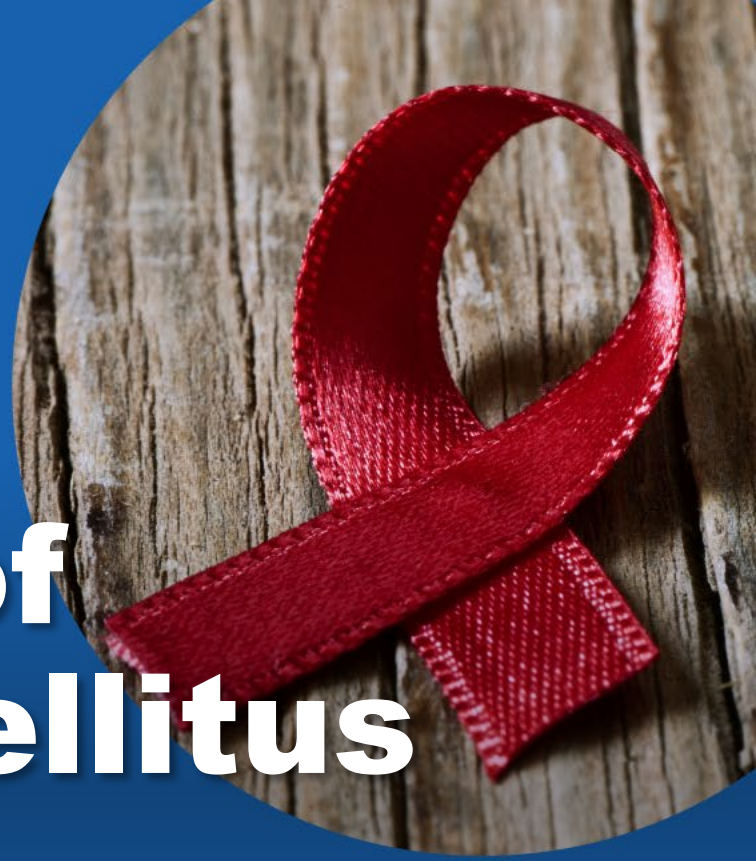
ashm



Management of Type 2 Diabetes Mellitus

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Overview

- Overview of T2DM & glycaemic targets
- Treatment after metformin – newer agents on the market
  - SGLT2 inhibitors
  - DPP4 agonists
  - GLP1 antagonists
- Insulin options
  - Newer options – coformulation

Diagnosis

- ADS position statement
- Criteria:
  - HbA1c $\geq$ 6.5%
  - Fasting glucose $\geq$ 7mmol/L.
  - Random glucose $\geq$ 11.1mmol/L
  - GTT showing fasting $\geq$ 7 or 2hr $\geq$ 11.1mmol/L
- Patients with IGT have an increased risk of death and vascular disease (regardless of progression to diabetes) as well as microvascular complications
  - Risk of progression to T2DM is reduced by 58% with lifestyle modification and 31% with metformin

1.The DECODE Study. *Arch Intern Med* 2001; 161:397-405 2. Singleton JR *et al.* Diabetes 2003;52(12):2867-2873 3. Diabetes Prevention Program Research Group. *N Engl J Med* 2002; 346:393-403

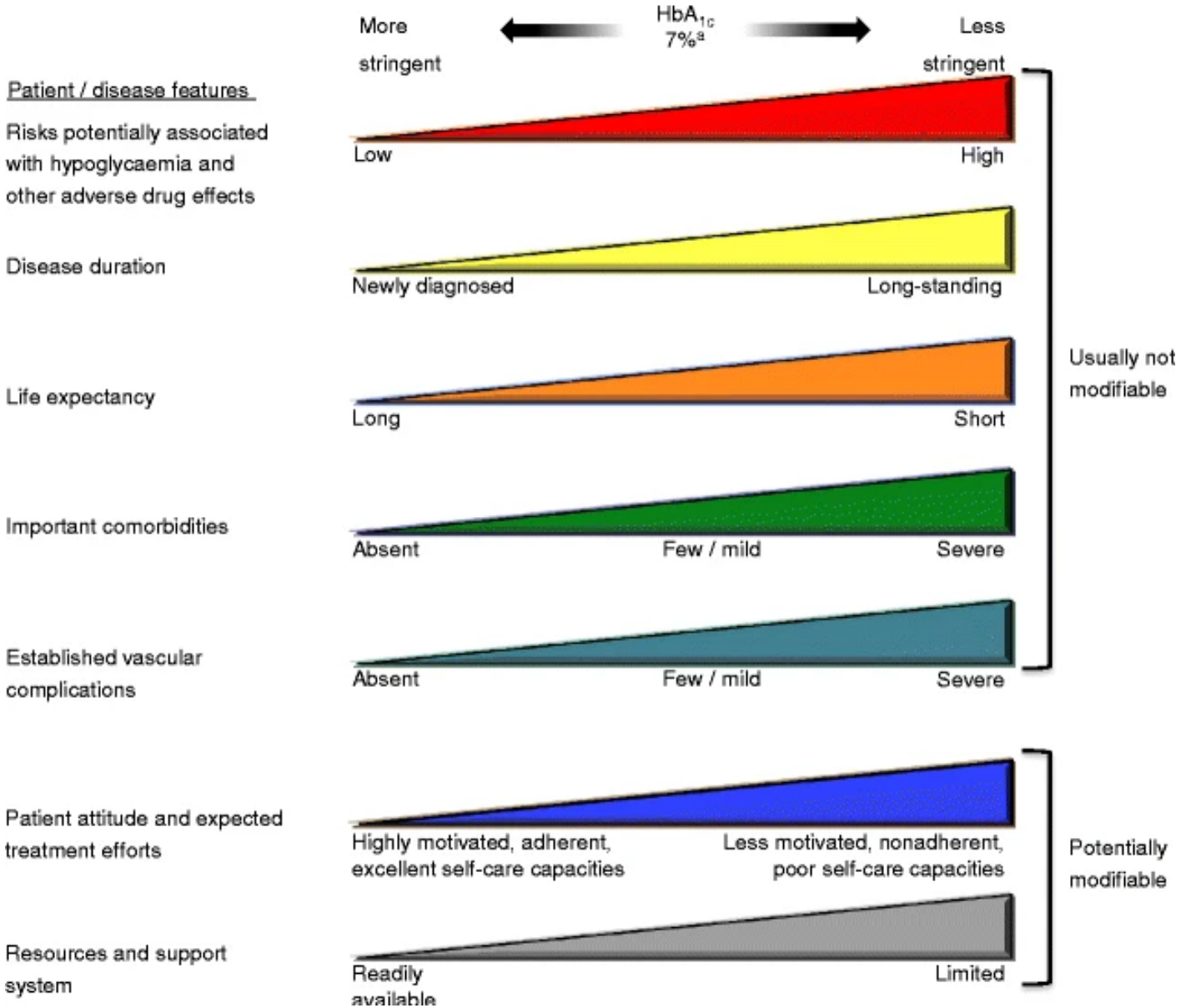
Optimising health outcomes in diabetes

- Glucose control
- Smoking cessation
- Blood pressure control
- Lipid management with priority to statins
- Some circumstances, antiplatelet therapy

ADA/EASD – 2015 position statement

- Glycaemic targets need to be individualised
- Based on modifiable and non-modifiable factors

1. Inzucchi S.E., Bergenstal R.M., Buse J.B., Diamant M., Ferrannini E., Nauck M. *et al Diabetologia.* 2015; **58**: 429-442



1. Inzucchi S.E. et al. *Diabetologia.* 2015; **58**: 429-442

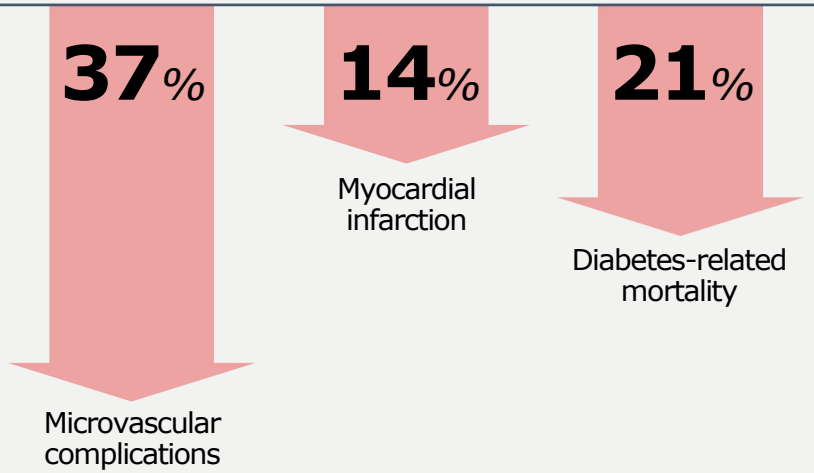
Importance of glycaemic control

GOOD GLYCAEMIC CONTROL

Reduces diabetes-related complications

UKPDS[1]

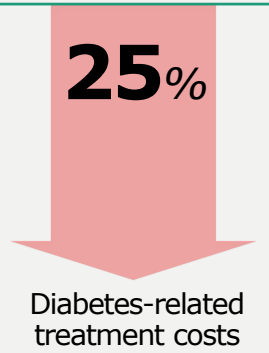
1% mean HbA_{1c} reduction results in:



Reduces total diabetes-related costs

Retrospective database analysis[2]

HbA_{1c} ≤7% continuously for 1 year results in . . .



Which included:

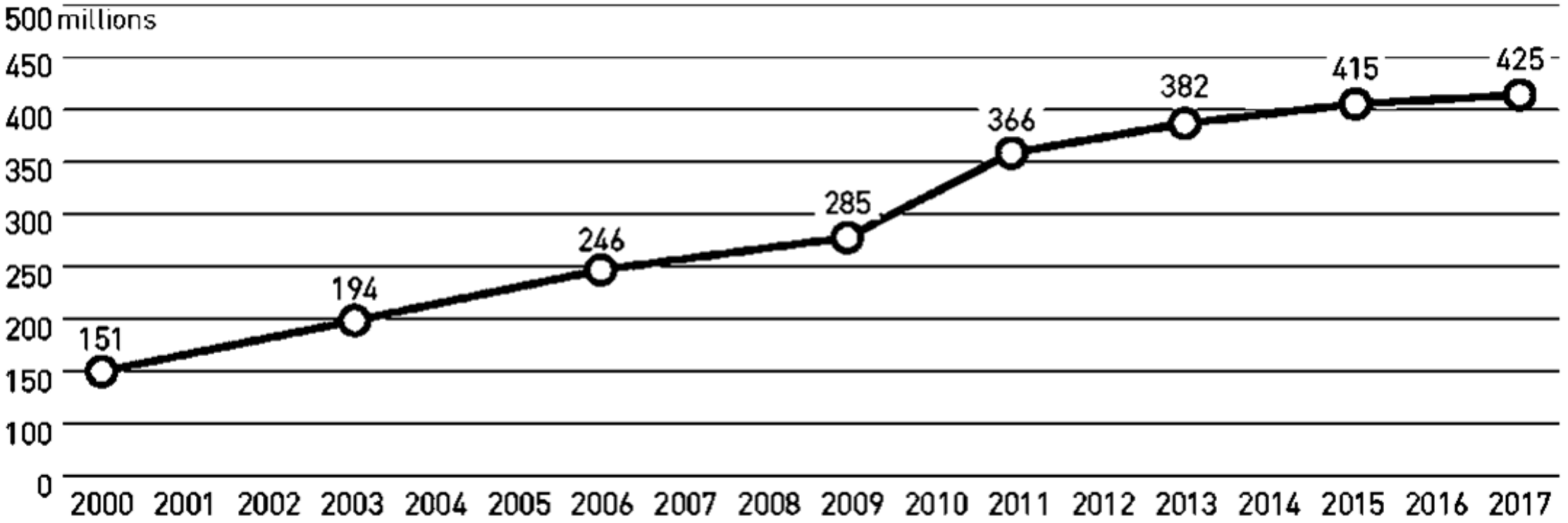
- ✓ 22% lower diabetes medical costs
- ✓ 28% lower diabetes pharmacy costs

