Recent paradigm shifts in the management of diabetes and its complications

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ACADI
Australian Centre for Accelerating Diabetes Innovations

Disclosures

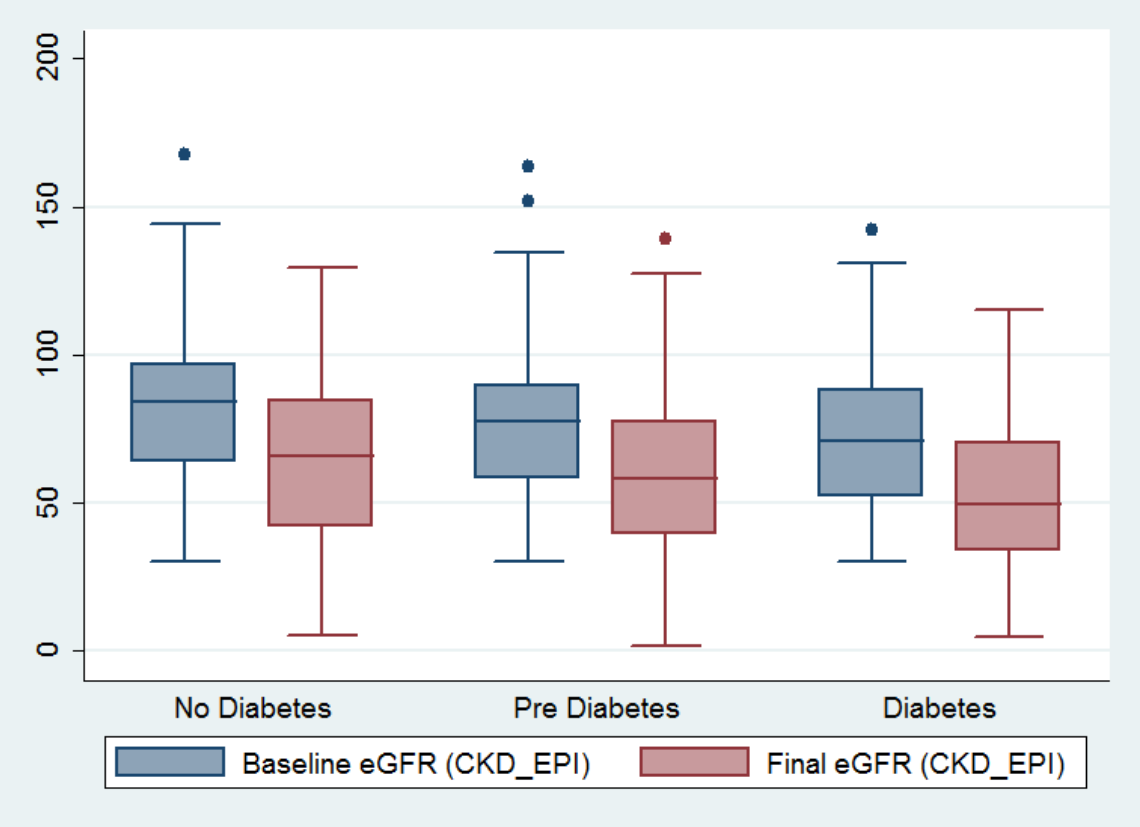
- Prof Ekinci discloses that in addition, to NHMRC, MRFF, JDRF funding, her institute receives research funding from Eli Lilly, Boehringer, NovoNordisk, Amgen, Versanis.
- Prof Ekinci sits on advisory boards of Eli Lilly, and Bayer and that she has given presentations for Eli Lilly, Bayer, Amgen, Boehringer.
- The funds received for advisory board and presentation activities are donated towards diabetes research at Prof Ekinci's institution.

Overview

- SGLT2i in CKD
- SGLT2i use in inpatients with heart failure
- SGLT2i safety in people without diabetes
- Need to improve prescription rates of SGLT2i
- Finerinone, Fidelity
- Tirzepatide in DKD
- DKD in T1 DM
- Associations between CGM and diabetes complications
- Insulin pumps
- ACADI
- Impact of DKD in Australia – ACADI and DA report on DKD

Glycaemic status and renal function decline over time in inpatients at Austin Health (n=4126)

- Median follow up of 514 days (IQR: 254, 740).
- Presence of diabetes compared to no diabetes was associated with:
  - **75% higher odds of progressing to eGFR< 30 ml/min**
- 1% increase in HbA1c level was associated with
  - **12% higher odds of eGFR< 30 ml/min**



Diabetes and diabetic kidney disease are a major cause of morbidity in the community and in the inpatient setting.

Torkamani, …. Ekinci- J Diabetes Complications. 2020 Jan;34(1):107465

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

N Engl J Med 2023;388:117-27.

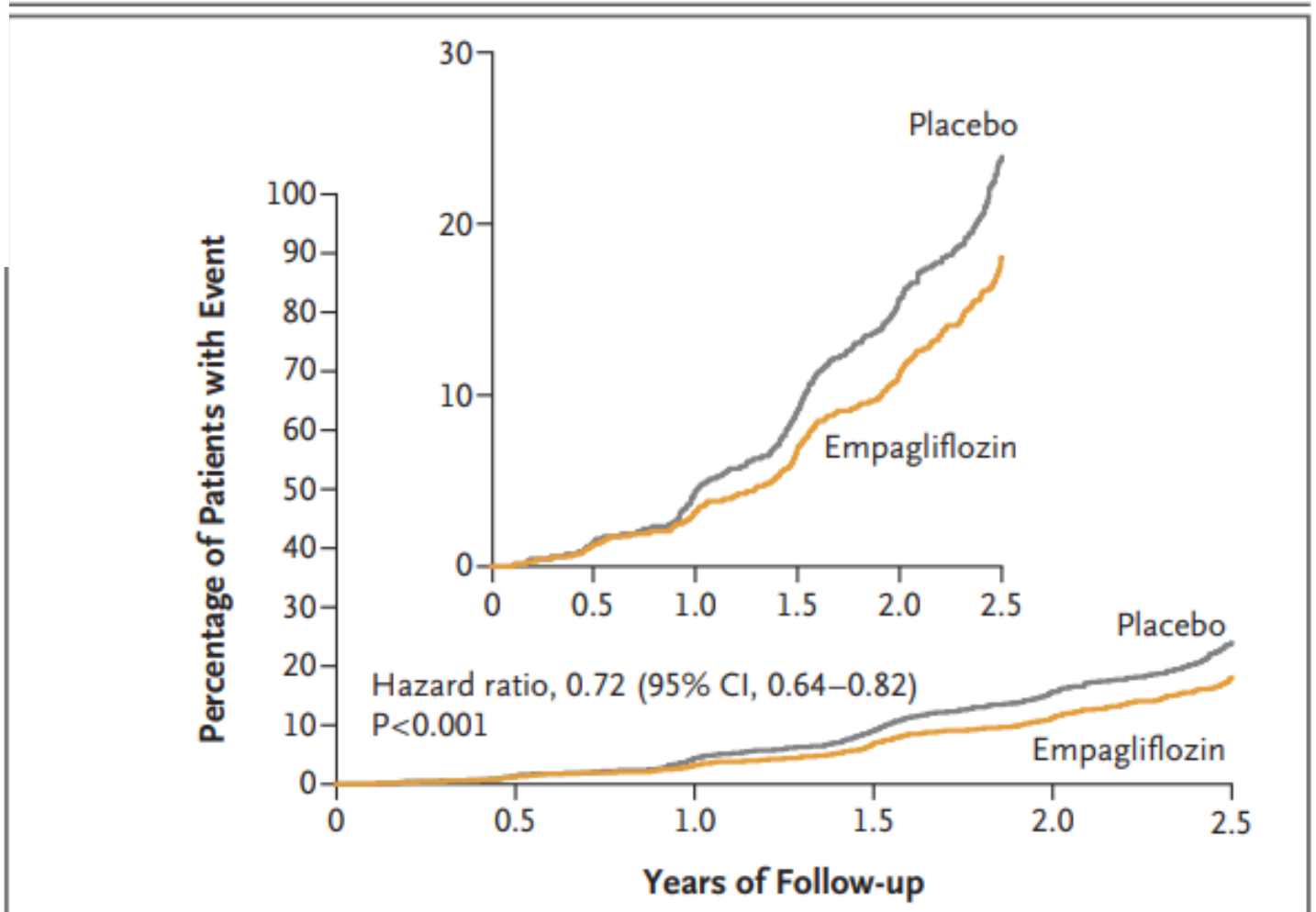
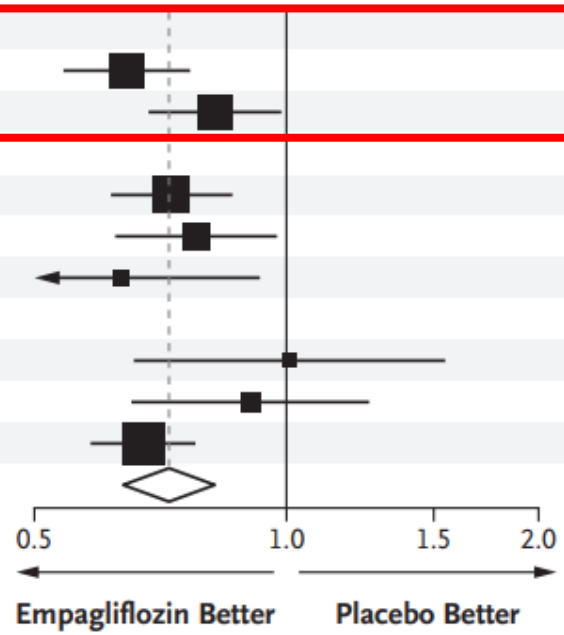


Figure 1. Progression of Kidney Disease or Death from Cardiovascular Causes.

Subgroup	Empagliflozin	Placebo	Hazard Ratio for Progression of Kidney Disease or Death from Cardiovascular Causes (95% CI)
	no. of patients with event/total no.		
Diabetes mellitus			
Present	218/1525	306/1515	0.64 (0.54–0.77)
Absent	214/1779	252/1790	0.82 (0.68–0.99)
Estimated GFR			
<30 ml/min/1.73 m^2	247/1131	317/1151	0.73 (0.62–0.86)
≥30 to <45 ml/min/1.73 m^2	140/1467	175/1461	0.78 (0.62–0.97)
≥45 ml/min/1.73 m^2	45/706	66/693	0.64 (0.44–0.93)
Urinary albumin-to-creatinine ratio			
<30	42/665	42/663	1.01 (0.66–1.55)
≥30 to ≤300	67/927	78/937	0.91 (0.65–1.26)
>300	323/1712	438/1705	0.67 (0.58–0.78)
All patients	432/3304	558/3305	0.72 (0.64–0.82)

