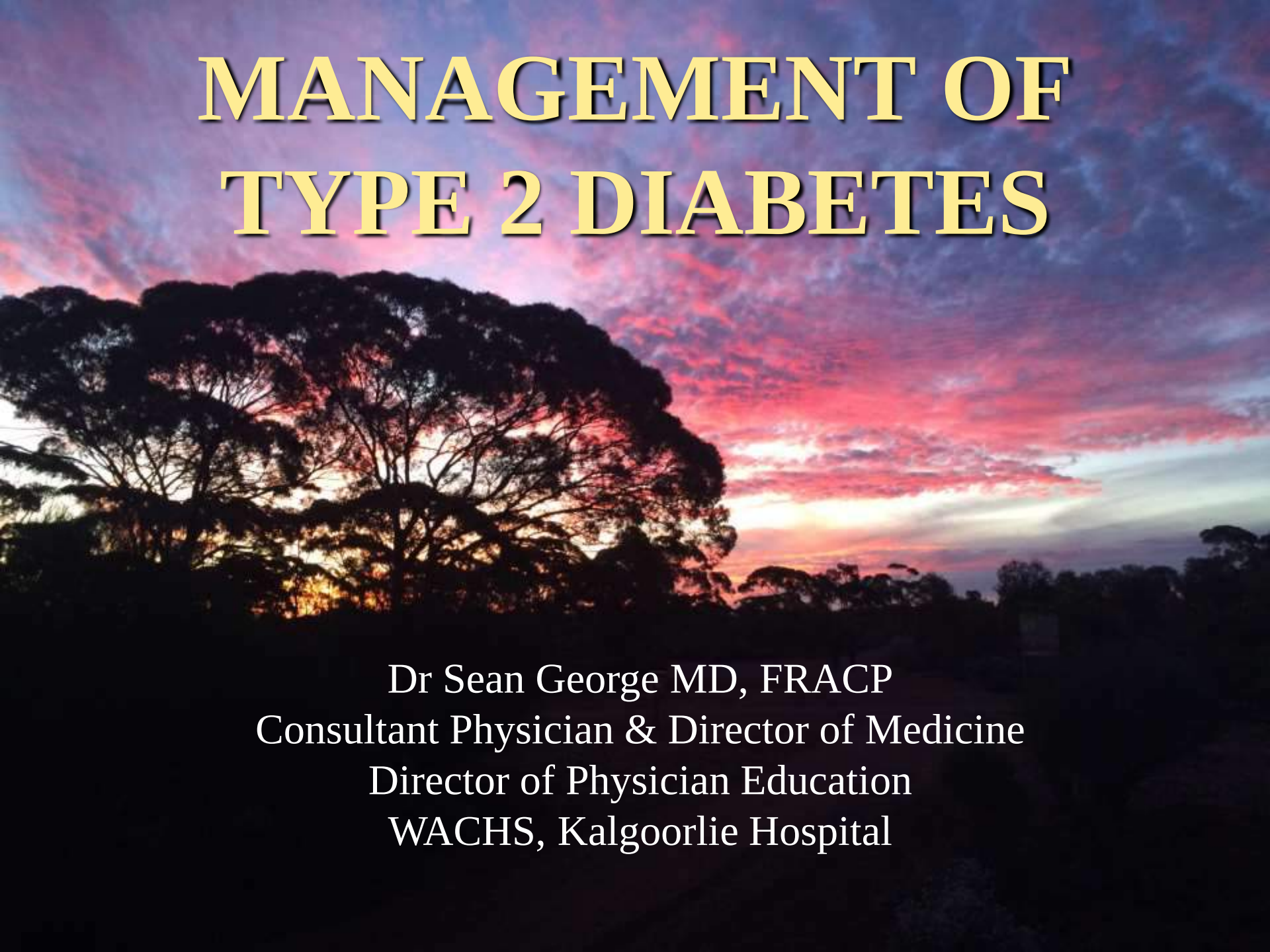
MANAGEMENT OF TYPE 2 DIABETES



Dr Sean George MD, FRACP
Consultant Physician & Director of Medicine
Director of Physician Education
WACHS, Kalgoorlie Hospital

I acknowledge Australia's Aboriginal and Torres Strait Islander peoples as the traditional custodians and first scientists, makers and innovators of this land and their continuing connection to Country. I pay respect to Elders past, present and emerging and extend my respect to all Aboriginal and Torres Strait Islander people attending today.

Disclosures

- I have no funding disclosures or conflict of interest
- A few slides have been obtained from pharmaceutical companies

DEFINITION & STATS

“ A group of metabolic diseases that are characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both”.

- In 2017-18, **one in twenty Australians** (4.9% or 1.2 million people) had diabetes. Since 2001, this rate has increased from 3.3%, however, has remained relatively stable since 2014-15 (5.1%).

- Diabetes continued to be **more common among males than females** (5.5% and 4.3% respectively). The prevalence of diabetes has increased for both males and females since 2001 (both 3.3%).

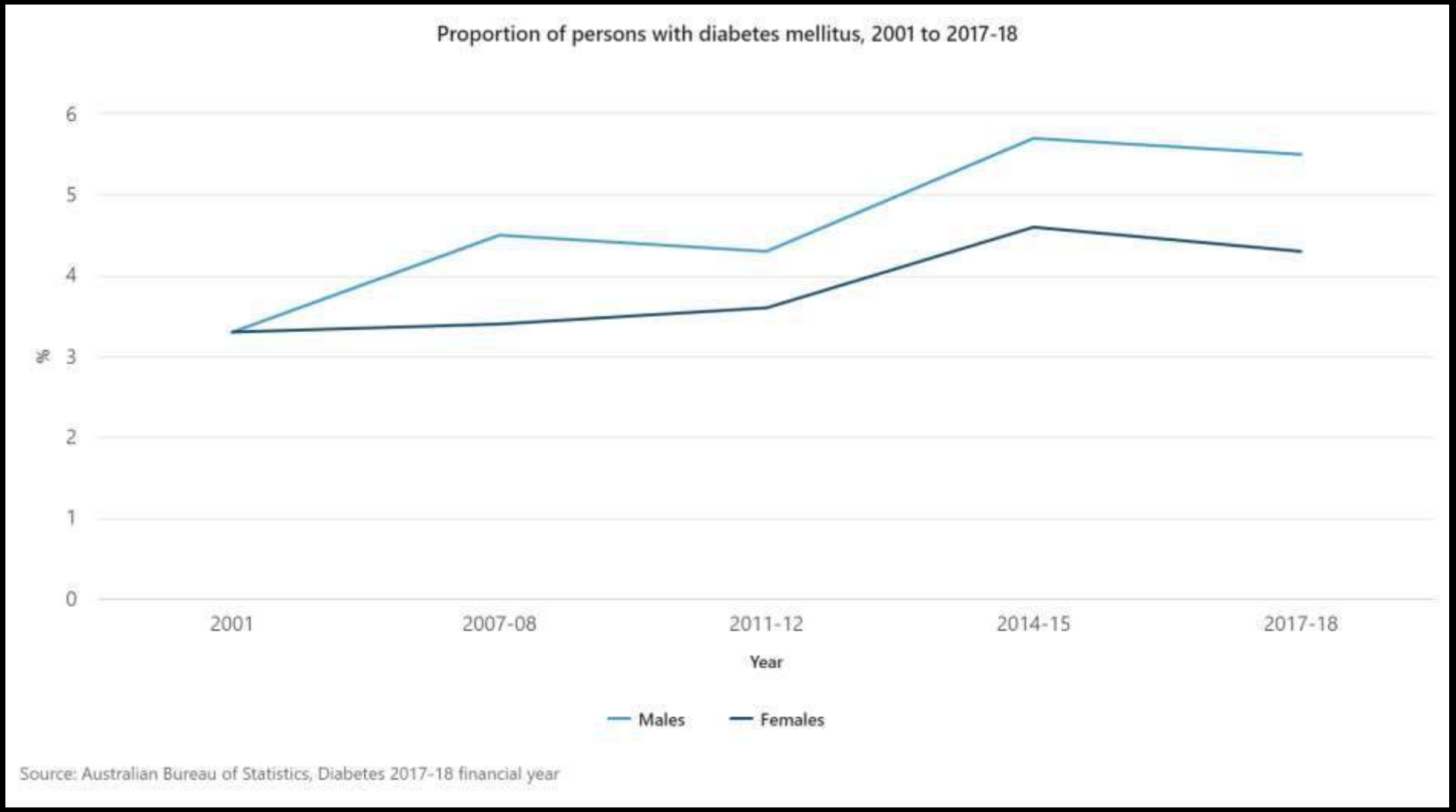
- Diabetes is Australia's **seventh leading cause of death**, accounting for 3% of all deaths in 2016. However, diabetes was mentioned as a contributory factor in 10.4% of all deaths.

- The rate of diabetes amongst adults **aged 65-74 year olds increased** from **12.5% in 2001 to 15.4% in 2017-18**. Meanwhile, of **adults aged 75 years** and over, **almost one in five (18.7%) had diabetes in 2017-18**; which was an increase from 11.2% in 2001.

