OBESITY MASTERCLASS

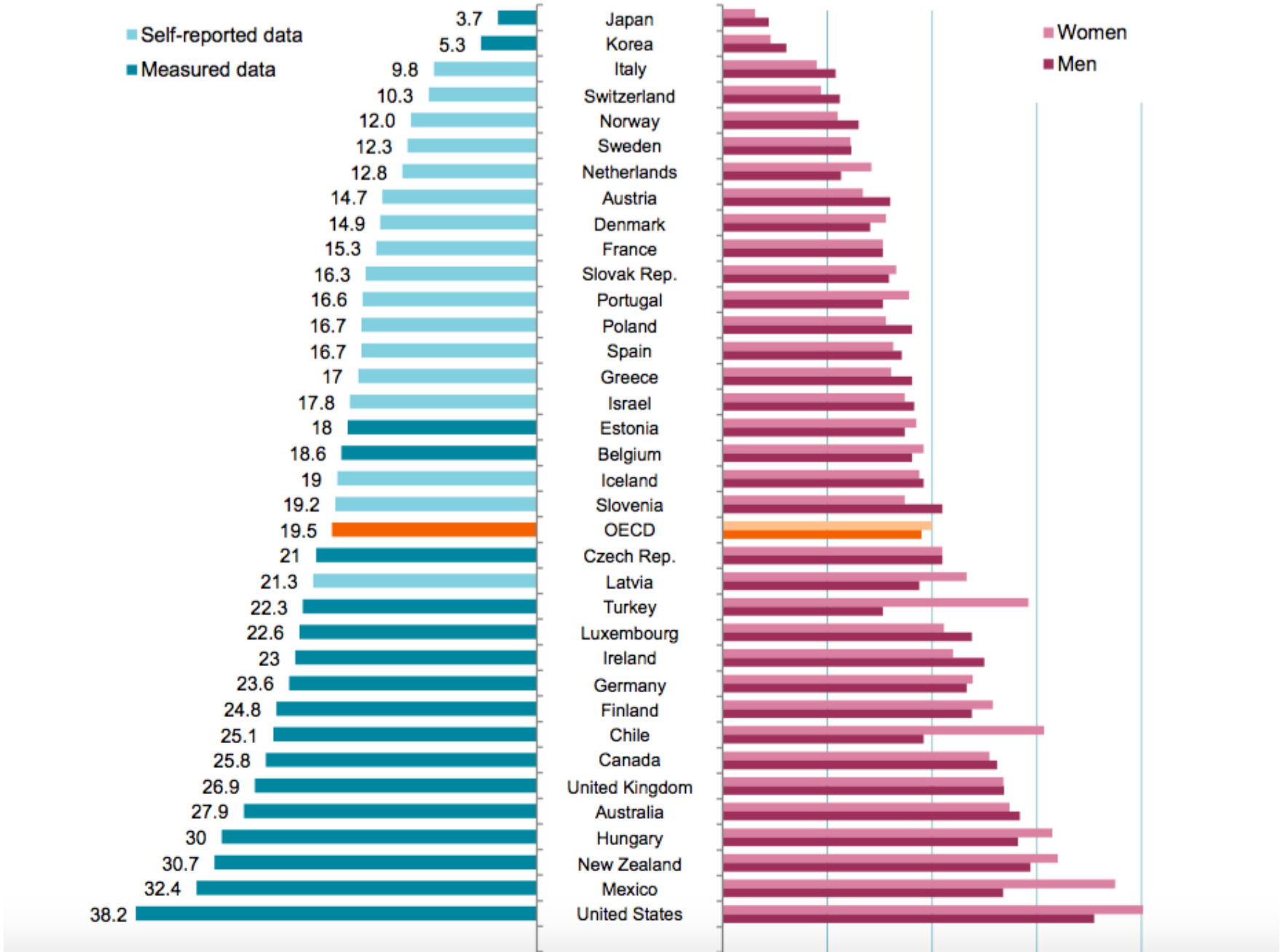
AN UPDATE ON COMPLEX OBESITY 2020

Dr Ole Schmiedel MRCP MD FRACP

Physician and Endocrinologist

SCD Auckland Diabetes Centre

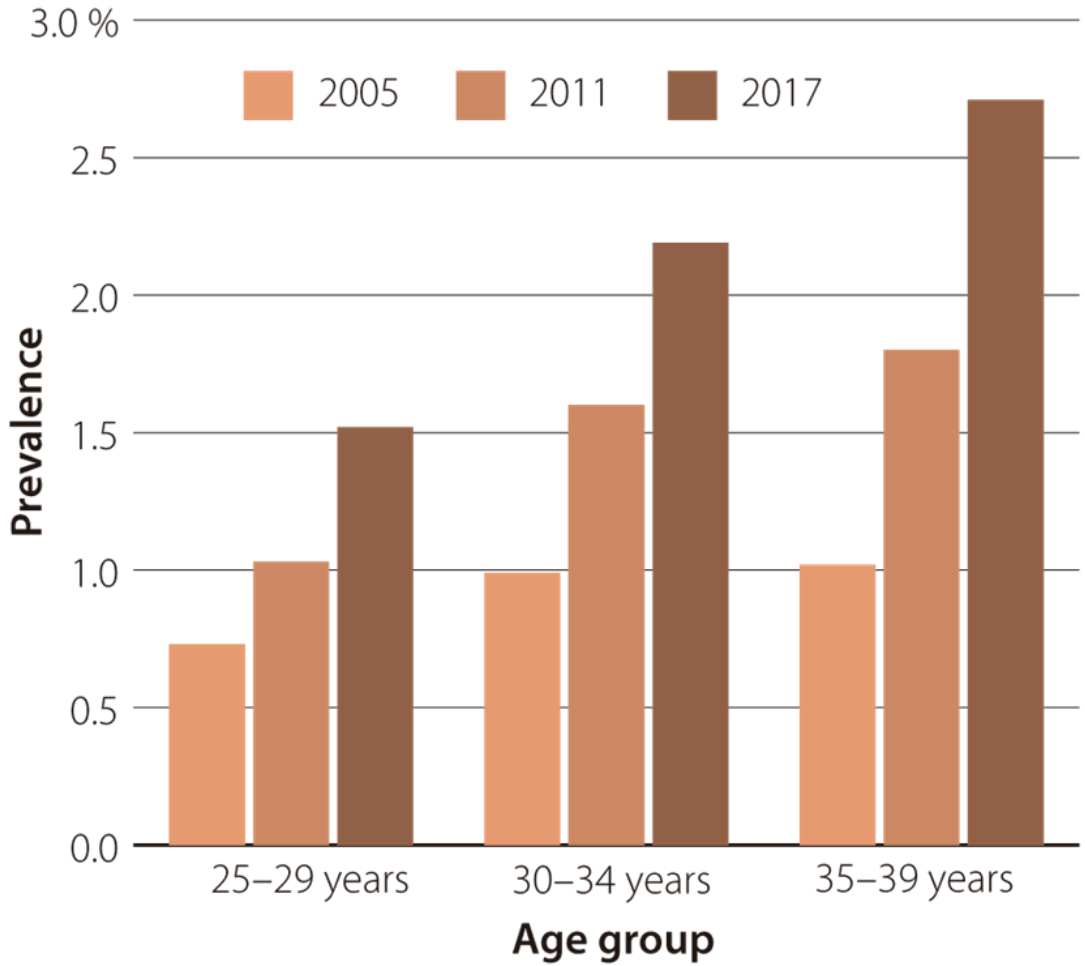
Figure 1: Obesity among adults, 2015 or nearest year



Changes in the prevalence of diabetes from 2005-2017 in adults aged 25-39 years in New Zealand

- The incidence of type 2 diabetes in younger adults and adolescents in New Zealand is increasing; people of Māori, Pacific and South-Asian ethnicities are particularly at risk

- People with early onset type 2 diabetes have increased morbidity and mortality compared to those with a later onset *or to those of similar age with type 1 diabetes*



T2DM in children, adolescents and young adults

- The incidence of type 2 diabetes in **young adults and adolescents** in New Zealand is increasing
- Māori, Pacific and South-Asian ethnicities are particularly at risk
- Early presentation - associated with an aggressive phenotype

- **higher morbidity and mortality than T1DM diagnosed at any age group, or T2DM diagnosed in older age groups**

1. Test HbA1c levels in patients at high risk, **regardless of their age** (screening guide)
2. Treatments need to be more assertive, e.g. pharmacological treatment escalated sooner
3. Preventing, or delaying, onset of type 2 diabetes - to reduce the burden of diabetes complications
4. A high degree of patient engagement is crucial

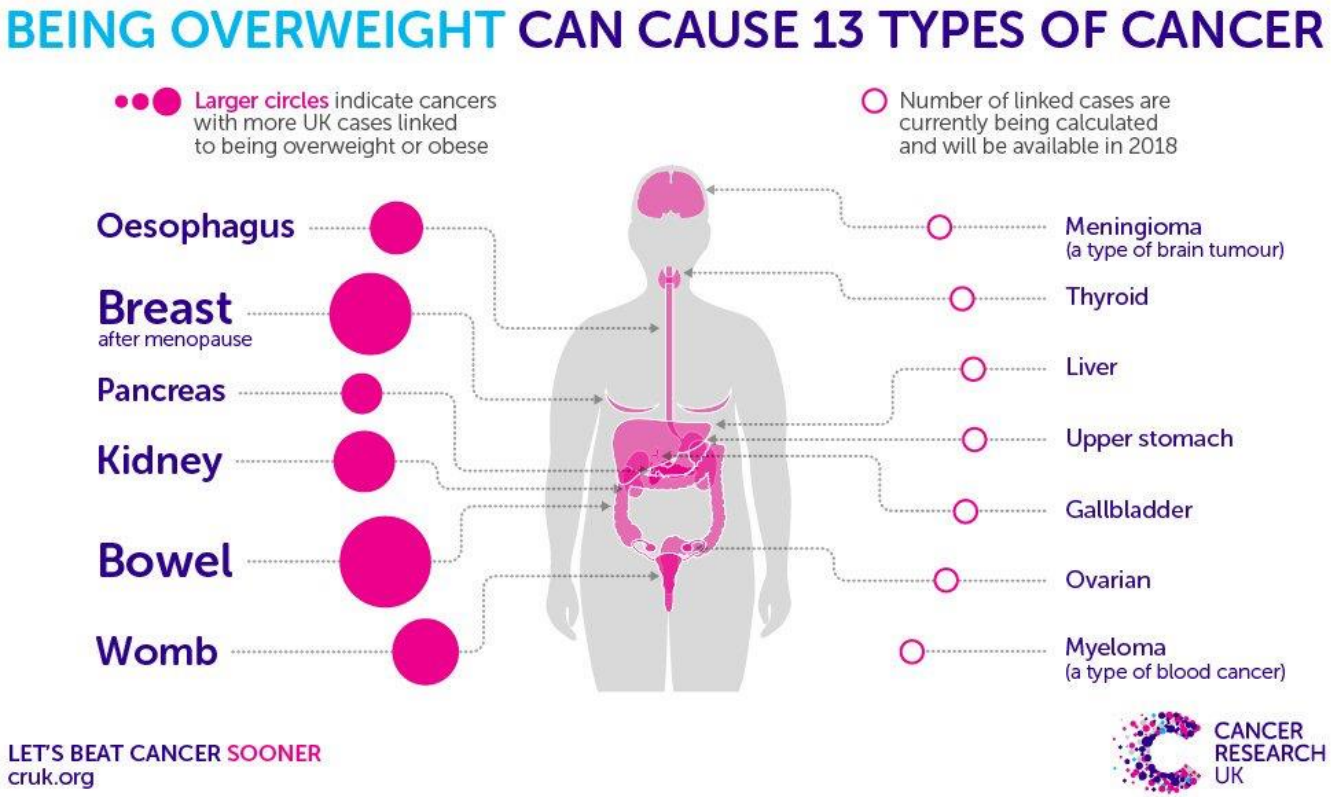
Key Principles

Obesity is a Chronic Condition

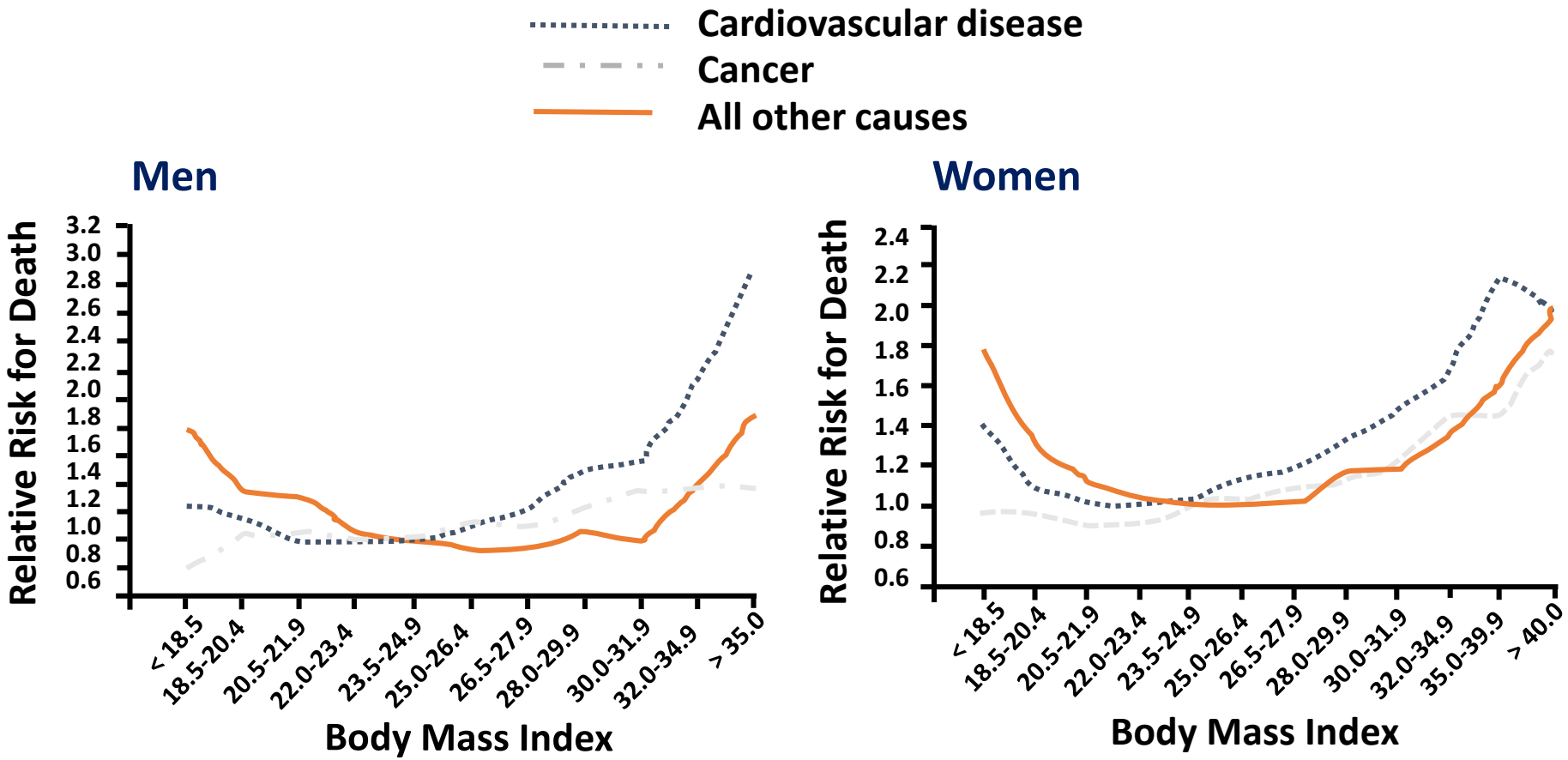
- Obesity is a chronic and often progressive condition not unlike diabetes or hypertension.
- Successful obesity management requires realistic and sustainable treatment strategies.
- Short-term "quick-fix" solutions focusing on maximizing weight loss are generally unsustainable and therefore associated with high rates of weight regain.