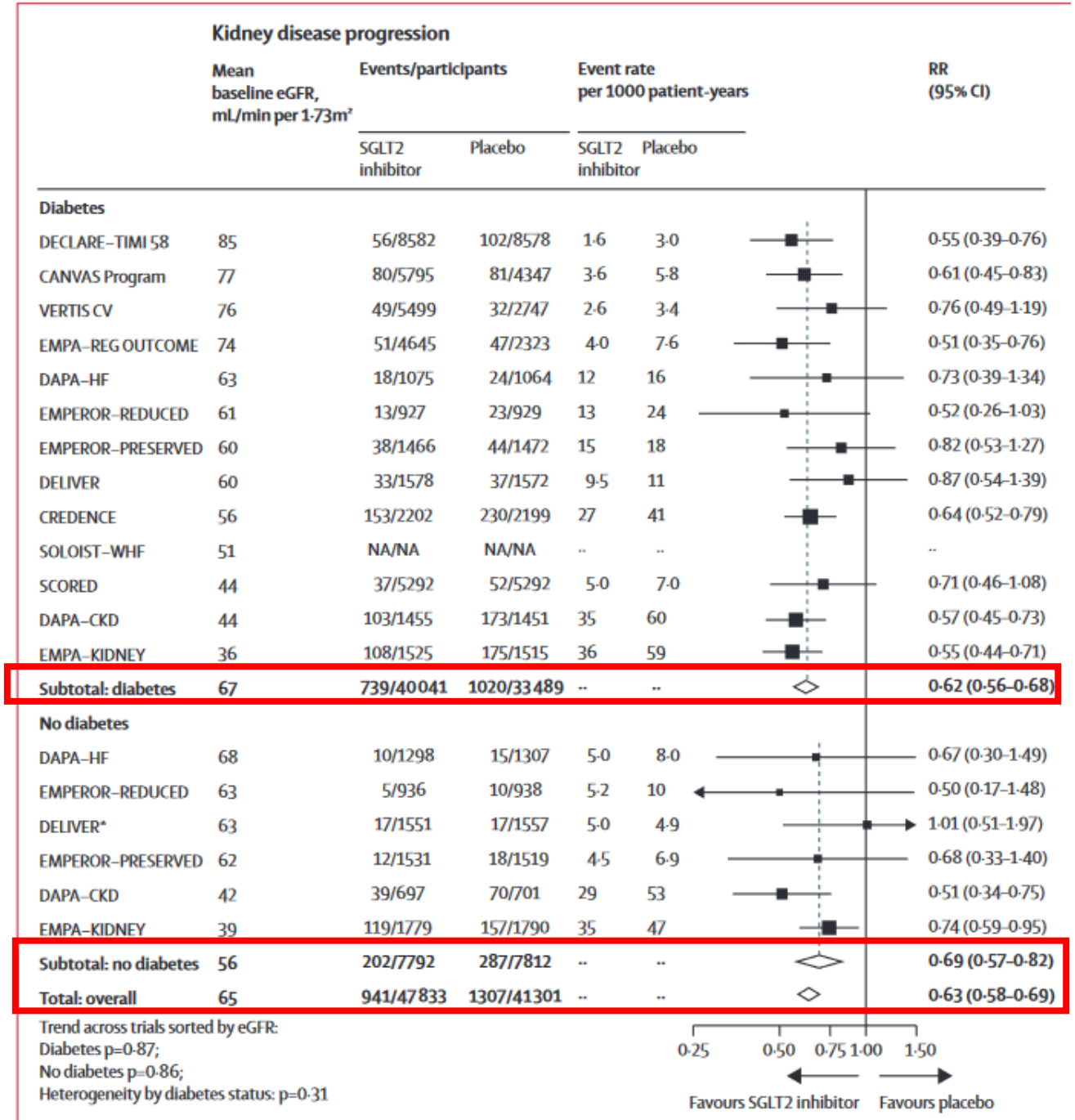


Background

- 90 409 randomly assigned patients
  - 13 RCTs
  - 74 804 with diabetes

- Composite endpoint
  - Sustained eGFR decrease ≥50% from randomization
  - end-stage kidney disease,
  - sustained low eGFR (<15 mL/min per 1·73 m^2 or <10 mL/min per 1·73 m^2)
  - death from kidney failure

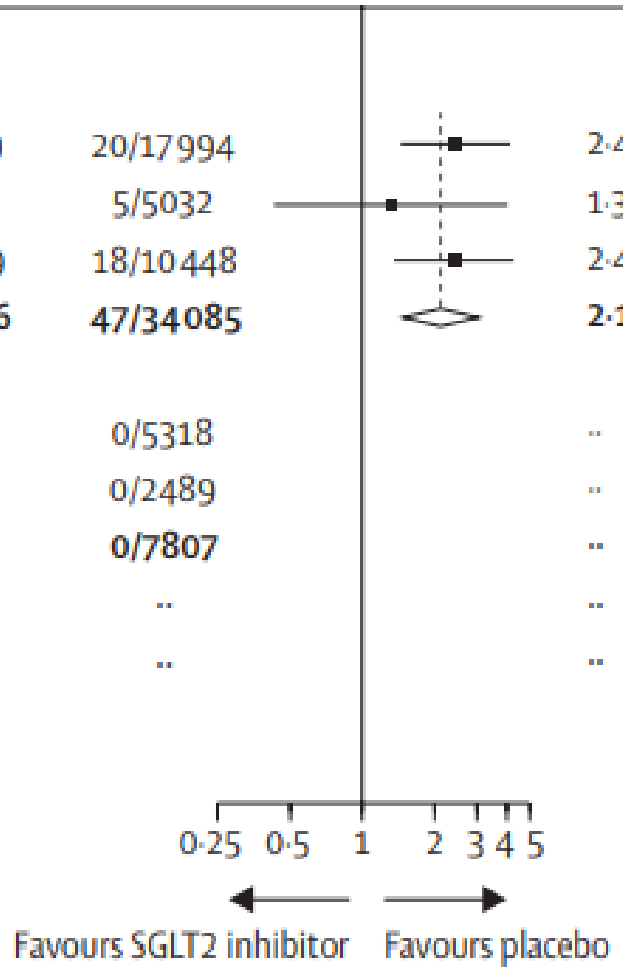
Lancet Nov 2022



Lancet Nov 2022

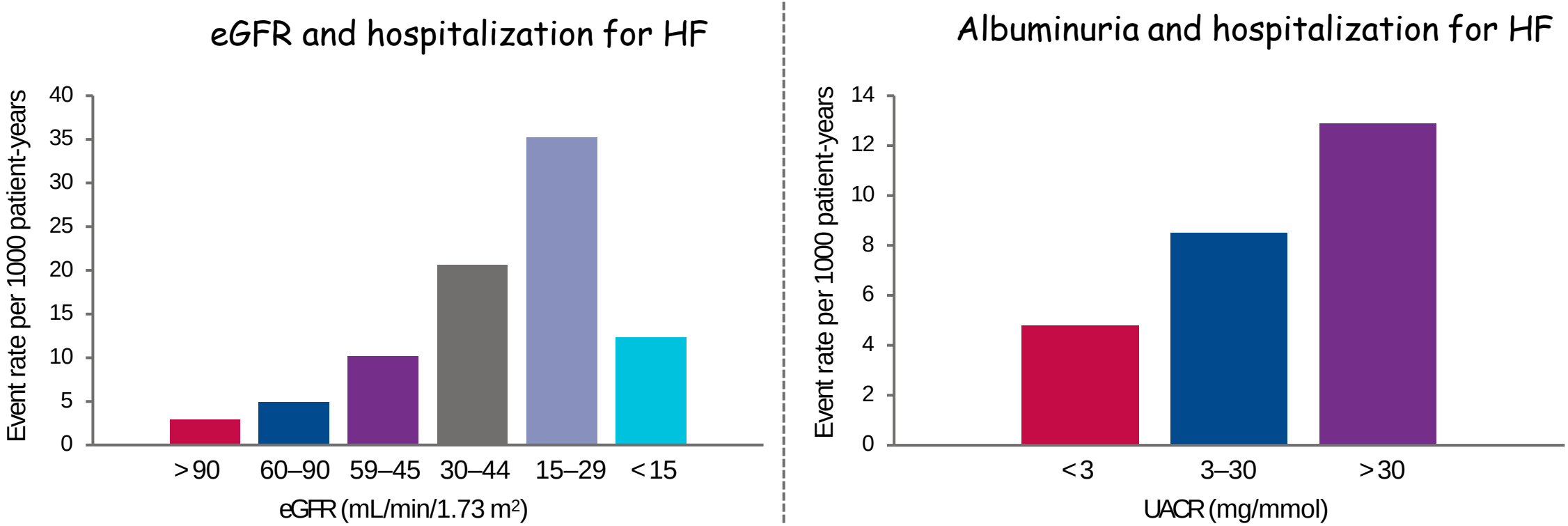
Ketoacidosis

	Mean baseline eGFR, mL/min per 1·73m²	Events/participants: SGLT2 inhibitor	Events/participants: Placebo	RR (95% CI)
Diabetes				
High atherosclerotic cardiovascular risk trials	80	63/24549	20/17994	2·44 (1·44–4·12)
Stable heart failure trials*	61	9/5043	5/5032	1·31 (0·43–4·02)
Chronic kidney disease trials	45	46/10469	18/10448	2·40 (1·36–4·25)
Subtotal: diabetes	**67**	**120/40666**	**47/34085**	**2·12 (1·49–3·04)**
No diabetes				
Stable heart failure trials	64	0/5313	0/5318	..
Chronic kidney disease trials	40	1/2475	0/2489	..
Subtotal: no diabetes	**56**	**1/7788**	**0/7807**	..
Total: overall	**65**	..	..	..
Total: overall (excluding CANVAS)†	**64**	..	..	..



Lancet Nov 2022

Renal impairment in patients with T2D increases the risk of hospitalization for heart failure



Population-matched Swedish database study; N = 266 305, median follow-up: 5.6 years

eGFR, estimated glomerular filtration rate; HF, heart failure; UACR, urine albumin:creatinine ratio

Rosengren A et al. Diabetologia 2018;61:2300–9

Almost half of the heart failure admissions have diabetes- Austin Health Diabetes Discovery Data

Clinical characteristics	N (episodes)	Diabetes	Pre-diabetes	No diabetes	p value[¶]
Number	1191	581 (49%)	408 (34%)	202 (17%)	
Male (%)	1191	323 (55.6%)	206 (50.5%)	90 (44.6%)	0.02
Age (years)	1191	79 (72, 84)	84 (77, 88)	83 (74, 88)	0.0001
HbA1c (%)	1191	7.0 (6.5, 8.0)	6.0 (5.8, 6.1)	5.4 (5.2, 5.5)	0.0001
HbA1c (mmol/mol)	1191	53 (48, 64)	42 (40, 43)	36 (33, 37)	0.0001
Haemoglobin (g/L)	1187	117 (104, 131)	124 (111, 137)	114 (103, 129)	0.0001
eGFR* (CKD-EPI) (ml/min/1.73 m2)	1187	39 (24, 60)	47 (29, 66)	39 (18, 71)	0.0013
Charlson comorbidity score (excluding diabetes and age)[#]	1191	3 (1, 3)	1 (1, 2)	1 (1, 3)	0.0001

