Prevention of Type 2 Diabetes

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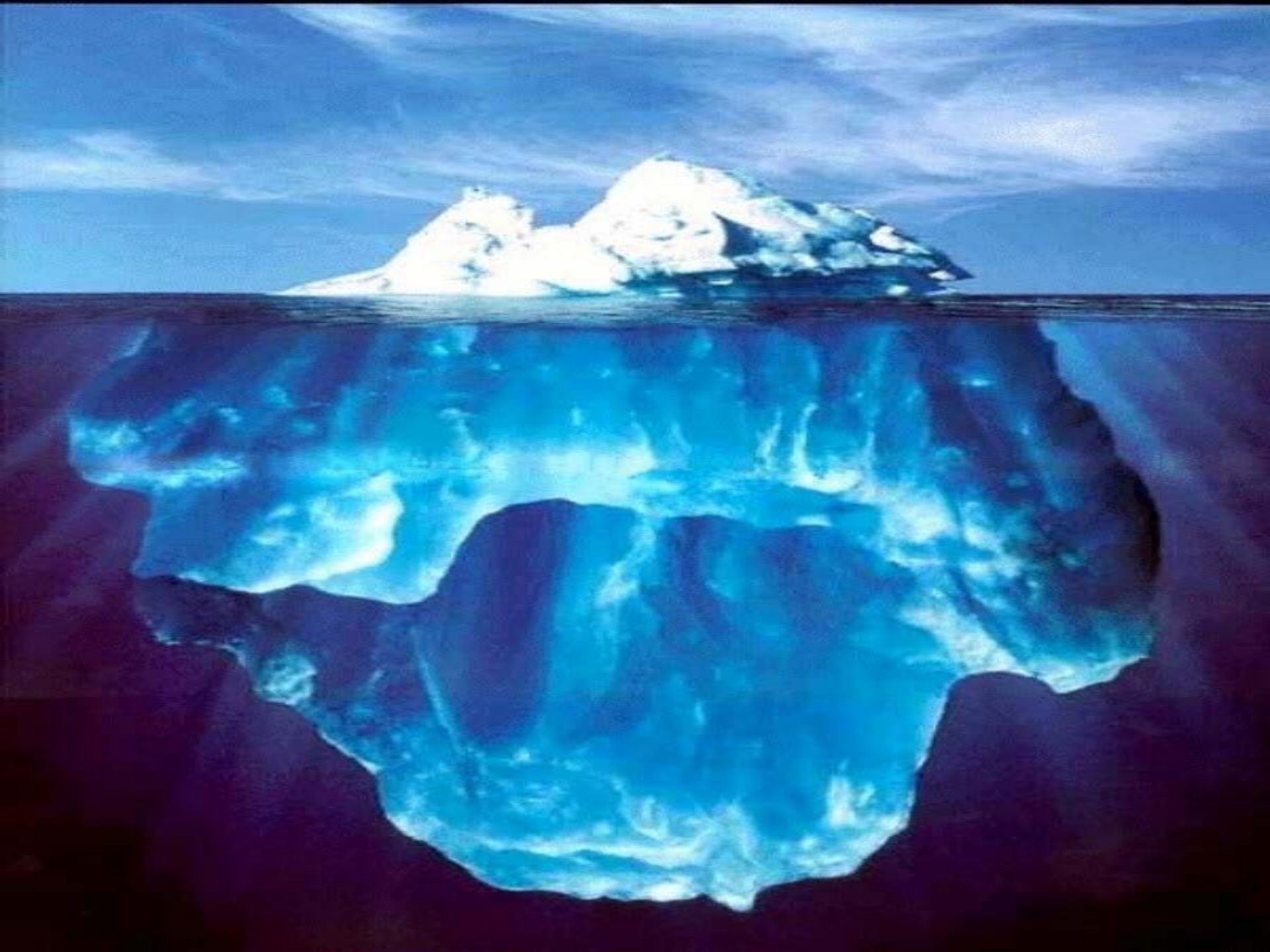
Presenter Disclosure Information

In compliance with accrediting board policies, the American Diabetes Association requires the following disclosure to participants:

Fran Broyles:

Speaker's Bureau: AstraZeneca



"TYPE 2 DIABETES IS PART OF A WORLDWIDE HEALTH CRISIS OF NONCOMMUNICABLE DISEASE THAT IS REPLACING PANDEMICS AND INFECTIOUS DISEASES AS THE GREATEST THREAT TO PUBLIC HEALTH"

50%

UNITED STATES HAS PRE DIABETES OR DIABETES

JAMA SEPT 8, 2015.VOL314,NUMBER10

JAMA 2015/ 2011 to 2012

Prevalence of Diabetes 12 to 14 % (29 million, of those 8.1 million undiagnosed, 36%)

Prevalence of Pre diabetes 38% (86 million)

NHANES Between 1988-1994 and 2011-2012, Prevalence of DM increased :

- Among overall population
- Among each age group (20-44, 45-64, > 65)
- Both sexes
- Every Racial / Ethnic Group
- Every Education level
- Every income level

Highest Prevalence was seen in Non-Hispanic black, Non-Hispanic Asian, and Hispanic

Total cost in 2012 of diagnosed DM $ 245 billion

DM pts cost 2.3 x more than pts without DM

Toddler May Be Youngest Ever Diagnosed With Type 2 Diabetes

The case report was session at the European Association for the Study of Diabetes (EASD) 2015 Meeting by Michael Yafi, MD, director of pediatric endocrinology at the University of Texas Health Science Center at Houston. presented September 16 in a poster discussion

The child, a 3-year-old Hispanic girl weighing 35 kg (77 pounds; > 95th percentile for age) presented at Dr Yafi's pediatric endocrinology clinic for evaluation of obesity. She didn't seem ill, she had polyuria and polydipsia, so he screened her and found she had a fasting plasma glucose of 230 mg/dL, and an HbA_{1c} of 7.2%. Her C-peptide was positive, Anti GAD and islet cell antibodies were negative

Pediatric and Adolescent Type 2 DM

Type 1 DM is still the most common

Type 2 in Children in the US is 12/100,000 with majority in AA, Hispanics, Asian/Pacific Islanders, and American Indians with Pima Indians 22/100,000 9 to 14 yo

The prevalence although still lower has tripled in the last decade and closely mimics increase obesity in children

Majority were Obese

Usually diagnosed in middle to late puberty

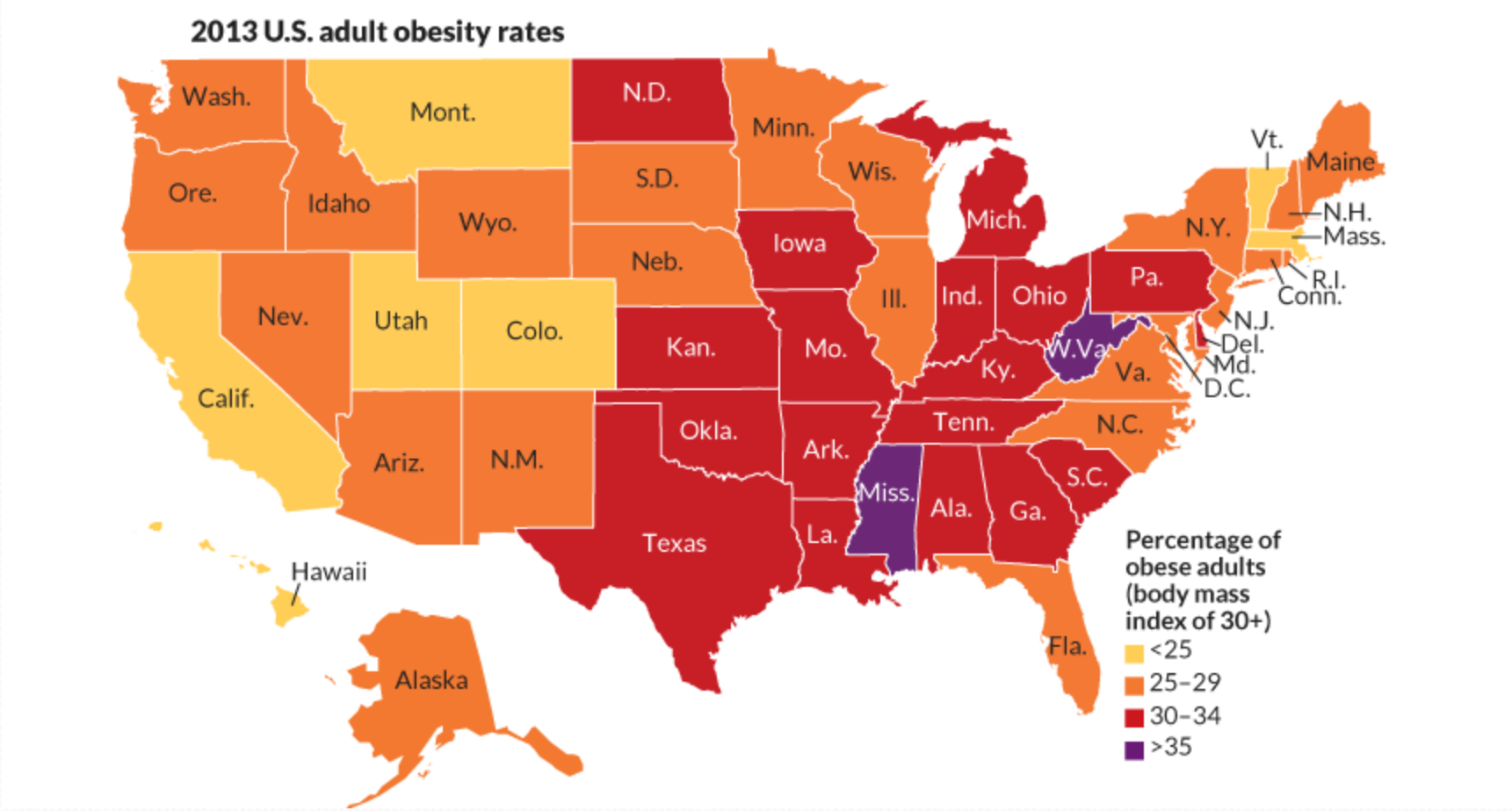
1/3 diagnosed on UA during PE

5 to 25 % present in DKA

Differentiation from Type 1 DM (85 to 98 % + Beta cell antibodies and low C peptide) and MODY

OBESITY

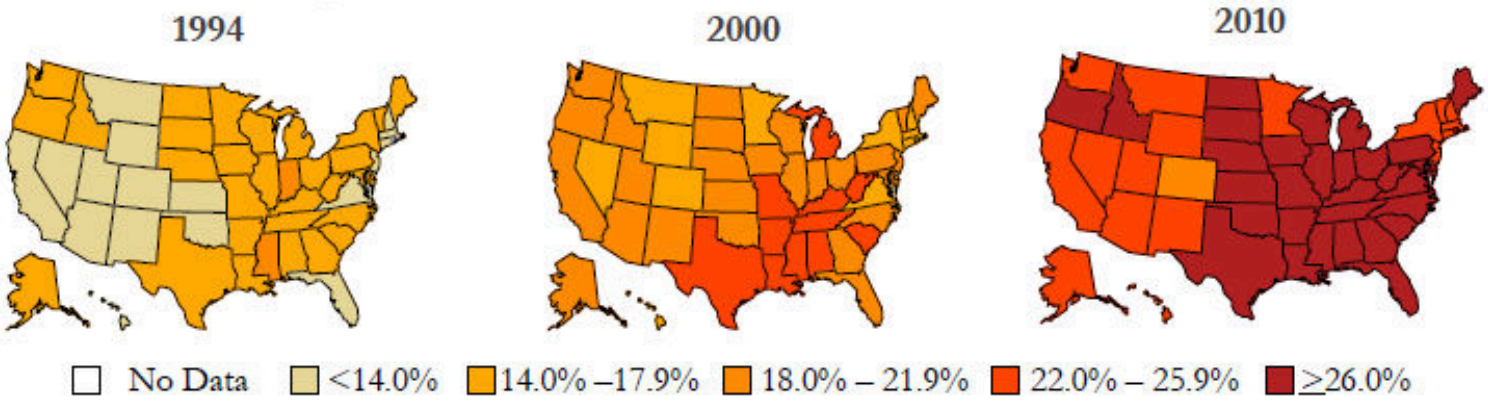
THE INCREASE IN DIABETES MAY BE DUE TO THE INCREASE IN OBESITY, THE MOST IMPORTANT RISK FACTOR FOR TYPE 2 DM, AFFECTING 30 TO 35% OF AMERICANS, WITH ANOTHER 35% BEING OVERWEIGHT, FOR A TOTAL OF 70% ADULT AMERICANS OVERWEIGHT OR OBESE, AND 17% OF CHILDREN



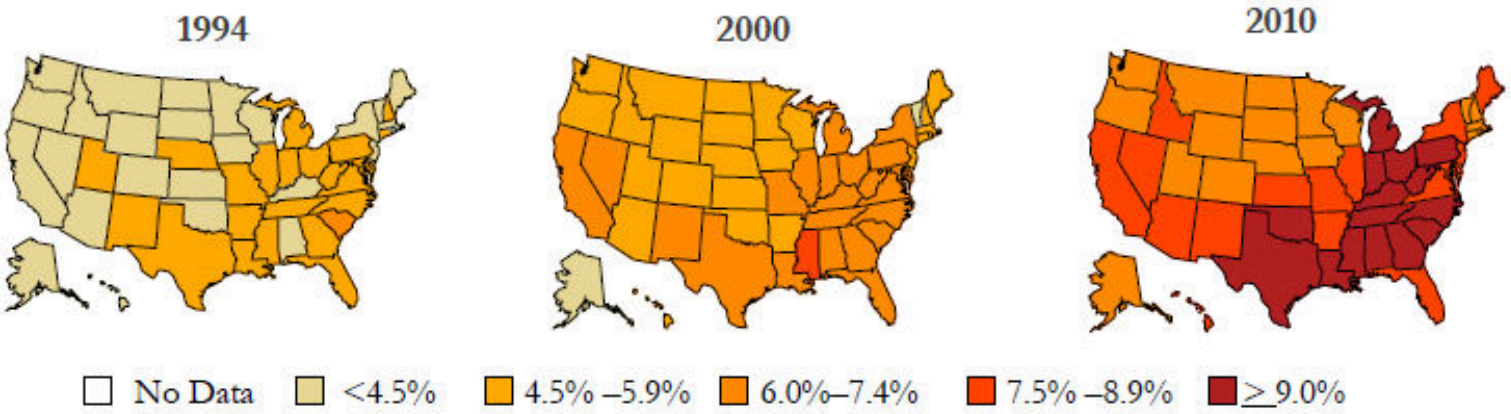
T2DM along with Obesity, may yet be the greatest chronic disease epidemic in the history of human existence. The basis for this claim is the meteoric rise of the global estimate, a greater than 2 fold increase, from 151 million people with DM in 2000 to the current estimate of 415 million, to the 2040 prediction of 642 million.

Age–Adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults Aged 18 years or older

Obesity (BMI ≥30 kg/m²)



Diabetes



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

Obesity at Swedish

Population	Recommendation	Grade (What's This?)
Adults aged 40 to 70 years who are overweight or obese	The USPSTF recommends screening for abnormal blood glucose as part of cardiovascular risk assessment in adults aged 40 to 70 years who are overweight or obese. Clinicians should offer or refer patients with abnormal blood glucose to intensive behavioral counseling interventions to promote a healthful diet and physical activity.	B

29%

HbA1c testing in overweight and obese patients

Total patients meeting criteria*: 107,772
Patients without HbA1c Measured: 76,622

*All SMG active patients aged 40-70 with BMI > 25

Paradigm Shift/When to Intervene

PREVENT TYPE 2 DIABETES/AGGRESSIVE TREATMENT PRE DM /OVERWEIGHT AND OBESITY

Categories of Increased Risk for Type 2 Diabetes (Prediabetes)

FPG	2-hr PG*	A1C
100-125 mg/dL 5.6-6.9 mmol/L Impaired fasting glucose (IFG)	140-199 mg/dL 7.8-11.0 mmol/L Impaired glucose tolerance (IGT)	5.7-6.4% 39-46 mmol/mol

Risk is continuous, extending below lower limit of range and becoming disproportionately greater at higher ends of range

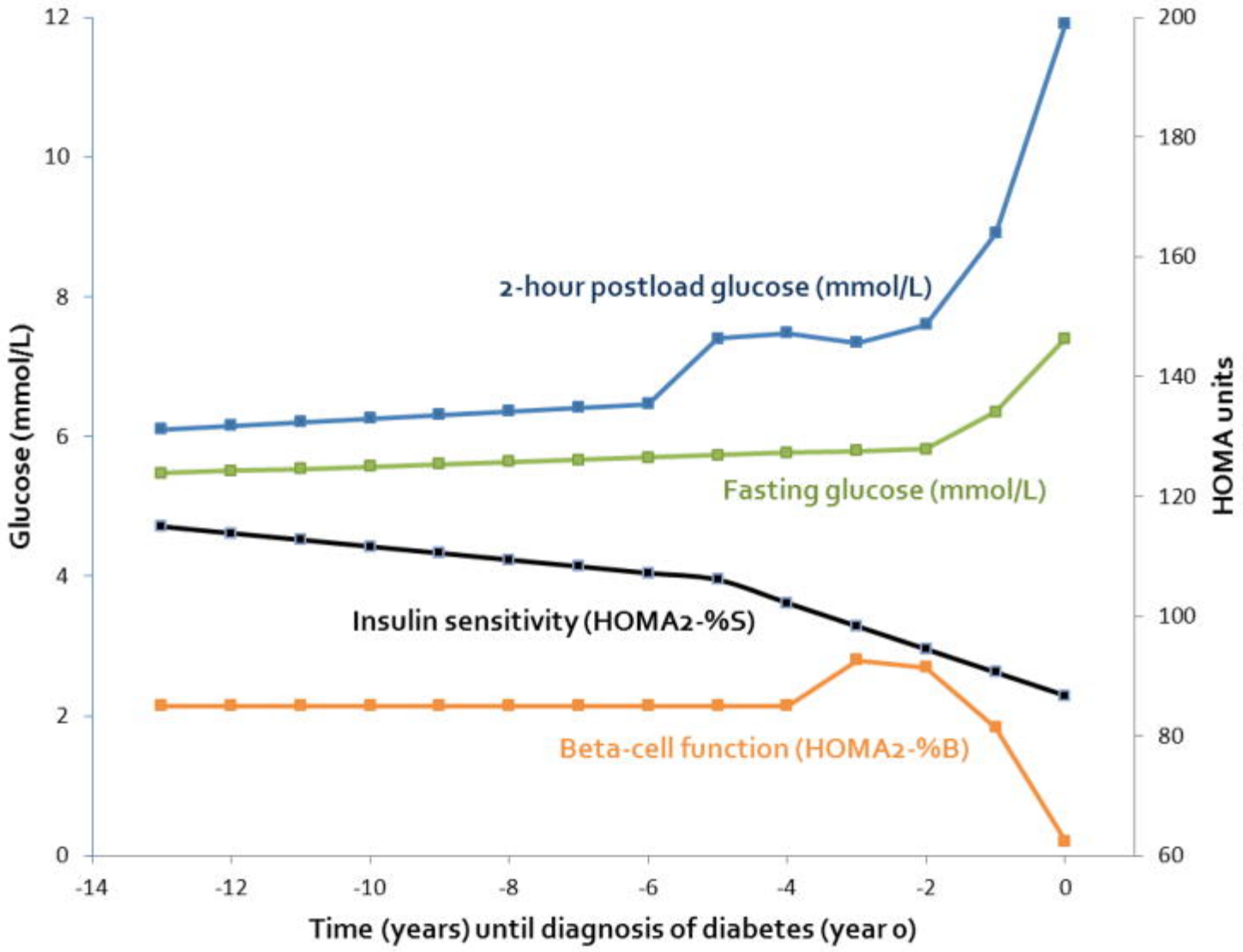
*In 75-g OGTT
FPG=fasting plasma glucose; OGTT=oral glucose tolerance test; PG=plasma glucose

American Diabetes Association. *Diabetes Care*. 2016;39(suppl 1):S1-S106.

