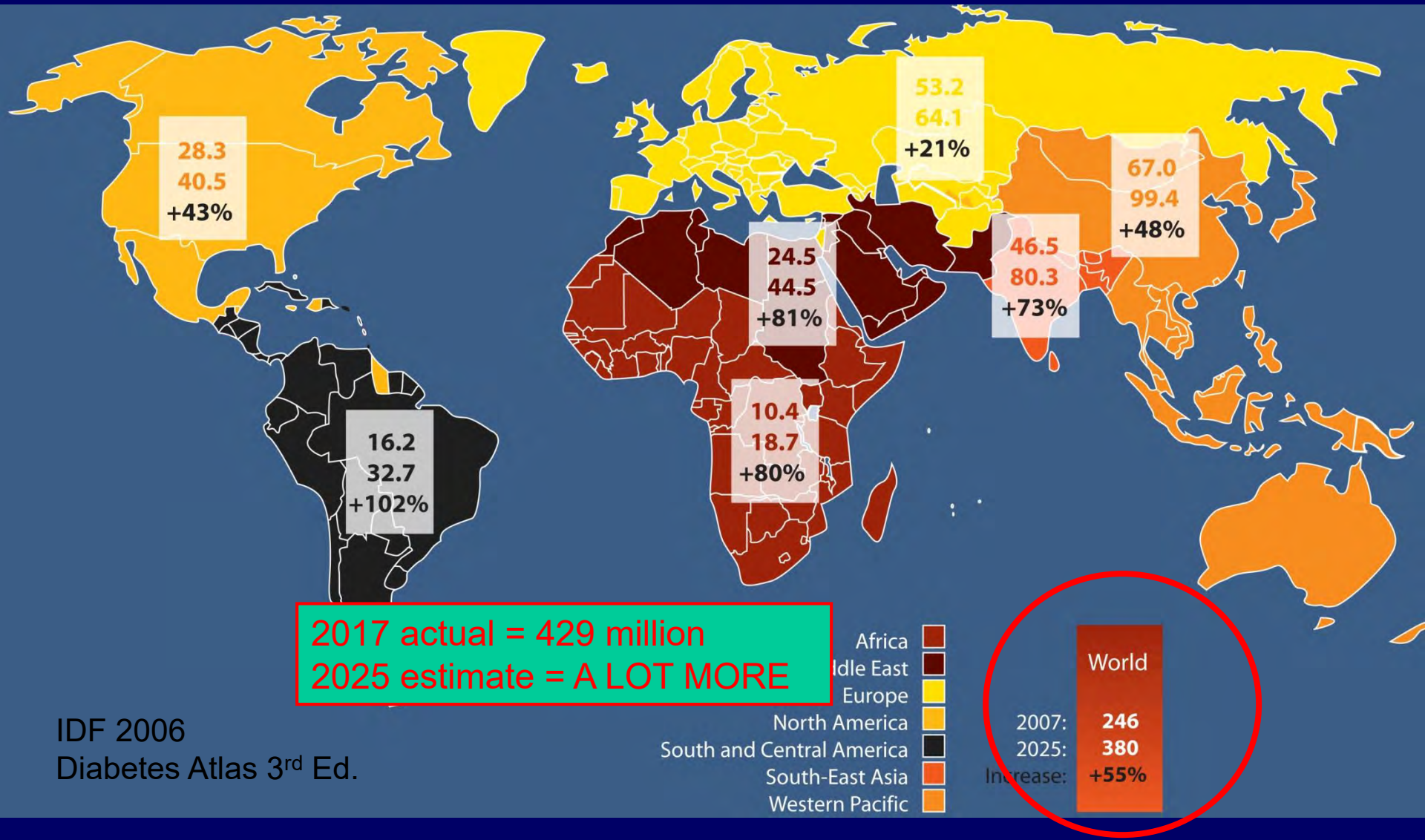


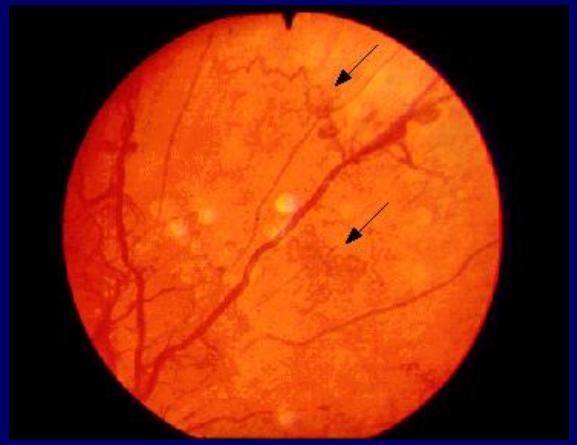
Figure 1. Effects of Insulin Therapy.
These photographs from 1922, in a case described by Geyelin,[11] show a young girl with insulin-deficient diabetes before treatment with insulin (Panel A) and after treatment (Panel B).

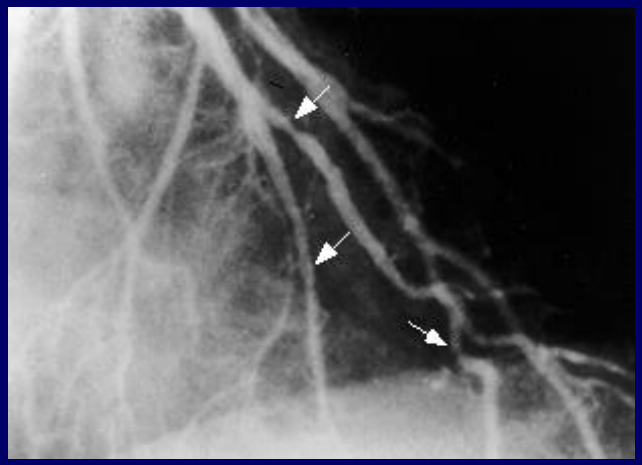
Projected vs actual global diabetes increase

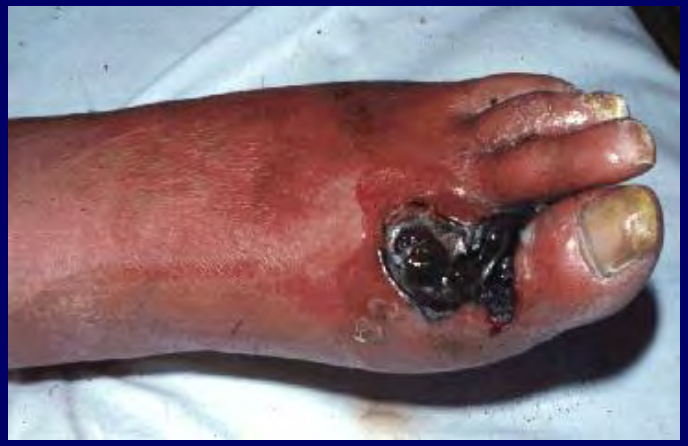


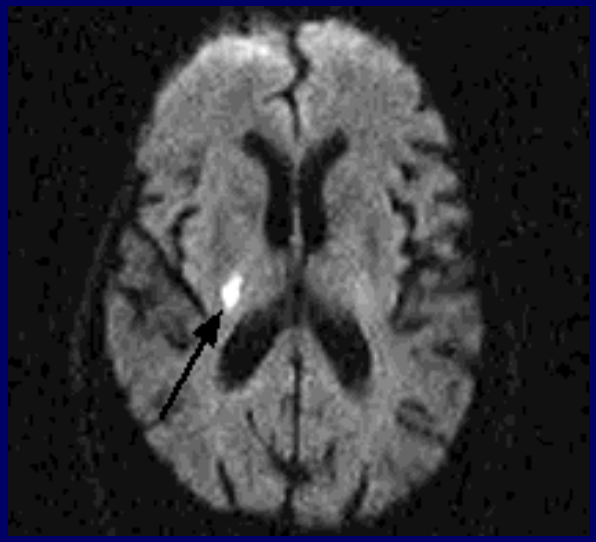
IDF 2006
Diabetes Atlas 3rd Ed.

Micro and macrovascular disease

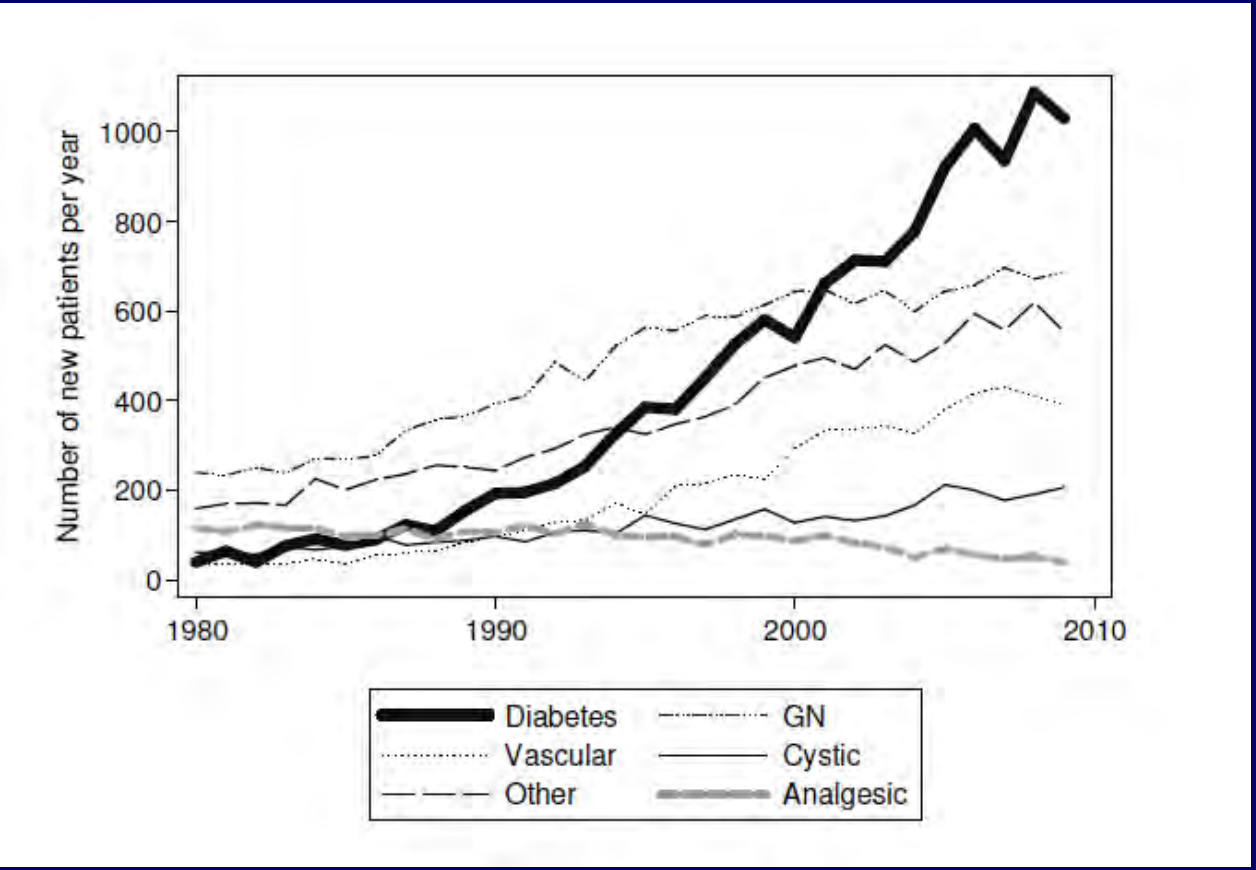






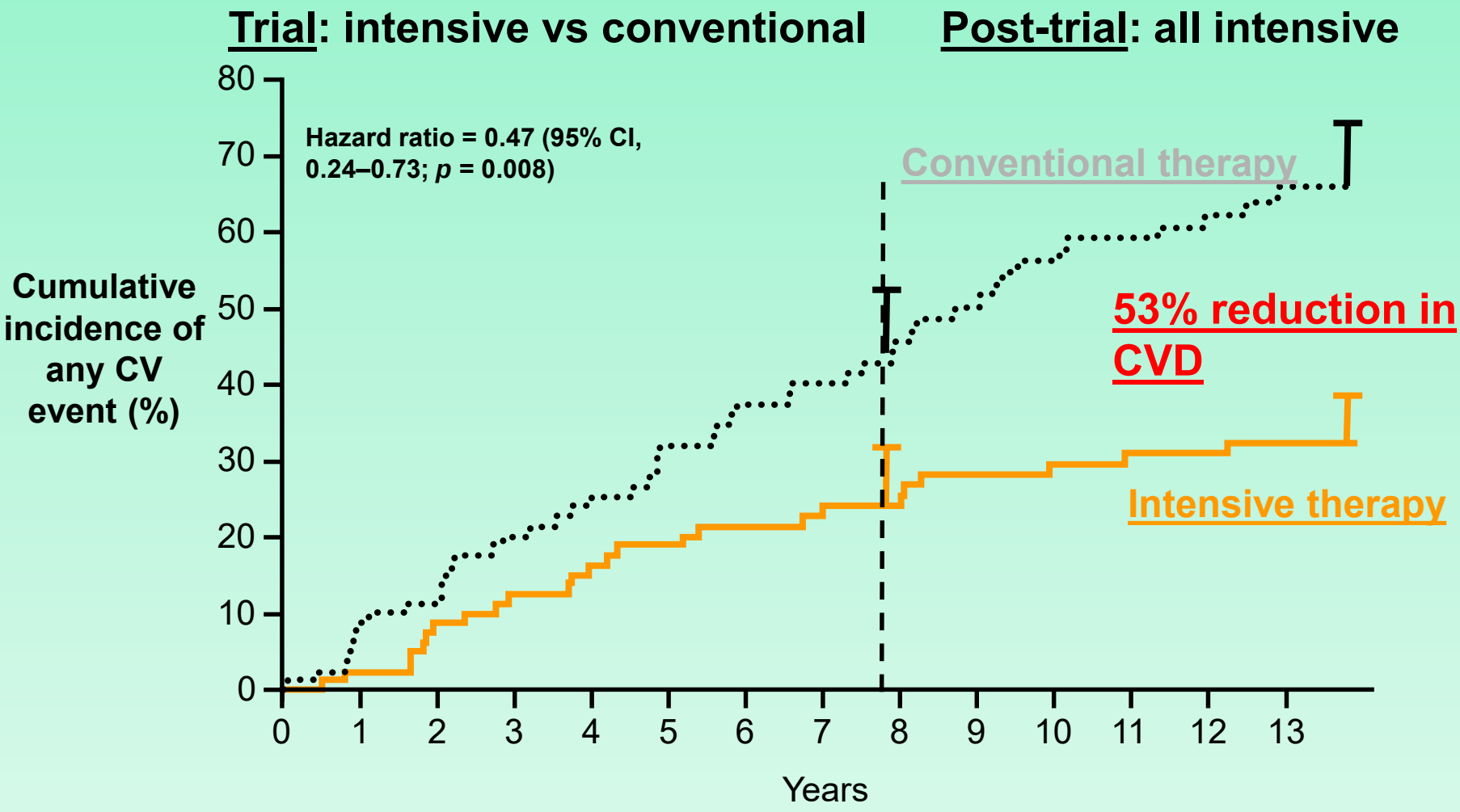


Diabetic ESKD: bullet performer



ANZDATA 2010

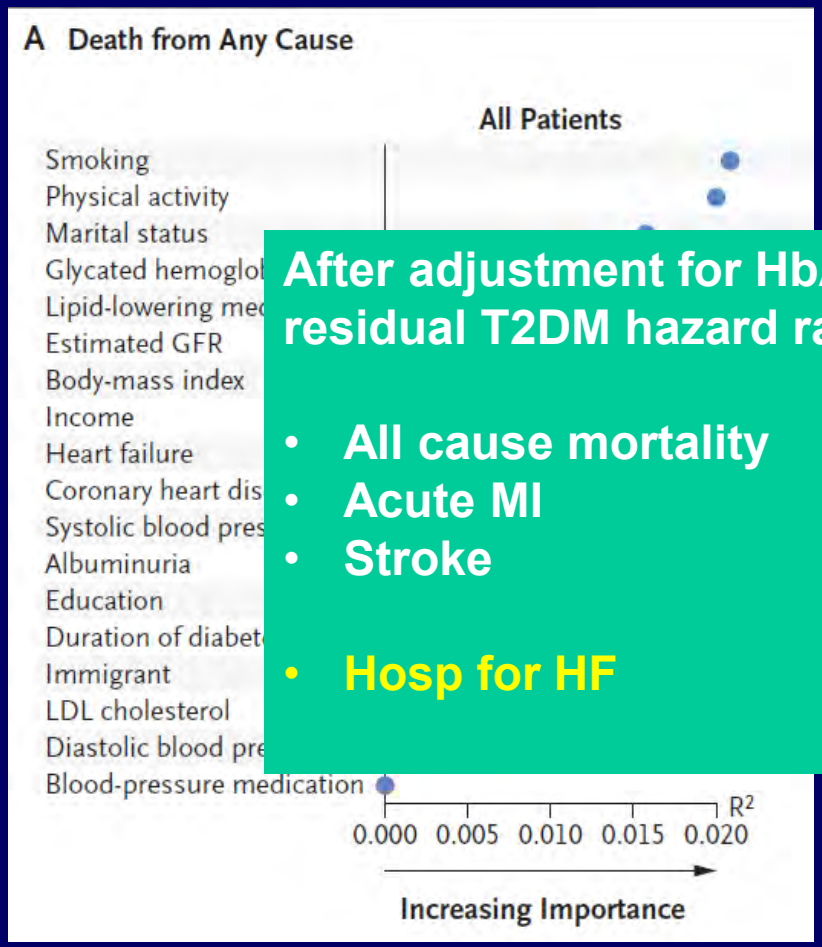
Multifactorial Rx in T2DM & legacy effect

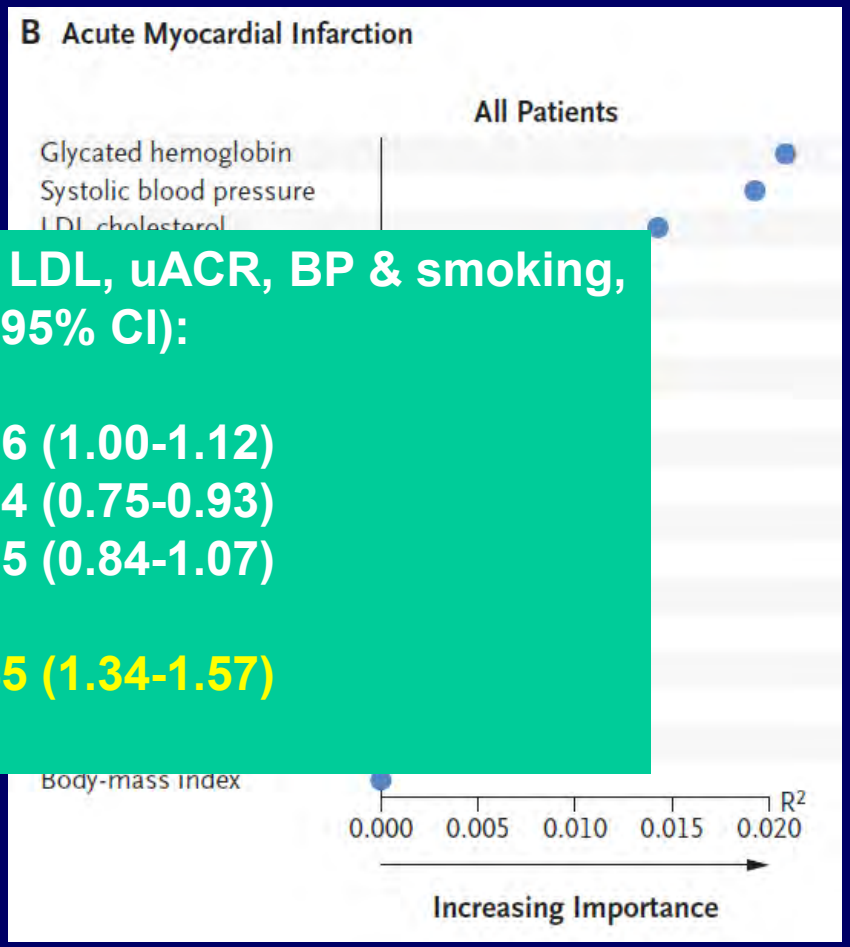


N=160 T2DM microalbuminuria

STENO 2 TRIAL
N Engl J Med 2008;358:580–591.