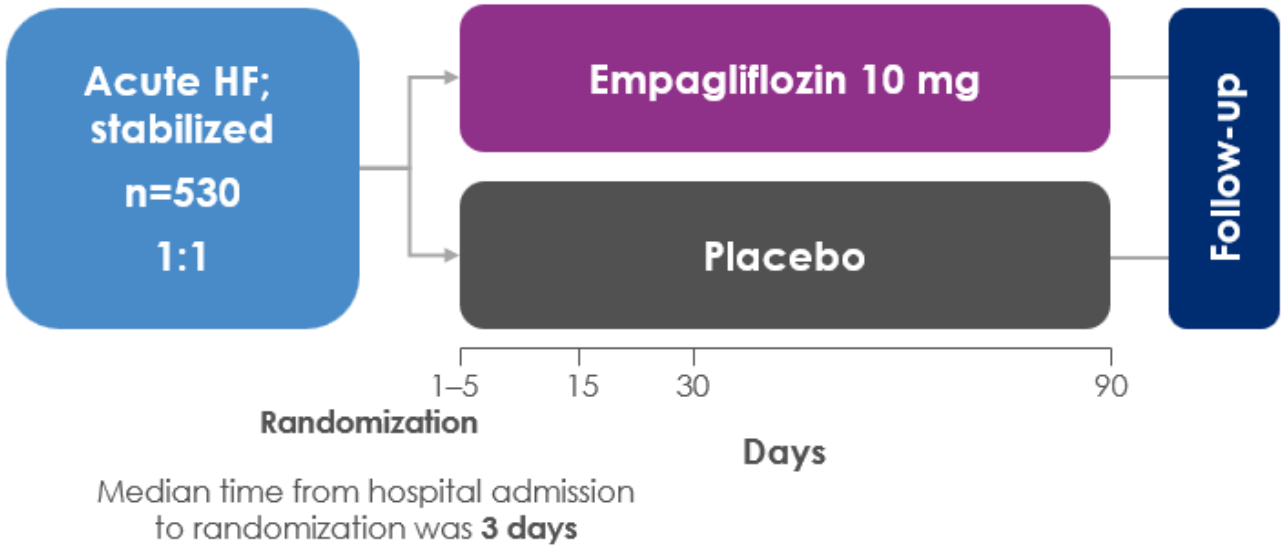
Khoo…. Ekinci *Scientific Reports* **volume 8**, Article number: 13564 (2018)

ARTICLES
https://doi.org/10.1038/s41591-021-01659-1
nature medicine
Check for updates

OPEN

The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial

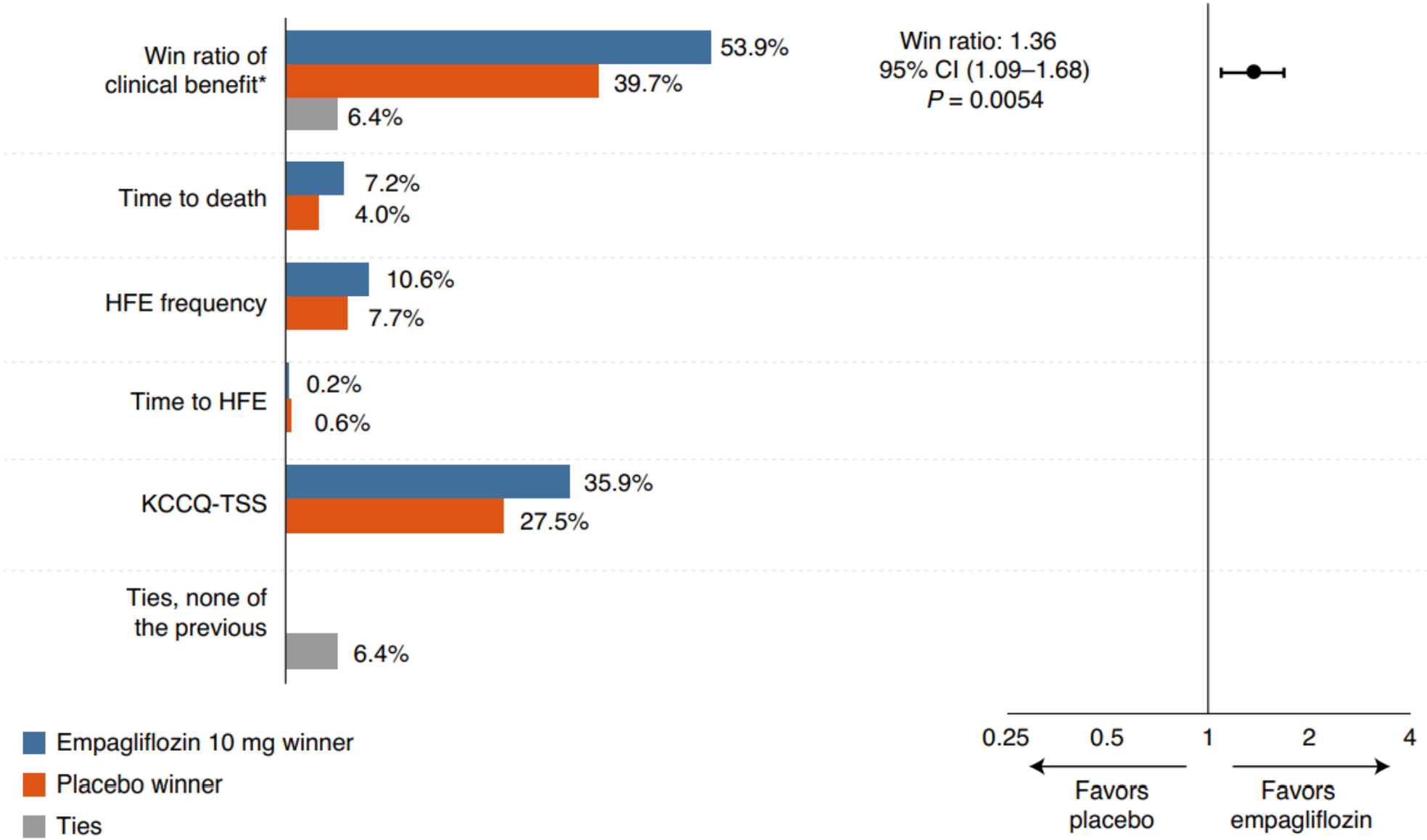
Adriaan A. Voors[1]✉, Christiane E. Angermann[2], John R. Teerlink[3], Sean P. Collins[4], Mikhail Kosiborod[5,6,7,8], Jan Biegus[9], João Pedro Ferreira[10,11], Michael E. Nassif[5,6], Mitchell A. Psotka[12], Jasper Tromp[13], C. Jan Willem Borleffs[14], Changsheng Ma[15], Joseph Comin-Colet[16], Michael Fu[17], Stefan P. Janssens[18], Robert G. Kiss[19], Robert J. Mentz[20,21], Yasushi Sakata[22], Henrik Schirmer[23], Morten Schou[24], P. Christian Schulze[25], Lenka Spinarova[26], Maurizio Volterrani[27], Jerzy K. Wranicz[28], Uwe Zeymer[29], Shelley Zieroth[30], Martina Brueckmann[31,32], Jonathan P. Blatchford[33], Afshin Salsali[34,35] and Piotr Ponikowski[9]



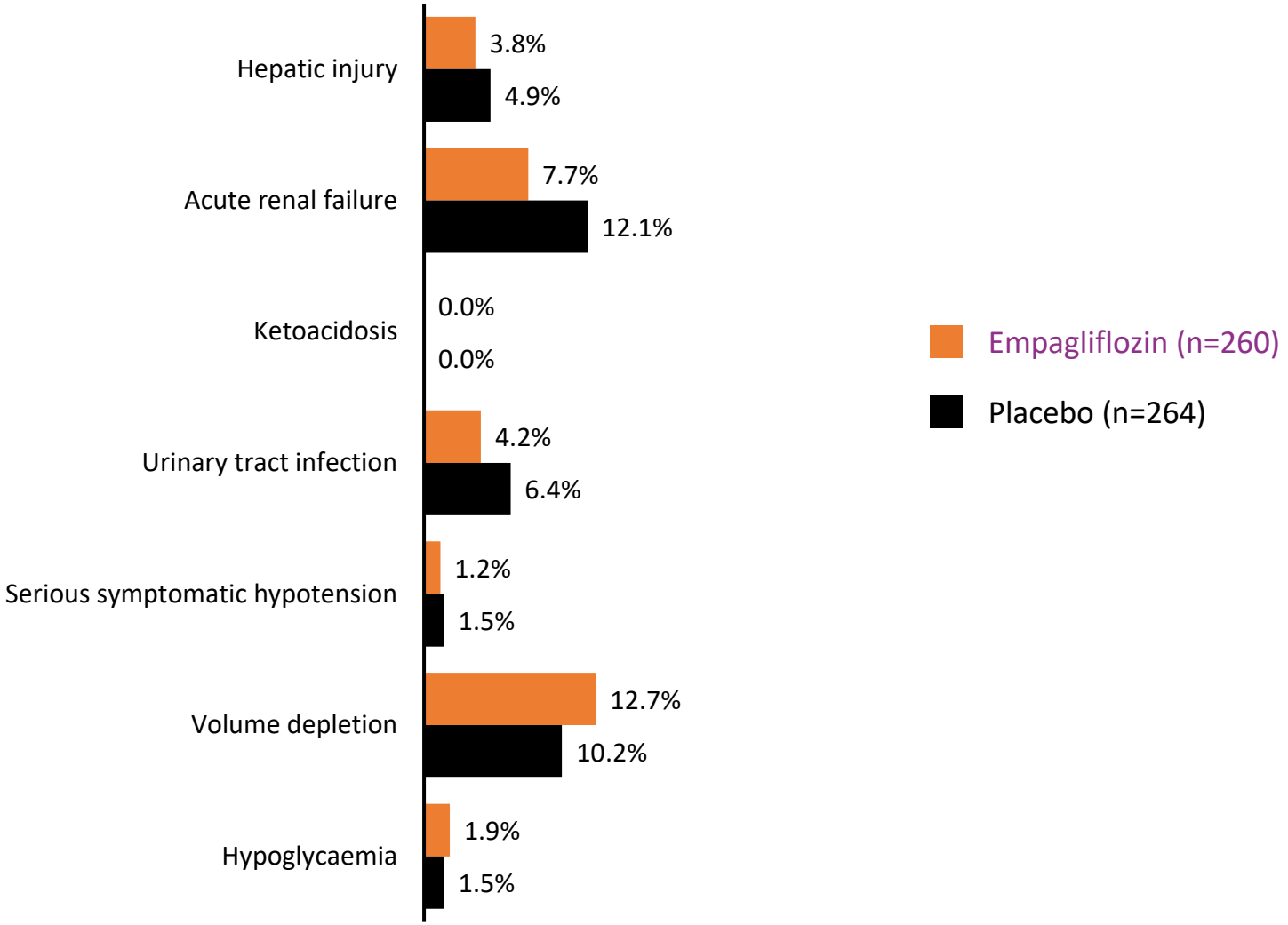
Median time from hospital admission to randomization was **3 days**

Primary endpoint

- **Clinical benefit evaluated with a win ratio based on a composite of:**
  - Death
  - Number of HFEs (including HHFs, urgent HF visits and unplanned outpatient visits)
  - Time to first HFE
  - ≥5 point difference in the KCCQ-TSS change from baseline after 90 days of treatment


Win ratio of clinical benefit*
53.9%
39.7%
6.4%
Time to death
7.2%
4.0%
HFE frequency
10.6%
7.7%
Time to HFE
0.2%
0.6%
KCCQ-TSS
35.9%
27.5%
Ties, none of the previous
6.4%
Empagliflozin 10 mg winner
Placebo winner
Ties
Win ratio: 1.36
95% CI (1.09–1.68)
P = 0.0054
0.25
0.5
1
2
4
Favors placebo
Favors empagliflozin