Progression of Pre DM to DM

- DPPPT 11% conversion annually
- ADA expert panel 70% of pts with pre DM will get DM
- In the Chinese DM prevention trial it was 90%
- Gestational DM 20 to 60% of women had DM within 5 to 10 years
- Multifactorial DM risk scores are promising future tools
- RF include gestational DM, first degree relative, metabolic syndrome, BMI, ethnicity, age, physical activity, Waist circumference

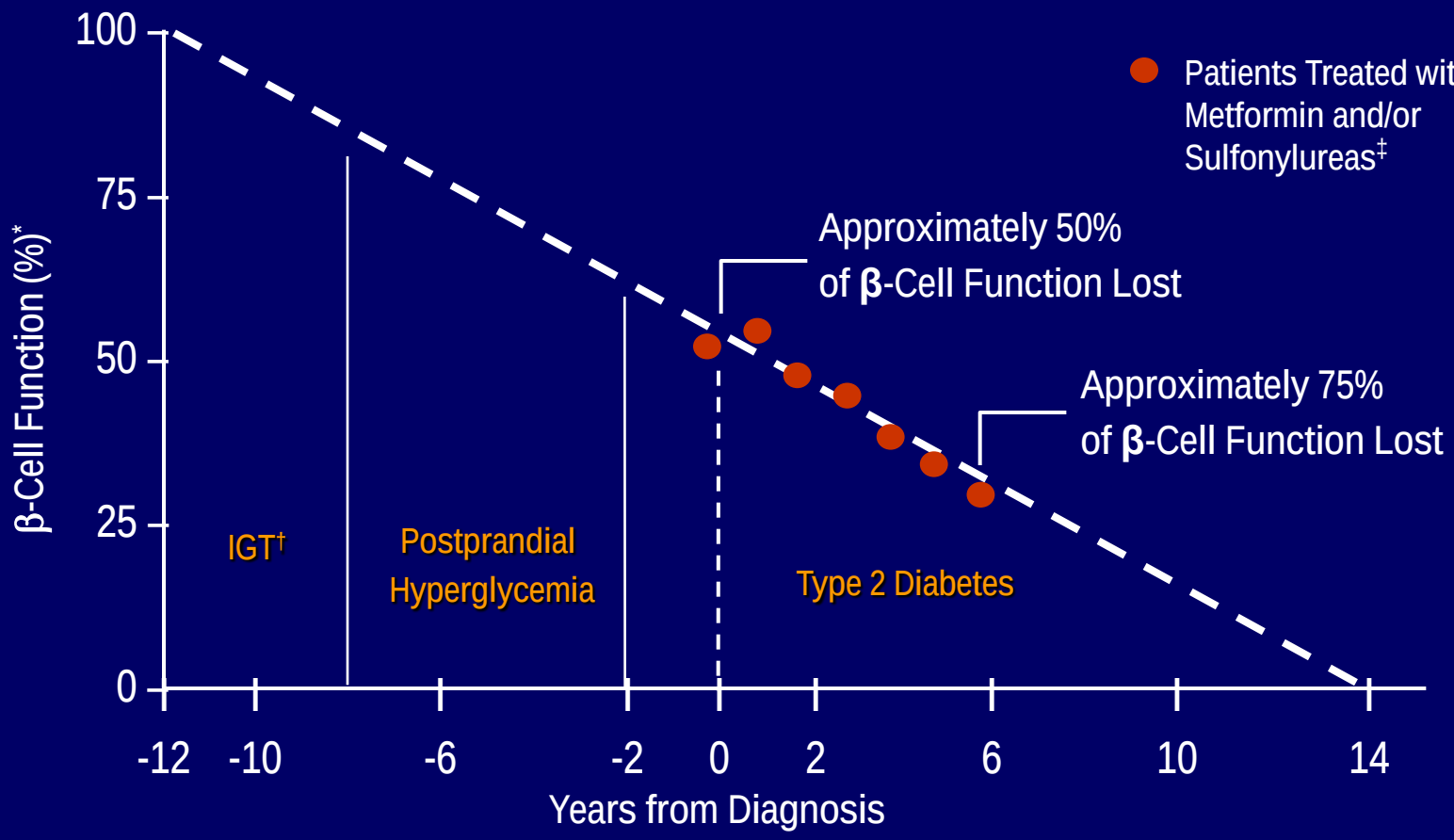
Pathophysiology of Pre Diabetes (British Whitehall II)



MULTISTAGE MODEL

- Stage I - long compensatory period when IR is present and accompanied by increased insulin secretion and beta cell mass
- Stage II – stable adaptation, B cells no longer fully compensating for increased IR, FPG and /or post glucose load BS not completely maintained, initially BS are normal
- Stage III – Unstable decompensation period glucose levels begin to rise with Beta Cell inability to compensate for IR and glucose levels rise rapidly

β-Cell Function Declines Over Time



*Dashed line shows extrapolation backward from year 0 and forward from year 6 from diagnosis based on Homeostasis Model Assessment (HOMA) data from UKPDS. †IGT = impaired glucose tolerance. ‡The data points for the time of diagnosis (0) and the subsequent 6 years are taken from the obese subset of the UKPDS population and were determined by the HOMA model. Adapted with permission from Lebovitz HE. *Diabetes Rev.* 1999;7:139-153.

Beta cell function

- Beta cell dysfunction already present in the Pre DM stage
- Studies using different measures of beta cell function have reported severely abnormal (up to 80% decreased) insulin secretion in pre DM people
- Autopsy data report a 50% decrease in beta cell volume in pts with IFG

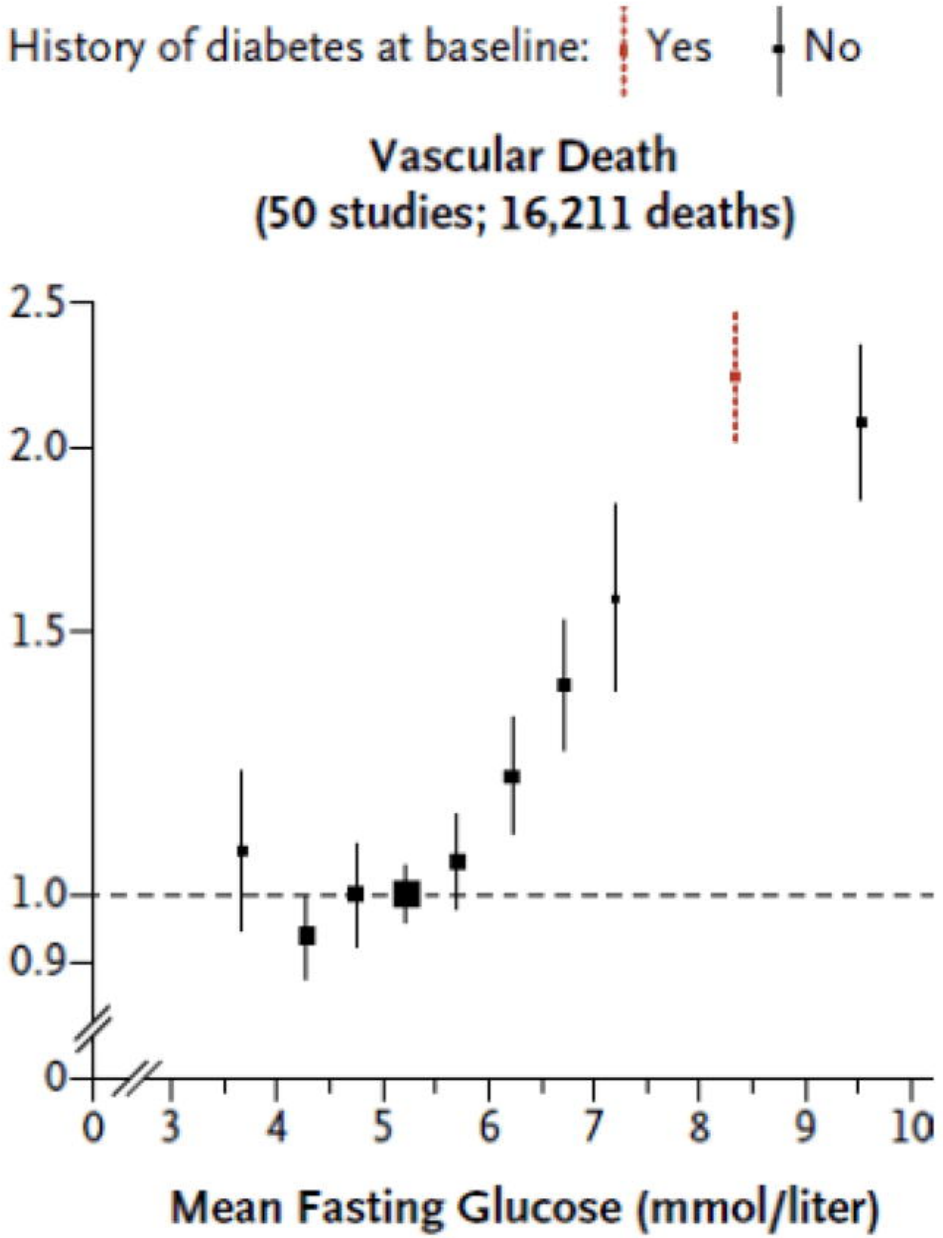
Why treat Pre DM

Decrease or prevent progression to DM

DM complications:

- Kidney – albuminuria, and decreased GFR
- Neuropathies – autonomic, sensorimotor
- DR
- Macrovascular DECODE Trial Increased Coronary death and total CV death related to IFG and IGT

FBG, A1c and post load Glucose are all robust predictors of vascular mortality independent of other vascular RFs(data from prospective trials) 5 .6 =100



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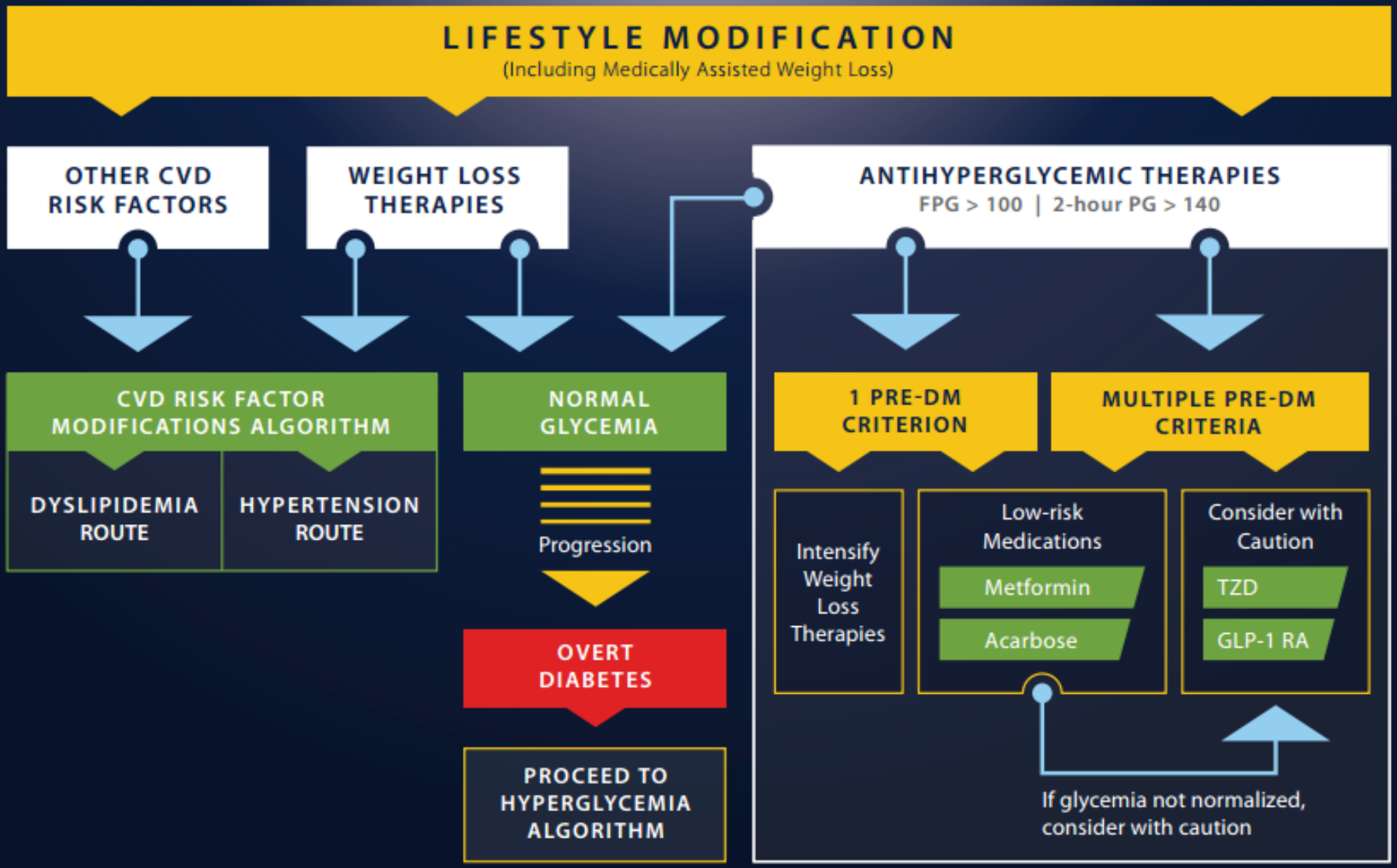
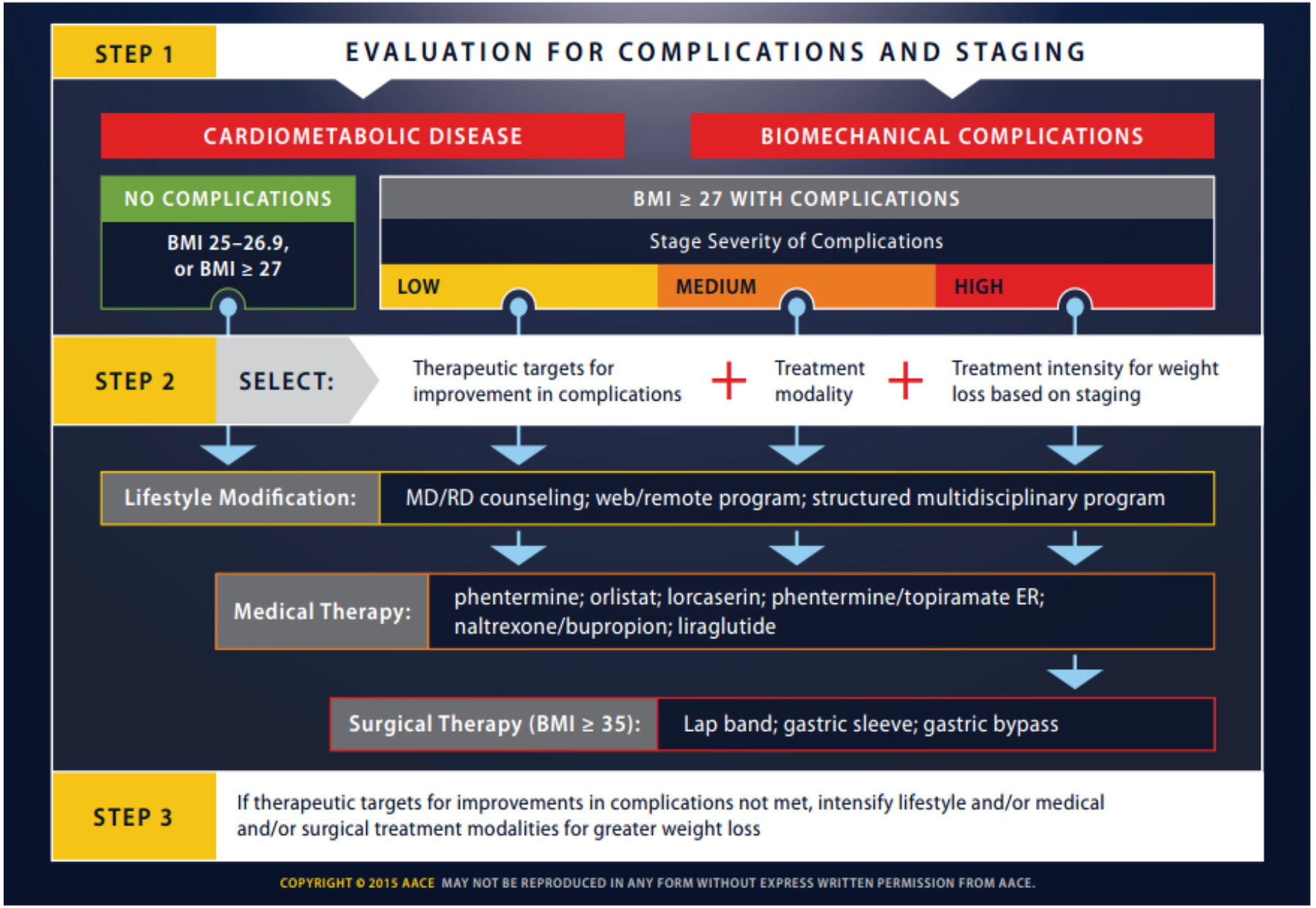
PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2005)



Complications-Centric Model for Care of the Overweight/Obese Patient



AACE/ACE Comprehensive Diabetes Management Algorithm, *Endocr Pract.* 2015;21(No. 4) e3

Diabetes Prevention Program Trial (NEJM 2/2002)

3234 pts x 3 years to 3 arms, Standard lifestyle recommendations with placebo bid, Standard lifestyle recommendations with Metformin 850 mg bid, and intensive lifestyle

Standard lifestyle - written instructions and a 30 min annual visit that emphasized healthy lifestyle, follow the Food pyramid and NCEP Step 1 Diet, and to increase activity

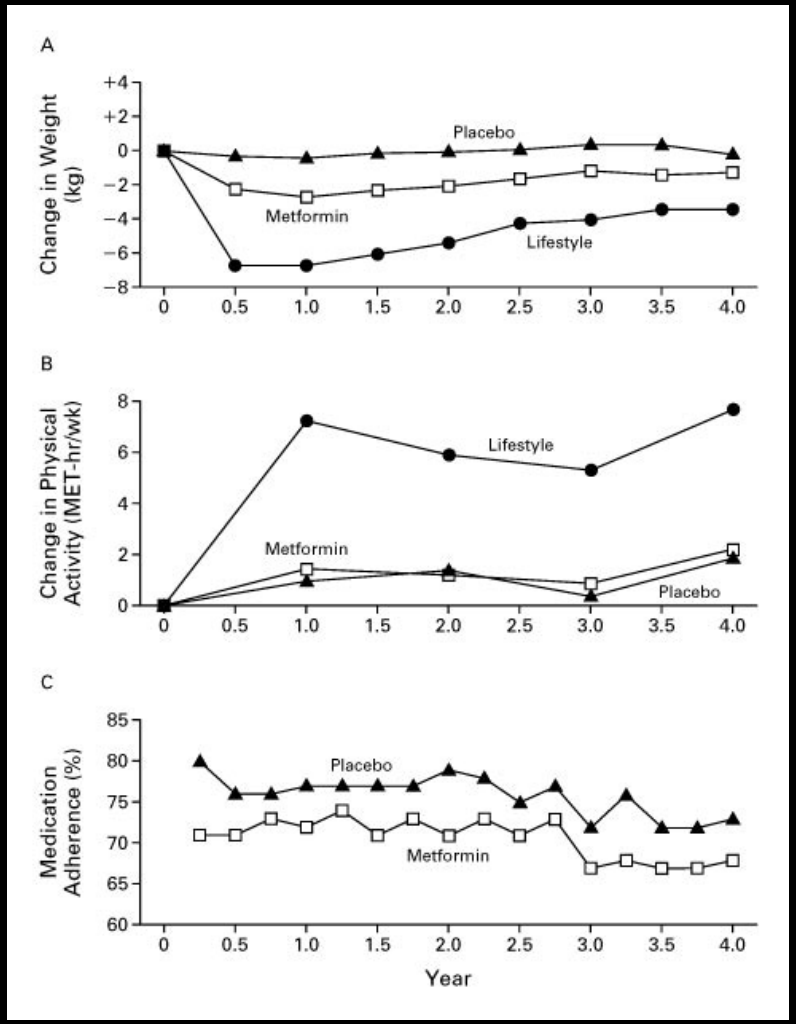
Intensive lifestyle – goal to achieve and maintain 7 % wt loss through low calorie, low fat diet and moderate intensity exercise such as walking for 150 min per week, 16 wk of diet, , exercise and behavior modification 1:1 visit, followed by monthly 1:1 and grp sessions to reinforce behavior

Incidence of T2DM was reduced by 58% in the Intensive lifestyle grp, by 31% in Metformin grp versus placebo

1 kg of weight loss decreased conversion by 16 %

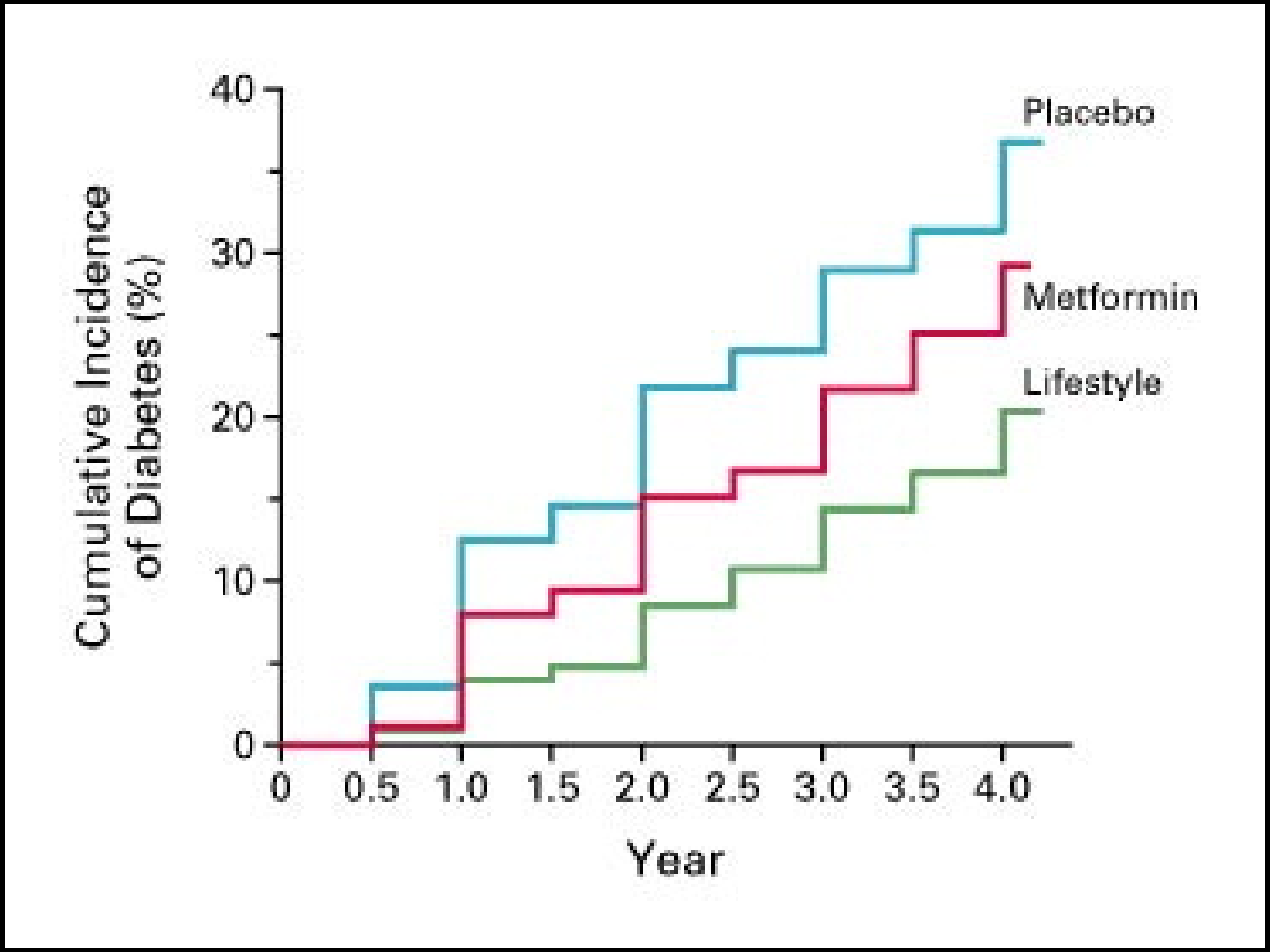
Findings consistent with the Finnish DM Prevention Study with lifestyle intervention 58% reduction in DM

Changes in Body Weight (Panel A) and Leisure Physical Activity (Panel B) and Adherence to Medication Regimen (Panel C) According to Study Group.



