phn NORTH WESTERN MELBOURNE

An Australian Government Initiative

Updates in diabetes and kidney disease for the primary care physician

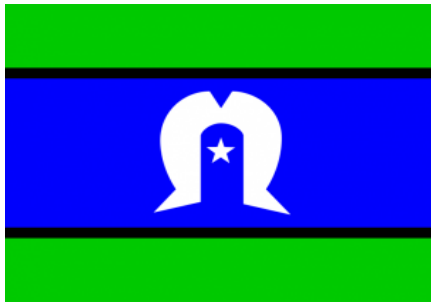
Thursday 23 May 2024

The content in this session is valid at date of presentation

Acknowledgement of Country

North Western Melbourne Primary Health Network would like to acknowledge the Traditional Custodians of the land on which our work takes place, The Wurundjeri Woi Wurrung People, The Boon Wurrung People and The Wathaurong People.

We pay respects to Elders past, present and emerging as well as pay respects to any Aboriginal and Torres Strait Islander people in the session with us today.



Collaboration

FUTURE HEALTH TODAY
Changing the course of chronic disease

FHT

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NORTH WESTERN MELBOURNE
An Australian Government Initiative

Western Health

WESTERN HEALTH CHRONIC DISEASE ALLIANCE

The Royal Melbourne Hospital

ACADI
Australian Centre for Accelerating Diabetes Innovations

THE UNIVERSITY OF MELBOURNE

Speakers

Dr Hannah Wallace, Western Health

- Dr Hannah Wallace is a nephrologist in Melbourne's west. She is undertaking her PhD with the University of Melbourne, exploring models of care to improve detection and management of kidney disease.

Dr Christopher Preston, Western Health

- Dr Christopher Preston is an endocrinologist at Western Health, with clinical interests in diabetes and modern data analytical and patient-interface technologies. He is currently undertaking a PhD exploring innovative models of care aimed at improving clinical outcomes in diabetes.

Associate Professor Spiros Fourlanos, MBBS, FRACP, PhD

- Spiros Fourlanos is Director of the Royal Melbourne Hospital Department of Diabetes and Endocrinology, and honorary Associate Clinical Professor with the University of Melbourne.
- He obtained his medical and PhD degrees at the University of Melbourne. His doctoral thesis -- Latent Autoimmune Diabetes in Adults (LADA): New Clinical, Immunogenetic and Metabolic Perspectives -- was performed at the Walter & Eliza Hall Institute.
- He has authored over 100 peer-reviewed papers and is currently a stream lead in the University of Melbourne Australian Centre for Accelerating Diabetes Innovations (ACADI) collaborative. He is currently a board member and honorary treasurer of the Australian Diabetes Society.

Updates in diabetes and kidney disease for the primary care physician

North-West PHN
23 May 2024

Dr Hannah Wallace & Dr Chris Preston

WESTERN HEALTH CHRONIC DISEASE ALLIANCE

Western Health

Outline

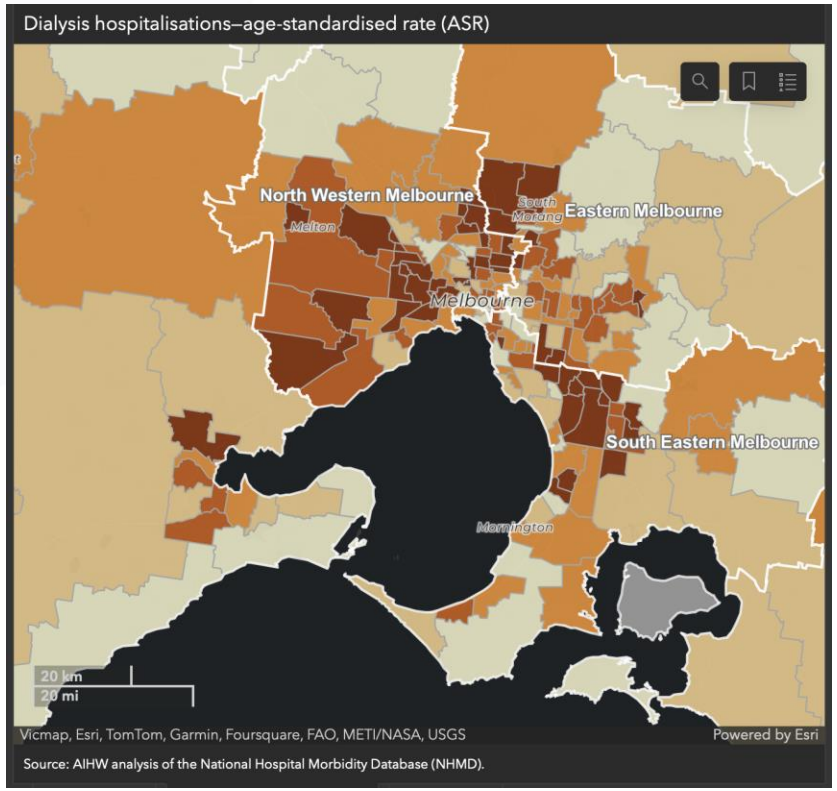
1. Local burden of T2DM and CKD
2. Updates in diabetes care
    1. Annual cycle of diabetes care
    2. Latest treatment algorithms
    3. Looking beyond glycemic control
    4. Practical tips
3. Updates in kidney disease care
    1. Why diagnose CKD?
    2. 4 pillars of CKD care
    3. Referral guidelines
4. Partnering with primary care in chronic disease management
    1. Future Health Today Program – WH
    2. New CKD Nurse Practitioner Clinic – WH
    3. Diabetes Remission Endo-Telehealth Rapid Access Clinics (Endo-TRACS) – RMH
5. Questions

A growing problem

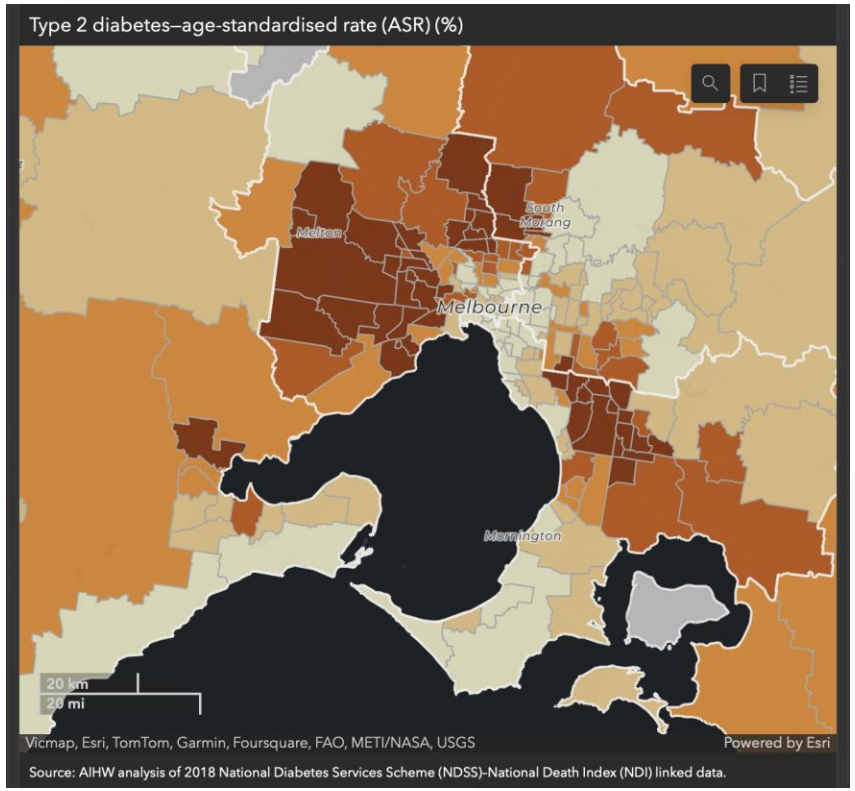
- Approx. 10% of the world's population has CKD
- >8.5% have diabetes (2014 data)
- No improvement in mortality from CKD from 1990 to 2017
- Increase in age standardized mortality form diabetes by 3% from 2000 to 2019
- CKD expected to be the 5th leading cause of years of life lost by 2040

Jager *et al.* Kidney Int 2019
WHO Fact Sheet 2023
Bikbov *et al*. Lancet. 2020
Roth *et al*. Lancet. 2019

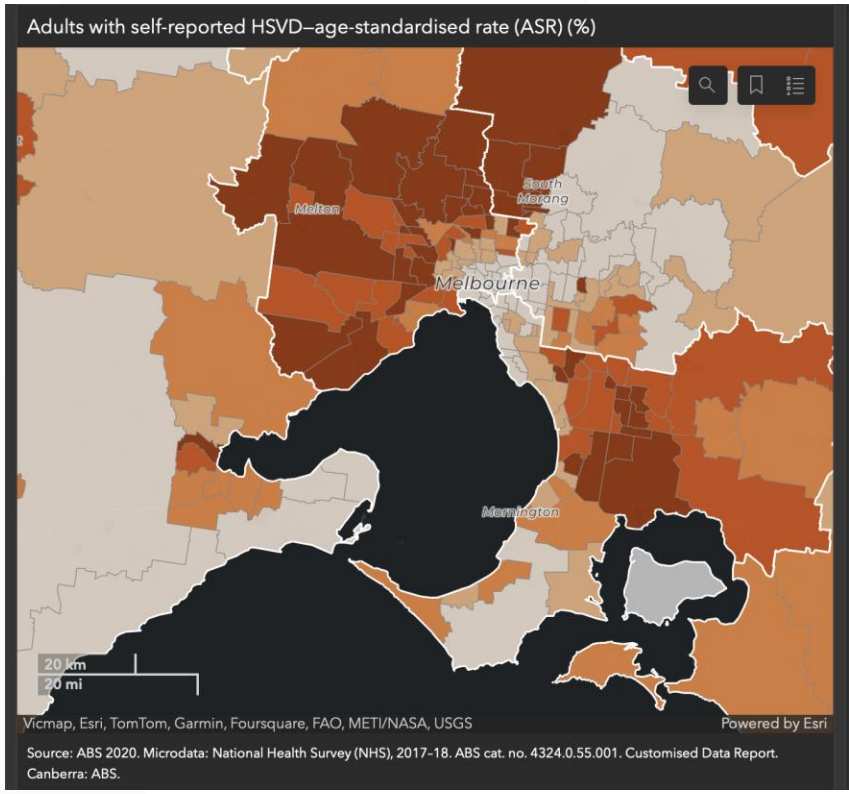
Chronic Disease in Melbourne



Dialysis



T2DM



Ischemic heart disease

AIHW Chronic Disease Maps

What can be done?

- Appropriate testing in those at risk
- Monitoring of cardio-renal-metabolic disease
- Treatments to reduce risk of progressive disease
- Identification of complications and referral to specialist services

Case 1: Mr MS

- 46M new patient to clinic: *“I want to get my diabetes back under control”*

- Past History
  - T2DM dx age 40
  - Hypertension
  - Obesity

- Medications
  - Metformin
  - Gliclazide
  - Perindopril

- Social History
  - Separated with new partner
  - Truck driver, poor diet and exercise
  - Ex-smoker, social EtOH

- Examination
  - Centrally obese, 112kg, BMI 38
  - BP 150/90 BSL 10.0
  - Pedal pulses +, sensation intact

Case 1: Mr MS

- 46M new patient to clinic: *“I want to get my diabetes back under control”*

Hb	140		115 – 160	g/L
HbA1c	8.5%		4.4 – 5.6	%
Cr	88		49 – 90	umol/L
eGFR	>90		>60	mL/min/1.73m2
uACR	2.0		<2.5	mg/mml
TC	5.2		3.5 – 5.5	mmol/L
HDL	1.0		>1.2	mmol/L
LDL	3.2		<3.5	mmol/L
TG	1.8		<1.5	mmol/L

- What should be our treatment recommendations?

Current Guidelines – Annual Cycle of Care

Check	When	Target
HbA1c	At least every 6-12 months	53mmol/mol (7%) or less
Blood pressure	At least every six months	130/80 or less
Foot assessment	Low risk feet: At least every year High risk feet: At least every 3-6 months	Foot health maintained
Eye examination	At least every two years	Eye health maintained
Kidney health	At least every year	Urine albumin levels in target range Kidney function test in target range
Blood fats	At least every year	Total cholesterol less than 4mmol/L LDL less than 2mmol/L HDL 1mmol/L or above Triglycerides less than 2mmol/L
Weight	At least every six months	BMI 18.5-24.9
Waist circumference*	At least every six months	Less than 94cm (men) Less than 80cm (women)
Healthy eating review	At least every year	Following a healthy eating plan
Physical activity review	At least every year	At least 30 minutes of moderate physical activity, five or more days a week and minimise time spent sitting
Medication review	At least every year	Safe use of medications
Smoking	At least every year	No smoking
Diabetes management	At least every year	Self-management of diabetes maintained
Emotional health	As needed	Emotional health and well-being maintained

- Treatment Principles
  - Treat to Target

  - HbA1c <7.0%
  - BP <130/80
  - BMI <25
  - Cr and uACR Normal
  - Lipids*
    - TC <4, LDL <2 HDL >1 TG <2

Current Guidelines – Treatment Algorithms

MONOTHERAPY: Metformin is the usual monotherapy unless contraindicated or not tolerated

- Metformin
- SU
- Insulin

Less commonly used: acarbose, DPP-4 inhibitor, SGLT2 inhibitor GLP-1RA, or TZD. Only acarbose is PBS reimbursed for monotherapy.

DUAL THERAPY: Choice of treatment – add on an oral agent or injectable therapy

Choice of dual therapy should be guided by clinical considerations (presence of, or high risk of, cardiovascular disease, heart failure, chronic kidney disease, hypoglycaemia risk, obesity), side effect profile, contraindications and cost.

- SGLT2 inhibitor
- GLP-1RA
- DPP-4 inhibitor
- SU
- Insulin

Less commonly used are: acarbose or TZD.

Current Guidelines – Treatment Algorithms

MULTIPLE THERAPIES: Choice of treatment : include additional oral agent or GLP-1 RA or insulin

Choice of agents should be guided by clinical considerations as above. Note: combinations not approved by PBS include GLP-1RA with SGLT2i. Consider reviewing any previous medication that has not reduced HbA1c by ≥0.5% after 3 months and take into consideration **glycaemic AND non-glycaemic benefits**.

SGLT2 inhibitor	GLP-1RA	DPP-4 inhibitor	SU	Insulin	Less commonly used are: acarbose or TZD.