Safety outcomes



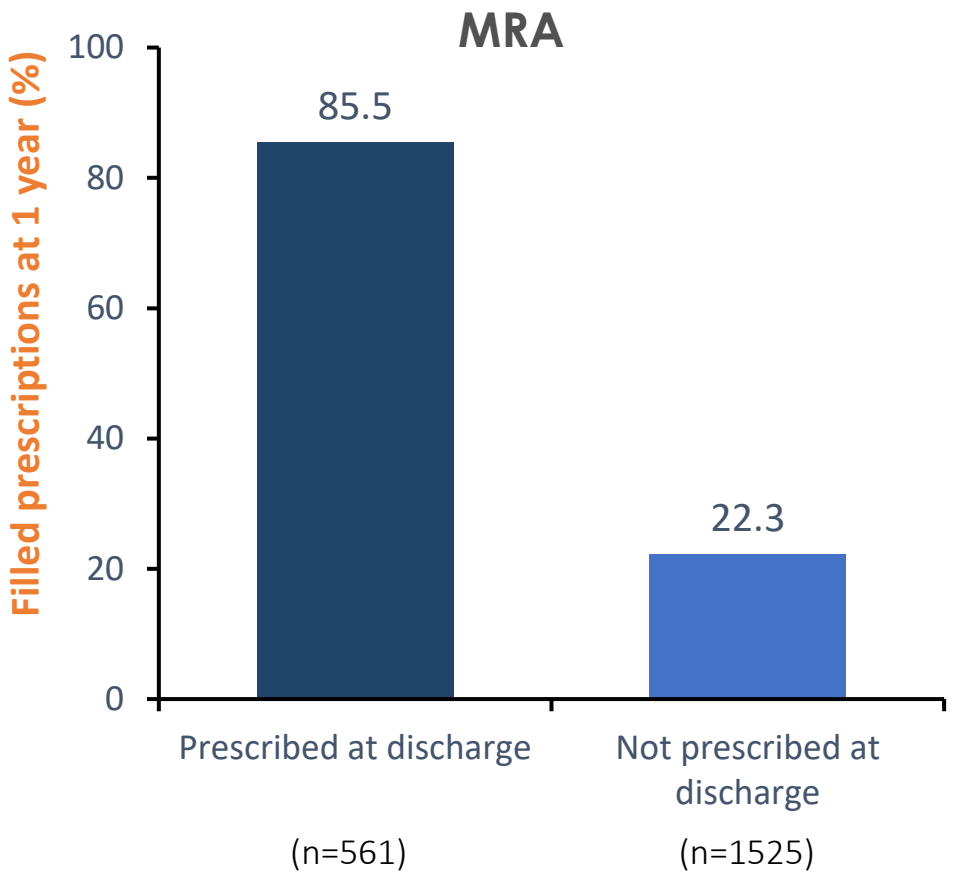
Prescription Patterns of Cardiovascular- and Kidney-Protective Therapies Among Patients With Type 2 Diabetes and Chronic Kidney Disease

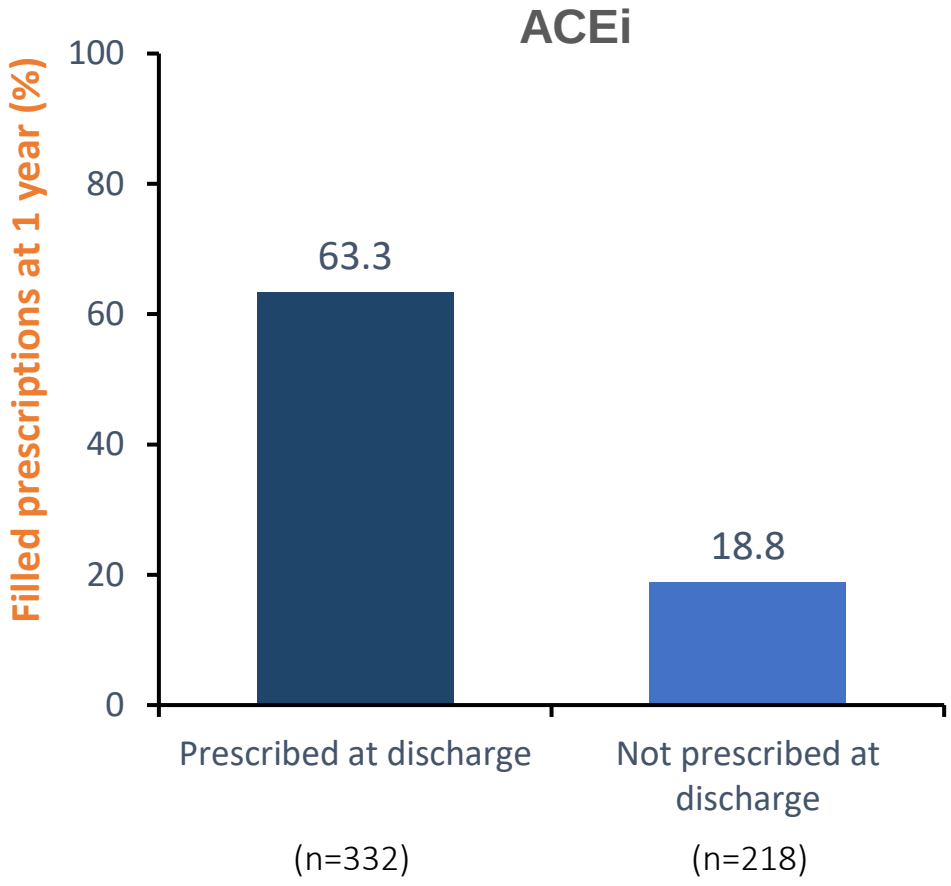
Diabetes Care 2022;45:2900–2906 | https://doi.org/10.2337/dc22-0614

Table 2—Association between the presence of CKD and prescription of SGLT2i and GLP1-RA among VA patients with T2DM during the years 2019 and 2020

		SGLT2i prescription		GLP1-RA prescription	
	n	% Prescribed	Multivariable model* OR (95% CI)	% Prescribed	Multivariable model* OR (95% CI)
CKD†					
Absent	610,528	11	Reference	7	Reference
Present	424,680	12	0.98 (0.97, 1.00)	10	1.13 (1.12, 1.15)
Unknown	162,672	8	0.85 (0.81, 0.90)	5	0.81 (0.75, 0.86)

Early treatment initiation in the hospital is associated with improved adherence





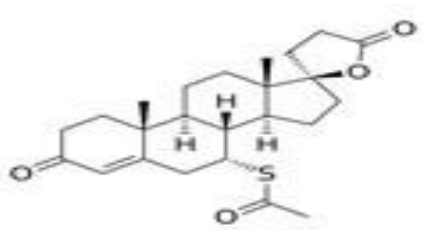
1. Curtis LH *et al. Am Heart J.* 2013;165:979; 2. Butler J *et al. J Am Coll Cardiol.* 2004;43:2036.

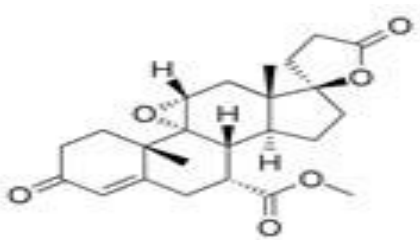
How do we improve prescribing rates?

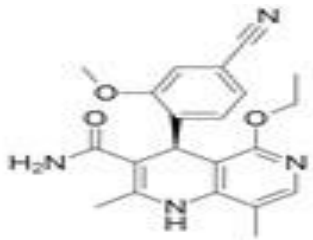
- Consideration of discharge script in a safe way

- Systematic review assessing safety of SGLT2i use in hospital/on discharge underway – Dr Frank Gao, PhD student. Preliminary results:
  - 15 RCTs with 3520 participants (1846 participants (52.4%) with type 2 diabetes)
  - No individual study reported higher rates of hypotension or acute kidney injury with SGLT2i
  - Similar rates of DKA

Finerinone



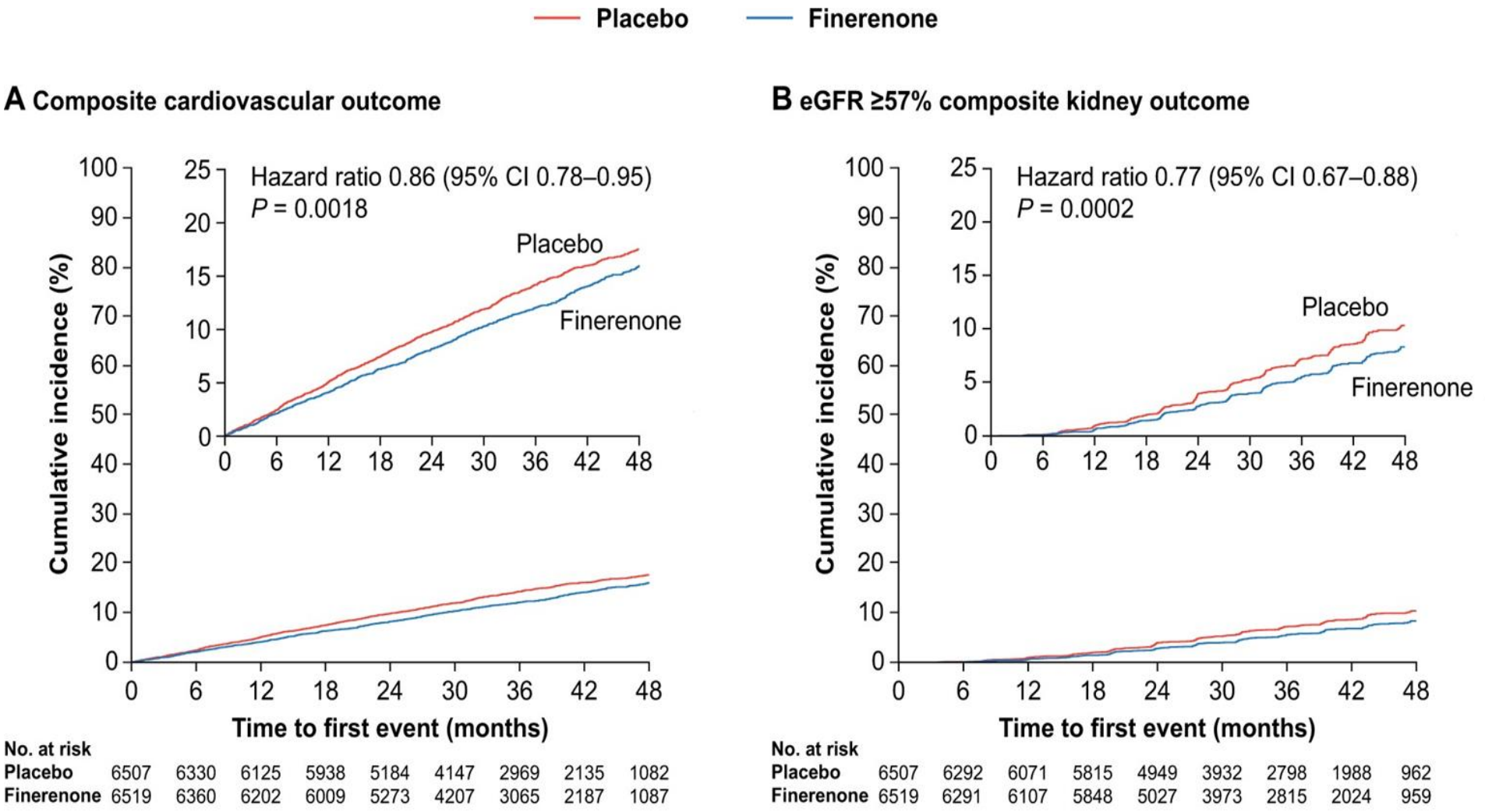




	Spironolactone	Eplerenone	Finerenone
Structure	Flat (steroidal)	Flat (steroidal)	Bulky (non-steroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
Tissue distribution	Kidney > heart	Kidney > heart	Balanced kidney-heart
Active metabolites	+++	-	-
Half-life	Long*	4-6 hours	2-3 hours
Sexual side-effects	++	+	-