Diabetes Prevention Program Research Group. N Engl J Med 2002;346:393-403.

Cumulative Incidence of Diabetes According to Study Group.



Diabetes Prevention Program Research Group. N Engl J Med 2002;346:393-403.

DPP Outcomes study

- Reversion of pre DM to normoglycaemia during the randomized phase of the study even if transient, was associated with a 56% reduced future risk of DM, independent of whether the reversion happened spontaneously, with lifestyle or Metformin during 5.7 years of follow up
- Those who remained pre DM despite intensive lifestyle had an even higher risk of developing DM than those on metformin or placebo

Medical and Surgical Interventions Shown to Delay or Prevent T2D

Intervention	Follow-up Period	Reduction in Risk of T2D (*P* value vs placebo)
Antihyperglycemic agents		
Metformin[1]	2.8 years	31% (*P*<0.001)
Acarbose[2]	3.3 years	25% (*P*=0.0015)
Pioglitazone[3]	2.4 years	72% (*P*<0.001)
Rosiglitazone[4]	3.0 years	60% (*P*<0.0001)
Weight loss interventions		
Orlistat[5]	4 years	37% (*P*=0.0032)
Phentermine/topiramate[6]	2 years	79% (*P*<0.05)
Bariatric surgery[7]	10 years	75% (*P*<0.001)

Lifestyle modification should be used with all pharmacologic or surgical interventions.

T2D, type 2 diabetes.

1. DPP Research Group. *N Engl J Med*. 2002;346:393-403. 2. STOP-NIDDM Trial Research Group. *Lancet*. 2002;359:2072-2077.
3. Defronzo RA, et al. *N Engl J Med.* 2011;364:1104-15. 4. DREAM Trial Investigators. *Lancet*. 2006;368:1096-1105.
5. Torgerson JS, et al. *Diabetes Care*. 2004;27:155-161. 6. Garvey WT, et al. *Diabetes Care*. 2014;37:912-921.
7. Sjostrom L, et al. *N Engl J Med*. 2004;351:2683-2693.

ADA Statement June of 2016

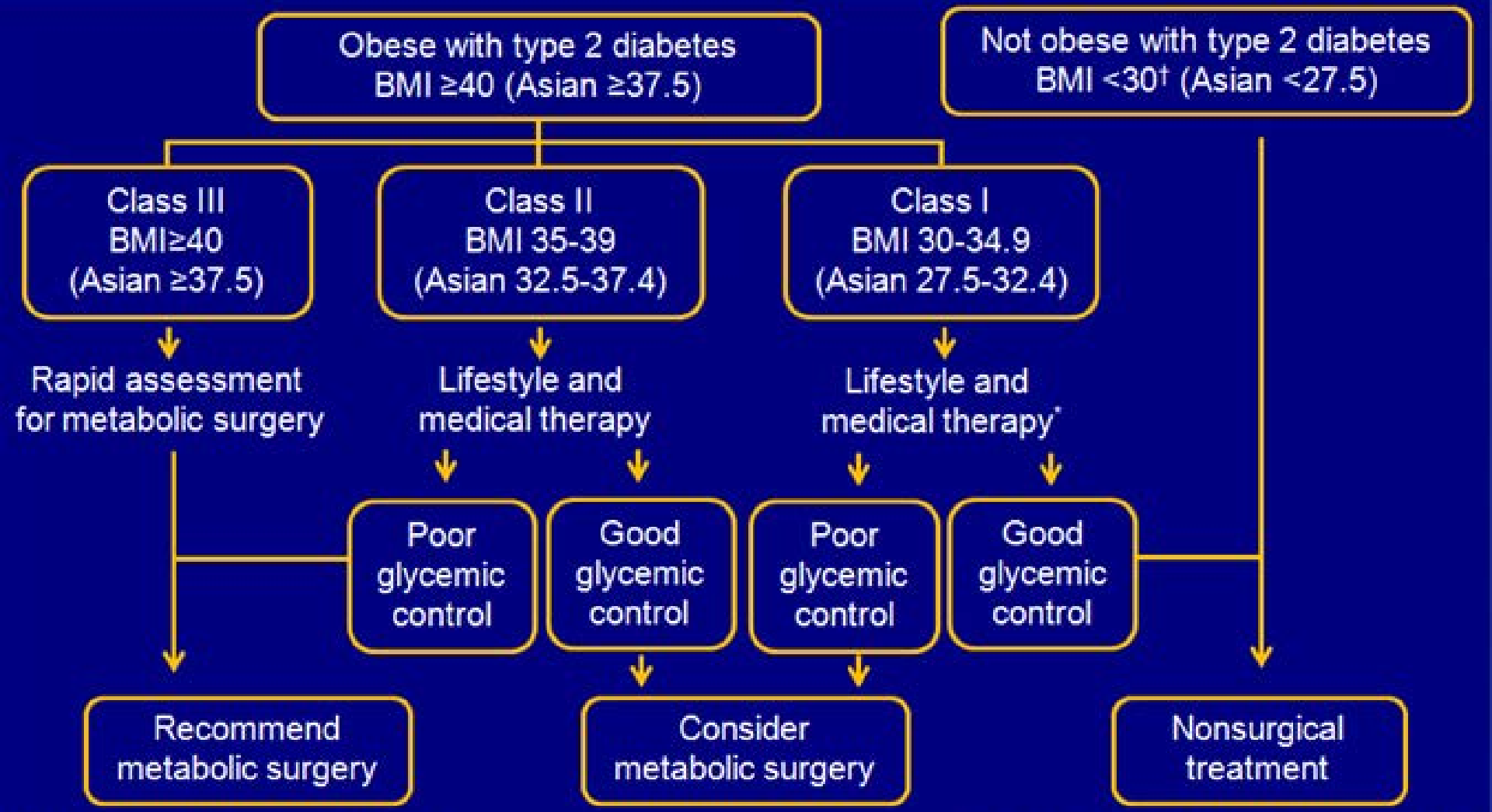
- Multidisciplinary group of 48 international clinicians /scholars (75 % non surgeons) including representatives of leading DM organizations, reviewed data from January 2005 to September of 2015.
- *Given its role in metabolic regulation, the GI tract constitutes a meaningful target to manage T2DM. Numerous clinical trials, albeit mostly short term/midterm, demonstrate that metabolic surgery achieves excellent glycemic control, and reduces CV RFs. Although additional studies are needed to further demonstrate long-term benefits, there is sufficient clinical and mechanistic evidence to support metabolic surgery among anti diabetes interventions for people with T2DM and obesity. Available data, based predominantly on modeling studies, suggest that bariatric/metabolic surgery is also cost effective, especially in patients with T2DM.*

ADA Bariatric Surgery Recommendations to Treat Type II Diabetes Joint Statement June of 2016

- BMI >/= 40 (Class III) Bariatric Surgery **Recommended regardless of glycemic control** (Asian 37.5)
- BMI 35-39.9 (Class II) & inadequate glycemic control Bariatric Surgery **Recommended** (Asian 32.5 – 37.5)
- BMI 30-34.9 (Class I) & inadequate glycemic control Bariatric Surgery **Considered** (Asian 27.5 to 32.5)
- For pts of Asian descent subtract 2.5 kg/m2 from above BMI recommendations
- Surgery should be performed in only high volume centers with multidisciplinary teams, who understand and are experienced in DM and GI surgeries with capability for long term follow up(mortality 0.1 to 0.5% and major complx 2 to 6 %)
- Diabetes Care June 2016

Metabolic Surgery for Type 2 Diabetes – Joint Statement from The 2nd Diabetes Surgery Summit (DSS-II)

Type 2 Diabetes Treatment Algorithm



*Including injectable medications and insulin

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

Patient Selection for Metabolic Surgery for the Treatment of Type 2 Diabetes

Contraindications for metabolic surgery:

- Type 1 diabetes diagnosis*
- Current drug or alcohol abuse
- Uncontrolled psychiatric illness
- Lack of comprehension of the risks/benefits, expected outcomes, alternatives
- Lack of commitment to nutritional supplementation, long-term follow-up
- In adolescent patients, GI surgery is inappropriate

Metabolic surgery is recommended as a treatment option in patients with:

- Class III obesity (BMI ≥40 kg/m^2)† regardless of the level of glycemic control or complexity of glucose-lowering regimens
- Class II obesity (BMI 35.0-39.9)† with poor glycemic control despite lifestyle and optimal medical therapy

Metabolic surgery may be considered as a treatment option in patients with:

- Class I obesity (BMI 30.0-34.9)† with poor glycemic control despite optimal medical treatment by oral or injectable medications

*Unless surgery is otherwise indicated, such as for severe obesity
†BMI thresholds should be reconsidered depending on ancestry; reduce by 2.5 for Asian patients
GI=gastrointestinal

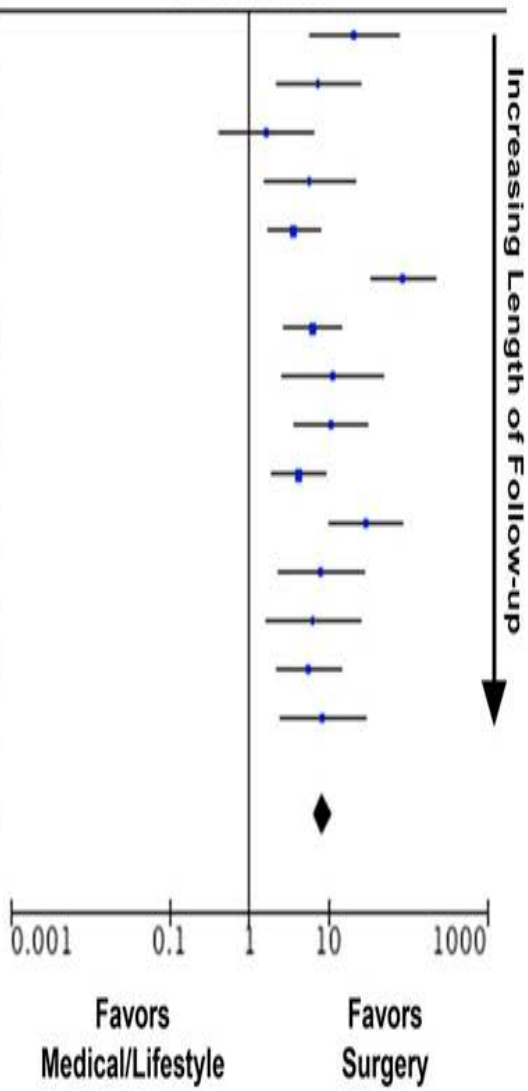
Rubino F, et al. *Diabetes Care*. 2016;39:861-877.

RCT data showing consistent superior efficacy of Surgery over med/lifestyle interventions for up to 5 years

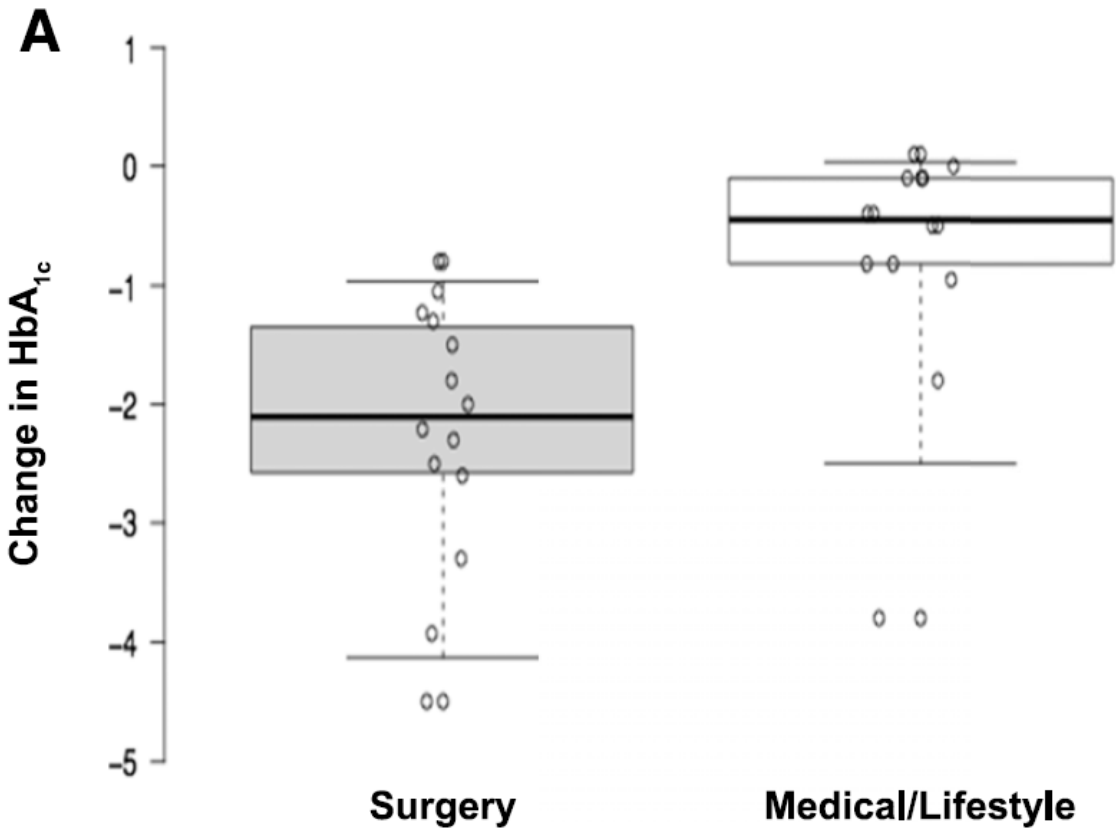
Study (Operation) [Follow-up; HbA_{1c} end point]	Surgery Glyc. Endp.	Surgery N	Medical/ Lifestyle Glyc. Endp.	Medical/ Lifestyle N	Weight	Peto, Fixed, 95% CI
Parikh 2014 (RYGB/LAGB/SG) [6 mo; ≤6.5% off meds] (18)	13	20	0	24	4.5%	21.15 [5.85, 76.51]
Courcoulas 2014 (RYGB/LAGB) [12 mo; ≤6.5% off meds] (14)	18	41	0	17	5.1%	7.51 [2.24, 25.21]
Ding 2015 (LAGB) [12 mo; ≤6.5%] (22)	6	18	5	22	3.9%	1.68 [0.42, 6.66]
Halperin 2014 (RYGB) [12 mo; ≤6.5% off meds] (15)	11	19	3	19	4.4%	5.82 [1.59, 21.39]
Ikramuddin 2013 (RYGB) [12 mo; ≤7.0%] (13)	28	57	11	57	12.5%	3.72 [1.72, 8.04]
Liang 2013 (RYGB) [12 mo; ≤7.0% off meds] (16)	28	31	0	70	8.4%	86.76 [33.89, 222.08]
Schauer 2012 (RYGB/SG) [12 mo; ≤6.0%] (12)	34	99	0	41	10.4%	6.39 [2.74, 14.88]
Cummings 2016 (RYGB) [12 mo; ≤6.5% off meds] (23)	9	15	1	17	3.4%	11.48 [2.63, 50.13]
Dixon 2008 (LAGB) [24 mo; ≤6.2% off meds] (10)	22	29	4	26	6.7%	10.83 [3.79, 30.96]
Ikramuddin 2015 (RYGB) [24 mo; ≤7.0%] (21)	26	60	8	59	11.8%	4.25 [1.92, 9.38]
Mingrone 2012 (RYGB/BPD) [24 mo; ≤6.5% off meds] (11)	34	40	0	20	6.4%	30.08 [10.28, 88.06]
Wentworth 2014 (LAGB) [24 mo; ≤7.0%] (17)	12	23	2	25	4.9%	8.11 [2.37, 27.84]
Courcoulas 2015 (RYGB/LAGB) [36 mo; ≤6.5% off meds] (24)	14	37	0	14	4.0%	6.44 [1.65, 25.21]
Schauer 2014 (RYGB/SG) [36 mo; ≤6.0%] (19)	27	97	0	40	8.7%	5.73 [2.28, 14.42]
Mingrone 2015 (RYGB/BPD) [60 mo; ≤6.5% off meds] (20)	19	38	0	15	4.9%	8.44 [2.46, 29.01]
Fixed-Effects Model		**624**		**466**	**100.0%**	**8.45 [6.44, 11.10]**

Heterogeneity: $Chi^2 = 45.43$, $df = 14$ ($P < 0.0001$); $I^2 = 69\%$

Test for overall effect: $Z = 15.36$ ($P < 0.00001$)



11 RCTs/ Median A1c drop of 2 % for surgery vs 0.5% medical/ Final A1c in surgical groups was near 6%



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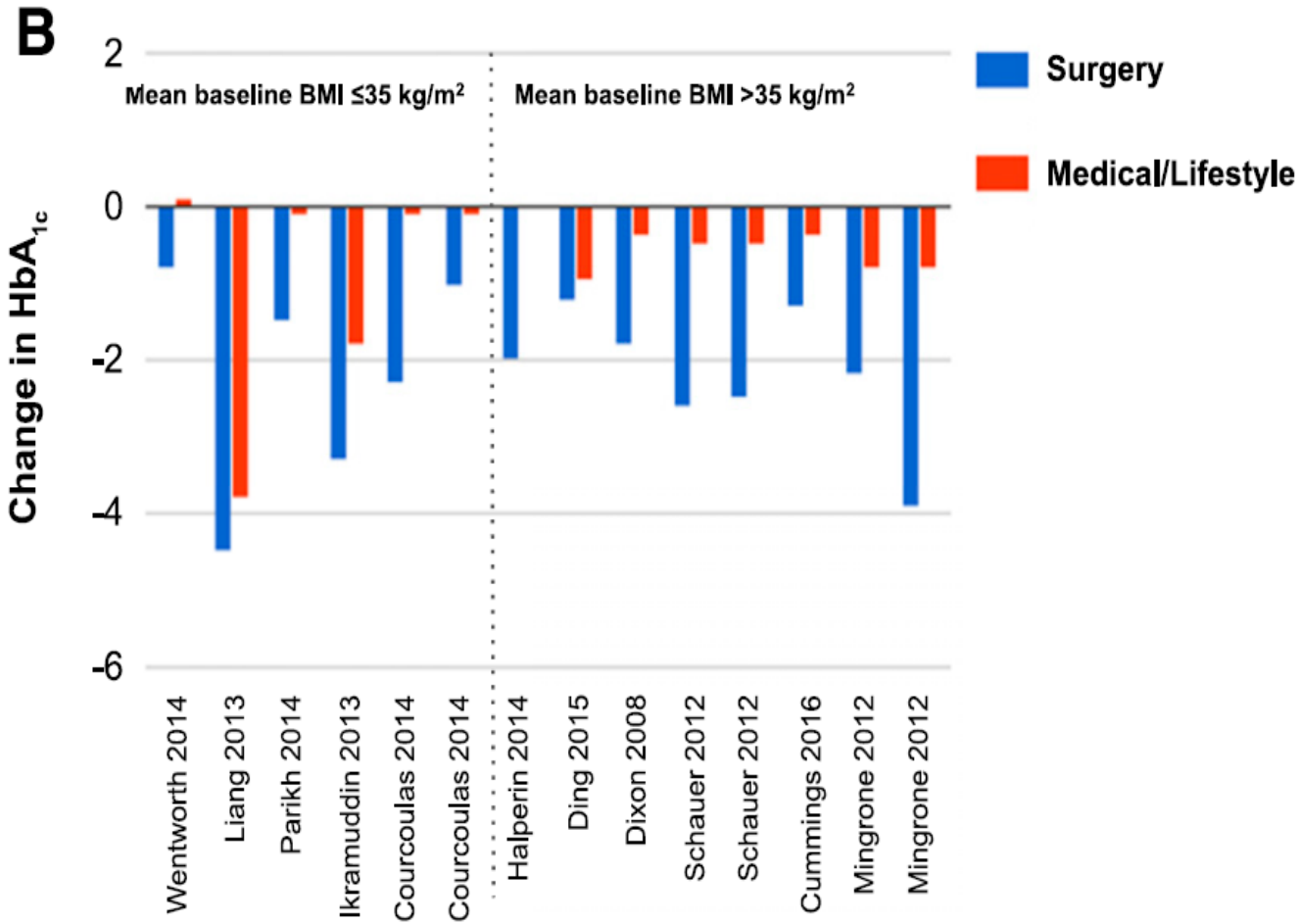
11 RCTs Change from baseline A1c