Co-morbidities and complications

- Increased morbidity and mortality (premature death), several (>100) significant associated co-morbidities (including several cancers)
- Significant impact on quality of life and wellbeing



Relative Risk for Death From Cardiovascular Disease, Cancer, and All Other Causes



The reference category consisted of participants with BMIs of 23.5-24.9 kg/m^2.

Calle EE, et al. *N Engl J Med.* 1999;341:1097-1105.

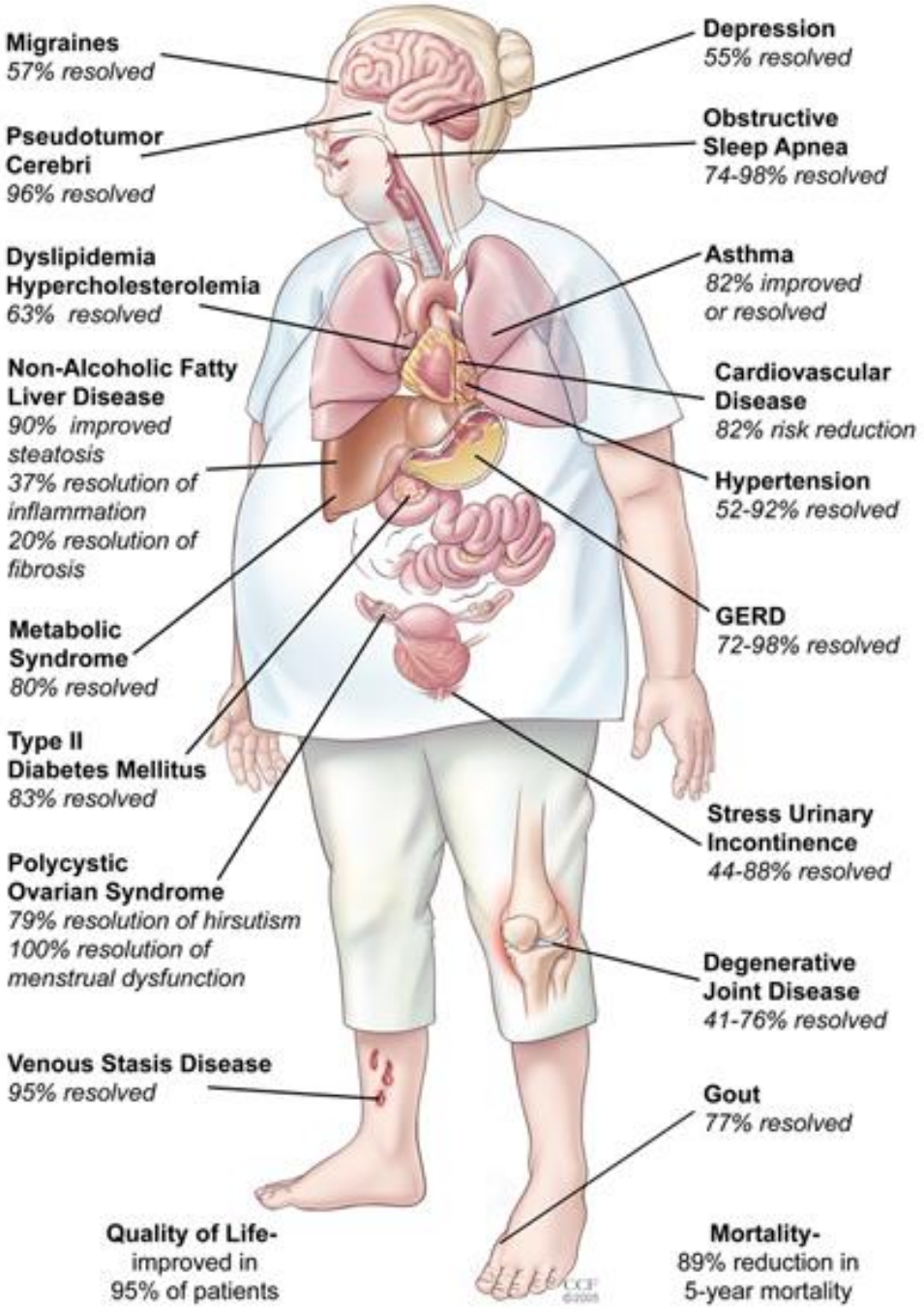
Obesity as a disease (clinicians approach)

- Inheritability
  - Genetics (40-70% inherited)
  - Epigenetics
- Pathophysiology:
  - Dysregulation of gut-brain axis that controls food intake
  - Obesity – mechanical and metabolic effects
- Chronic and relapsing
  - *Why? - mechanisms behind* the 'vicious cycle' & set-weight concept
  - Need for long-term management and prevention of weight cycling

- Environmental factors
  - Obesogenic environments

Obesity complications

- Mechanical
- Metabolic
- Cancer
- Psychological & QOL
- Functional
- Mortality



EOSS: EDMONTON OBESITY STAGING SYSTEM - *Staging Tool*

STAGE 0

- **NO** sign of obesity-related risk factors
- **NO** physical symptoms
- **NO** psychological symptoms
- **NO** functional limitations

Case Example:
Physically active female with a BMI of 32 kg/m², no risk factors, no physical symptoms, no self-esteem issues, and no functional limitations.

Class I, Stage 0 Obesity

EOSS Score

WHO Obesity Classfication

STAGE 1

- Patient has obesity-related **SUBCLINICAL** risk factors
  (borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.)
  - *OR* -
- **MILD** physical symptoms - patient currently not requiring medical treatment for comorbidities
  (dyspnea on moderate exertion, occasional aches/pains, fatigue, etc.) - *OR* -
- **MILD** obesity-related psychological symptoms and/or mild impairment of well-being
  (quality of life not impacted)

Case Example:
38 year old female with a BMI of 59.2 kg/m², borderline hypertension, mild lower back pain, and knee pain. Patient does not require any medical intervention.

Class III, Stage 1 Obesity

WHO CLASSIFICATION OF WEIGHT STATUS (**BMI kg/m²**)

Obese Class I ..... 30 - 34.9
Obese Class II ..... 35 - 39.9
Obese Class III ..... ≥40

Stage 0 / Stage 1 Obesity

Patient ***does not meet clinical criteria for admission*** at this time.
Please refer to primary care for further preventative treatment options.

STAGE 2

- Patient has **ESTABLISHED** obesity-related comorbidities requiring medical intervention
  (HTN, Type 2 Diabetes, sleep apnea, PCOS, osteoarthritis, reflux disease) - *OR* -
- **MODERATE** obesity-related psychological symptoms
  (depression, eating disorders, anxiety disorder) - *OR* -
- **MODERATE** functional limitations in daily activities
  (quality of life is beginning to be impacted)

Case Example:
32 year old male with a BMI of 36 kg/m² who has primary hypertension and obstructive sleep apnea.

Class II, Stage 2 Obesity

STAGE 3

- Patient has **significant** obesity-related end-organ damage (myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis) - *OR* -
- **SIGNIFICANT** obesity-related psychological symptoms
  (major depression, suicide ideation) - *OR* -
- **SIGNIFICANT** functional limitations
  (eg: unable to work or complete routine activities, reduced mobility)
- **SIGNIFICANT** impairment of well-being
  (quality of life is significantly impacted)

Case Example:
49 year old female with a BMI of 67 kg/m² diagnosed with sleep apnea, CV disease, GERD, and suffered from stroke. Patient's mobility is significantly limited due to osteoarthritis and gout.

Class III, Stage 3 Obesity

STAGE 4

- **SEVERE** (potential end stage) from obesity-related comorbidities - *OR* -
- **SEVERELY** disabling psychological symptoms - *OR* -
- **SEVERE** functional limitations

Case Example:
45 year old female with a BMI of 54 kg/m² who is in a wheel chair because of disabling arthritis, severe hyperpnea, and anxiety disorder.

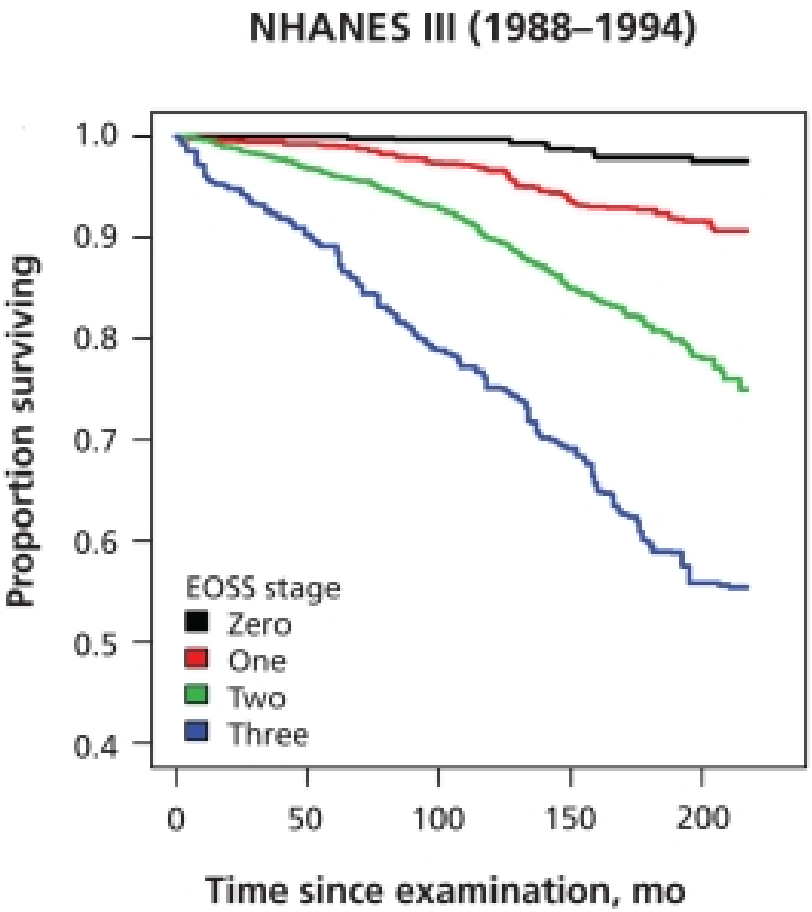
Class III, Stage 4 Obesity

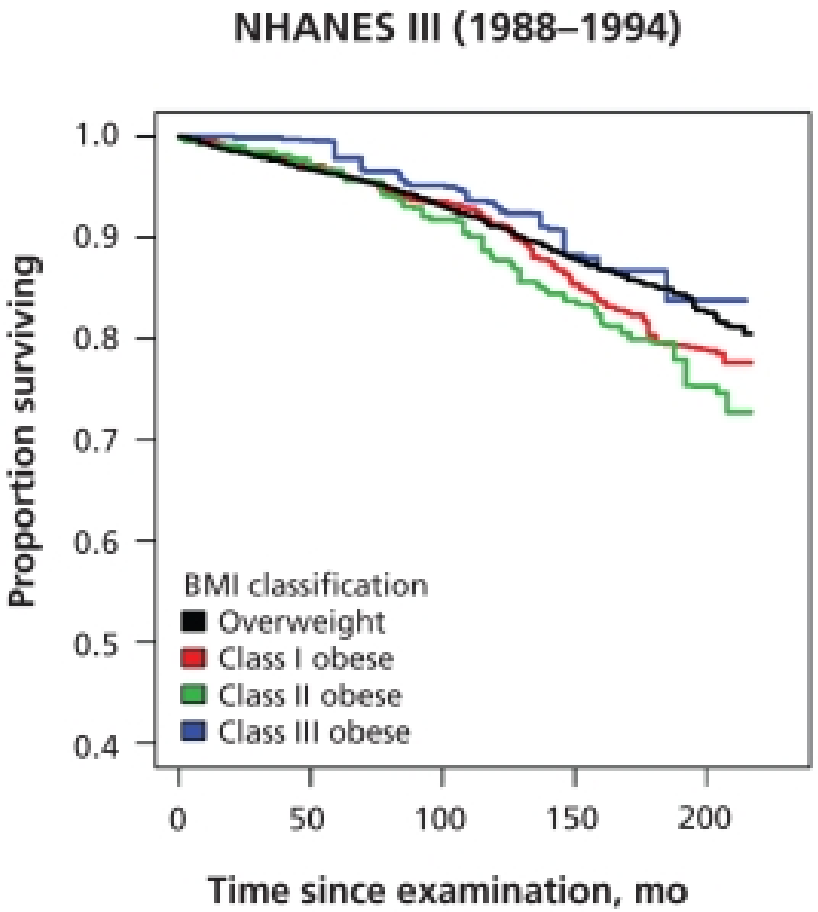
Alberta Health Services

UNIVERSITY OF ALBERTA

Sharma AM & Kushner RF, *Int J Obes* 2009

Edmonton Staging System Can Predict Mortality Better than BMI

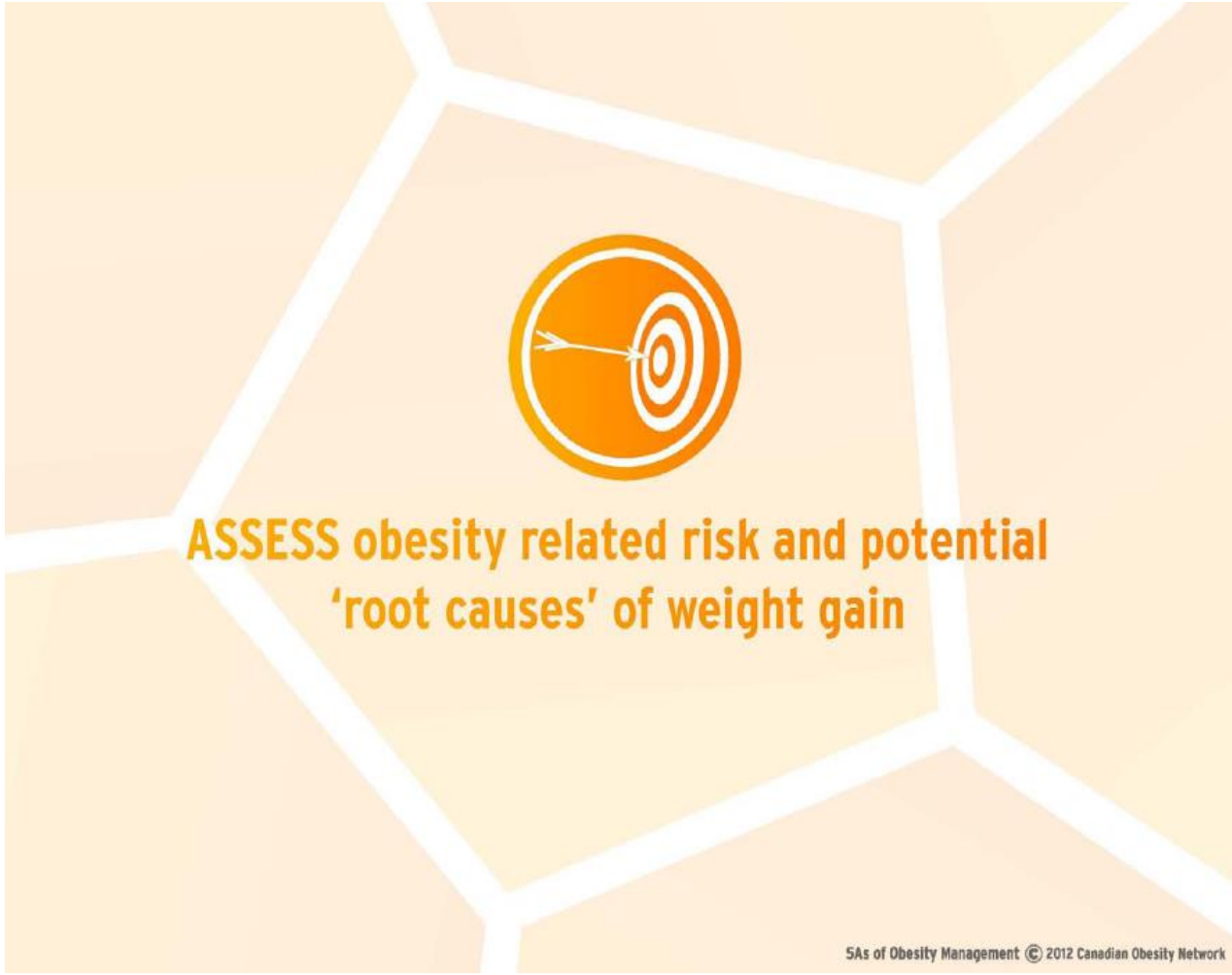




Padwal R et al. CMAJ. 2011

Bariatric assessment

- Structured
- Pre-clinic ‘patient assessment tools’
- Comprehensive clinic assessment
- Investigations
- Agreed management plan