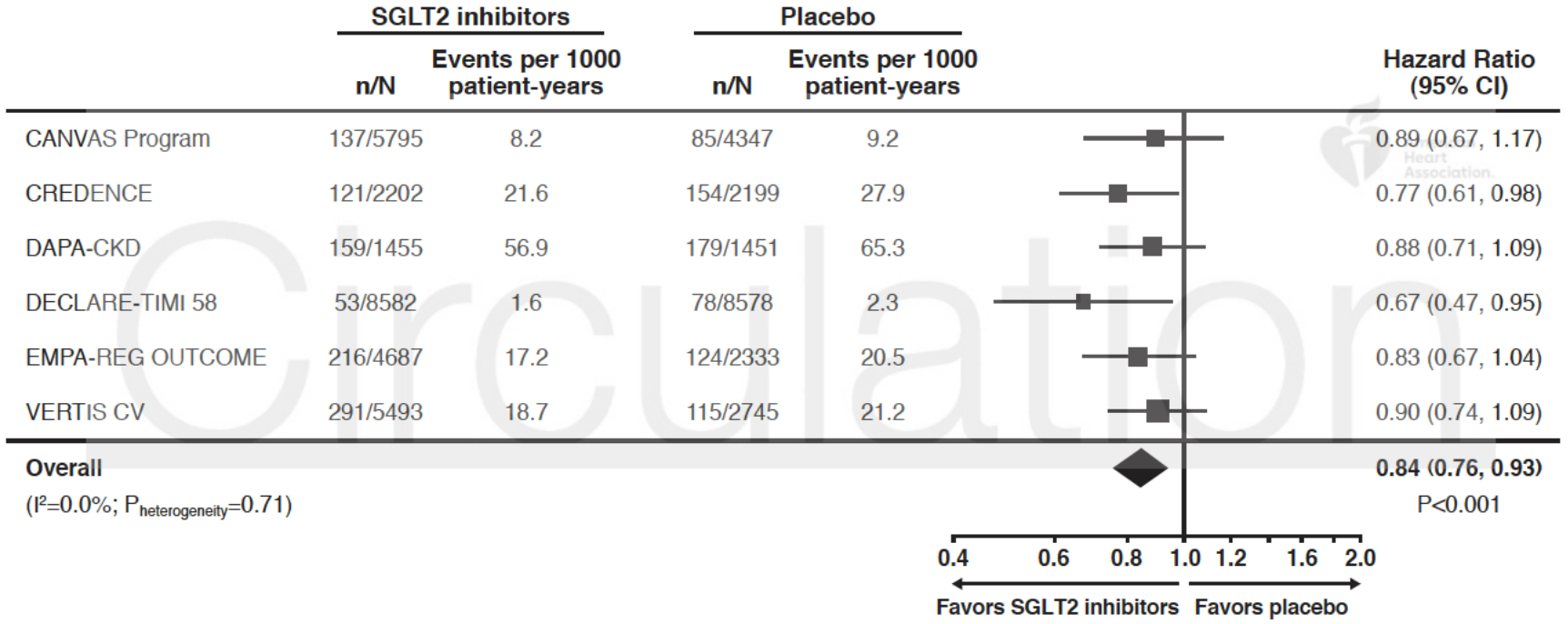
Sourced from: The Nonsteroidal Mineralocorticoid-Receptor-Antagonist Finerenone in Cardiorenal Medicine: A State-of-the-Art Review of the Literature. American Journal of Hypertension. 2023.

FIDELITY pooled analysis



Agarwal et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis Eur Heart J 2022,

Effects of SGLT2 Inhibitors on Serious Hyperkalemia (Central Laboratory Determined Serum Potassium ≥6.0 mmol/L).



Circulation. 2022 May 10;145(19):1460-1470.

Finerenone PBS

- Chronic kidney disease with Type 2 diabetes
- Diagnosis of CKD for at least 3 months prior to initiating treatment
- No known significant non-diabetic renal disease, prior to initiating treatment
- eGFR ≥25 mL/min/1.73 m^2
- Urinary albumin-to-creatinine ratio ≥ 200 mg/g (22.6 mg/mmol)
- Must discontinue treatment with this drug prior to initiating renal replacement therapy
- Stabilised for at least 4 weeks, on either: (i) an ACE inhibitor or (ii) an angiotensin II receptor antagonist, unless medically contraindicated
- Must be in combination with an SGLT2i unless medically contraindicated or intolerant
- Patient must not be receiving treatment with another selective nonsteroidal mineralocorticoid receptor antagonist, a renin inhibitor or a potassium-sparing diuretic,
- Patient must not have established heart failure with reduced ejection fraction with an indication for treatment with a mineralocorticoid receptor antagonist

Effects of Tirzepatide Versus Insulin Glargine on Cystatin C–Based Kidney Function: A SURPASS-4 Post Hoc Analysis

Hiddo J.L. Heerspink, Naveed Sattar, Imre Pavo, Axel Haupt, Kevin L. Duffin, Zhengyu Yang, Russell J. Wiese, Jonathan M. Wilson, Andrea Hemmingway, David Z.I. Cherney, Katherine R. Tuttle

Tirzepatide slowed the cystatin–C based eGFRdecline rate compared with insulin glargine

Context

Tirzepatide reduces body weight and eGFR-creatinine compared with insulin glargine

However, eGFR-creatinine may be influenced by muscle mass changes

Aim

Examine effects of tirzepatide on kidney function assessed by eGFR-cystatin C, which is not affected by muscle mass changes

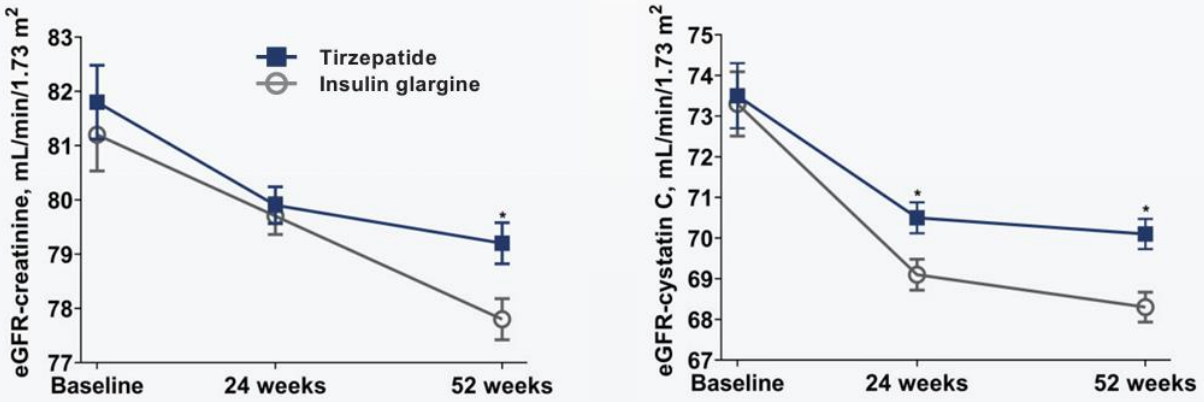
Population

Type 2 diabetes
High cardiovascular risk

n = 995	*n* = 1,000
Tirzepatide 5, 10, 15 mg (pooled for analysis)	Titrated insulin glargine 100 U/mL

Key Result

Tirzepatide slowed the eGFR decline rate when assessed by both creatinine–and cystatin C–based eGFR



*P < 0.05 for tirzepatide vs. insulin glargine

Effects on eGFR-cystatin C were consistent across subgroups defined by demographics, and by baseline glycemic control, SGLT2 inhibitor use, body weight, albuminuria status, and eGFR

Correlation Analyses

Baseline, 1-year, and 1-year change from baseline values correlated between eGFR-creatinine and -cystatin C

There were no significant correlations between changes in either eGFR measure and body weight changes

eGFR, estimated glomerular filtration rate; SGLT2, sodium-glucose co-transporter 2.
eGFR-creatinine, creatinine-derived eGFR
eGFR-cystatin C, cystatin C–derived eGFR

Diabetes Care Jun 2nd 2023

These data support a kidney-protective effect of tirzepatide

Background and Objective

Background

- Chronic kidney disease (CKD), defined by decreased estimated glomerular filtration rate (eGFR)[a] and increased albuminuria, [b] is common in people with type 2 diabetes (T2D)[1]
- In SURPASS-4, the glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide showed a potential kidney protective effect in people with T2D and high cardiovascular risk[2]
- Tirzepatide slowed the rate of eGFR decline and reduced urine albumin-creatinine ratio (UACR) vs. insulin glargine over 2 years[2]

Objective

- To examine the effects of tirzepatide vs. comparator treatments on UACR across the SURPASS-1 through -5 trials

[a]<60 mL/min/1.73 m^2; prevalence: 19.6-29.6%; [b]UACR >30 mg/g; prevalence: 15.4-38.8%.

Tirzepatide Reduced UACR vs. All Comparators in Patients With T2D and Baseline UACR ≥30 mg/g[a]

Baseline UACR ≥30 mg/g	n	Mean (SE)	UACR Difference, % (95% CI)
All comparators (reference, S2-S4)	497	-45.3 (2.7)	
TZP 5 mg	335	-61.4 (2.4)	-29.4 (-39.6, -17.6)**
TZP 10 mg	339	-67.5 (2.0)	-40.6 (-49.0, -30.7)**
TZP 15 mg	327	-70.9 (1.8)	-46.8 (-54.4, -37.9)**
PBO (reference, S1 and S5)	43	-39.0 (8.7)	
TZP 5 mg	59	-62.9 (4.4)	-40.1 (-58.9, -12.7)*
TZP 10 mg	60	-70.4 (3.5)	-52.7 (-67.5, -31.2)**
TZP 15 mg	52	-70.8 (3.7)	-53.3 (-68.3, -31.1)**
Active comparators (reference, S2-S4)	454	-45.8 (2.9)	
TZP 5 mg	276	-61.1 (2.7)	-28.1 (-39.4, -14.8)**
TZP 10 mg	279	-66.7 (2.2)	-38.5 (-48.0, -27.3)**
TZP 15 mg	275	-70.7 (2.0)	-46.0 (-54.4, -36.0)**
Insulin comparators (reference, S3 and S4)	373	-41.4 (3.5)	
TZP 5 mg	177	-60.5 (3.4)	-32.6 (-45.2, -17.3)**
TZP 10 mg	188	-66.7 (2.7)	-43.3 (-53.5, -30.8)**
TZP 15 mg	190	-70.7 (2.4)	-50.0 (-59.1, -39.0)**

*p<0.01 for pairwise comparisons; **p<0.001 for pairwise comparisons.
[a]All data are percent change from baseline estimated difference (95% CI) at Week 40.
Note: All comparators included PBO and active comparators in the S-1 through S-5 studies.
CI=confidence interval; PBO=placebo; S-1=SURPASS-1; S-2=SURPASS-2; S-3=SURPASS-3; S-4=SURPASS-4; S-5=SURPASS-5; SE=standard error; T2D=type 2 diabetes; TZP=tirzepatide; UACR=urine albumin-creatinine ratio.