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Types of Metabolic Surgery Procedures for Treating Type 2 Diabetes

RYGB (gastric bypass)	➢ More favorable risk-benefit profile vs other options in most patients with type 2 diabetes
Vertical sleeve gastrectomy (VSG)	➢ Effective weight loss ➢ Major improvement of type 2 diabetes in short to medium term (1-3 years – longer-term studies requried) • Valuable option for patients concerned about risk of operations with bowel diversion
Laparoscopic adjustable gastric banding (LAGB)	➢ Effective in improving glycemia in patients with obesity and type 2 diabetes primarily by causing weight loss • Greater risk for reoperation/revision due to failure, complications
Biliopancreatic diversion (BPD)	➢ Most complex surgery – most effective for glycemic control/weight loss but risk-benefit profile is less favorable • Significant risk of nutritional deficiencies • Highest perioperative morbidity/mortality • Should be considered only in patients with BMI >60

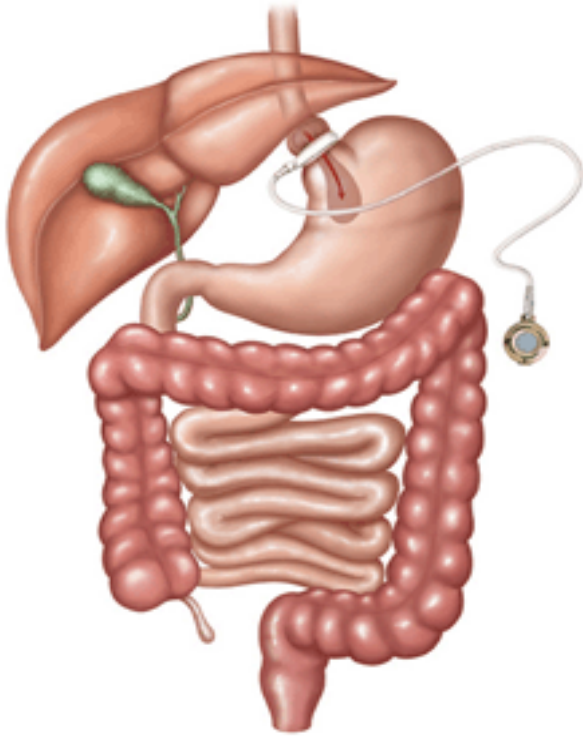
RYGB=Roux en-Y gastric bypass

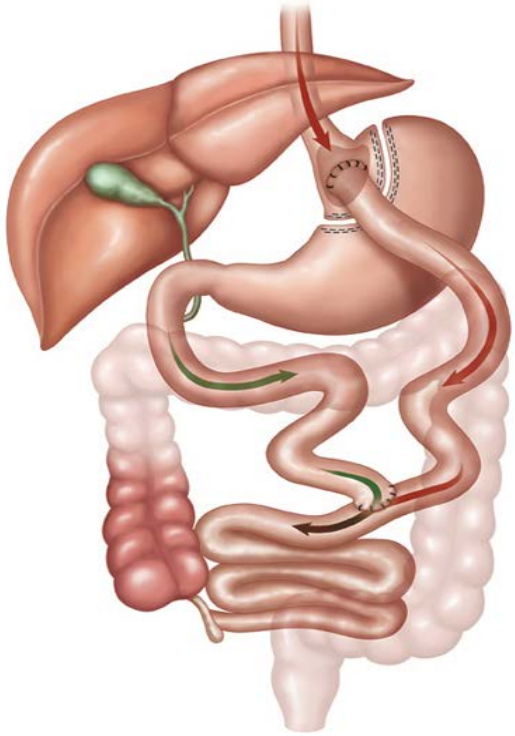
Rubino F, et al. *Diabetes Care*. 2016;39:861-877.

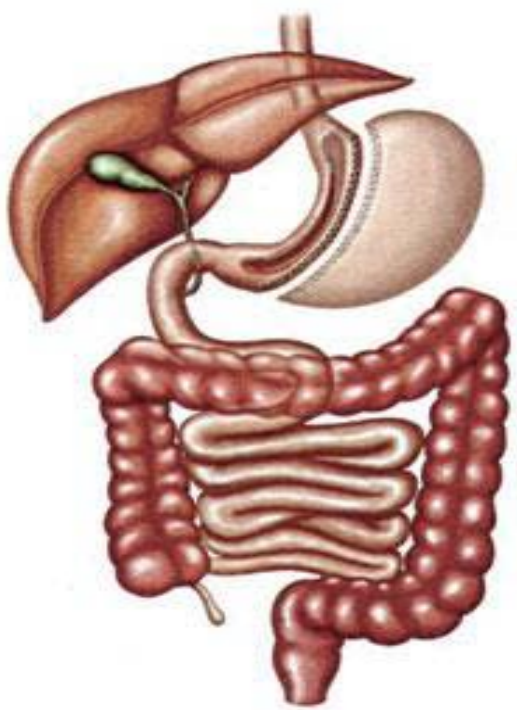
Adjustable Gastric Band

Roux-en-Y Gastric Bypass

Vertical Sleeve Gastrectomy







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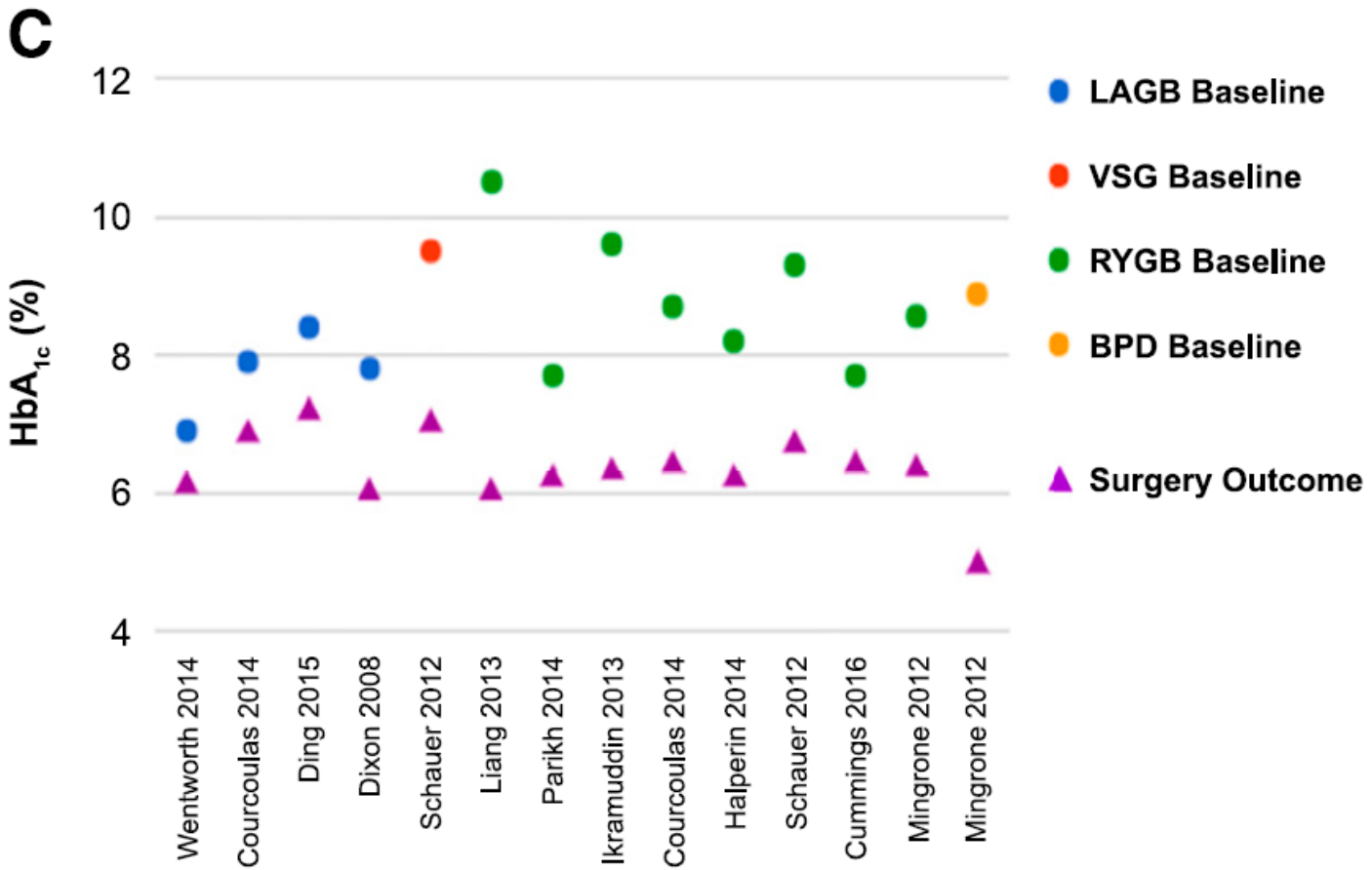
Baseline vs final A1c following surgery



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How much weight loss?

- 5-10% achieved with lifestyle reduces CVD RFs, prevents or delays DM, and improves other health outcomes of obesity
- Clinically meaningful is >/= 5 %
- Long term weight maintenance of loss is difficult
- There are now multiple medications approved by the FDA to treat weight
- FDA indications considering meds if BMI>/= 27 with complications of wt, and if >/= 30

The New York Times

Why Do Obese Patients Get Worse Care? Many Doctors Don't See Past the Fat

By GINA KOLATA SEPT. 25, 2016

FDA approved medications for weight loss

- Xenical (Orlistat) – longterm
- Diethylpropion (Tenuate)
- Lorcaserin (Belviq)- longterm
- Wellbutrin/Naltrexone (Contrave) –longterm
- Phentermine (adipex P, Fastin)
- Phentermine/Topamax (Qysmia) – longterm
- Liraglutide (Saxenda) - longterm

- Combine with lifestyle changes, with FUV monthly x first 3 months then every 3 months

Assessing Efficacy and Safety of Weight Loss Medications

Effective

Weight loss ≥5% body weight at 3 months and safe

↓

Continue medication

Ineffective

Weight loss <5% at 3 months
or
Safety or tolerability issue

↓

Discontinue medication
Seek alternate medication or refer for alternative therapy

Apovian CM, et al. *J Clin Endocrinol Metab*. 2015. doi: 10.1210/jc.2014-3415.

Treating Patients With Type 2 Diabetes Who Are Overweight or Obese

- Use antihyperglycemic medications that promote weight loss or weight neutrality
  - GLP-1 receptor agonists*
  - SGLT2 inhibitors†
  - Metformin‡
  - DPP-4 inhibitors (weight neutral)
  - Pramlinitide§
- Type 2 patients who require insulin:
  - Add metformin, pramlinitide, or GLP-1 RA to mitigate insulin-associated weight gain
  - First-line insulin: basal (consider prior to premixed or combination insulin therapy)
- Type 2 diabetes & hypertension:
  - ACEIs, ARBs, calcium channel blockers preferred over beta-adrenergic blockers

*Liraglutide is the only GLP-1 receptor agonist approved by the FDA for weight loss in the United States
†SGLT2 inhibitors are not approved by the FDA for weight loss in the United States
‡Metformin is not approved by the FDA for weight loss in the United States
§Pramlinitide is not approved by the FDA for weight loss in the United States
ACEI=angiotensin-converting enzyme inhibitor; ARB=angioten receptor blocker

Apovian CM, et al. *J Clin Endocrinol Metab*. 2015. doi: 10.1210/jc.2014-3415.

Breaking the cycle of Obesity and Diabetes

- Genetic and Epigenetics Obesity/Gestational DM/Increased Obesity and DM in offspring
- Public Health Policy
- School Interventions
- Food Industry

SUGAR IS THE 0LD CRACK

Big Sugar's Sweet Little Lies

How the industry kept scientists from asking: Does sugar kill?

GARY TAUBES AND CRISTIN KEARNS COUZENSNOVEMBER/DECEMBER 2012 ISSUE

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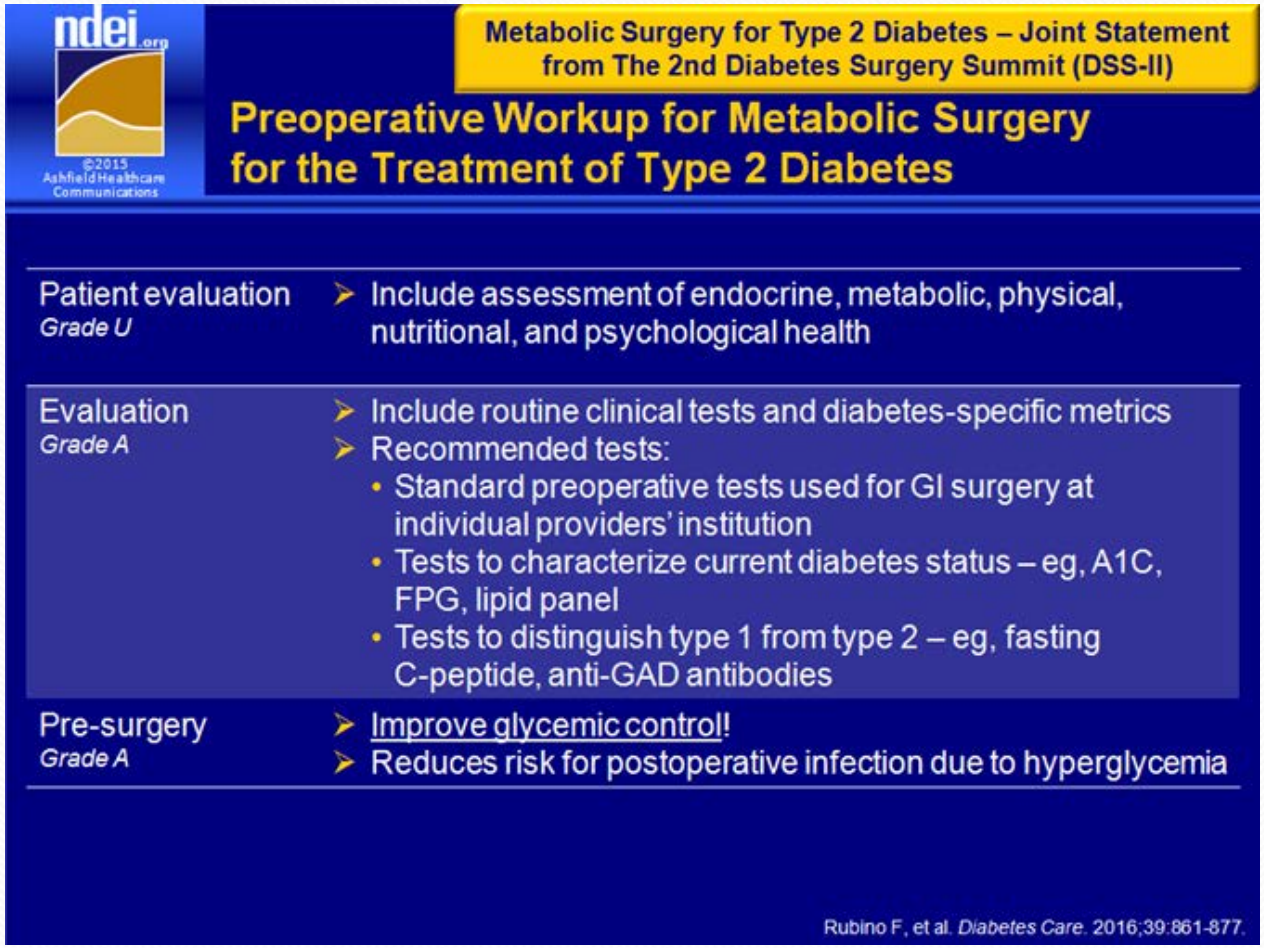
2016 US Dietary Guidelines

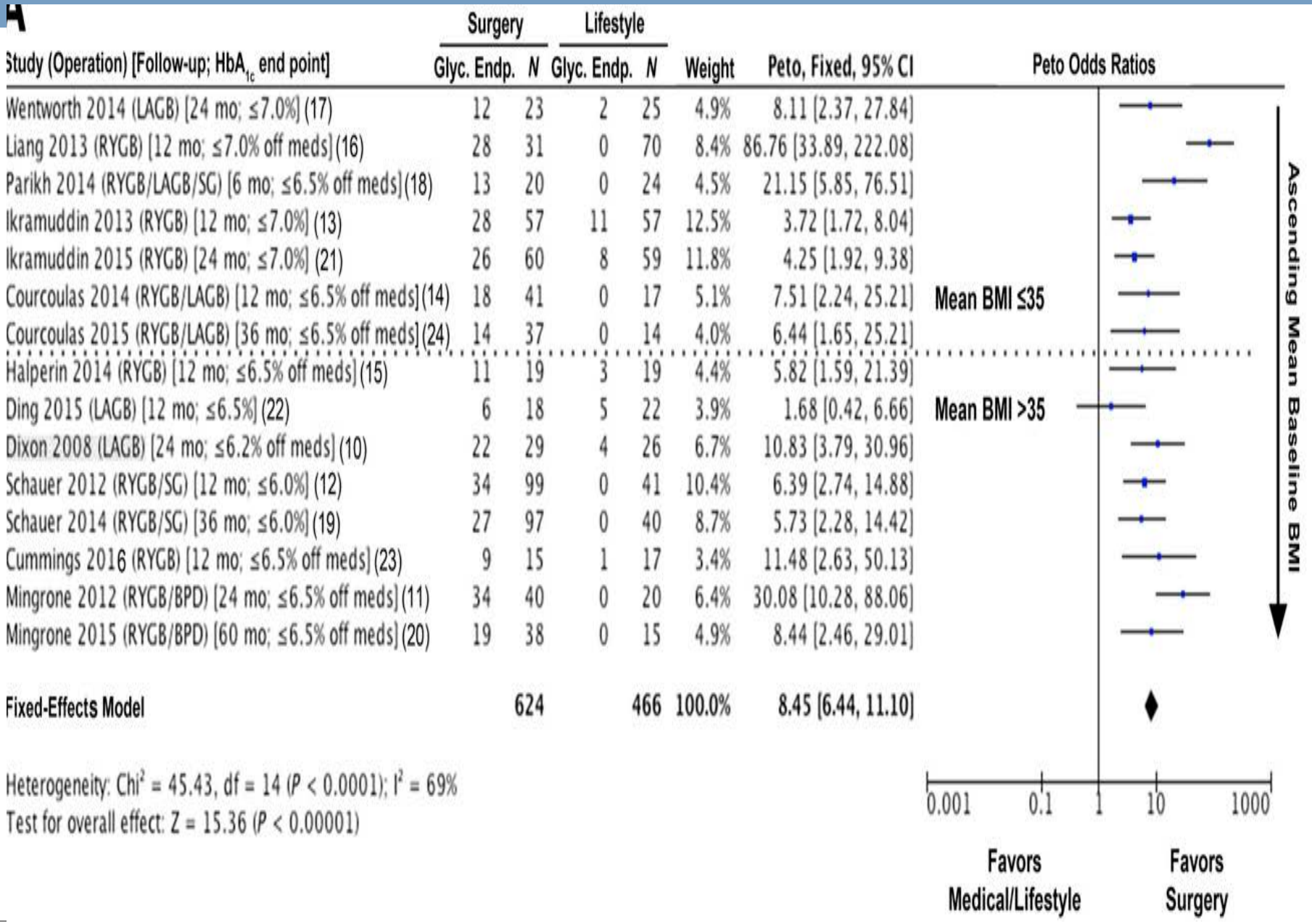
- Average American gets 25 teaspoons of added sugar per day 100% more than recommended, = 500 calories per day = 3500 calories per week = 1 pound of weight per week
- Goal is not more than 12 tsp per day in men
- Not more than 10 tsp per day in women
- Not more than 6 tsp per day in children
- One can of Coke is 10 teaspoons
- Kids fruit juice < 6mos none, 1 to 6 yo 4 to 6 oz, 7 to 18 yo 8 to 12 oz (high fructose corn syrup linked to fatty liver, obesity and insulin resistance)