- *The obesity consultation*
- *Use of patient self-assessment tools*
- *Assessment process (1)*

1st visit

- *Obesity timeline* (age of onset, changes in childhood and adolescence, triggers for weight gain and weight loss attempts, what worked and what didn't (show my timeline – insert picture)

Kamal in 2016

- **29yo male** presented to ACH with vomiting, central abdominal cramps, dehydration, constipation, decreased appetite and headaches.
- 1 month history of polyuria and polydipsia.
- 3 week history of vomiting every day, unable to keep food/fluids down-saw GP 5 days prior and received anti-emetics.
- Reports weight gain after high school.
- Dx with depression and subsequent 40-50kg weight gain over 3 months. Started on fluoxetine

Investigations and progress:

Investigations:

- ECG: sinus tachycardia
- Haematology: **Hb 183,** platelets 262, WBC 10.28, **HbA1c 118**
- Biochemistry: Na+ 130, **K+ 2.9, Glucose 24.3,** urea 3.9, Cr 159, bilirubin 9, GGT 43, **ALP 148,** lipase 114. Serum B-hydroxybutyrate >8. **pH 7.21, bicarb 12, lactate 1.4.**
- Urinalysis: Glucose 2+, ketones 4+, protein 2+, nitrate negative, Leu negative.

- **Impression:** DKA with acidosis , also severe dehydration, AKI and ongoing hypokalaemia secondary to vomiting and insulin.

- Dramatic improvement with GIK infusion and IVF and BSL stabilised. Transitioned to insulin injections with diabetes nurse input and education around self-administration. BSL stabilised.
-
- **Final regime 50units mane, 20units midi, 50units nocte.** Educated around hypoglycaemia and management.

Kamal in 2016

- diagnosed diabetes (May 2016), HbA1c 44 mmol/mol on 19.07.2016; probable type 2 diabetes
  - Admission serum hydroxybutyrate >8 on 15.05.2016 with glucose 24.3
  - **GAD antibody IA2 antibody negative**
  - 30 kg weight loss in the month preceding Hospital admission with osmotic symptoms
  - C- peptide 1950pmol/L (ref 970-1470) indicating **type 2 diabetes**

- Obesity – current 140.6 kg, height 1.77 metres
- Pre-diabetes with HbA1c of 44 on 31.07.2015
- Depression – diagnosed 2012, currently controlled on fluoxetine
- peak weight of 170 kg prior to his illness

Kamal 2016

Current Medications

- Fluoxetine 20 mg once daily
- Omeprazole 40 mg nocte - for probable reflux dyspepsia
- Metformin 500 mg bd – advised to increase to 1 gram bd
- PenMix 30, 45 units bd – **advised to reduce to 20 units bd** and subsequently to **trial stopping** if blood glucose levels under 10 and to start **glipizide 10 mg bd**

<u>History & examination:</u>

- mother is overweight as is her sister and his brother with truncal obesity, no family history of diabetes
- snoring at night and has some daytime somnolence (possible OSA)
- acanthosis nigricans affecting his posterior neck
- blood pressure was normal at 105/60 mmHg.

Kamal 2016

- **<u>Phone review: 19.9.2016</u>** – on no insulin, just metformin 1g bd and glipizide 10mg bd, has been getting hypoglycaemia around 11pm.

- **Advised to stop glipizide in the evening**. Pre-breakfast around 5.5, but 2 hours after breakfast is around 7-9.

- HbA1c 33, indicating return to normal glucose control. **May stop glipizide altogether**.

Kamal 2017

- experiences quite significant hunger sensations and cravings, mostly first thing in the morning after getting up as well as at night-time
- snoring significantly and daytime sleepiness
- HbA1c is 36mmol/mol
- His lipid profile shows an excellent LDL with an increased triglyceride to HDL ratio, a sign of his metabolic syndrome
- *This will improve with a further reduction of carbohydrate intake. Consider fibrate in the future*

Kamal 2017

- **05 2017:** started on a low dose of Duromine. He had negative cardiac investigations. We normally start with a very low dose and titrate it up in a stepwise fashion.

- **12 2017:** He commenced Duromine after our last review. He was tolerating alternate day dosing well, however when he increased the dose to 15mg per day he *noticed sleeping problems, tachycardia and headaches.* He also noted a dry mouth and sometimes unspecific body shaking that reminded him of hypoglycaemia.

- Continued low dose Duromine 7.5 mg and added Topiramate 25mg (he signed the appropriate consent forms)

- **04 2018:** tolerating the Topiramate and Metformin well. He had a recent stress event, which caused worsening of his underlying depression / anxiety.

- discussed appropriateness of Topiramate, concerned about his mood changes, phase out Topiramate

Progress: - 05 2019 referred for bariatric surgery

“He was invited to attend the bariatric information seminar on 31 July 2019 and 25 September 2019. Unfortunately he did not attend these two appointments.

Bariatric surgery requires a high level of commitment and motivation by the patient to make significant and consistent lifestyle changes. Non-attendance at hospital appointment is an indication of poor commitment.

We are therefore discharging Shamal from the bariatric programme back to your care. If Shamal would like to reconsider bariatric surgery in the future we would require a re-referral.”

Progress : 11 2019

Medications

- Metformin 500mg bd
- **Orlistat 120mg bd**
- Topiramate (reduced)
- Escitalopram 10mg
- Pravastatin 20mg

Results

- **Testosterone 6.7, oestradiol 140, LH 4.3, FSH 3.1**
- **HbA1c 37mmol/mol**, LDL 2.3, HDL 0.77, eGFR 72, TSH 2.7, ACR<1

Comment:

- borderline testosterone value of 6.7, an effect of his obesity, not recommended treatment at present
- Topiramate phased out
- Referred to psychology

Questions:

- Possible treatment options?
- Treatment for depression
- Treatment for obesity
  - Medications
  - Procedures, surgery

Sophia, 36

- **Diagnoses**
- Type 2 diabetes diagnosed August 2015 in the setting of acute renal failure
  - Strong family history for type 2 diabetes
- Renal impairment secondary to post *streptococcal* glomerulonephritis
- Obesity Edmonton Obesity Stage 3, weight reduced recently
  - **Currently enrolled in the bariatric programme and preparing for surgery**
- Mild left ventricular hypertrophy
- Hypertension on treatment
- Possible NAFLD (echogenic liver on ultrasound)

- **Medications**
- Metformin 1 g bd
- Cilazapril plus 5/12.5 mg od
- Allopurinol 100 mg od (new medication)
- Cholecalciferol 1.25 mg monthly
- Duromine 15 mg od (new medication)

Sophia 36

- She **struggles from significant hunger and cravings**.

- blood pressure 125/80 and HbA1c is 52 mmol/mol
- renal function relatively stable with an eGFR of 55 – 57
- uric acid has been rising to 0.73 & recent episode of gout, treated with prednisone. I commenced low dose of allopurinol.

- 15 mg of duromine to help with hunger and cravings and to prevent weight regain before the surgery.
- *This medication should be stopped once she proceeds to surgery. She needs to continue with her vitamin D as she initially was significantly vitamin D deficient.*
- She also shall continue with the same dose of metformin until surgery. She might be able to come off metformin post-operatively.

Sophia, 36

- **gastric bypass surgery 04/06/2019, follow-up Bariatric Services (**Single anastomosis gastric bypass)
- Bulky Omentum and a large floppy stomach and a large liver.

- Type 2 diabetes improved and medication discontinued (HbA1c 37mmol/mol)
- Hypertension improved *and medication reduced*
- Recent fall with trauma to chest wall and rib fracture
- Hyperparathyroidism due to Vitamin D deficiency or CKD – (PTH of 11.1, borderline corrected calcium of 2.56)
- Iron deficiency, on treatment
- Liver function improved

Sophia 36

- **Medications**
- Metformin 1g bd (reduced dose)
- Centrum Multi-Vitamin Strong two tablets daily.
- Cholecalciferol 1.25 mg every second week.
- Ferrous sulphate 325 mg od.
- Omeprazole 40 mg od.
- **Topiramate 25 mg nocte.**
- Paracetamol and tramadol prn.
- Ondansetron prn.

Recommendation

1. Start vitamins, 25OH D3, iron, and reduce dose of metformin
2. recheck BP (note renal impairment)
3. Start topiramate 25 mg for migrainous headaches prohylaxis and help with significant nocturnal cravings

Sophia 36

- The first couple of weeks were great; however, over the last few weeks she has been struggling with general tiredness, fatigue, malaise, weak legs and significant nocturnal hunger and cravings.
- She also complains about frequent right-sided migrainous headaches.
- her weight has reduced from 170 to 152 kg over two months but now reaching a plateu
- She missed a number of appointments with the bariatric team; hence, I added her standard post-bariatric supplement regimen.
-
- To help her with migraines and nocturnal cravings, I started topiramate as detailed above. There are no contraindication (no glaucoma, no risk of pregnancy), and I explained possible side effects of this medication.
- She has been advised about contraceptive measures
- Her diabetes now well controlled, reduced her metformin to 500 mg twice daily, and subsequently stop metformin completely

The utility of weight loss medications after bariatric surgery for weight regain or inadequate weight loss: A multi-center study

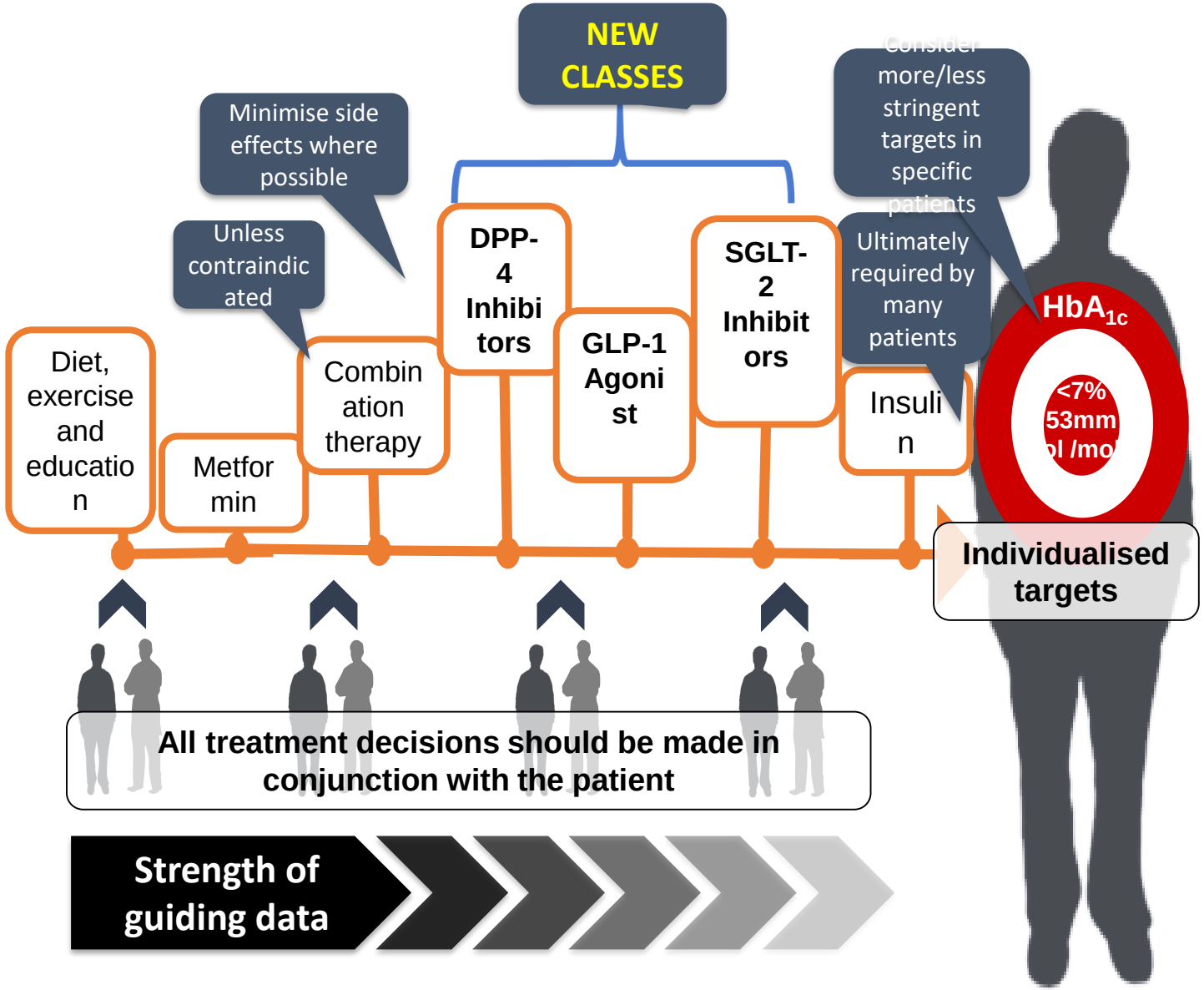
October 2016, Surgery for Obesity and Related Diseases 13(3

- Topiramate was the only medication that demonstrated a statistically significant response for weight loss with patients being twice as likely to lose at least 10% of their weight when placed on this medication (odds ratio = 1.9; P = .018).

- Regardless of the postoperative body mass index, patients who underwent RYGB were significantly more likely to lose≥5% of their total weight with the aid of weight loss medications.