. . . compared with patients above target HbA_{1c} ≤7%

1. Stratton *et al. BMJ* 2000;321:405–12. 2. Shetty *et al. J Manag Care Pharm* 2005;11:559–64.

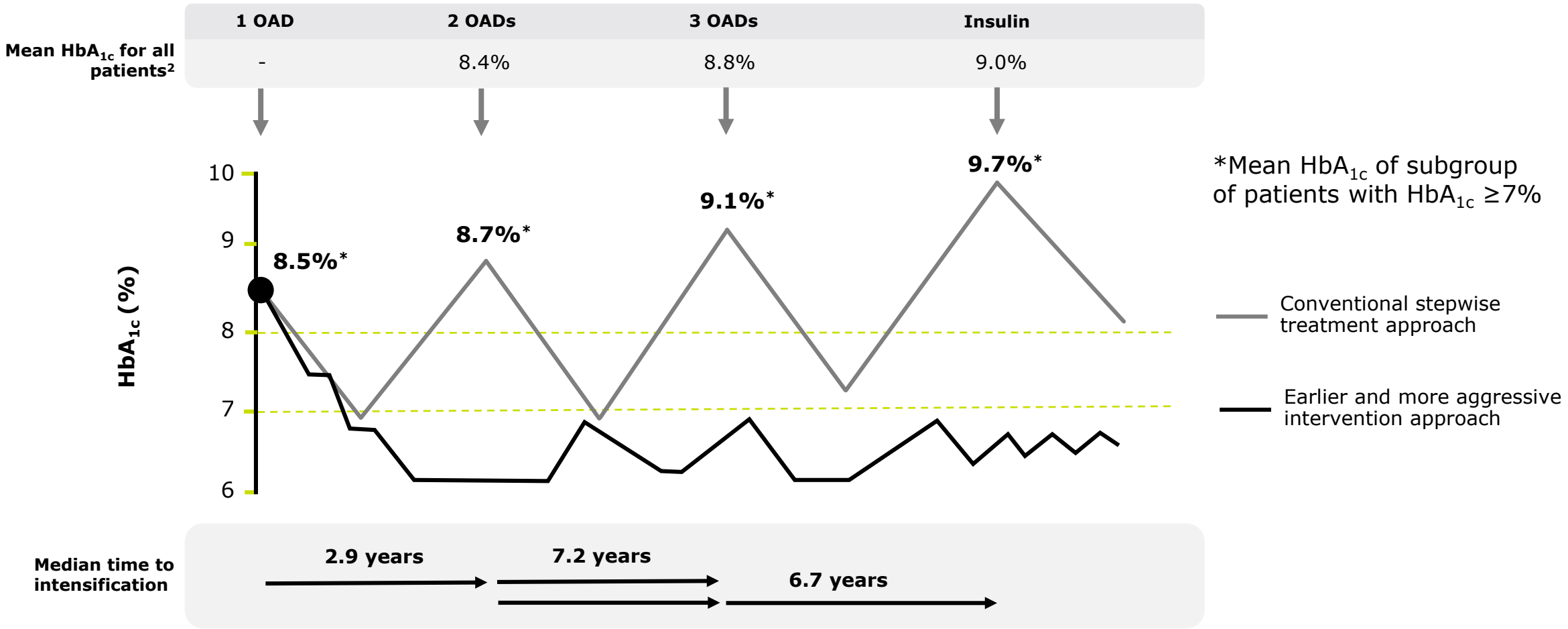
The increasing burden of T2DM

Total number of adults with diabetes (20-79 years)



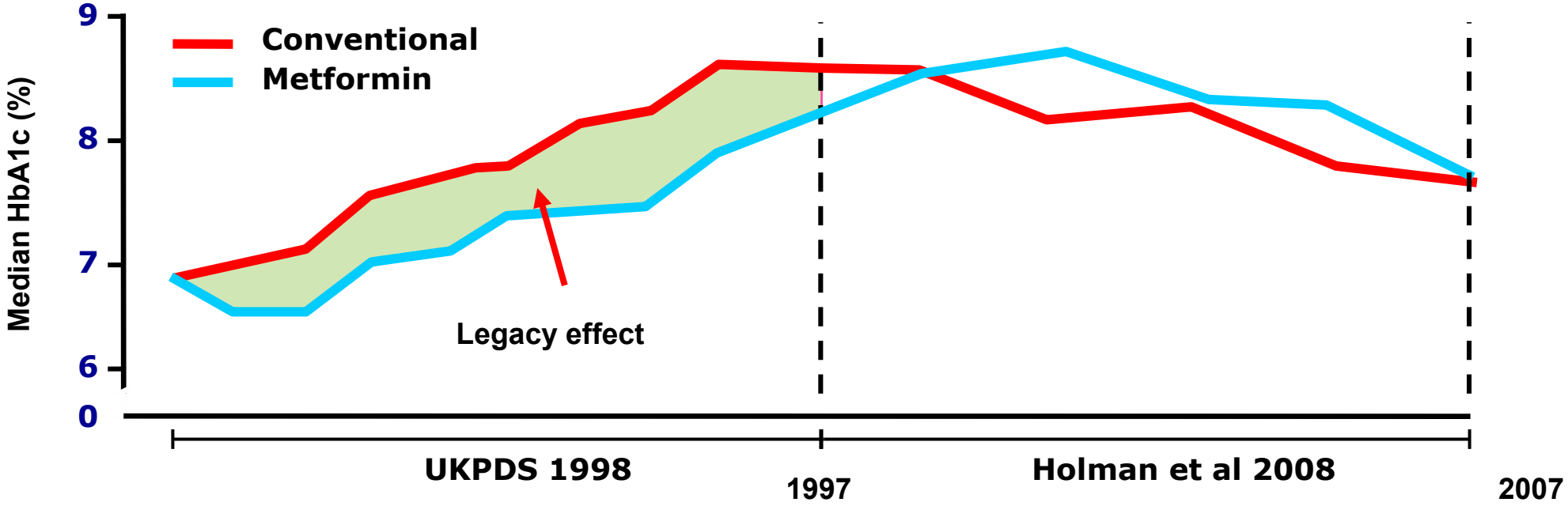
1. World Health Statistics 2017. Monitoring Health for the SDGs. *World Health Organization* 2017.
2. International Diabetes Federation. *IDF Diabetes Atlas*, 8th ed. Brussels, Belgium: International Diabetes Federation, 2017. http://www.diabetesatlas.org.

Clinical inertia



1. Del Prato S *et al. Int J Clin Pract* 2005;59(11):1345–55. 2. Khunti K *et al. Diabetes Care* 2013;36(11):3411–7. 3. Khunti K and Millar-Jones D. *Prim Care Diabetes* 2017;11(1):3–12.

Legacy effect



Similar HbA1c after 1st year but in intensive arm

- 24% ↓ microvascular Cx
- 15% ↓ MI
- 13% ↓ all cause mortality

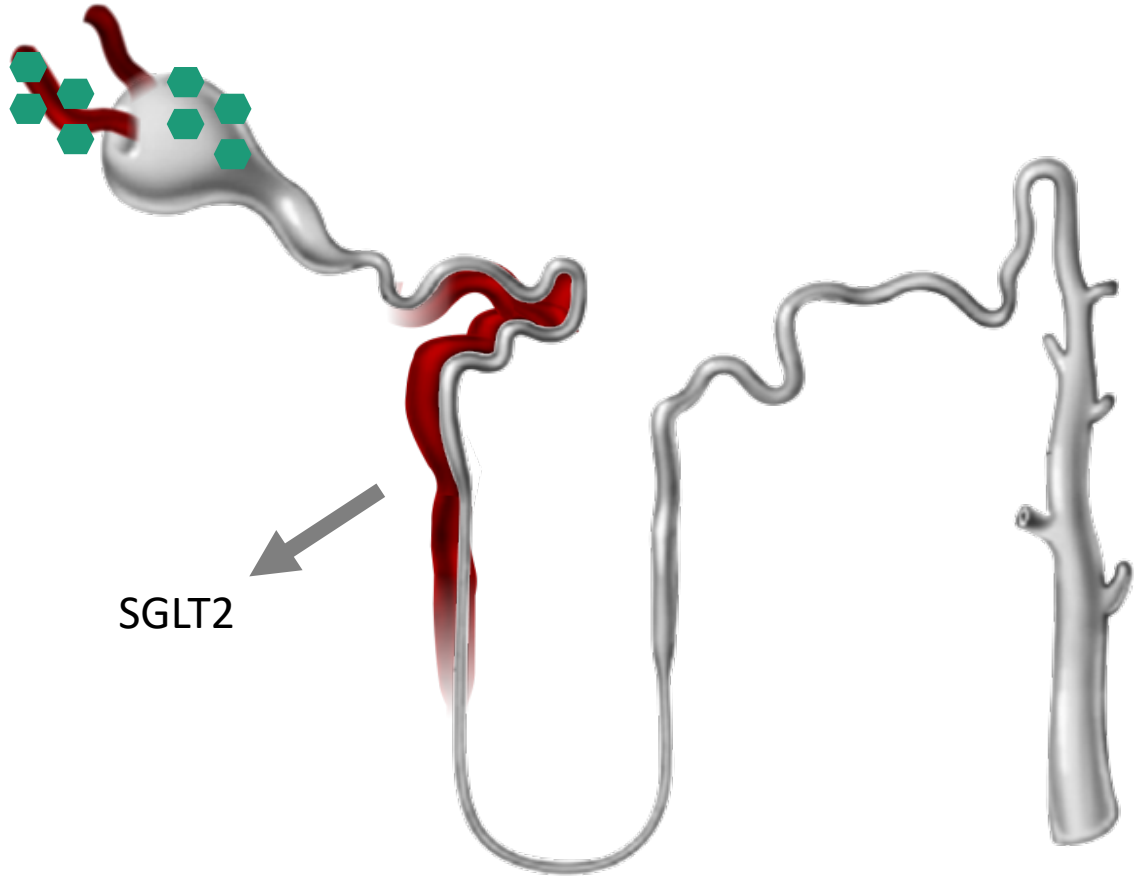
1. Holman RR *et al. N Engl J Med* 2008;359:1577–89 2. UKPDS 33. *Lancet* 1998;352:837–53.