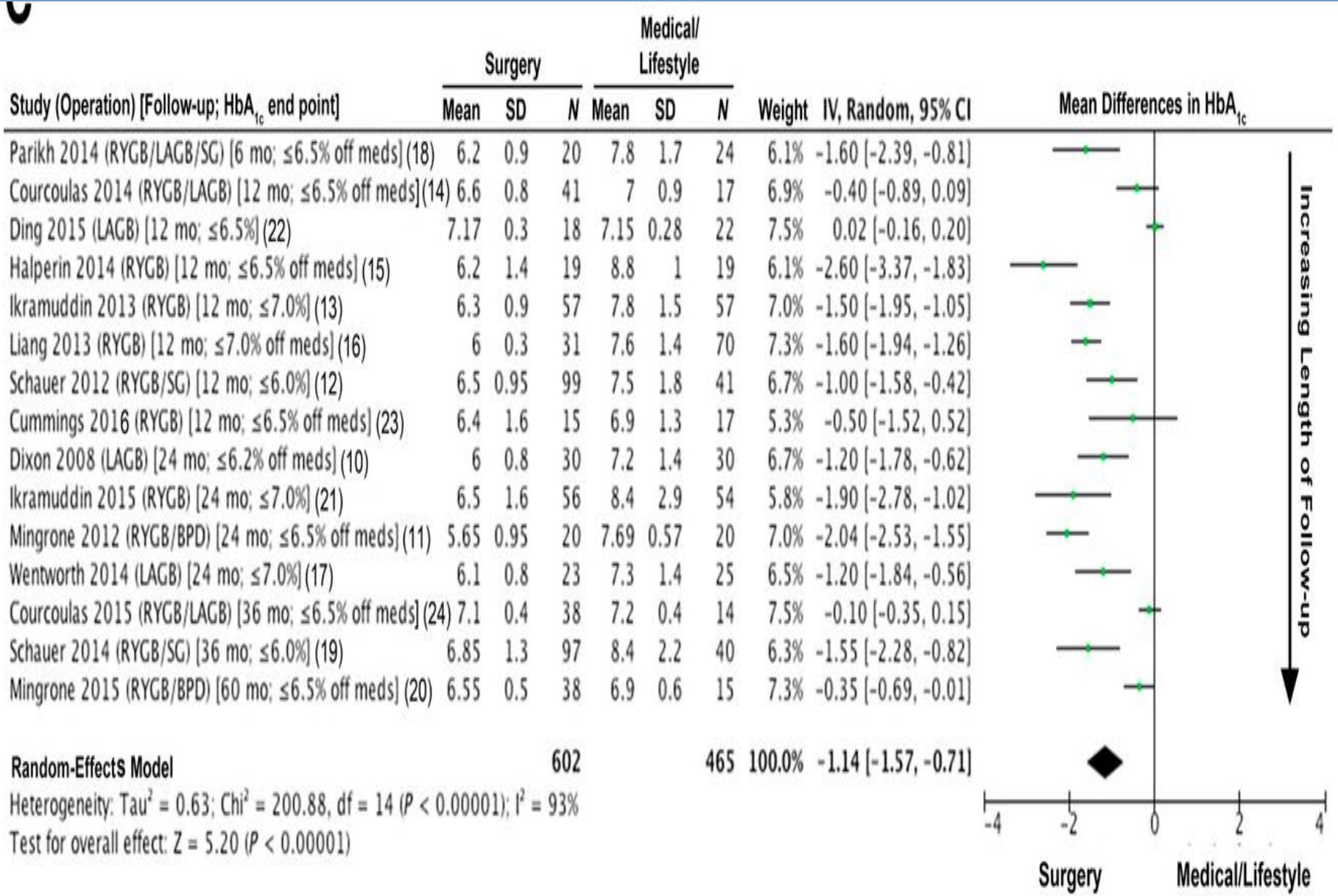
2016 American Dietary Habits

- 70% above the added sugar recommendations
- 71% above the saturated fat intake
- 89% above the sodium intake
- 87% below the vegetable goal intake
- 75% below the fruit goal intake

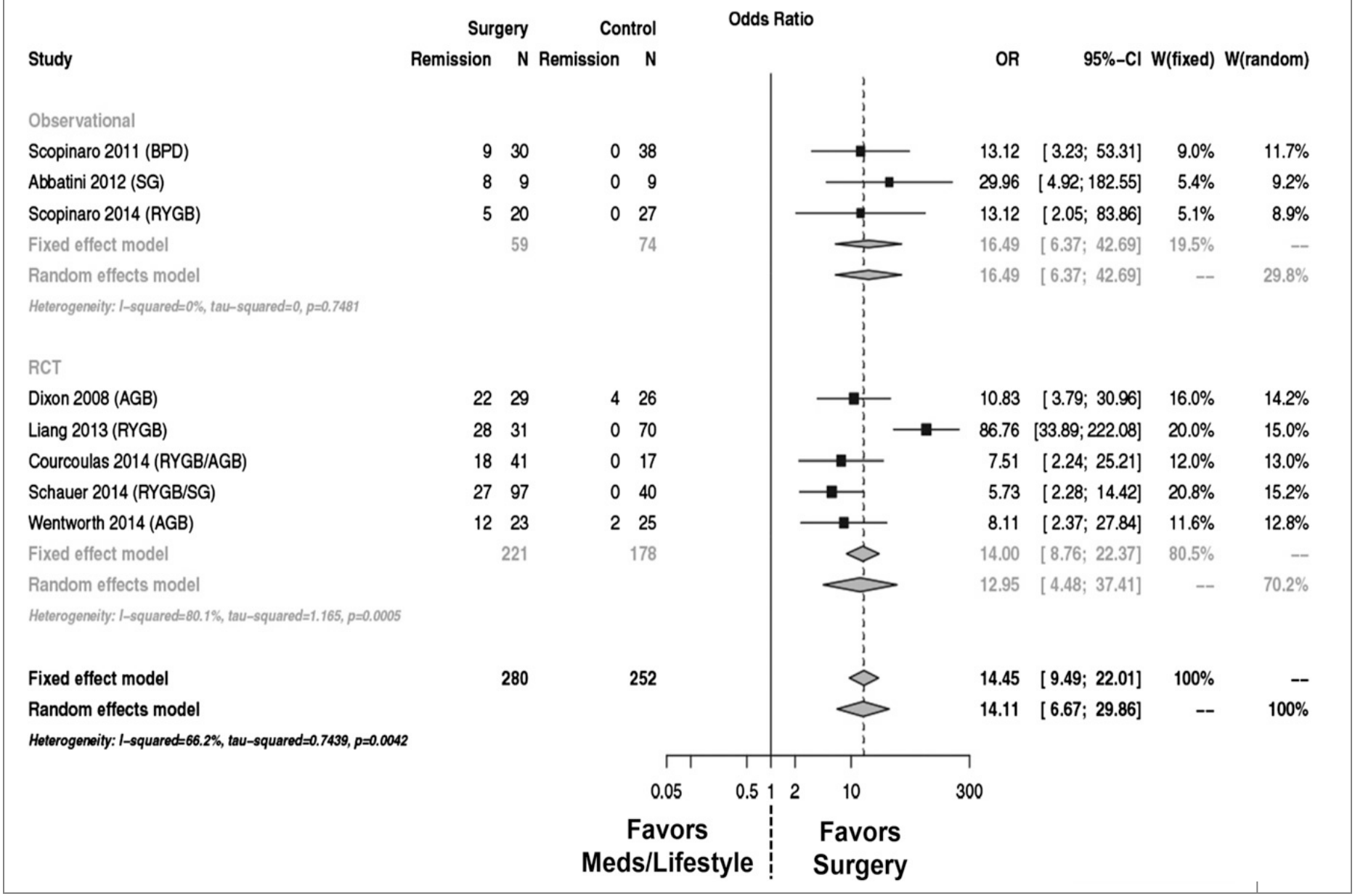
THANK YOU!




A
Surgery
Lifestyle
Study (Operation) [Follow-up; HbA1c end point]
Glyc. Endp. N
Glyc. Endp. N
Weight
Peto, Fixed, 95% CI
Peto Odds Ratios
Wentworth 2014 (LAGB) [24 mo; ≤7.0%] (17) 12 23 2 25 4.9% 8.11 [2.37, 27.84]
Liang 2013 (RYGB) [12 mo; ≤7.0% off meds] (16) 28 31 0 70 8.4% 86.76 [33.89, 222.08]
Parikh 2014 (RYGB/LAGB/SG) [6 mo; ≤6.5% off meds] (18) 13 20 0 24 4.5% 21.15 [5.85, 76.51]
Ikramuddin 2013 (RYGB) [12 mo; ≤7.0%] (13) 28 57 11 57 12.5% 3.72 [1.72, 8.04]
Ikramuddin 2015 (RYGB) [24 mo; ≤7.0%] (21) 26 60 8 59 11.8% 4.25 [1.92, 9.38]
Courcoulas 2014 (RYGB/LAGB) [12 mo; ≤6.5% off meds] (14) 18 41 0 17 5.1% 7.51 [2.24, 25.21]
Courcoulas 2015 (RYGB/LAGB) [36 mo; ≤6.5% off meds] (24) 14 37 0 14 4.0% 6.44 [1.65, 25.21]
Mean BMI ≤35
Halperin 2014 (RYGB) [12 mo; ≤6.5% off meds] (15) 11 19 3 19 4.4% 5.82 [1.59, 21.39]
Ding 2015 (LAGB) [12 mo; ≤6.5%] (22) 6 18 5 22 3.9% 1.68 [0.42, 6.66]
Mean BMI >35
Dixon 2008 (LAGB) [24 mo; ≤6.2% off meds] (10) 22 29 4 26 6.7% 10.83 [3.79, 30.96]
Schauer 2012 (RYGB/SG) [12 mo; ≤6.0%] (12) 34 99 0 41 10.4% 6.39 [2.74, 14.88]
Schauer 2014 (RYGB/SG) [36 mo; ≤6.0%] (19) 27 97 0 40 8.7% 5.73 [2.28, 14.42]
Cummings 2016 (RYGB) [12 mo; ≤6.5% off meds] (23) 9 15 1 17 3.4% 11.48 [2.63, 50.13]
Mingrone 2012 (RYGB/BPD) [24 mo; ≤6.5% off meds] (11) 34 40 0 20 6.4% 30.08 [10.28, 88.06]
Mingrone 2015 (RYGB/BPD) [60 mo; ≤6.5% off meds] (20) 19 38 0 15 4.9% 8.44 [2.46, 29.01]
Ascending Mean Baseline BMI
Fixed-Effects Model 624 466 100.0% 8.45 [6.44, 11.10]
Heterogeneity: Chi² = 45.43, df = 14 (P < 0.0001); I² = 69%
Test for overall effect: Z = 15.36 (P < 0.00001)
0.001
0.1
1
10
1000
Favors Medical/Lifestyle
Favors Surgery


Surgery
Medical/ Lifestyle
Study (Operation) [Follow-up; HbA1c end point] Mean SD N Mean SD N Weight IV, Random, 95% CI
Mean Differences in HbA1c
Parikh 2014 (RYGB/LAGB/SG) [6 mo; ≤6.5% off meds] (18) 6.2 0.9 20 7.8 1.7 24 6.1% -1.60 [-2.39, -0.81]
Courcoulas 2014 (RYGB/LAGB) [12 mo; ≤6.5% off meds] (14) 6.6 0.8 41 7 0.9 17 6.9% -0.40 [-0.89, 0.09]
Ding 2015 (LAGB) [12 mo; ≤6.5%] (22) 7.17 0.3 18 7.15 0.28 22 7.5% 0.02 [-0.16, 0.20]
Halperin 2014 (RYGB) [12 mo; ≤6.5% off meds] (15) 6.2 1.4 19 8.8 1 19 6.1% -2.60 [-3.37, -1.83]
Ikramuddin 2013 (RYGB) [12 mo; ≤7.0%] (13) 6.3 0.9 57 7.8 1.5 57 7.0% -1.50 [-1.95, -1.05]
Liang 2013 (RYGB) [12 mo; ≤7.0% off meds] (16) 6 0.3 31 7.6 1.4 70 7.3% -1.60 [-1.94, -1.26]
Schauer 2012 (RYGB/SG) [12 mo; ≤6.0%] (12) 6.5 0.95 99 7.5 1.8 41 6.7% -1.00 [-1.58, -0.42]
Cummings 2016 (RYGB) [12 mo; ≤6.5% off meds] (23) 6.4 1.6 15 6.9 1.3 17 5.3% -0.50 [-1.52, 0.52]
Dixon 2008 (LAGB) [24 mo; ≤6.2% off meds] (10) 6 0.8 30 7.2 1.4 30 6.7% -1.20 [-1.78, -0.62]
Ikramuddin 2015 (RYGB) [24 mo; ≤7.0%] (21) 6.5 1.6 56 8.4 2.9 54 5.8% -1.90 [-2.78, -1.02]
Mingrone 2012 (RYGB/BPD) [24 mo; ≤6.5% off meds] (11) 5.65 0.95 20 7.69 0.57 20 7.0% -2.04 [-2.53, -1.55]
Wentworth 2014 (LAGB) [24 mo; ≤7.0%] (17) 6.1 0.8 23 7.3 1.4 25 6.5% -1.20 [-1.84, -0.56]
Courcoulas 2015 (RYGB/LAGB) [36 mo; ≤6.5% off meds] (24) 7.1 0.4 38 7.2 0.4 14 7.5% -0.10 [-0.35, 0.15]
Schauer 2014 (RYGB/SG) [36 mo; ≤6.0%] (19) 6.85 1.3 97 8.4 2.2 40 6.3% -1.55 [-2.28, -0.82]
Mingrone 2015 (RYGB/BPD) [60 mo; ≤6.5% off meds] (20) 6.55 0.5 38 6.9 0.6 15 7.3% -0.35 [-0.69, -0.01]
Random-Effects Model 602 465 100.0% -1.14 [-1.57, -0.71]
Heterogeneity: Tau² = 0.63; Chi² = 200.88, df = 14 (P < 0.00001); I² = 93%
Test for overall effect: Z = 5.20 (P < 0.00001)
Increasing Length of Follow-up
-4 -2 0 2 4
Surgery
Medical/Lifestyle

BMI < 35 T2DM remission



Choosing Nutritional Therapy for Obesity

- Nutritional approaches for weight loss typically focus on the manipulation of the three macronutrients: protein, fat, or carbohydrate
- Very low-calorie diets contain less than 800 kcal/day and require close medical supervision for safety reasons
- Low calorie diets range from 1200-1800 kcal/day (1200-1500 for women, 1500-1800 for men).
- Restricting dietary fat leads to a greater reduction in total and LDL cholesterol, whereas restricting dietary carbohydrate leads to a greater reduction in serum triglycerides and an increase in HDL-cholesterol
- Reduction of carbohydrates can lead to a greater reduction in serum glucose and hemoglobin A1C

Reference/s: [8] [55] [91] [93]

ADA 2016 Guidelines

Recommendations for Preventing or Delaying Type 2 Diabetes

Individuals with prediabetes: IGT, IFG, or A1C 5.7%-6.4%	Refer to intensive diet & physical activity behavior counseling program targeting • Weight loss (7% of body weight) • Increased physical activity (≥150 min/week moderate activity)
Consider metformin therapy for type 2 diabetes prevention in individuals with prediabetes	Especially in presence of • BMI >35 kg/m^2 • Age <60 years • Women with prior GDM

At least annual monitoring of individuals with prediabetes

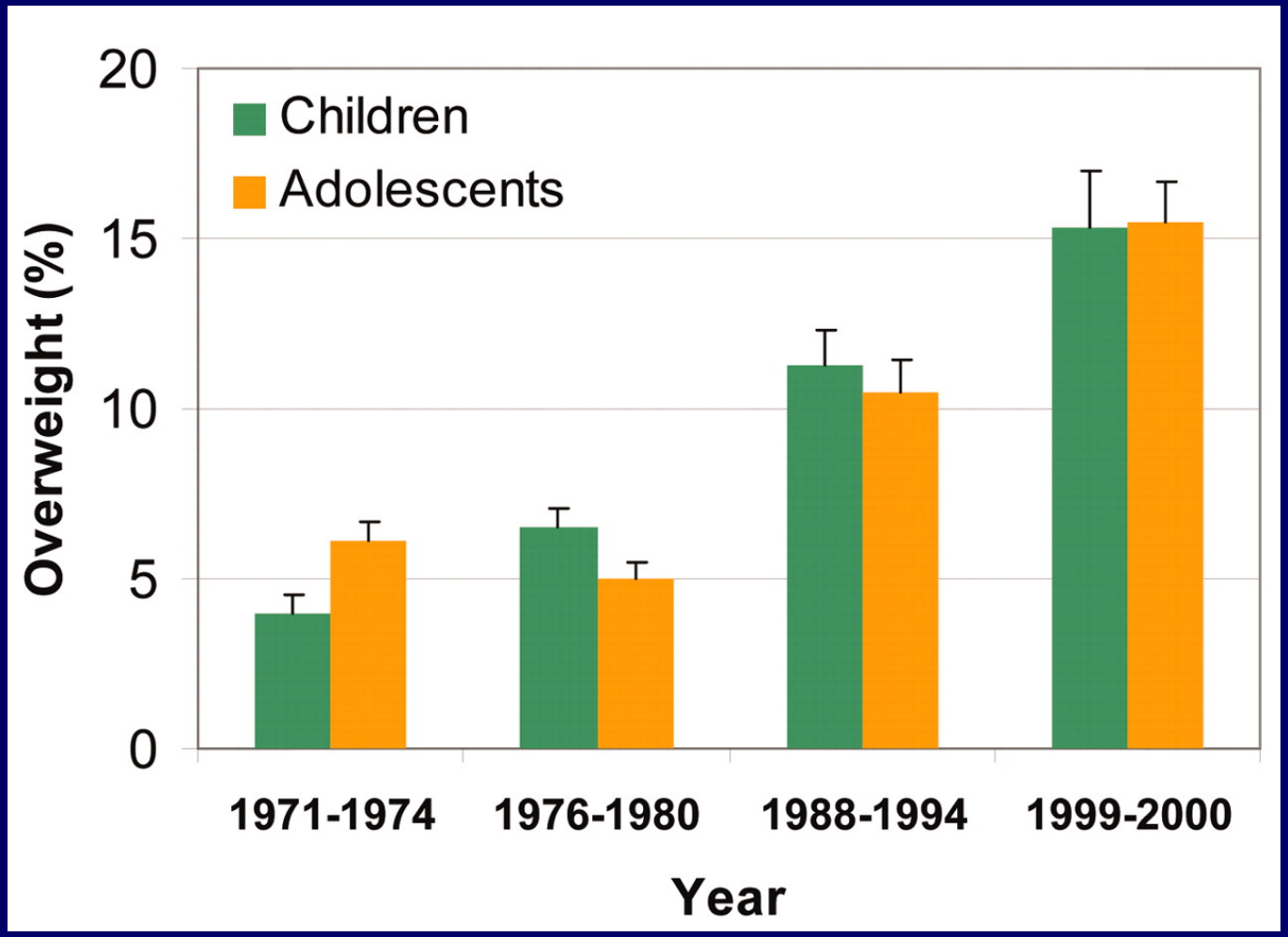
Screen for and treat modifiable CVD risk factors: obesity, hypertension, dyslipidemia

DSME & DSMS appropriate for prediabetes to receive education and support for diabetes prevention or delay

Metformin is not FDA approved in the United States for type 2 diabetes prevention

CVD=cardiovascular disease; GDM=gestational diabetes mellitus; IFG=impaired fasting glucose; IGT=impaired glucose tolerance

American Diabetes Association. *Diabetes Care*. 2016;39(suppl 1):S1-S106.


20
15
10
5
0
Overweight (%)
Children
Adolescents
1971-1974
1976-1980
1988-1994
1999-2000
Year

Screening for Type 2 Diabetes & Prediabetes in Asymptomatic Individuals

- Type 2 diabetes testing
  - Adults of any age who are overweight or obese* and who have ≥1 diabetes risk factor
  - Begin testing at age 45
  - Normal test? Repeat at ≥3-year intervals
- Prediabetes testing
  - A1C, FPG, or 2-h PG after 75-g OGTT
  - Identify & treat other CVD risk factors
  - Consider testing in children and adolescents who are overweight or obese and have ≥2 diabetes risk factors

Diabetes Risk Factors

- Physical inactivity
- First-degree relative with diabetes†
- High-risk race/ethnicity
- Women who delivered a baby >9 lb or prior GDM diagnosis
- HDL-C <35 mg/dL ± TG >250 mg/dL
- A1C ≥5.7%, IGT, or IFG
- Hypertension (≥140/90 or on treatment)
- CVD history
- Conditions associated with insulin resistance‡

*BMI ±25 kg/m² or ≥23 kg/m² for Asian Americans
†African-American, Latino, Native American, Asian American, Pacific Islander
‡Severe obesity, acanthosis nigricans, polycystic ovarian syndrome

American Diabetes Association. *Diabetes Care*. 2016;39(suppl 1):S1-S106.

Postoperative Follow-Up for Metabolic Surgery for Treating Type 2 Diabetes

After surgery, patients should be managed by multidisciplinary teams.