THEN...

To intensify treatment to meet glycaemic targets

- If on metformin+SU+DPP-4i, consider *adding* SGLT2i, or *switching* DPP-4i to a GLP-1RA, or an SGLT2i.
- When adding incretin therapy, use either a DPP4i or GLP-1RA (not both together).
- If on basal insulin, consider *adding* SGLT2i or GLP-1RA or bolus insulin with meals, or *change* to premixed/coformulated insulin.
- If on metformin+DPP4i+SGLT2i *consider* adding SU or insulin.

With increasing clinical complexity consider specialist endocrinology consultation

Statewide Referral Criteria

- T2DM not responding to a combination of dietary AND medical management (i.e. at least three glucose-lowering medicines) with HbA1c >8.0%

- T2DM with complications (e.g. cardiovascular disease, kidney disease, retinopathy, cerebral vascular disease, neuropathy)

- Planning for pregnancy
- Unstable glycaemic control due to concomitant use of medicines that impact on glycaemic control (e.g. corticosteroids, chemotherapy protocols)
- Assessment for commercial driver's licence
- Diagnosis of type of diabetes

Beyond glycaemic control – The Evidence

- Sulfonylureas
- Metformin
- DPP4i
- SGLT2i
- GLP1-RA
- ...

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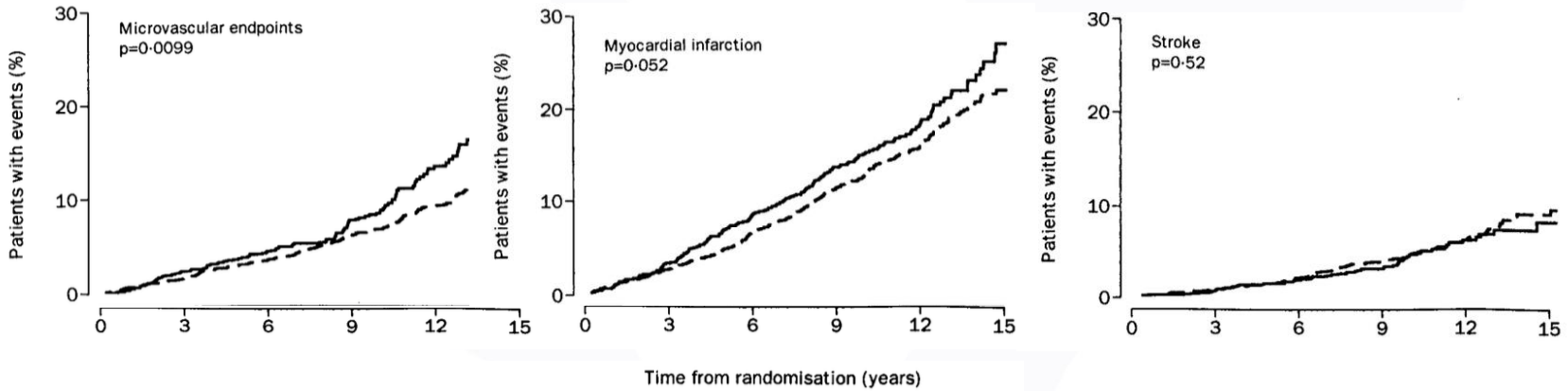

Figure 7: **Kaplan-Meier plots of aggregate endpoints: microvascular disease, myocardial infarction, and stroke for intensive and conventional treatment and by individual intensive therapy**
Microvascular disease=renal failure, death from renal failure, retinal photocoagulation, or vitreous haemorrhage. Myocardial infarction=non-fatal, fatal, or sudden death. Stroke=non-fatal and fatal. Key as for figures 3 and 4.

UKPDS Group 1998

Beyond glycaemic control – The Evidence

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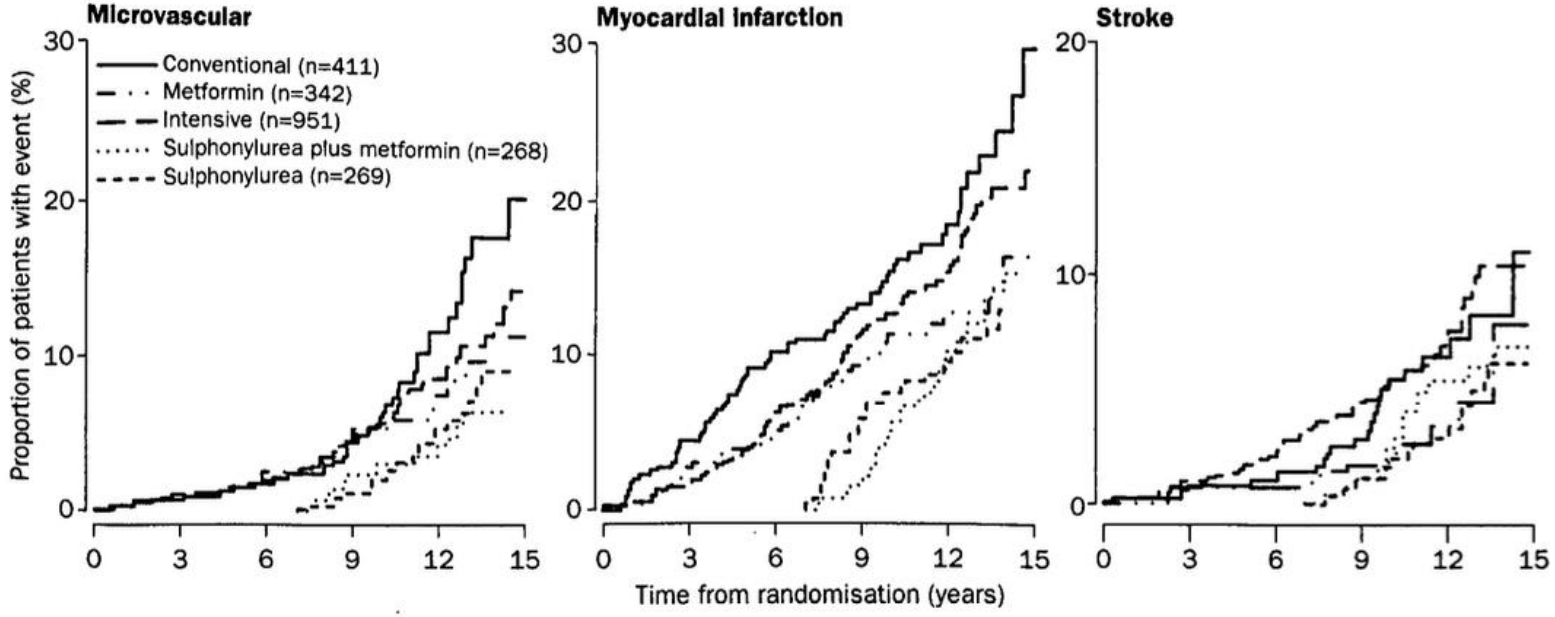

Figure 7: **Kaplan-Meier plots in diet/metformin study for microvascular disease (renal failure or death from renal failure, retinopathy requiring photocoagulation, or vitreous haemorrhage), myocardial infarction (non-fatal and fatal, including sudden death), stroke (non-fatal and fatal) and cataract extraction**

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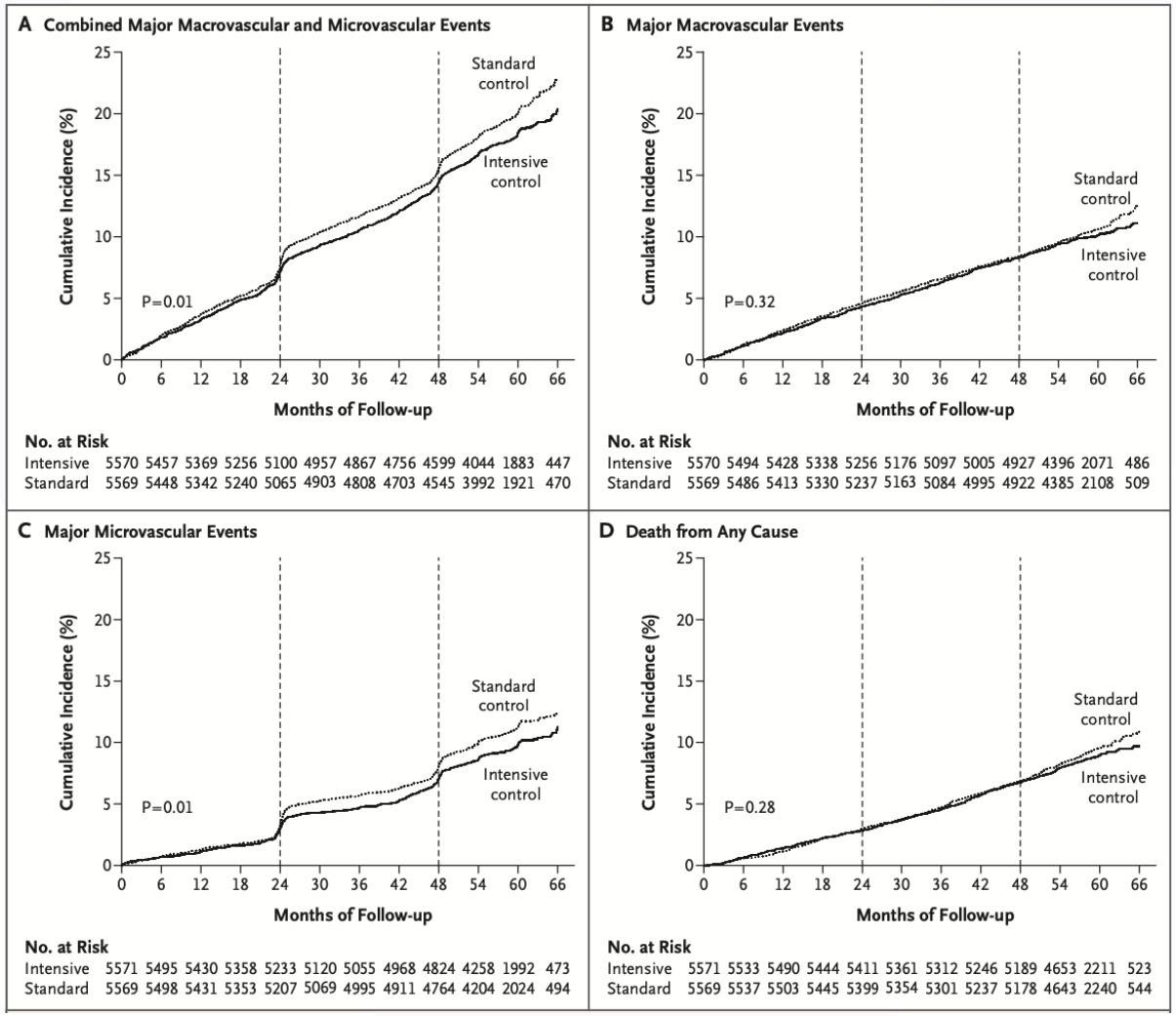

ADVANCE Collaborative Group 2008

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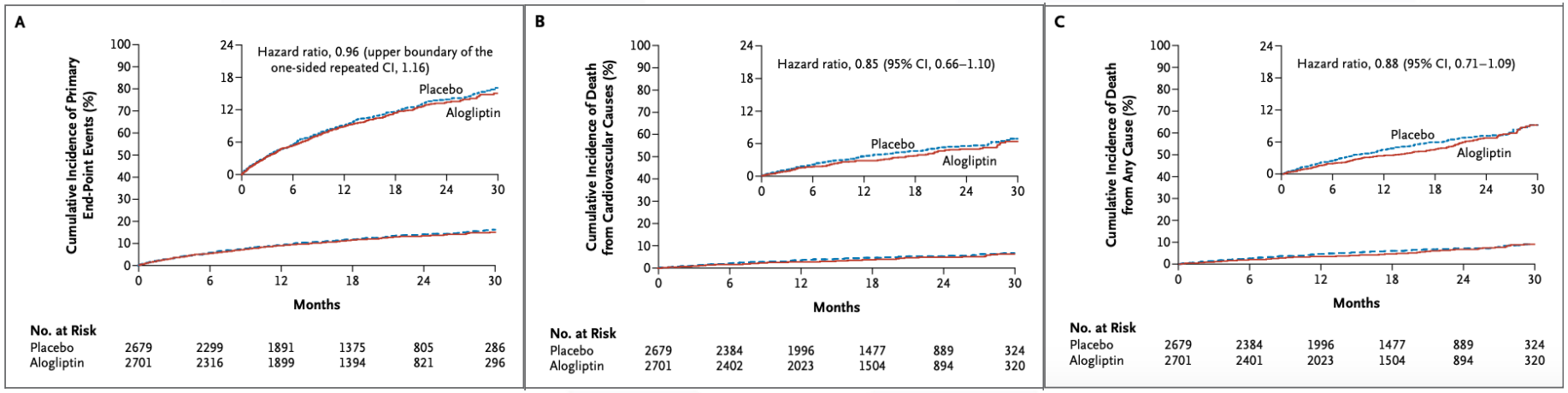

White et al 2013

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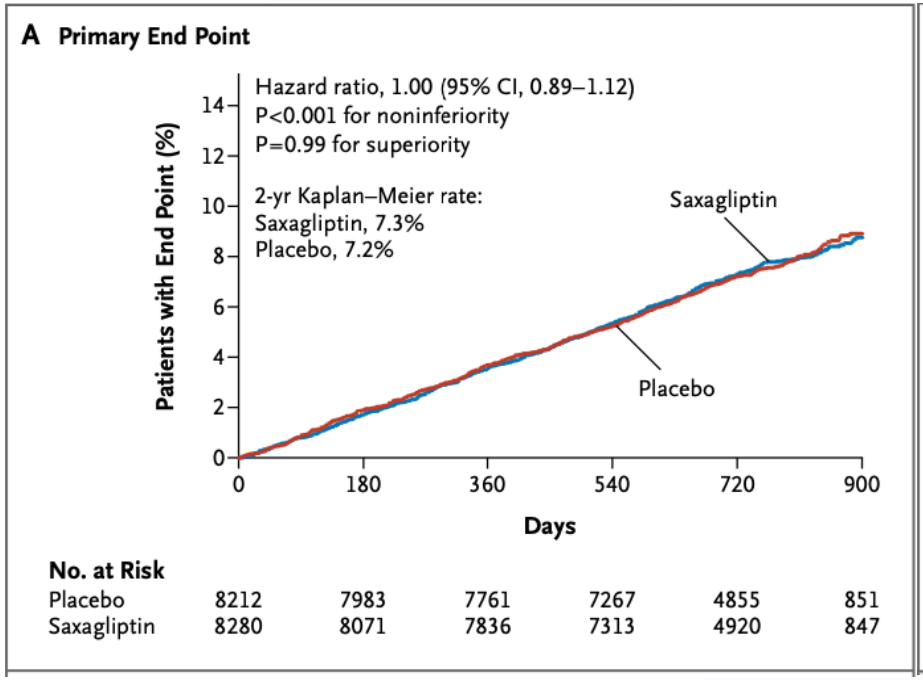