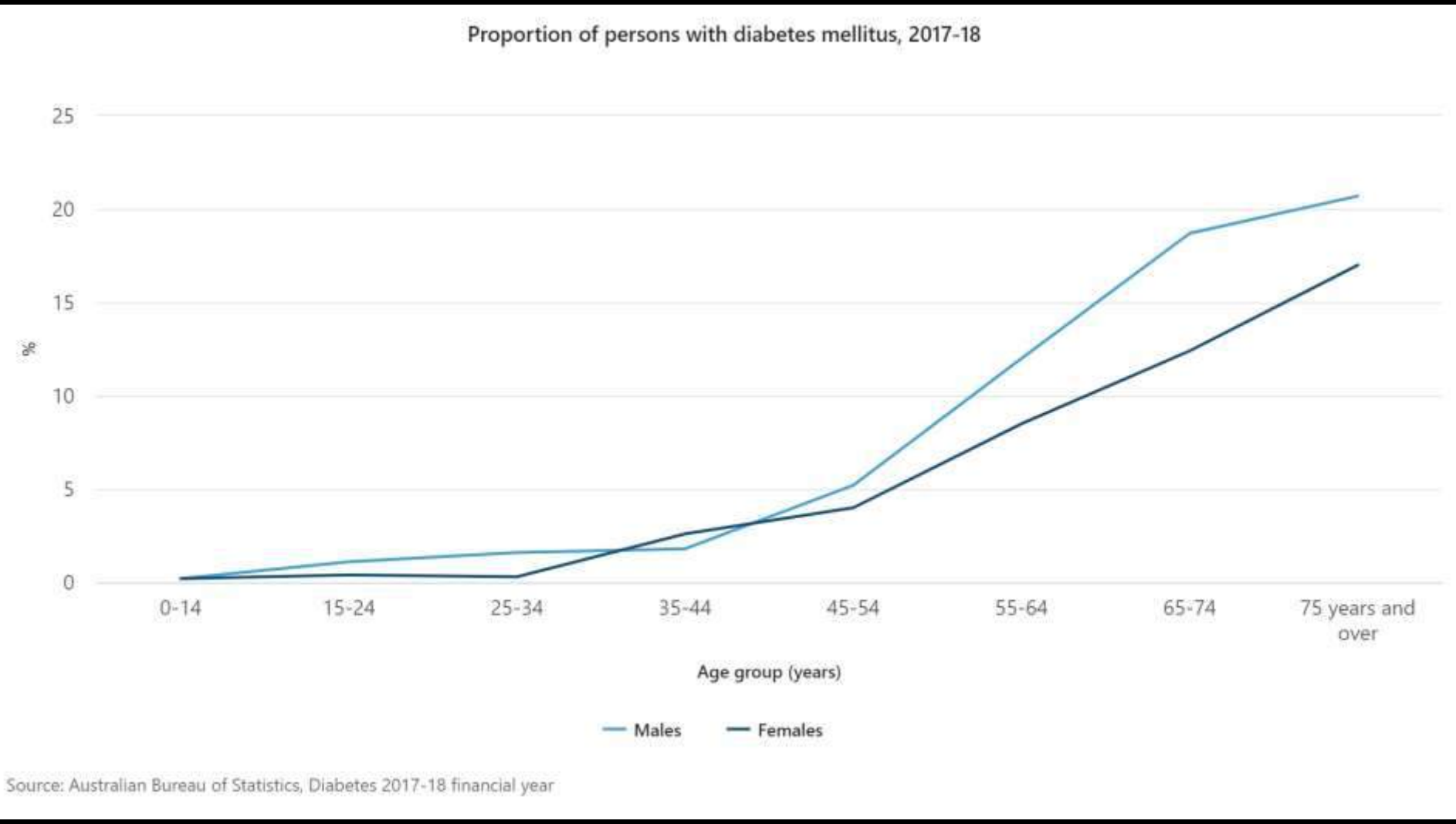
- **Type 2 diabetes was more common than Type 1 diabetes with 4.1% or 1.0 million people having Type 2 diabetes compared with around 145,000 people (0.6%) with Type 1 diabetes in 2017-18**. Over the past decade, the proportion of people with Type 2 diabetes has increased from 3.5% in 2007-08. However, the prevalence has remained relatively stable since 2014-15 (4.4%). In contrast, Type 1 diabetes has remained fairly constant; in 2007-08 the rate was 0.4%.

- In 2017-18, adults aged 18 years and over who were **obese were almost five times** as likely as those who were of normal weight to have Type 2 diabetes (9.8% compared to 2.0%). Similarly, adults who were **overweight were more than twice as likely to have Type 2 diabetes** (4.6% compared to 2.0%) than adults of a normal weight.

https://www.abs.gov.au/statistics/health/health-conditions-and-risks/diabetes/2017-18



Source: Australian Bureau of Statistics, Diabetes 2017-18 financial year



Source: Australian Bureau of Statistics, Diabetes 2017-18 financial year

- **Diabetes was the second leading cause of death for Aboriginal and Torres Strait Islander people in 2018.**

- The proportion of people who reported having diabetes remained steady at **8%, the same as in 2012–13**.

- The proportion of people with diabetes was the same for males and females (both 8%) & **higher for people living in remote areas (12%) than in non-remote areas (7%).**

- The proportion of people with diabetes generally increased with age. **By 55 years and over, 35% of people had diabetes, more than 11 times higher than** the proportion for people aged 25–34 years (3%).

https://www.abs.gov.au/statistics/people/aboriginal-and-torres-strait-islander-peoples/national-aboriginal-and-torres-strait-islander-health-survey/latest-release#diabetes

Results from the 2018-19 National Aboriginal and Torres Strait Islander Health Survey (NATSIHS)

Western Australia

- Compared to 2012-13, around 4 in 10 (44%) Aboriginal and Torres Strait Islander people aged 15+ continued to rate their own health as excellent or very good.
- Around 1 in 3 (36%) young people aged 2-17 were overweight or obese, with similar rates for males and females.
- Hypertension affects **8% of people**, in line with the national average.
- **Diabetes affects 11% of people. This was higher than the national average (8%).**

CLASSIFICATION

- Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance)
- Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
- Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

American Diabetes Association
Diabetes Care 2018 Jan; 41(Supplement 1): S13-S27.https://doi.org/10.2337/dc18-S002

TYPE 2 DIABETES

- Insulin Resistance
- Inadequate insulin secretory response rather than absolute deficiency
- No autoimmune β cell destruction
- Adult Onset Diabetes
- 80-90% obese
- Onset of hyperglycemia and diagnosis of Type 2 DM is 9-12yrs

TYPE 2 DIABETES

- 20% have micro vascular and neuropathic complications at diagnosis
- Usually ketosis resistant
- Genetic component of Insulin resistance
- Prevalence doubles for every 20% increase over desirable body weight and for each decade after the 4^{th}.

MANAGEMENT

- Genetic factors do play a role as diabetics with poor control for 25yrs
  - 20% no retinopathy
  - 80% no nephropathy
  - 35% no neuropathy
- ↑ A1C of 1% conferred an 11% ↑ risk of CAD.
- **1% reduction in the mean A1C levels was associated with reduction in risk of 21%** for any end point related to DM.

TREATMENT

- Nutrition and Physical Activity
- Oral Hypoglycemic Agents
- Insulin
- Surgery
- Management of Complications *

NUTRITION AND PHYSICAL ACTIVITY

- Meta-analysis of 89 studies illustrated that weight loss in Type 2 DM improved A1C by 2.7% *

- Sedentary lifestyle increases the risk for Type 2 DM. Major research trials have found that changing diet and increasing physical activity can reduce this risk as much as 58%.

* Brown S, Upchurch S, Anding R et al: Promoting weight loss in Type 2 diabetes. Diabetes Care 19: 613, 1996

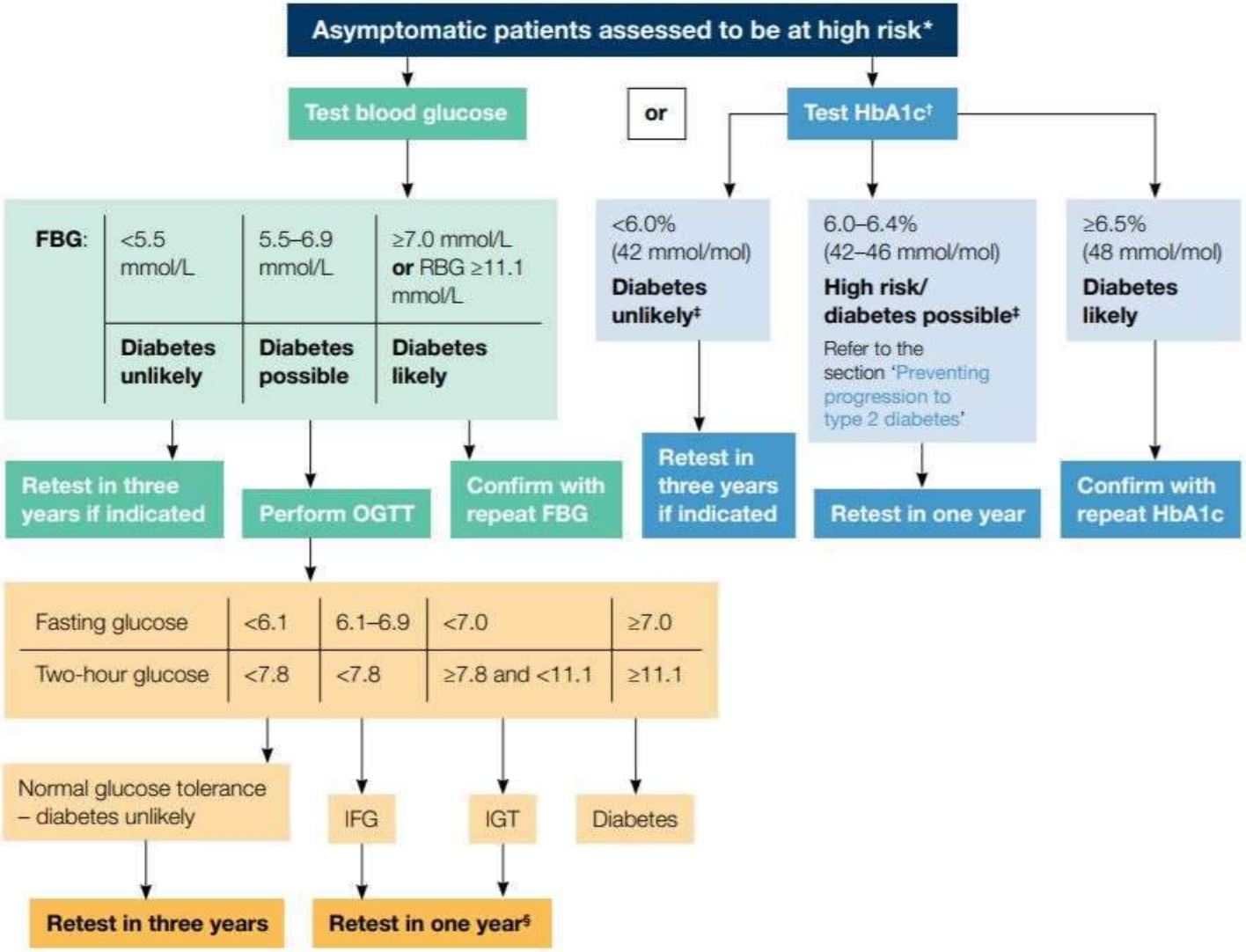
DIET & EXERCISE

- ↓ Calories 250-500 kcal from usual
- Consistent Carbs at meals (60-70%)
- Glycemic index: The *glycemic index* or GI ranks carbohydrates according to their effect on blood glucose levels
  - Low GI foods are foods with a GI less than 55.
  - Intermediate GI foods are foods with a GI between 55 and 70.
  - High GI foods are foods with a GI greater than 70