Evaluations	➢ At least every 6 months during the first 2 postoperative years ➢ At least annually thereafter

Monitor glycemic control to avoid potential hyperglycemia relapse

Stable nondiabetic glycemic for < 5yrs	➢ Monitor for complications ➢ 5-yr remission: reduce monitoring frequency ➢ Persistent normoglycemia & no complications: cease screening for complications

In first 6 months, evaluate for glycemic control and tapering of diabetes medications

- ➢ After 6 months, further diabetes treatment should be dosed accordingly
- ➢ Discontinue meds only after stable normoglycemia for at least two 3-month A1C cycles

If glucose levels quickly reach normoglycemic range early post-surgery:

- ➢ Adjust therapy to prevent hypoglycemia*

Ongoing and long-term monitoring of micronutrient status, nutritional supplementation, patient support

*Metformin, TZDs, GLP-1 receptor agonists, DPP-4 inhibitors, alpha-glucosidase inhibitors, and SGLT2 inhibitors are suitable for early postoperative diabetes care)

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

Summary of Recommendations for Treating Type 2 Diabetes With Metabolic Surgery

Metabolic surgery is recommended to treat:

- Type 2 diabetes in patients with Class II and Class III obesity
  when glycemia is inadequately controlled by lifestyle and optimal medical therapy

Metabolic surgery should be considered to treat:

- Type 2 diabetes in patients with Class I obesity
  if glycemic control is poor despite optimal treatment with oral or injectable medications

Surgery should be performed in high-volume centers with multidisciplinary teams that understand and are experienced in the management of diabetes and GI surgery

Mortality rates with bariatric/metabolic operations are typically 0.1%-0.5%

Major complications rates are 2%-6%, with minor complications in up to 15%

Postoperative follow-up: Ongoing and long-term monitoring of micronutrient status, nutritional supplementation, and support

Short/mid-term RCTs have shown that metabolic surgery achieves excellent glycemic control and reduces CV risk factors. Surgical value is more related to improved glucose homeostasis than weight loss. Additional studies are needed to demonstrate long-term benefits.

GI=gastrointestinal

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

Strategies for Long-Term Weight Loss

Use approved weight loss medications to:

- Ameliorate comorbidities
- Increase adherence to lifestyle
- Improve physical functioning

Individuals with:

- BMI ≥30
- BMI ≥27 with ≥1 weight-related comorbidity*

Combined use of weight loss medication with lifestyle changes can produce greater weight loss and cardiometabolic improvements vs lifestyle alone

Assess efficacy and safety of pharmacotherapy at least monthly for first 3 months, then at least every 3 months

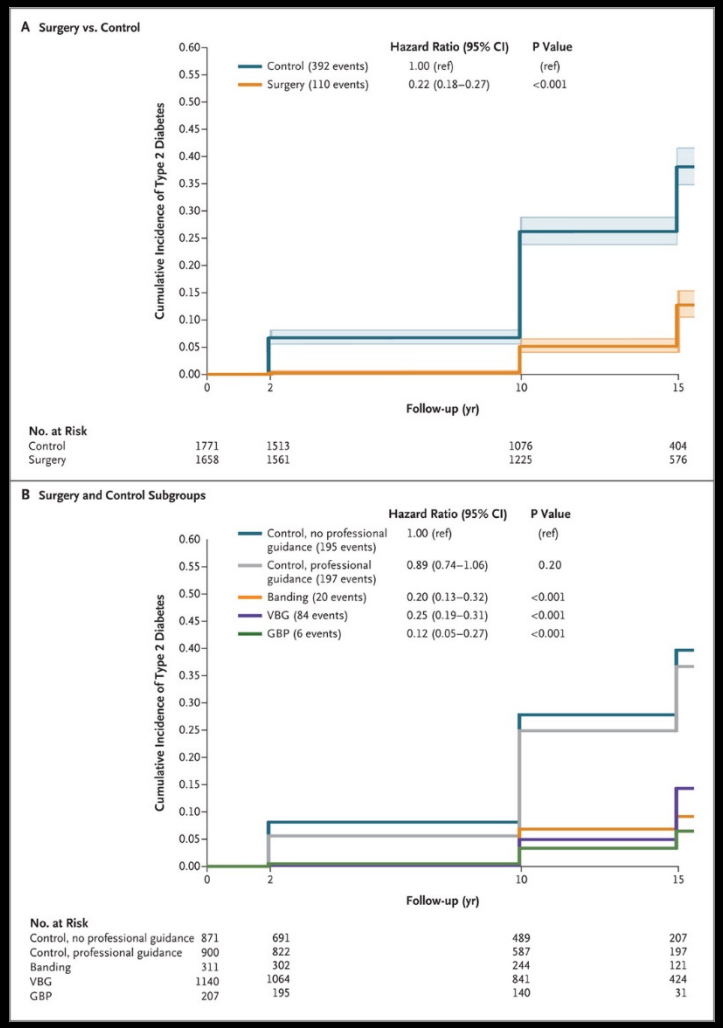
Weight loss medications available in the United States

Phentermine†,‡ • Phentermine/topiramate • Diethylpropion • Lorcaserin • Orlistat • Naltrexon/bupropion • Liraglutide

*Hypertension, dyslipidemia, type 2 diabetes, obstructive sleep apnea
†Use of phentermine and diethylpropion not recommended in patients with uncontrolled hypertension, history of CVD, history of cardiac arrhythmia, or seizures
‡Phentermine is not FDA approved for long-term use in the United States

Apovian CM, et al. *J Clin Endocrinol Metab.* 2015. doi: 10.1210/jc.2014-3415.

Cumulative Incidence of Type 2 Diabetes.



Carlsson LM et al. N Engl J Med 2012;367:695-704.

The NEW ENGLAND JOURNAL of MEDICINE

Identify and Manage Concomitant Pharmacotherapy That Might Alter Body Weight

Cardiovascular Medications

May increase body weight:

- Some beta-blockers
  - Propranolol
  - Atenolol
  - Metoprolol
- Dihydropyridine (“dipine”) calcium channel blockers
  - Nifedipine
  - Amlodipine
  - Felodipine

Diabetes Mellitus Medications

May increase body weight:

- Most insulins
- Sulfonylureas
- Thiazolidinediones
- Meglitinides

May decrease body weight:

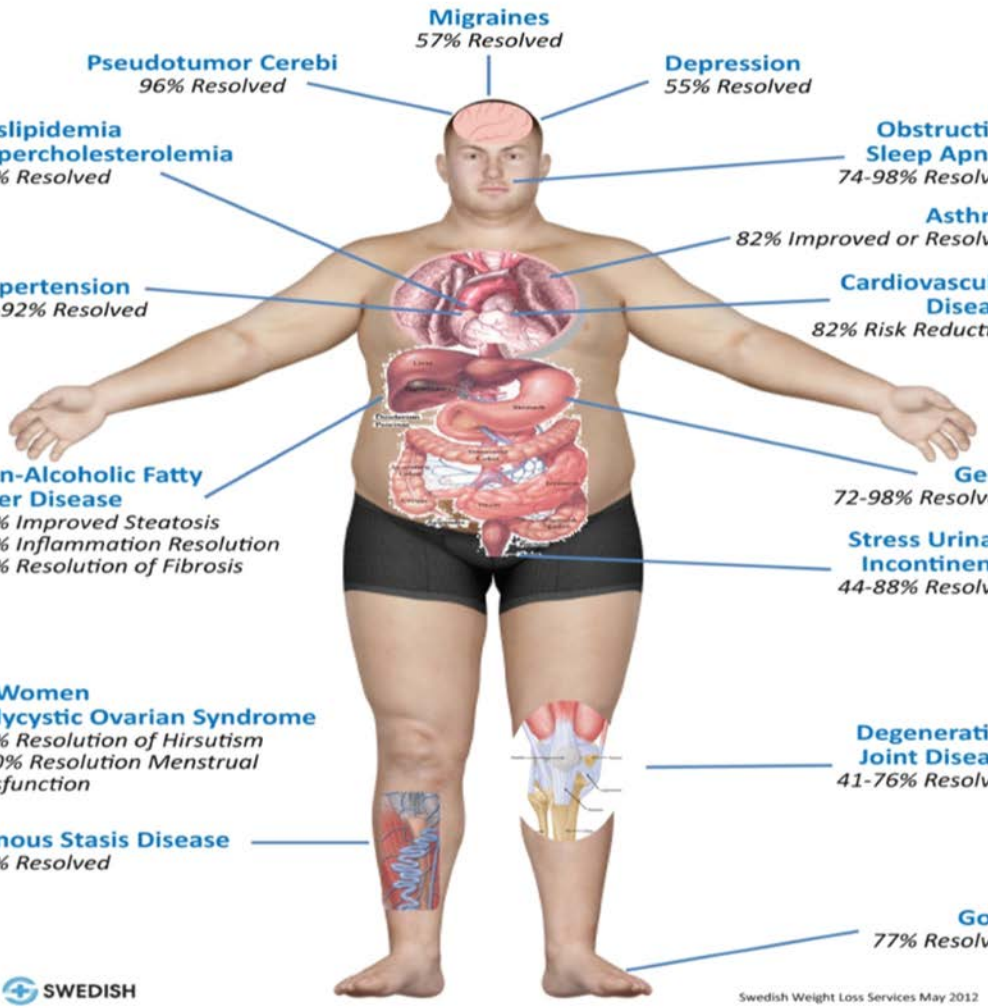
- Metformin
- Glucagon-like peptide-1 agonists
- Sodium glucose co-transporter 2 inhibitors
- Alpha glucosidase inhibitors

Reference/s: [7] [18] [63] [76]

Obesity

* Leading cause of preventable death in the US
* The American Medical Association (AMA), World Health Organization (W.H.O.), along with National and International medical and scientific societies, recognize obesity as a chronic progressive ***disease***
* U.S. spent $190 billion on obesity-related health care expenses in 2005

Obesity and Related Illness and Disease

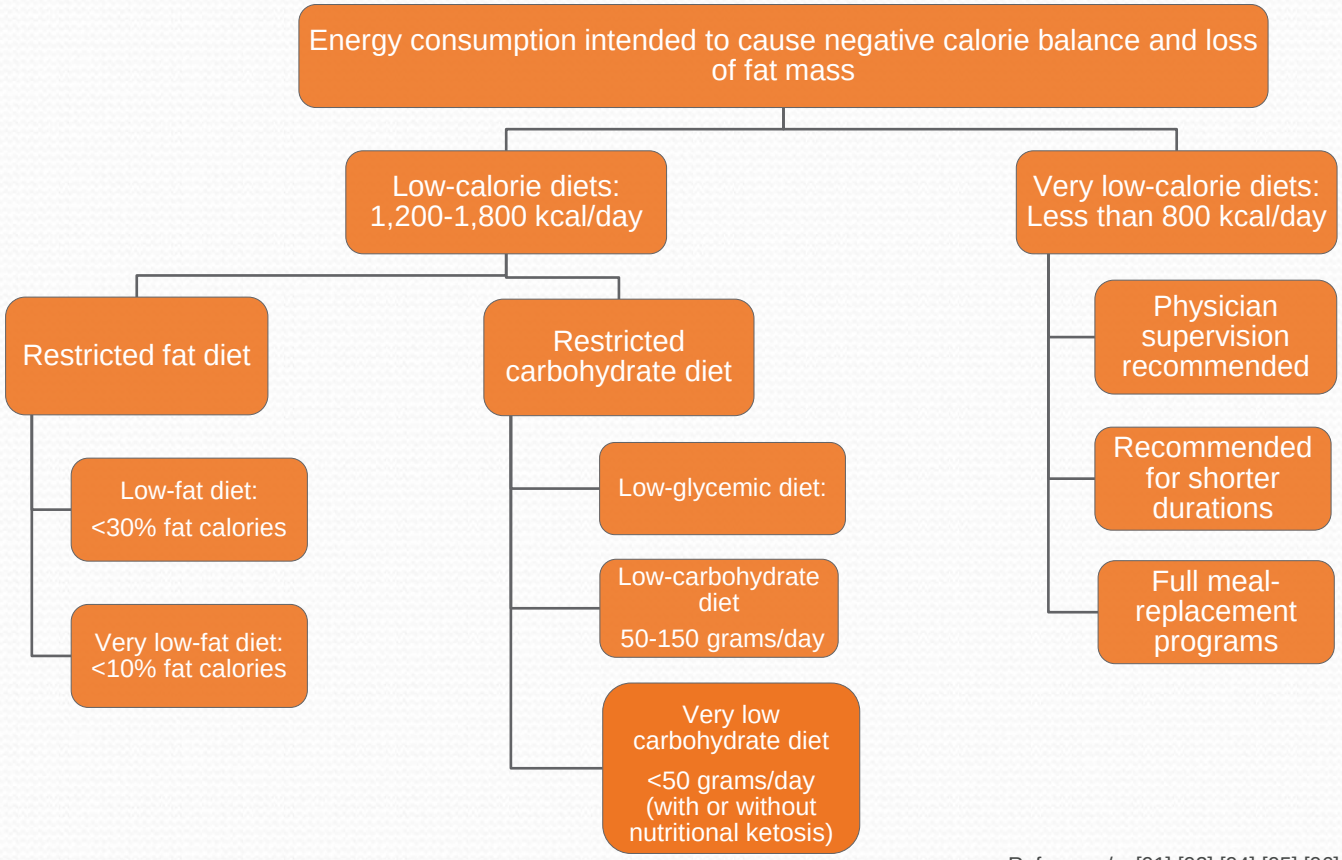


Type II Diabetes
83% Resolved

Quality of Life
Improved 95% in Patients

Metabolic Syndrome
80% Resolved

Nutritional Therapy for Obesity



Reference/s: [91] [92] [94] [95] [96] [97] [509]

Obesity Algorithm®. ©2015-2016 Obesity Medicine Association.

Definition of Obesity

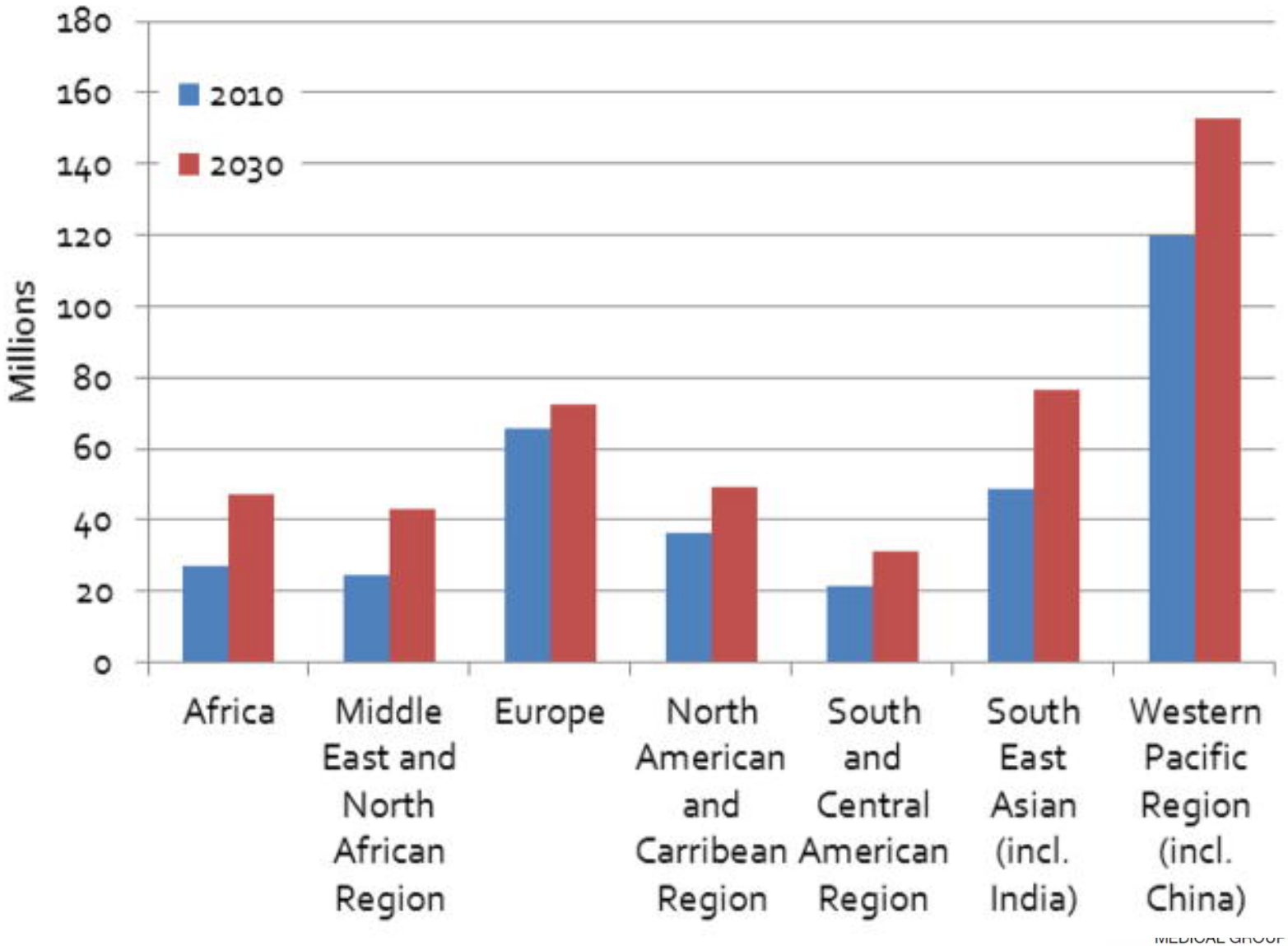
BMI = Weight kg/Height m^2

Underweight	≤ 19
Normal	19 - 25
Overweight	26 - 29
Obese Class I	30 - 35
Obese Class II	35 - 39.9
Morbid Obesity	≥ 40
Super Obesity	≥ 50

BMI 40 = approximately 100 lbs above ideal weight

SWEDISH

IGT aged 20-79 by region 2010 and 2030



Long-Term Mortality after Gastric Bypass

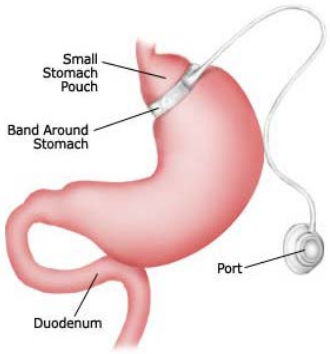
* 7.1 years follow-up
* Overall deaths dropped 40% with Surgery
* Heart Disease Deaths dropped 56%
* Diabetes deaths dropped 92%
* Cancer deaths dropped 60%

Kearsten lost over 130 pounds along with multiple medical conditions and prescriptions pills!

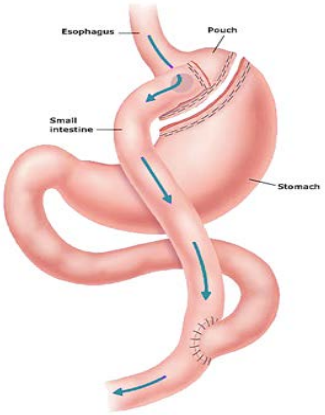
SWEDISH

Successful Weight Loss Surgery

Restrictive Procedures

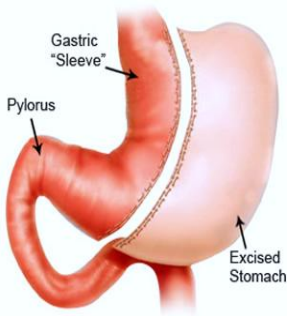


- Adjustable Gastric Band (AGB)
  - Advanced platform Standard (APS) and Large (APL)
  - Realize C



- Roux-en-Y Gastric Bypass

(Roux 100 cm)



- Vertical Sleeve Gastrectomy (VSG)

SWEDISH
MEDICAL GROUP

How Dangerous is Surgery?

- BOLD National Data – 57918 patients…
- Average in hospital mortality = 0.043%
- Average mortality 30 days = 0.089%
- **Surgery is less risky than the disease itself for 1 month**

DeMaria EJ et al SOARD 6(2010) 347-355

SWEDISH
MEDICAL GROUP

Screening Children for Type 2 Diabetes and Prediabetes

Consider for all children who are overweight* and have ≥2 of any of the following risk factors:

- Family history of type 2 diabetes in first- or second-degree relative
- Native American, African American, Latino, Asian American or Pacific Islander
- Signs of insulin resistance or conditions associated with insulin resistance†
- Maternal history of diabetes or GDM during child's gestation

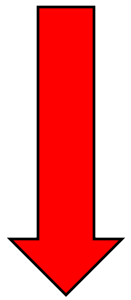
Test every 3 yrs using A1C beginning at age 10 or puberty onset

Children: age ≤18 yrs
*BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% ideal for height
†Acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome, or small-for-gestational-age birth weight
BMI=body mass index; GDM=gestational diabetes mellitus

American Diabetes Association. *Diabetes Care*. 2016;39(suppl 1):S1-S106.

How Dangerous is Surgery?