T2DM CV risk is mainly modifiable





After adjustment for HbA1c, LDL, uACR, BP & smoking, residual T2DM hazard ratio (95% CI):

- **All cause mortality** **1.06 (1.00-1.12)**
- **Acute MI** **0.84 (0.75-0.93)**
- **Stroke** **0.95 (0.84-1.07)**

- **Hosp for HF** **1.45 (1.34-1.57)**

Swedish National Diabetes register, n = 271,174, 5.1yrs f/up, NEJM 2018

Diabetic CKD: the dark decade

Year	Agent	Trial	Cardio	Renal
1993	ACEi	Collaborative Study Group	Y	Y
2001	ARB	IDNT	Y	Y
2007	Rosiglitazone	RECORD	N **+ HF**	N
2008	ACEi & ARB	ONTARGET, VA-NEPHRON-D	N	N **+ AKI**
2008	Tighter BSL control	ACCORD, ADVANCE & VADT	N **+ hypo's**	N
2010	Avosentan	ASCEND	N **+ HF**	N
2011	Sulodexide	SUN-Micro/Macro	N	N
2012	Aliskiren	ALTITUDE	N **+ HF**	N
2013	Bardoxelone	BEACON	N **+ HF**	N
2013	Saxagliptin	SAVOR-TIMI	N **+ HF**	N

Individualise and prioritise therapy targets

Individualise targets

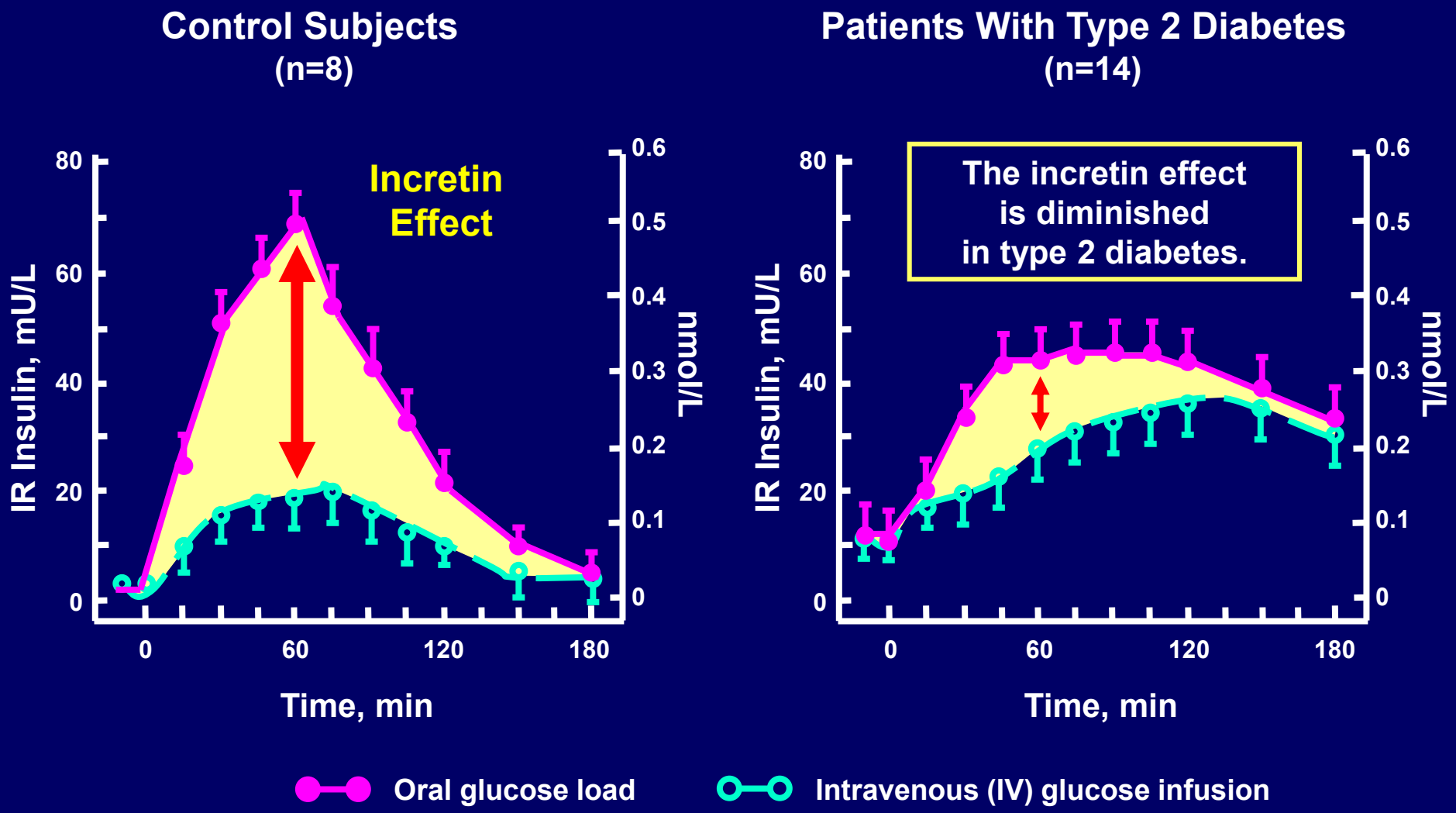
- **Tight targets:** for young motivated compliant patients, short duration of DM, no micro/macrovascular disease, few co-morbidities
- **Gentle targets**: treat the elderly with respect
  - E.g. Systolic BP 110 vs 140, HbA1c 6 vs 8%

Prioritise targets

1. BP and lipids: easier to achieve, bigger mortality benefit
2. Glucose control and weight loss

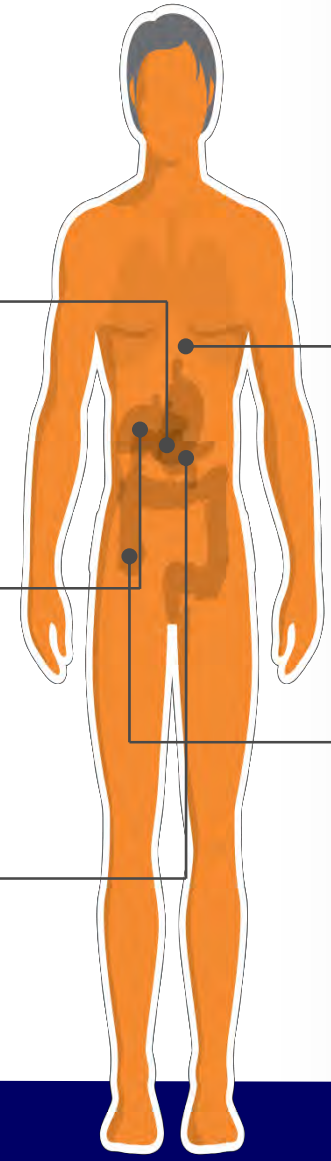
Mealtime

Incretin Effect: normal vs T2DM



IR=Immune Reactive.

Effects of incretins and incretin-based therapy[1]



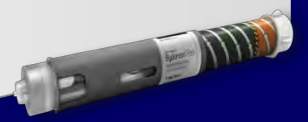
Alpha cells:
Less glucagon

Stomach:
Slowed gastric emptying

Liver:
Less gluconeogenesis

Small bowel:
GLP-1 secretion occurs after food

Beta cells:
More insulin (but only if glucose raised)



Adapted from DeFronzo RA, 2009[1]

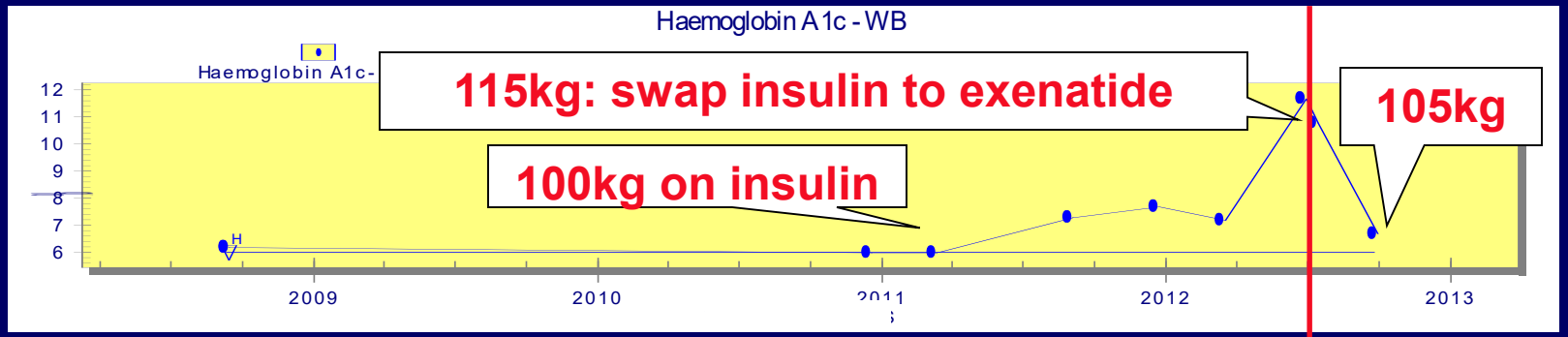
Reference 1. DeFronzo RA, *Diabetes* 2009; 58: 773-95.

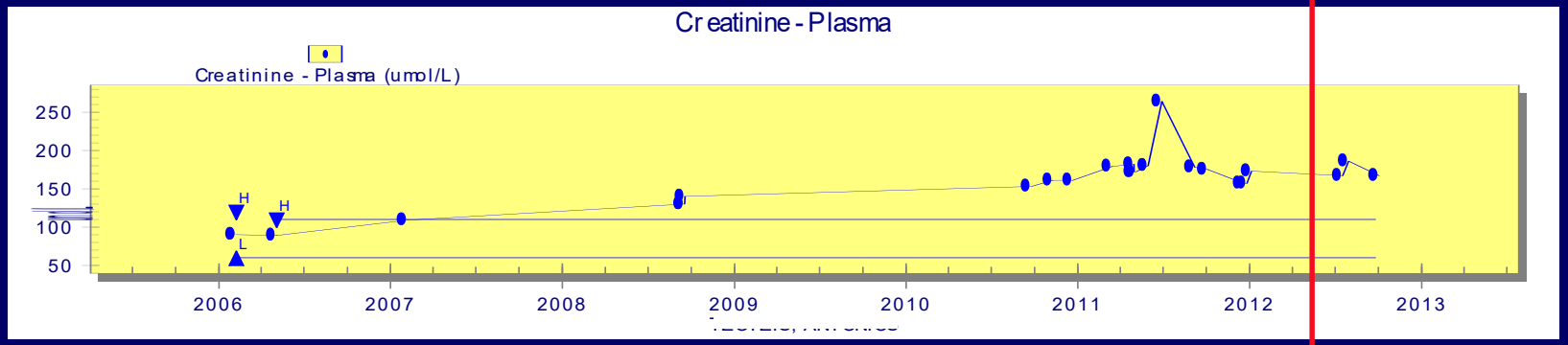
DPP4i safety – watch the BNP, not the lipase

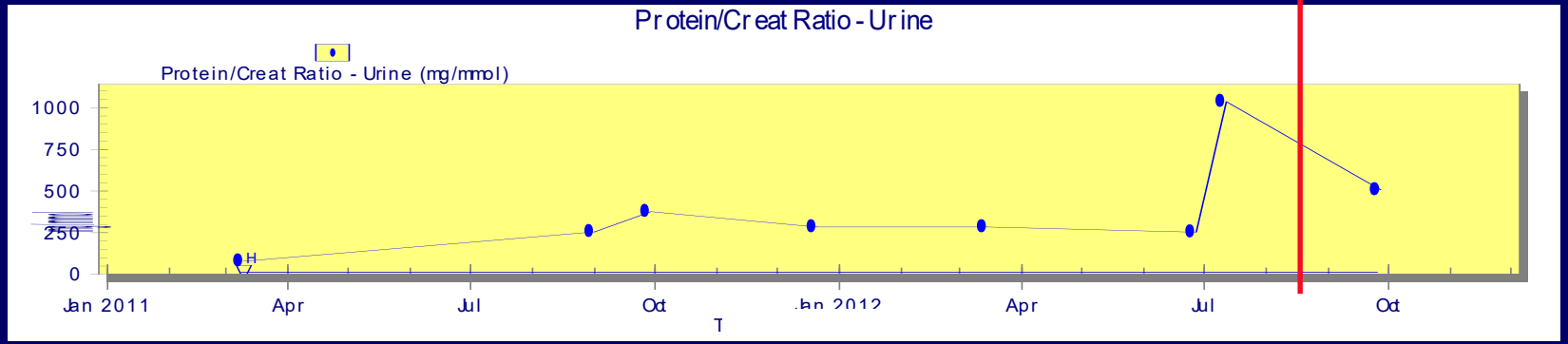
	EXAMINE[1,2]	SAVOR-TIMI[3]	TECOS[4]
	Alogliptin vs Placebo	*Saxagliptin vs Placebo*	*Sitagliptin vs Placebo*
Primary endpoint	11.3% vs 11.8% (*P*=0.32) MACE	7.3% vs 7.2% (*P*=0.99) MACE	11.4 vs 11.6 (P=0.99) MACE+
Baseline HF	28.0% vs 27.8% 757 vs 744	12.8% vs 12.8% 1056 vs 1049	17.8% vs 18.3% 1303 vs1340
Incidence of hospitalization for heart failure	3.9% vs 3.3% 106 vs 89 HR: 1.19, 95% CI: 0.90, 1.58	3.5% vs 2.8% 289 vs 228 HR 1.28 (*P*=0.007)	3.1% vs 3.1% 228 vs 229 HR 1.00 95% CI: 0.83, 1.20

	EXAMINE[1,2]	SAVOR-TIMI[3]	TECOS[4]
	Alogliptin vs Placebo	*Saxagliptin vs Placebo*	*Sitagliptin vs Placebo*
Acute Pancreatitis	0.4% vs 0.3% (*P*=0.50)	0.2% vs 0.1% (*P*=0.18)	0.3% vs 0.2% (P=0.07)
Pancreatic Cancer	0 vs 0	5 vs 12 0.1% vs 0.2% (P=0.95)	9 vs 14 0.1% vs 0.2% (P=0.32)

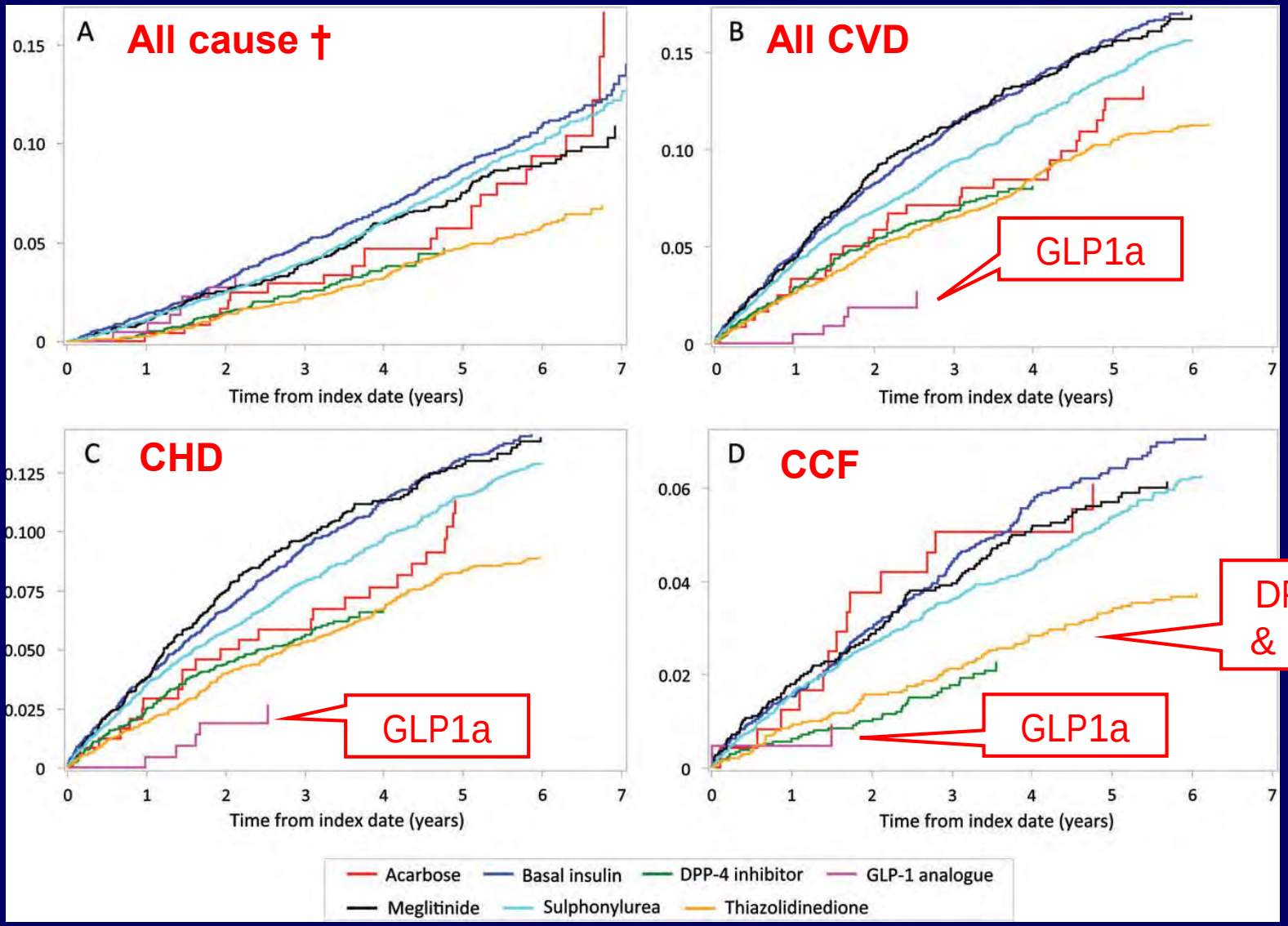
45 yr man, 175cm, 100kg = 25kg overweight