- Reduce fat 25-35%
- Physical Activity 150-250 min/wk 5 or more days/wk

RACGP Guidelines General practice management of Type 2 diabetes

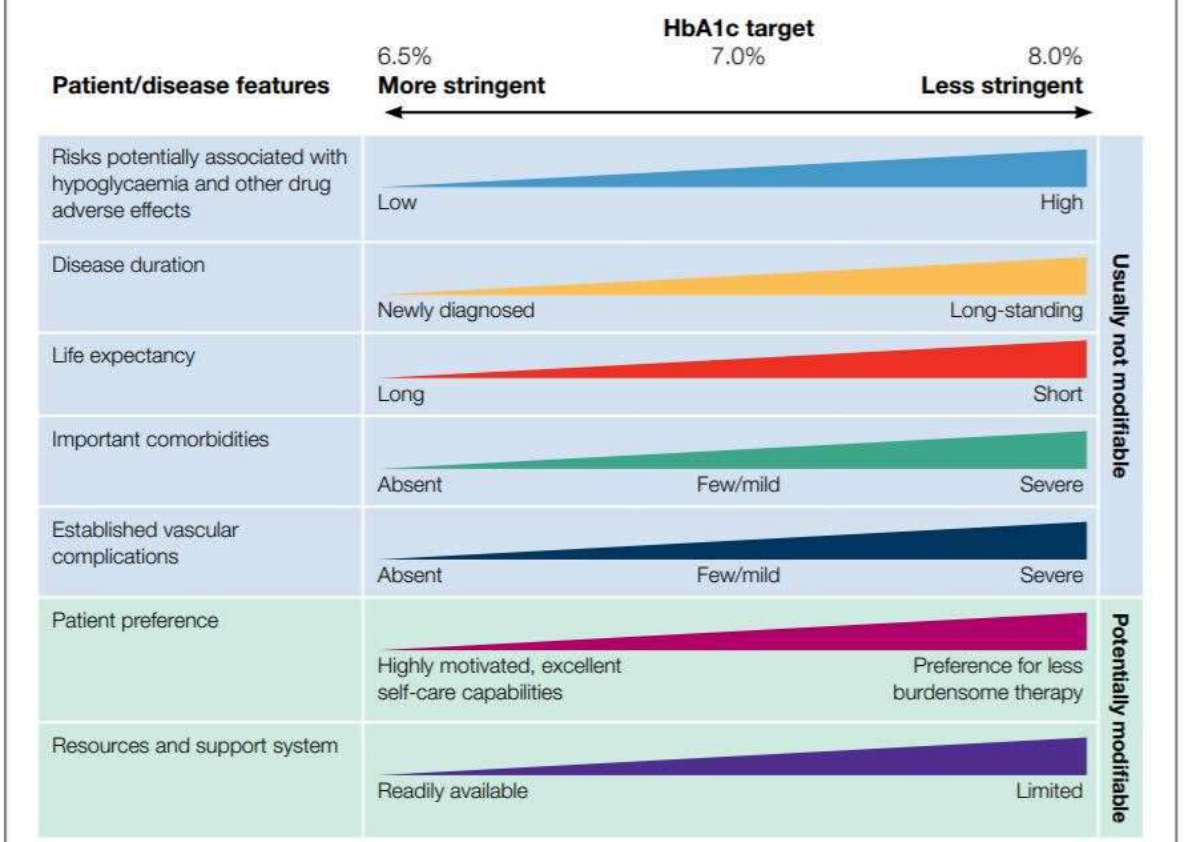
Figure 1. Screening and diagnosing type 2 diabetes in asymptomatic people[1,21–23]



Not all patients are the same

RACGP Guidelines General practice management of Type 2 diabetes

Figure 1. Approach to individualising HbA1c targets



Some important patient characteristics to consider when individualising HbA1c targets are listed on the left. More stringent efforts to lower HbA1c are justified for people who fall to the left of the range; those toward the right may have other priorities and require less stringent efforts.

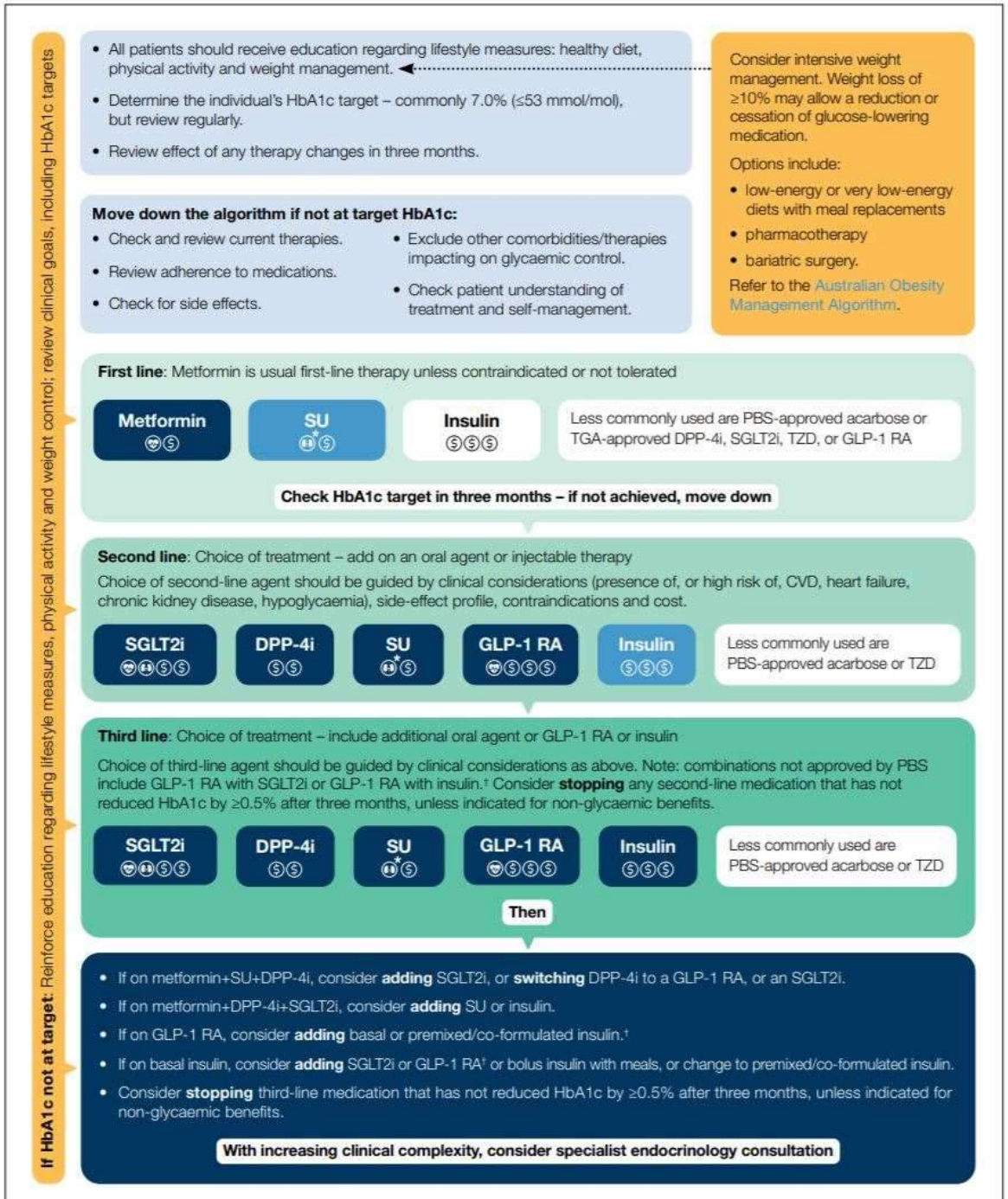
Source: Adapted from Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach: Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38(1):140–49, with permission of the American Diabetes Association.

OHA'S

- Earlier treatment of Type 2 DM – Insulin Deficiency but missed treatment of Insulin Resistance
- OHA is divided into
  - Insulin Secretagogues
  - Non Secretagogues

RACGP Guidelines General practice management of Type 2 diabetes

Figure 1. Australian type 2 diabetes management algorithm



SULFONYLUREA AGENTS

- World War II
- Carbutamide 1955 Germany

First Generation Agents:

- Tolbutamide
- Chlorpropamide
- Acetohexamide

Second Generation Agents:

- Glibenclamide
- Glipizide
- Gliclazide
- Glimiperide

Mechanism of Action:

•Requires a functioning Pancreas

•Side Effects: Prevalence 5%, most common GI and Cutaneous

•Not to be used in patients with Sulpha Allergy

NON SECRETAGOGUES

BIGUANIDES

- Phenformin & Metformin – late 1950s
- More accurately described as antihyperglycemics rather than hypoglycemics
- Doesn’t increase insulin levels but rather improves insulin sensitivity
- Hence useful in insulin resistance
- No weight gain has an anorexic effect and is beneficial in weight loss

- In UKPDS 34 Metformin had a greater benefit in CAD compared to SU's and insulin in a cohort of overweight patients
- A systematic review of 29 trails of Metformin as monotherapy as compared to other OHA's , Insulin, Diet, Placebo found that Metformin in overweight and Obese diabetics resulted in ↓ all cause mortality and ↓ rate of AMI *
- 100% excreted by kidney hence contraindicated in renal failure, creat > 124umol/l

* Cochrane Database Syst Rev 2005

THIAZOLIDINEDIONES

- Troglitazone: 1st to be introduced and taken off the market due to severe hepatic toxicity and failure
- Rosiglitazone and Pioglitazone 1999
- Mechanism of Action:
  - Enhances the effect of insulin in muscle, adipose tissue and liver (Peroxisome Proliferator-Activated Receptor gamma agonist)
  - Known as insulin sensitizers which work by ↓ insulin resistance
  - Circulating insulin must be present for its action

- ↓ BP, ↓ PVR, ↑ HDL, ↓ TG & exerts a beneficial affect on vascular smooth muscle proliferation and ↓ carotid intimal medial thickness

- ↑ plasma volume: contraindicated in heart failure NYHA class III or IV

- Contraindicated in active liver disease or transaminases > 2.5X normal

- Can cause fluid retention and weight gain

- Pioglitazone ↓ TG but Rosiglitazone ↑ HDL & LDL

- The results of a recent placebo-controlled randomized trial involving pioglitazone (PROactive study) with respect to CVS demonstrated that after two years of pioglitazone therapy in high-risk Type 2 pts there was a 16% relative risk reduction in the combined end-point of time to death, MI, and stroke ($p<0.05$).

- Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. Lincoff AM; Wolski K; Nicholls SJ; Nissen SE JAMA. 2007 Sep 12;298(10):1180-8.

  Conclusion: *Pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of patients with diabetes. Serious heart failure is increased by pioglitazone, although without an associated increase in mortality*

- Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. Nissen SE; Wolski K N Engl J Med. 2007 Jun 14;356(24):2457-71. Epub 2007 May 21.

  Conclusion: *Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance*

- RECORD Study: designed to evaluate the effect of rosiglitazone on cardiovascular events and mortality, in Europe and Australia, with 4458 patients.