DKD in T1DM

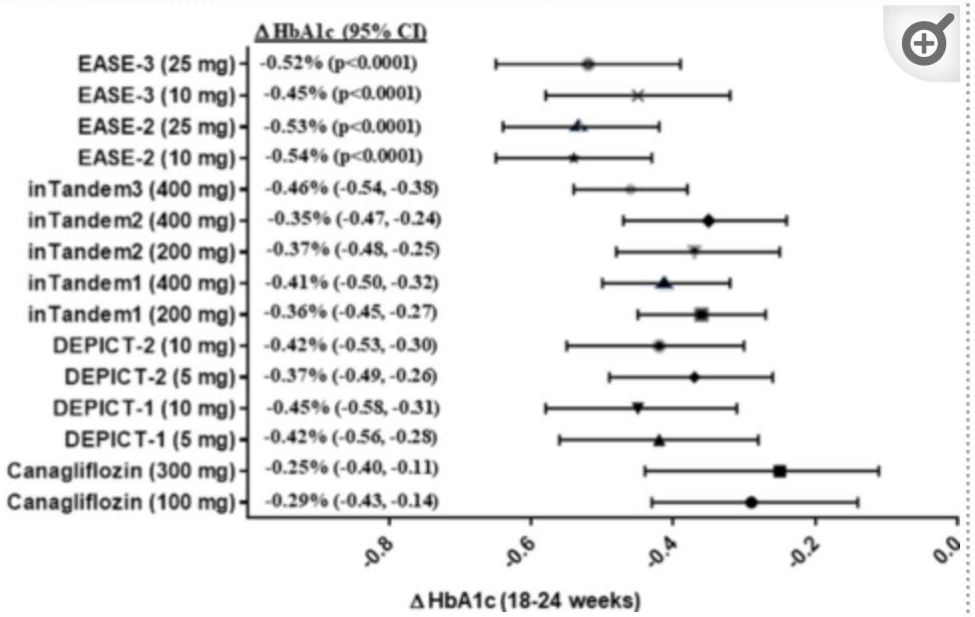
- Intensive glucose management is associated with :
  - Weight gain
  - Higher insulin resistance
  - Central obesity
  - Dyslipidaemia
  - Higher blood pressure
  - Higher inflammation

Purnell, Circulation2013; 127;180-187

SGLT2i have similar effects on eGFR and albuminuria in T2D and T1D but increase risk of DKA

Numbers of Research Subjects in Each Arm of Clinical Trials

Study	Placebo	Low Dose	High Dose
EASE-3	238	244	242
EASE-2	239	243	241
inTandem3	703	--	699
inTandem2	258	261	263
inTandem1	268	263	262
DEPICT-2	272	271	270
DEPICT-1	260	259	259
Canagliflozin	117	117	117



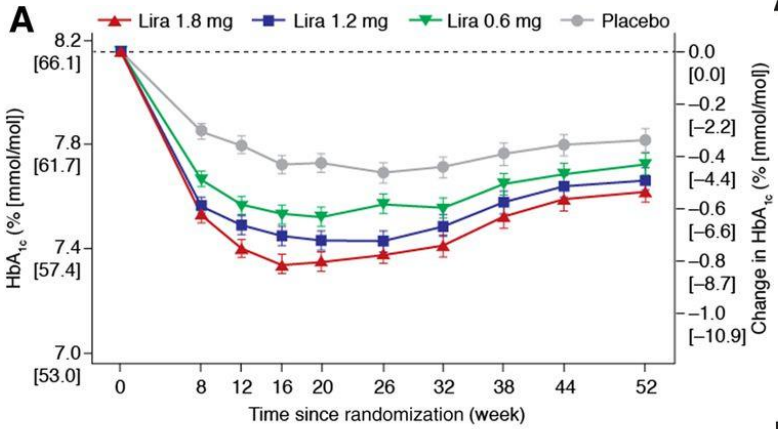
Taylor et al Lancet Diabetes Endocrinology 2019;7:949-958
Groop PH et al Lancet Diabetes Endocrinology 2020; 8:845-854
Van Raalte DH et al Diabetes Care 2019;42:1921-1929
Cherney DZI et al CJASN 2021; 16:1715-1719

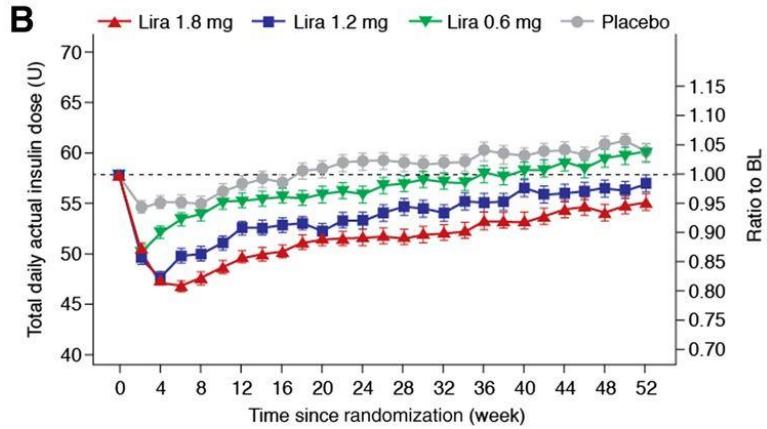
nsMRA in T1D and DKD- FINE-ONE

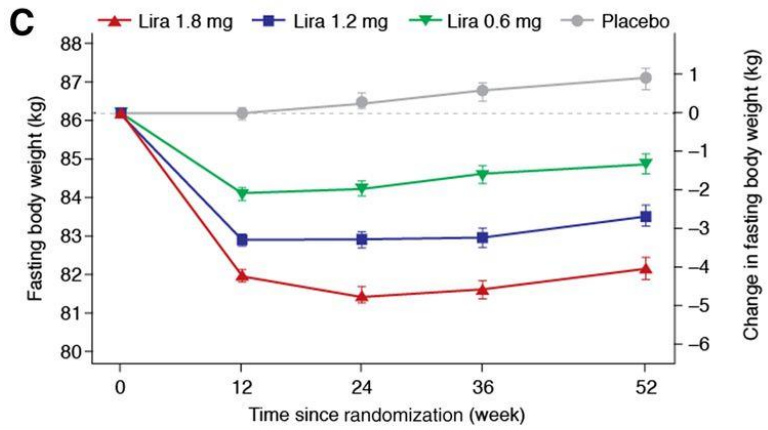
- Parallel group, randomized double-blinded, placebo controlled trial of 220 patients with T1D and DKD
- eGFR > 25 to <90ml/min/1.73m2 and UACR >200 to < 5000mg/g
- Primary endpoint at 6months – UACR
- Secondary endpoints safety and tolerability