Swedish Registry outcome data to 2012



N = 20, 442, 2005-2012. Ekstrom *Diab Obes Metab* 2016

Diabetic CKD: from dark decade to new golden era

Year	Agent	Trial	Cardio	Renal
1993	ACEi	Collaborative Study Group	Y	Y
2001	ARB	IDNT	Y	Y
2007	Rosiglitazone	RECORD	N + HF	N
2008	ACEi & ARB	ONTARGET, VA-NEPHRON-D	N	N + AKI
2008	Tighter BSL control	ACCORD, ADVANCE & VADT	N + hypo's	N
2010	Avosentan	ASCEND	N + HF	N
2011	Sulodexide	SUN-Micro/Macro	N	N
2012	Aliskiren	ALTITUDE	N + HF	N
2013	Bardoxelone	BEACON	N + HF	N
2013	Saxagliptin	SAVOR-TIMI	N + HF	N
2015	SGLT2i	EMPA-REG	Y - HF	Y
2016	GLP1a	LEADER	Y - MI	Y
2017	SGLT2i	CANVAS	Y - HF	Y
2018	GLP1a	Sustain 6	Y - MI	Y
2019	SGLT2i	DECLARE, CREDENCE	Y - HF	Y

New targets


HALLUS HANDICRAFT
Sopsokha, Punakha : Bhutan
Deals: Antique, Jewellery, Postcard,Mask
and gift items from Bhutan.Contact No.17214178

Sodium glucose co-transporter (SGLT2) inhibitors

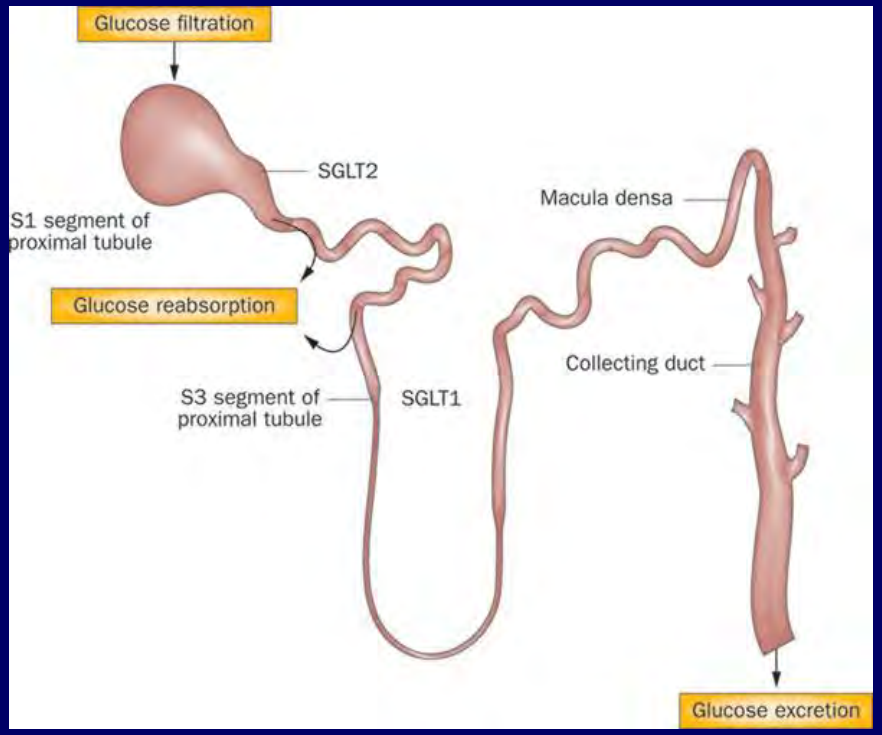
Induce prox tubular glycosuria

Benefits:

- reduce HbA1c ≈ 1% with few or no hypo's if used alone
- lower body weight & BP

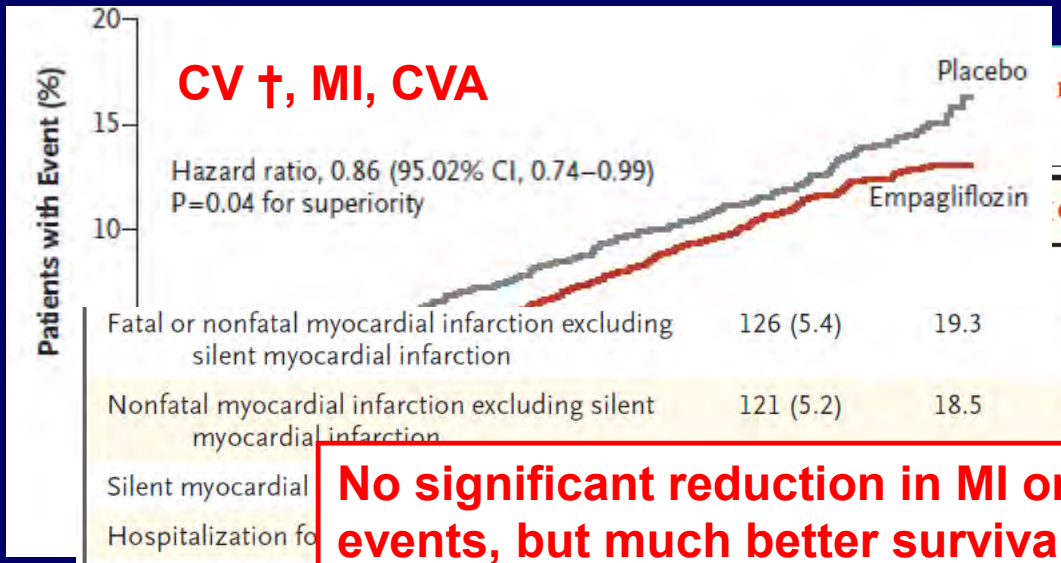
Risks:

- dehydration (esp if on diuretics)
- hypo's with SU or insulin
- UTIs, vulvovaginitis, balanitis
- DKA if ↓insulin & beta-cell defic



Cefalu, *Lancet* Sept 2013

SGLT2i: CV benefit in high CV risk

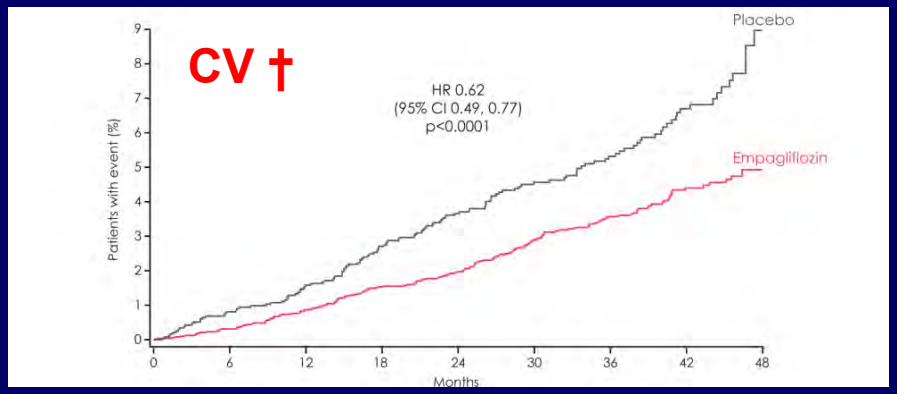


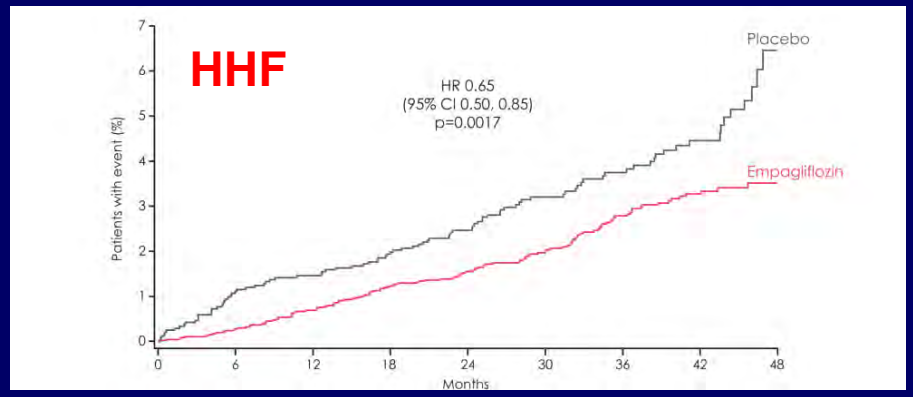
L of MEDICINE

CLE

Fatal or nonfatal myocardial infarction excluding silent myocardial infarction	126 (5.4)	19.3	223 (4.8)	16.8	0.87 (0.70–1.09)	0.23
Nonfatal myocardial infarction excluding silent myocardial infarction	121 (5.2)	18.5	213 (4.5)	16.0	0.87 (0.70–1.09)	0.22
Silent myocardial				7.0	1.28 (0.70–2.33)	0.42
Hospitalization fo				10.0	0.99 (0.74–1.34)	0.97
Coronary revascularization procedure	186 (8.0)	29.1	329 (7.0)	25.1	0.86 (0.72–1.04)	0.11
Fatal or nonfatal stroke	69 (3.0)	10.5	164 (3.5)	12.3	1.18 (0.89–1.56)	0.26
Nonfatal stroke	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92–1.67)	0.16

No significant reduction in MI or CVA events, but much better survival





Zinman, *NEJM*, Sept 2015

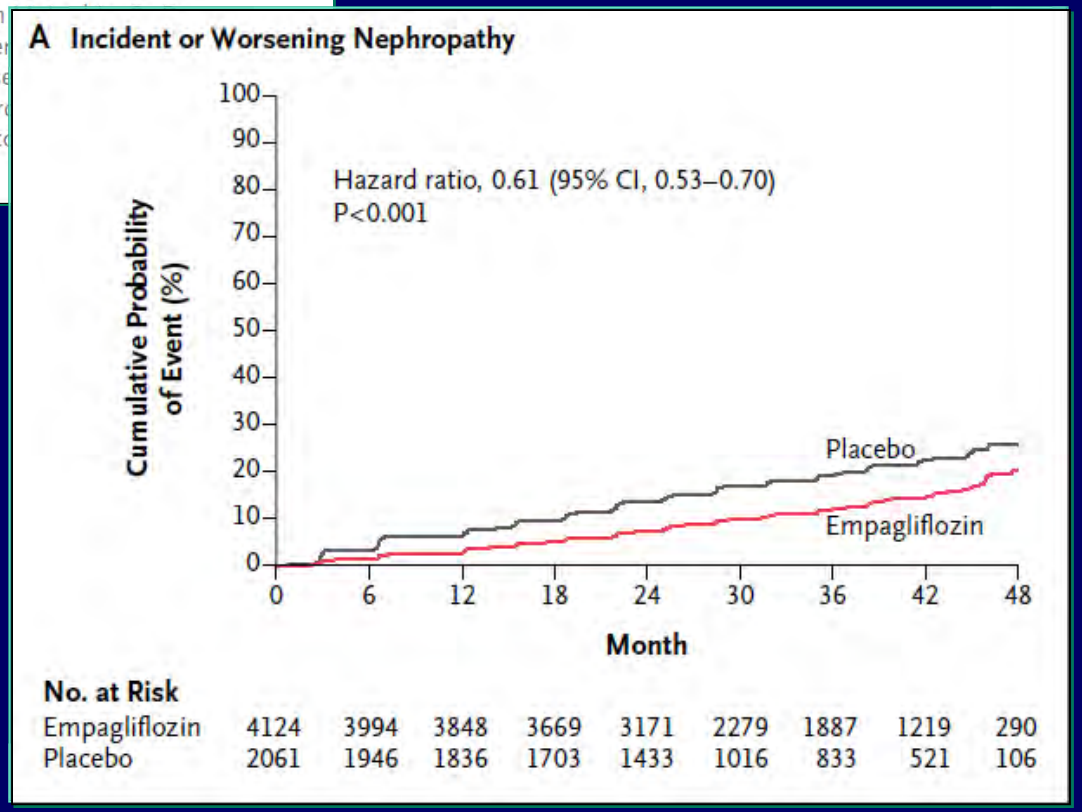
SGLT2i: CKD benefit in high CV risk

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John
David Fitchett, M.D., Maximilian von Eynatten
Michaela Mattheus, Dipl. Biomath., Odd Erik Johanse
Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernar
for the EMPA-REG OUTCOME Investigato



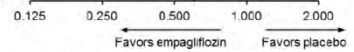
Wanner, *NEJM*, June 2016

CKD benefits for all sub-groups

Figure S1. Pre-specified subgroup analyses for incident or worsening nephropathy.

Cox regression analyses in patients treated with ≥1 dose of study drug. p-value is for test of homogeneity of treatment group difference among subgroups (test for treatment group by covariate interaction) with no adjustment for multiple testing.

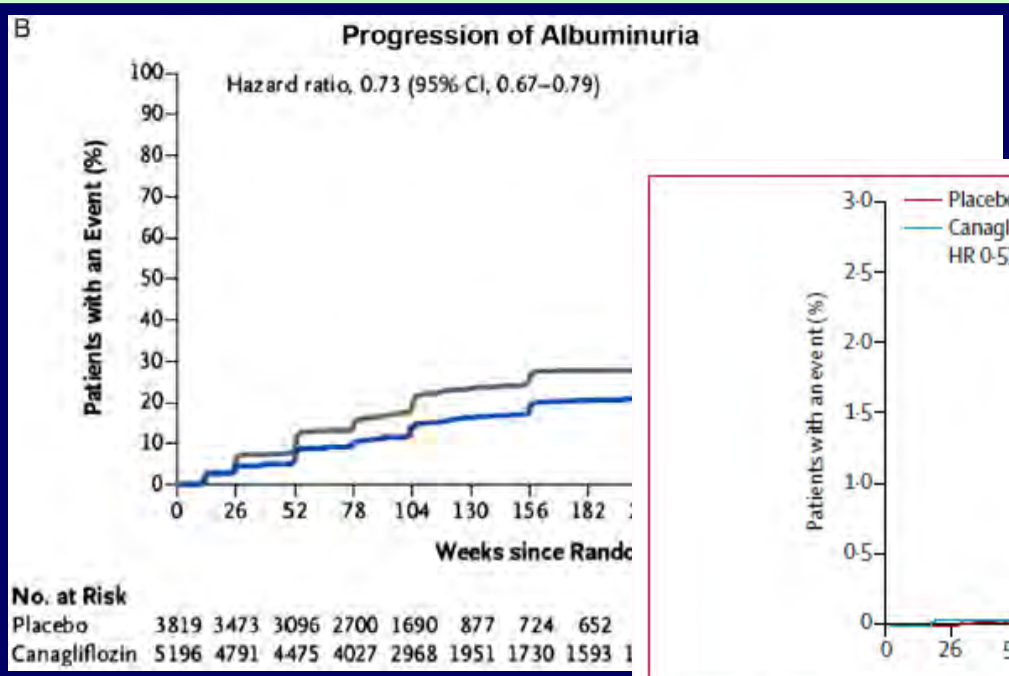
	Empagliflozin	Placebo	Hazard ratio (95% CI)	p-value for interaction
	Patients analyzed			
All patients	4124	2061		
Estimated glomerular filtration rate				0.40
≥90 mL/min/1.73m^2	962	452		
60 to <90 mL/min/1.73m^2	2179	1112		
45 to <60 mL/min/1.73m^2	707	341		
<45 mL/min/1.73m^2	276	156		
Urine albumin-to-creatinine ratio				0.87
<30 mg/g	2737	1361		
≥30 mg/g	1344	687		
Glycated hemoglobin				0.89
<8.5%	2847	1453		
≥8.5%	1277	608		
Body mass index				0.39
<30 kg/m^2	2009	985		
≥30 kg/m^2	2115	1076		
Blood pressure control				0.55
SBP ≥140 mmHg and/or DBP ≥90 mmHg	1476	794		
SBP <140 mmHg and DBP <90 mmHg	2648	1267		
Diuretic				0.95
No	2350	1197		
Yes	1774	864		



ACE, angiotensin-converting enzyme. ARB, angiotensin-receptor blocker. DBP, diastolic blood pressure. SBP, systolic blood pressure.