Cardiovascular endpoints - Summary

- Primary endpoint non-inferiority criterion satisfied:
  - HR 0.99 (0.85- 1.16) for rosiglitazone vs metformin or sulfonylurea in dual combination therapy.
- Secondary endpoints
  - statistically significant increase in heart failure
  - effect on myocardial infarction inconclusive
  - no excess of CV death, all-cause death, stroke
  - Increased fracture risk in women

NEWER THERAPIES

- Glucose Homeostasis is dependent on a complex interplay of multiple hormones: insulin and amylin: Beta cells
- Glucagon: Alpha cells
- Gastrointestinal peptides: Glucagon like peptide-1 & Gastric inhibitory peptide
- Amylin is deficient in Type 1 and relatively in Insulin requiring Type 2

GLP-1 THERAPIES

- Incretin Effect: oral glucose has a greater stimulatory effect on insluin secretion than IV glucose. This effect is mediated by GLP-1
- GLP-1 is produced from proglucagon gene in L-cells of the small intestine and is secreted in response to nutrients.
- GLP-1 levels are ↓ in Type 2 DM.
- Mechanism:
  - Its main effect is by stimulating glucose dependent insulin release from the pancreatic islets.
  - Slow gastric emptying
  - ↓inappropriate postmeal glucagon release
  - Reduce food intake
  - Animal models GLP-1 stimulates beta-cell proliferation, preventing diabetes.
- Short half life due to degradation by enzyme dipeptidyl peptidase IV (DDP-IV)

EXENATIDE
BYETTA

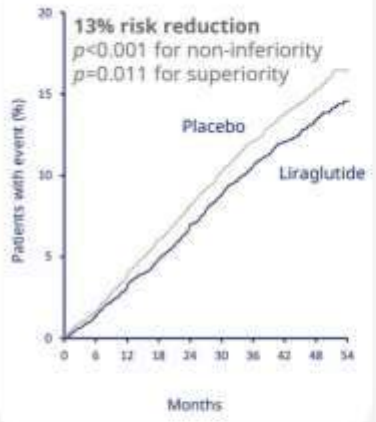
- Exendin-4 is a naturally occuring component of the Gila monster saliva which is very similar to GLP-1
- It is resistant to DPP-IV degradation so has a long half life.
- Exenatide is a synthetic exendin-4 and the first GLP-1 based therapy approved by US FDA for Type 2 DM. Available on PBS as Byetta.
- Shown to promote beta cell regeneration and differentiation in prediabetic and diabetic rats

- HBA1c: reduction by 0.8-1.1%
- Weight Loss was sustained at 30 weeks
- Nausea and Vomiting
- 36 postmarketing reports of Acute Pancreatitis about 1 in 3000 and necrotizing pancreatitis 1 in 10000.
- 78 cases of ARF but most patients on ACE and diuretics
- Dose: 5-10mcg sc twice daily
- Long Acting GLP-1 Agonists:
  - Semaglutide- OZEMPIC
  - Dulaglutide- TRULICITY once weekly
  - Liraglutide once daily sc

GLP-1 RA cardiovascular outcome trials

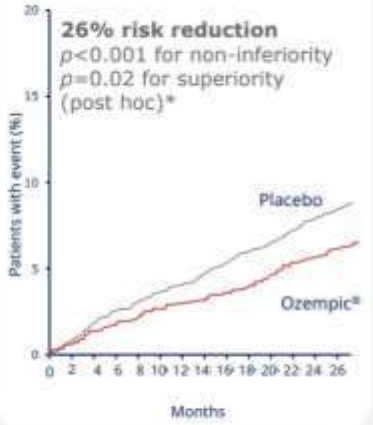
LEADER[1]

Liraglutide (Victoza®) vs placebo
for time to CV death, non-fatal MI and non-fatal stroke



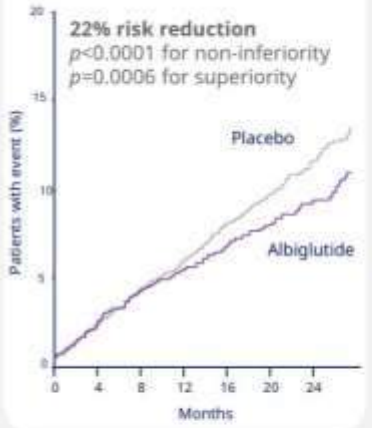
SUSTAIN 6[2]

Ozempic® (semaglutide) vs placebo*
for time to CV death, non-fatal MI and non-fatal stroke



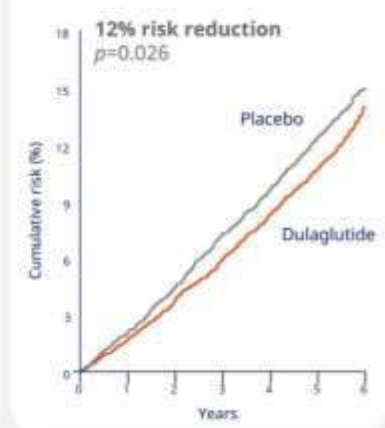
HARMONY Outcomes[3]

Albiglutide vs placebo
for time to CV death, non-fatal MI and non-fatal stroke



REWIND[4]

Dulaglutide vs placebo
for time to CV death, non-fatal MI and non-fatal stroke



*Not pre-specified.
Albiglutide was withdrawn from the worldwide market in July 2018. Ozempic® is not indicated for the prevention of CV events.

CV, cardiovascular; GLP-1 RA, glucagon-like peptide 1 receptor agonist; MI, myocardial infarction.

1. Marso SP *et al. N Engl J Med* 2016;375:311–22. 2. Marso SP *et al. N Engl J Med* 2016;375:1834–44. 3. Hernandez AF *et al. Lancet* 2018;392:1519–29. 4. Gerstein HC *et al. Lancet* 2019; S0140-6736:31149-31153.

DPP-IV inhibitors

- Enzyme expressed on the surface of most cell types that deactivates GIP and GLP-1
- Oral administration
- HBA1c: reduction of 0.6%
- Sitagliptin (Januvia) 100mg once daily and 50mg once daily for GFR<30 to 50ml/min and 25mg for severe renal insufficiency
- Vildagliptin 50mg to 100mg daily (Galvus)
- Saxagliptin 2.5 to 5mg once daily (Onglyza)
- Linagliptin 5mg daily (renal safety) (Trajenta)
- Alogliptin 25mg/day (Nisena)

Side Effects:

- Small increased risk of Nasopharyngitis (RR 1.2 95% CI 1.0-1.4)
- Urinary Tract Infection (RR 1.5, 95% CI 1.0-2.2)
- Headache (RR 1.4, 95% CI 1.1-1.7)
- 88 postmarketing reports of acute pancreatitis
- Vildagliptin: Hepatic dysfunction
- Serious skin reactions with Vildagliptin and Saxagliptin have been seen with higher doses
- Sitagliptin: Anaphylaxis, Angioedema, Steven Johnson Syndrome

SGLT2 INHIBITION-GLIFLOZINS

DAPAGLIPFLOZIN (FORXIGA) & CANAGLIFLOZIN (INVOKANA), EMPAGLIFLOZIN (JARDIANCE)

- Majority of the glucose is reabsorbed into the blood stream in the PT by SGLT2 and SGLT1 molecules
- SGLT2 inhibitors block the reabsorption of glucose in the kidney, increase glucose excretion, and lower blood glucose levels

SGLT2 INHIBITORS

- Dapa: 5 & 10mg
- Cana: 100 & 300mg
- Empa: 10 & 25mg
- Ertugliflozin: 5 & 15 mg

ADVERSE EFFECTS & WARNINGS:

- DKA post surgery, Low Carb Diet, Excess alcohol
- ↑ Risk of Toe Amputation (CANVAS)
- Possible ↑ risk of fractures (CANVAS)
- **Female & Male genital mycotic Infections, UTI**
- Volume depletion, Hypersensitivity
- Photosensitivity
- Fournier's Gangrene

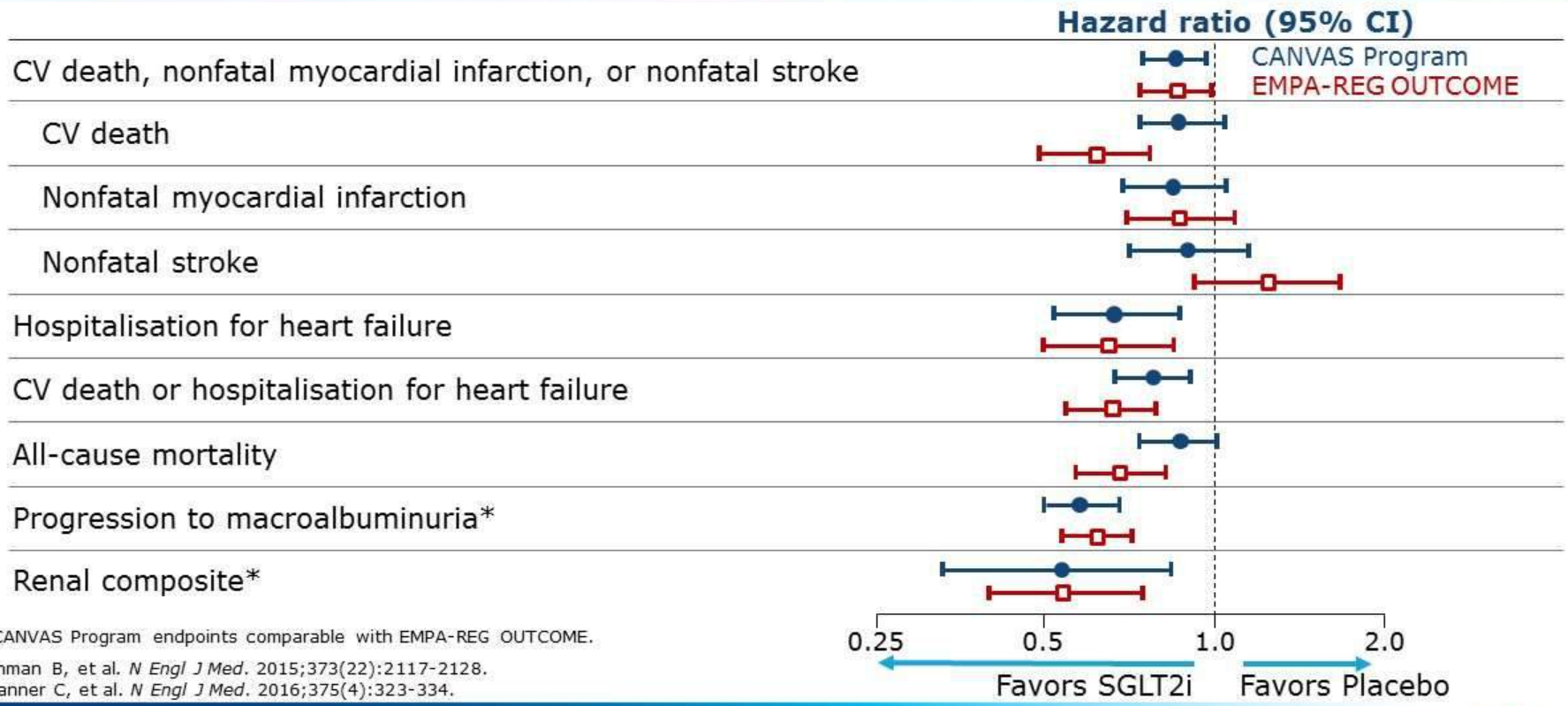
EMPA-REG OUTCOME

- **38% reduction in CV death, 32% reduction in all-cause mortality**

- Empagliflozin prevented more than one-third of CV deaths, with a 38% relative reduction. A total of 3.7% of empagliflozin-treated subjects experienced CV death vs 5.9% for placebo: HR=0.62 (95% CI: 0.49, 0.77); $P<0.001$.
- Additionally, empagliflozin significantly reduced all-cause mortality by 32%, with an occurrence of 5.7% vs 8.3% with placebo: HR=0.68 (95% CI: 0.57-0.82); $P<0.001$. CV mortality was a component of the primary endpoint, which also included nonfatal myocardial infarction and nonfatal stroke

CANVAS VRS EMPA-REG

Key Outcomes in the CANVAS Program and EMPA-REG OUTCOME



*CANVAS Program endpoints comparable with EMPA-REG OUTCOME.