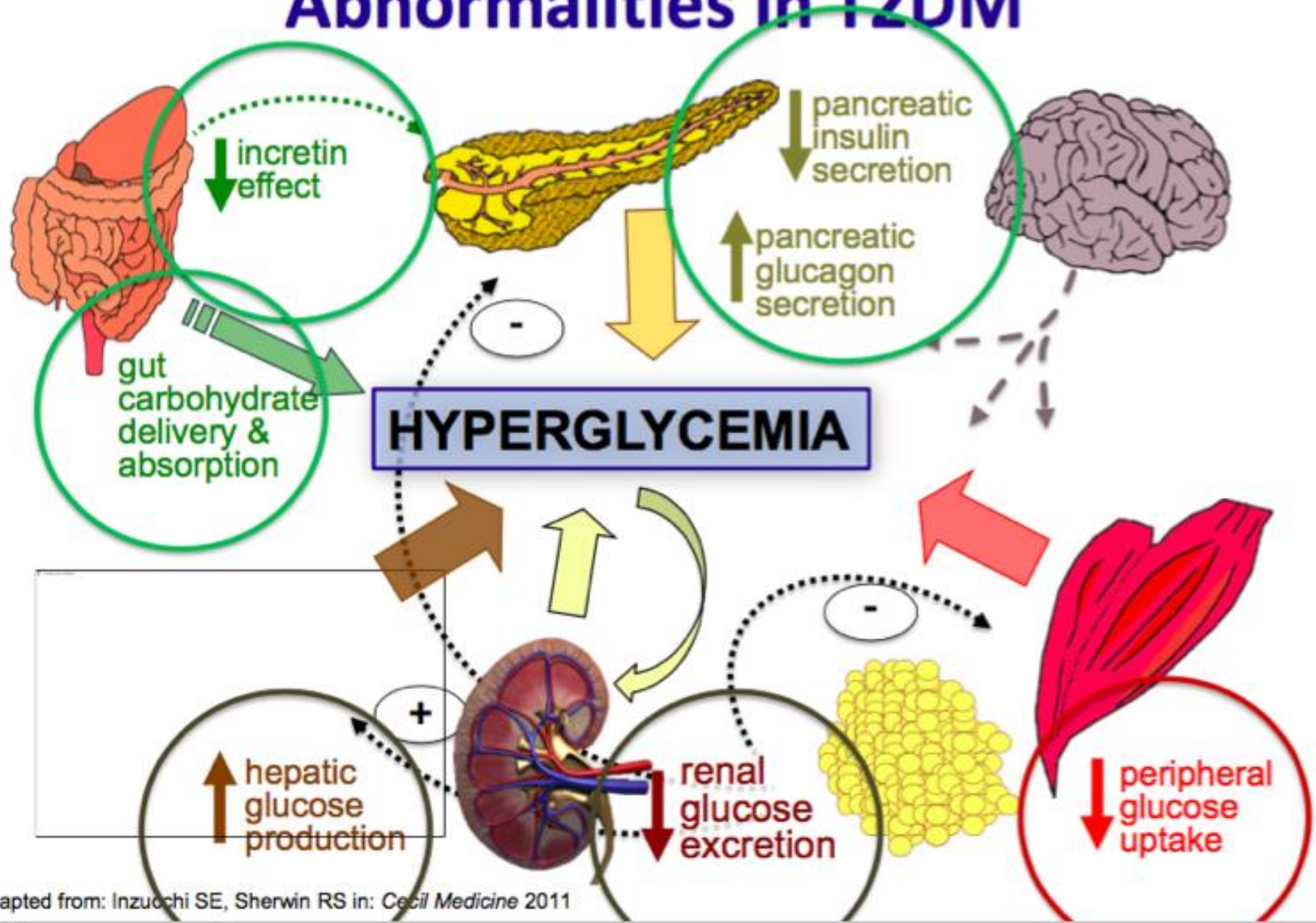
- Conclusions: Weight loss pharmacotherapy serves as a useful adjunct to bariatric surgery in patients with inadequate weight loss or weight regain.

Diabetes medications



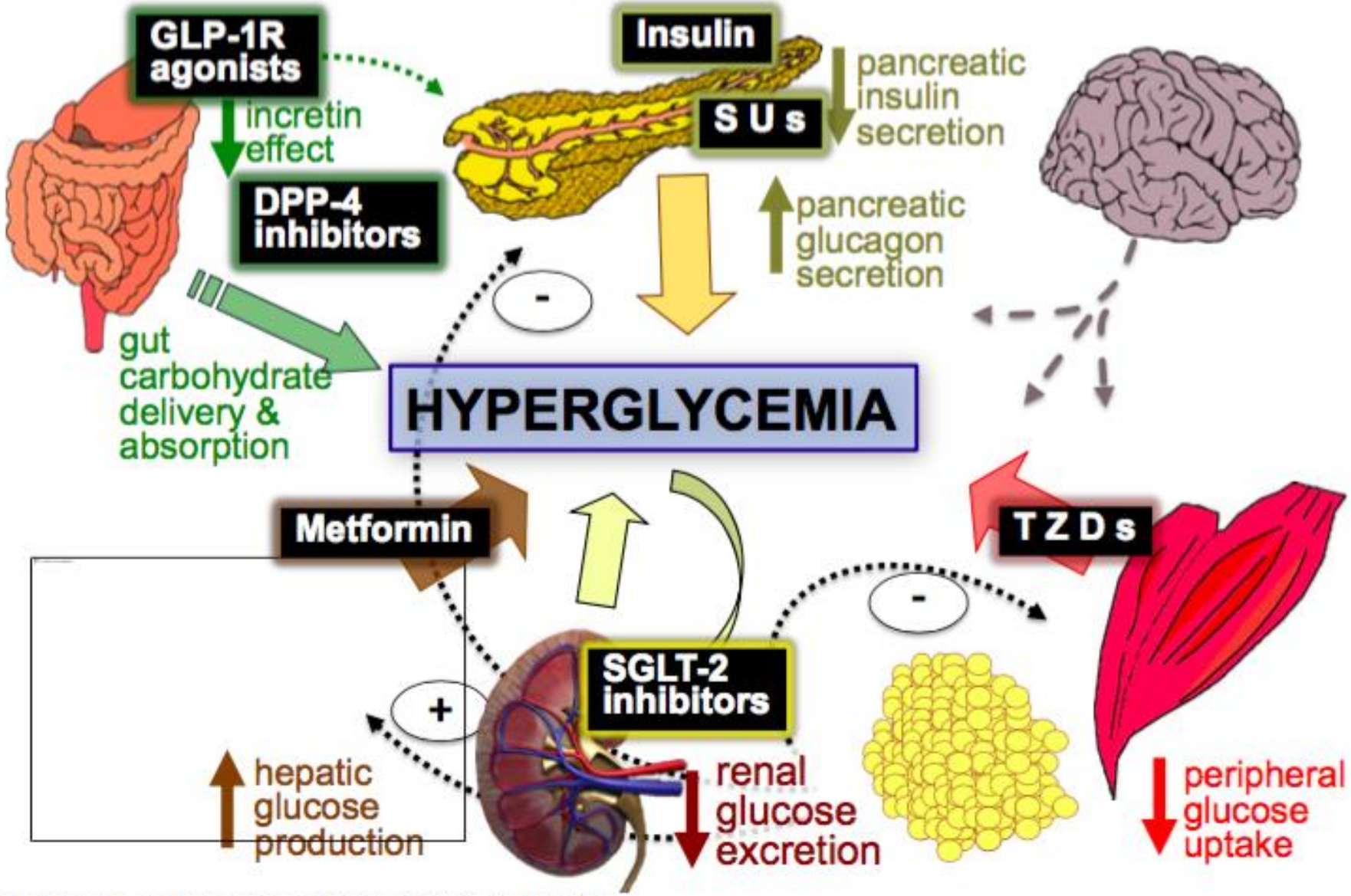
ADA, American Diabetes Association; CV, cardiovascular; EASD, European Association for the Study of Diabetes.
Adapted from: Inzucchi SE, *et al. Diabetes Care* 2012;**35**:1364–79.

Multiple Complex Pathophysiological Abnormalities in T2DM



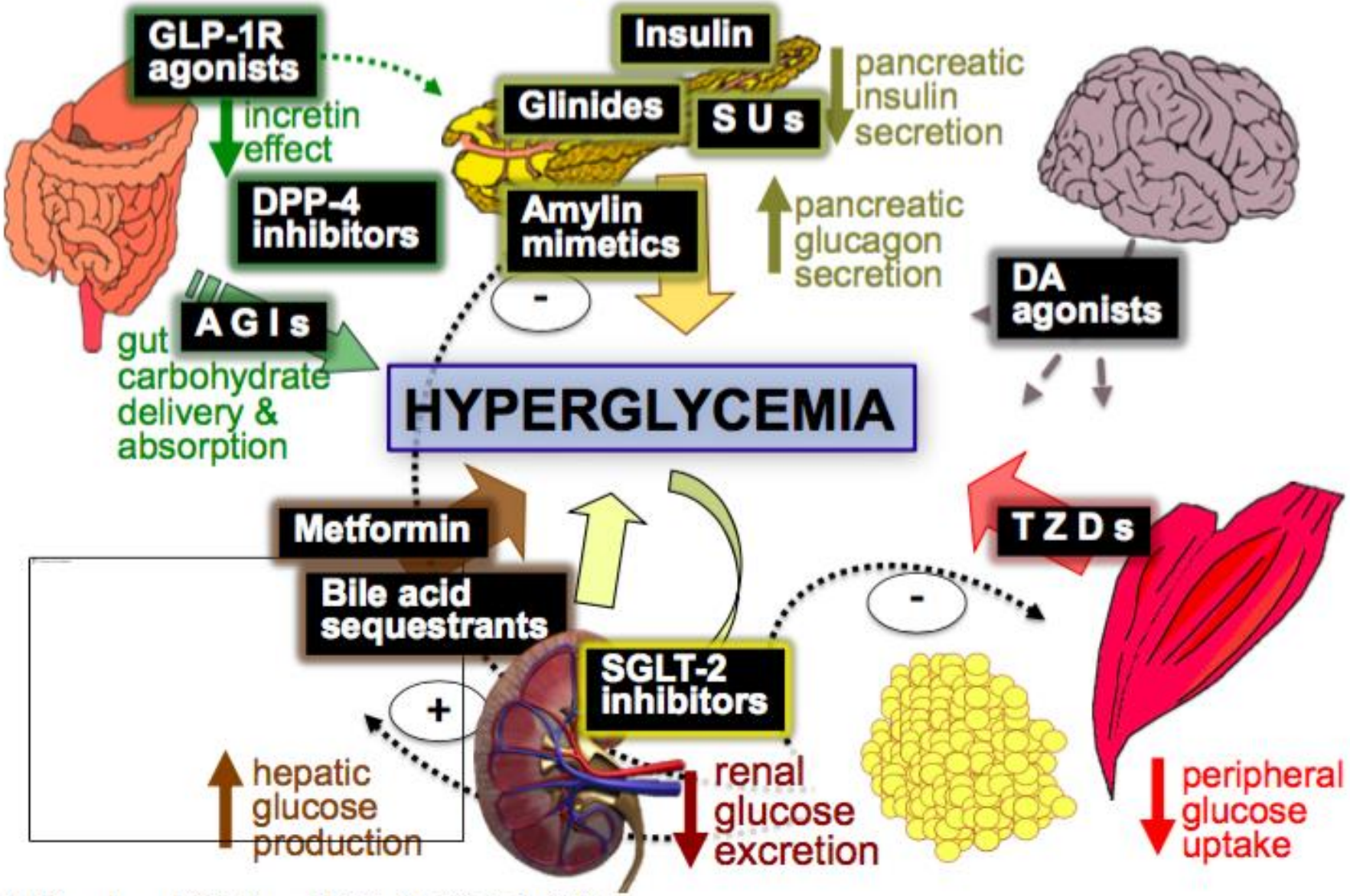
Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