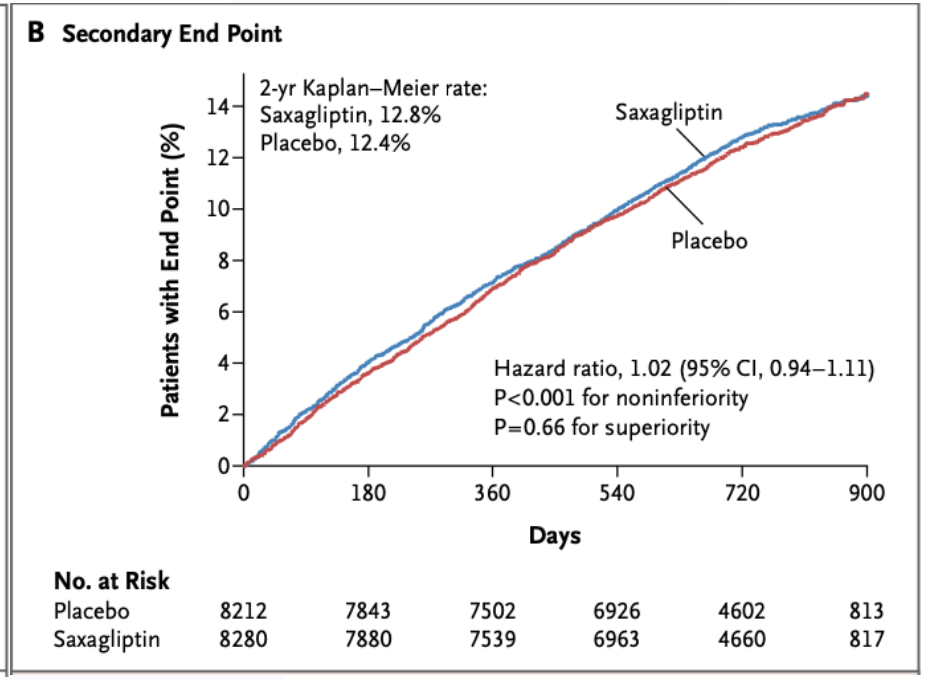

Scirica et al 2013

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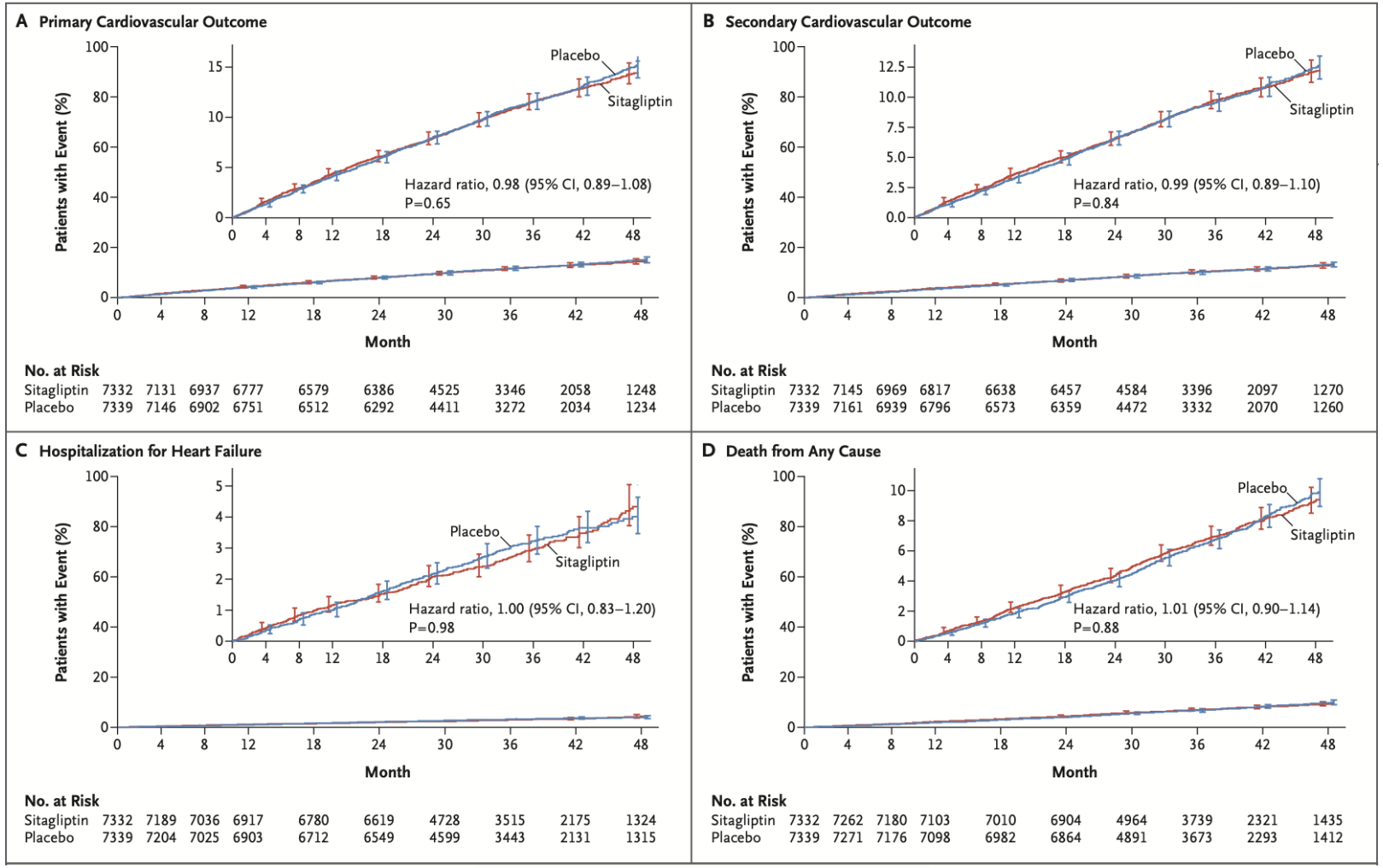

Green et al 2015

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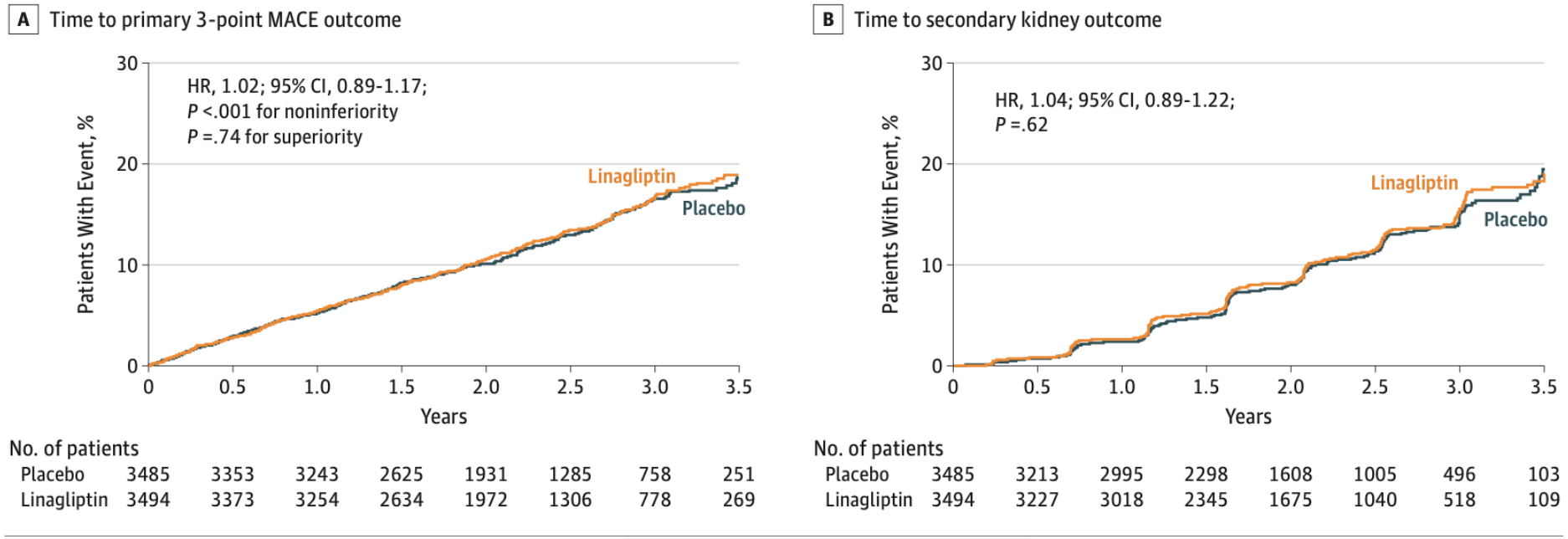

Rosenstock et al 2018

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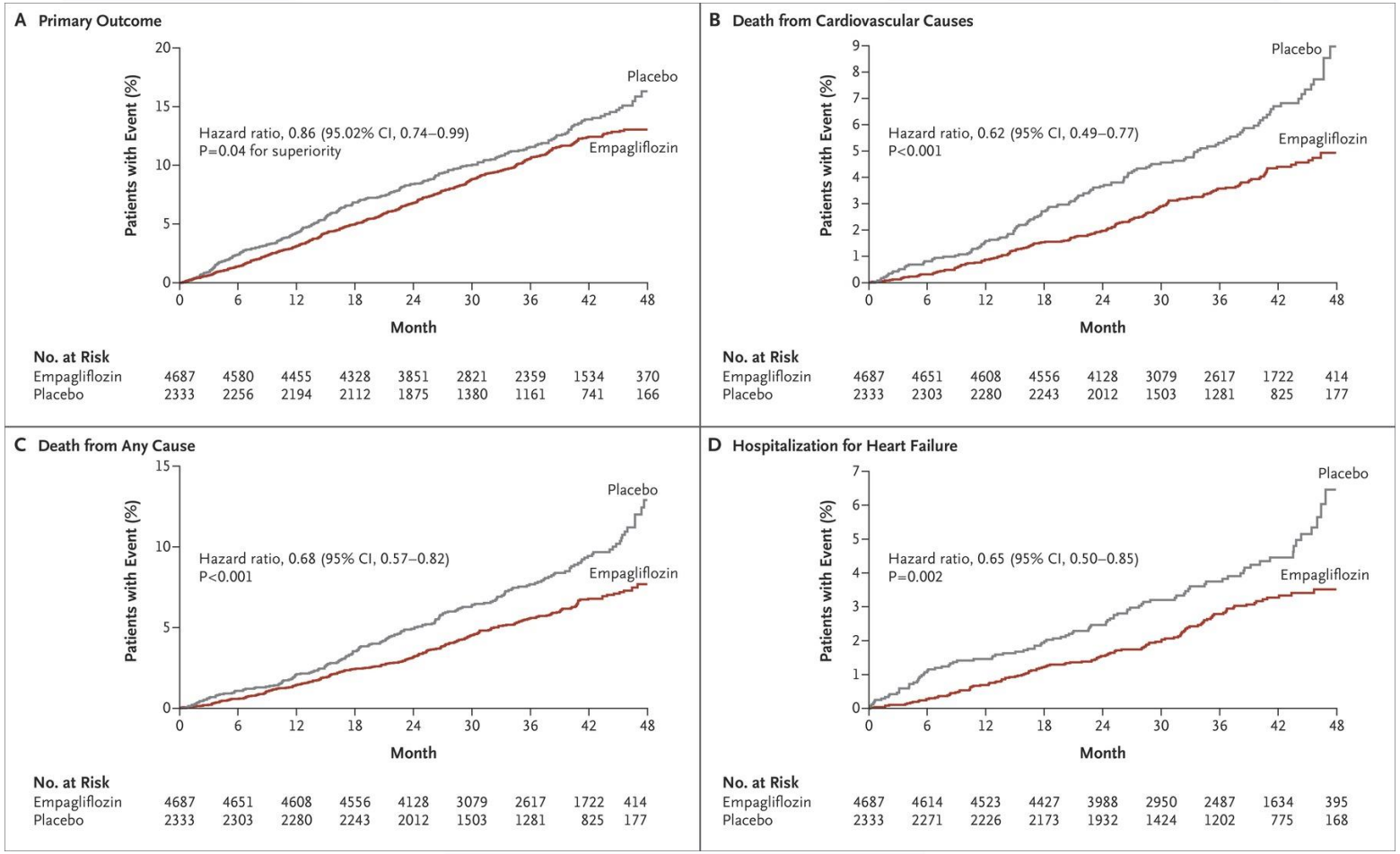