Oral agents after metformin

- Sulphonylureas
- Thiazolidiones
- SGLT2 inhibitors
  - Dapagliflozin
  - Empagliflozin
- DPP4 antagonists
  - Sitagliptin
  - Linagliptin
  - Saxogliptin
  - Aloglipitin
  - Vildagliptin
- (Acarbose)

SGLT2 inhibitors

Filtered glucose load > 180 g/day



reduces glucose reabsorption in the proximal tubule, leading to urinary glucose excretion*[1]

*A loss of approximately 78 g of sugar per day on 25 mg dose

1. Bakris GL *et al. Kidney Int*. 2009;75;1272–7.

DPPIV antagonists

- DPP4 inactivates a number of incretins
- Inhibition of breakdown results in higher levels of incretins
  - Results in glucose-dependent insulin secretion
- Weight neutral, no risk of hypoglycaemia (unless used with SU/insulin)
- Generally well tolerated
  - Occasional nausea
  - ? pancreatitis
- Safe in renal failure (most require dose adjustment except linagliptin)
- CV safe (trend to increased HF in some agents)

1. Mulvihill, EE and Drucker DJ. Endocri Rev. 2014; 35(6):992-1019

5 Steps in managing T2DM

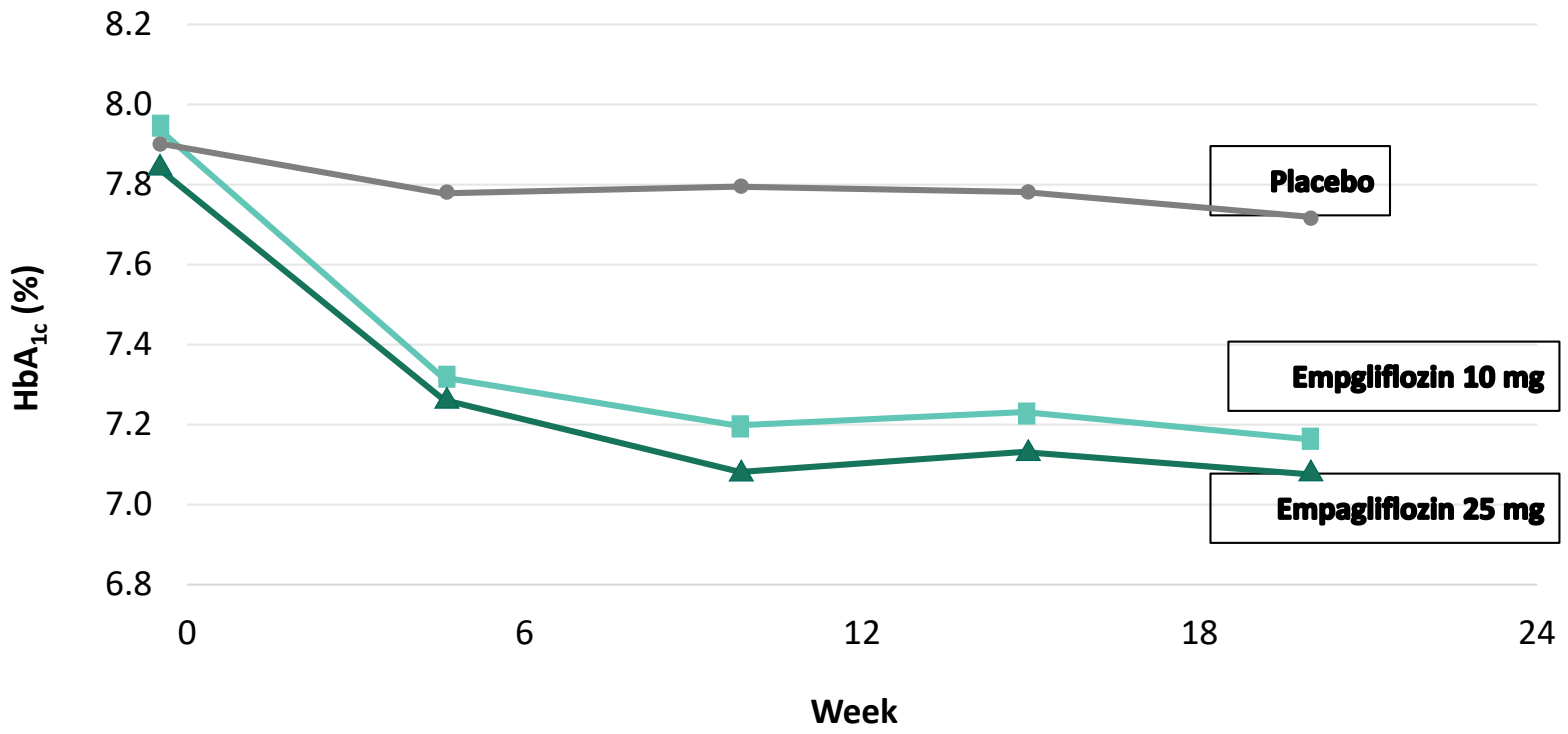
- 1st – metformin and lifestyle
- 2nd – if HbA1c over target: determine if the patient has established vascular disease
  - If yes – empagliflozin as preferable agent
  - Consider screening for occult disease as this affects the best treatment option for patients
- 3rd – if HbA1c over target: determine if the patient has HF or CKD
  - If yes – empagliflozin as preferable agent
- 4th – if HbA1c over target: determine if there is a need to reduce the risk of hypoglycaemia
  - If yes – either SGLT-2 inhibitor or DPP4
- 5th – if HbA1c over target: determine if there is a need to minimise weight gain or promote weight loss
  - If yes – SGLT2 inhibitors (as oral agents) or GLP1 agonists (injectable)

Now we have agents that address more than just glycaemic control but also can assist with reducing diabetic-related complications, hypoglycaemia and can enable weight loss

Glycaemic benefits of empagliflozin

Empagliflozin provides established HbA_{1c} efficacy*[1]

*vs placebo, as add-on to metformin (p<0.001) at 24 weeks (primary endpoint).[1]



Empagliflozin provides significant weight loss

- Empagliflozin 25mg: -2.5kg
- Empagliflozin 10mg: -2.1kg
- Placebo -0.5kg

Empagliflozin reduces systolic blood pressure

- Empagliflozin 25mg: -5.2mmHg
- Empagliflozin 10mg: -4.5mmHg
- Placebo -0.4mmHg

1. Haring HU et al. Diabetes Care 2014;37:1650–9.

Empa-reg study

Randomised and treated 7020 patients

- Inclusion
  - Adults with T2DM
  - Established CVD
  - HbA1c 7-10%
  - eGFR >30
- Subgroups
  - Standard of care + placebo (2333)
  - Standard of care + empagliflozin 10mg (2345)
  - Standard of care + empagliflozin 25mg (2342)

1. Zinman B *et al. N Engl J Med* 2015;373:2117–28.

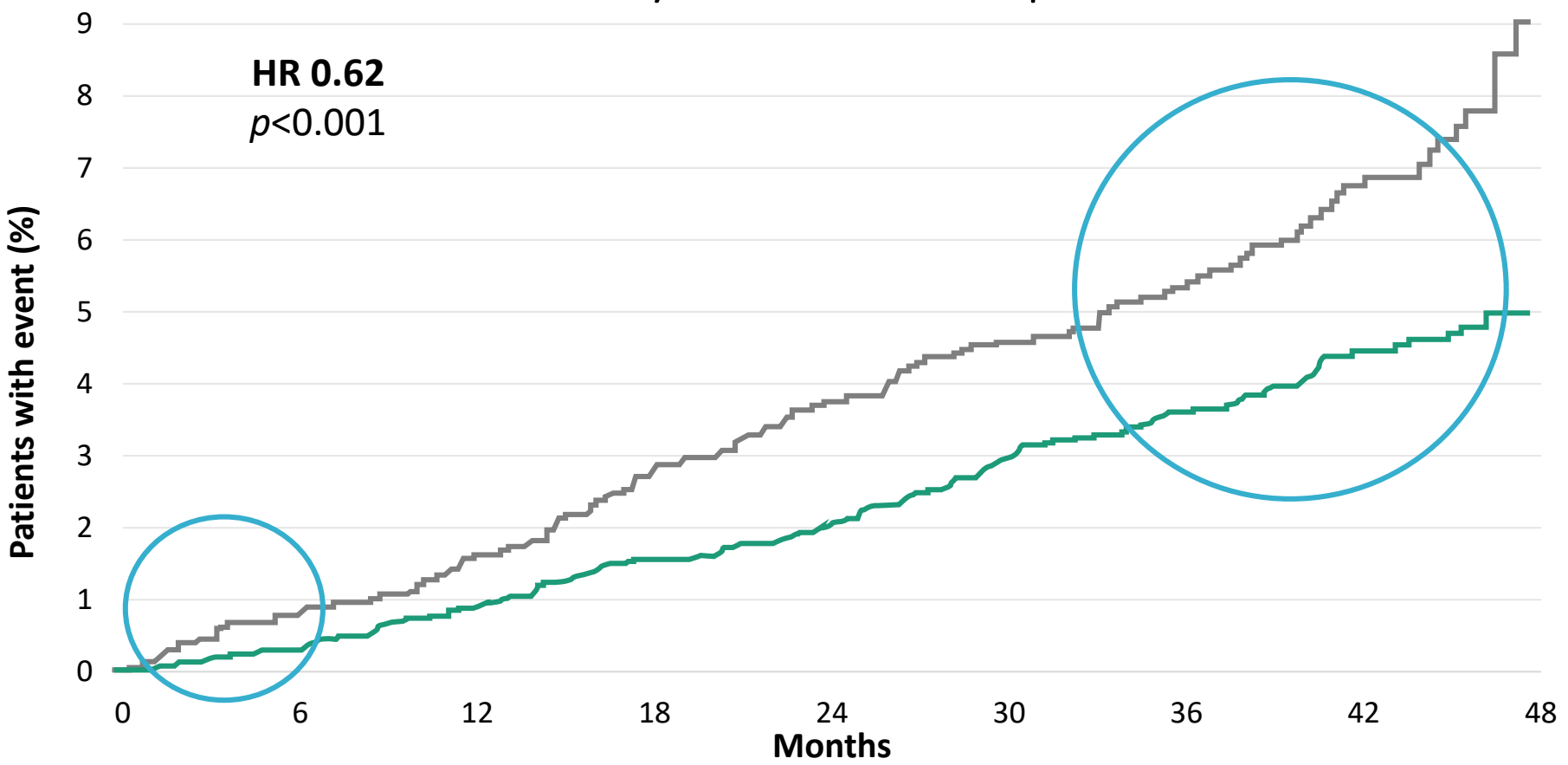
CV death

Empagliflozin reduced the risk of CV death by 38%

vs placebo on top of standard of care in patients with T2D and established CV disease[1†]

†CAD, PAD, MI or stroke.

Early* and sustained# response



Standard of care + Placebo

Standard of care + empagliflozin

Standard of care

- **CV medications (eg statins, ACEi/ARBs)**
- **Glucose lowering agents**

Adapted from Zinman B *et al.* 2015.[1]

*Within 6 months from start. #Up to 48 months from start.