Major Pathophysiologically-Based Therapies for T2DM

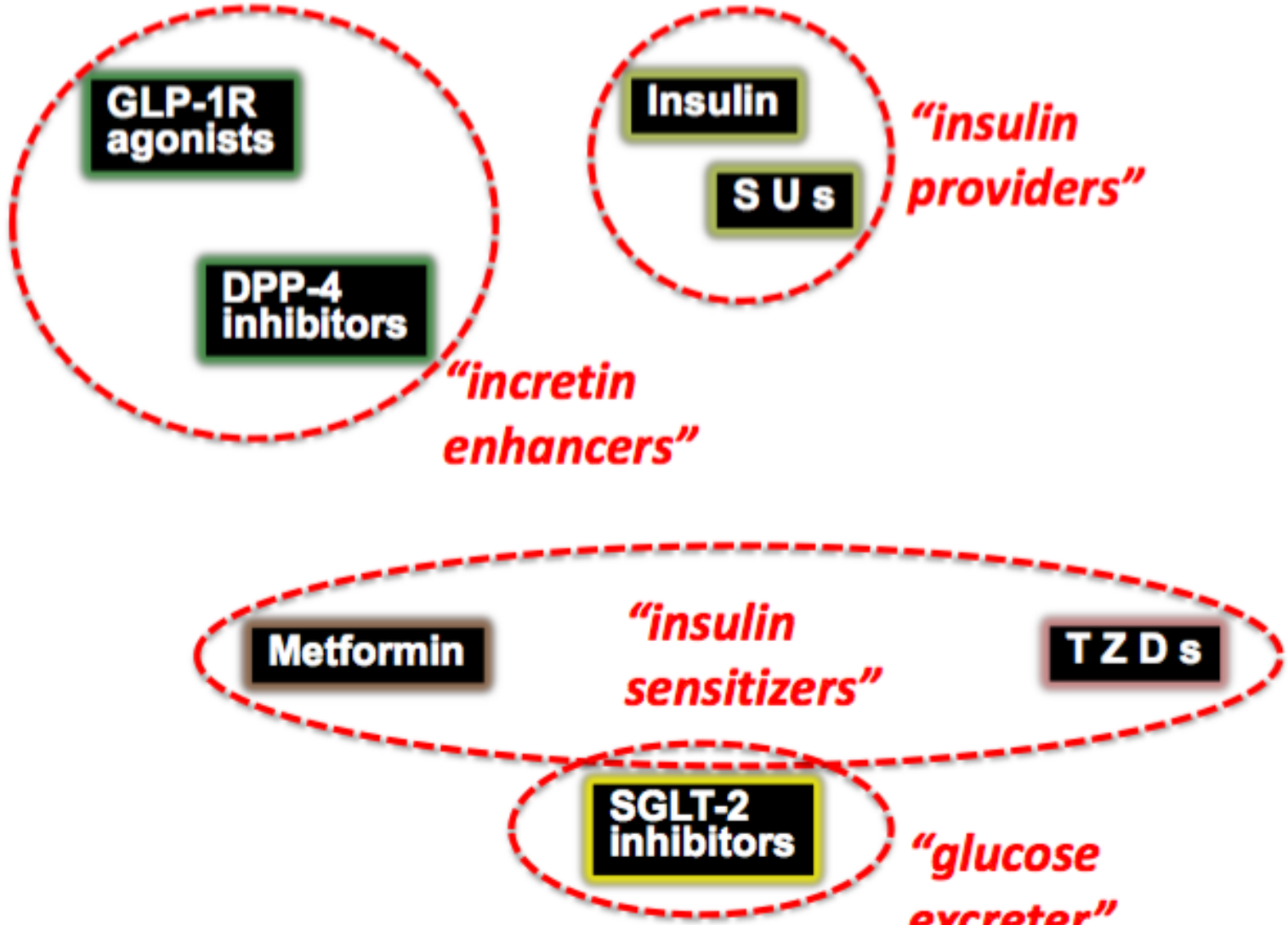


Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

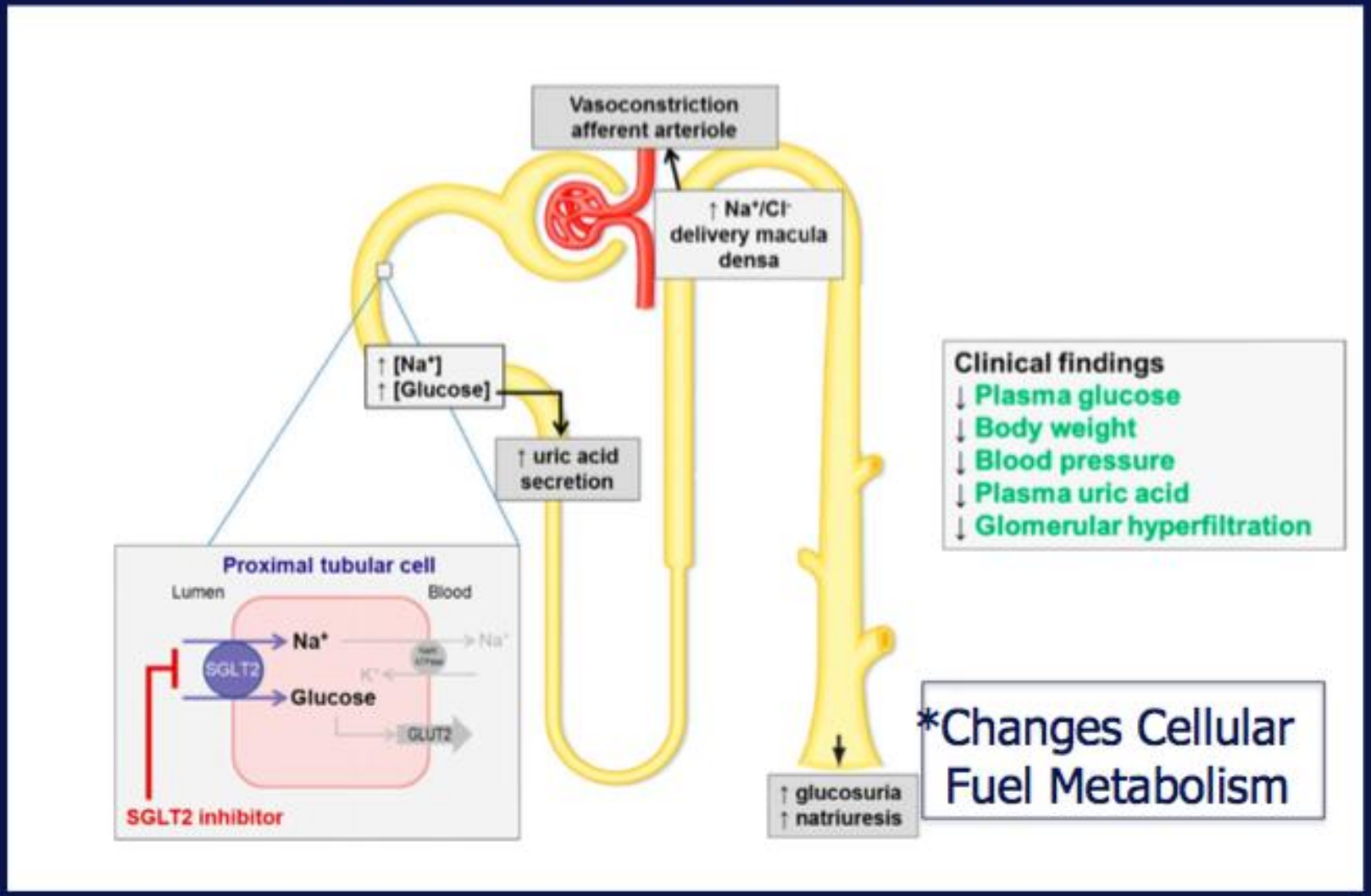
Multiple Pathophysiologically-Based Therapies for T2DM



Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011


GLP-1R agonists
DPP-4 inhibitors
"incretin enhancers"
Insulin
S U s
"insulin providers"
Metformin
"insulin sensitizers"
T Z D s
SGLT-2 inhibitors
"glucose excreter"

Effects of SGLT2 Inhibitors



van Bommel et al Clinical J. Amer. Soc. Nephrol. 12:700-710, 2017

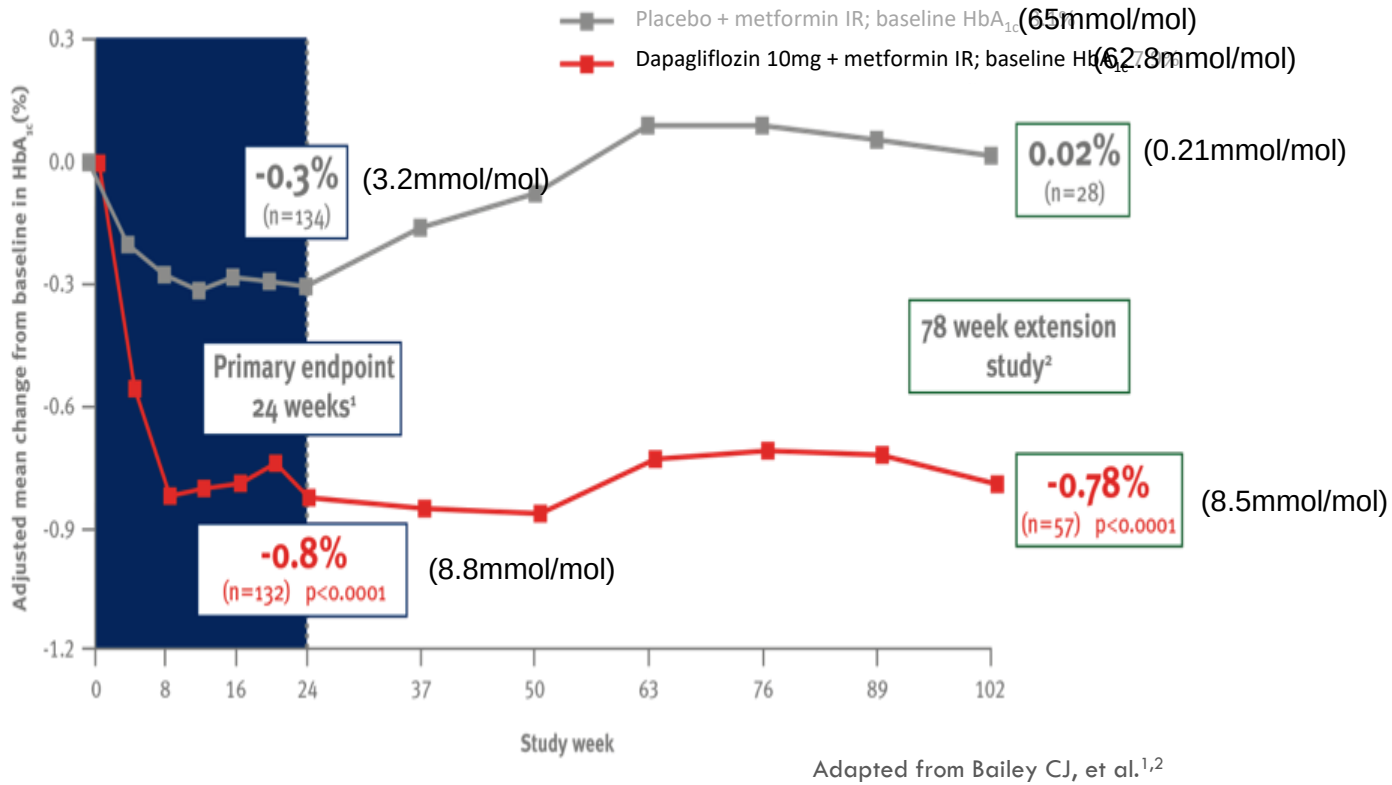
*Mudaliar et al Diabetes Care:1115-1122, 2016

Joslin Diabetes Center

Dapagliflozin plus metformin IR:

Significant HbA_{1c} reduction sustained out to 102 weeks[1,2]

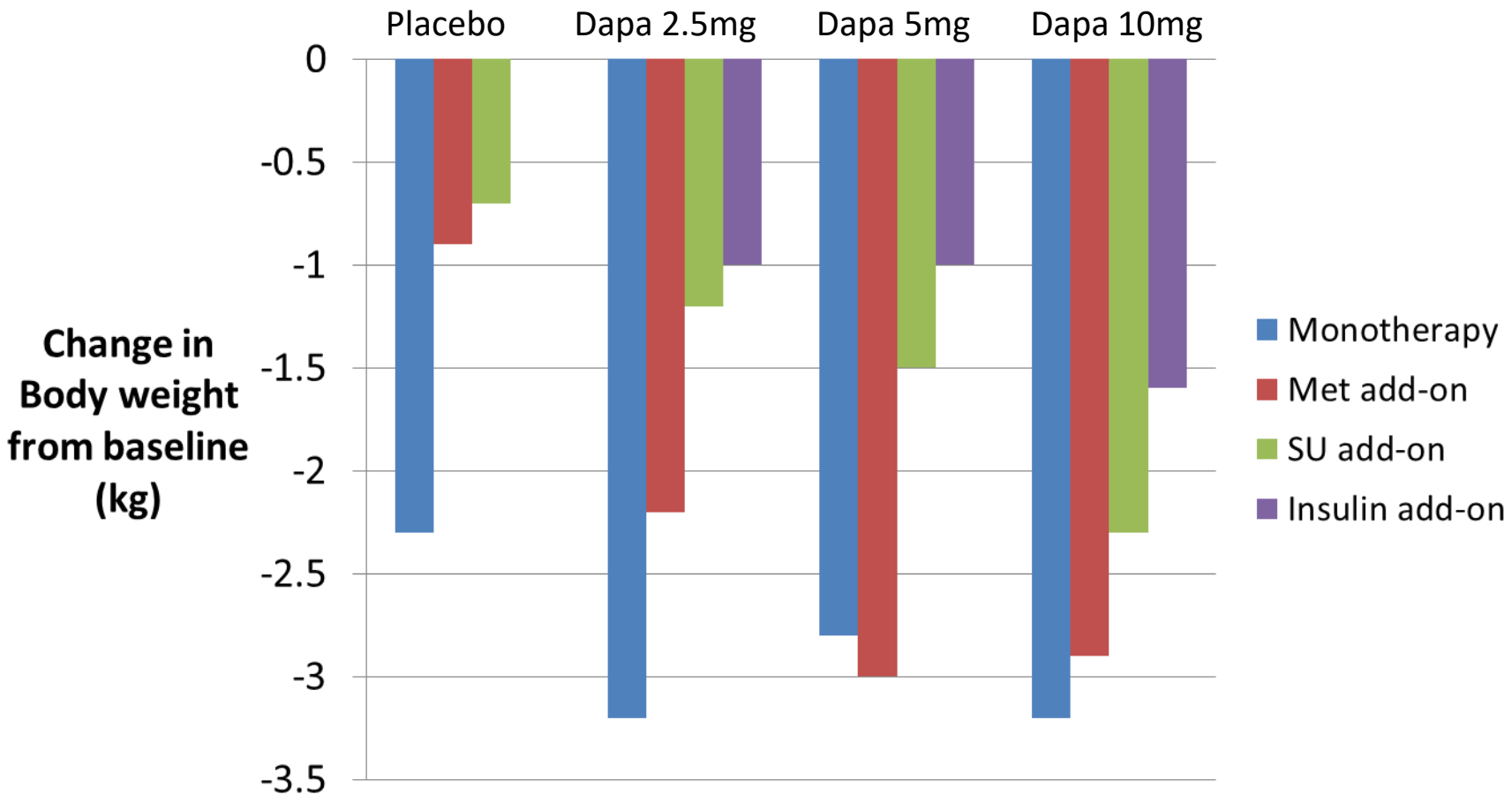
(compared with placebo, in patients taking metformin IR)



Adapted from Bailey CJ, et al.[1,2]

1. Bailey CJ, et al. BMC Medicine 2013;11:43:1-10.
2. Bailey CJ, et al. Lancet 2010;375:2223−2233.

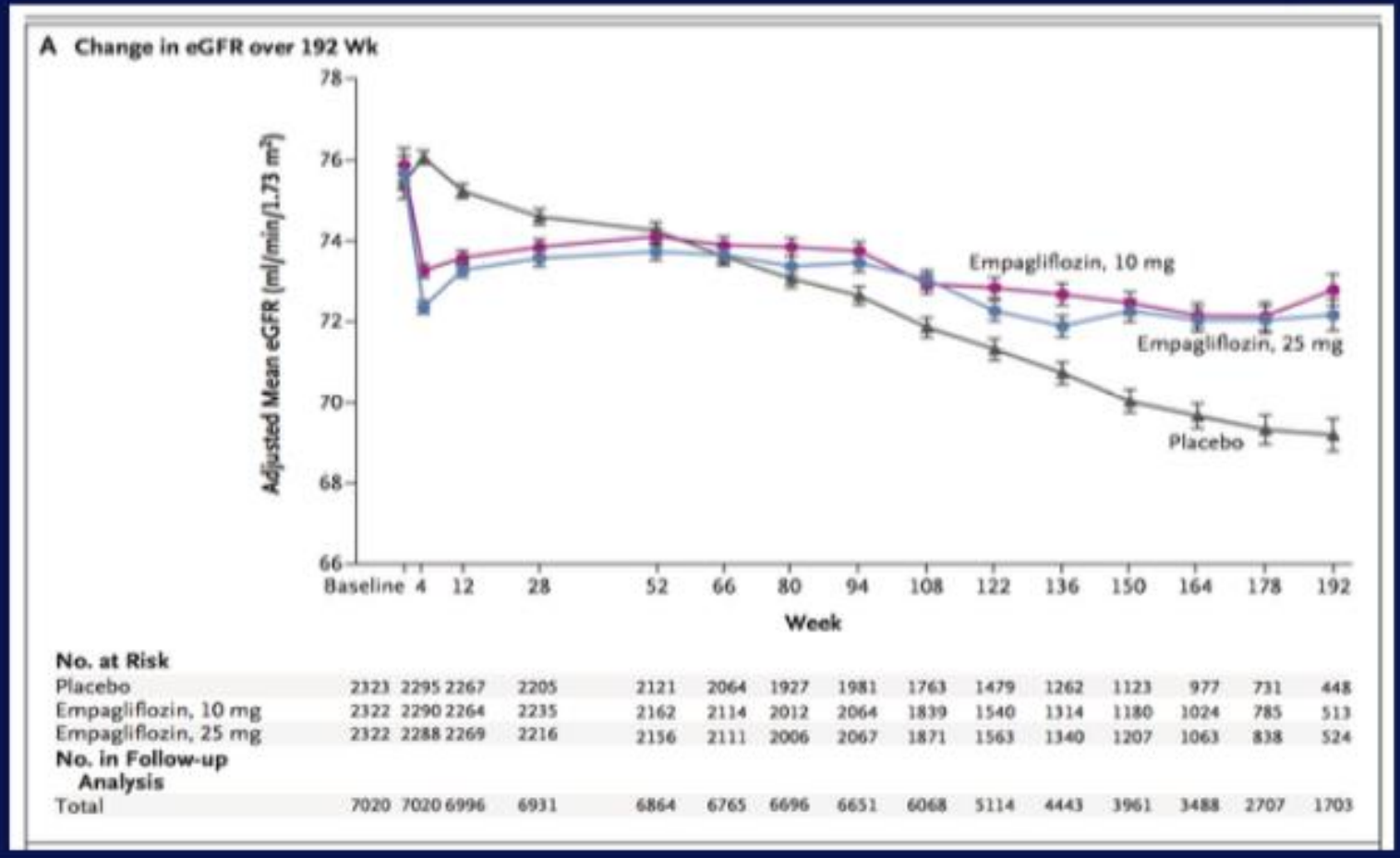
Changes from Baseline in Body Weight in Phase 3 Dapagliflozin Studies



Wilding JPH, et al. Abstract 78-OR. ADA 2010; Strojek K, et al. Abstract 870. EASD 2010; Ferrannini E, et al. *Diabetes Care.* 2010;33(10):2217-2224; Bailey CJ, et al. *Lancet.* 2010;375(9733):2223-2233.