Zinman et al 2015

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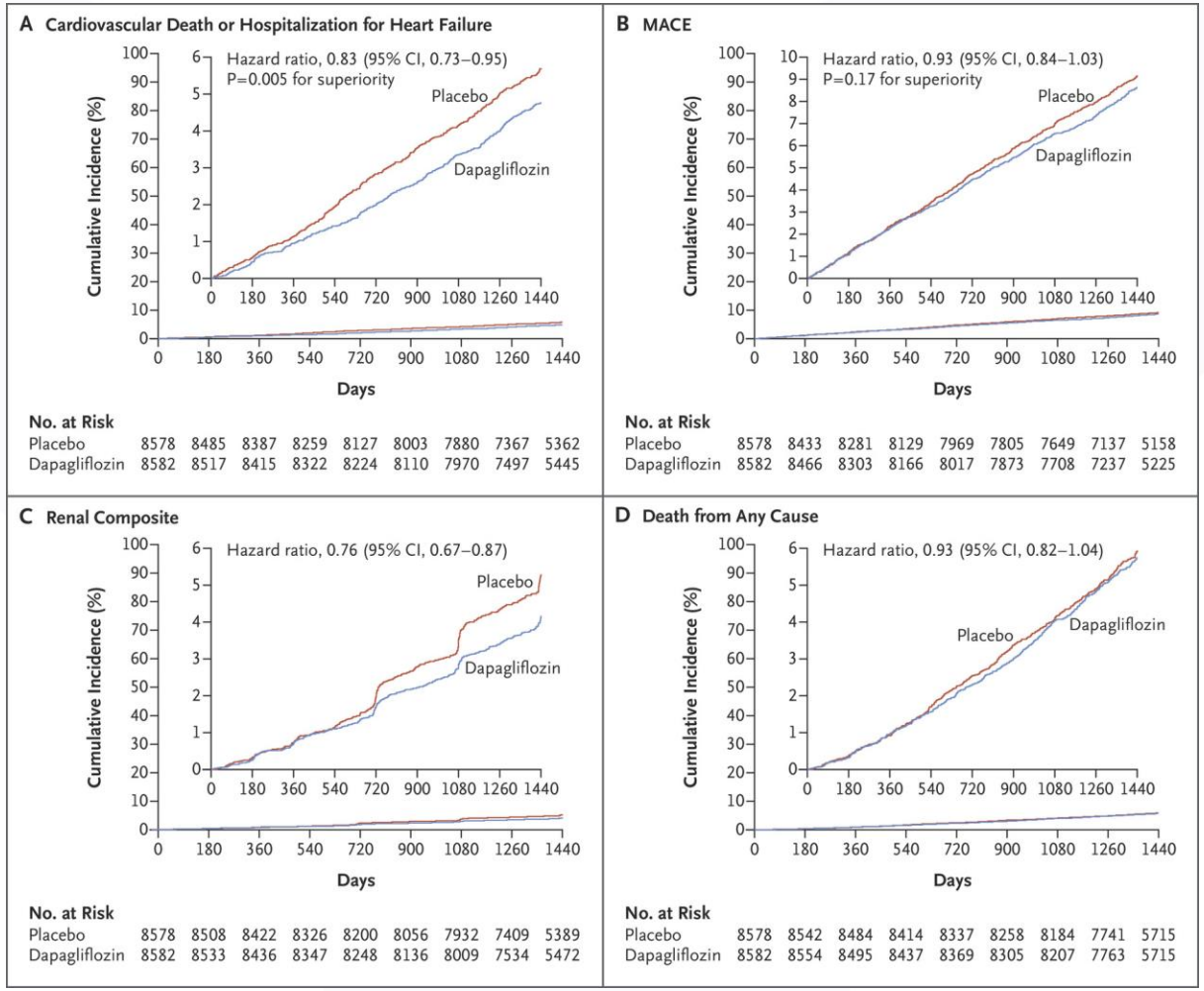

Wiviott et al 2019

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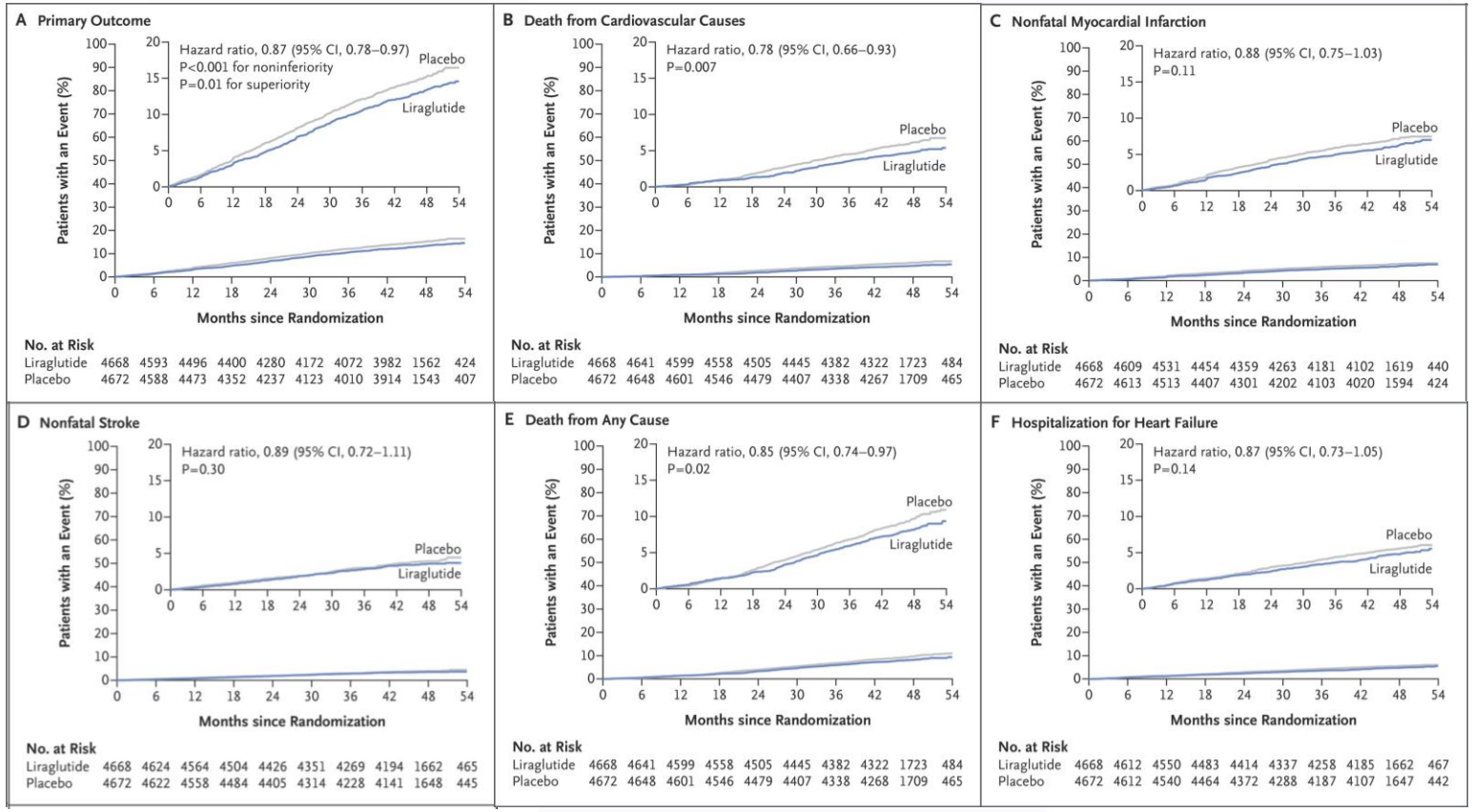

Marso et al 2016

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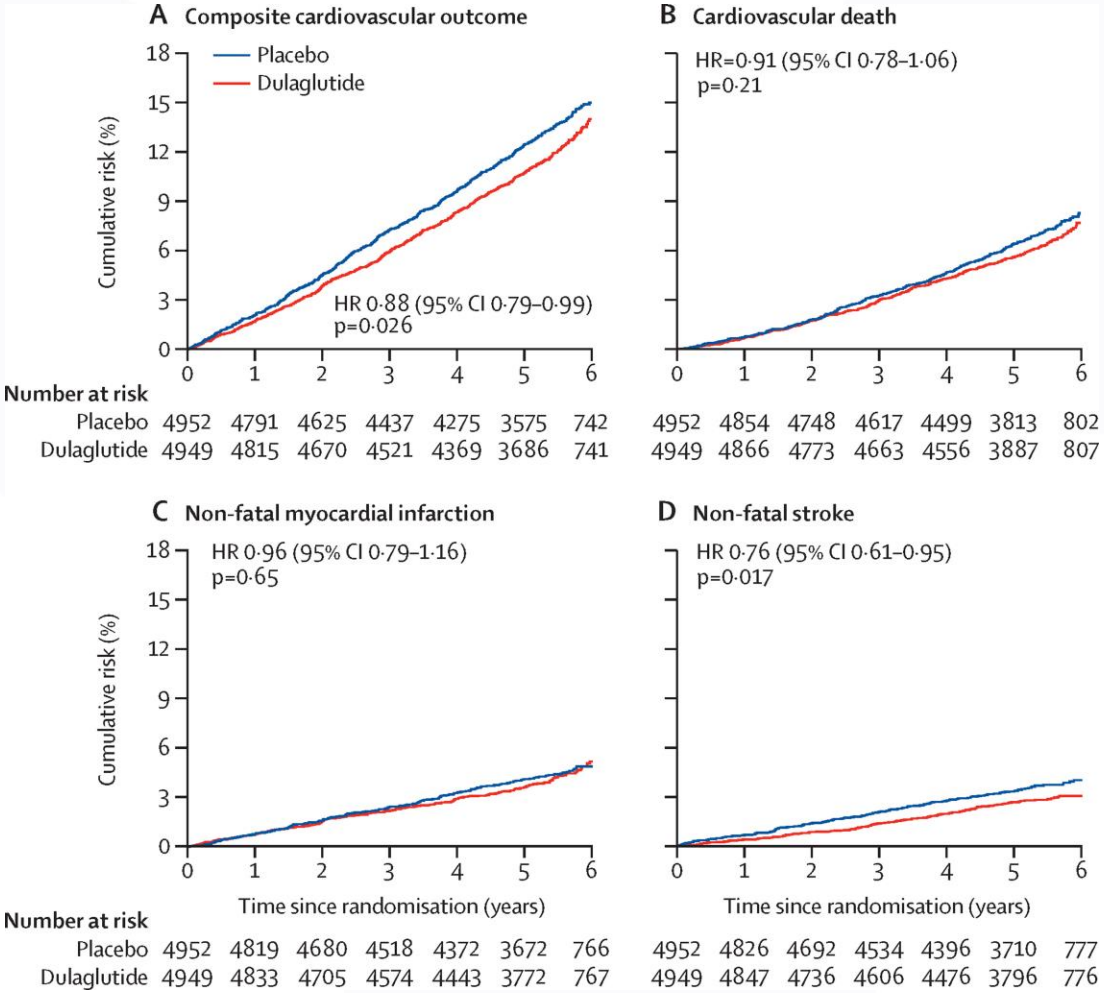

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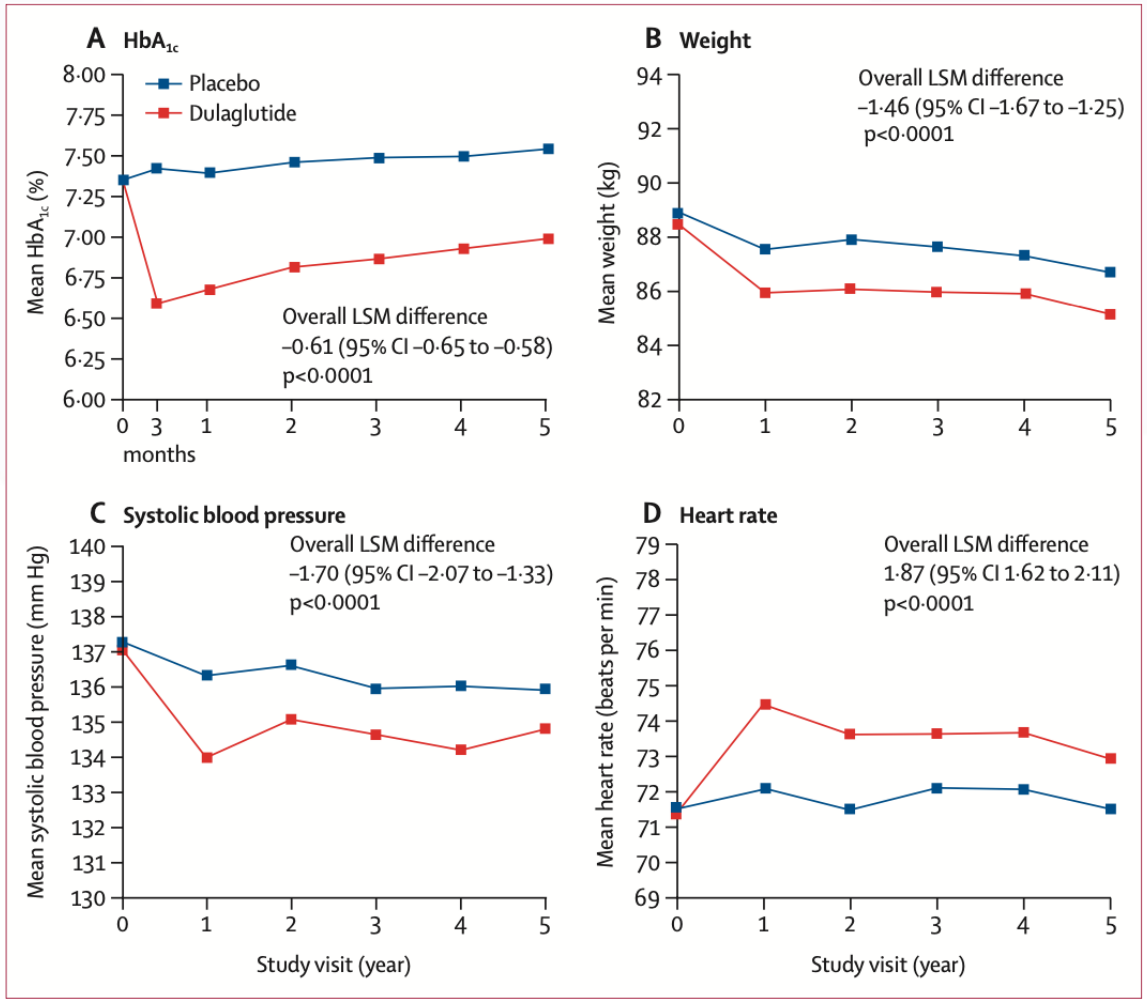