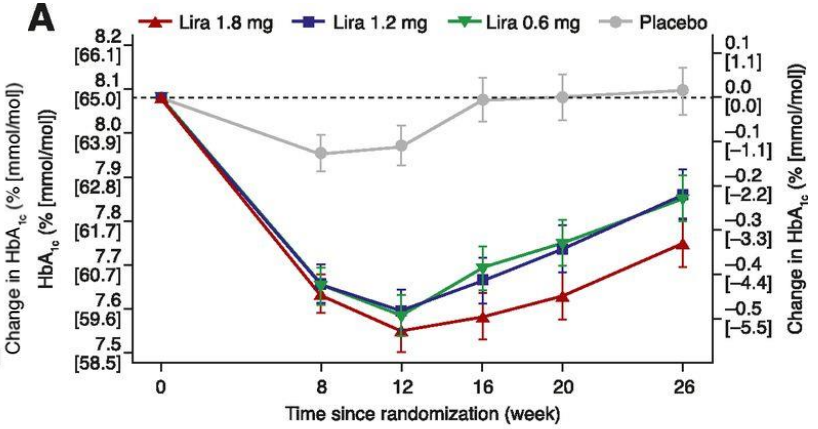
Clinical Trials.gov

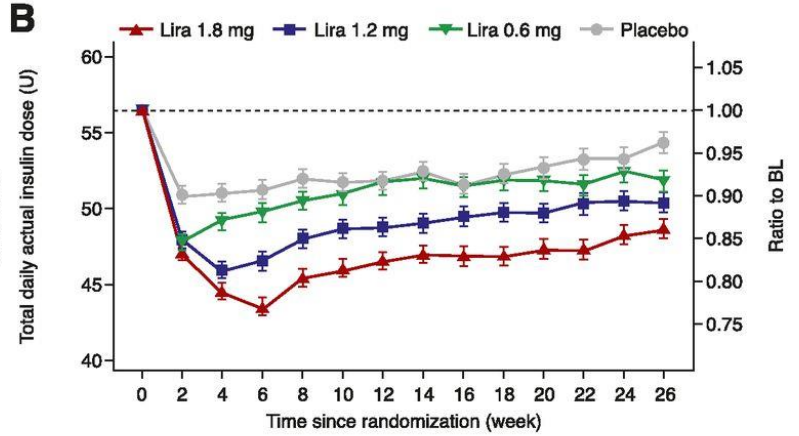
GLP-1RA have beneficial effects in T1DM

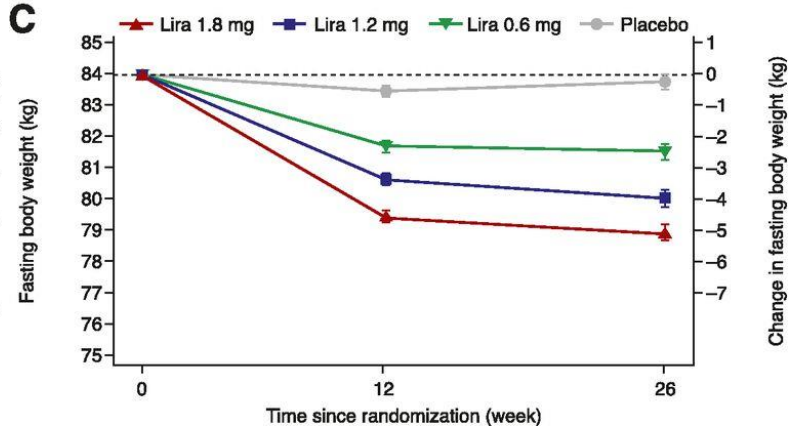








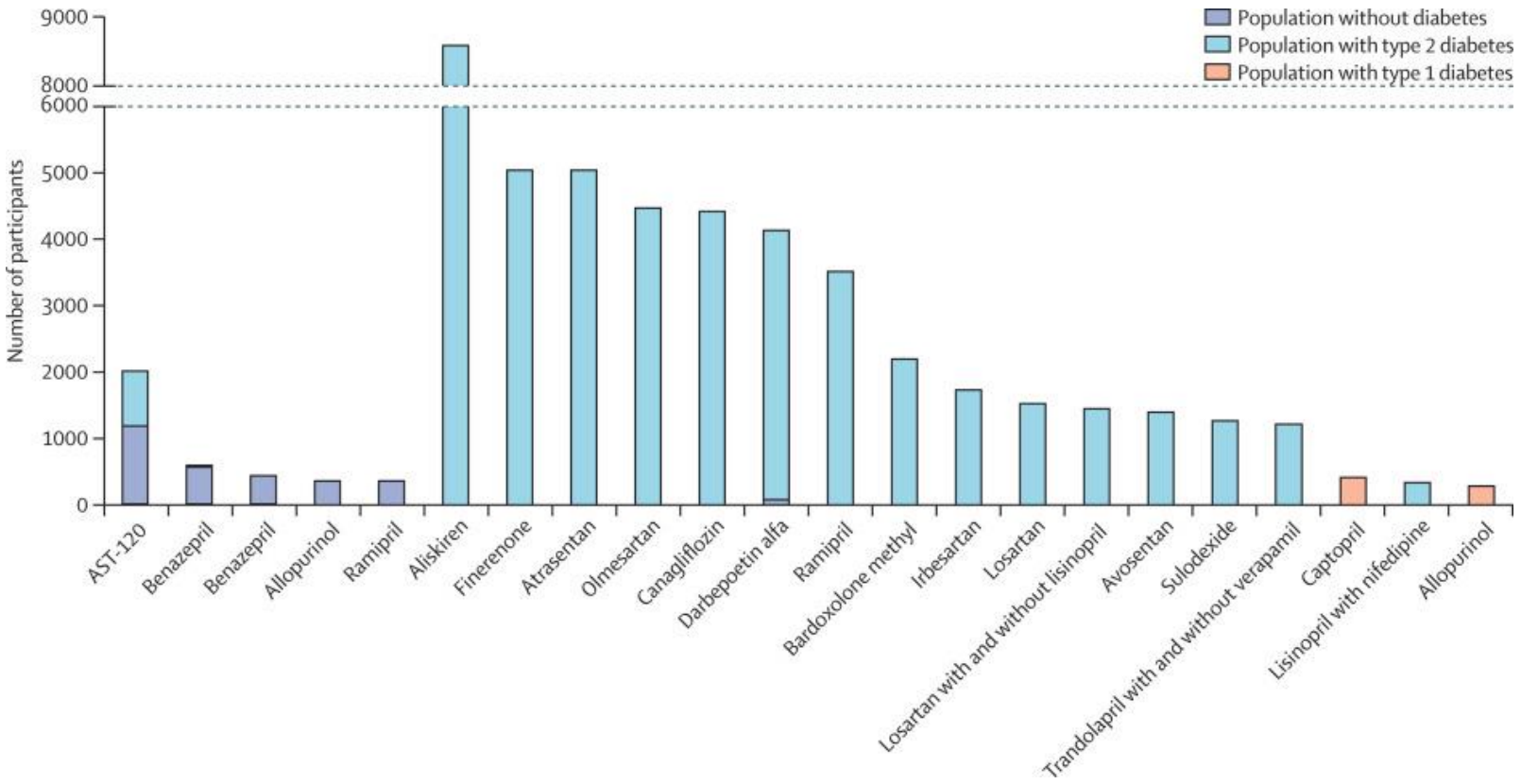




Mathieu C et al Diabetes Care 2016; 39-1702-1710

Ahren B et al Diabetes Care 2016; 39:1693-1701

More trials are needed in T1D and DKD



Heerspink et al Lancet Diabetes Endocrinology,
Published online June 23, 2023

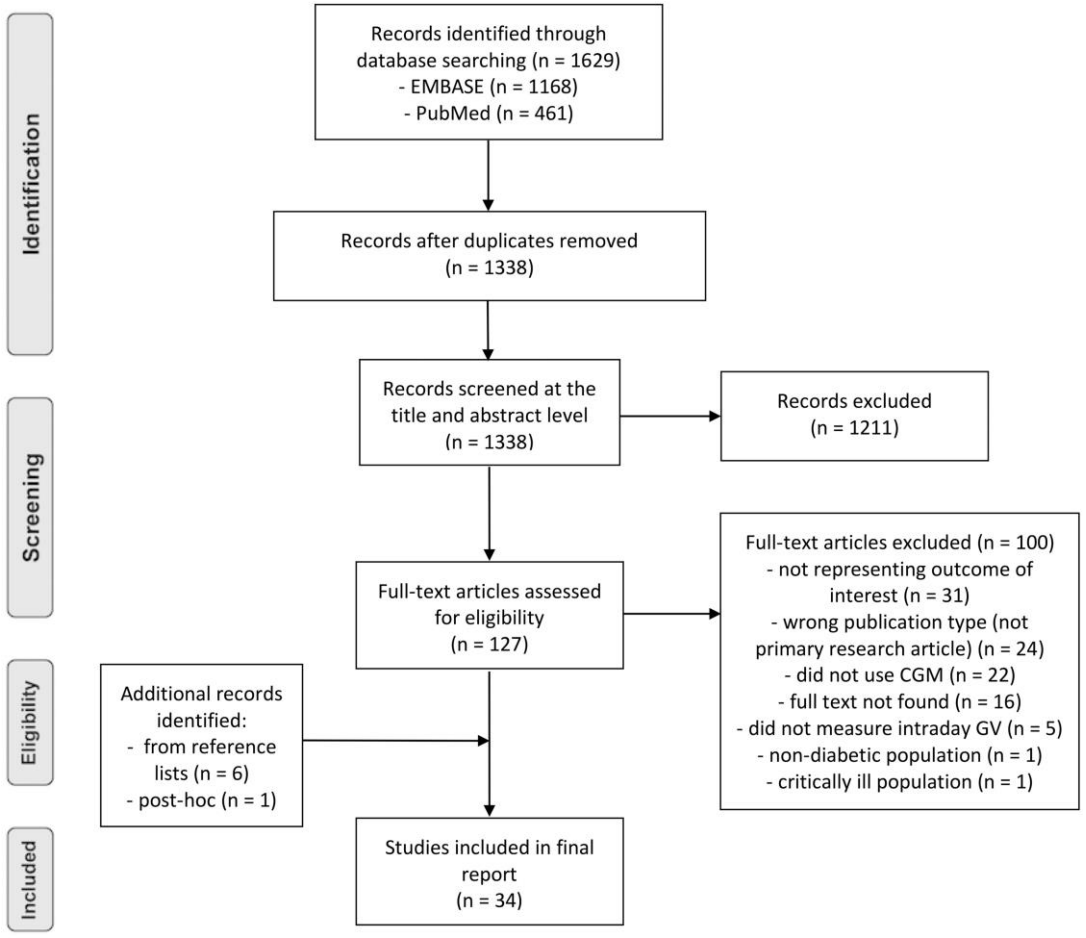
JOURNAL ARTICLE

Complications of Diabetes and Metrics of Glycemic Management Derived From Continuous Glucose Monitoring

Michael Yapanis, Steven James, Maria E Craig, David O'Neal, Elif I Ekinci

The Journal of Clinical Endocrinology & Metabolism, Volume 107, Issue 6, June 2022, Pages e2221–e2236, https://doi.org/10.1210/clinem/dgac034

Published: 30 January 2022 **Article history**



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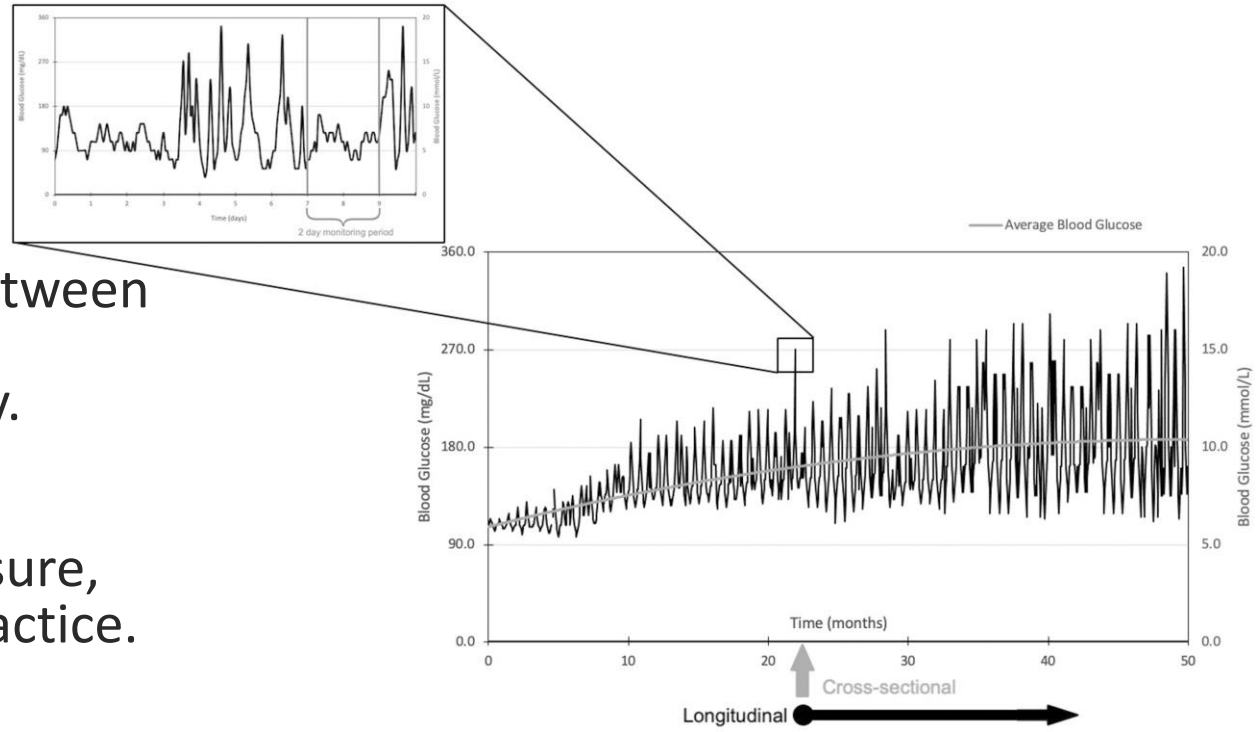
Observational vs longitudinal studies. Thirty out of the 34 papers included in this review used ...



- The evidence supports the association between diabetes complications and CGM-derived measures of intraday glycaemic variability.
- TIR emerged as the most consistent measure, supporting its emerging role in clinical practice.
- More longitudinal studies and trials are required to confirm these associations, particularly for T1D, for which there are limited data.

J Clin Endocrinol Metab, Volume 107, Issue 6, June 2022, Pages e2221–e2236, https://doi.org/10.1210/clinem/dgac034

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Insulin pumps

Commercially Available in Australia

HYBRID CLOSED LOOP

MiniMed™ 780G system

t:slim X2 pump with Control-IQ™

YpsoPump mylife CamAPS | FX

PATCH PUMPS

omnipod

FlashGM Study

- NHMRC funded national randomised controlled clinical trial (Clinical Trials and Cohorts Grant $3.15m).
- 350 Indigenous Australians with type 2 diabetes on injectable therapies
- 6 visits over 6 months
- Randomised to receive flash glucose monitoring or usual care (SMBG).
- Metro, regional, rural and remote Australia.

- **AIMS:** To assess the effects of using flash glucose monitoring on (i) haemoglobin A1c (HbA1c) and (ii) achieving blood glucose targets and reducing low blood glucose (hypoglycaemic) episodes; and (iii) to determine whether this strategy is cost effective in an Australian Indigenous health setting.
- **PRIMARY OUTCOME:** Change in HbA1c level from baseline to 6 months.
- **CURRENTLY:** 140 screened, 18 clinical trial sites in VIC, NSW, QLD, WA and NT (Aboriginal Medical Services, tertiary hospitals, community clinics).