Zinman B, et al. *N Engl J Med*. 2015;373(22):2117-2128.
Wanner C, et al. *N Engl J Med*. 2016;375(4):323-334.

Presented at the 53rd Annual Meeting of the European Association for the Study of Diabetes; 15 September 2017; Lisbon, Portugal.

CANVAS Program

DECLARE TIMI 58

FARXIGA Achieved a Positive Result in the Phase III DECLARE-TIMI 58 Trial, a Large Cardiovascular Outcomes Trial in 17,000 Patients with Type 2 Diabetes

FARXIGA met the primary composite endpoint of a statistically-significant reduction in hospitalization for heart failure or CV death in a broad patient population

Results confirmed the well-established safety profile of FARXIGA

September 24, 2018 07:00 AM Eastern Daylight Time

WILMINGTON, Del.--(BUSINESS WIRE)--AstraZeneca today announced positive results from the Phase III DECLARE-TIMI 58 cardiovascular (CV) outcomes trial (CVOT) for FARXIGA® (dapagliflozin), the broadest SGLT-2 inhibitor CVOT conducted to date. The trial evaluated the CV outcomes of FARXIGA vs. placebo over a period of up to five years, across 33 countries and in more than 17,000 adults with type 2 diabetes (T2D) who have multiple CV risk factors or established CV disease.

"Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes – Mechanisms, Management, and Clinical Considerations."

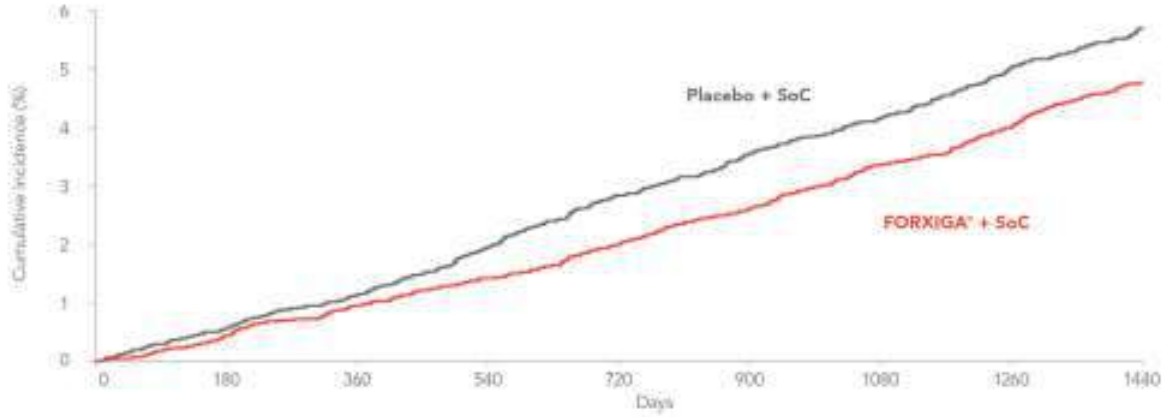
Tweet this

In the DECLARE (Dapagliflozin Effect on Cardiovascular Events)-TIMI 58 trial, FARXIGA met its primary safety endpoint of non-inferiority for major adverse cardiovascular events (MACE). FARXIGA achieved a statistically-significant reduction in the composite endpoint of hospitalization for heart failure (hHF) or CV death, one of the two primary efficacy endpoints. Additionally, fewer MACE events were observed with FARXIGA for the other primary efficacy endpoint, however, this did not reach statistical significance. FARXIGA is not indicated to reduce the risk of CV events or hHF.

Patients with T2D and established CVD or risk factors for CVD*

DECLARE primary composite outcome: CV death and hospitalisation for HF[1,2†]

†FORXIGA® is not indicated for CV death.



No. at Risk									
Placebo + SoC	8578	8485	8387	8259	8127	8003	7880	7367	5362
FORXIGA® + SoC	8582	8517	8415	8322	8224	8110	7970	7497	5445

Adapted from Wiviott et al. 2019.[1]

17% RRR

(0.9% ARR)‡

(HR 0.83; 95% CI: 0.73, 0.95; P=0.005)
‡Due to a lower rate of hHF in the FORXIGA® group (HR 0.73; 95% CI: 0.61, 0.88)

FORXIGA® significantly reduced the risk of CV death and hospitalisation for HF vs placebo[1,2]

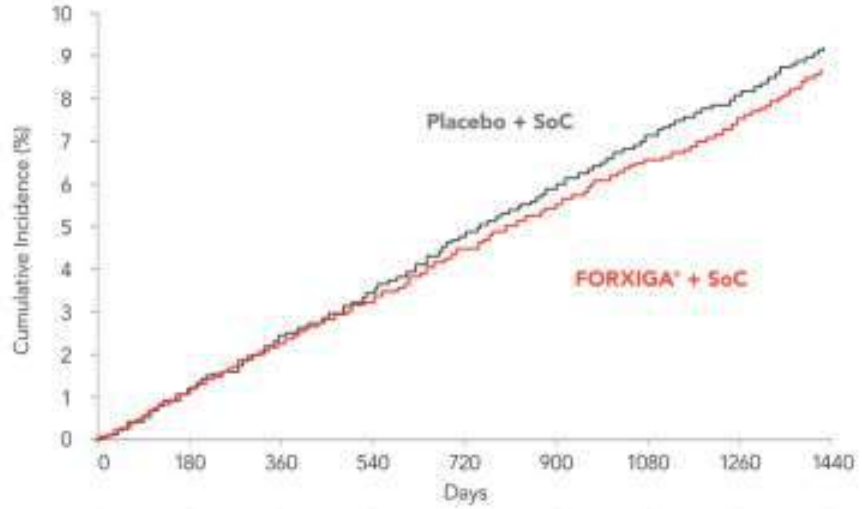
*In the DECLARE study, risk factors for cardiovascular disease included: age ≥55 years in men or ≥60 years in women and one or more of dyslipidaemia, hypertension or current tobacco use, without having had a CV event at baseline.
ARR=absolute risk reduction; CV=cardiovascular; CVD=cardiovascular disease; HF=heart failure; RRR=relative risk reduction; SoC=standard of care; T2D=type 2 diabetes.
References: 1. Wiviott SD et al. *N Engl J Med* 2019; 380:347–357. **2.** FORXIGA® Approved Product Information.

forxiga
(dapagliflozin)

Patients with T2D and established CVD or risk factors for CVD*

DECLARE primary composite outcome: MACE[1,2†]

†Because FORXIGA® resulted in a significantly lower rate of CV death and hospitalization for HF than placebo but did not result in a significantly lower rate of MACE, analyses of additional outcomes are hypothesis-generating.[1]



No. at Risk									
Placebo + SoC	8578	8433	8281	8129	7969	7805	7649	7137	5158
FORXIGA* + SoC	8582	8466	8303	8166	8017	7873	7708	7237	5225

7% RRR

(0.6% ARR)

(HR 0.93; 95% CI: 0.84, 1.03; P=0.17 [not significant])

Adapted from Wiviott et al 2019[1]

*In the DECLARE study, risk factors for cardiovascular disease included: age ≥55 years in men or ≥60 years in women and one or more of dyslipidaemia, hypertension or current tobacco use, without having had a CV event at baseline.[1]

ARR=absolute risk reduction; CV=cardiovascular; CVD=cardiovascular disease; HF=heart failure; MACE=major adverse cardiovascular events; RRR=relative risk reduction; SoC=standard of care; T2D=type 2 diabetes

References: 1. Wiviott SD et al. *N Engl J Med* 2019; 380:347–357. **2.** FORXIGA® Approved Product Information.

forxiga
(dapagliflozin)

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

John J.V. McMurray, M.D., Scott D. Solomon, M.D., Silvio E. Inzucchi, M.D., Lars Køber, M.D., D.M.Sc., Mikhail N. Kosiborod, M.D., Felipe A. Martinez, M.D., Piotr Ponikowski, M.D., Ph.D., Marc S. Sabatine, M.D., M.P.H., Inder S. Anand, M.D., Jan Bělohlávek, M.D., Ph.D., Michael Böhm, M.D., Ph.D., Chern-En Chiang, M.D., Ph.D., et al., for the DAPA-HF Trial Committees and Investigators*