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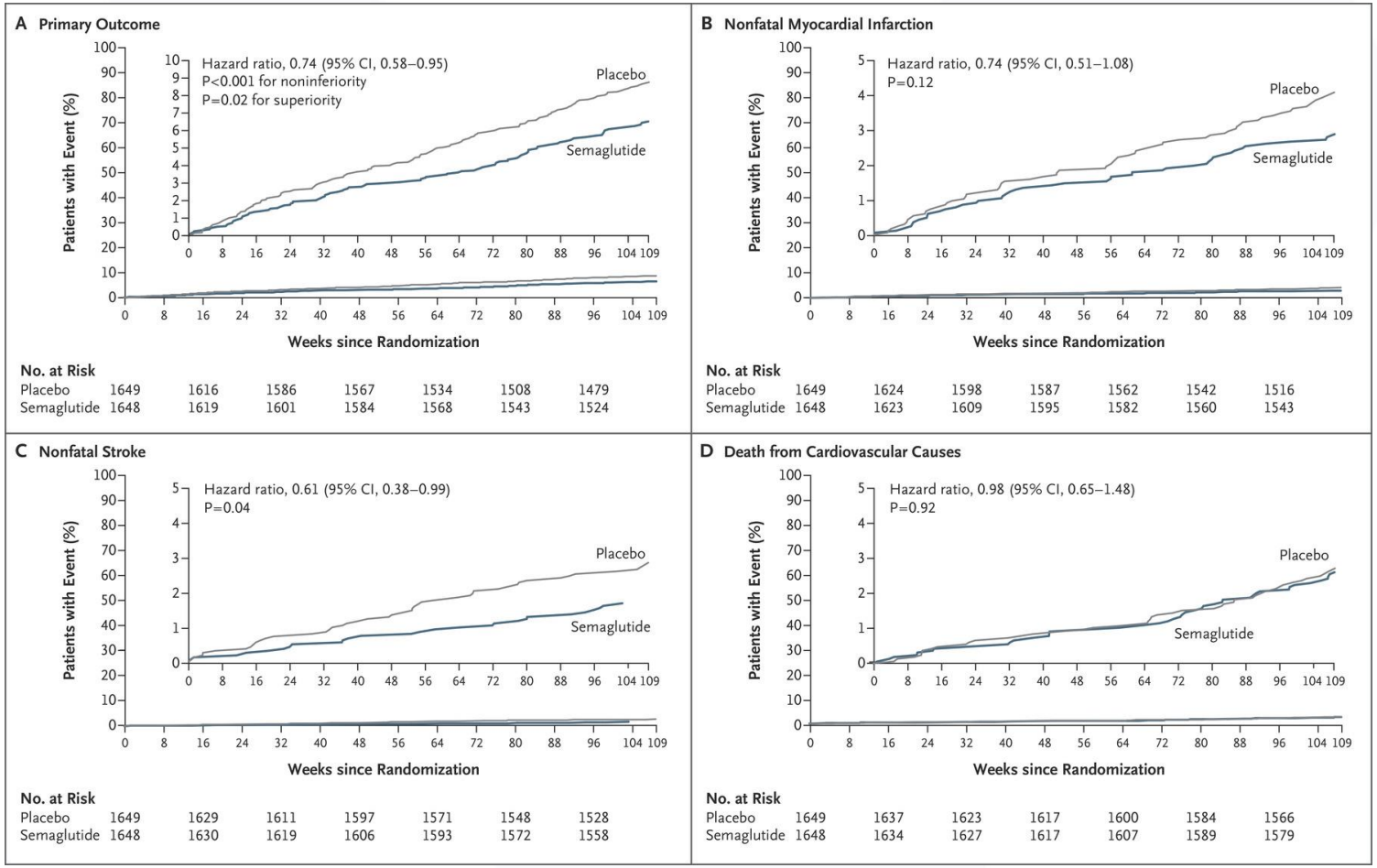

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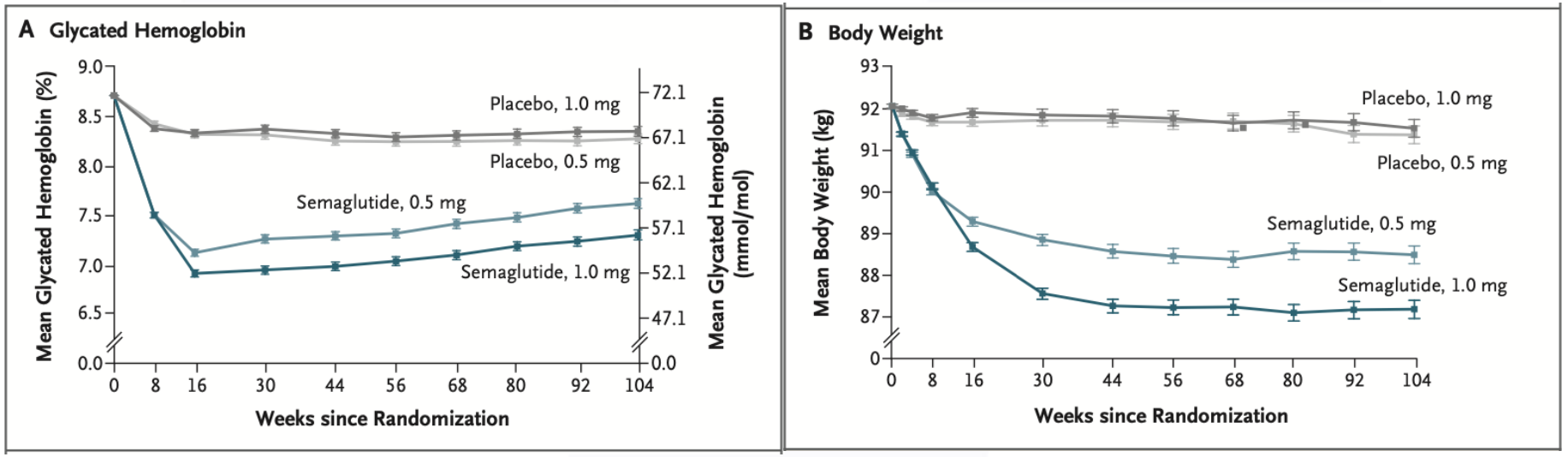

Marso et al 2016

Some Practical Points

- Intensifying treatment
  - Think: Could my patient benefit from a different glucose-lowering agent?
  - Is there a good reason why my patient is not on either an SGLT2i or GLP1-RA?

- Initiating GLP1-RA
  - Prepare patients for potential GI side effects; start low, go slow
  - Expect to reduce insulin when starting (will often be able to wean and cease)

- Combining therapy
  - When adding incretin therapy, use either a DPP4i or GLP1-RA (not both together)

Some Practical Points

- PBS indications
  - GLP1-RA + SGLT2i not approved as combination solely for T2DM
  - Consider non-diabetes indications for SGLT2i (covered soon)

- Sick day management
  - WH SGLT2 inhibitors while unwell
  - WH GLP1-RAs for 3-5 half lives before elective procedures

- De-prescribing
  - Review any medication that has not reduced HbA1c >0.5% after 3 months

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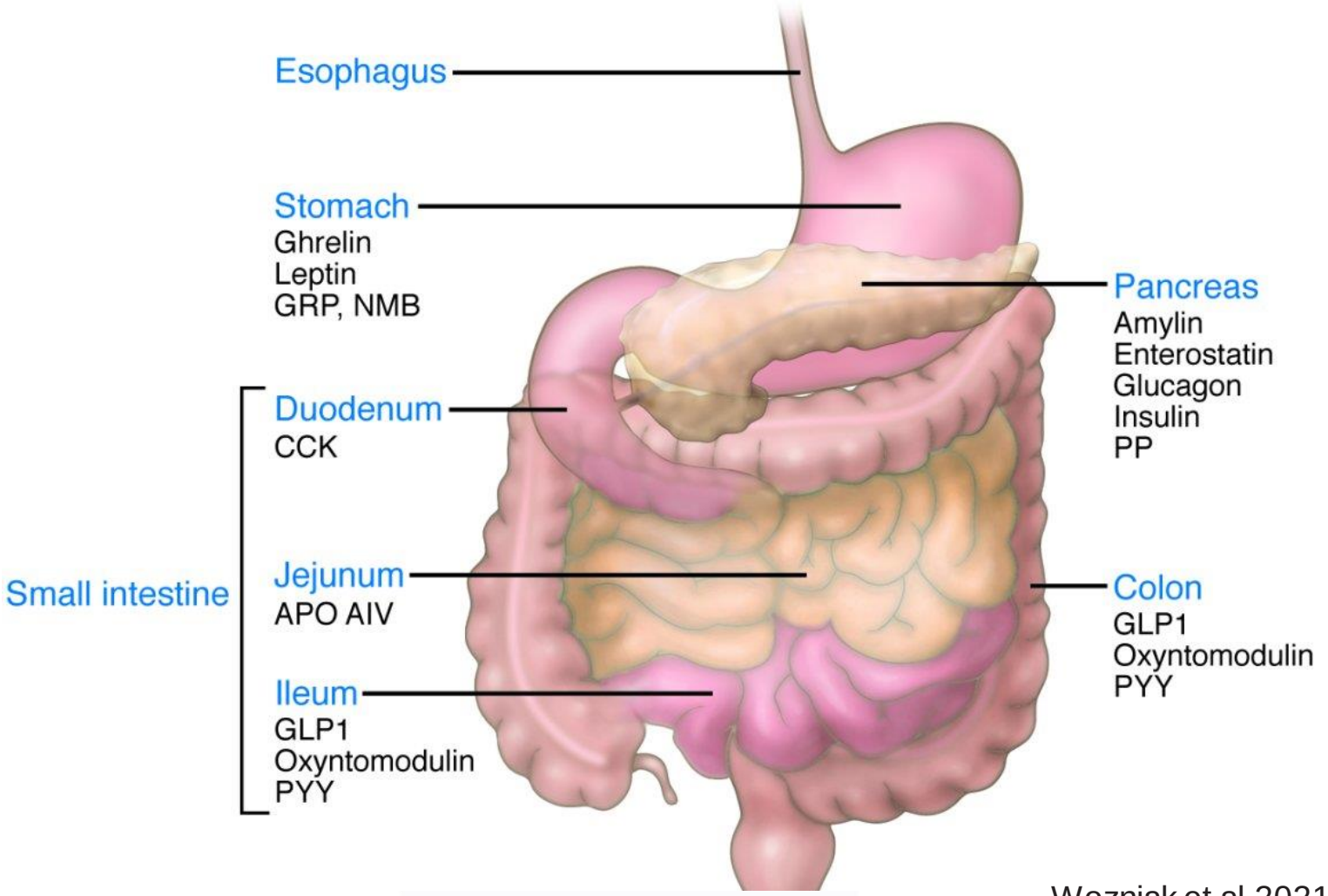

Wozniak et al 2021

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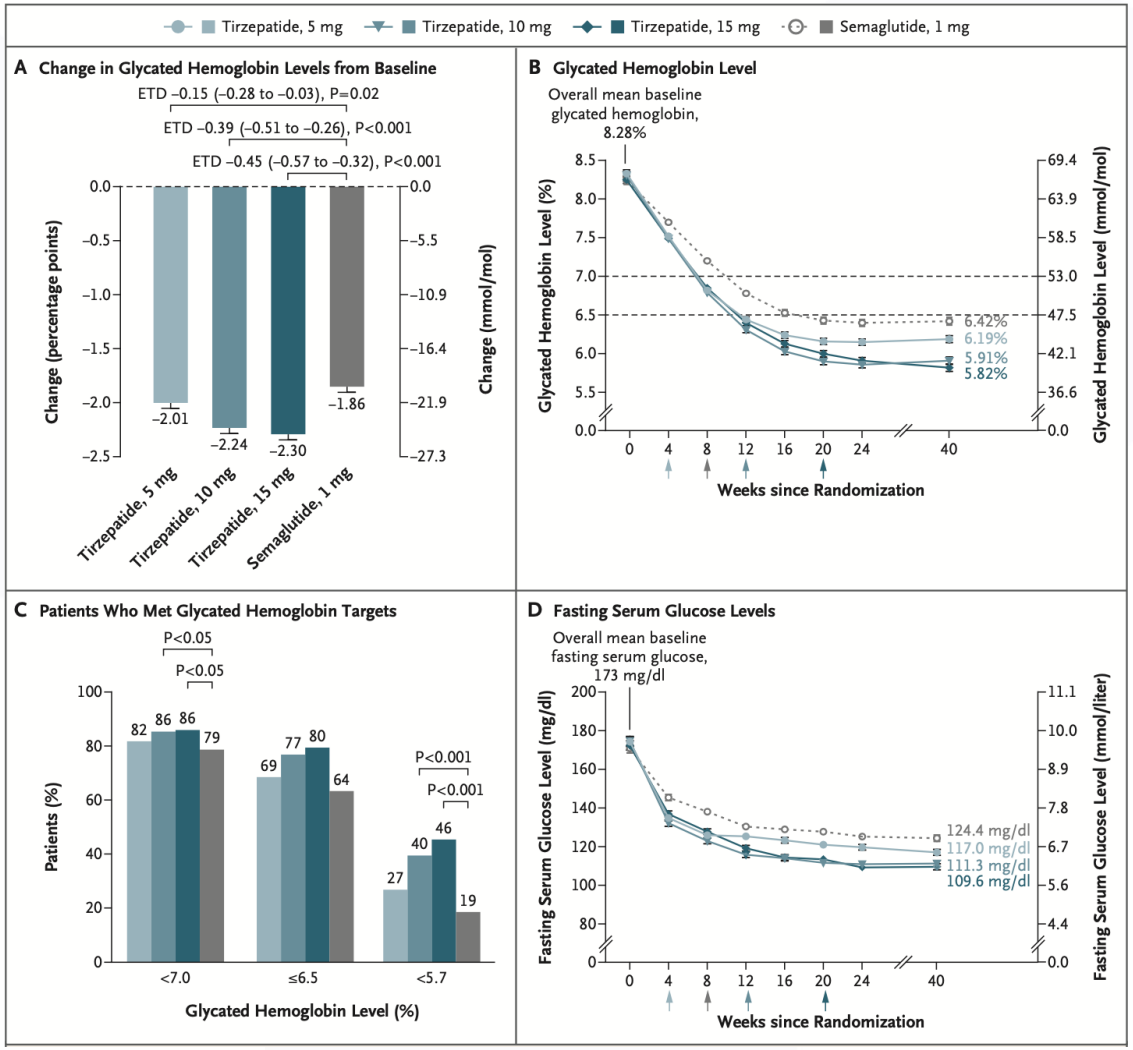