STUDY OVERVIEW VIDEO

Summary

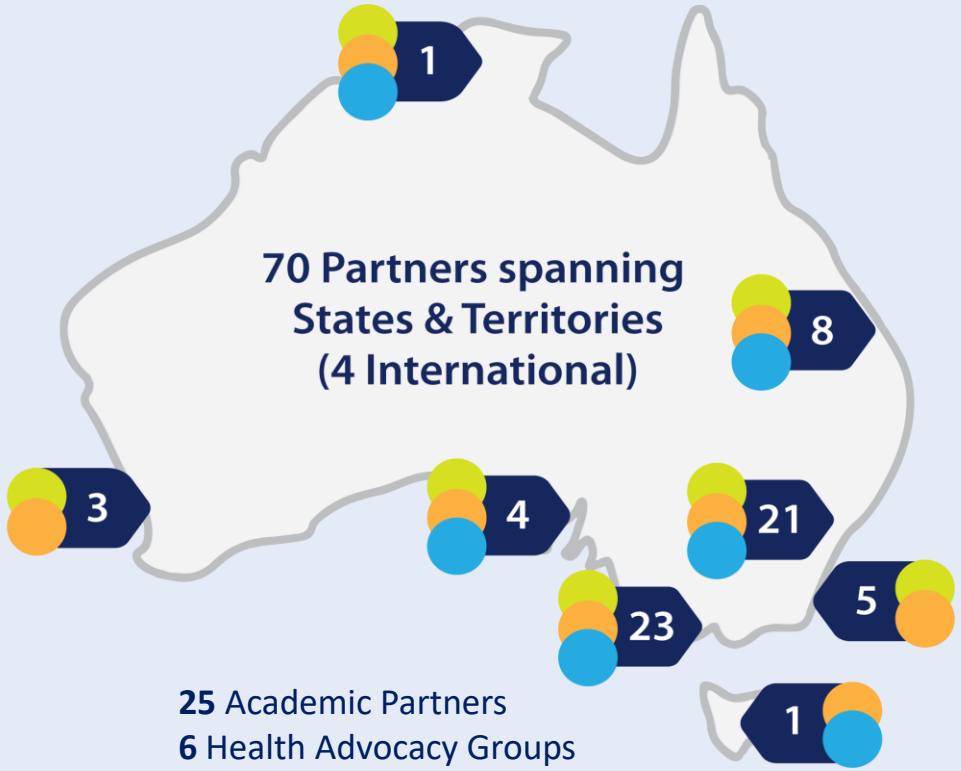
- SGLT2i have consistently shown cardio- renal protective effects but are underutilised in clinical practice
- Finerinone is now listed on the PBS
- GLP1 analogues and incretins such as tirzepatide are likely to be associated with improved kidney function - watch this space
- More trials are needed in people with type 1 diabetes
- Continuous/Flash glucose monitoring improve day to day management of diabetes and improve glucose control and may be particularly important for high risk populations.
- Insulin pump therapies increase time in target range and over time likely reduce diabetes complications but are limited to individuals with private insurance
- The future is bright for people living with diabetes.

ACADI

Australian Centre for Accelerating Diabetes Innovations

NATIONAL REACH

- # Number and location of ACADI Partners
- PRIORITY 1 Activity Site
- PRIORITY 2 Activity Site
- PRIORITY 3 Activity Site



25 Academic Partners
6 Health Advocacy Groups
14 Health Services
25 Industry Partners

ACADI Australian Centre for Accelerating Diabetes Innovations

COLLABORATIVE GAIN

ENABLING PLATFORMS & NETWORKS

Health Economics	Co-Design	Biostatistics
Behavioural	Implementation	Epidemiology

National and International Clinical, Research, Industry, Community and Investor Networks

Independent Scientific & Commercialisation Advisory

International Advisory

ACADI COUNCIL

Indigenous Advisory

Community Advisory

Training Program Advisory

ACADI Deputy Director

ACADI Director

ACADI Management Committee

Senior Program Manager

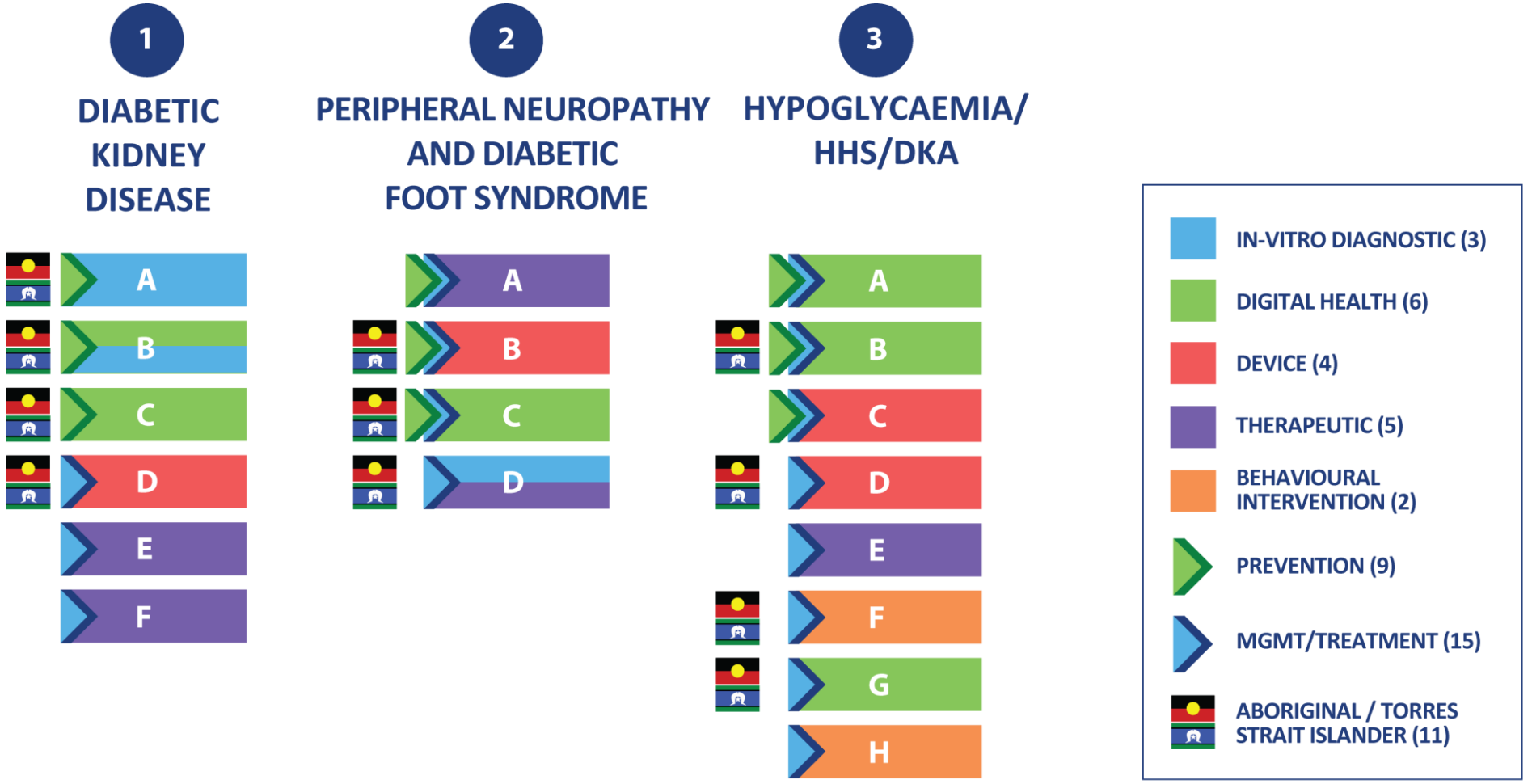
Training Manager

Administration & Finance Officer

Training Program	Research Portfolio	Platforms
Training Leads	**Priority Leads Project Leads**	**Platform Leads**

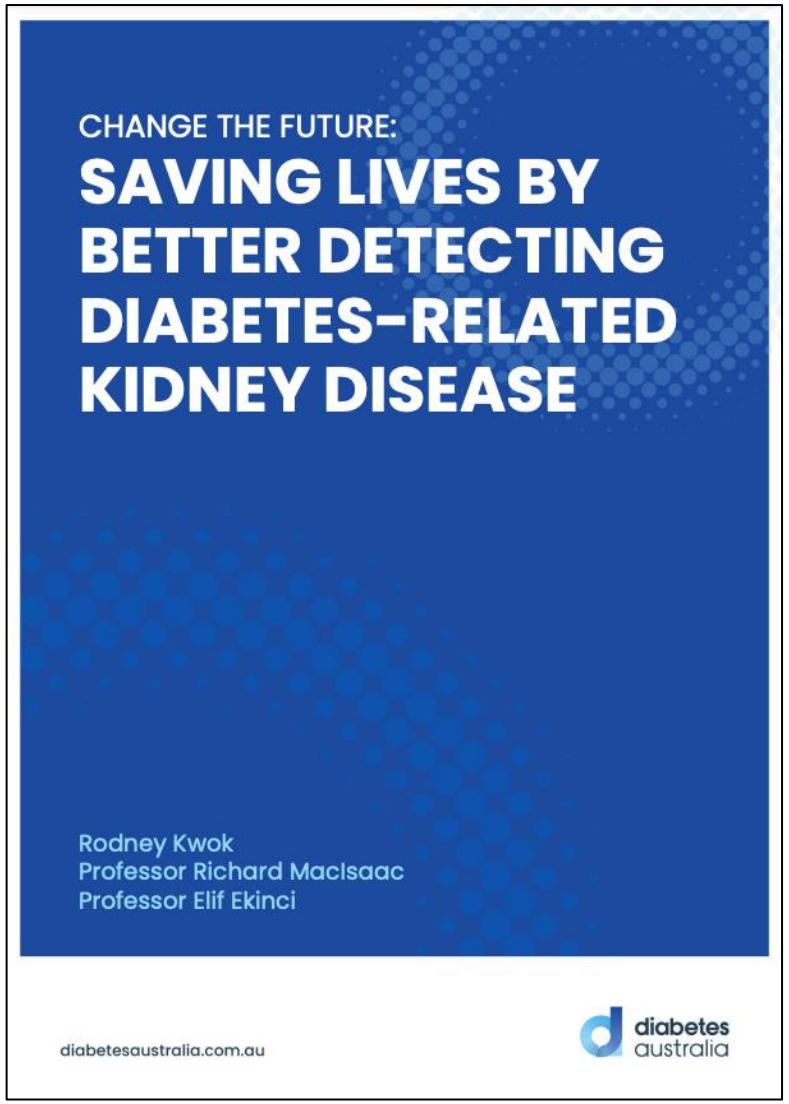
ACADI Australian Centre for Accelerating Diabetes Innovations

RESEARCH PORTFOLIO



ACADI Australian Centre for Accelerating Diabetes Innovations

Further detail



SCAN ME!

ACADI Australian Centre for Accelerating Diabetes Innovations

Challenges of kidney function measurement

Accuracy of estimated glomerular filtration rate :

- CKD-EPI equation inaccurate in diabetes
  - May be from presence of diabetes specific factors such as presence of hyperfiltration, increased creatinine and changed in creatinine concentration
  - Only 30% of the developmental and validation dataset had people with diabetes

- Significant proportion of people develop reduction in eGFR without albuminuria

ID-DKD Consortium

The international dataset:

- 5 international cohorts with direct measurement of kidney function (n = 11,151)
  - Spain, Germany, Korea, America and Australia (Austin Health)

Projects:

- Intra-individual participant data meta-analysis
  - Assessing the agreement between direct measurements of kidney function and CKD-EPI eGFR estimates
  - Using AI to improve eGFR estimates – **RenoTrue®**

Stay in touch

ACADI Partnering Summit – World Diabetes Day 14th November 2023

ACADI Monthly Seminar Series

ACADI video at ADA

- https://youtu.be/LTtU3ooJyYQ

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