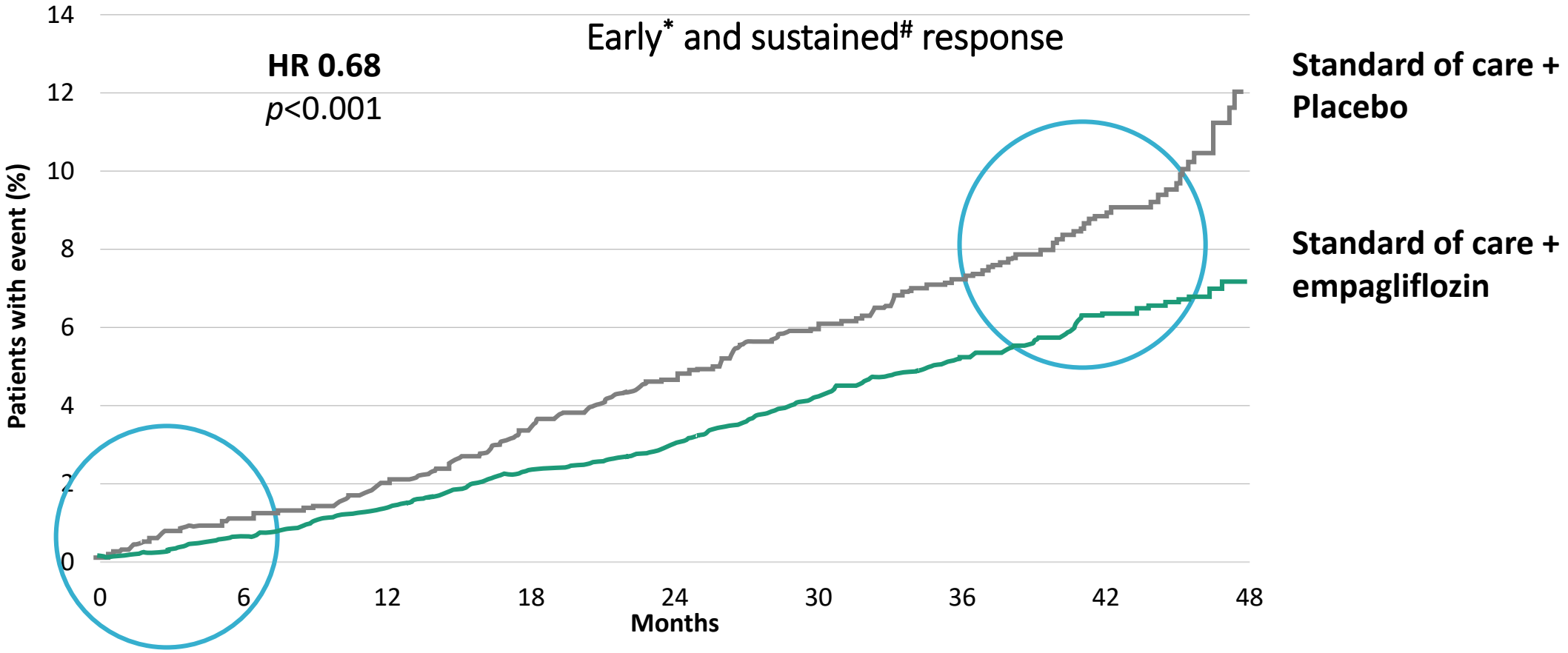
1. Zinman B *et al. N Engl J Med* 2015;373:2117-28.

All-cause mortality

Empagliflozin reduced the risk of all-cause mortality by 32%

vs placebo on top of standard of care in patients with T2D and established CV disease[1†]

[†]CAD, PAD, MI or stroke. JARDIANCE® is not indicated to reduce all-cause mortality



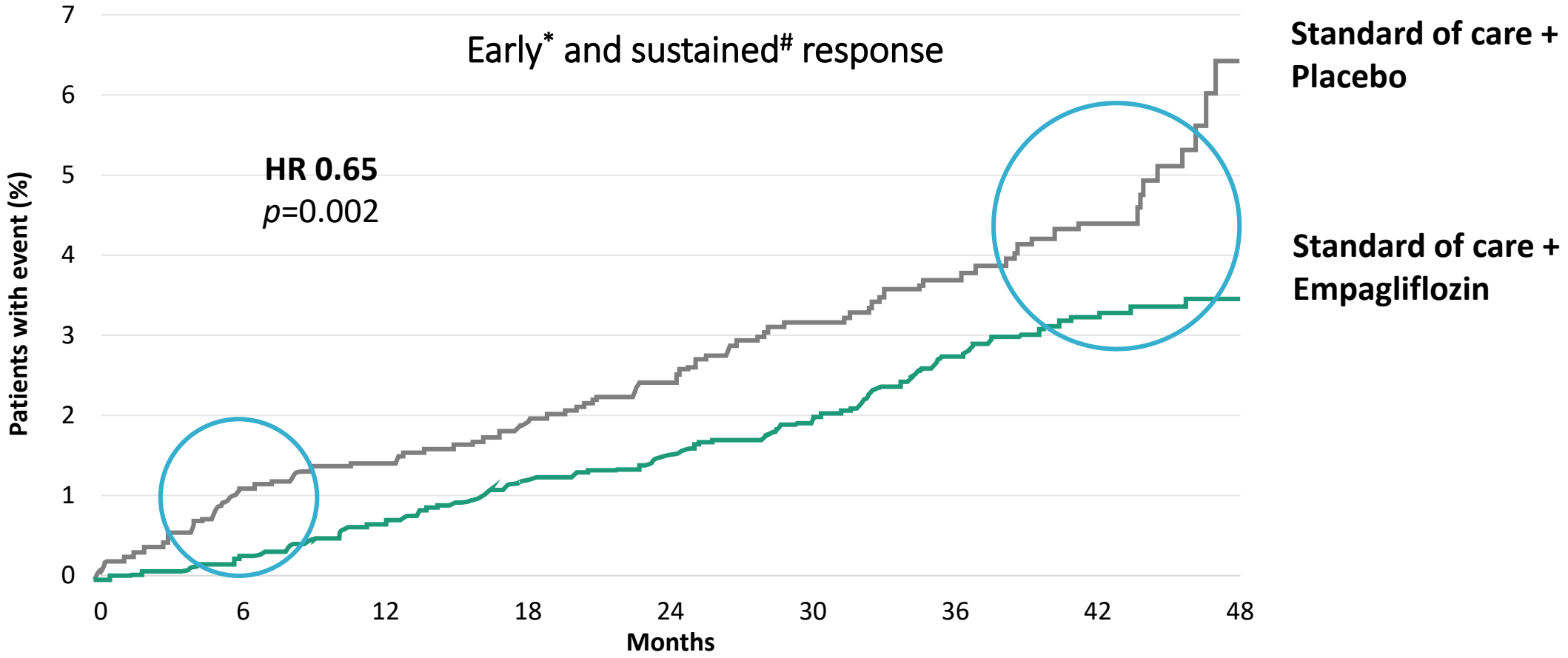
Adapted from Zinman B *et al*. 2015.[1]

Hospitalisation for heart failure

empagliflozin reduced the risk of hospitalisation for heart failure by 35%

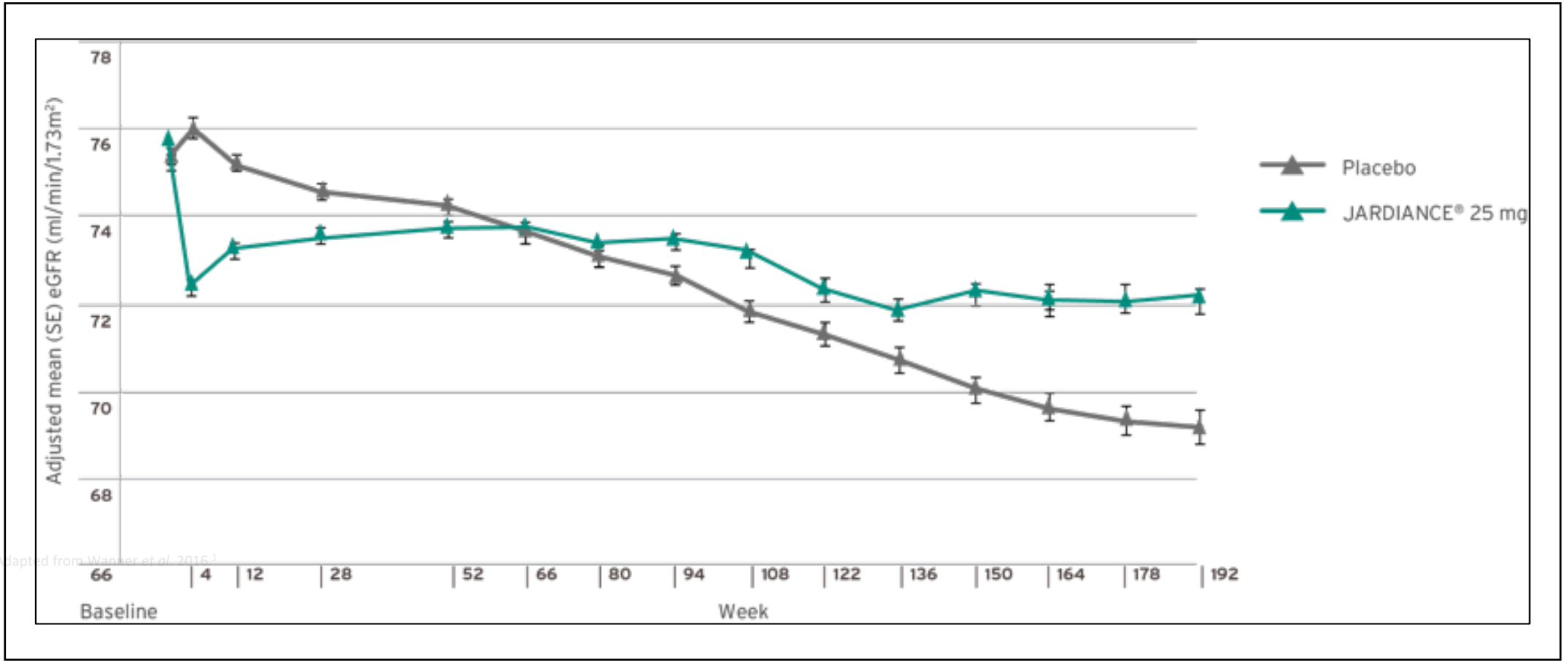
vs placebo on top of standard of care in patients with T2D and established CV disease[1†]

†CAD, PAD, MI or stroke. JARDIANCE® is not indicated to reduce hospitalisation for heart failure



Adapted from Zinman B *et al.* 2015.[1]

Empagliflozin and renal outcomes



- 1. Wanner C *et al. N Engl J Med* 2016; 373:323-34. 2. JARDIANCE Approved Product Information. 3. Zinman B *et al. N Engl J Med* 2015; 373:2117-28
  4. Wiviott SD *et al. N Engl J Med* 2018 Nov 10. doi: 10.1056/NEJMoa1812389. 5. Forxiga Approved Product Information.

Safety considerations

- No increase in the overall rate of UTI, complicated UTI or pyelonephritis with empagliflozin vs placebo in EMPA-REG OUTCOME[1]
  - **UTI**: 18.0% vs 18.1%, respectively
  - **Complicated UTI**:* 1.7% vs 1.8%, respectively
  - **Pyelonephritis**: 0.3% vs 0.2%, respectively

- Increased rate of genital infections with empagliflozin vs placebo in EMPA-REG OUTCOME[1]
  - 6.4% with empagliflozin vs 1.8% with placebo ($p<0.001$)