Frias et al 2021

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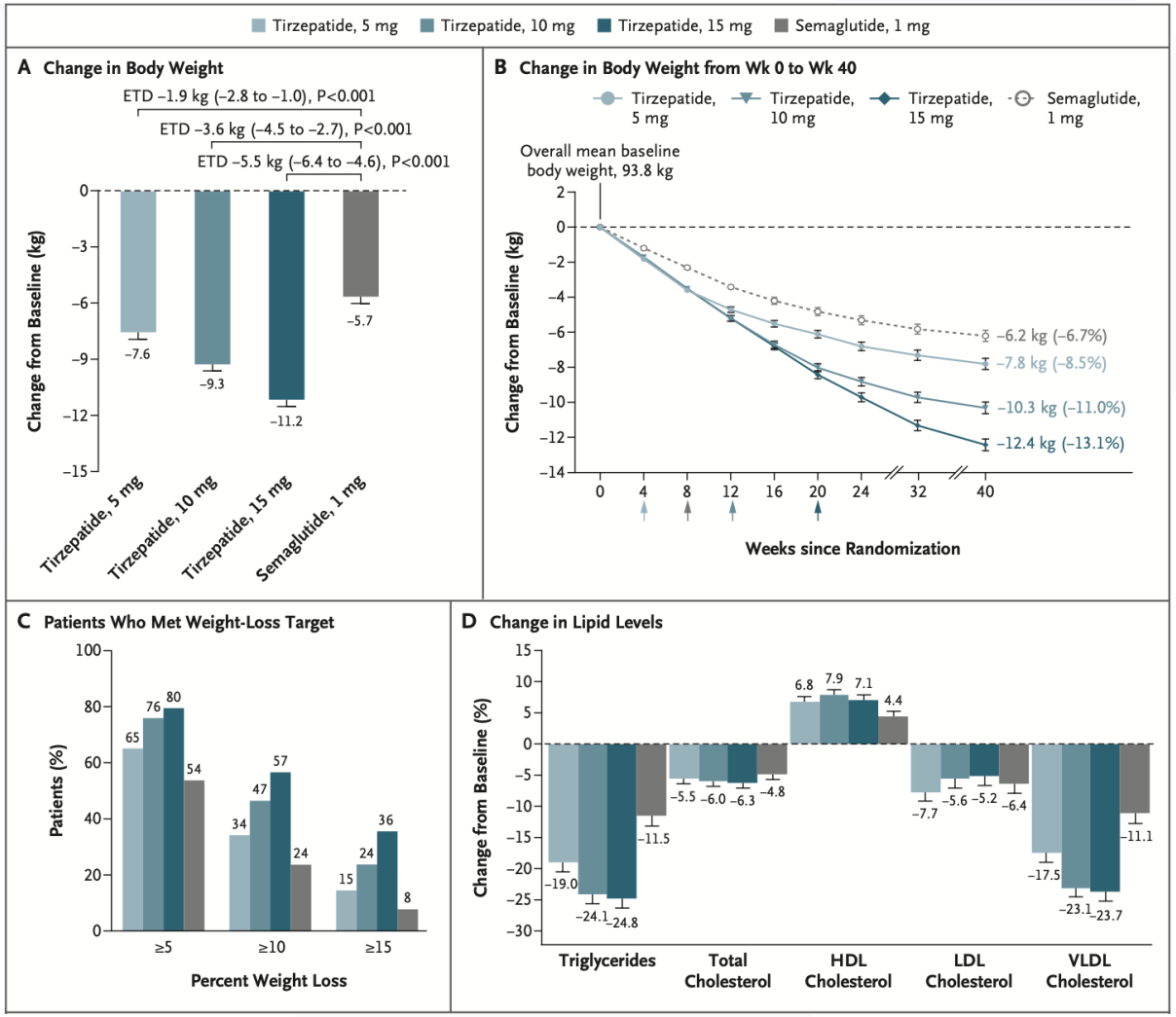

Frias et al 2021

What else is new?

- Ultra-long acting insulin: Insulin Icodec (Awiqli)
  - Once weekly dosing
  - Non-inferior to daily glargine in insulin naïve patients
  - Approved in Europe, FDA approval pending...

- Combination injectables
  - Multiple in research phase...

What's coming?

Mechanism of Action	Therapeutic Agonist	Dosing
Dual GLP-1RA /GIP RA	Tirzepatide (LY3298176)	Weekly SC
Dual GLP-1RA /Glucagon RA	Survodutide (BI 456906)[2] Efinopegdutide (HM12525A) [3] Cotadutide (MEDI0382)[1 2] Mazdutide (BI 456906)[2 3]	Weekly SC Weekly SC Daily SC Weekly SC
Triple GIP RA/ GLP-1RA /Glucagon RA	Retatrutide (LY3437943)[2]	Weekly SC
Dual GLP-1RA/Amylin	Semaglutide/Cagrilinitide[2] (CagriSema NovoNordisk)	
Dual GLP-1RA/Insulin	Semaglutide/Insulin Icodec[2] (Icosema NovoNordisk) Liraglutide/Insulin Degludec (IDegLira NovoNordisk) Lixisenatide/Insulin glargine 100U/ml (IGlarLixi)	

- GIP: Gastric Inhibitory Polypeptide; GLP-1: Glucagon Like Peptide 1; GLP-2: Glucagon-Like Peptide - 2;
- [1]Exendin analogue GLP1.
  [2]Phase III Trials In progress/Only Phase II published.
  [3]No further development planned for type 2 diabetes mellitus

Back to our case

Case 1: Mr MS

- 46M new patient to clinic: *“I want to get my diabetes back under control”*

- Progress
  - Improved adherence, diet, exercise
  - Commenced Semaglutide 0.25mg weekly, uptitrated monthly to 1mg
  - Experienced initial GI upset, now resolved and tolerating well

- Screening
  - Attended optometry review: no retinopathy
  - Podiatry: no loss of protective sensation, normal pulses and toe pressures

Case 1: Mr MS

- 46M new patient to clinic: *“I want to get my diabetes back under control”*

Hb	140	**144**	115 – 160	g/L
HbA1c	8.5%	**7.0%**	4.4 – 5.6	%
Cr	88	**90**	49 – 90	umol/L
eGFR	>90	**88**	>60	mL/min/1.73m2
uACR	2.0	**1.8**	<2.5	mg/mml
TC	5.2	**3.8**	3.5 – 5.5	mmol/L
HDL	1.0	**1.5**	>1.2	mmol/L
LDL	3.2	**3.0**	<3.5	mmol/L
TG	1.8	**1.4**	<1.5	mmol/L

- BP 130/75; Weight 112kg --> 108kg

Case 1: Mr MS

- 46M new patient to clinic: *“I want to get my diabetes back under control”*

- Progress
  - Welcomes baby son with new partner
  - Busy with new parenthood, fails to attend follow-up appointment
  - Lost to follow-up for several years...

WESTERN HEALTH CHRONIC DISEASE ALLIANCE

Western Health

Updates in Chronic Kidney Disease

Case 1: Mr MS

- Mr MS returns to clinic after several years
- Aged 52, with a young family
- No recent blood tests, stopped a number of his mdications
- Recent visit to the optometrist for new glasses and concern for diabetic eye changes has prompted a return to the GP

- Past History
  - T2DM dx aged 40
  - Diabetic retinopathy
  - HTN
  - Obesity

- Medications
  - Metformin
  - Perindopril 2mg

- Examination

  Centrally obese, weight 110 kg, BMI 37

  BP: 155/90

  Random BSL 15

Case 1: Mr MS

- 52 M

Hb	140		115 – 160	g/L
HbA1c	9.5%		4.4 – 5.6	%
Cr	126		49 – 90	umol/L
eGFR	59		>60	mL/min/1.73m2
TC	5.2		3.5 – 5.5	mmol/L
HDL	1.0		>1.2	mmol/L
LDL	3.2		<3.5	mmol/L
TG	1.8		<1.5	mmol/L

- Does this gentleman have CKD? And what are the implications?

Why diagnose CKD?

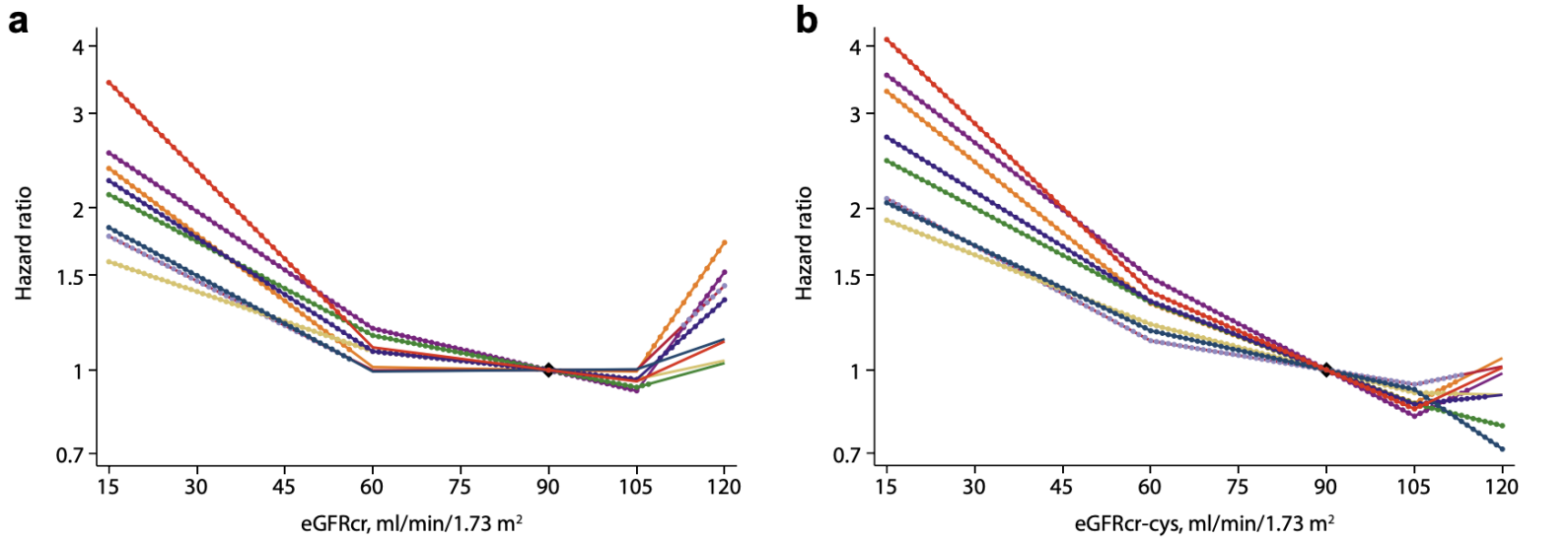

Figure 7 | Hazard ratios for adverse outcomes using the continuous model of estimated glomerular filtration rate (eGFR), comparison of the shape of associations between creatinine-based eGFR (eGFRcr) and creatinine and cystatin C–based eGFR (eGFRcr-cys) in the population with cystatin C (eGFRcr-cys population). (**a**) Associations of eGFR based on creatinine alone with all-cause mortality, cardiovascular mortality, all-cause hospitalizations, myocardial infarction, stroke, heart failure, atrial fibrillation, and peripheral artery disease; (**b**) Associations of eGFR based on creatinine and cystatin C with all-cause mortality, cardiovascular mortality, all-cause hospitalizations, myocardial infarction, stroke, heart failure, atrial fibrillation, and peripheral artery disease. Reproduced with permission from *JAMA*, Writing Group for the CKD Prognosis Consortium; Grams ME, Coresh J, Matsushita K, et al. Estimated glomerular filtration rate, albuminuria, and adverse outcomes: an individual-participant data meta-analysis. *JAMA*. 2023;330(13):1266–1277.[12]

Why diagnose CKD?

WESTERN HEALTH CHRONIC DISEASE ALLIANCE

Western Health

Overall	Urine albumin-creatinine ratio, mg/g					Urine albumin-creatinine ratio, mg/g				
eGFRcr	<10	10–29	30–299	300–999	1000+	<10	10–29	30–299	300–999	1000+
	All-cause mortality: 82 cohorts 26 444 384 participants; 2 604 028 events					Myocardial infarction: 64 cohorts 22 838 356 participants; 451 063 events				
105+	1.6	2.2	2.9	4.3	5.8	1.1	1.4	2.0	2.7	3.8
90–104	ref	1.3	1.8	2.6	3.1	ref	1.3	1.6	2.2	3.2
60–89	1.0	1.3	1.7	2.2	2.8	1.1	1.3	1.6	2.2	3.1
45–59	1.3	1.6	2.0	2.4	3.1	1.4	1.7	2.0	2.8	3.7
30–44	1.8	2.0	2.5	3.2	3.9	1.9	2.0	2.4	3.2	4.3
15–29	2.8	2.8	3.3	4.1	5.6	2.7	3.1	3.1	4.2	5.1
<15	4.6	5.0	5.3	6.0	7.0	4.6	5.6	4.8	6.0	6.0
	Cardiovascular mortality: 76 cohorts 26 022 346 participants; 776 441 events					Stroke: 68 cohorts 24 746 436 participants; 461 785 events				
105+	1.4	2.0	3.0	4.1	5.4	1.2	1.6	2.2	3.1	4.3
90–104	ref	1.3	1.9	2.7	3.6	ref	1.3	1.6	2.4	3.1
60–89	1.0	1.4	1.7	2.4	3.2	1.1	1.3	1.7	2.2	3.0
45–59	1.4	1.7	2.2	2.8	3.8	1.4	1.6	1.9	2.3	2.9
30–44	2.0	2.3	2.8	3.7	4.6	1.6	1.7	2.0	2.4	3.0
15–29	3.2	3.1	3.5	5.0	6.5	1.8	2.1	2.1	2.7	3.0
<15	6.1	6.4	6.4	7.3	8.2	3.2	2.8	2.9	3.2	3.8
	Kidney failure with replacement therapy: 57 cohorts 25 466 956 participants; 158 846 events					Heart failure: 61 cohorts 24 603 016 participants; 1 132 443 events				
105+	0.5	1.2	2.9	7.7	25	1.2	1.7	2.7	4.2	6.9
90–104	ref	1.8	4.3	12	43	ref	1.3	2.0	2.8	4.2
60–89	2.3	4.9	10	27	85	1.1	1.4	1.9	2.7	4.2
45–59	13	19	37	89	236	1.6	1.8	2.4	3.4	5.0
30–44	50	58	115	240	463	2.2	2.5	3.1	4.2	6.5
15–29	283	301	443	796	1253	3.6	3.5	4.1	5.8	8.1
<15	770	1040	1618	2297	2547	5.1	5.7	5.8	7.9	9.9

US – UACR mg/g	<10	15-29	30-299	300-999	>1000
AUS – UACR mg/mmol	<1.13	1.2-3.28	3.39-33.79	33.9-112	>113