Empagliflozin (SGLT2 Inhibitor) Slowed Decline in eGFR

Normal Rate of GFR Decline: 0.5 – 1 ml/year

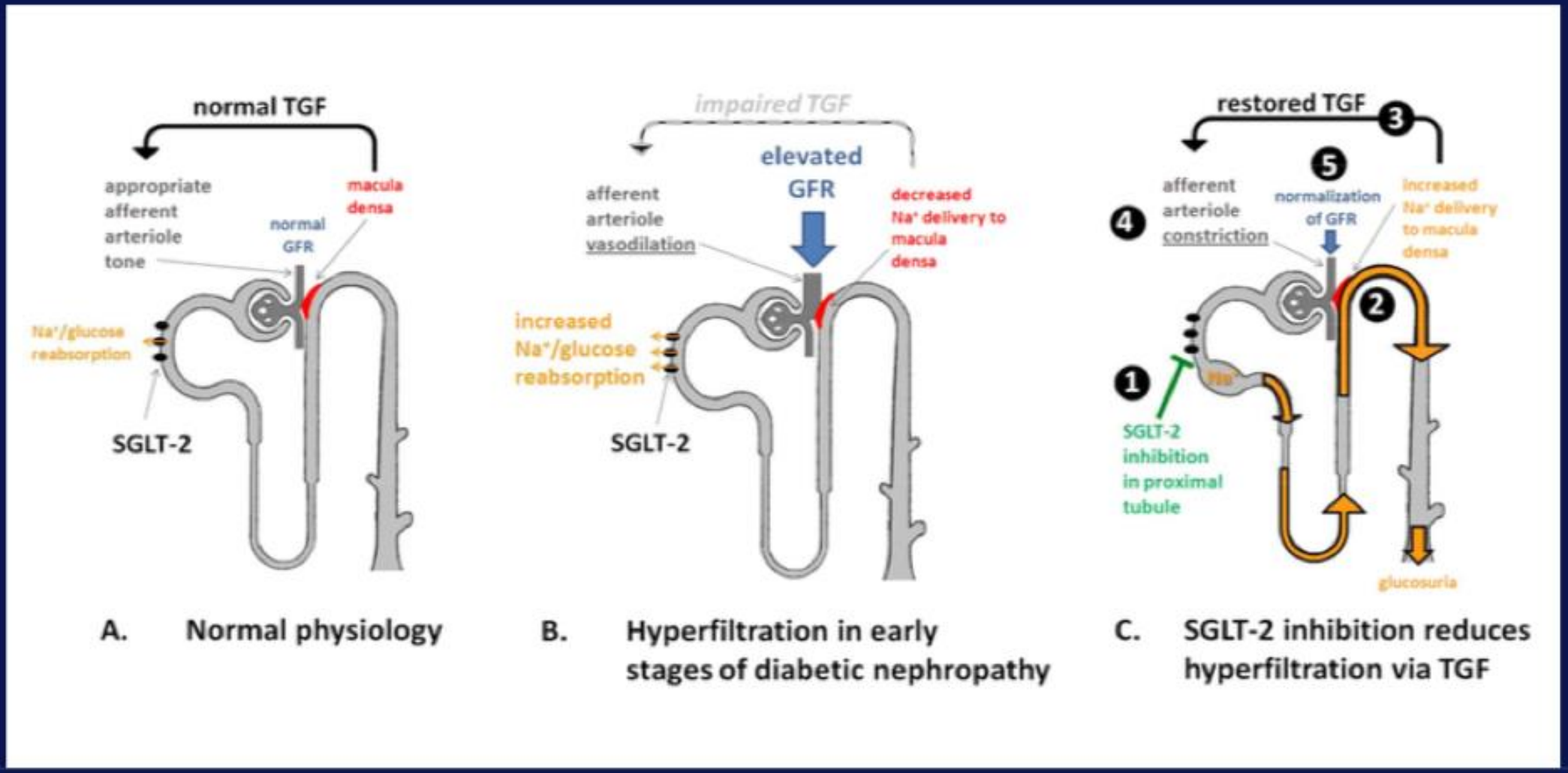


No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

Wanner et al NEJM 375:323-334, 2016

Joslin Diabetes Center

Empagliflozin Decreased Glomerular Hyperfiltration in 8 Week Study in People with Type 1 Diabetes Possibly by Altering Tubulo-Glomerular Feedback



A. Normal physiology

B. Hyperfiltration in early stages of diabetic nephropathy

C. SGLT-2 inhibition reduces hyperfiltration via TGF

Cherney et al Circulation 129:587-597, 2014

Joslin Diabetes Center

Monotherapy

adjunct to diet and exercise in patients with T2DM

Add-on combination therapy

In combination with MET, when MET alone with diet and exercise does not provide adequate glycaemic control

In combination with a SU, when a SU alone with diet and exercise does not provide adequate glycaemic control

In combination with insulin (alone or with one or both of MET or a SU) when the existing therapy, along with diet and exercise, does not provide adequate glycaemic control

1. FORXIGA® (dapagliflozin propanediol monohydrate) data sheet avail able at http://www.medsafe.govt.nz/profs/datasheet/f/forxigatab.pdf

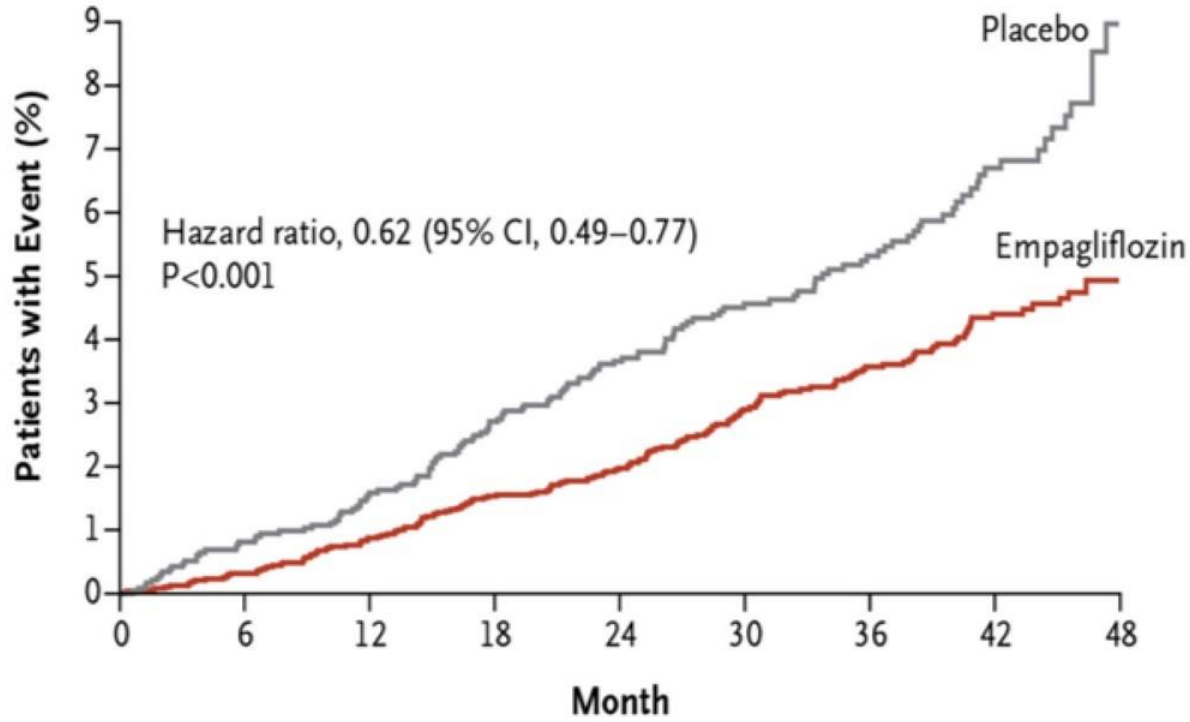
EMPA-REG OUTCOME
Baseline Characteristics—CVD

Characteristic	PBO (n = 2333)	Empa 10 mg (n = 2345)	Empa 25 mg (n = 2342)
Any CV risk factor, n (%)	2307 (98.9)	2333 (99.5)	2324 (99.2)
CAD, n (%)	1763 (75.6)	1782 (76.0)	1763 (75.3)
Multivessel CAD, n (%)	1100 (47.1)	1078 (46.0)	1101 (47.0)
History of MI, n (%)	1083 (46.4)	1107 (47.2)	1083 (46.2)
CABG, n (%)	563 (24.1)	594 (25.3)	581 (24.8)
History of stroke, n (%)	553 (23.7)	535 (22.8)	549 (23.4)
PAD, n (%)	479 (20.5)	465 (19.8)	517 (22.1)
Single-vessel CAD, n (%)	238 (10.2)	258 (11.0)	240 (10.2)
Cardiac failure,* n (%)	244 (10.5)	240 (10.2)	222 (9.5)

Data are n (%) in patients treated with ≥1 dose of study drug.
*Based on narrow standardized MedDRA query "cardiac failure."
Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

EMPA-REG OUTCOME

CV Death



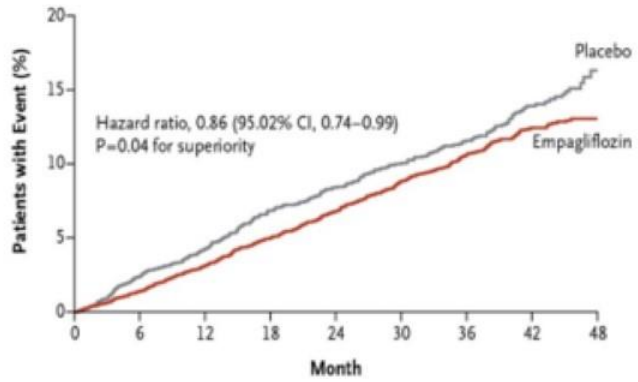
No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

From N Engl J Med, Zinman B, et al., Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes, 373., 2117-2128.

EMPA-REG OUTCOME

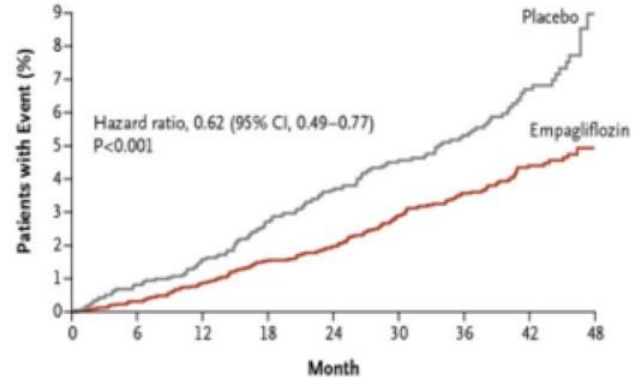
CV Outcomes and Death From Any Cause

Primary Outcome



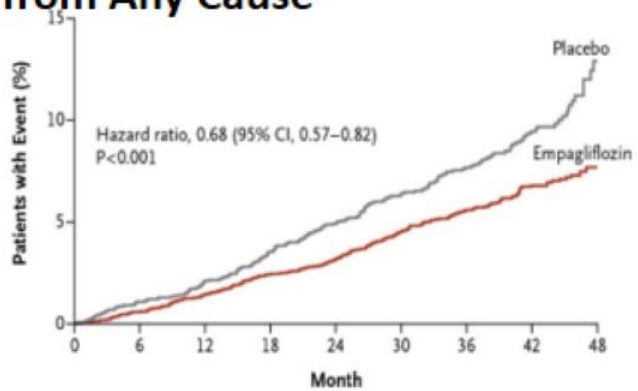
No. at Risk									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Death from CV Causes



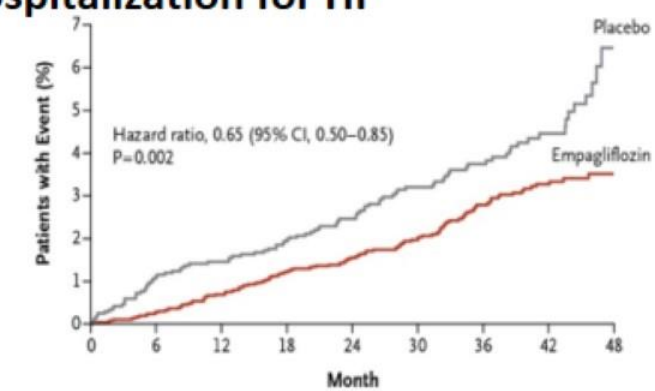
No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Death from Any Cause



No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Hospitalization for HF

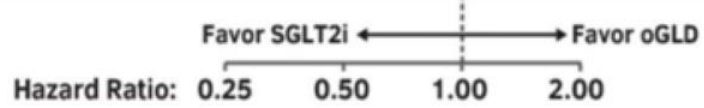


No. at Risk									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

CVD-REAL Study: SGLT2 Inhibitors are Associated With a Significantly Reduced Risk for All-Cause Mortality

- Secondary outcome: risk of all-cause mortality between treatment groups

Database	N	# of events	HR (95% CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)
Total	215,622	1334	0.49 (0.41, 0.57)



P-value for SGLT2i vs oGLD: <0.001

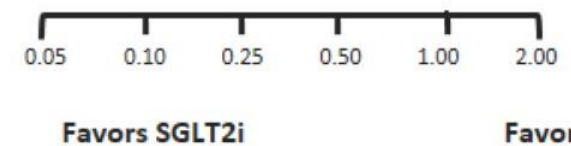
Heterogeneity p-value: 0.09

Kosiborod M, et al. Circulation. 2017. [Epub ahead of print] With permission from Wolters Kluwer Health.

CVD-REAL Study: SGLT2 Inhibitors Are Associated With a Significantly Reduced Risk for hHF

- Primary outcome: Risk for hHF in patients with T2D newly initiated on SGLT2 inhibitors vs other glucose-lowering drugs

Database	N	No. of events	HR (95% CI)
USA	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2900	11	0.14 (0.03, 0.68)
Total	309,056	961	0.61 (0.51, 0.73)

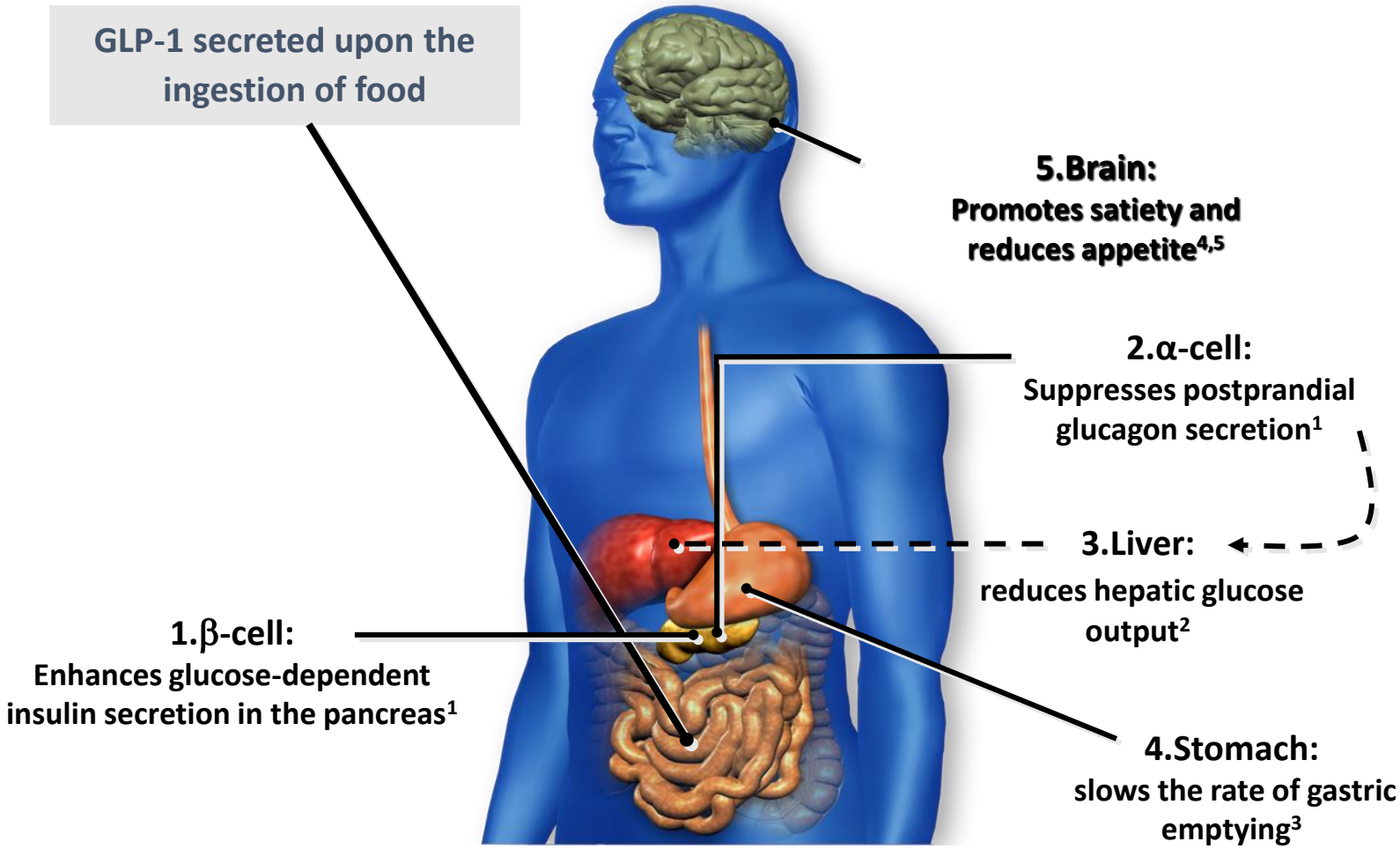


***P* value for SGLT2i vs oGLD: < .001**

Kosiborod M, et al. Circulation. 2017. [Epub ahead of print] With permission from Wolters Kluwer Health.