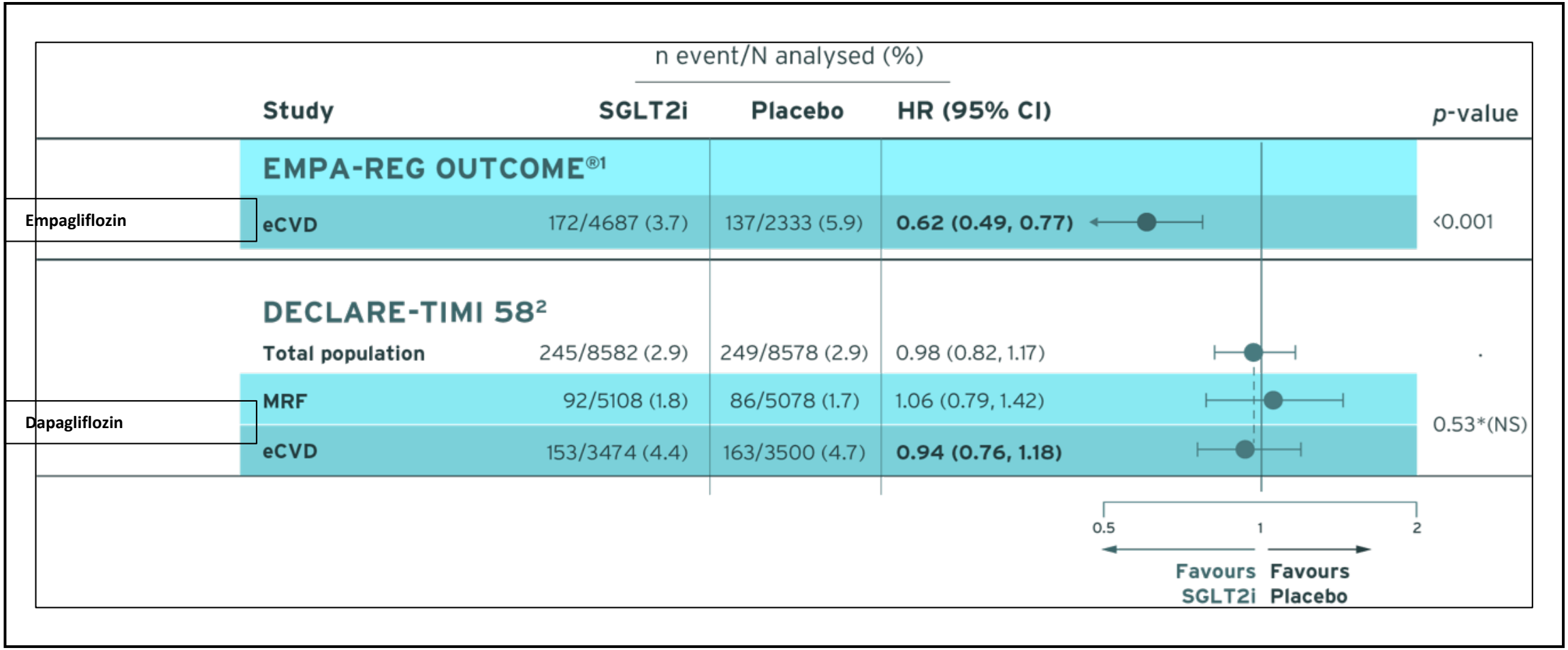
1. Zinman *B et al. N Engl J Med* 2015;373:2117-28.

SGLT2i and (DKA)

- In patients taking SGLT2 inhibitors, rare cases of DKA have been reported
- Discontinuation or temporary interruption should be considered until the situation is clarified
- The Australian Diabetes Society recently released an alert outlining a series of cases of

SGLT2i be ceased at least 3 days pre-operatively (2 days prior to surgery and the day of surgery) or in other physically stressful situations

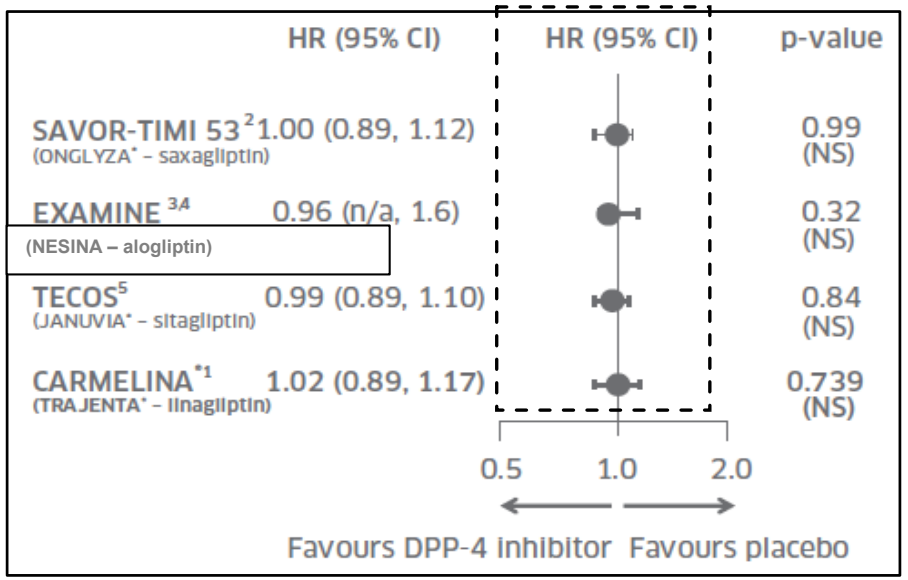
Death Outcomes from SGLT2 inhibitor



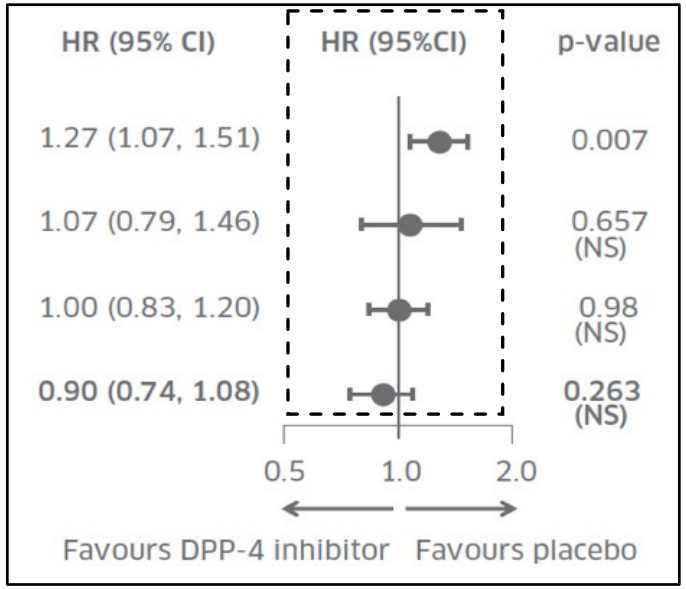
1. Zinman B *et al*. 2015[1] 2. Wiviott *et al.* 2018.[2]

DPP4 inhibitors and CV outcomes

Risk of CV death, MI and ischaemic stroke



Risk of hospitalisation for heart failure



. Rosenstock J *et al*. *JAMA* 2019;321:69–79. 2. Scirica BM *et al*. *N Engl J Med* 2013;369:1317. 3. White WB *et al*. *N Engl J Med* 2013;369:1327–36. 4. Zannad F *et al*. *Lancet* 2015;385;2067–76. 5. Green JB *et al*. *N Engl J Med* 2015;373:232–42.

Selected oral agents after metformin

PBS listed	Evidence of cardioprotection	Key adverse events	Risk of hypoglycaemia	Effect on weight	Renal Impairment eGFR (ml/min/1.73m^2
SGLT2 inhibitors	✔ empagliflozin demonstrated cardioprotection	Genital infections, UTI, postural hypotension	Low with metformin Increased risk when combined with insulin/SU	Loss	Empagliflozin Stop when < 45[8] dapagliflozin Stop when < 60[9]
DPP4 inhibitors	X	Potential risk of pancreatitis	Low with metformin Increased risk when combined with insulin/SU	Neutral	Dose adjustments (except linagliptin)
SUs	X	Hypoglycaemia, weight gain	Yes (common)	Gain	Stop when < 30

Injectable options

GLP1 Receptor Agonists

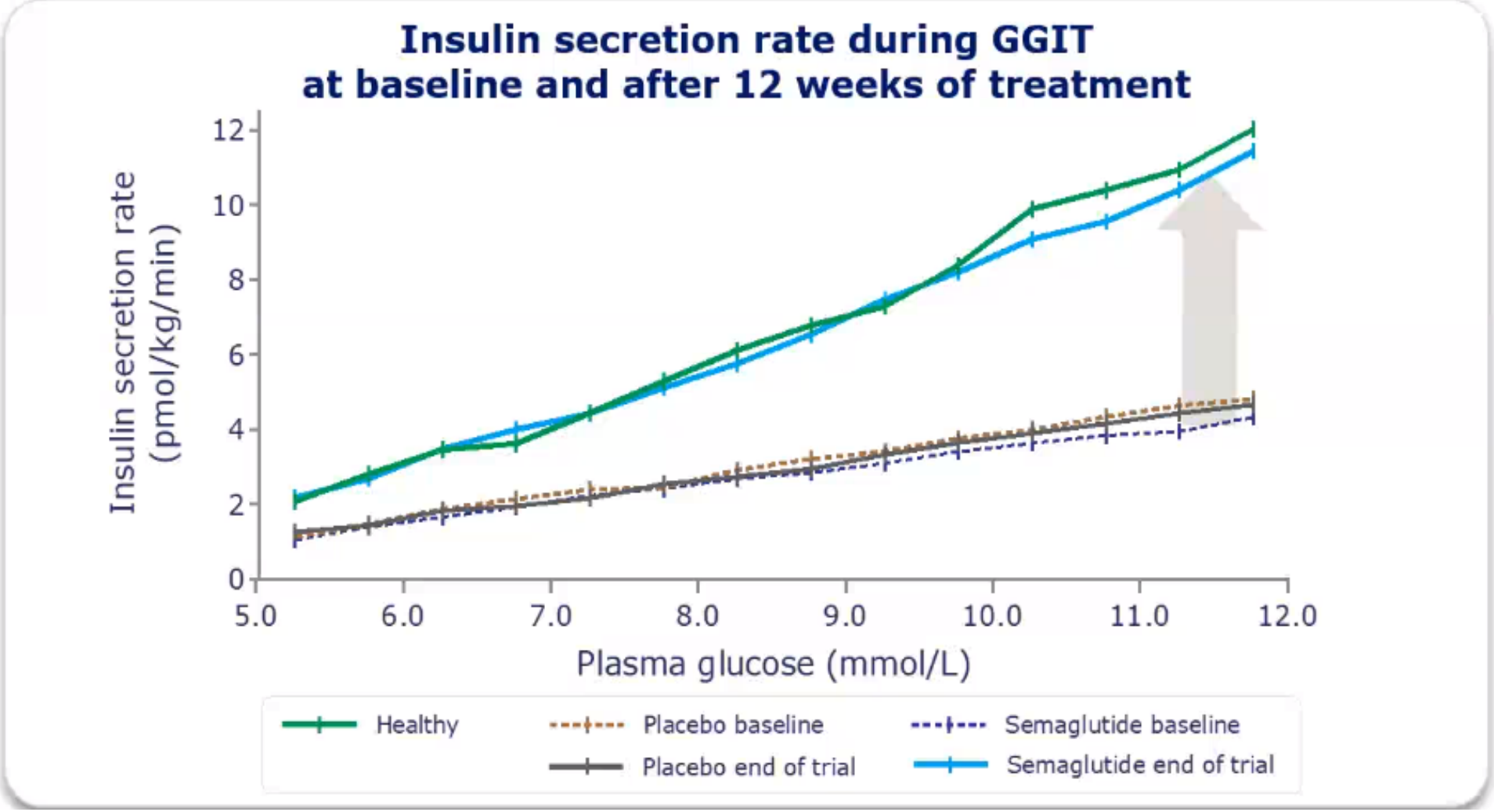
- Exenatide (byetta or bydureon) – exendin-4-based GLP1 RA
- Dulaglutide (trulicity) – large human GLP-1 RA, semaglutide (ozempic) – small GLP-1 RA
  - However, **only** byetta (twice daily) is PBS approved for the use with insulin
- Act on both FPG and PPG levels to varying degrees
- Effects
  - Decreased insulin secretion (beta cells)
  - Increased glucagon secretion (alpha cells)
  - Increased hepatic glucose production
  - Reduced appetite
  - Decreased incretin effect
  - Decreased glucose uptake

Effects

- Advantages
  - Weight loss or weight neutral
  - Lower hypoglycaemia vs rapid-acting insulin addition
  - Lower daily dose of insulin
- Disadvantages
  - Number of injections and complexity of regime (extra two daily)
  - GIT side effects
  - Possibly less effective long-term or patients with initial very poor glycaemic control
  - Cost of GLP1 RA