	Acute kidney injury: 49 cohorts 23 914 614 participants; 1 408 929 events					Atrial fibrillation: 50 cohorts 22 886 642 participants; 1 068 701 events				
05+	1.0	1.6	2.4	3.7	5.5	1.1	1.3	1.7	2.4	3.5
0–104	ref	1.4	2.1	3.2	5.0	ref	1.2	1.5	1.9	2.3
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0–44	5.6	5.9	6.8	8.6	11	1.4	1.5	1.7	2.0	2.4
5–29	8.3	8.0	8.5	9.9	10	1.9	1.8	2.0	2.6	3.0
:15	8.5	11	7.9	5.5	5.7	2.6	2.5	3.1	3.6	4.2
	Hospitalization: 49 cohorts 25 426 722 participants; 8 398 637 events					Peripheral artery disease: 54 cohorts 24 830 794 participants; 378 924 events				
05+	1.4	1.7	2.1	2.1	2.3	0.9	1.4	1.9	2.8	5.0
0–104	ref	1.1	1.3	1.5	1.7	ref	1.3	1.9	2.8	4.3
0–89	1.0	1.1	1.3	1.5	1.8	1.0	1.3	1.8	2.5	3.8
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:15	2.7	2.8	3.0	3.2	3.8	9.1	9.0	9.6	13	14

Figure 5 | Associations of chronic kidney disease (CKD) staging by estimated glomerular filtration rate by creatinine (eGFRcr) and albumin-to-creatinine ratio (ACR) categories and risks for 10 common complications in multivariable-adjusted analyses. Numbers reflect the adjusted hazard ratio compared with the reference cell. Adjustment variables included age, sex, smoking status (current, former, or never), systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, body mass index, use of antihypertensive medications, and a medical history of diabetes, coronary heart disease, stroke, heart failure, atrial fibrillation, peripheral artery disease, cancer, and chronic obstructive pulmonary disease, where relevant. The colors were determined for each outcome separately using the following rule: the percentile shaded the darkest green color corresponds to the proportion of cells in the grid without CKD (e.g., 6 of 35 cells with eGFR ≥60 ml/min per 1.73 m^2 and ACR <30 mg/g [<3 mg/mmol]), and the percentile shaded the darkest red color corresponds to proportion expected to be at highest risk (e.g., 11 of 35 cells with eGFR <15 ml/min per 1.73 m^2 and albumin-to-creatinine ratio 1000+ mg/g [100+ mg/mmol]). In this manner, the numbers of green and red cells are consistent across outcomes, but the patterns are allowed to differ. ref, reference cell. Reproduced with permission from *JAMA*, Writing Group for the CKD Prognosis Consortium; Grams ME, Coresh J, Matsushita K, et al. Estimated glomerular filtration rate, albuminuria, and adverse outcomes: an individual-participant data meta-analysis. *JAMA*. 2023;330(13):1266–1277.[12]

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Who should I test?

Patients with risk factors for CKD

- Diabetics*
- Hypertension*
- Established cardiovascular disease
- Family history of kidney failure
- Obesity
- Smoker
- Aboriginal or Torres Strait Islander origin ≥30
- History of AKI

Kidney Health Check:

- eGFR
- Urine albumin creatinine ratio (uACR)
- Blood pressure

How often:

Kidney Health Check every 1-2 years.

* Patients with DM and HTN should all be screened yearly.

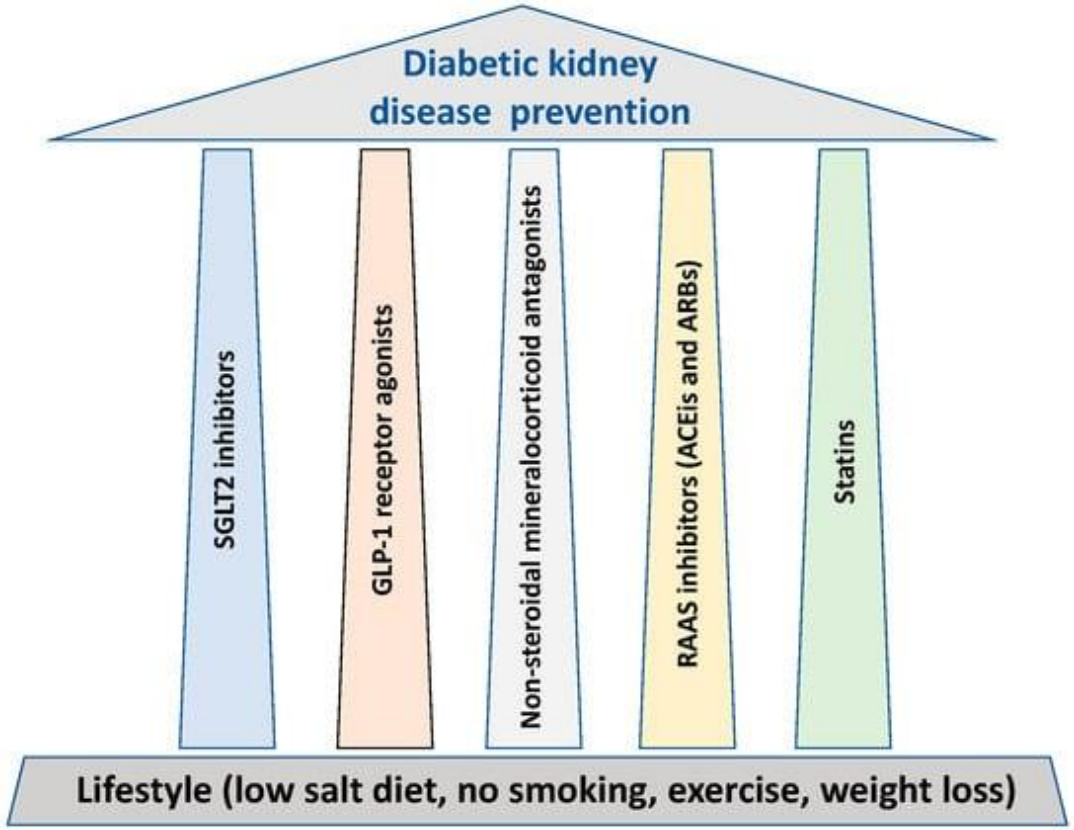
CKD Management

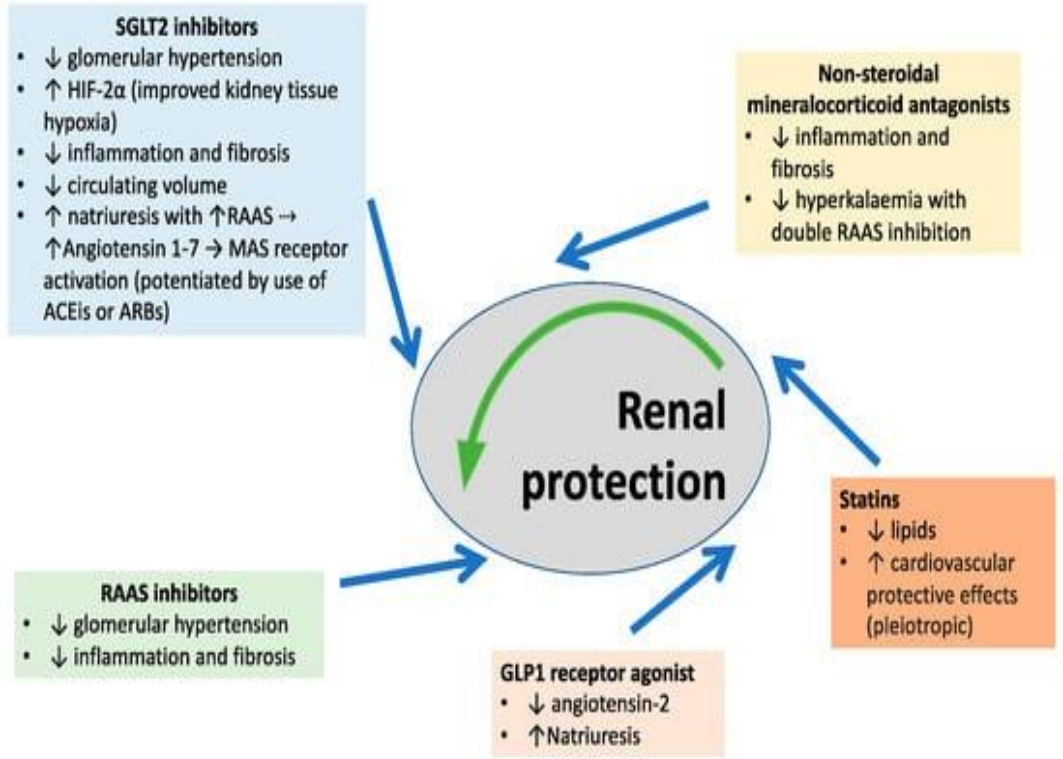
WESTERN HEALTH CHRONIC DISEASE ALLIANCE

Western Health

Lifestyle	Blood pressure	Cardiovascular risk	Medications
• Smoking cessation • Physical activity • Weight reduction if overweight • Salt reduction	• <130/80mmHg *being updated to <120/80 • ACEi / ARB first line	• Mod-severe CKD (eGFR < 45 OR macroalbuminia = highest CVD risk • Statin therapy as per CVD guidelines • LDL < 2 (primary) & <1.8 (secondary)	• ACEi / ARB • SGLT2i • MRAs • *GLP1-agonists*

The Pillars of CKD pharmacotherapy





Kearney & Gnudi, Pharmaceutics 2023.

Our patient

- Mr MS had his metformin up-titrated and re-started on gliclazide. Perindopril was increased to the maximum dose.

- His first UACR was 100, second 88.

- 3 months later on maximum ACEI dose UACR is 50mg/mmol.
- Urine MCS – no red cells or leukocytes
- Normal renal tract US

Step-wise initiation: ACEi / ARB

- Angiotensin converting enzyme inhibitors and angiotensin receptor blockage
  - MOA: decrease glomerular hypertension, decrease inflammation and fibrosis
  - Reduce proteinuria
  - Reduce progression of CKD
  - Risk >> benefit in combination ACE inhibitor & ARB (ie use one or the other)
  - Benefits are over and above their blood pressure lowering effects

- Practical tips
  - Start low - particularly in the elderly or normotensive patient
  - **Check UEC 2-4 weeks after starting**
    - Up to 20% decline in function acceptable
  - Sick day plan: withhold in context of prolonged fasting or dehydrating illness
  - ACEi cough → try change to ARB

Step-wise initiation: SGLT2 inhibitors

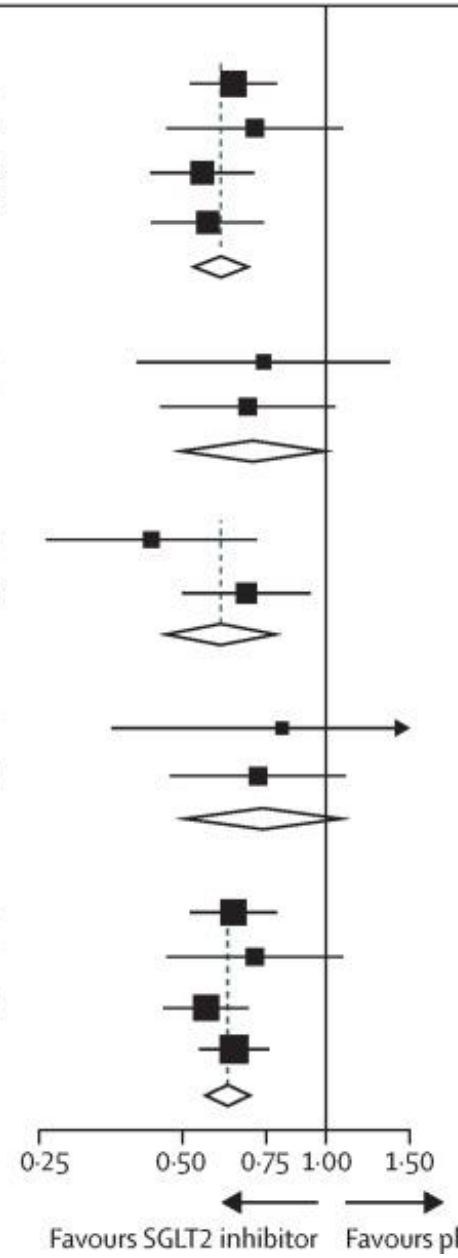
- Proposed MOA:
  - Reduced glomerular hypertension
  - Reduced inflammation and fibrosis
  - Reduce circulating volume

- Benefits
  - Reduced the risk of progressive CKD 37% - with similar results between diabetes and non diabetes patients
  - Risk of cardiovascular death or heart failure hospitalization reduced by 23%

Figure: Effect of sodium glucose co-transporter-2 inhibition on kidney disease progression by presumed primary kidney disease (chronic kidney disease trials only)