Wanner, *NEJM*, June 2016

CANVAS: renoprotection in both high & low CV risk



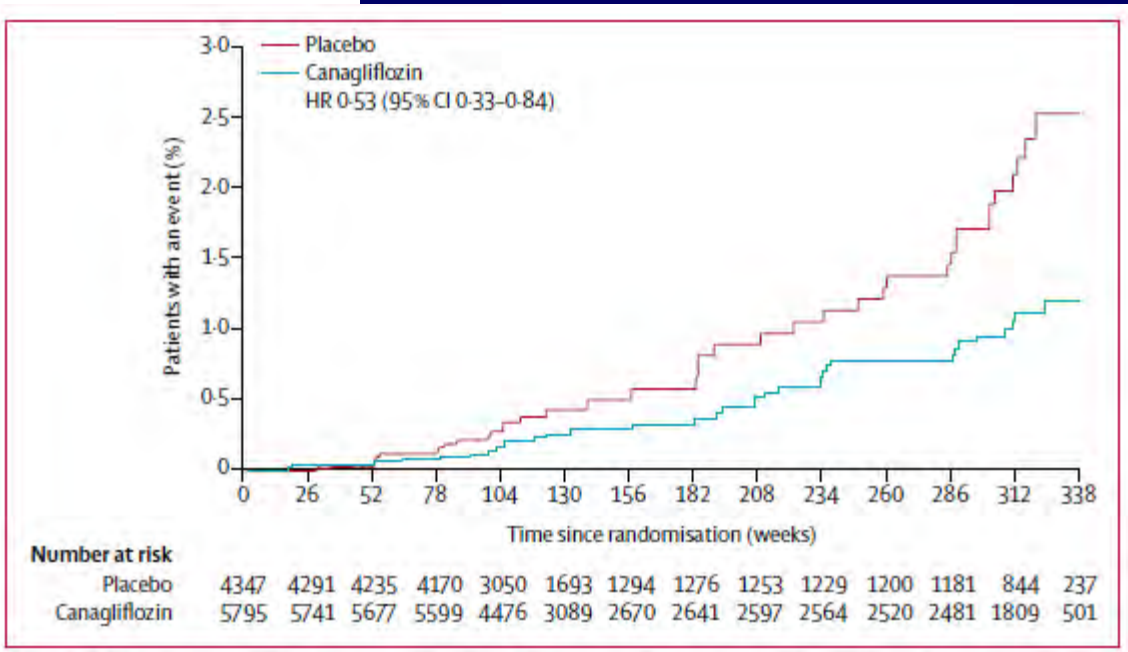


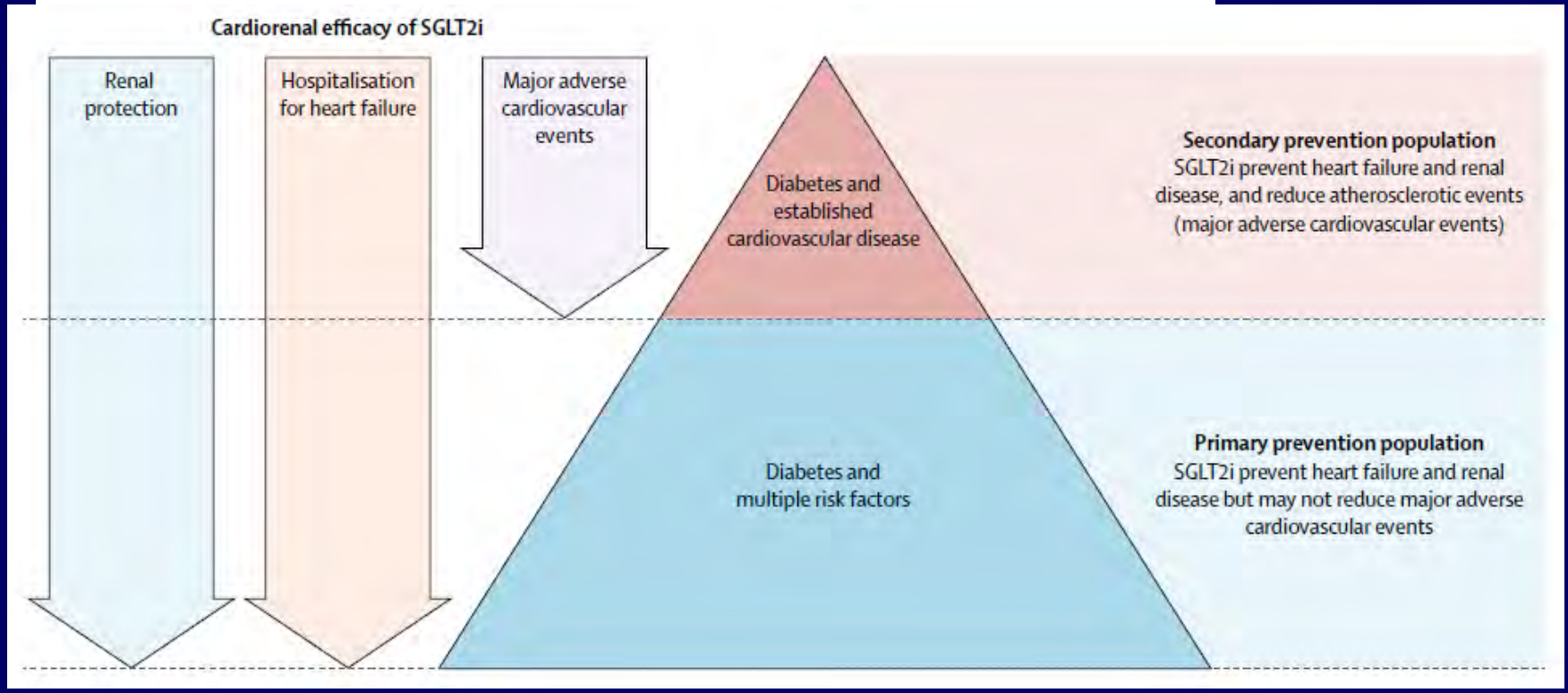
Figure 1: **Effects of canagliflozin versus placebo on the composite outcome of doubling of serum creatinine, ESKD, or death from renal causes in the CANVAS Program**

Time to the first event was counted, with any subsequent events disregarded. Doubling of serum creatinine was required to be sustained, defined as being present on at least two consecutive measurements more than 30 days apart. End-stage kidney disease (ESKD) was defined as the composite of maintenance dialysis sustained for at least 30 days, renal transplantation, or a sustained eGFR of less than 15 mL/min per 1·73 m^2, and adjudicated by an expert committee. Death from renal causes was defined as death where the proximate cause was renal, as defined by the endpoint adjudication committee. HR=hazard ratio.

Perkovic, CANVAS *Lancet* June 2018

And adding DECLARE: in low > high CV/CKD risk?

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes:



Zelniker T et al, *Lancet* 2018

Verma S et al, editorial, *Lancet* 2018

Current and future kidney outcome trials

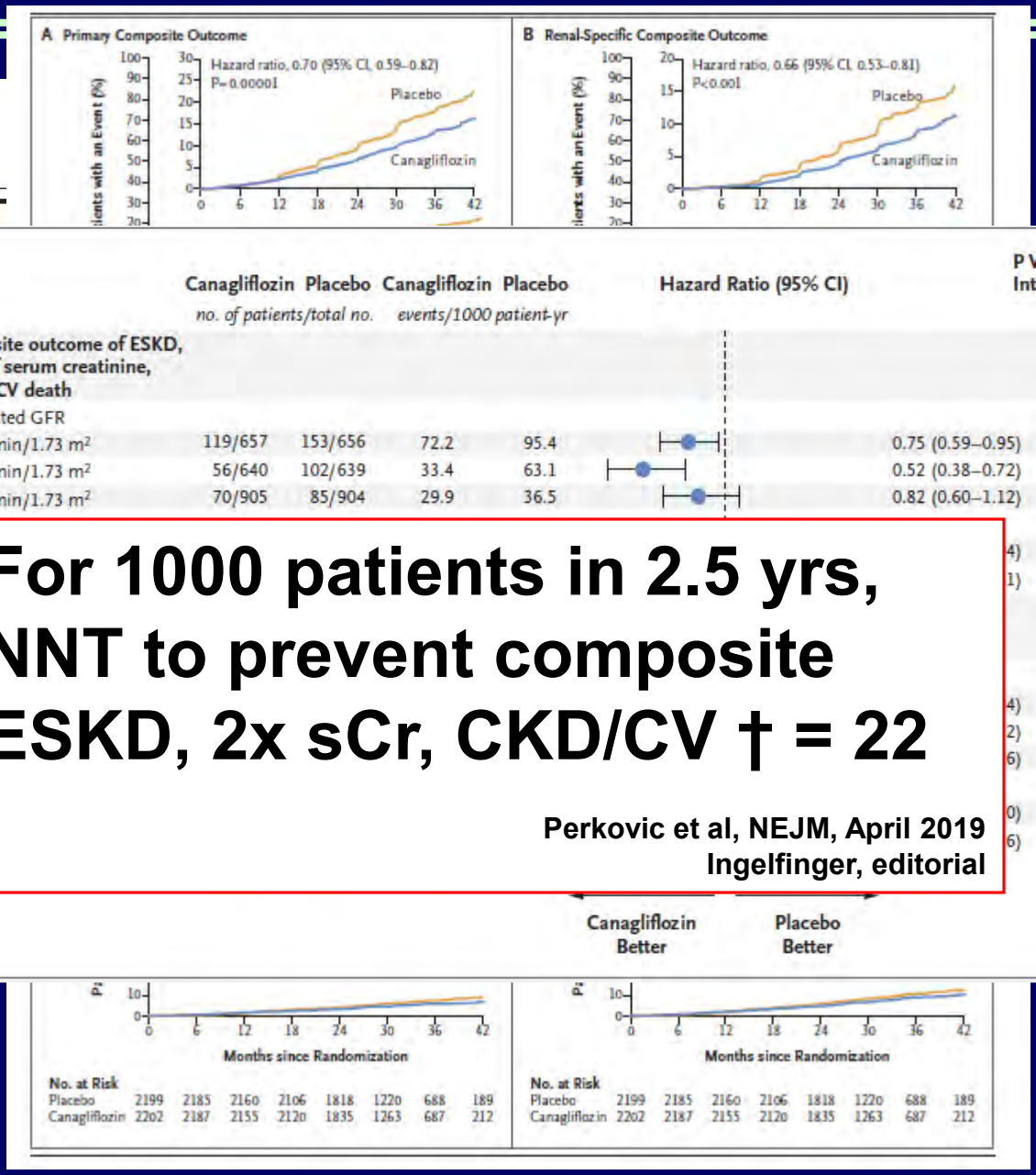
Table 1. Kidney Outcomes in Clinical Trials of SGLT2 Inhibitors

Study	Intervention	Study Population	Outcomes
EMPA-REG OUTCOME (NCT01131676)[56,84]	Empagliflozin	T2DM, eGFR ≥ 30; high CV risk	• 44% RR reduction of Scr doubling (1.5% vs 2.6%) • 38% RR of progression to UACR > 300 (11.2% vs 16.2%) • 55% RR reduction of initiation of KRT (0.3% vs 0.6%) • Slowing of decline in GFR (annual decrease of 0.19 ± 0.11 vs 1.67 ± 0.13; $P < 0.001$)
CREDENCE (NCT02065791)[86]	Canagliflozin	T2DM; HbA_{1c} [6.5%, 12%]; high CV risk; UACR [300, 5,000]; eGFR [30, 90]	• Trial in progress; estimated completion in June 2019 • Primary outcome: time to the 1st occurrence of an event in the primary composite end point (ESRD, Scr doubling, kidney or CV death)
CANVAS, CANVAS R (NCT01032629, NCT01989754)[85]	Canagliflozin	T2DM; HbA_{1c} [7%, 10.5%], high CV risk; median UACR 12.3; mean eGFR 76.5	• ↓ progression of albuminuria (HR, 0.73; 95% CI, 0.67-0.79) • ↓ composite outcome of 40% reduction in eGFR, KRT, or kidney death (HR, 0.60; 95% CI, 0.47-0.77)
Dapa-CKD (NCT03036150)[87]	Dapagliflozin	T2DM; eGFR [25, 75]; UACR [200, 5,000]	• Trial in progress; estimated completion in November 2020 • Primary outcome: time to 1st occurrence of any of the components of the primary composite end point (ESRD, ≥50% sustained decline in eGFR, kidney or CV death)
DECLARE-TIMI-58 (NCT01730534)[93]	Dapagliflozin	T2DM; high CV risk	• Trial in progress; estimated completion in April 2019 • Secondary outcome measures: time to 1st event of kidney composite end point (confirmed sustained ≥ 40% decrease in eGFR to eGFR < 60 and/or ESRD and/or kidney or CV death [time frame: up to 6 y])

Abbreviations: CANVAS, A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus; CANVAS-R, A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus; CI, confidence interval; CREDENCE, A Randomized, Double-blind, Event-driven, Placebo-Controlled, Multicenter Study of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Subjects With Type 2 Diabetes Mellitus and Diabetic Nephropathy; CV, cardiovascular; Dapa-CKD, A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; DECLARE-TIMI-58, Effect on Cardiovascular Events A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients With Type 2 Diabetes; eGFR, estimated glomerular filtration rate (in mL/min/1.73 m^2); EMPA-REG, A Phase III, Multicentre, International, Randomised, Parallel Group, Double Blind Cardiovascular Safety Study of BI 10773 (10 mg and 25 mg Administered Orally Once Daily) Compared to Usual Care in Type 2 Diabetes Mellitus Patients With Increased Cardiovascular Risk; ESRD, end-stage renal disease; HbA_{1c}, hemoglobin A_{1c}; HR, hazard ratio; KRT, kidney replacement therapy; RR, relative risk; Scr, serum creatinine; SGLT2, sodium/glucose co-transporter 2; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UACR, urine albumin-creatinine ratio (in mg/g).

Alicic et al, *AJKD* June 2018

Renoprotection even in CKD



For 1000 patients in 2.5 yrs, NNT to prevent composite ESKD, 2x sCr, CKD/CV † = 22

Perkovic et al, NEJM, April 2019
Ingelfinger, editorial

eGFR prescribing guidelines

Table 2. Kidney Function Dose Adjustments for Approved SGLT2 Inhibitors

SGLT2 Inhibitor	Dose	Kidney Dose Adjustment
Dapagliflozin	5-10 mg	Avoid initiating if eGFR < 60 Not recommended with eGFR 30-60 Contraindicated with eGFR < 30
Empagliflozin	10-25 mg	No dose adjustment if eGFR ≥ 45 Avoid use, discontinue with eGFR persistently <45
Canagliflozin	100-300 mg	No dose adjustment if eGFR > 60 100 mg daily if eGFR 45-59 Avoid use, discontinue with eGFR persistently <45
Ertugliflozin	5-15 mg	Avoid initiating if eGFR 30-60 Continued use is not recommended with persistent eGFR 30-60 Contraindicated with eGFR < 30

Abbreviations: eGFR, estimated glomerular filtration rate (in mL/min/1.73 m^2); SGLT2, sodium/glucose transporter inhibitor 2.

Alicic et al, *AJKD* June 2018

eGFR: estimate or guess-timate?

Can't apply if s. creatinine unstable, different assay

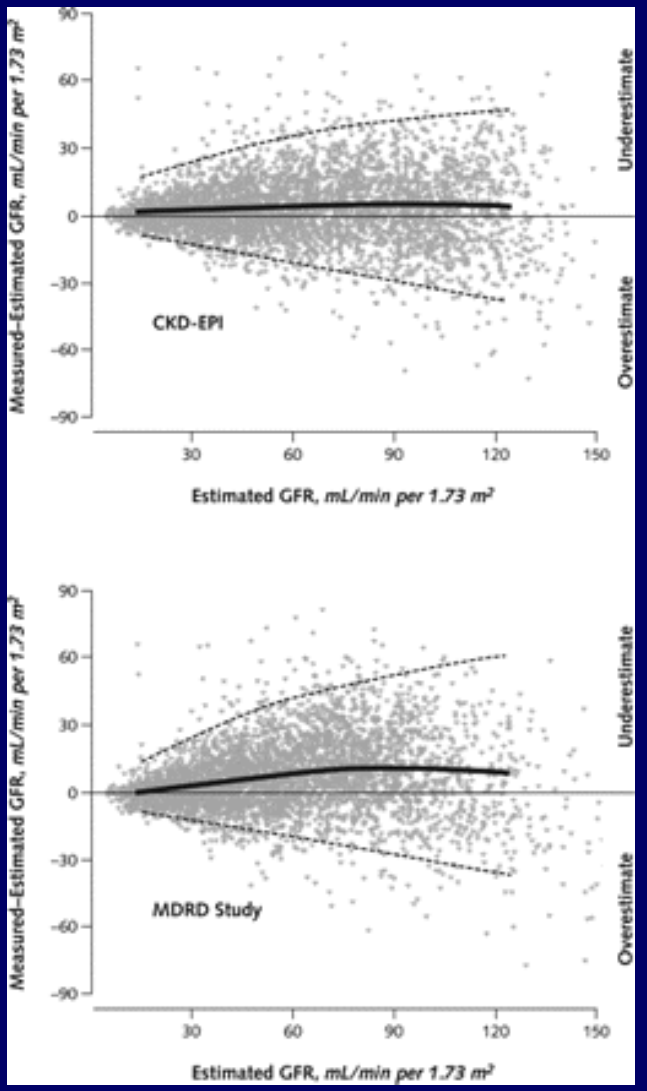
50-100% false high/low eGFR in outliers:

- True GFR higher: muscular, tall
- True GFR lower:

  muscle wasting, short

CKD-EPI better on average than MDRD formula

Levey, *Ann Int Med* 2009



The bigger picture

Renal glucose physiology

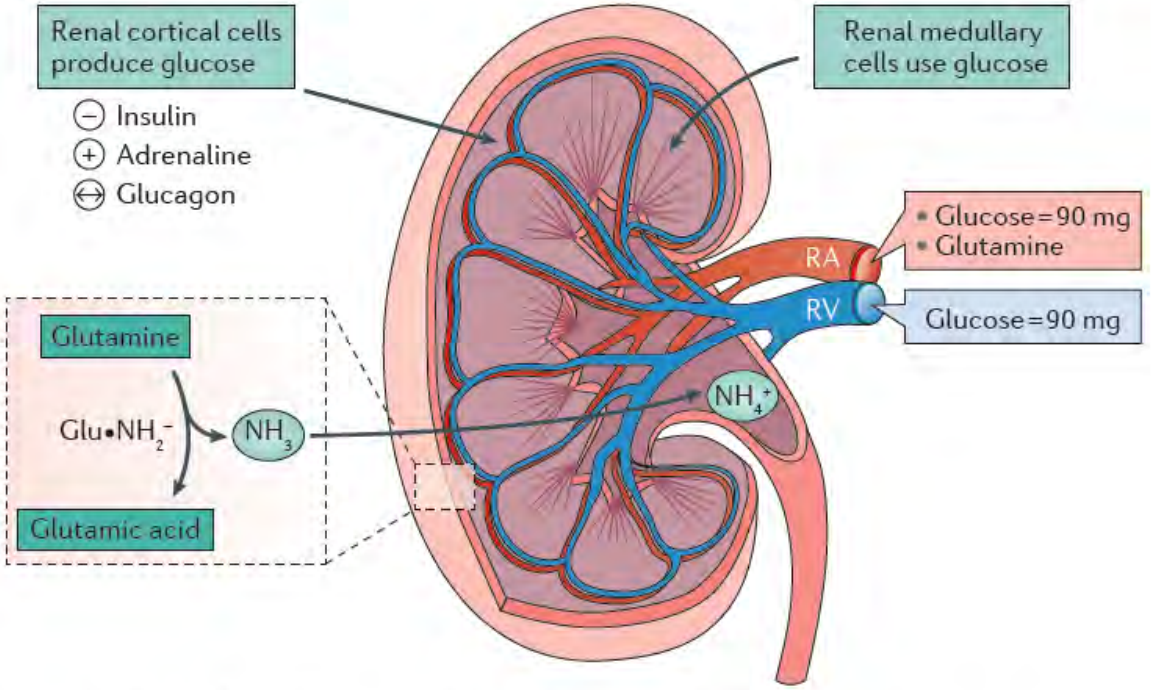


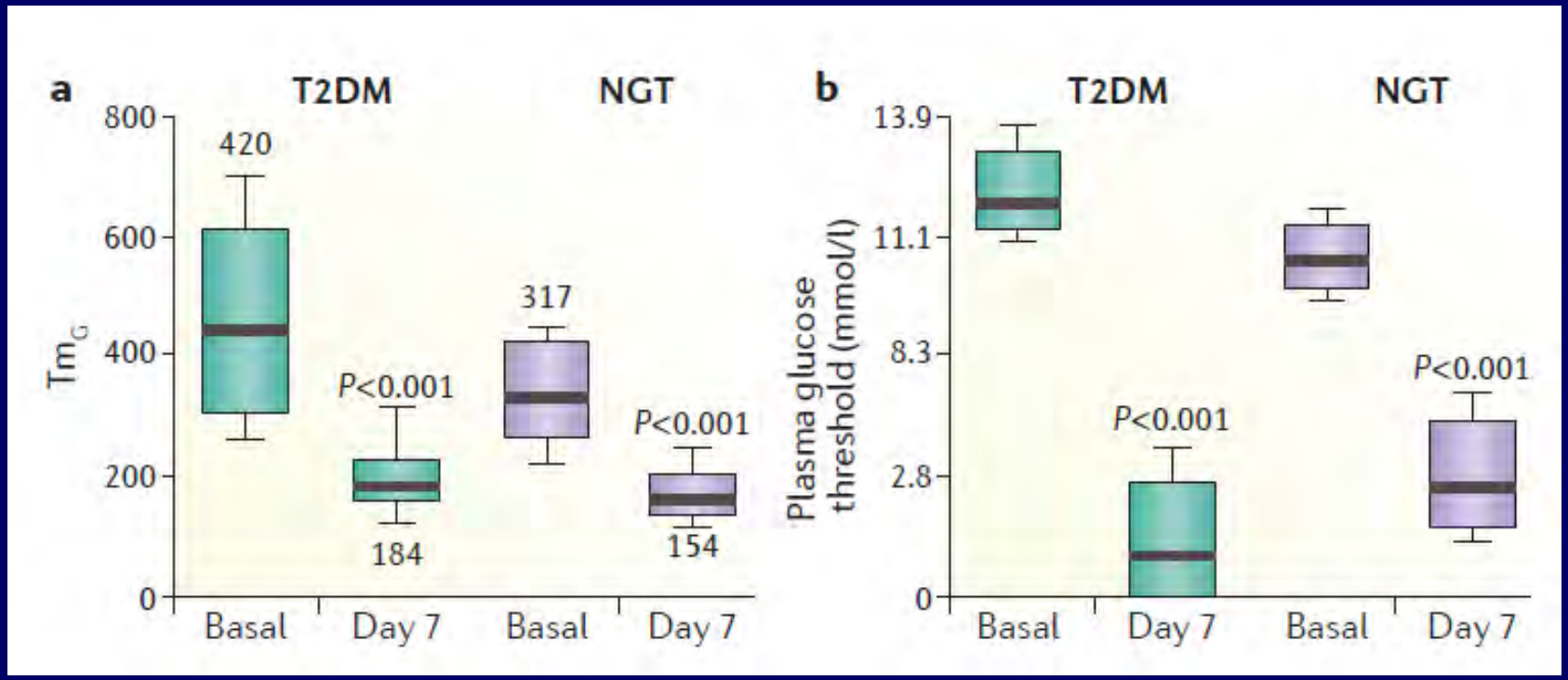
Figure 1 | **Role of the kidney in glucose homeostasis.** The kidney utilizes glucose as an energy source (renal medullary cells) and produces glucose via gluconeogenesis (renal cortical cells). The net result is that the net arteriovenous balance of glucose across the kidney is zero. Glucose production by the renal cortical cells is inhibited by insulin and stimulated by adrenaline. Glucagon has no effect on renal glucose production. Glutamine is extracted by renal tubular cells and used to generate ammonia (NH_3), which has an important role in acid excretion (NH_4^+). RA, renal artery; RV, renal vein.

de Fronzo et al, *Nature Reviews Nephrology* 2017

Works in diabetics & non-diabetics

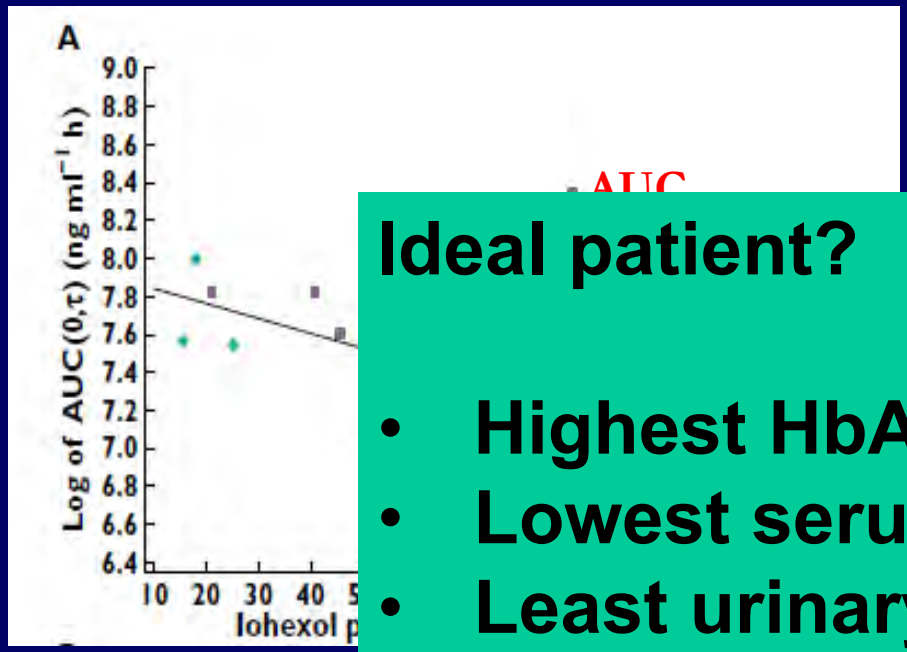
↓Tubular glucose re-absorption

↓Plasma glucose threshold



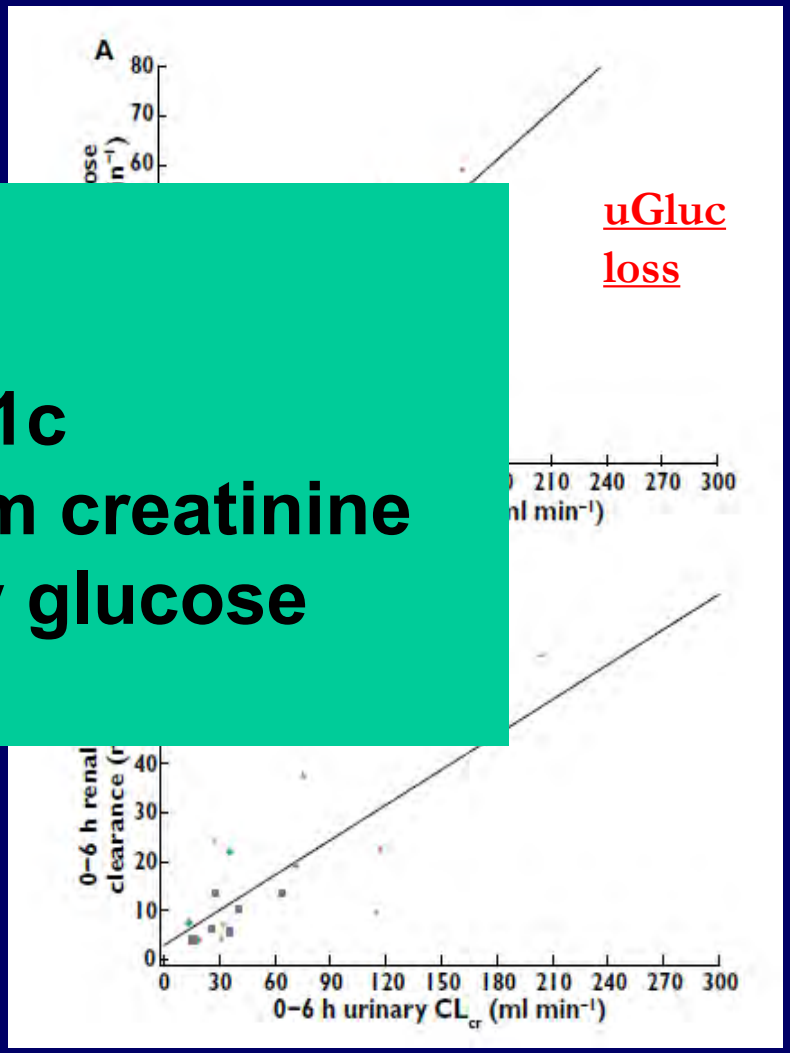
de Fronzo et al, *Nature Reviews Nephrology* 2017

↓GFR →↑retention but ↓efficacy



AUC

uGluc loss

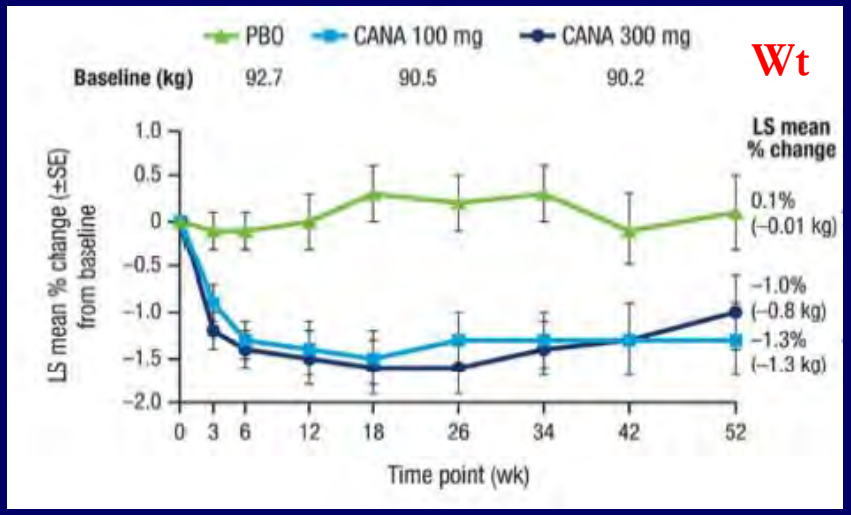


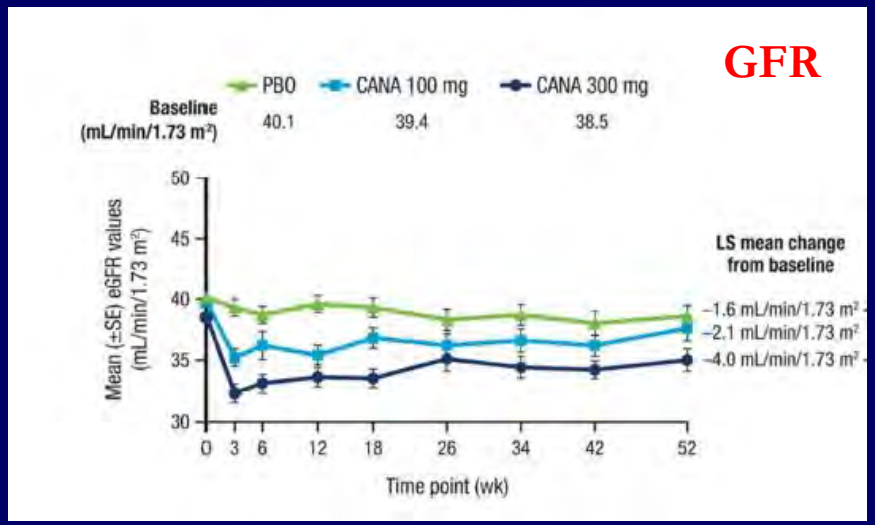
Ideal patient?

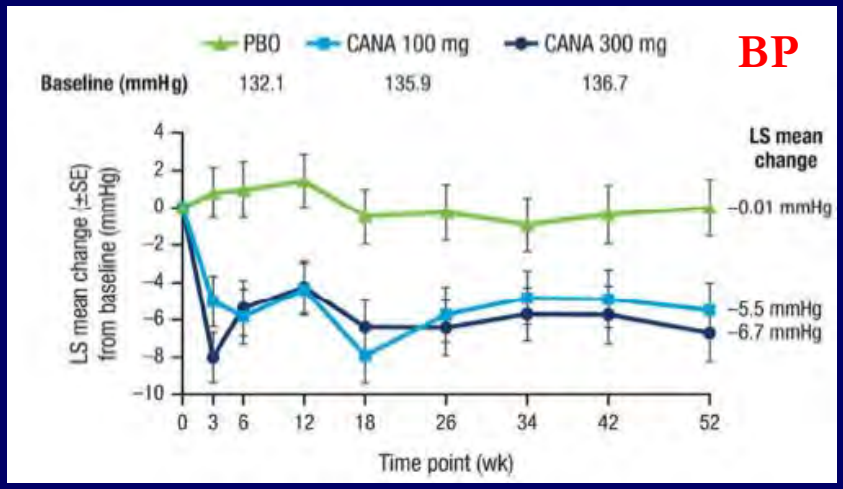
- Highest HbA1c
- Lowest serum creatinine
- Least urinary glucose

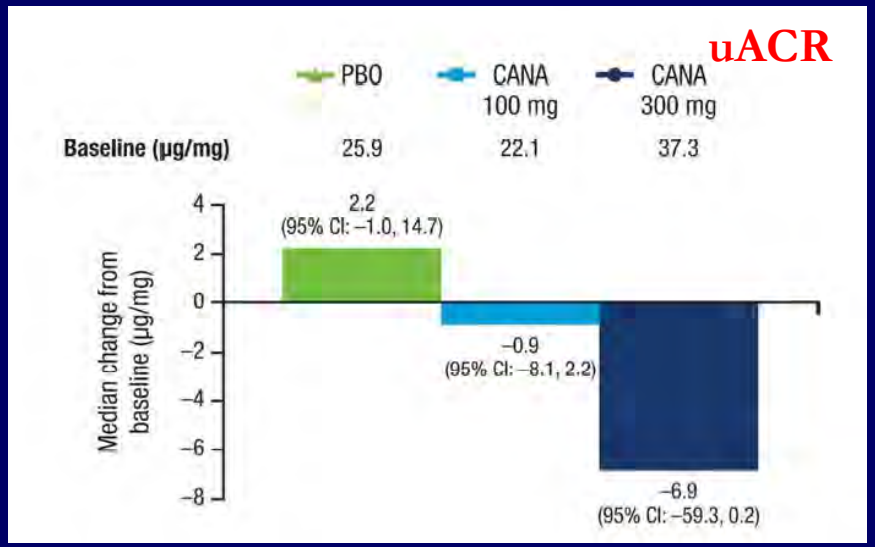
Kasichayanulaet al, Dapagliflozin pharmacokinetics in moderate and severe CKD, *BJCP* 2012