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

Semaglutide normalises insulin



Kapitza C et al Diabetologia 2017;60:1390-9

Semaglutide change in HbA1c

- SUSTAIN 1 – vs placebo (30/52, baseline HbA1 8.1%)
  - Placebo -0.02
  - Semaglutide 0.5mg -1.5
  - Semaglutide 1mg -1.6
- SUSTAIN 2 – vs sitagliptin (56/52, baseline HbA1c 8.1)
  - Sitagliptin -0.5
  - Semaglutide 0.5mg -1.3
  - Semaglutide 1mg -1.6
- SUSTAIN 3 – vs exenatide ER (56/52, baseline HbA1c 8.3%)
  - Exenatide -0.9
  - Semaglutide 1mg -1.5
- SUSTAIN 7 – vs dulaglutide
  - Dulaglutide 0.75mg -1.1
  - Dulaglutide 1mg -1.4
  - Semaglutide 0.5mg -1.5
  - Semaglutide 1mg -1.8

Semaglutide change in HbA1c

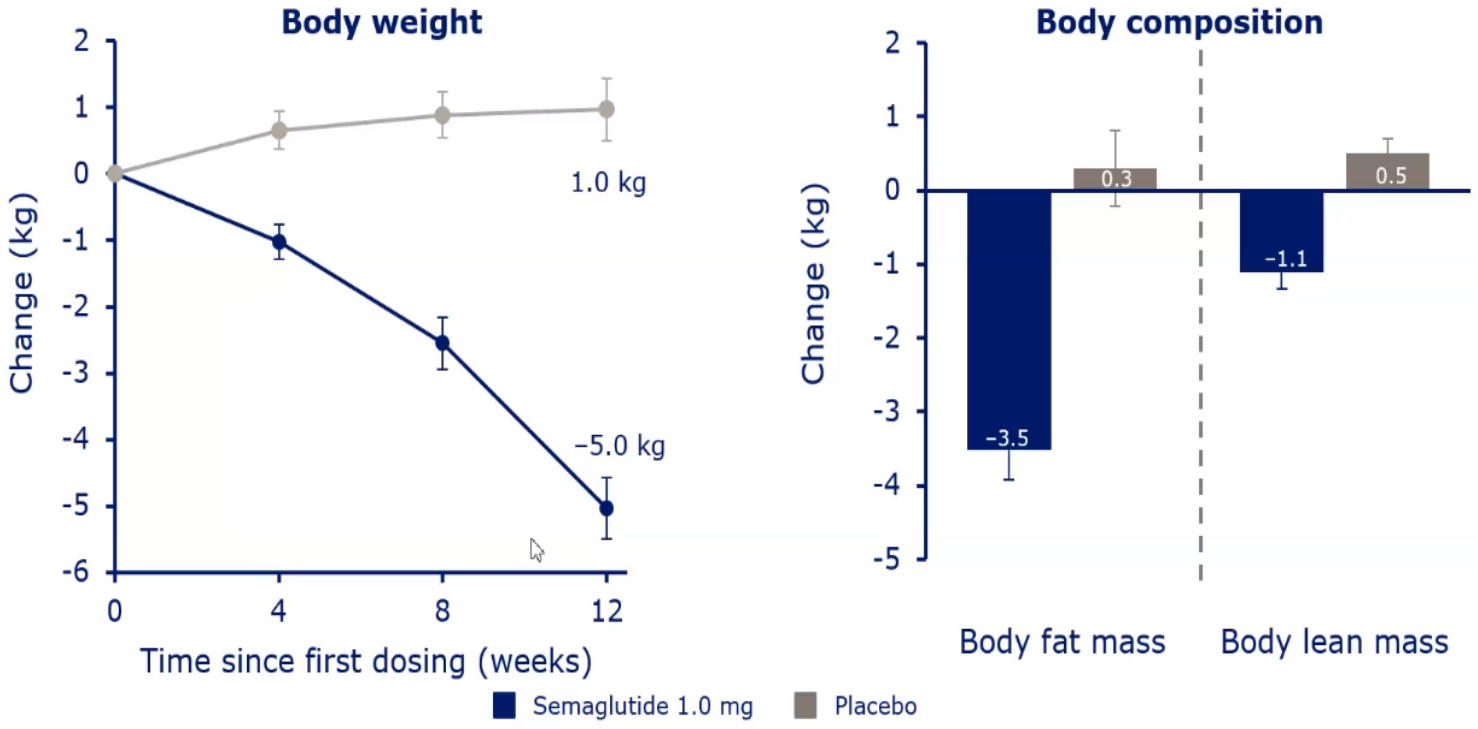
- SUSTAIN 8 – vs canagliflozin (52/52, baseline HbA1 8.3%)
  - Canagliflozin -1.0
  - Semaglutide 1mg -1.5
- SUSTAIN 9 – vs placebo (30/52, baseline HbA1c 8.0)
  - Placebo -0.1
  - Semaglutide 1mg -1.5
- SUSTAIN 4 – vs lantus (30/52, baseline HbA1c 8.2%)
  - Lantus -0.8
  - Semaglutide 0.5mg -1.2
  - Semaglutide 1mg -1.6
- SUSTAIN 5 – vs placebo
  - Placebo -0.1
  - Semaglutide 0.5mg -1.4
  - Semaglutide 1mg -1.8

1. Soreli C et al Lancet Diabetes Endocrinol 2017;5:251-60 2. Ahren B et al Lancet Diabetes Endocrinol 2017;S:341-54 3. Ahmann AJ et al Diabetes Care 2018;41:258-66 4. Pratley RE et al Lancet Diabetes Endocrinol 2018;6;275-86 5. Lingvay I et al Lancet Diabetes Endocrinol 2019;7:834-44 6. Zinman B et al Lancet Diabetes Endocrinol 2019;7;356-67 7. Capehorn MS et al Diabetes Metab 2019 8. Aroda VR eg at Lancet Diabetes Endocrinol 2017;5:355-66 9. Rodbard HW et al. J clin Endocrinol Metab 2018;103:2291-301

Semaglutide change in HbA1c

- Reductions in HbA1c > with semaglutide than comparitors
  - Placebo, sitagliptin, exenatide ER, glargine, dulaglutide, canagliflozin, liraglutide
- SUSTAIN 1-5 reductions in HbA1c greater in patients with higher baseline HbA1c
  - No influence from baseline BMI, background treatment, diabetes duration or age
- Consistently reduced FPG and/or PPG across all studies

Semaglutide reduces fat mass

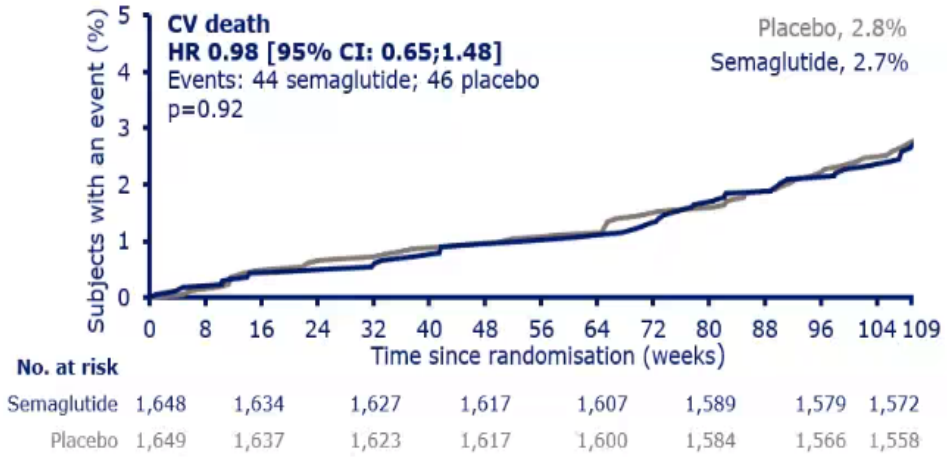


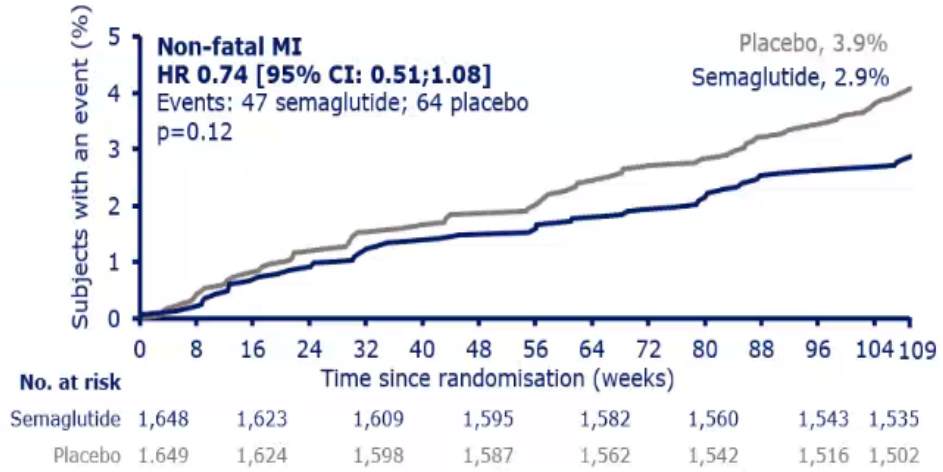
- SUSTAIN 1-5 and 7-10
  - Reductions in weight more than comparators
  - Placebo, sitagliptin, exenatide ER, glargine, dulaglutide, canagliflozin, liraglutide
- SUSTAIN 1-5 and 7 reductions in weight greater with higher baseline BMI and the higher dose
- SUSTAIN 1-5 weight reduction was due to the effect of the drug and not nausea/vomiting

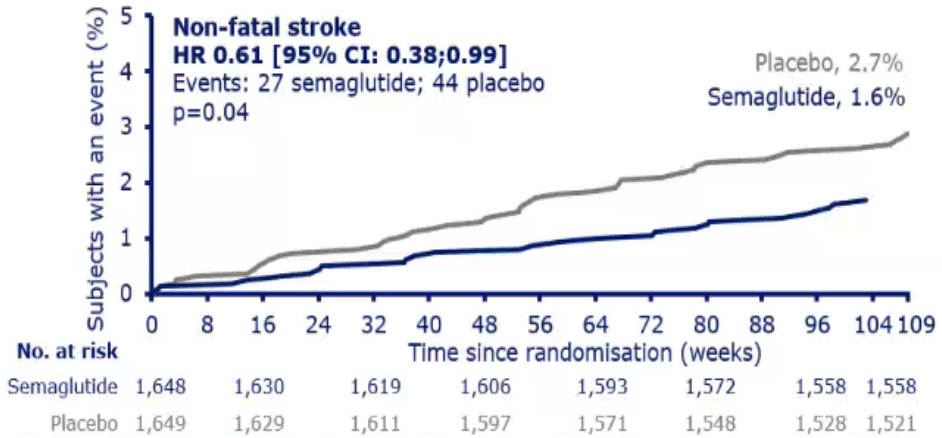
1. Blundell J et al Diabetes Obes Metab 2017;19:1242-51