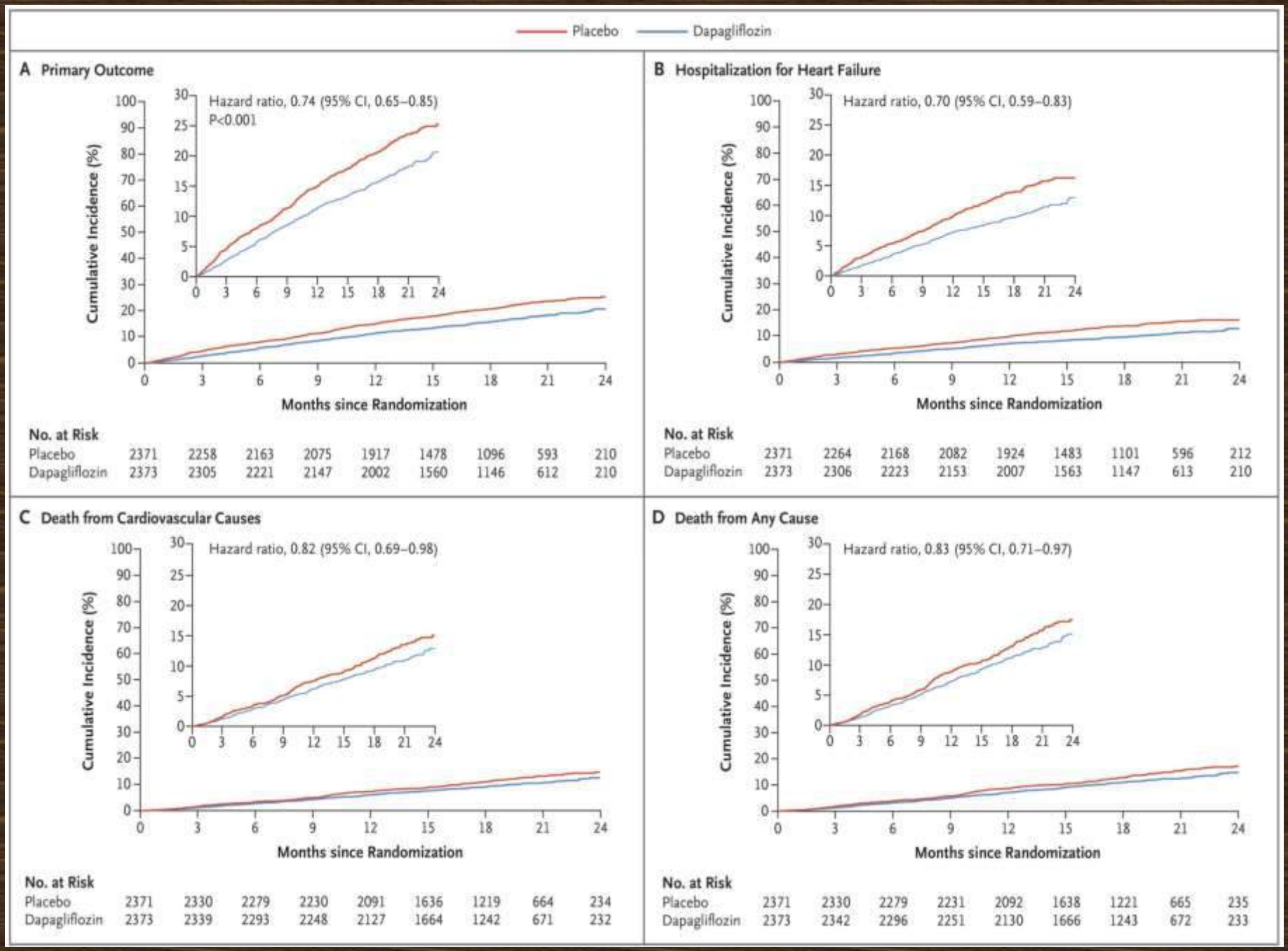
November 21, 2019 N Engl J Med 2019; 381:1995-2008
DOI: 10.1056/NEJMoa1911303

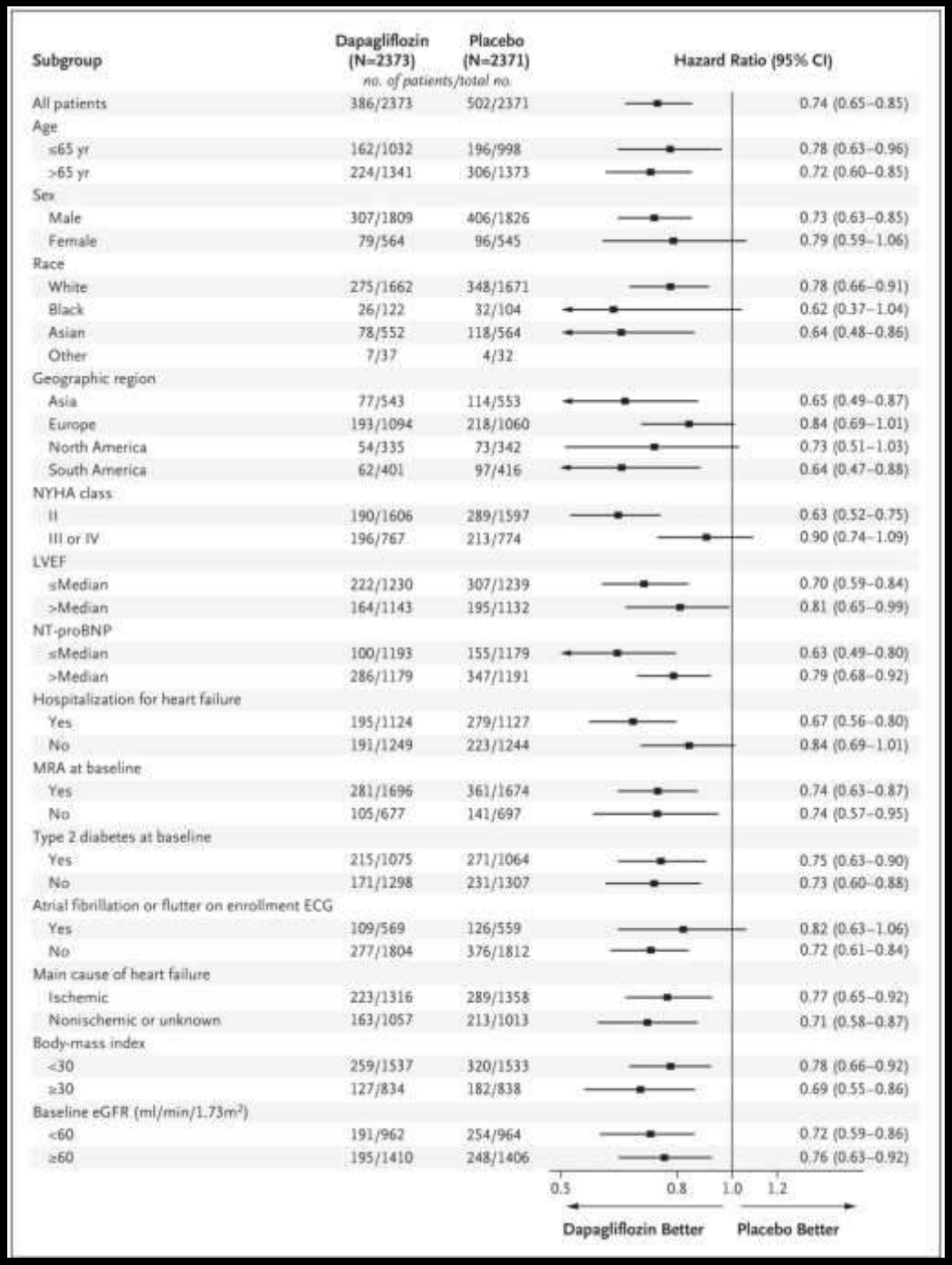
BACKGROUND

In patients with type 2 diabetes, inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of a first hospitalization for heart failure, possibly through glucose-independent mechanisms. More data are needed regarding the effects of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction, regardless of the presence or absence of type 2 diabetes.

METHODS

In this phase 3, placebo-controlled trial, we randomly assigned 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.


Placebo
Dapagliflozin
A Primary Outcome
Hazard ratio, 0.74 (95% CI, 0.65–0.85)
P<0.001
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2258 2163 2075 1917 1478 1096 593 210
Dapagliflozin 2373 2305 2221 2147 2002 1560 1146 612 210
B Hospitalization for Heart Failure
Hazard ratio, 0.70 (95% CI, 0.59–0.83)
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2264 2168 2082 1924 1483 1101 596 212
Dapagliflozin 2373 2306 2223 2153 2007 1563 1147 613 210
C Death from Cardiovascular Causes
Hazard ratio, 0.82 (95% CI, 0.69–0.98)
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2330 2279 2230 2091 1636 1219 664 234
Dapagliflozin 2373 2339 2293 2248 2127 1664 1242 671 232
D Death from Any Cause
Hazard ratio, 0.83 (95% CI, 0.71–0.97)
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2330 2279 2231 2092 1638 1221 665 235
Dapagliflozin 2373 2342 2296 2251 2130 1666 1243 672 233


Subgroup
Dapagliflozin (N=2373)
Placebo (N=2371)
no. of patients/total no.
Hazard Ratio (95% CI)
All patients 386/2373 502/2371 0.74 (0.65–0.85)
Age
≤65 yr 162/1032 196/998 0.78 (0.63–0.96)
>65 yr 224/1341 306/1373 0.72 (0.60–0.85)
Sex
Male 307/1809 406/1826 0.73 (0.63–0.85)
Female 79/564 96/545 0.79 (0.59–1.06)
Race
White 275/1662 348/1671 0.78 (0.66–0.91)
Black 26/122 32/104 0.62 (0.37–1.04)
Asian 78/552 118/564 0.64 (0.48–0.86)
Other 7/37 4/32
Geographic region
Asia 77/543 114/553 0.65 (0.49–0.87)
Europe 193/1094 218/1060 0.84 (0.69–1.01)
North America 54/335 73/342 0.73 (0.51–1.03)
South America 62/401 97/416 0.64 (0.47–0.88)
NYHA class
II 190/1606 289/1597 0.63 (0.52–0.75)
III or IV 196/767 213/774 0.90 (0.74–1.09)
LVEF
≤Median 222/1230 307/1239 0.70 (0.59–0.84)
>Median 164/1143 195/1132 0.81 (0.65–0.99)
NT-proBNP
≤Median 100/1193 155/1179 0.63 (0.49–0.80)
>Median 286/1179 347/1191 0.79 (0.68–0.92)
Hospitalization for heart failure
Yes 195/1124 279/1127 0.67 (0.56–0.80)
No 191/1249 223/1244 0.84 (0.69–1.01)
MRA at baseline
Yes 281/1696 361/1674 0.74 (0.63–0.87)
No 105/677 141/697 0.74 (0.57–0.95)
Type 2 diabetes at baseline
Yes 215/1075 271/1064 0.75 (0.63–0.90)
No 171/1298 231/1307 0.73 (0.60–0.88)
Atrial fibrillation or flutter on enrollment ECG
Yes 109/569 126/559 0.82 (0.63–1.06)
No 277/1804 376/1812 0.72 (0.61–0.84)
Main cause of heart failure
Ischemic 223/1316 289/1358 0.77 (0.65–0.92)
Nonischemic or unknown 163/1057 213/1013 0.71 (0.58–0.87)
Body-mass index
<30 259/1537 320/1533 0.78 (0.66–0.92)
≥30 127/834 182/838 0.69 (0.55–0.86)
Baseline eGFR (ml/min/1.73m²)
<60 191/962 254/964 0.72 (0.59–0.86)
≥60 195/1410 248/1406 0.76 (0.63–0.92)
0.5
0.8
1.0
1.2
Dapagliflozin Better
Placebo Better

CONCLUSIONS

Among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes.