* McGill University: Compared 5,746 morbidly obese patients managed medically with 1,035 patients who underwent surgery
* sex, age, and duration matched
* Medical: 5-year mortality was **6.17%**
* Surgical: 5-year mortality was **0.68%**



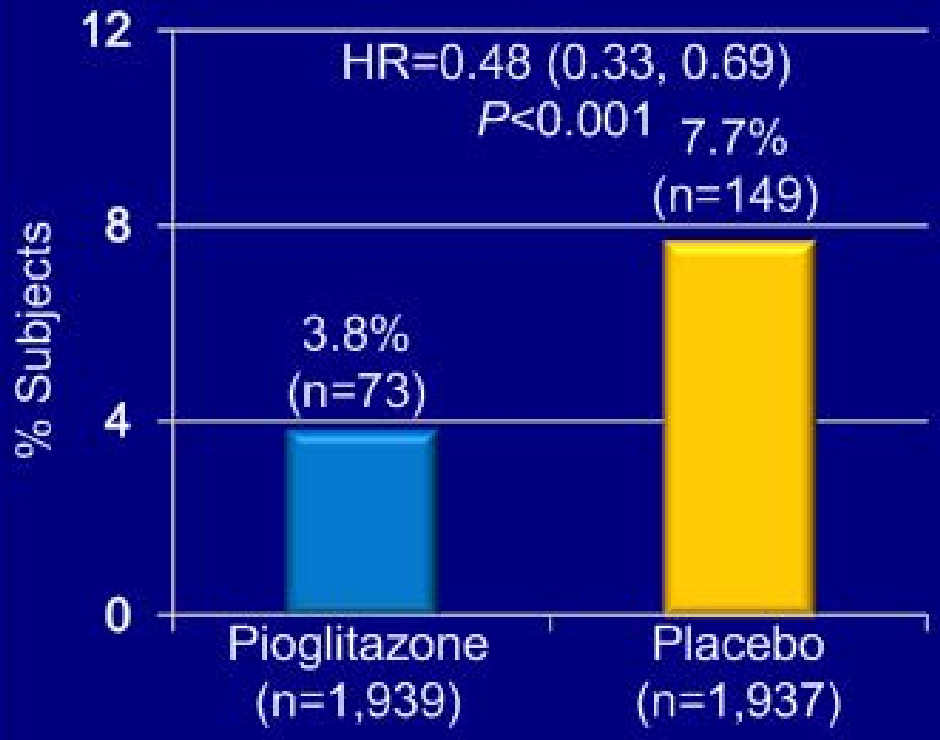
>9 X

SWEDISH

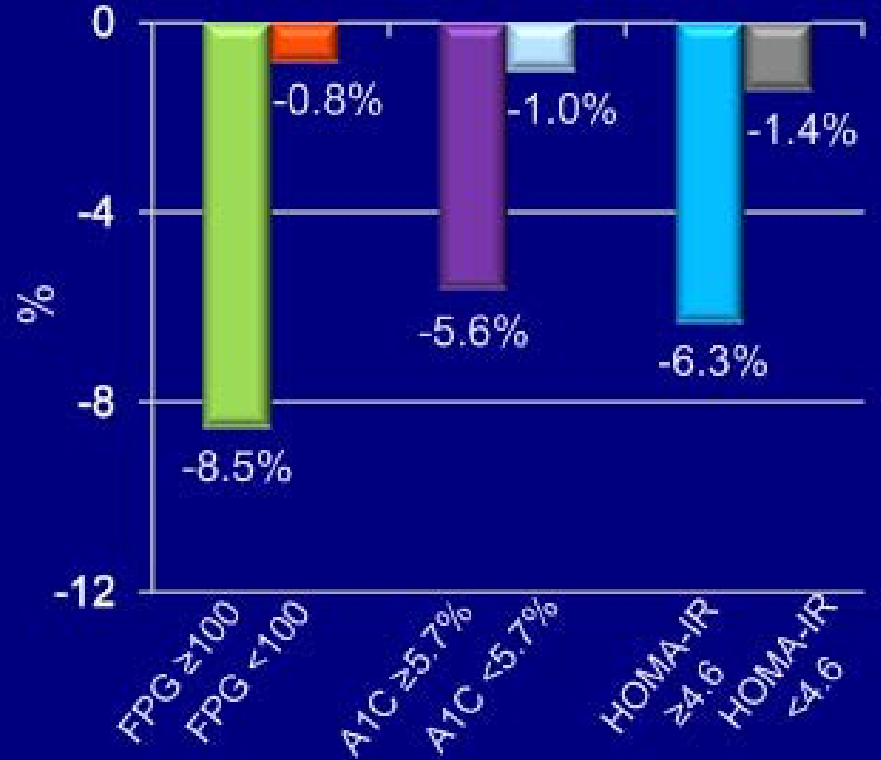
Christou NV, et al.: Ann. Surg., 240: 416-422, 2004

IRIS: Pioglitazone Lowers Rate of Progression to Diabetes Vs Placebo

Rate of progression to diabetes



Absolute risk reduction[1]

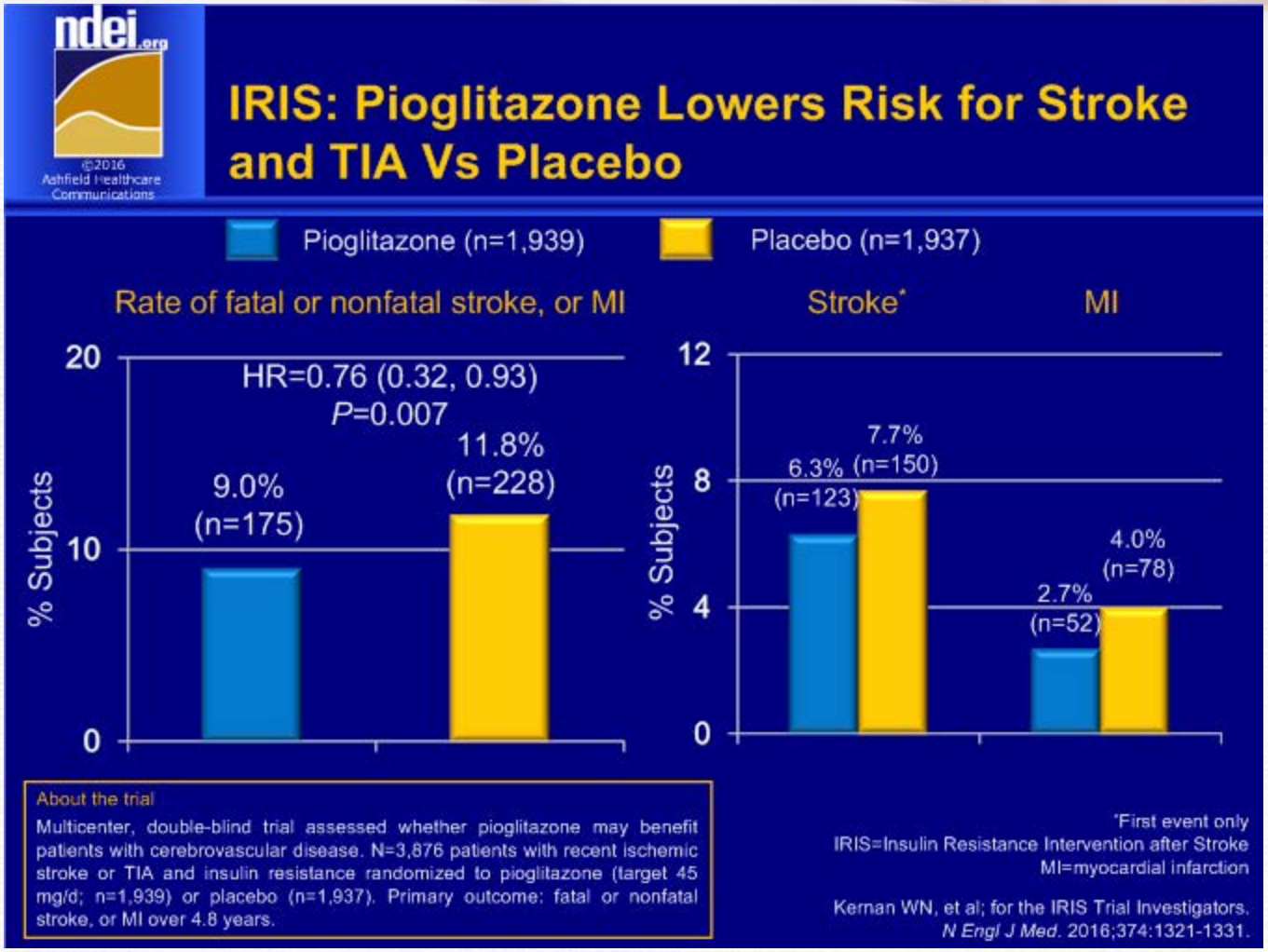


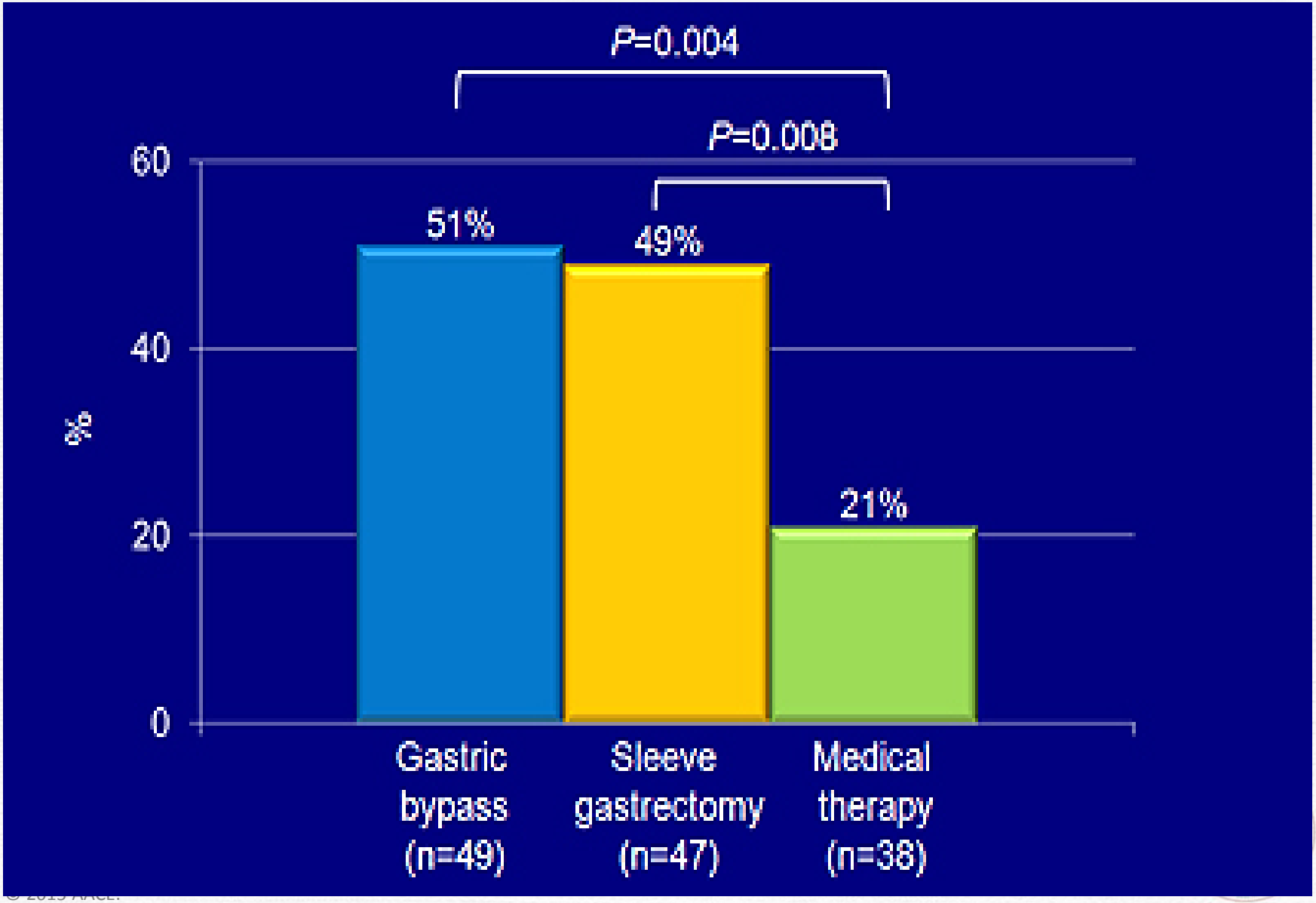
About the trial

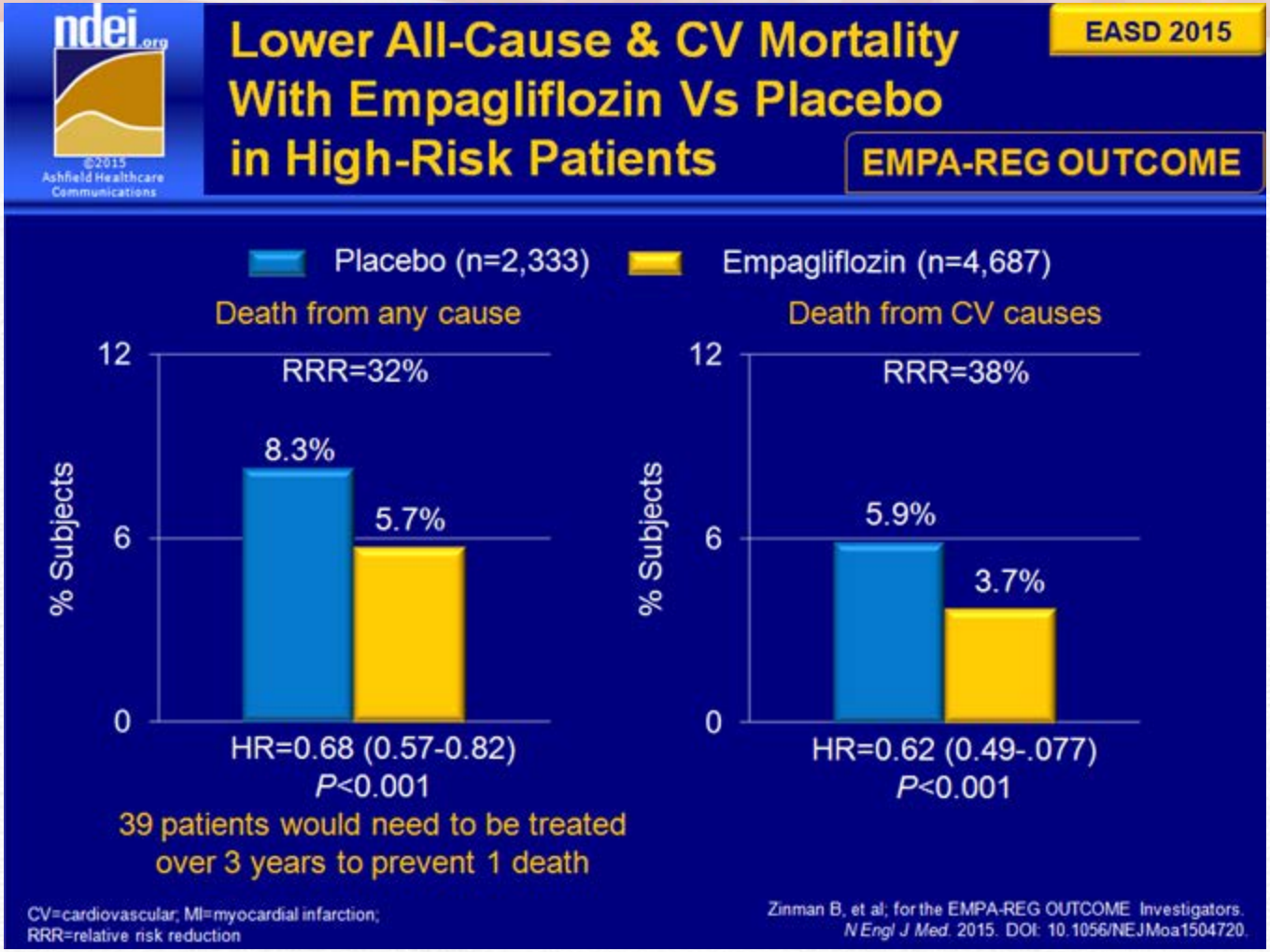
Multicenter, double-blind trial assessed whether pioglitazone may benefit patients with cerebrovascular disease. N=3,876 patients with recent ischemic stroke or TIA and insulin resistance randomized to pioglitazone (target 45 mg/d; n=1,939) or placebo (n=1,937). Primary outcome: fatal or nonfatal stroke, or MI over 4.8 years.

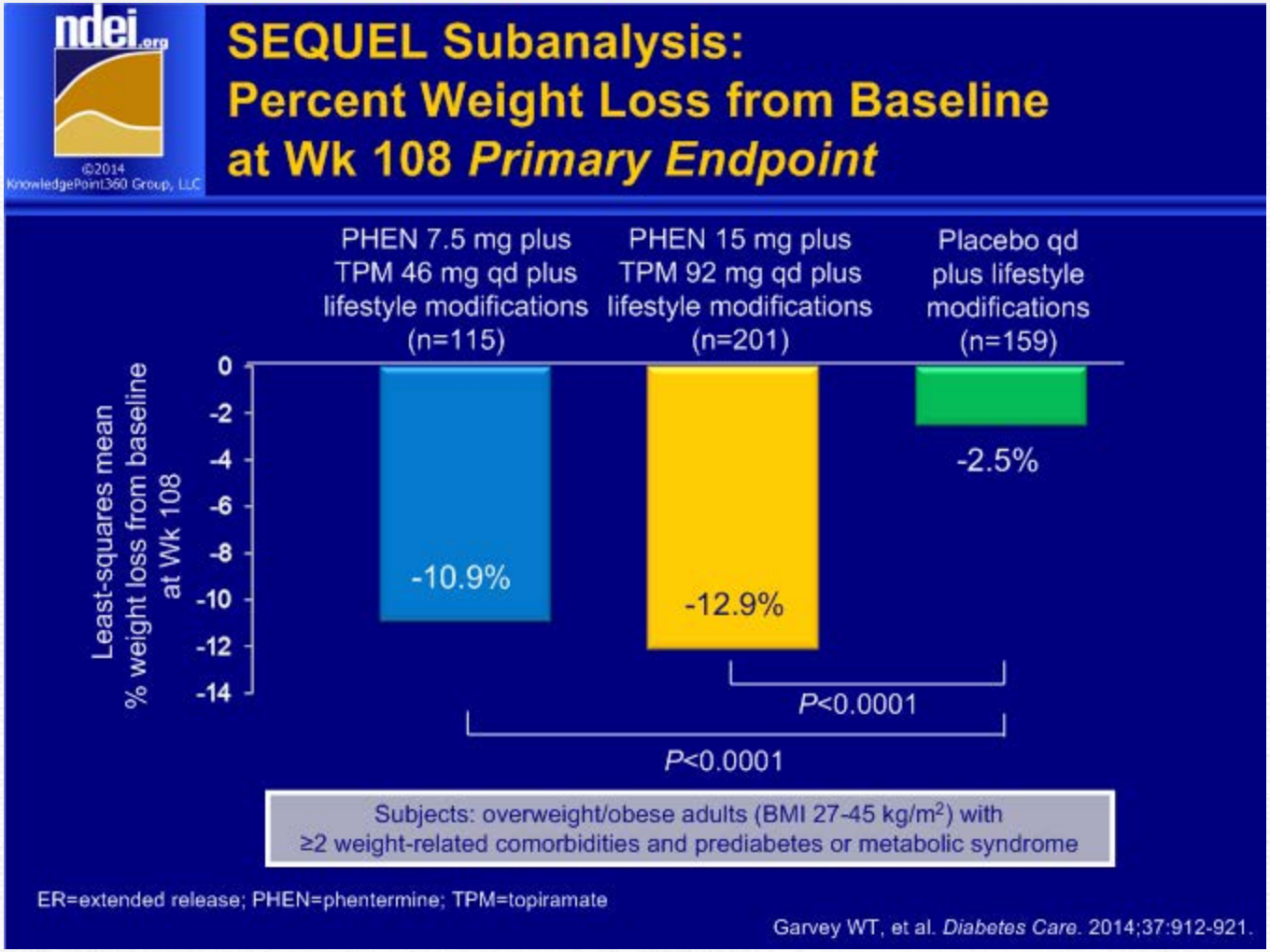
IRIS=Insulin Resistance Intervention after Stroke
MI=myocardial infarction; SBP=systolic blood pressure

1. Inzucchi SI, et al. Presented at the American Diabetes Association 75th Scientific Sessions. June 5-9, 2015; Boston, Massachusetts. 380-OR
Kernan WN, et al; for the IRIS Trial Investigators. *N Engl J Med*. 2016;374:1321-1331.