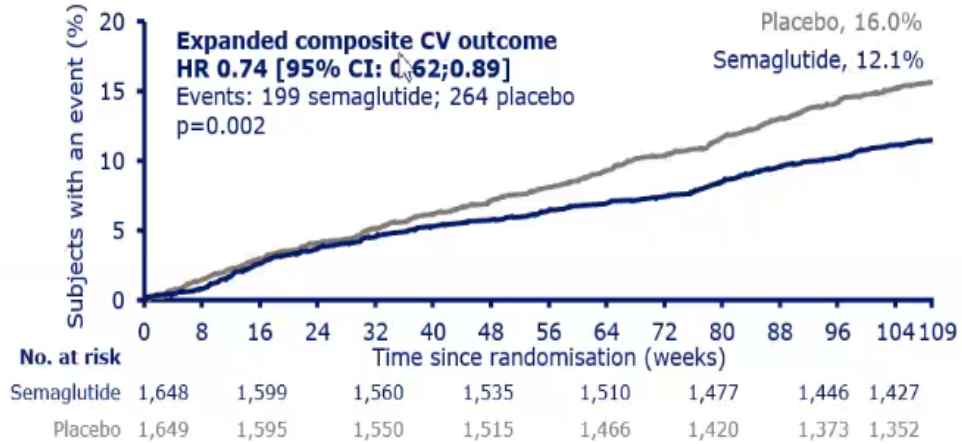
Semaglutide and CV outcomes

SUSTAIN 6









1. Marso SP *et al. N Engl J* Med 2016;375:1834-44

SUSTAIN 6: adverse effects

- GI disorders
  - Diarrhoea: 17.9% (semaglutide 0.5mg) vs 18.4% (semaglutide 1mg) vs 11.9% (placebo)
  - Nausea: 17.3% (semaglutide 0.5mg) vs 21.9% (semaglutide 1mg) vs 7.5% (placebo)
  - Vomiting: 10.5% (semaglutide 0.5mg) vs 14.8% (semaglutide 1mg) vs 5.2% (placebo)
- Gallbladder disorders:
  - Cholelithiasis: 2.5% (semaglutide 0.5mg) vs 2.1% (semaglutide 1mg) vs 2.3% (placebo)
  - Cholecystitis acute: 0.5% (semaglutide 0.5mg) vs 0% (semaglutide 1mg) vs 0.7% (placebo)
- Acute pancreatitis: 0.7% (semaglutide 0.5mg) vs 0.4% (semaglutide 1mg) vs 0.4% (placebo)
  - Shown in other studies to not increase the risk

Insulin options

Types of insulin

- Basal insulin: long-acting or ultra-long acting
- Co-formulated: two separate insulins – rapid acting and ultra-long acting basal insulins
- Pre-mixed: suspension of rapid-acting insulin with crystalline version of the same insulin (protaminated to form an intermediate-acting insulin)
- Rapid-acting insulin
- Short-or intermediate acting insulins
- Initiating insulin options:
  - Basal insulin (eg glargine)
  - Co-formulation (ryzodeg)
  - Premixed (novomix, Humalog mix)

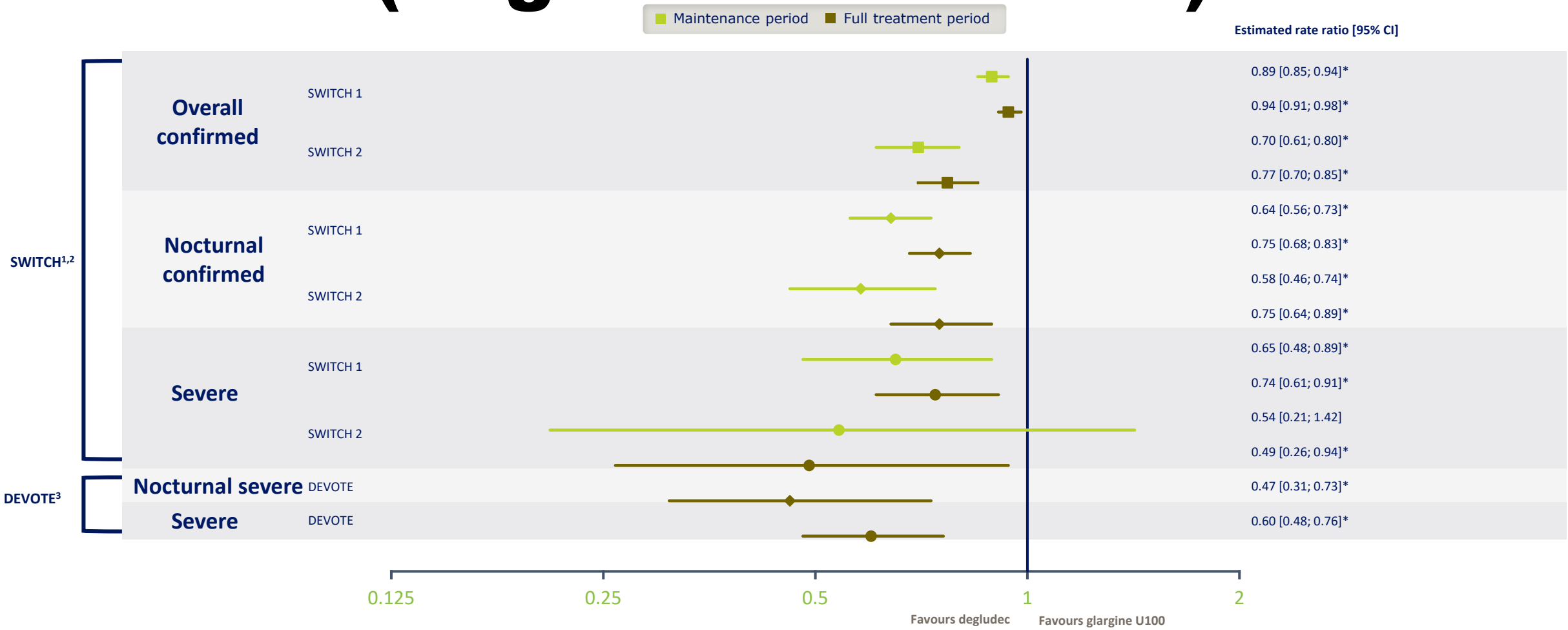
Co-formulation insulin

- Ryzodeg 30/70
- Only currently available co-formulation
- Soluble co-formulation of 70% insulin degludec and 30% insulin aspart
- Peak action due to aspart, stable basal effect from degludec >24hrs

Co-formulation insulin

- Advantages
  - Simplicity of regime (one pen)
  - Fewer daily injections than basal add on
  - Lower hypoglycaemia than premixed or basal add on
  - Lower daily dose of insulin compared to other insulin regimes
  - No resuspension required (cf premixed insulin)
  - Better 24hr coverage compared to premixed insulin and lantus (not toujeo)
  - Lower glycaemic variability compared to premixed insulin
- Disadvantages
  - Less flexibility (can’t adjust the dose of novorapid)
  - Indicated only once or twice daily

SR hypoglycaemia (degludec vs lantus)



1. Lane W, et al. *JAMA.* 2017; 318(1): 33-44. **2.** Wysham C, *et al*. *JAMA*. 2017; 318(1): 45-56. **3.** Marso SP, *et al*. *N Engl J Med.* 2017; 377(8): 723-32.

Patients on basal insulin

- Situations
  - Basal insulin titrated to target FBGL and HbA1 above target OR
  - Basal insulin dose limited by hypoglycaemia (and weight gain) (over-basalisation)
    - Particularly if >0.5U/kg – may not improve glycaemic control but increases hypoglycaemia and weight gain
- Options
  - Combination injectable therapy to cover postprandial glucose excursions
    - Adding a rapid-acting insulin with 1-3 meals
    - Changing to pre-mixed insulin
    - Adding GLP1 RA
    - Changing to co-formulation
- Usually sulfonylureas, possible DPP4I and GLP1RA are ceased
- Metformin and SGLT2 inhibitors should be continued particularly if large doses of insulin required (eg obese, highly-insulin resistant)

1. Inzucchi et al. *Diabetologia.* 2015; **58**: 429-442

Basal add on rapid-acting insulin

- Eg lantus/toujeo with novorapid, humalog, apidra or fiasp
- Controls PPG excursions
- Aims to mimic the physiological meal-simulated insulin release
- Start with one/two meals and upgrade to three if needed
- Advantages
  - Greater flexibility (dosing/timing) than premixed
  - Graduated introduction of prandial insulin
- Disadvantages
  - Risk of hypoglycaemia potentially greater than premixed
  - Weight gain often greater than premixed
  - Injection burden (potentially more daily injections)
  - Complexity of regime (two types of insulins/pens)

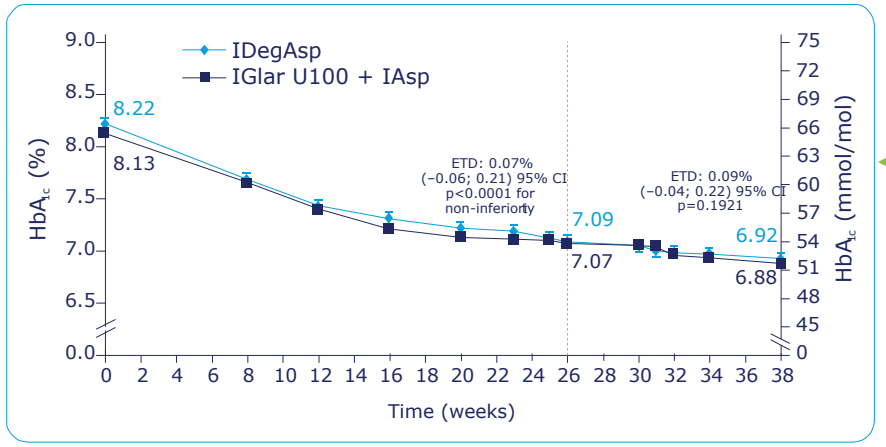
Ryzodeg vs basal add on

- 38/52, randomised, open-label, treat-to-target (HbA1c <7%)
- Basal insulin +/- OHAs, HbA1c 7-10%
- Ryzodeg vs insulin glargine U100 + aspart (lantus/novorapid)
- Results:
  - Number of injections:
    - W26 – one ryzodeg, two lantus/novorapid
    - W38 – 1.62 ryzodeg, 2.85 lantus/novorapid
  - Dose of insulin
    - Ryzodeg 83.4U vs lantus/NR 89.3 (6.6% reduction)
  - Similar estimated treatment difference of -1.1% HbA1c (confirmed non-inferiority)
  - At W26 and W38 target HbA1c, fasting and postprandial BGLs were similar
  - At W38 target HbA1c without hypoglycaemia
    - Ryzodeg: 22.5% vs lantus/novorapid 21.1%
  - At W38 nocturnal hypoglycaemia
    - Estimated rate ratio 0.61 in favour of ryzodeg