SGLT2i even in CKD: ↓wt, BP, GFR & uACR









Yale *et al.* doi:10.1111/dom.12348

Reversible acute ↓GFR, long-term stable GFR

Wanner, *NEJM*, June 2016

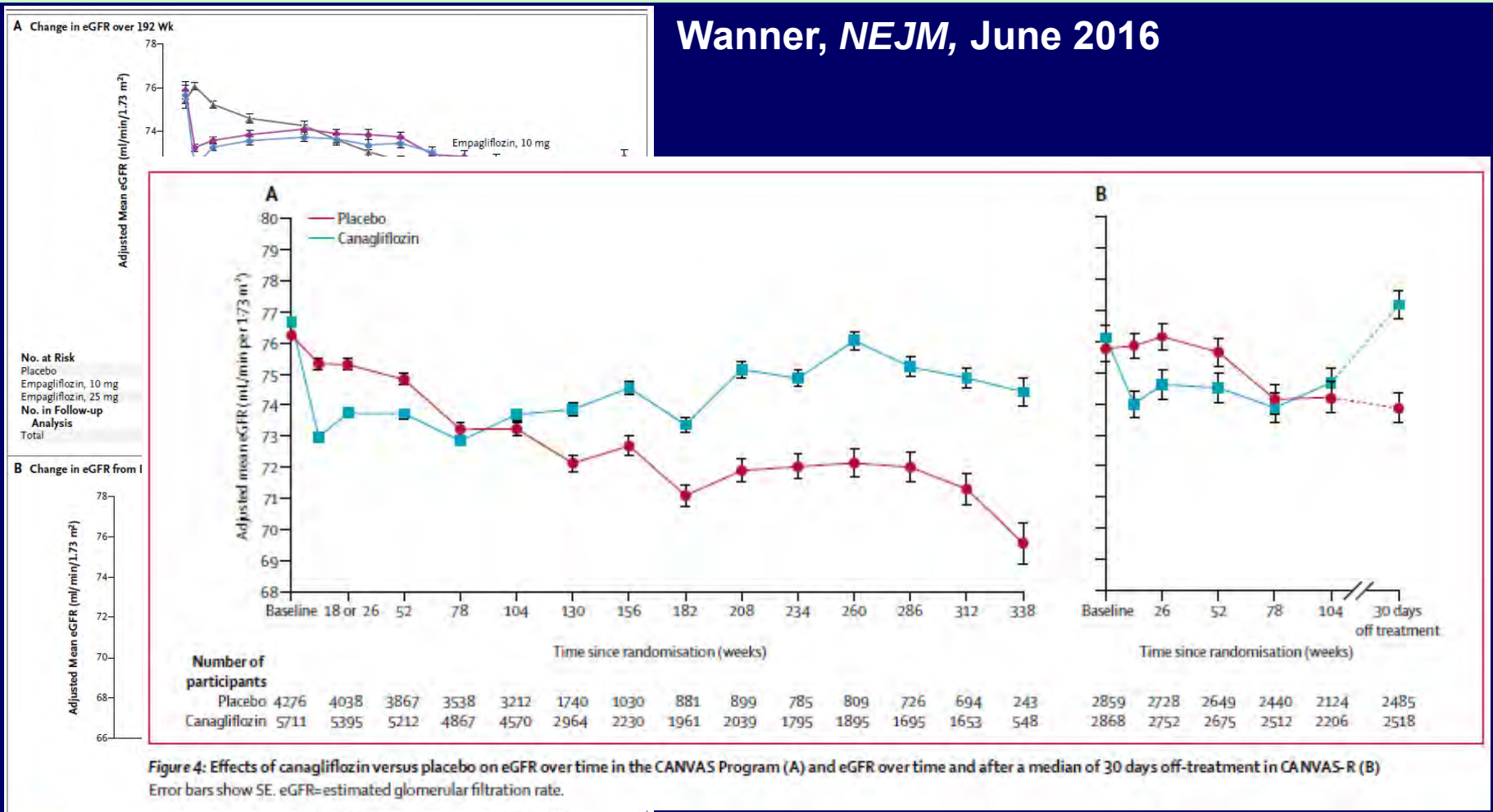


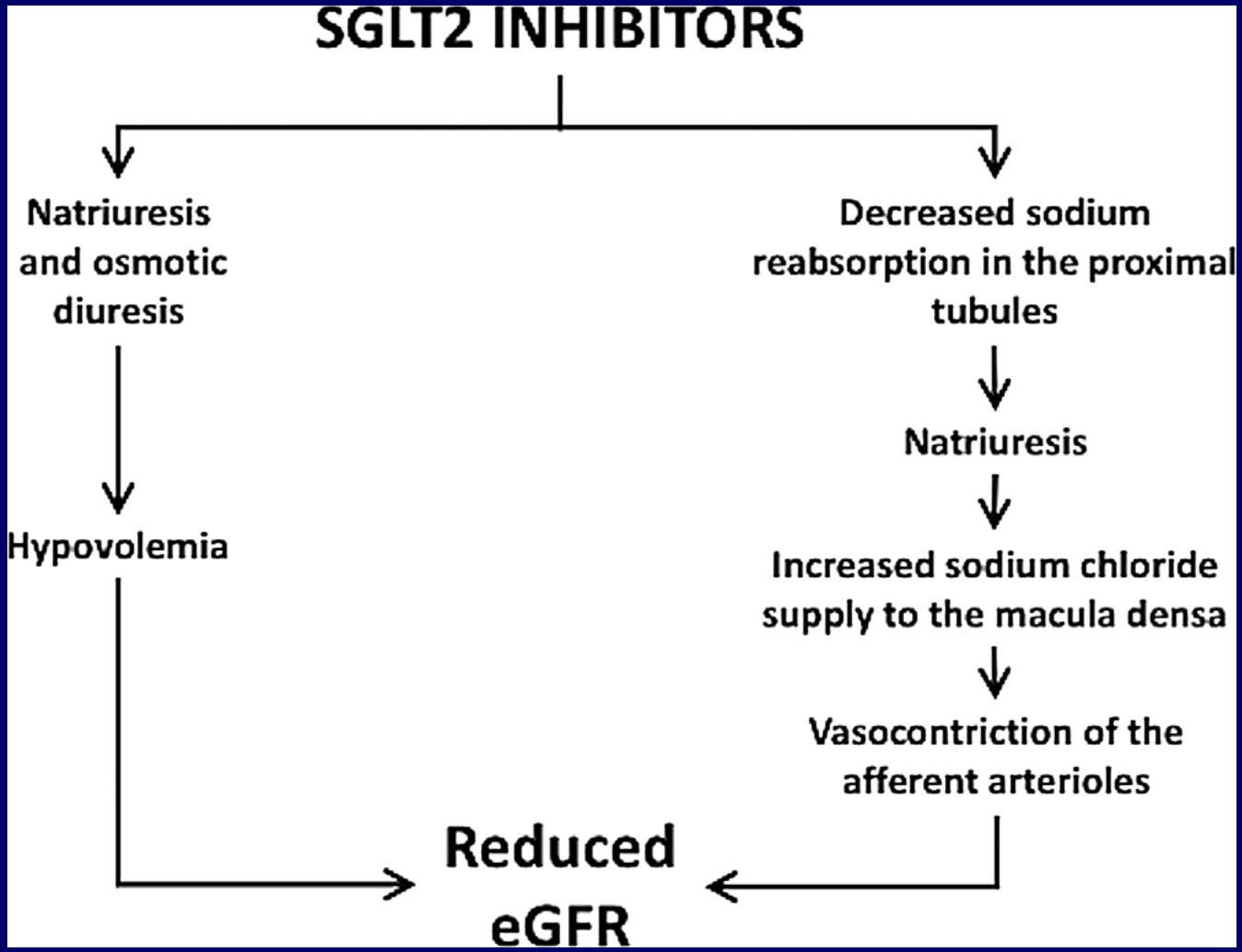
Figure 4: Effects of canagliflozin versus placebo on eGFR over time in the CANVAS Program (A) and eGFR over time and after a median of 30 days off-treatment in CANVAS-R (B)
Error bars show SE. eGFR=estimated glomerular filtration rate.

Figure 3. Renal Function over Time.

Shown are the adjusted means for the estimated glomerular filtration rate (eGFR) over a period of 192 weeks (Panel A) and at the last measurement during treatment and at follow-up (Panel B) among patients who received empagliflozin (at a dose of 10 mg or 25 mg) or placebo. Baseline values are means, and the I bars indicate standard errors. The eGFR was calculated according to the creatinine formula developed by the Chronic Kidney Disease Epidemiology Collaboration. Among patients in the empagliflozin group, the adjusted mean difference from placebo in the change from baseline at follow-up (Panel B) was 4.7 ml per minute per 1.73 m^2 in both the 10-mg and 25-mg groups ($P<0.001$ for both comparisons). Panel A is based on prespecified mixed-model, repeated-measures analysis in patients who received at least one dose of a study drug and had a baseline and postbaseline measurement. Panel B is based on a prespecified analysis of a covariance model (with the baseline eGFR and glycated hemoglobin level as linear covariates and baseline body-mass index, region, and study group as fixed effects) in patients who underwent measurements at all three time points.

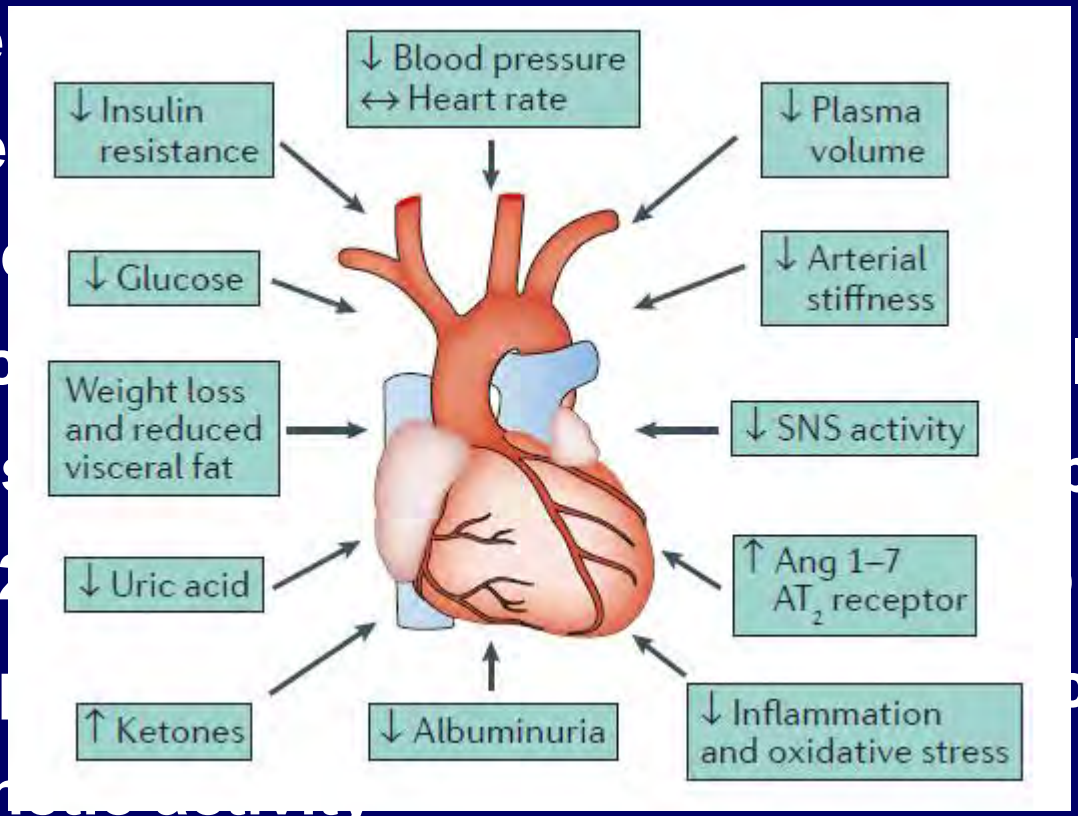
Perkovic, CANVAS *Lancet* June 2018

Initial acute GFR fall



Multiple long-term renoprotection possibilities

1. ↓Glomerular pressure: ↓TGF → ↓aff artery dilation
2. ↓BP lowe
3. ↓Glucose
4. Thrifty fu
5. Metabolic lucagon
6. ↑Natriures porter
7. ↑Renal O2
8. RAAS de ceptors
9. ↓Sympath



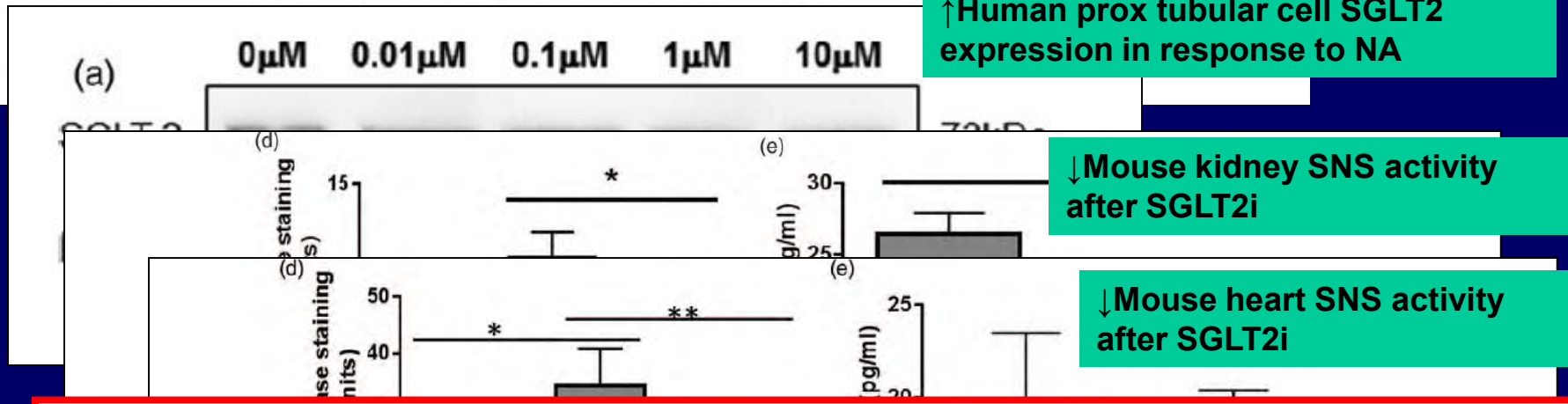
Tsimihodimos et al, *Diab & Met Synd*, 2018

de Fronzo et al, *Nature Reviews Nephrology* 2017

Bidirectional sympathetic NS & SGLT2 interaction

Role of the sympathetic nervous system in regulation of the sodium glucose cotransporter 2

↑Human prox tubular cell SGLT2 expression in response to NA



↓Mouse kidney SNS activity after SGLT2i

↓Mouse heart SNS activity after SGLT2i

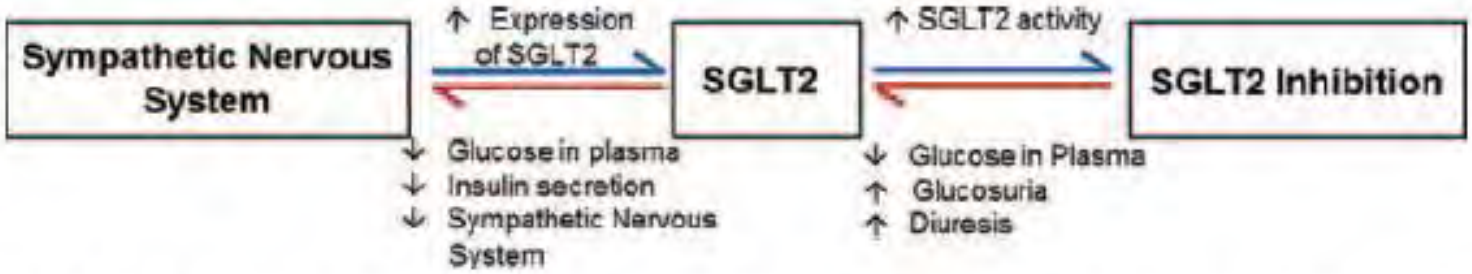
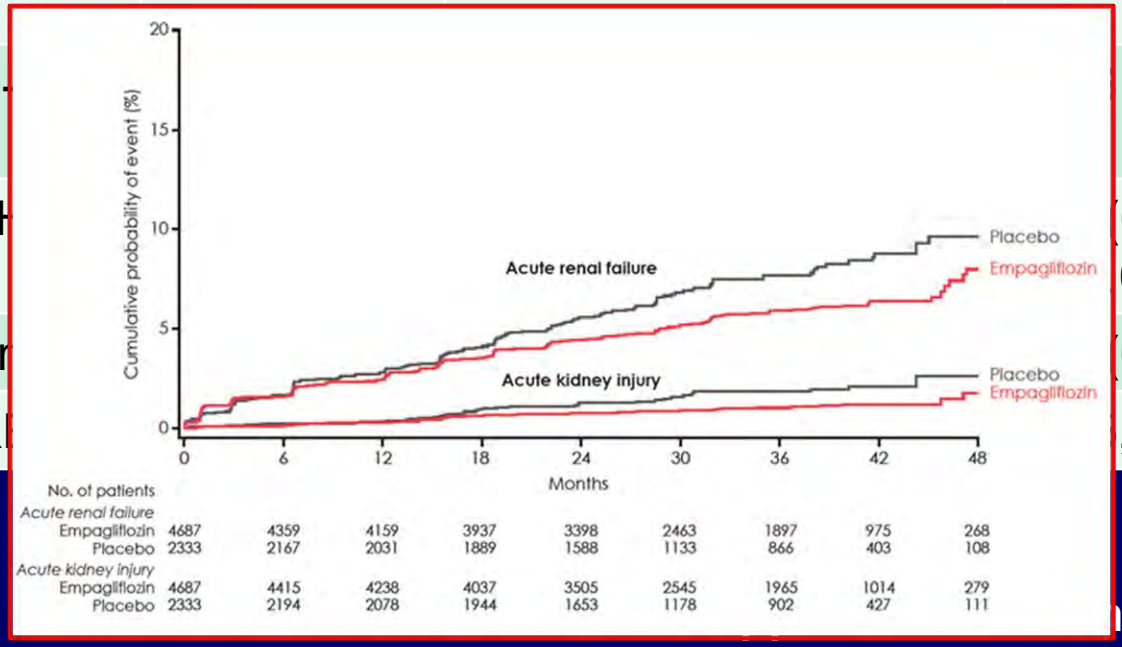


FIGURE 8 Proposed bidirectional interaction between the sympathetic nervous system, SGLT2 and SGLT2 inhibition.

Matthews & Schlaich et al, *J Hypertens* 2017

?Reduced rate of AKI vs SGLT2i non-users

Study	N	AKI % p.a. or total: SGLT2i vs placebo	HR (CI), p
EMPA-REG >60	5,199	3.2 vs 3.9%	0.77 (0.57-1.04)
EMPA-REG <60	1,819	11.2 vs 14.3%	0.75 (0.57-0.98)
CANVAS-			(0.39-1.11),
Mt Sinai H			(0.3-0.7), 004
Geisinger			(0.4-1.1), ns
DECLARI			, p = 0.002



nner et al, *NEJM* 2017
Nadkarni et al, *Diab Care* 2017
Perkovic et al, *Lancet Diab Endocrin* 2018
Wiviott et al, *NEJM* 2018

Enhanced recovery from experimental AKI

Non-diabetic mouse ischaemia-reperfusion

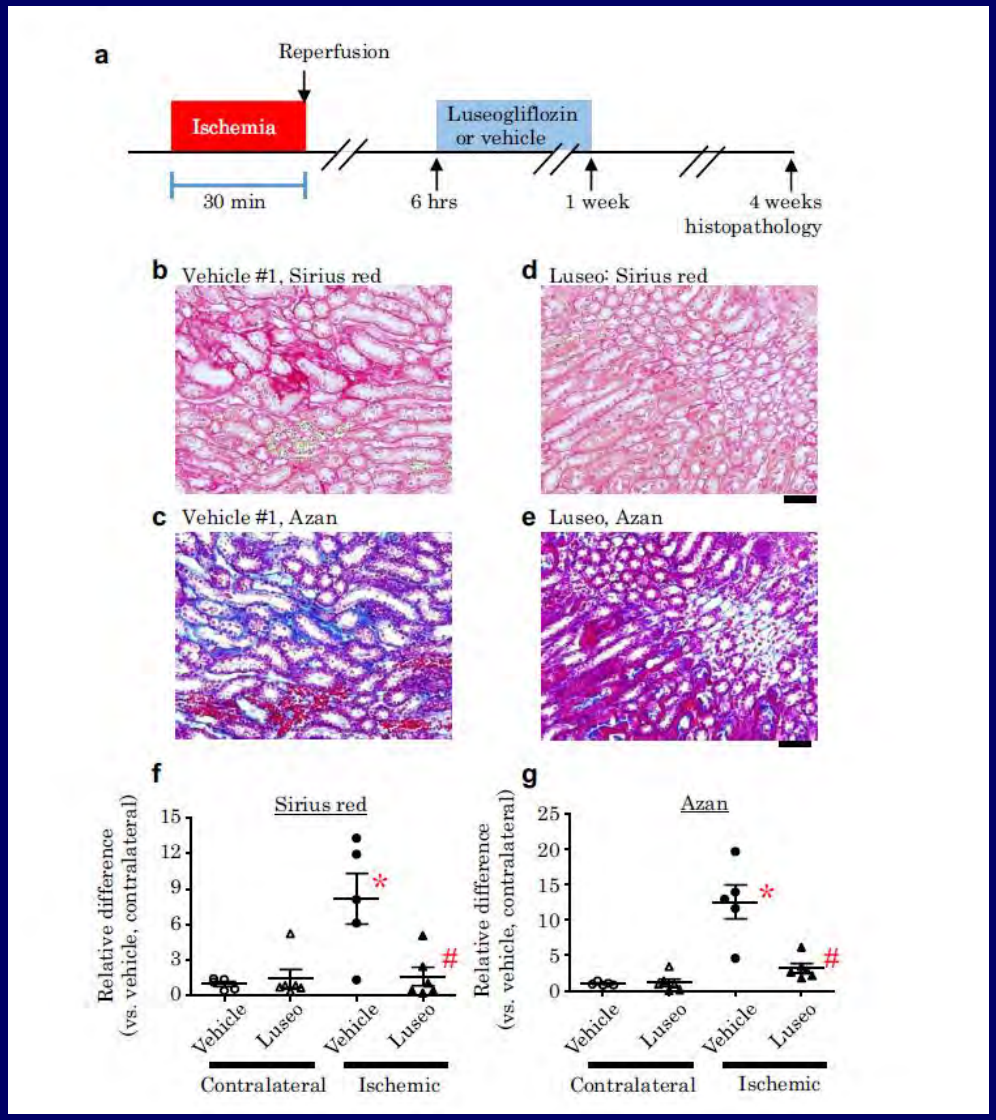
SGLT2i (luseogliflozin) given 6 hrs post-injury