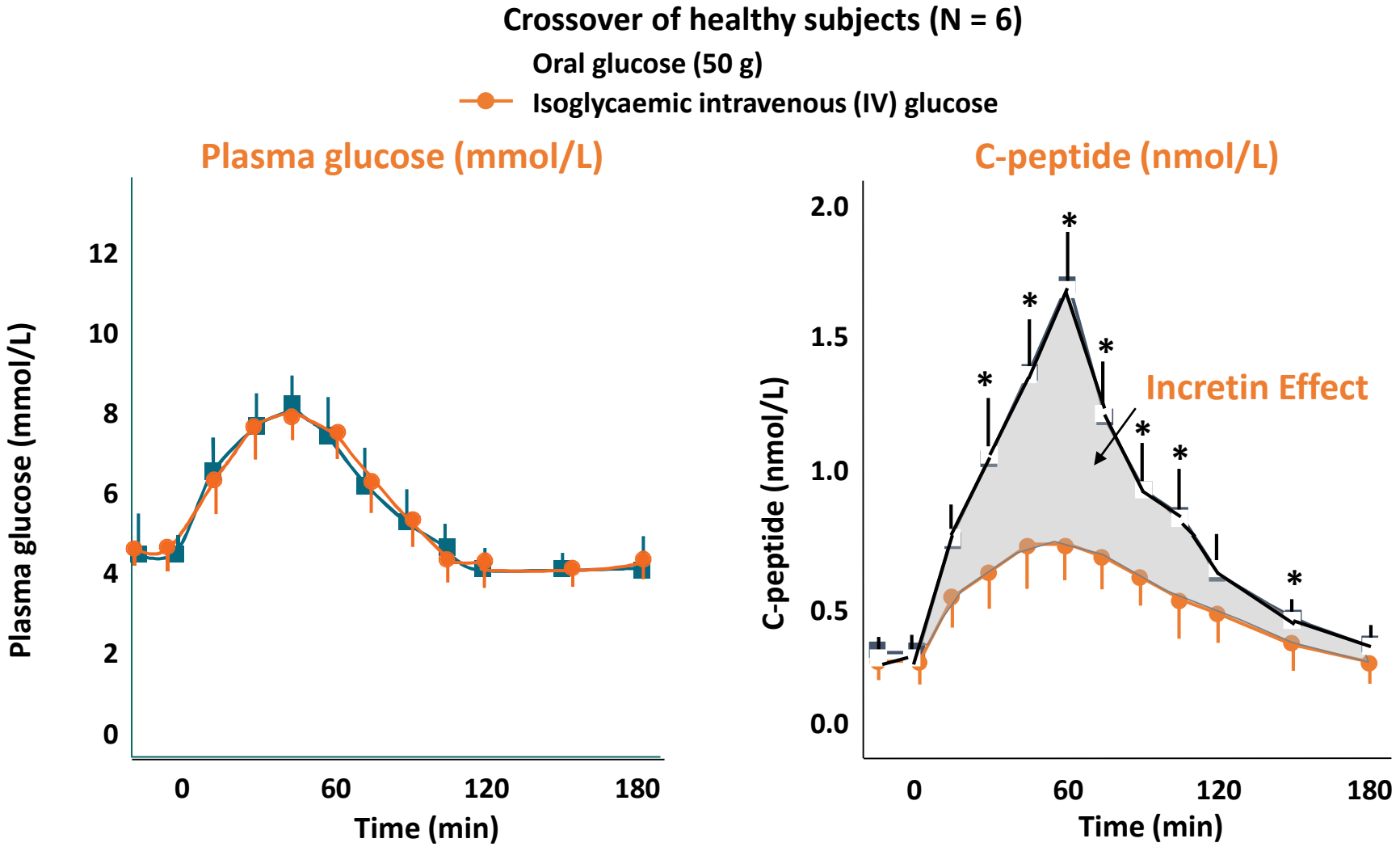
Incretin Therapies

GLP-1 effects in humans - the natural role of incretins



Adapted from [1]Nauck MA, et al. *Diabetologi*a 1993;36:741–744; [2]Larsson H, et al. *Acta Physiol Scand* 1997;160:413–422; [3]Nauck MA, et al. *Diabetologia* 1996;39:1546–1553; [4]Flint A, et al. *J Clin Invest* 1998;101:515–520; [5]Zander et al. *Lancet* 2002;359:824–830.

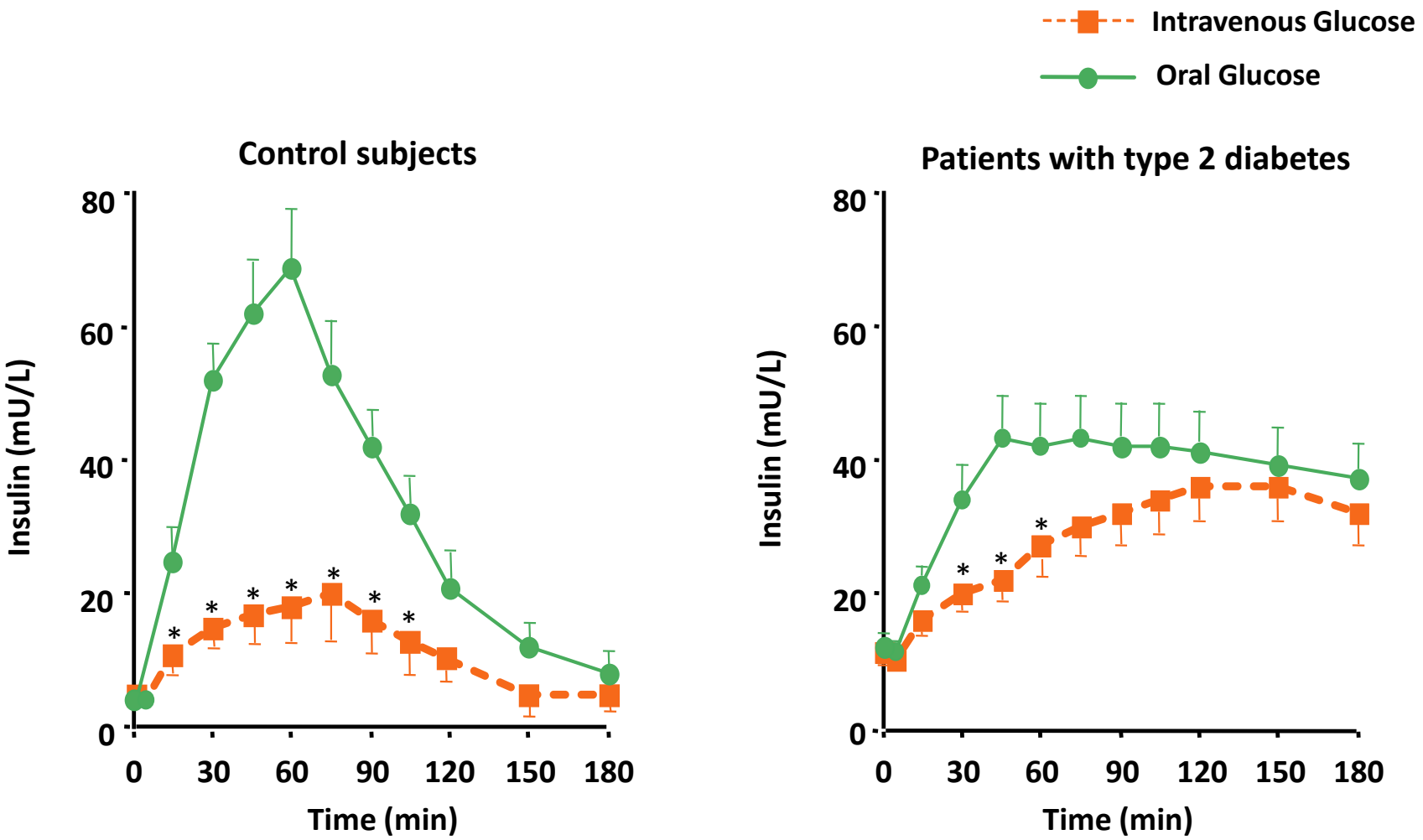
The incretin effect
β-cell response to oral vs IV glucose



Mean (SE); *$P \leq 0.05$

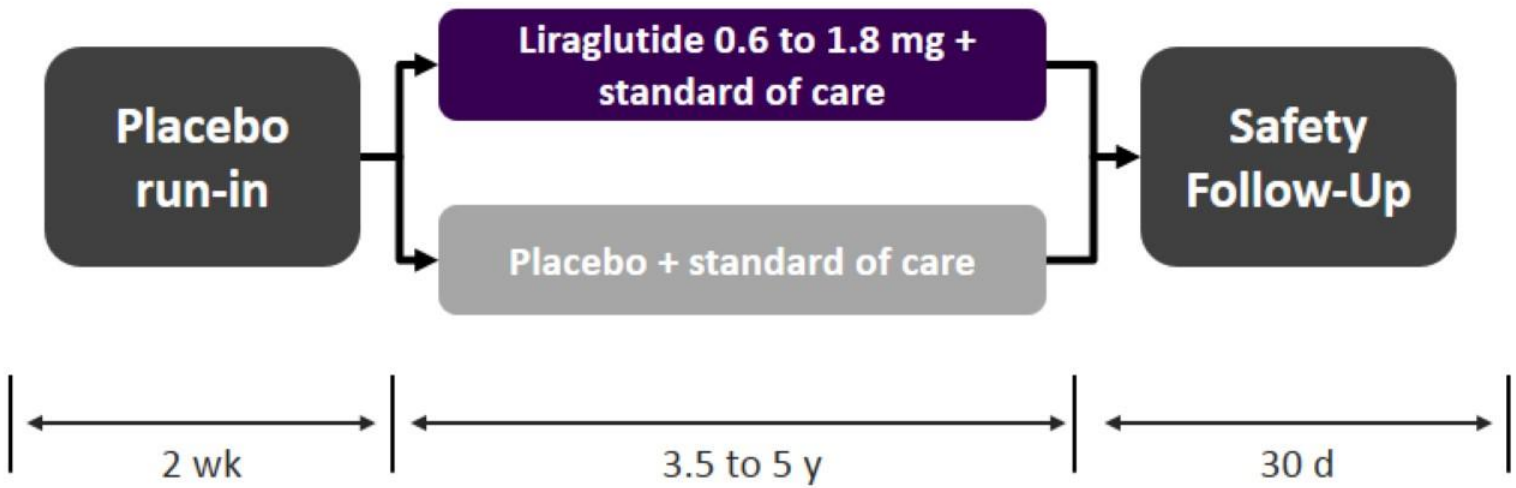
Data from Nauck MA, et al. *J Clin Endocrinol Metab* 1986;63:492–498. Plasma glucose values converted to mmol/L from mg/dL using conversion factor of 0.0555; C-peptide values converted to nmol/L from ng/mL using conversion factor 0.333.

The incretin effect is reduced in patients with type 2 diabetes



*$P \leq .05$ compared with respective value after oral load.
Nauck MA, et al. *Diabetologia* 1986;29:46–52.

LEADER
Study Design



Key inclusion criteria

- T2D, $HbA_{1c} \geq 7.0\%$
- Antidiabetic drug-naïve; OADs and/or basal/premix insulin
- Age ≥ 50 y and established CVD or chronic renal failure **OR**
- Age ≥ 60 y and risk factors for CVD

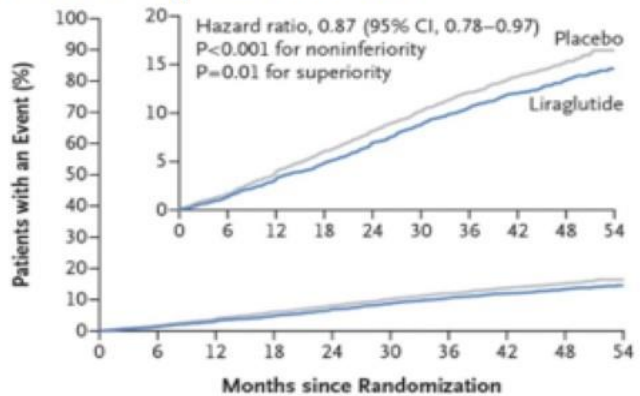
Key exclusion criteria

- T1D
- Use of GLP-1 RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familiar or personal history of MEN-2 or MTC

Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

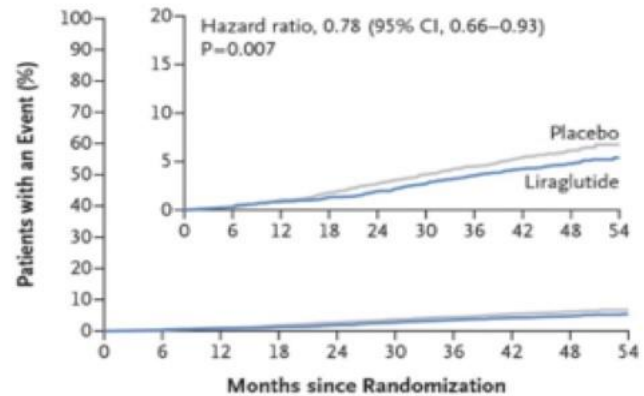
LEADER
Primary and Exploratory Outcomes

Primary Outcome



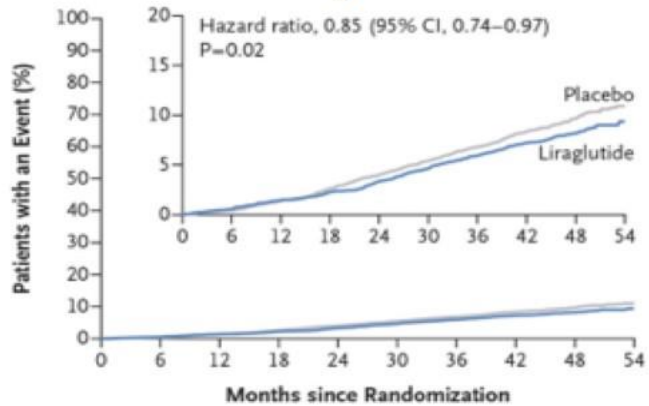
No. at Risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