1. Philis-Tsimikas A, *et al. Diabetes Res Clin Pract*. 2019; 147: 157–65.

Co-formulation vs BBT in Step-by-Step Trial: Results

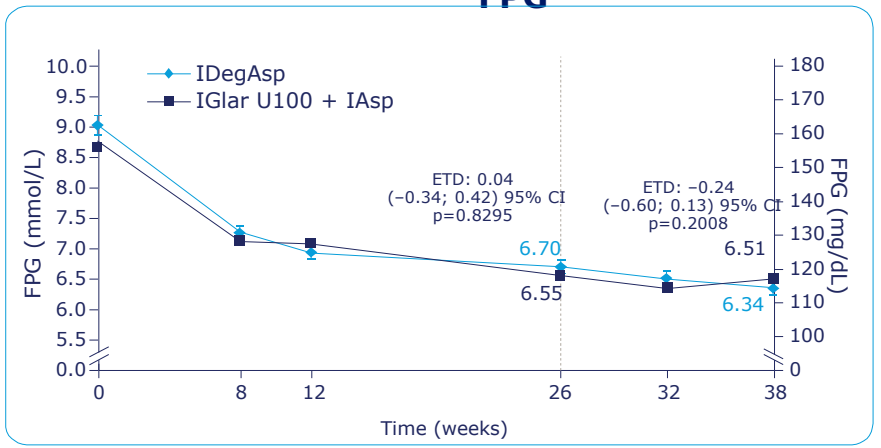
HbA_{1c}



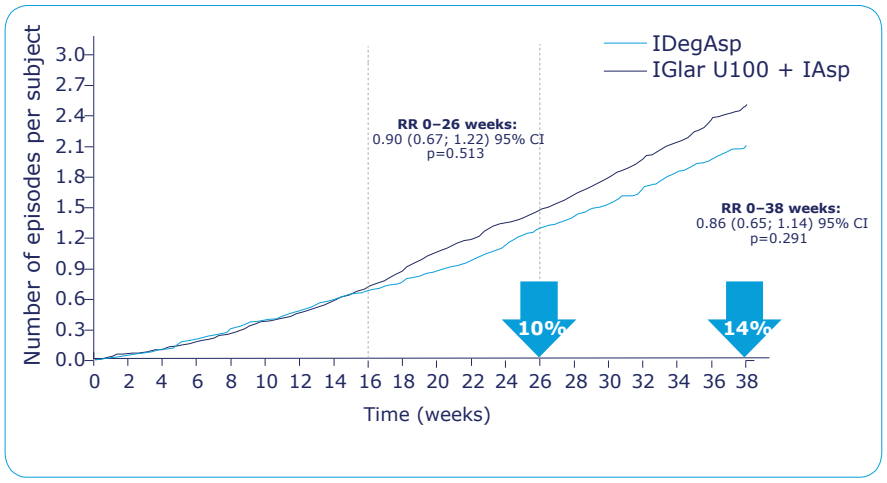
Similar reduction in HbA_{1c}

Similar reduction in FPG

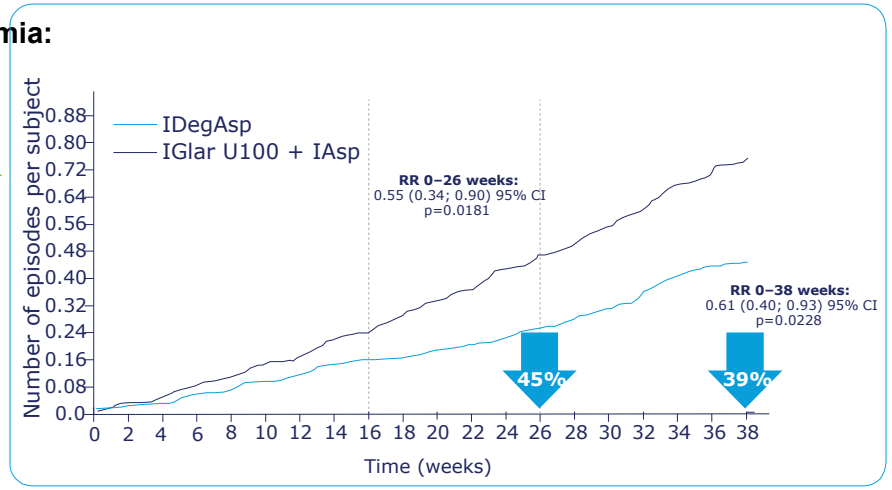
FPG



Confirmed hypoglycaemia: Numerically lower



Nocturnal confirmed hypoglycaemia: Significantly lower



Premixed insulins

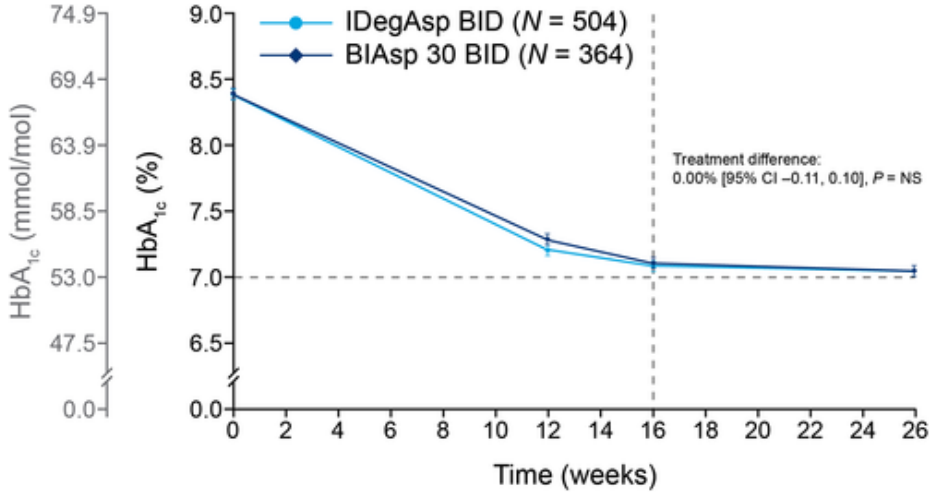
- Eg novomix, humalog mix
- Used 1-3 times daily with meals
- If twice daily roughly 50/50 with breakfast and dinner (preferably) to allow better basal coverage
- Premixed
  - Advantages
    - Simplicity – one pen
    - Potentially fewer injections than basal add on
  - Disadvantages
    - Less flexibility
    - Risk of inadequate 24hr coverage ie poorer glycaemic control and more variability
    - Need for resuspension

Ryzodeg vs premixed insulin

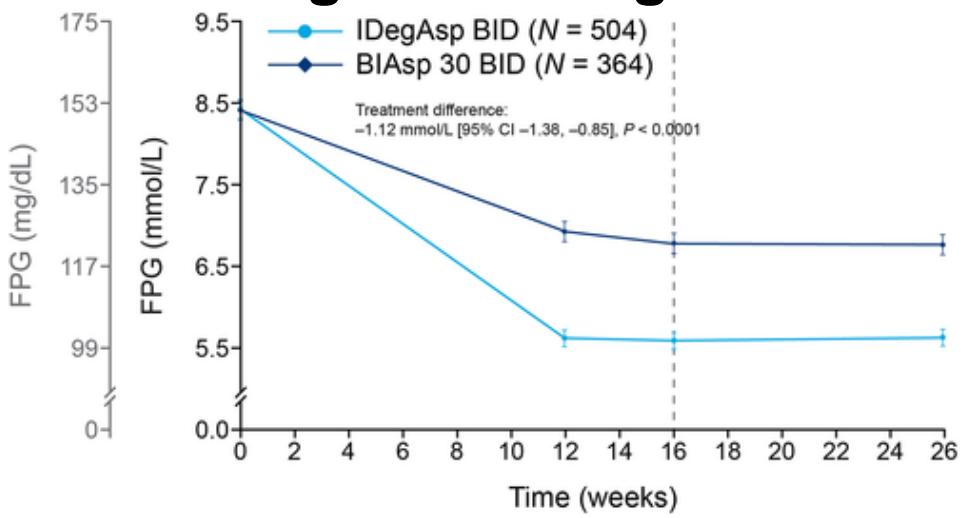
- Two RCT, open-label, treat-to-target in patients with T2DM
- Two doses of ryzodeg or novomix
- 26/52
- Results – ryzodeg group
  - Lower insulin 16% (0.9 vs 1.1U/kg)
  - Less weight gain -0.5kg
  - Greater reduction in FBG
  - Overall hypoglycaemia lower 19% (estimated rate ratio 0.81)
  - Nocturnal hypoglycaemia lower 57% (0.43)
  - Severe hypoglycaemia lower 39% (0.61)
  - Overall HbA1c comparable

1. Christiansen JS, *et al. J Diabetes.* 2016; 8(5): 720-8.

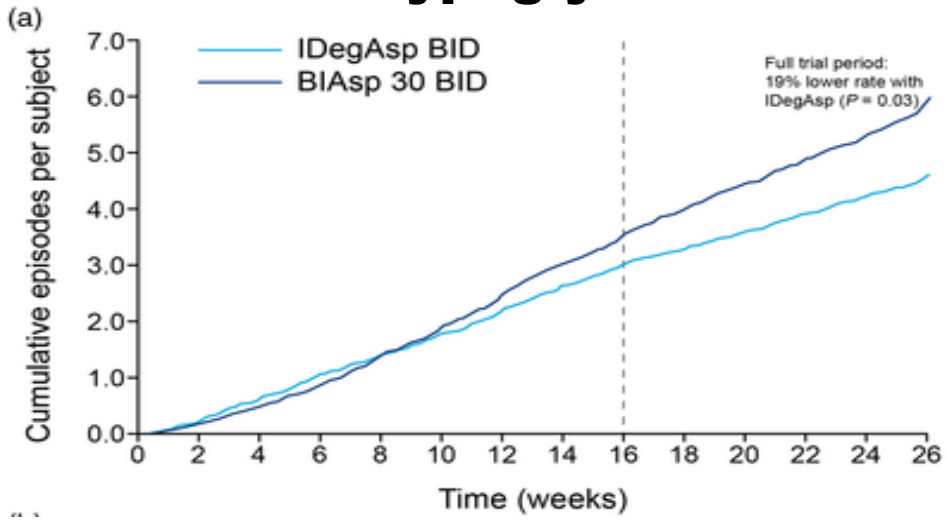
Change in HbA1c



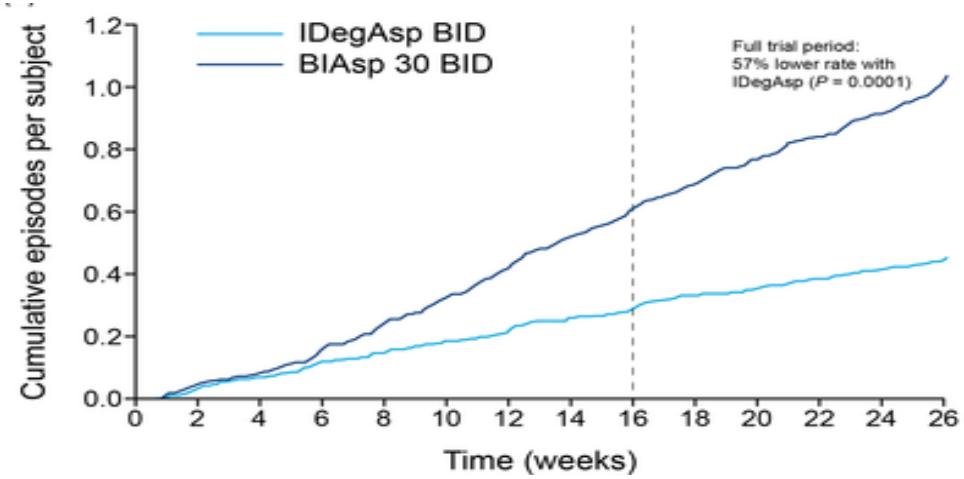
Change in fasting BGL



Overall hypoglycaemia



Nocturnal hypoglycaemia



Patient examples

- T2DM naïve to treatment
  - If HbA1c <9% -> metformin and lifestyle alone
  - If HbA1c >9% -> consider dual therapy from onset
- T2DM on metformin
  - If vascular disease, renal disease or heart failure -> empagliflozin
  - If concerns regarding weight -> semaglutide for 6-12 months -> SGLT2-I
- T2DM on maximal non-insulin therapy
  - If sugars are generally all elevated -> basal insulin
  - If postprandial elevations -> ryzodeg

Summary

- We need to set individualised targets for patients and be aggressive in our attempts to achieve these targets
- All vascular risk factors need to be treated to minimise the long-term risks of T2DM
- Today a plethora of drugs exist for the management of T2DM
  - We need to be proactive when screening for occult vascular disease
  - We need to consider the non-glycaemic benefits of drugs
    - Empagliflozin has a clear benefit in patients with vascular disease, heart failure and renal impairment
    - Semaglutide has a clear benefit in terms of weight reduction and glycaemic control
- We need to address the clinical inertia that exists regarding the initiation of insulin
  - Ryzodeg should be considered as an option for insulin initiation or intensification given its pharmokinetic profile

ashm

Thank you