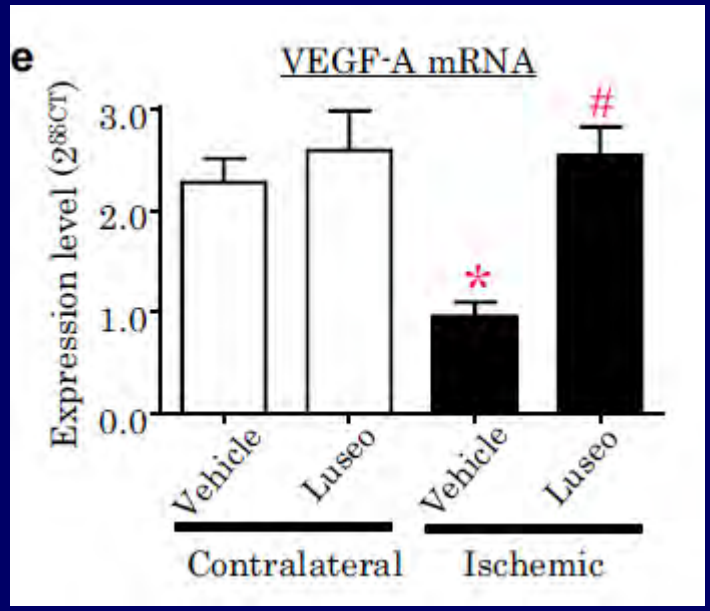
SGLT2i →

- ≈ Function (urea/CCl) in Wk 1
- ↑ uVol & uGluc in Wk 1
- ↓ Congestion-haem'ge in Wk 1*
- ↑ VEGF at Wk 1 & 4*
- ↓ Fibrosis at Wk 1 & 4*
- * = Blocked by sunitinib

Zhang et al, *Kidney Int,* Aug 2018

Enhanced recovery from experimental AKI





Zhang et al, *Kidney Int,* Aug 2018

Looking carefully

& safety

Effect
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Jason H Y Wu*

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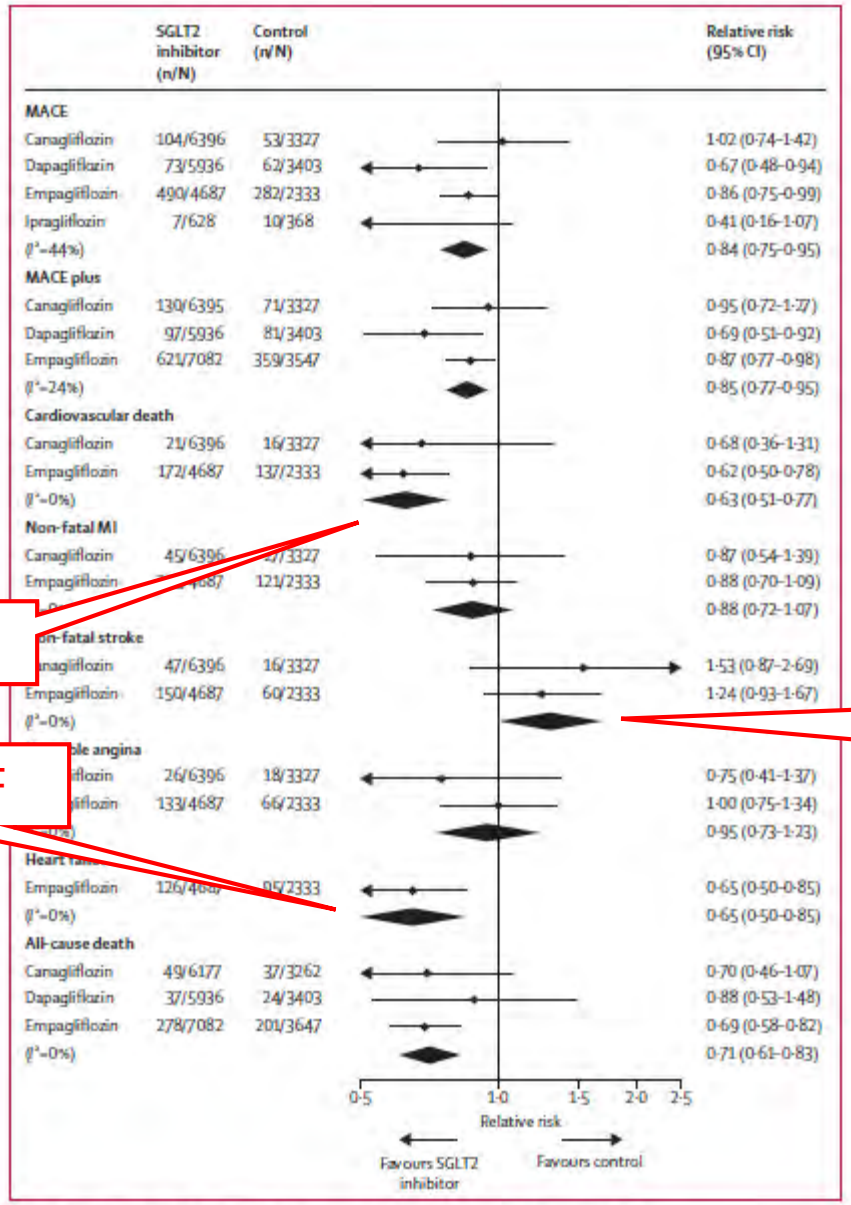


Figure 2: **Effects of SGLT2 inhibitors on vascular outcomes, overall and for each drug**
Estimates for each drug were derived directly from regulatory documents or fixed-effects meta-analysis of effect estimates from multiple sources. Summary effects for all compounds were obtained from fixed-effects meta-analysis. MACE=major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke). MACE plus=MACE and admission to hospital for unstable angina. SGLT2=sodium-glucose cotransporter-2. *Data available only for empagliflozin.

Less CV †

Less CCF

More stroke

& in CANVAS: more amputations

N= 37,525, 6 regulatory submissions, 7 drugs
Wu, *Lancet Diab Endocrin* 2016

Gliflozin guidelines

20% reduction in insulin/ SU if tight control

50% reduction in BP Rx/diuretic if tight control

Daily BP, weight, BSL next 2 months

Daily groin/apron wash, dry & baby powder

Zinc/castor oil if red; clotrimazole/fluconazole if thrush,

MSU pot & cephalexin; pre-emptive Rx if dysuria

Hold SGLT2i if too symptomatic, try alternate daily

Watch for DKA in long-standing T2DM

– & stop 3 days pre-op!

M Thomas, personal communication

Sliding Toward Euglycemic DKA

T2DM CKD & acidosis

70M

Controlled T2DM, BP, chol, stable Stage 2-3 CKD

Routine TKR, continued all usual pills

Post-op high K+ 6.8, low HCO3 12!

Differential Dx?

- Higher sCr = renal acidosis
- Higher lactate = metformin acidosis
- Higher ketones = SGLT2i acidosis
- Higher Cl- = N saline acidosis
- Higher pCO2 = opioid respiratory acidosis

Well day pills & sick day plans

Continue:

- Aspirin
- Ca2+ ch blocker
- Insulin (↓ dose)
- Statin

Stop if sick:

- ACEi/ARB
- Digoxin
- Diuretic
- Metformin
- NSAID
- SGLT2i

Therapy	PRO	CON
Metformin	**Experience / Proven outcomes / Cost**	**GI symptoms/ CKD**
Sulfonylurea	**Experience / Cost**	**Hypo's/ Wt. gain / CKD**
DPP4-i (gliptin)	**Wt. neutral / Low risk of hypo's**	**Cost / CCF (saxa, not sita) / GI CKD (except lina) / LFT's (vilda)**
TZD (glitazone)	**Low risk of hypo's**	**Cost / Fluid retention / Wt. gain / Fracture risk / ?Bladder ca (pio)**
SGLT2-i (gliflozin)	**Wt. loss / SBP reduction / Low risk of hypo's**	**New / Dehydration / DKA $ / UTI & thrush / CKD inefficacy**
Acarbose	**Low risk of hypo' / Wt. neutral / Cost**	**Limited efficacy / GI tolerability**
GLP-1 (incretin analogue)	**Wt. loss / Low risk of hypoglycaemia**	**Cost / Injection / GI symptoms**
Insulin	**Experience / Effective**	**Injection / Wt. gain / Hypo's**

Therapy	PRO	CON
Metformin	**Experience / Proven ou… Cost**	**BASELINE** **…toms/ CKD**
Sulfonylurea	**Experience / Cost**	**Hypo's/ Wt. gain / CKD**
DPP4-i (gliptin)	**Wt. neutral / Low risk of hypo's**	**Cost / CCF (saxa, not sita) / GI CKD (except lina) / LFT's (vilda)**
TZD (glitazone)	**Low risk of hypo's**	**TOO RISKY** **…ntion / Wt. gain / Fracture …adder ca (pio)**
SGLT2-i (gliflozin)	**Wt. loss / SBP reduction / Low risk of hypo'**	**New / Dehydration / DKA $ / UTI & thrush / CKD inefficacy**
Acarbose	**Low risk of hypo' / Wt. ne… Cost**	**TOO WEAK** **…ficacy / GI tolerability**
GLP-1 (incretin analogue)	**Wt. loss / Low risk of hypoglycaemia**	**Cost / Injection / GI symptoms**
Insulin	**Experience / Effective**	**Injection / Wt. gain / Hypo's**

Therapy	PRO	CON
Metformin	**Experience / Proven ou… / Cost**	**…toms/ CKD**
Sulfonylurea	**Experience / Cost**	**…ain / CKD**
DPP4-i (gliptin)	**Wt. neutral / Low risk of hypo's**	**Cost / CCF (saxa, not sita) / GI CKD (except lina) / LFT's (vilda)**
SGLT2-i (gliflozin)	**Wt. loss / SBP reduction / Low risk of hypo'**	**New / Dehydration / DKA $ / UTI & thrush / CKD inefficacy**
GLP-1 (incretin analogue)	**Wt. loss / Low risk of hypoglycaemia**	**Cost / Injection / GI symptoms**
Insulin	**Experience / Effectiv…**	**…gain / Hypo's**

BASELINE

HYPOs/WT GAIN

HYPOs/WT GAIN

Lower all-cause † with SGLT2i or GLP1a vs DPP4i, & fewer S/E's with SGLT2i or DPP4i's vs GLP1a

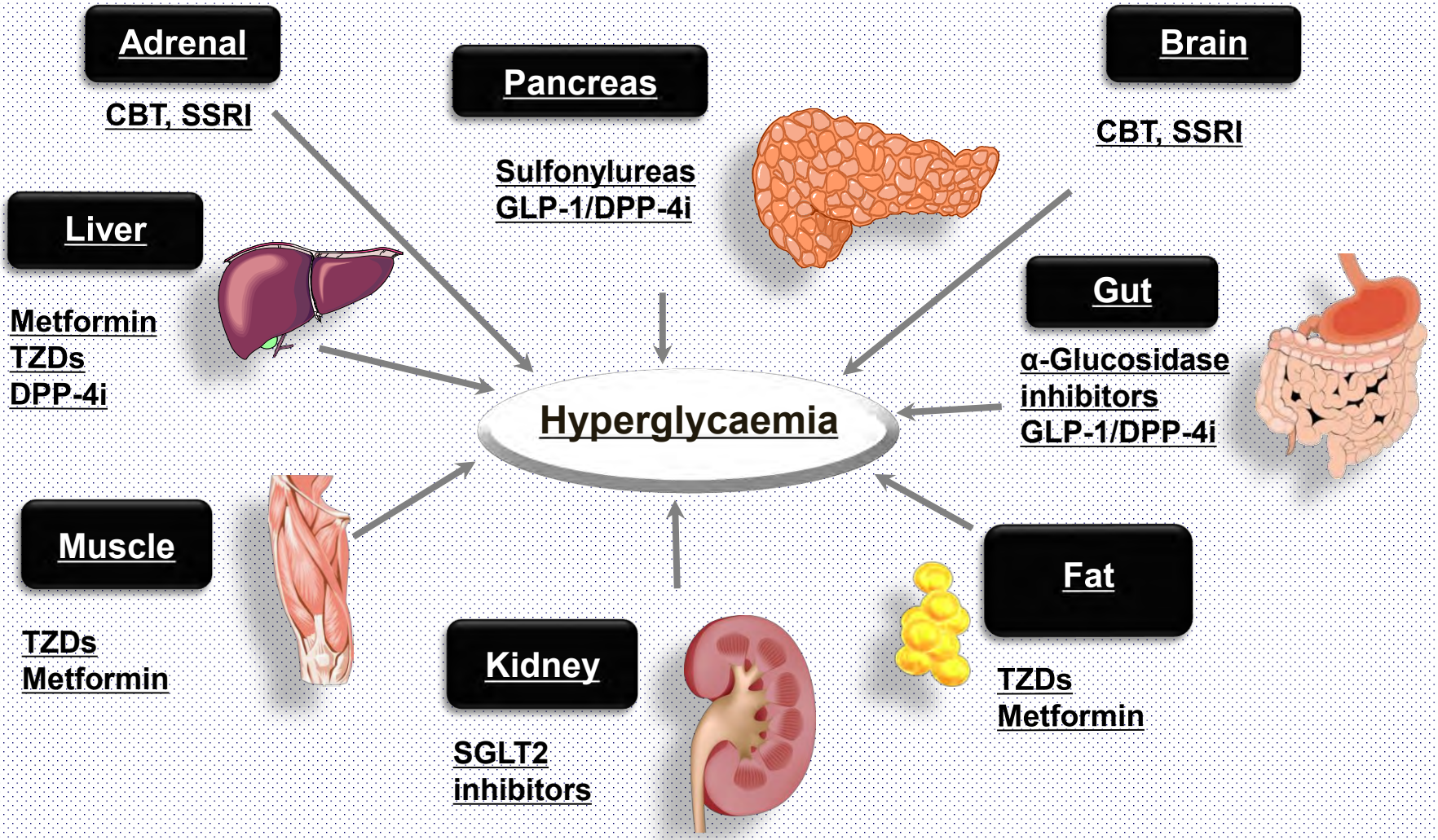
Agent	All-cause †	CV †	HF events	Side-effects
1. SGLT2i	-1.0%, 0.80 (0.71-0.89)	-0.8%, 0.79 (0.69-0.91)	-1.1%, 0.62 (0.54-0.72)	Comparator
2. GLP1a	-0.6%, 0.88 (0.81-0.94)	-0.5%, 0.85 (0.77-0.94)	Comparator	+5.8%, 1.80 (1.44-2.25) vs #1
3. DPP4i	0.1%, 1.02 (0.94-1.11)	Comparator	Comparator	+3.1%,1.93 (1.59-2.35) 2 vs #3

Network meta-analysis, 236 trials, 176,310 subjects

Absolute risk % & hazard ratio (CI) vs others or placebo

Zheng SL et al, JAMA 2018, doi:10.1001/jama.2018.3024

Sites/Modes of Action of Pharmacotherapy for T2DM



Adapted from DeFronzo RA. Diabetes. 2009;58:773-795.

5 Types of Diabetes

Cluster analysis of Swedish/UK new diabetics, n = 8980

*** Age, BMI, HbA1c, HOMA-β, HOMA-IR, Ab's, cmplx, genes**

*** Replicated x 3 independent databases: n = 14,775 total**

1. **Severe Autoimmune Diabetes (SAD)**
2. **Severe Insulin-Deficient Diabetes (SIDD) = Eye risk**
3. **Severe Insulin-Resistant Diabetes (SIRD) = CKD risk**
4. **Mild Obesity-related Diabetes (MOD)**
5. **Mild Age-Related Diabetes (MARD)**

Ahlquist et al, *Lancet Diab & Endocrin*, March 2018

Hiding in plain sight

Worse DM control & complications in ATSI vs non-ATSI despite same Rx: NEPHRON GP study

144 ATSI (53y) vs 449 non-ATSI (64y) at same GP (vs 3893 total)

Similarities:

Same obesity 50%, waist 106cm, DM duration 8yrs

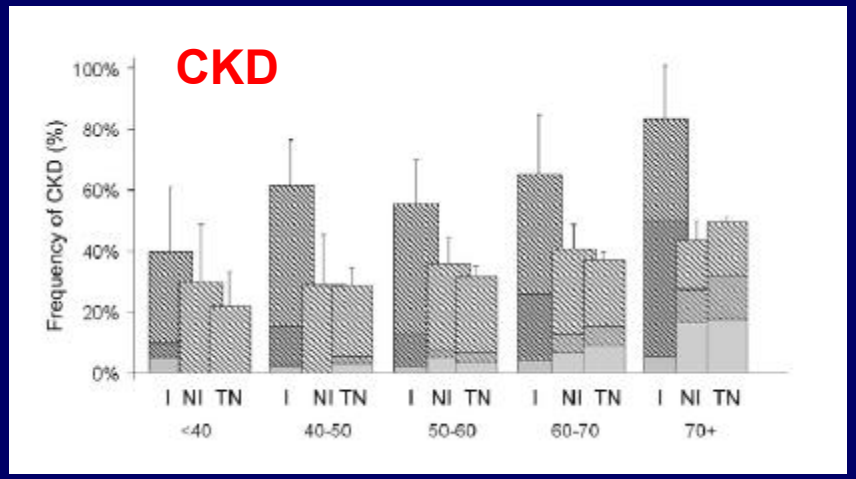
Same BP 132/80 & BP Rx, LDL 2.5 & lipid Rx

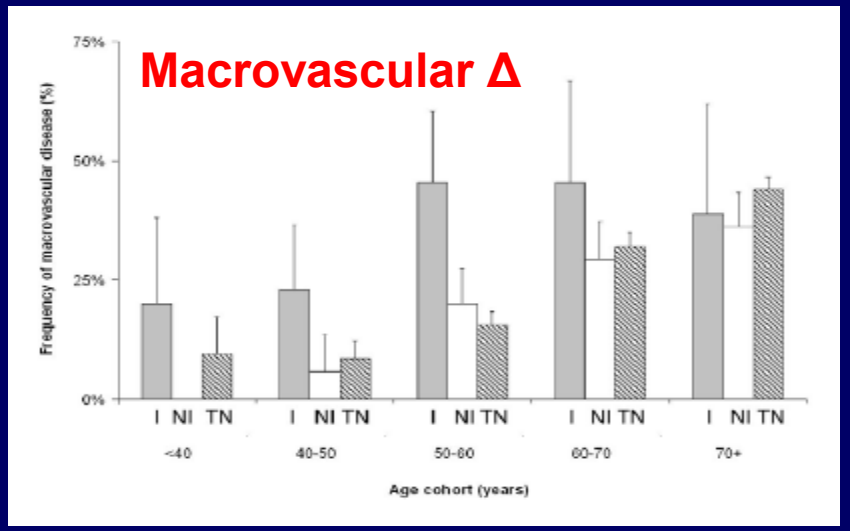
Differences:

More smoking (38 vs 9%), family history DM x2, CVD x3, CKD x5

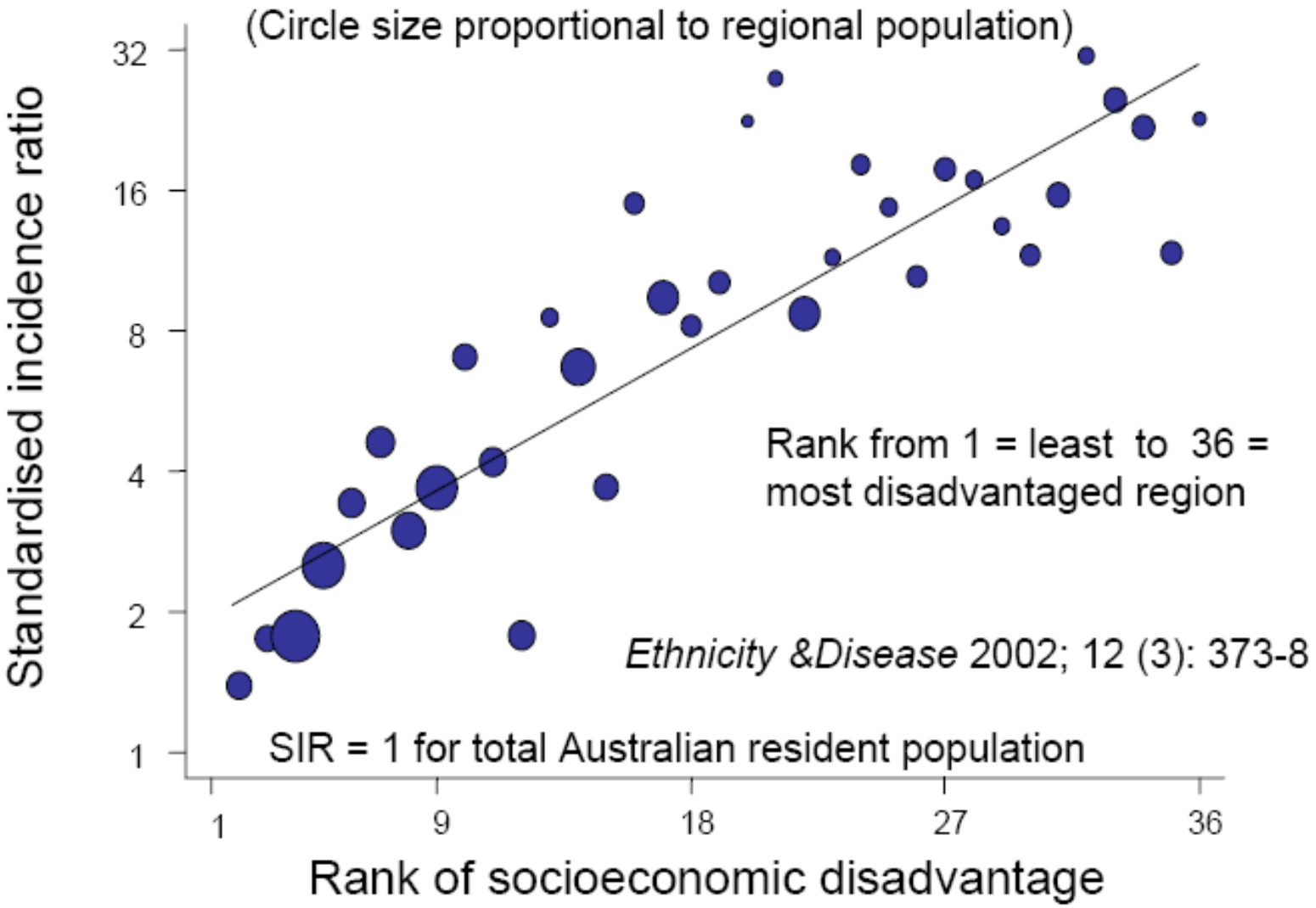
Worse HbA1c 8.9 vs 7.4%, but same Met/SU/insulin rates

M Thomas & M Thomas *BMC Pub Health* 2007





Disadvantage and ESRD incidence



Missing factors in ATSI T2DM: chronic stress

Cause: **Chronic stress**

- Socio-economic
- Family health

Consequence: **Cortisol**

- Insomnia
- Constant hunger with central obesity
- Insulin resistance with acanthosis
- Resistant hypertension with relatively low K+
- Muscle weakness and fatigue
- Recurrent infections

Schmitt & Spargo *Bio Soc Sci* 1995

Don’t make a bad situation worse

Stress: city hospital solo → outreach AMS & AHW

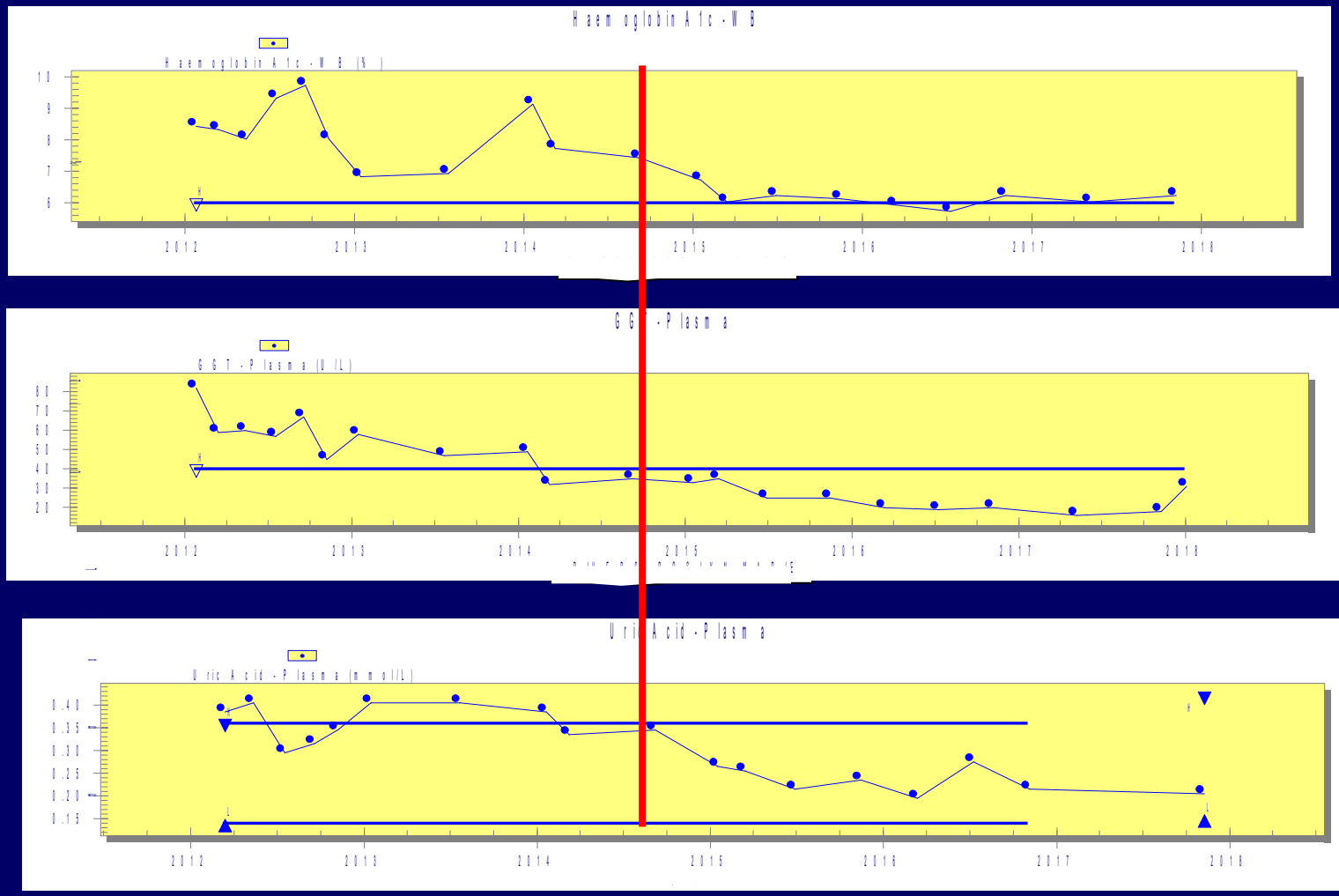
Cost: brand → generic, S100 & CTG

BMI/hypo’s: SU’s & insulin → gliptins, GLP1 & SGLT2i

Focus: HbA1c & obesity → BP & lipids

CV & CKD: ACEi/diuretic → ACEi/CCB

45F ATSI & SGLT2i Rx →↓BSL, BP, wt, GGT & UA



142kg	135kg	118kg	120kg

Lean Weight: Rule of Thumb

Height (cm)	155	165	175	185
Weight (kg) BMI = 25	60	68	76	85

Max lean weight (kg) = Ht (cm) - 100

Lifetime weight history

Birth

Young adult

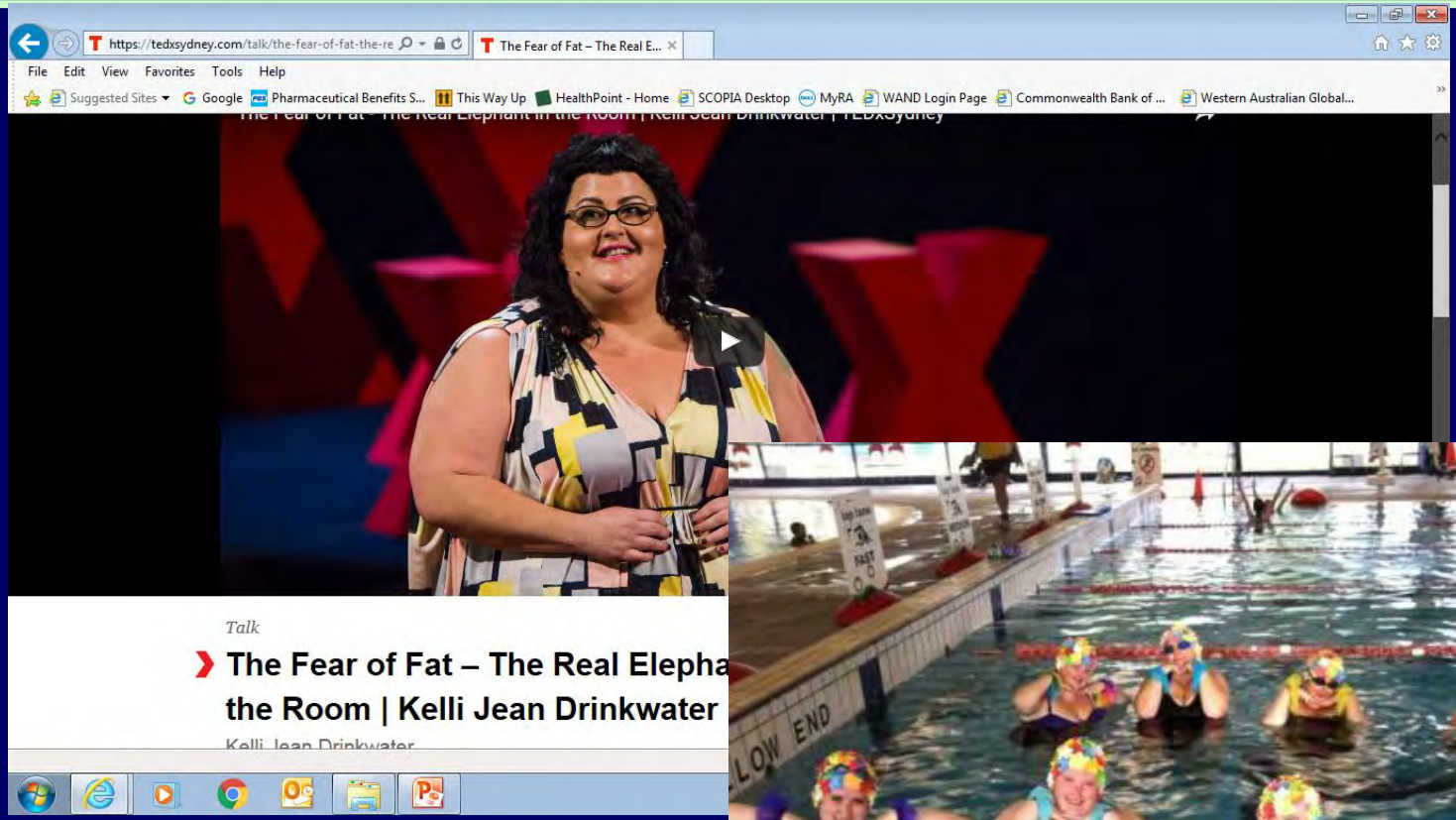
Maximum

Minimum

Current

What, when & why?

Praise the positive



Eat right

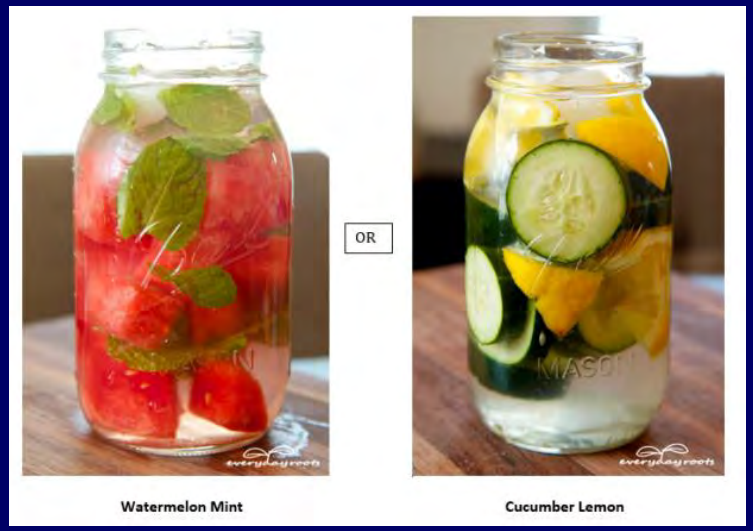
Quantity, quality & value

Pre-meal vinegar as anorectic

Eat like a hippie, not like a truckie

Make food crunchy and colourful

Traffic light detox drink



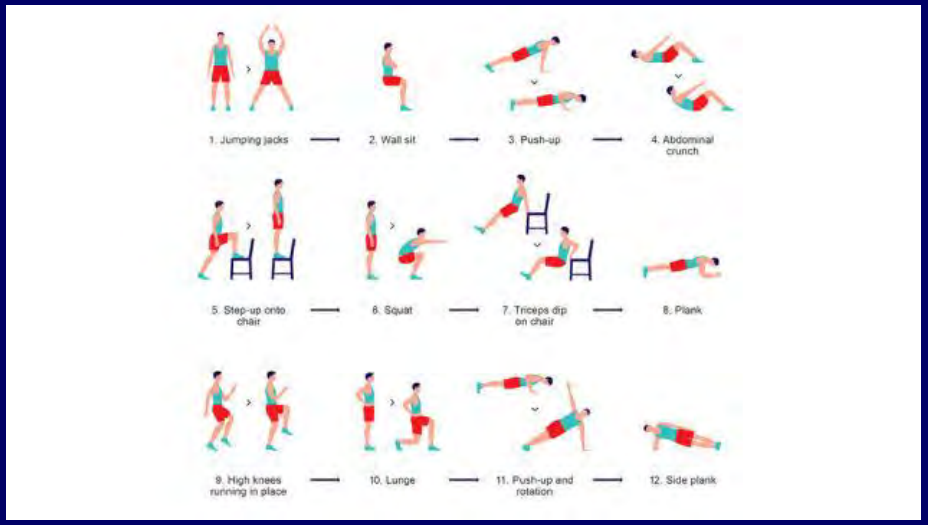
Move well

Motivation: age 20 vs 50 vs 80

Purpose: fit, strong, flexible, stable

Bird-rocket half-squats

“Seven”



Stay calm

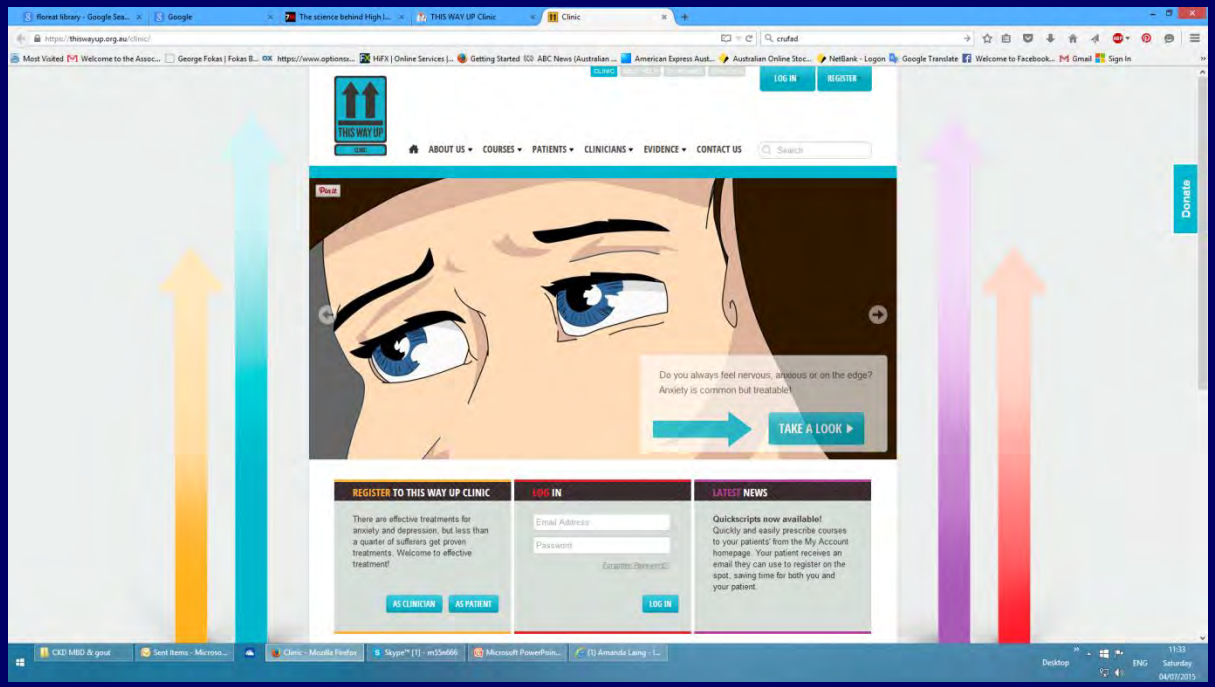
Friends & family, pets & plants

Movement, music & massage

DIY CBT: breathe, walk, smile, talk

CRUfAD.org

“This Way Up”



Simplicity and complexity