Death from CV Causes



No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

Death from Any Cause



No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

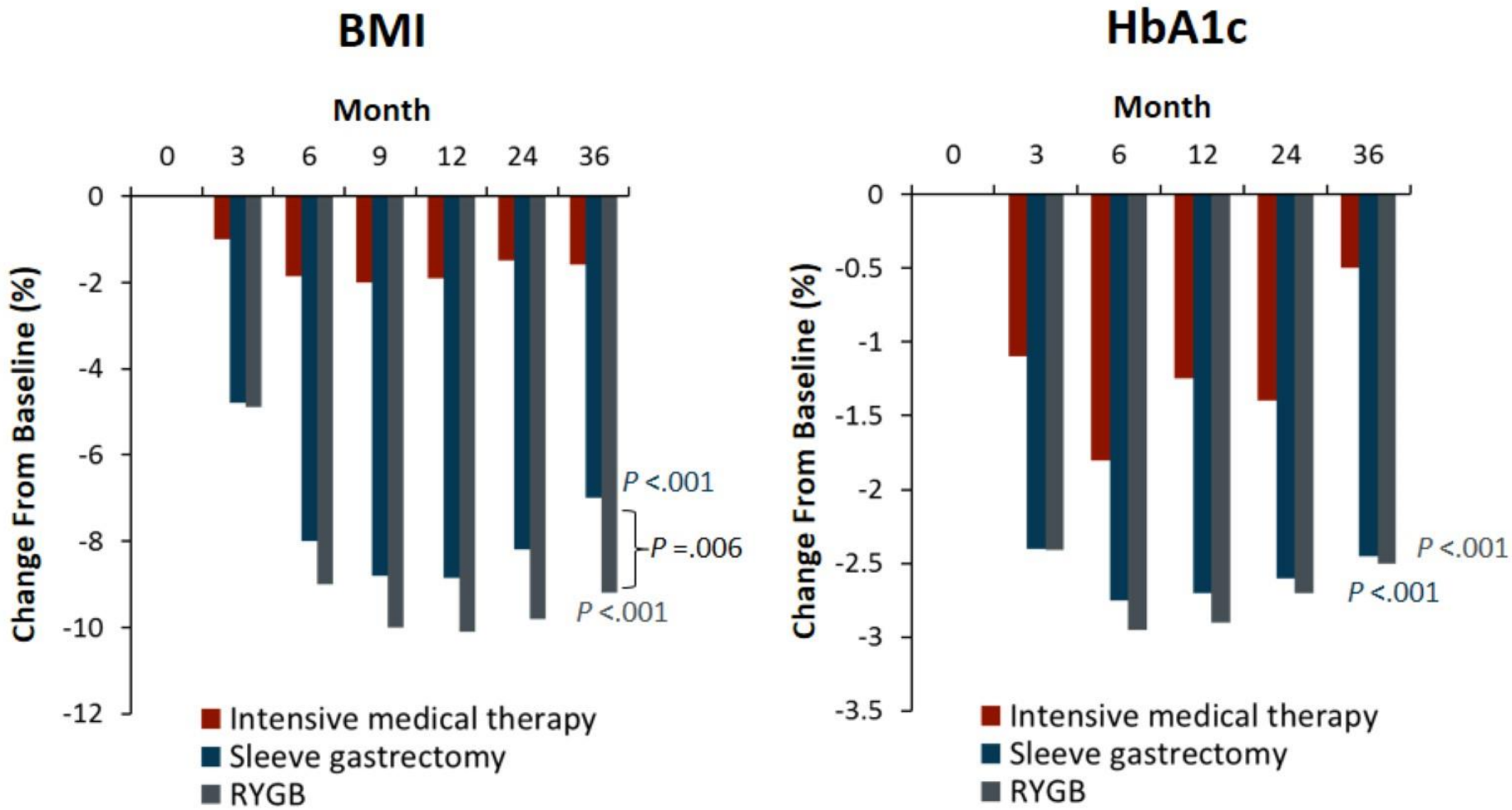
From N Engl J Med, Marso SP, et al, Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes, 375., 1834-1844. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Key Takeaways

- A significant number of the FDA-mandated CVOTs have been conducted
- In all FDA-mandated CVOTs, the antihyperglycemic agent studied achieved noninferiority compared with placebo
- 3 studies (EMPA-REG OUTCOME, LEADER, and SUSTAIN-6) have demonstrated superiority of CVD reduction with empagliflozin, liraglutide, and semaglutide*, respectively
- Other studies are in progress, and their results will provide information about whether the superior benefits seen in the above studies generally represent a class effect
- Still, it is conceivable that actual class effects might not be shown in some of these studies, even if they exist, because of differences in study population and design

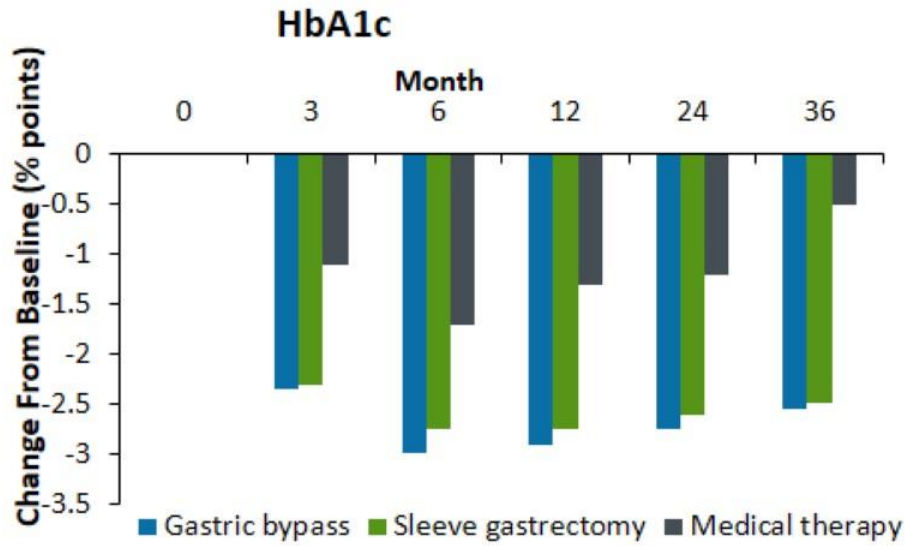
*FDA has not yet approved this medication for use.

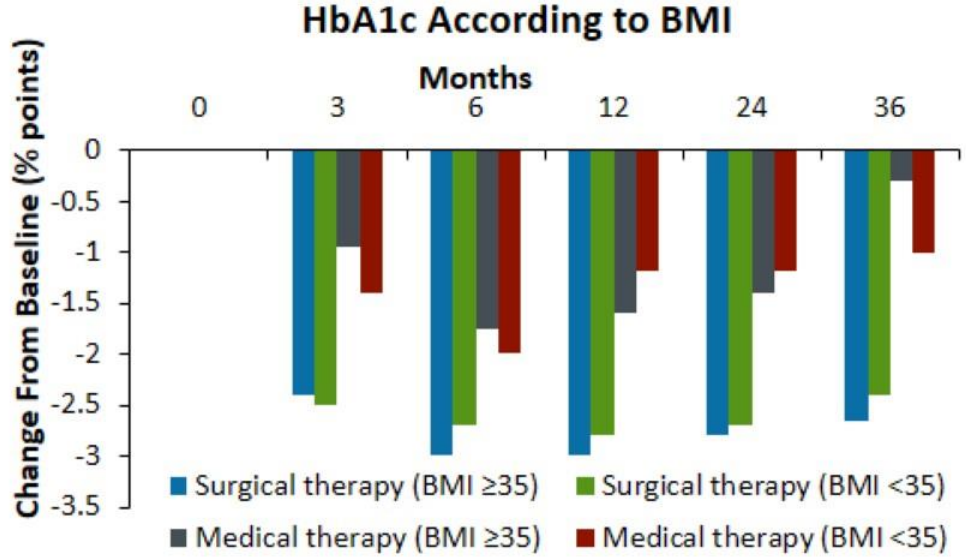
Weight Loss Surgery Improves T2DM

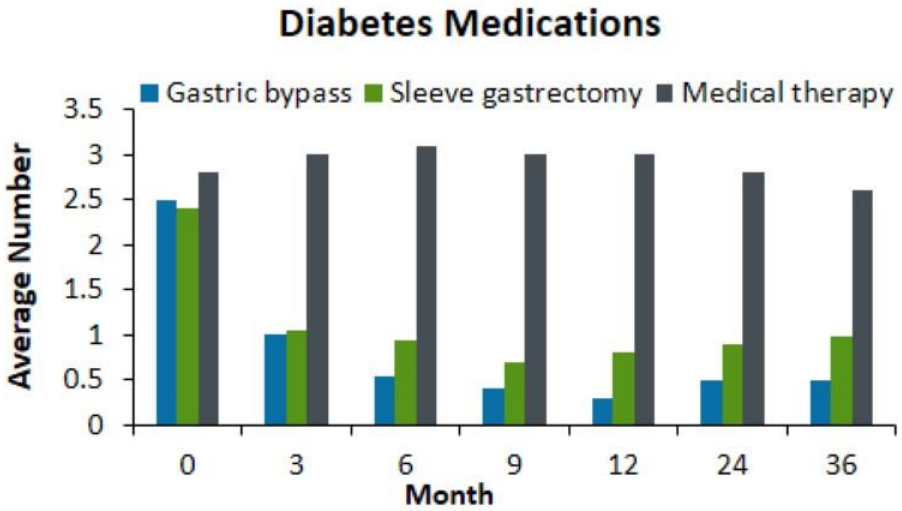


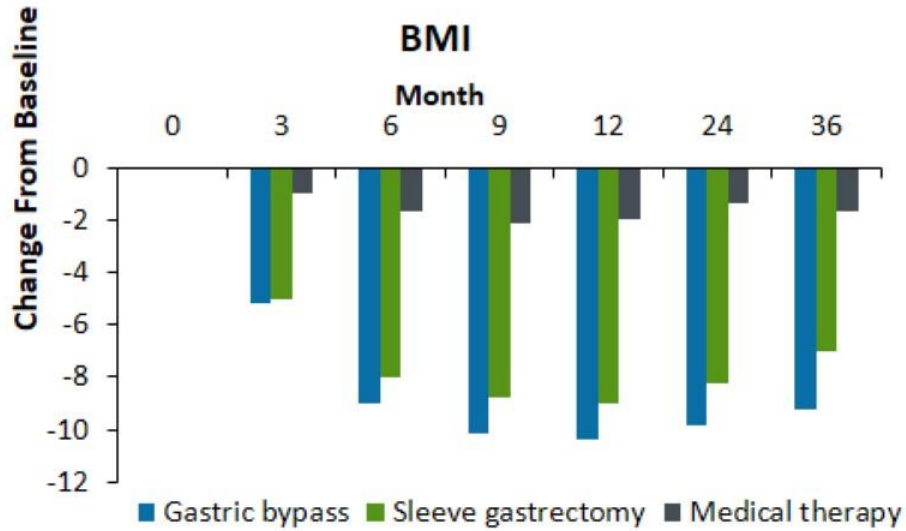
Schauer PR, et al. *N Engl J Med*. 2014;370:2002-2013.

Bariatric Surgery vs Intensive Medical Therapy for T2DM: STAMPEDE Trial



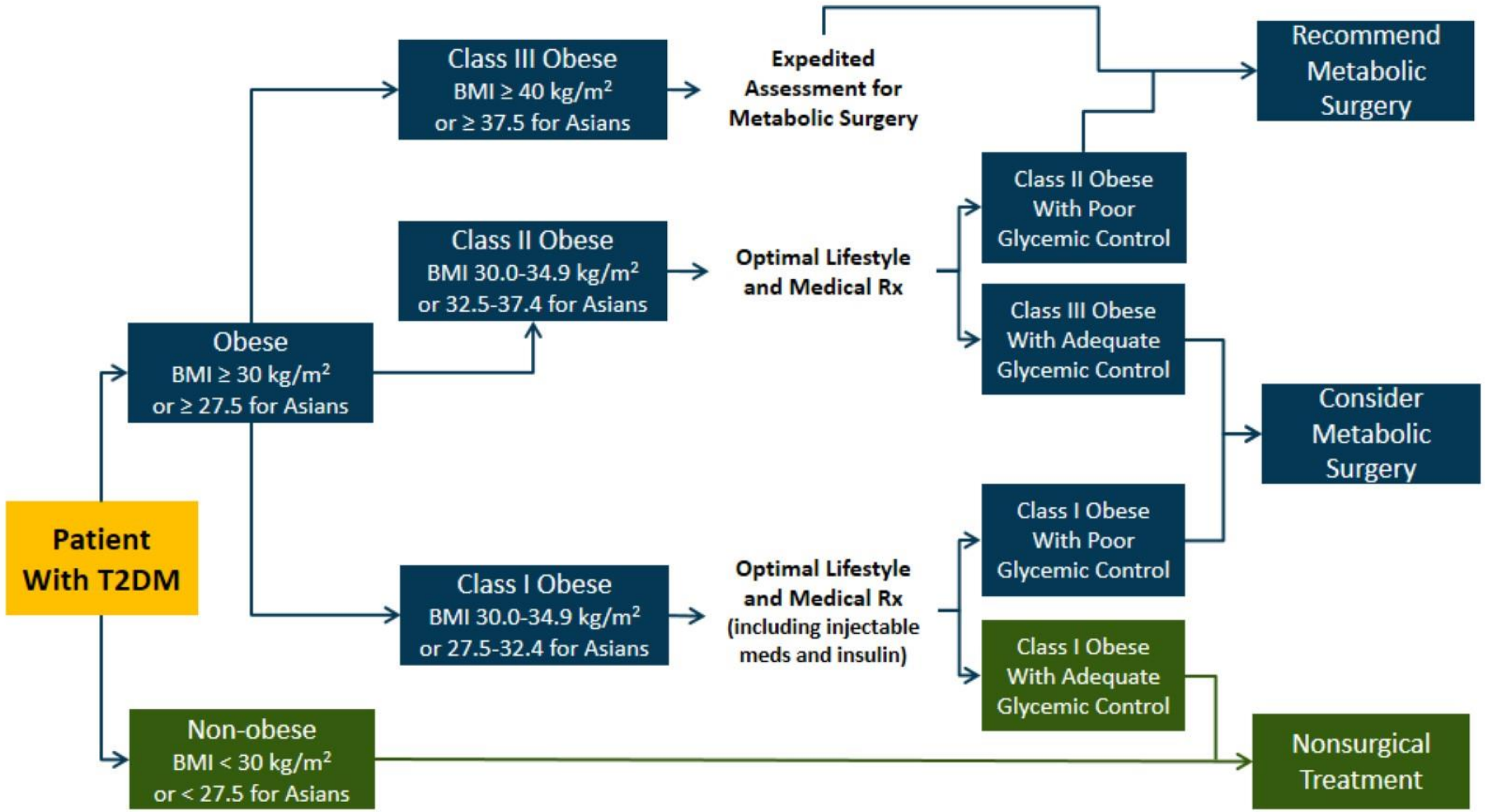






Schauer PR, et al. *N Engl J Med*. 2014;370:2002-2013.

Algorithm for the Treatment of T2DM as Endorsed by International Diabetes Organizations



Rubino F, et al. *Diabetes Care.* 2016;39:861-877.