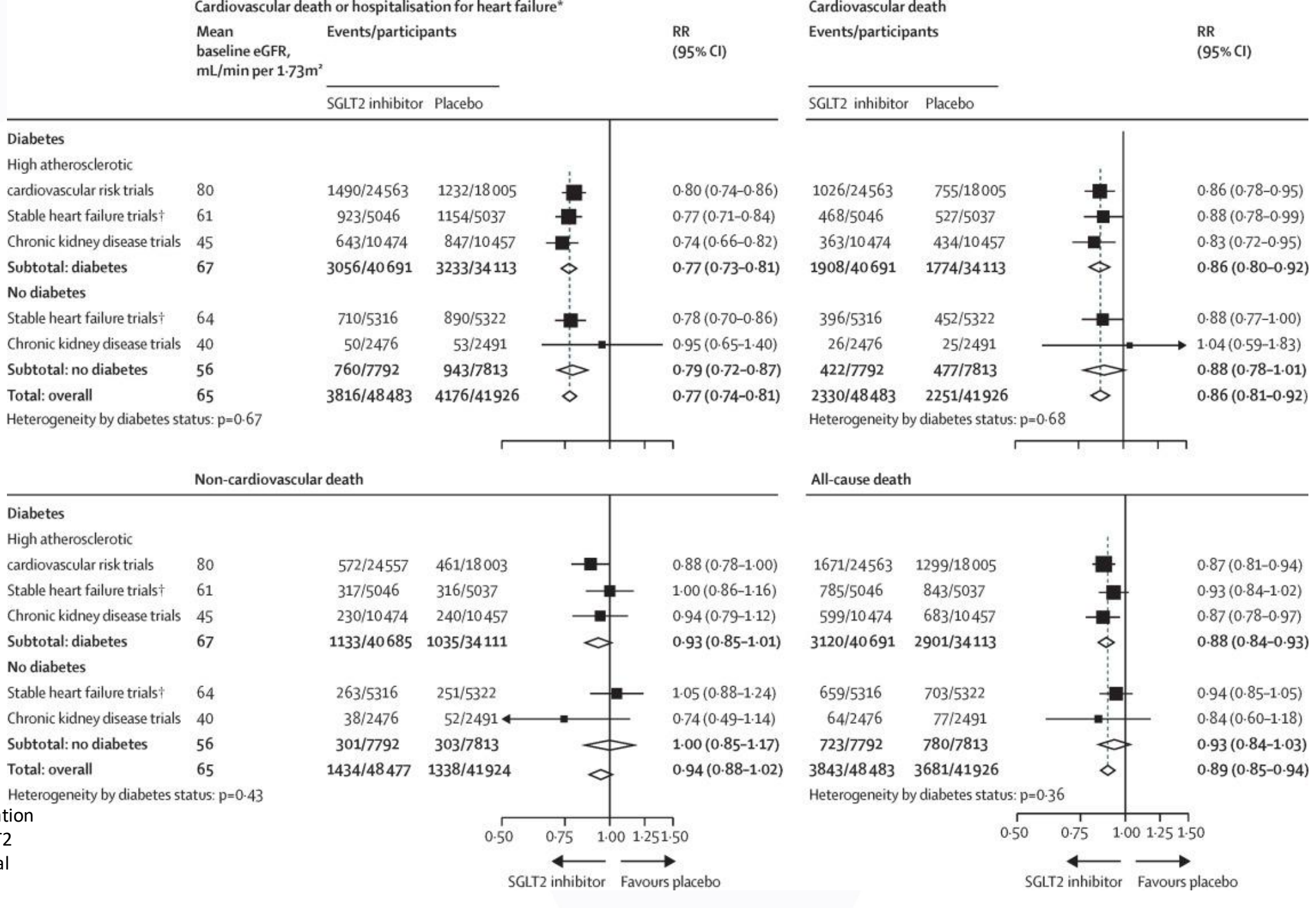
	Mean baseline eGFR, mL/min per 1·73m²	Events/participants		Event rate per 1000 patient-years		RR (95% CI)
		SGLT2 inhibitor	Placebo	SGLT2inhibitor	Placebo	
Diabetic kidney disease or nephropathy*						
CREDENCE	56	153/2202	230/2199	27	41	0·64 (0·52–0·79)
SCORED	44	37/5292	52/5292	5	7	0·71 (0·46–1·08)
DAPA-CKD	43	93/1271	157/1239	36	64	0·55 (0·43–0·71)
EMPA-KIDNEY	36	85/1032	133/1025	42	67	0·56 (0·43–0·74)
Subtotal	**46**	**368/9797**	**572/9755**	..	..	**0·60 (0·53–0·69)**
Ischaemic and hypertensive kidney disease						
DAPA-CKD	43	18/324	26/363	28	37	0·74 (0·40–1·36)
EMPA-KIDNEY	35	37/706	52/739	27	37	0·69 (0·45–1·05)
Subtotal	**38**	**55/1030**	**78/1102**	..	..	**0·70 (0·50–1·00)**
Glomerular disease						
DAPA-CKD	43	21/343	46/352	33	70	0·43 (0·26–0·72)
EMPA-KIDNEY	42	69/853	95/816	44	64	0·68 (0·50–0·93)
Subtotal	**42**	**90/1196**	**141/1168**	..	..	**0·60 (0·46–0·78)**
Other kidney disease or unknown						
DAPA-CKD	43	10/214	14/198	25	37	0·81 (0·35–1·83)
EMPA-KIDNEY	36	36/713	52/725	26	36	0·72 (0·47–1·10)
Subtotal	**38**	**46/927**	**66/923**	..	..	**0·74 (0·51–1·08)**
Any diagnosis						
CREDENCE	56	153/2202	230/2199	27	41	0·64 (0·52–0·79)
SCORED	44	37/5292	52/5292	5	7	0·71 (0·46–1·08)
DAPA-CKD	43	142/2152	243/2152	33	58	0·56 (0·45–0·68)
EMPA-KIDNEY	37	227/3304	332/3305	36	52	0·64 (0·54–0·76)
Total	**44**	**559/12 950**	**857/12 948**	..	..	**0·62 (0·56–0·69)**

Heterogeneity across groups of primary kidney disease: p=0·67
Trend across trials sorted by eGFR for any diagnosis: p=0·88



The Nuffield Department of Population Health Renal Studies Group & SGLT2 inhibitor Meta Analysis CardioRenal Trialist Consortium, Lancet, 2022

Figure: Effect of sodium glucose co-transporter-2 inhibition on heart failure and mortality outcomes by diabetes status



The Nuffield Department of Population Health Renal Studies Group & SGLT2 inhibitor Meta Analysis CardioRenal Trialist Consortium, Lancet, 2022

Step-wise initiation: SGLT2 inhibitors

- Who to initiate?

  - CKD specific PBS:
    - eGFR 25-75 (**to initiate)**
    - UACR 22.6-565mg/mmol (**to initiate)**
    - Stabilized on the maximum tolerated ACEi/ARB.
    - *Exclusions ADPKD, lupus, ANCA vasculitis or immunosuppression for kidney disease or transplantation.*

  - Other PBS:
    - T2DM: HbA1c > 7% in combination with metformin or sulfonylurea or insulin
    - Heart failure: heart failure NYHA Class II-IV (now on PBS for both HFrEF and HFpEF

Step-wise initiation: SGLT2 inhibitors

- Practical tips
  - Who is safe for an SGLT2i?
    - Contraindicated in T1DM
    - Caution in patients with frequent UTIs complicated by pyelonephritis / hospitalization
  - Review other diuretic or anti-HTN when initiating
    - If euvolemic consider diuretic dose reduction
    - If BP <120/80 prior to commencement, consider dose reduction of anti HTN
  - Sick day management
    - https://www.health.qld.gov.au/__data/assets/pdf_file/0022/1154380/SGLT2-inhibitor-Patient-Information.pdf

Step-wise initiation: MRA

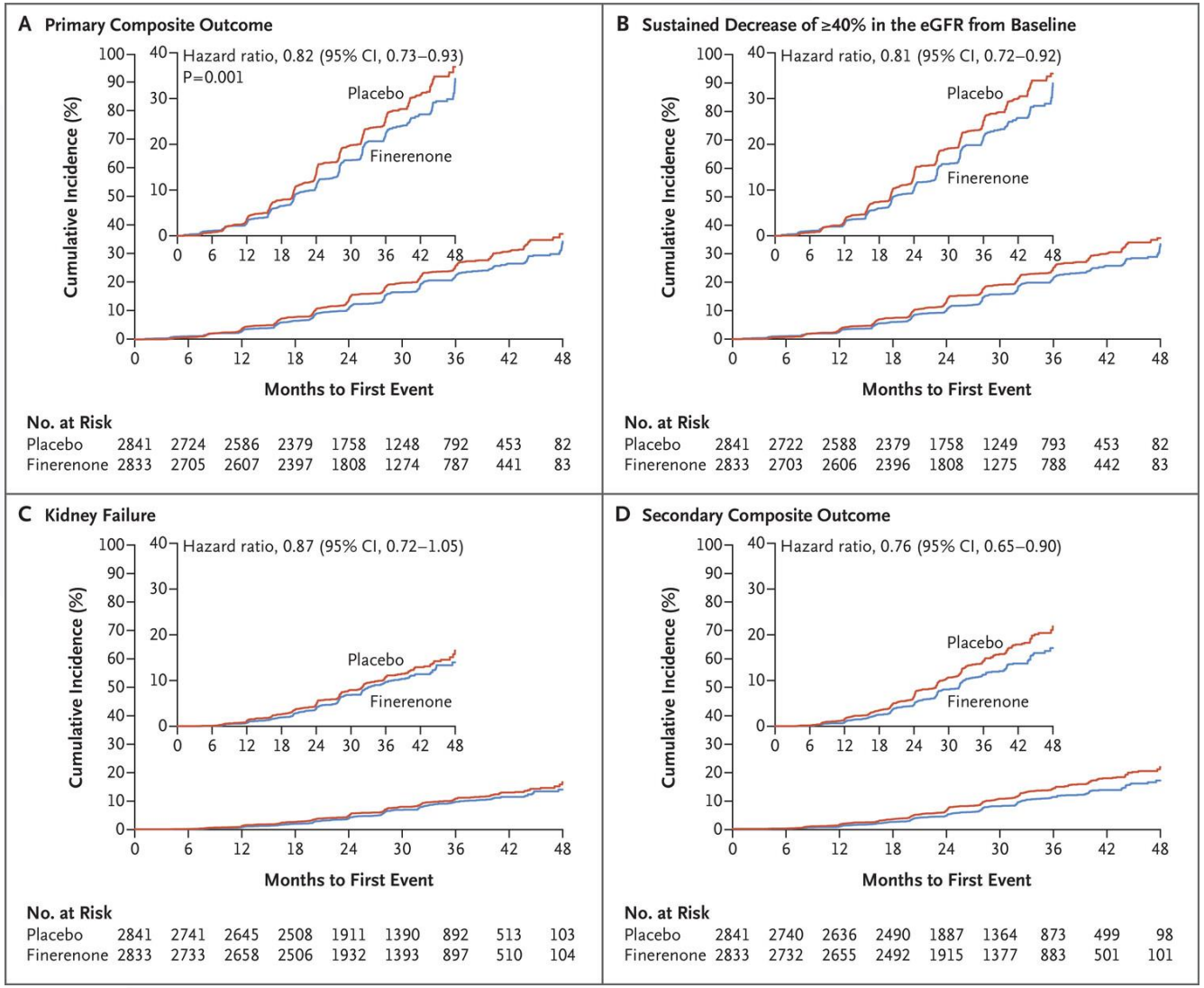
- MOA: decreased inflammation and fibrosis

- Renal benefit:
  - Proteinuria reduction
  - Historically use limited by side effect profile (particularly hyperkalemia)
    - New non steroidal MRAs thought to have less hyperkalemia

Step-wise initiation: MRA

FIDELIO-DKD

Reduction in the primary outcome which was a composite of kidney failure, 40% sustained decrease in eGFR and death from renal cause (HR 0.82, 95% CI 0.72-0.93)



Bakris etal NEJM 2020

Step-wise initiation: MRA

- Practical tips
  - Added with persistent proteinuria despite ACE inhibitor / ARB and SGLT2 inhibitor
  - PBS criteria for NS MRAs in diabetic CKD
    - CKD with T2DM
    - eGFR $\geq$ 25ml/min/1.83m2 & UACR $\geq$ 22.6mg/mmol
    - Already on max tolerated ACEi / ARB & SGLT2i (unless contraindicated)
  - Potassium
    - Do not initiate if potassium > 5
    - Check potassium at 1 month and minimum 4 monthly thereafter
    - K > 5.5, withhold, adjust diet and consider re-trialing if K $\leq$ 5

Step-wise initiation: GLP1-RA (emerging)

- MOA (postulated)
  - Improved glomerular hemodynamics
  - Naturesis
  - Alteration of RAAS
  - Anti-fibrotic benefits
  - Weight loss benefits
- Benefit:
  - Meta-analysis of RCTs in T2DM
    - 14% reduction in MACE (HR 0.86, 95% CI 0.80– 0.93)
    - Reduction in mortality from any cause
    - Reduction in HF hospitalizations
    - Reduction in the renal composite by 21% (HR 0.79, 95% CI (0.73-0.87)
  - Flow Trial (NCT03819153)

Step-wise initiation: GLP1-RA (emerging)

- PBS indication currently for diabetes
- Already in KDIGO 2024 guidelines for T2DM and CKD where indiviuals have not achieved glycemic target despite metformin and SGLT2i
- Should be priorities in patients with CKD and CVD

Case 1: Mr MS

- 52 yo male, with T2DM, new diagnosis of diabetic kidney disease, obesity and HTN.
- Taking: metformin, gliclazide, perindopril (max dose) with UACR 50mg/mmol
- SGLT2 inhibitor added

- 6 months later
  - Review post admission with NSTEMI requiring LAD stent, commenced on DAPT
  - Ongoing obesity – BMI 37
  - HbA1c improved to 8.5%, eGFR 52, Cr 135, K 5.1, UACR 35mg/mmol

  - GLP1 RA is added

When to refer

Statewide Referral Criteria – Found on Health Pathways

- Urgent: ED or call to nephrology registrar
  - Rapid reduction in kidney function
  - Malignant hypertension
  - Nephrotic or nephritic syndrome
  - Acutely unwell renal transplant patients & dialysis patients
- Acute (Category 1)
  - GFR < 30ml/min/1.73m2
  - Accelerated progression of CKD – decrease in GFR of 15ml/min/1.73m2 per year
  - Nephrotic range proteinuria (without nephrotic syndrome)
  - Systemic illness or immunological disease with suspected renal involvement
- Routine:
  - Persistent macroalbuminuria (despite appropriate initiation of treatment of HTN / T2DM)
  - Hematuria with preserved renal function
  - CKD 3a-3b if progressive fall in eGFR
  - Uncontrolled or resistant hypertension (minimum 3 agents with one being HCT)
  - Genetic causes – ADPKD

Where to get more information

- Health Pathways – is a great resource
  - https://melbourne.communityhealthpathways.org/
- Australian Type 2 Diabetes Glycemic Management Algorithm
  - https://www.racgp.org.au/getattachment/2938847a-968c-40bc-b147-df2d651ab508/Australian-type-2-diabetes-management-algorithm.pdf.aspx
- Kidney Health Australia - CKD Management in Primary care
  - https://kidney.org.au/health-professionals/ckd-management-handbook

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Questions

FUTURE HEALTH TODAY
Changing the course of chronic disease

WESTERN HEALTH CHRONIC DISEASE ALLIANCE

Western Health

THE UNIVERSITY OF MELBOURNE

Designed by GPs for GPs

- What does the trial involve?
  - Use of a clinical decision support software and quality improvement software
  - Modules for T2DM, CVD and CKD
    - Non interruptive real time clinical decision support to aid appropriate testing in those at risk, timely diagnosis & evidence-based management
    - Direct links to the clinical guidelines and patient information sheets
    - Ability to audit & recall
  - Seamless integration into Best Practice and Medical Director

If interested please contact: ClinicalSupportFHT@wh.org.au

FUTURE HEALTH TODAY
Changing the course of chronic disease

WESTERN HEALTH CHRONIC DISEASE ALLIANCE

Western Health

THE UNIVERSITY OF MELBOURNE

- What will Western Health provide?
  - Technical education – provided by FHT technical team at Melbourne University
  - Clinical education – tailored to needs and wants of practice
  - Nurse practitioner support
    - Chronic kidney disease
    - Diabetes
- Other potential benefits
  - CPD points through completion of clinical audits
  - Easy identification of MBS item numbers (and recalls) for chronic disease plans

If interested please contact: ClinicalSupportFHT@wh.org.au