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., et al., for the DAPA-CKD Trial Committees and Investigators*

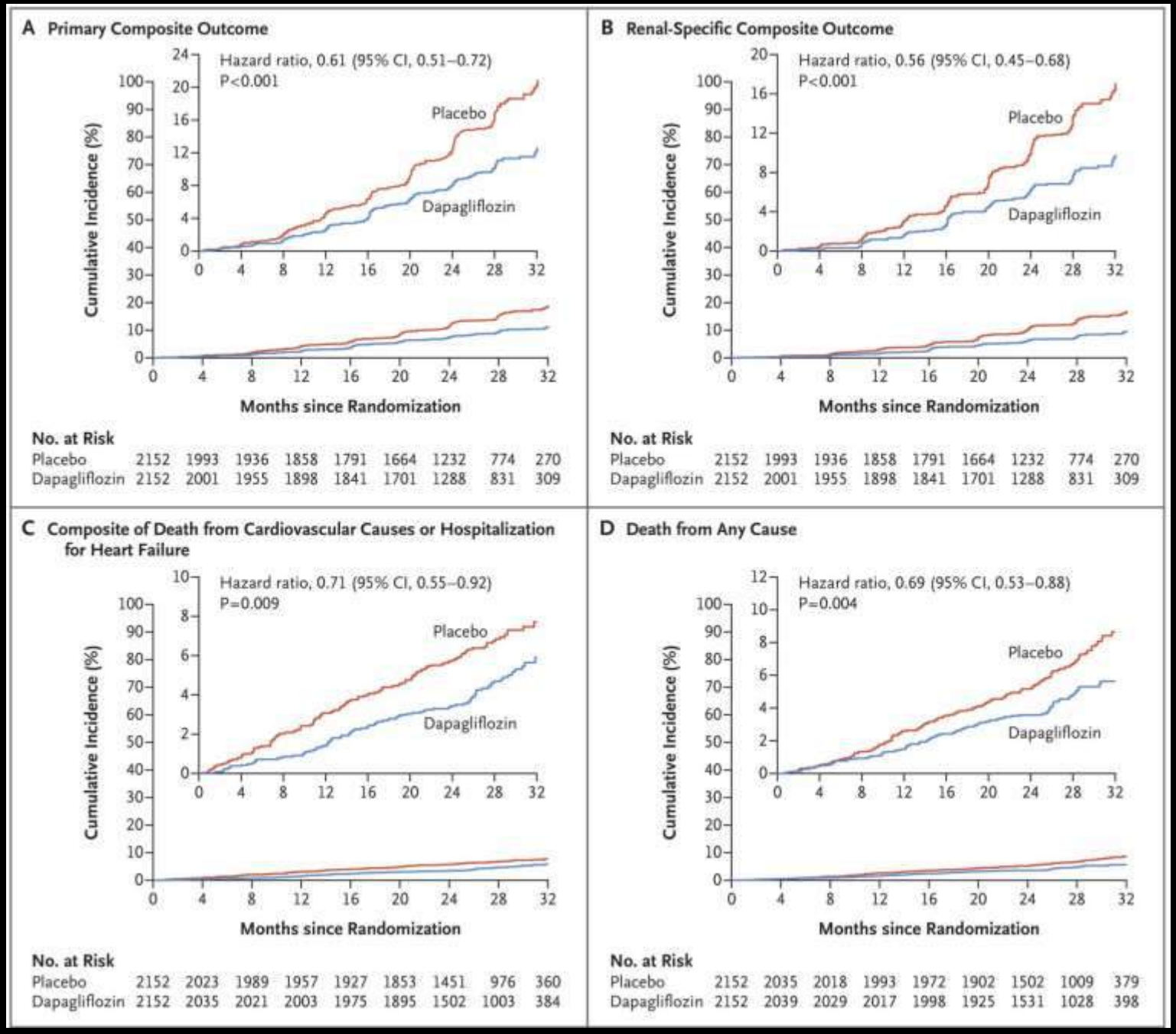
October 8, 2020 N Engl J Med 2020; 383:1436-1446
DOI: 10.1056/NEJMoa2024816

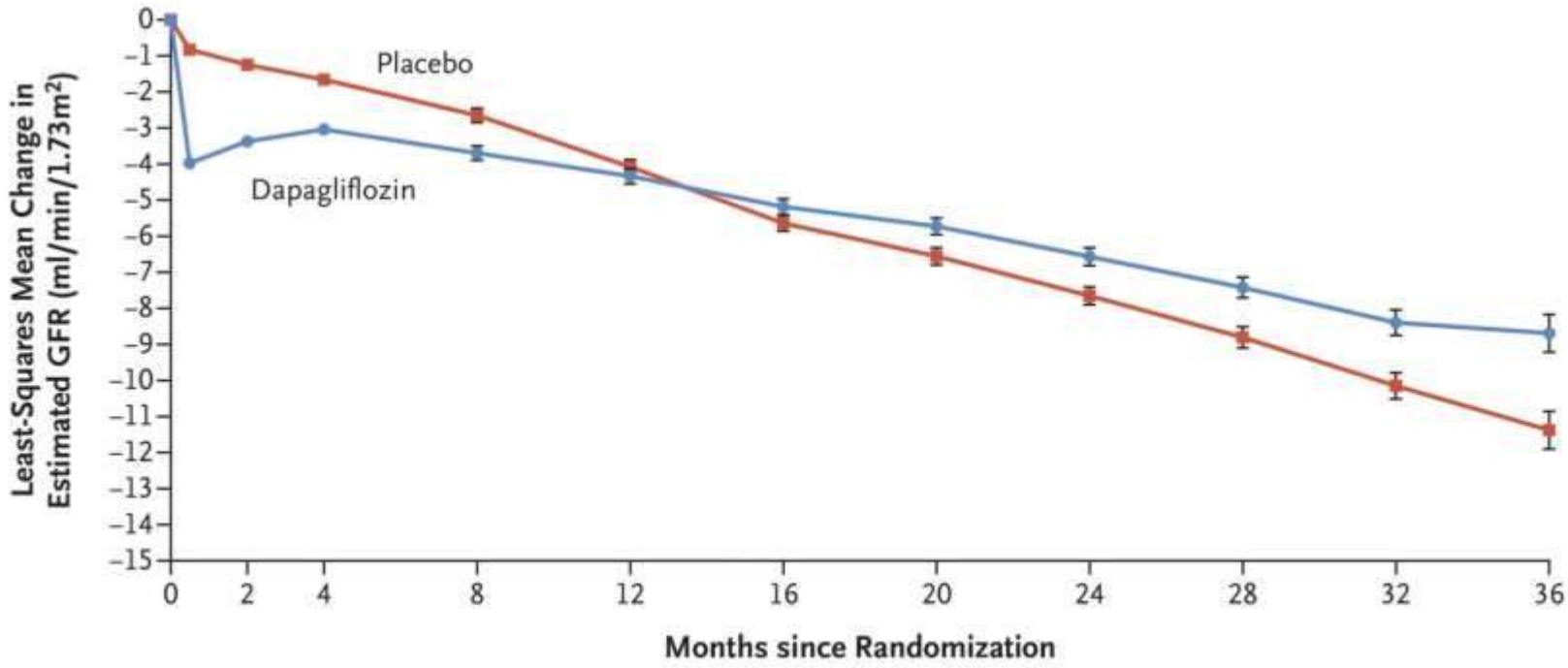
BACKGROUND

Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

METHODS

We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.


A Primary Composite Outcome
Hazard ratio, 0.61 (95% CI, 0.51–0.72)
P<0.001
Placebo
Dapagliflozin
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2152 1993 1936 1858 1791 1664 1232 774 270
Dapagliflozin 2152 2001 1955 1898 1841 1701 1288 831 309
B Renal-Specific Composite Outcome
Hazard ratio, 0.56 (95% CI, 0.45–0.68)
P<0.001
Placebo
Dapagliflozin
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2152 1993 1936 1858 1791 1664 1232 774 270
Dapagliflozin 2152 2001 1955 1898 1841 1701 1288 831 309
C Composite of Death from Cardiovascular Causes or Hospitalization for Heart Failure
Hazard ratio, 0.71 (95% CI, 0.55–0.92)
P=0.009
Placebo
Dapagliflozin
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2152 2023 1989 1957 1927 1853 1451 976 360
Dapagliflozin 2152 2035 2021 2003 1975 1895 1502 1003 384
D Death from Any Cause
Hazard ratio, 0.69 (95% CI, 0.53–0.88)
P=0.004
Placebo
Dapagliflozin
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2152 2035 2018 1993 1972 1902 1502 1009 379
Dapagliflozin 2152 2039 2029 2017 1998 1925 1531 1028 398



No. of Participants

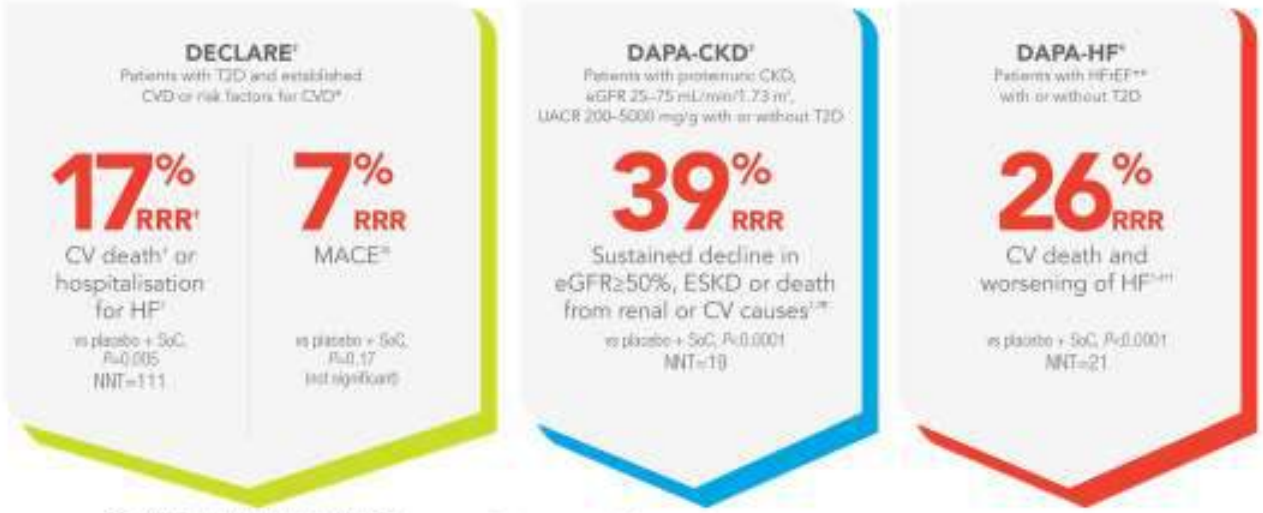
Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157
Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157

CONCLUSIONS

Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo.

Primary efficacy outcomes across trials[1–4]

Outcome overview



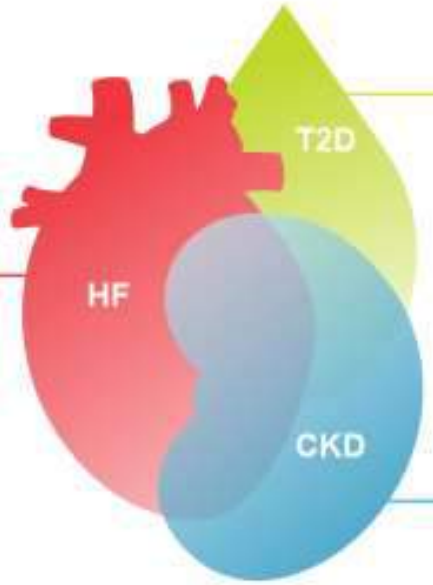
‡FORXIGA® is not indicated for CV death

FORXIGA®. Proven cardiovascular and renal PROTECTION across three landmark trials[1–4]

*In the DECLARE study, risk factors for cardiovascular disease included: age ≥55 years in men or ≥60 years in women and one or more of dyslipidaemia, hypertension or current tobacco use without having had a CV event at baseline.[1] †Due to a lower rate of hHF in the FORXIGA® group (HR 0.73, 95% CI: 0.61, 0.88).[1] §MACE was defined as cardiovascular death, myocardial infarction, or ischaemic stroke.[1] ¶ESKD defined as the need for maintenance dialysis (peritoneal or haemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15 mL/min/1.73 m² for at least 28 days.[2] **HFrEF defined as NYHA class II–IV HF and ejection fraction of ≤40%.[3] ††Worsening HF is defined as hHF or urgent HF visit requiring initiation or intensification of treatment specifically for HF.[3]
CKD=chronic kidney disease, CV=cardiovascular, CVD=cardiovascular disease, eGFR=estimated glomerular filtration rate, ESKD=end-stage kidney disease, HF=heart failure, hHF=hospitalisation for heart failure, MACE=major adverse cardiovascular events, NYHA=New York Heart Association, RRR=relative risk reduction, SoC=standard of care, T2D=type 2 diabetes. **References:** 1. FORXIGA® Approved Product Information. 2. Wiviott SD *et al. N Engl J Med* 2019; 380:347–357. 3. Havranek HJL *et al. N Engl J Med* 2020; 383(15):1436–1446. 4. McMurray JJV *et al. N Engl J Med* 2019; 381(21):1995–2008. 5. Protocol for: McMurray JJV *et al. N Engl J Med* 2019; 381:1995–2008. NEJM website. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1911303/suppl_file/nejmoa1911303_protocol.pdf. Last accessed May 2021.

forxiga (dapagliflozin)

FORXIGA® indications[1]



FORXIGA® indication in the treatment of symptomatic HFrEF[1]

Treatment of adults with symptomatic heart failure with reduced ejection fraction, as an adjunct to SoC therapy

FORXIGA® indication in type 2 diabetes[1]

Adults with type 2 diabetes mellitus as an adjunct to diet & exercise

- **Monotherapy** where metformin was not tolerated
- **Initial combination therapy** with metformin where there are poor prospects for response to metformin monotherapy
- **Add-on combination** with other anti-hyperglycaemic agents

Prevention of hospitalisation for heart failure

- Adults with type 2 diabetes mellitus and established cardiovascular disease or risk factors for cardiovascular disease to reduce the risk of hospitalisation for heart failure

FORXIGA® NEW indication in proteinuric chronic kidney disease[1]

To reduce the risk of progressive decline in kidney function in adults with proteinuric chronic kidney disease (CKD Stage 2, 3 or 4 and UACR ≥30 mg/g*)

FORXIGA® is the FIRST and ONLY treatment approved across three inter-related diseases[1–3]

*≥3.39 mg/mmol

CKD=chronic kidney disease. HbA1c=glycated haemoglobin. HFrEF=heart failure with reduced ejection fraction. SGLT2=sodium–glucose co-transporter-2 inhibitor. SoC=standard of care. UACR=urine albumin-to-creatinine ratio.

References: 1. FORXIGA® Approved Product Information. 2. JARDIANCE® Approved Product Information. 3. STEGLATRO® Approved Product Information.

forxiga
(dapagliflozin)

ORIGINAL ARTICLE FREE PREVIEW

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Ph.D., João P. Ferreira, M.D., Edimar Bocchi, M.D., Michael Böhm, M.D., Ph.D., Hans-Peter Brunner–La Rocca, M.D., Dong-Ju Choi, M.D., Vijay Chopra, M.D., Eduardo Chuquiure-Valenzuela, M.D., Nadia Giannetti, M.D., Juan Esteban Gomez-Mesa, M.D., et al., for the EMPEROR-Preserved Trial Investigators*

October 14, 2021 N Engl J Med 2021; 385:1451-1461
DOI: 10.1056/NEJMoa2107038

RESULTS

- Over a median of 26.2 months, a primary outcome event occurred in 415 of 2997 patients (13.8%) in the empagliflozin group and in 511 of 2991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001)

- The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001)

CONCLUSIONS

Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes.

SURPASS- 3

Lancet 2021; 398: 583-98
August 6th 2021

Bernhard Ludvik, Francesco Giorgino, Esteban Jódar, Juan P Frias, Laura Fernández Landó, Katelyn Brown, Ross Bray, Ángel Rodríguez

TWINCRETINS

- Tirzepatide is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist under development for the treatment of type 2 diabetes.

- To assess the efficacy and safety of tirzepatide versus titrated insulin degludec in people with type 2 diabetes inadequately controlled by metformin with or without SGLT2 inhibitors

SUMMARY

- In summary, tirzepatide-treated participants had clinically meaningful and superior improvements in glycaemic control and bodyweight, with lower risk of hypoglycaemia, than did participants treated with titrated insulin degludec, in a population with type 2 diabetes inadequately controlled by metformin with or without an SGLT2 inhibitor.

- These results support the use of tirzepatide for the treatment of type 2 diabetes and provide further evidence for the potential role of this dual GIP and GLP-1 receptor agonist as the next step in the treatment continuum when injectable therapy is considered.

INSULIN THERAPY

- Methods:
  - Basal Supplement
  - Pre-meal bolus
- Basal Supplement
  - Intermediate to Long acting (NPH, Glargine, Detemir)
  - Ultra Long Acting: Insulin Degludec & U300 Glargine, Toujeo

- Pre-meal bolus
  - Rapid acting (regular or short acting)
  - Very rapid acting (lispro, aspart, glulisine)

- Type 2 basal supplements are often adequate
- Basal + One
- Premixed Insulin Combinations (Ryzodeg, Novomix 30/70, Humalog Mix 25/75)
  - Useful in Type 2 whose requirement is not high
  - Watch out for Hypoglycemia

Ultra long acting insulin

- **Insulin Degludec** is an ultralong-acting basal insulin analogue developed by Novo Nordisk under the brand name **Tresiba**
- duration of action that lasts up to 40 hours
- peakless, extended and highly predictable glucose-lowering effect, once-daily dosing on a flexible schedule may be feasible with degludec
- well suited to patients with unpredictable social or work schedules, those who travel frequently and those who find rigid scheduling of their insulin injections a burden or barrier to regular treatment.

Bariatric Surgery

Sleeve gastrectomy and type 2 diabetes mellitus: a systematic review.

Gill RS[1], Birch DW, Shi X, Sharma AM, Karmali S.
Author information

RESULTS:
A total of 27 studies and 673 patients were analyzed. The baseline mean body mass index for the 673 patients was 47.4 kg/m(2) (range 31.0-53.5). The mean percentage of excess weight loss was 47.3% (range 6.3-74.6%), with a mean follow-up of 13.1 months (range 3-36). DM had resolved in 66.2% of the patients, improved in 26.9%, and remained stable in 13.1%. The mean decrease in blood glucose and hemoglobin A1c after sleeve gastrectomy was -88.2 mg/dL and -1.7%, respectively.

CONCLUSION:
Most patients with type 2 DM experienced resolution or improvement in DM markers after LSG. LSG might play an important role as a metabolic therapy for patients with type 2 DM.

Surg Obes Relat Dis. 2010 Nov-Dec;6(6):707-13. doi: 10.1016/j.soard.2010.07.011. Epub 2010 Aug 6.

Bariatric Surgery

OBJECTIVE

To compare the effect of Roux-en-Y gastric bypass (RYGB) surgery versus intensive medical diabetes and weight management (IMWM) on clinical and patient-reported outcomes in obese patients with type 2 diabetes (T2D).

CONCLUSIONS

Three years after randomization to RYGB versus IMWM, surgery produced greater weight loss, lower HbA_{1c}, reduced cardiovascular risk, and improvements in obesity-related quality of life in obese patients with type 2 diabetes.

*Clinical and Patient-Centered Outcomes in Obese Type 2 Diabetes Patients 3 Years After Randomization to Roux-en-Y Gastric Bypass Surgery Versus Intensive Lifestyle Management: The SLIMM-T2D Study

Donald C. Simonson, Florencia Halperin, Kathleen Foster, Ashley Vernon and Allison B. Goldfine

Diabetes Care 2018 Feb; dc170487.https://doi.org/10.2337/dc17-0487

Original Investigation

ONLINE ONLY

March 4, 2020

Comparing the 5-Year Diabetes Outcomes of Sleeve Gastrectomy and Gastric Bypass

The National Patient-Centered Clinical Research Network (PCORNet) Bariatric Study

Kathleen M. McTigue, MD[1,2]; Robert Wellman, MS[3]; Elizabeth Nauman, MPH, PhD[4]; et al

» Author Affiliations | Article Information

JAMA Surg. 2020;155(5):e200087. doi:10.1001/jamasurg.2020.0087

Editorial Comment

Key Points

Question How do type 2 diabetes (T2DM) outcomes compare across the 2 most common bariatric procedures?

Findings In this cohort study of 9710 adults with T2DM who underwent bariatric surgery, most patients who had Roux-en-Y gastric bypass or sleeve gastrectomy experienced T2DM remission at some point over 5 years of follow-up. Patients who had Roux-en-Y gastric bypass showed slightly higher T2DM remission rates, better glycemic control, and fewer T2DM relapse events than patients who had sleeve gastrectomy.

Meaning Understanding diabetes outcomes of different bariatric procedures will help surgeons and patients with diabetes make informed health care choices.