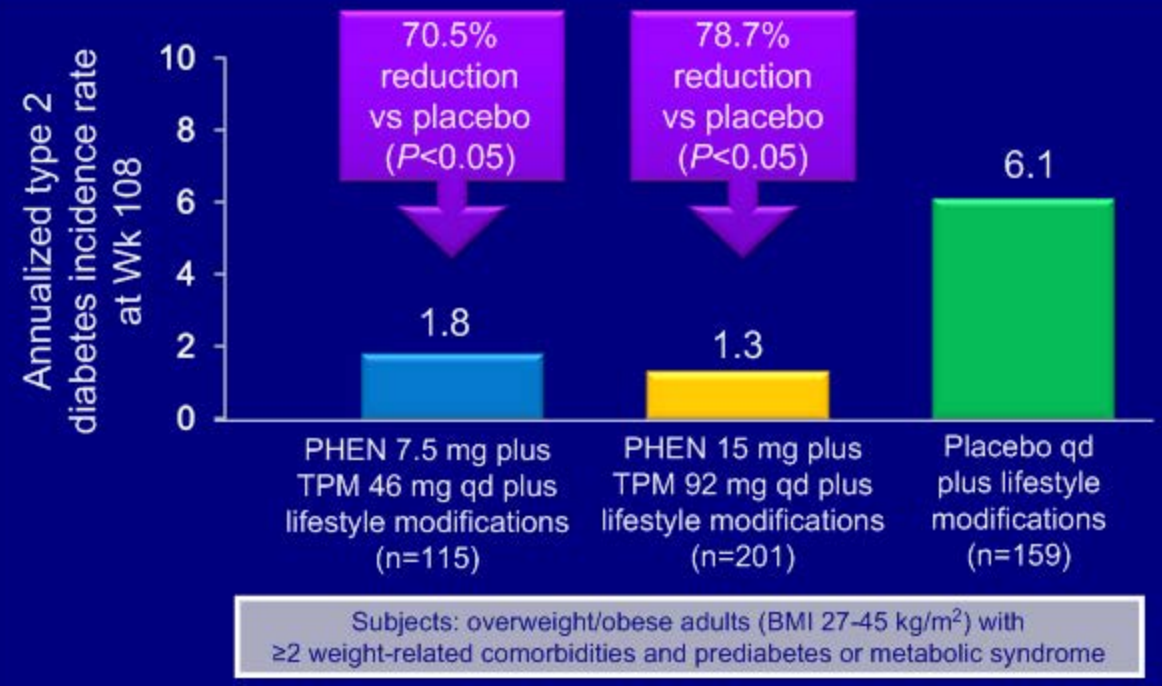






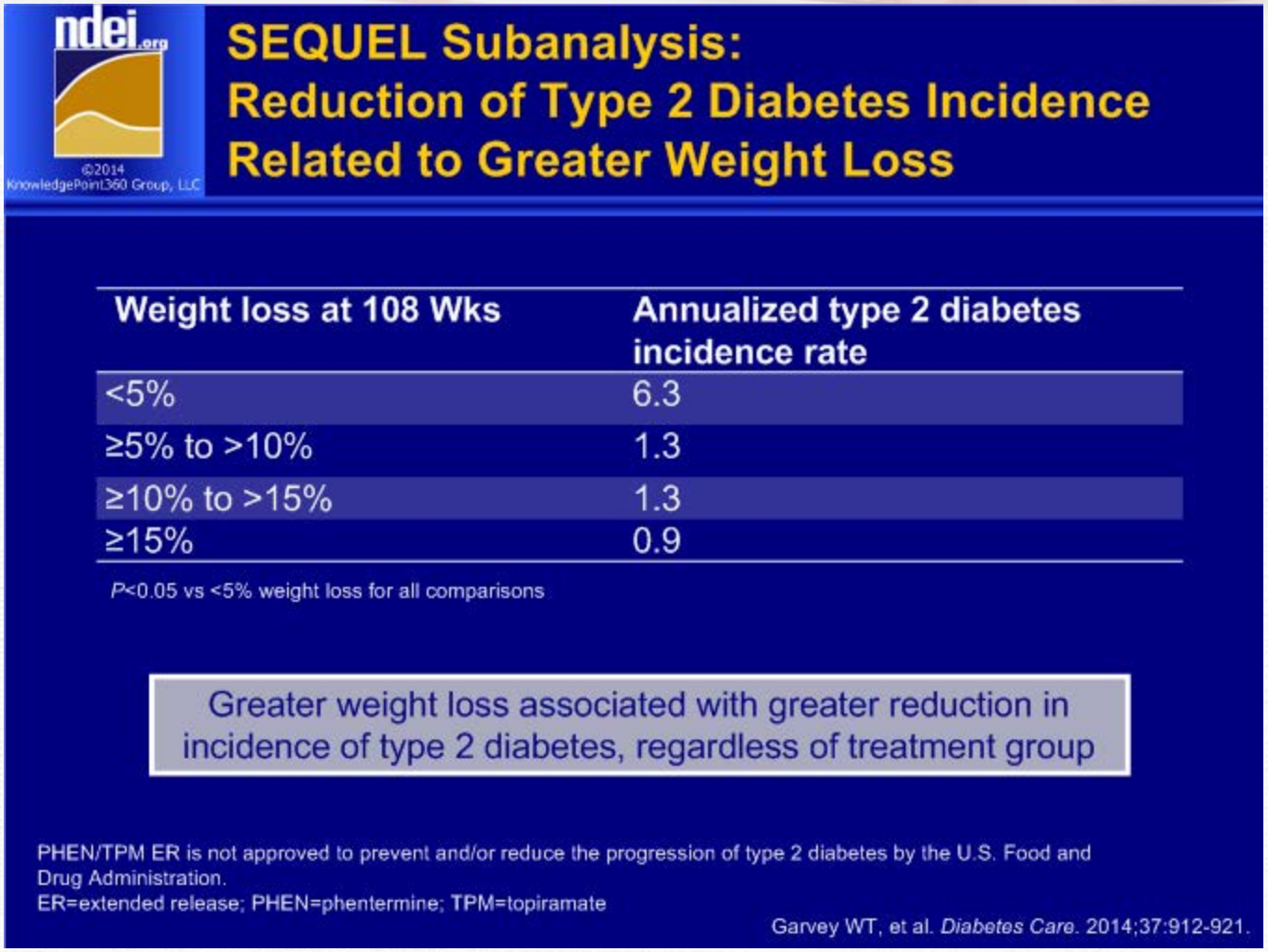


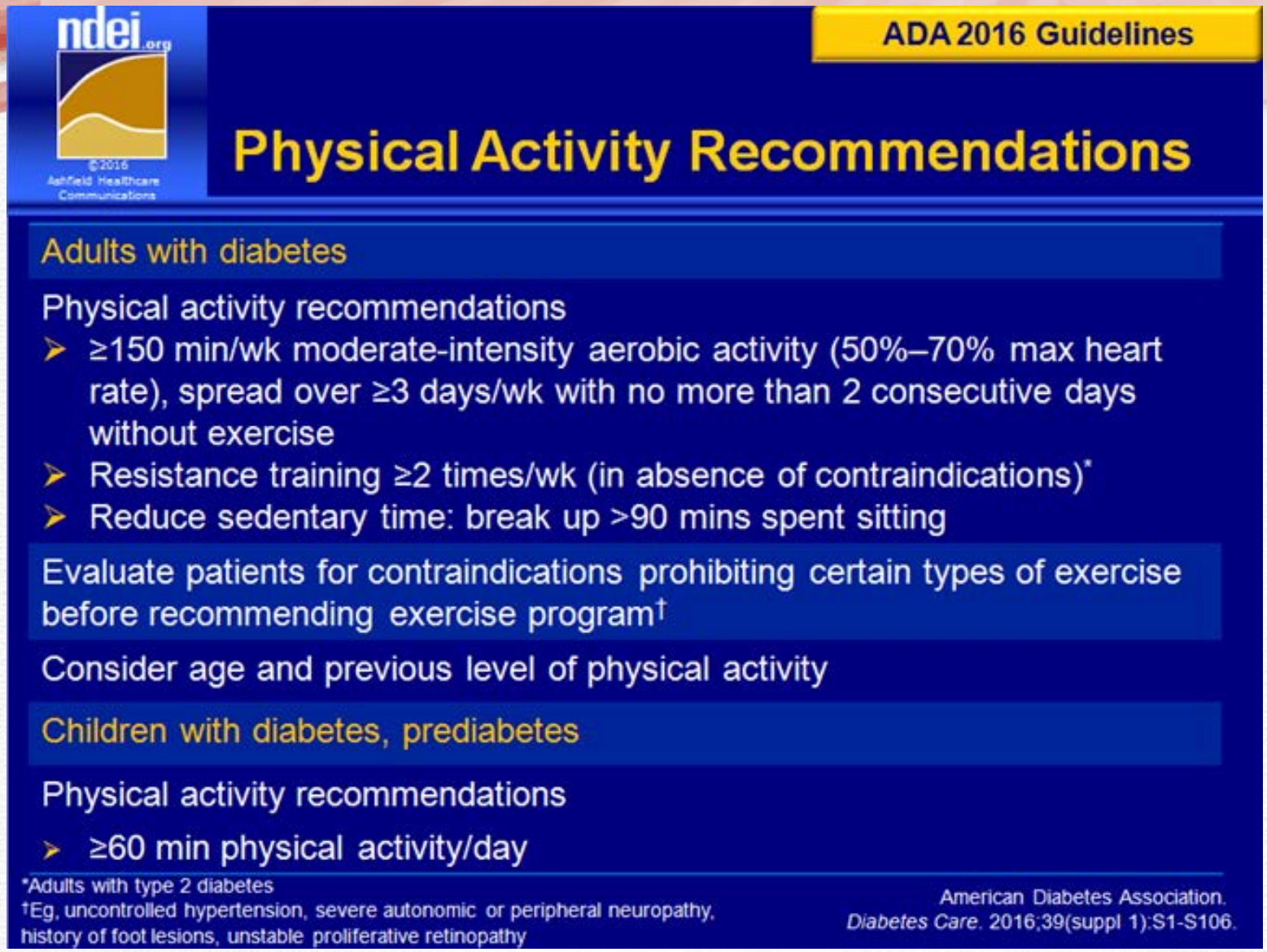
SEQUEL Subanalysis: Annualized Incidence of Type 2 Diabetes at Wk 108

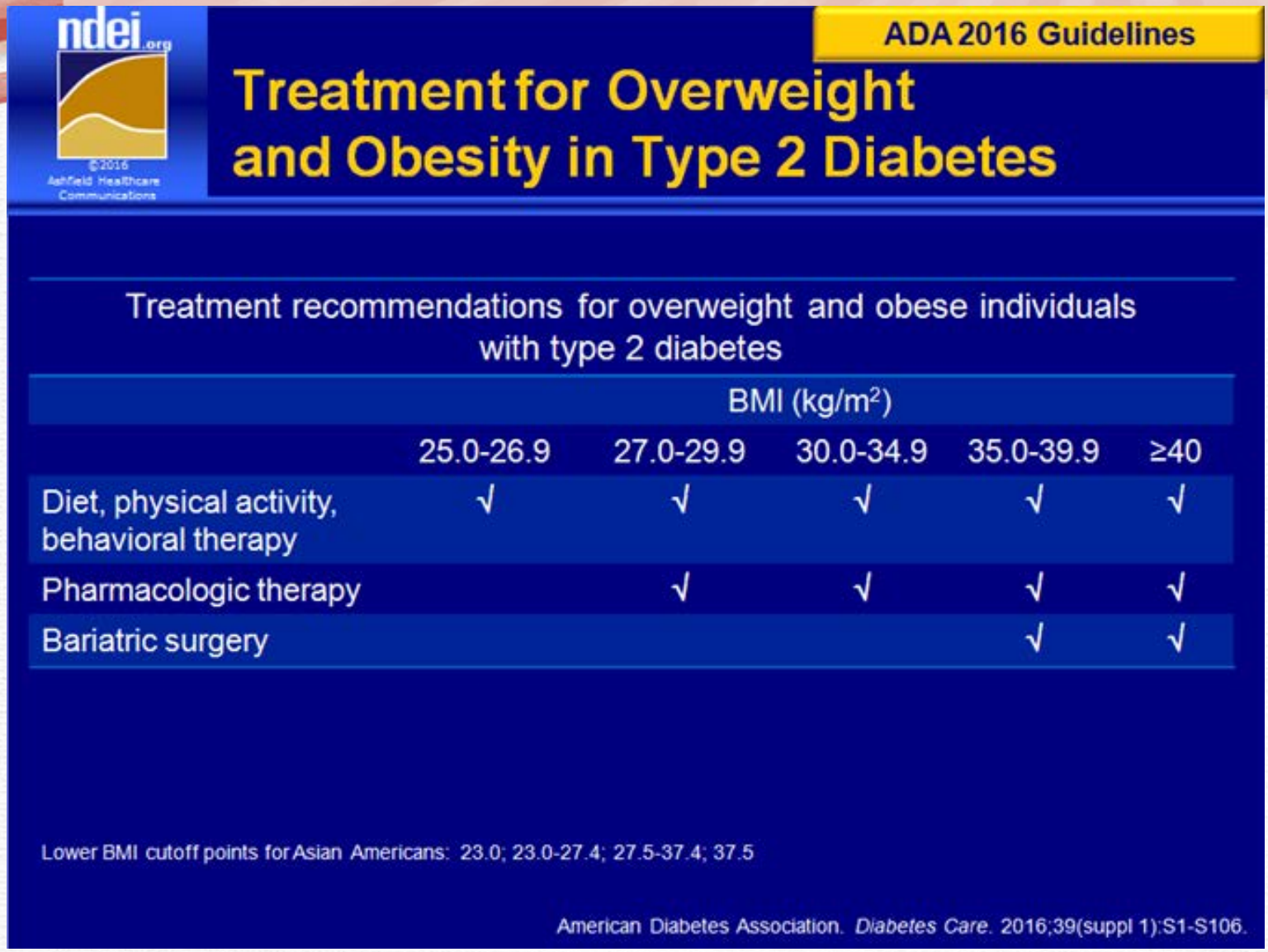


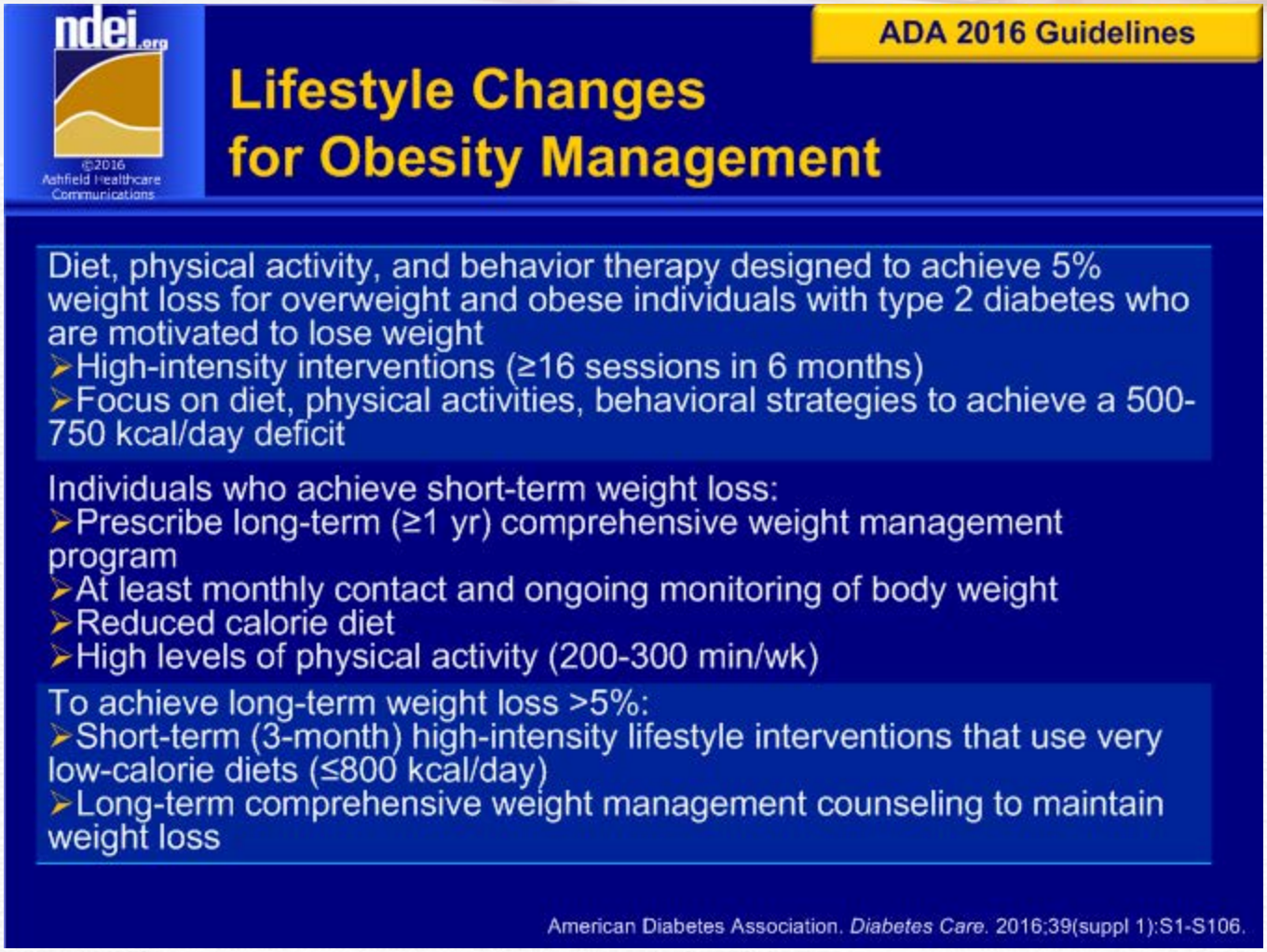
PHEN/TPM ER is not approved to prevent and/or reduce the progression of type 2 diabetes by the U.S. Food and Drug Administration. ER=extended release; PHEN=phentermine; TPM=topiramate

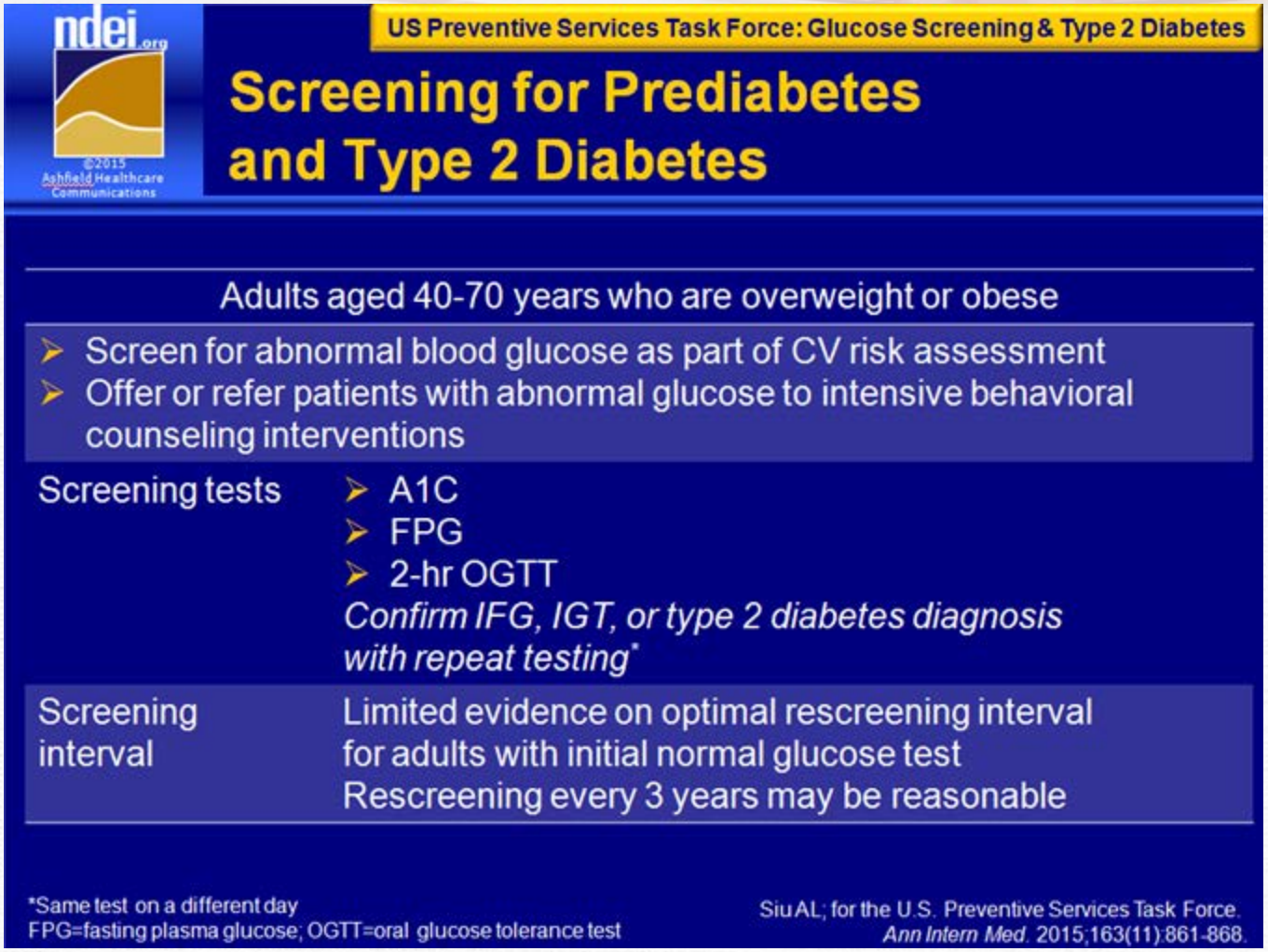
Garvey WT, et al. *Diabetes Care*. 2014;37:912-921.

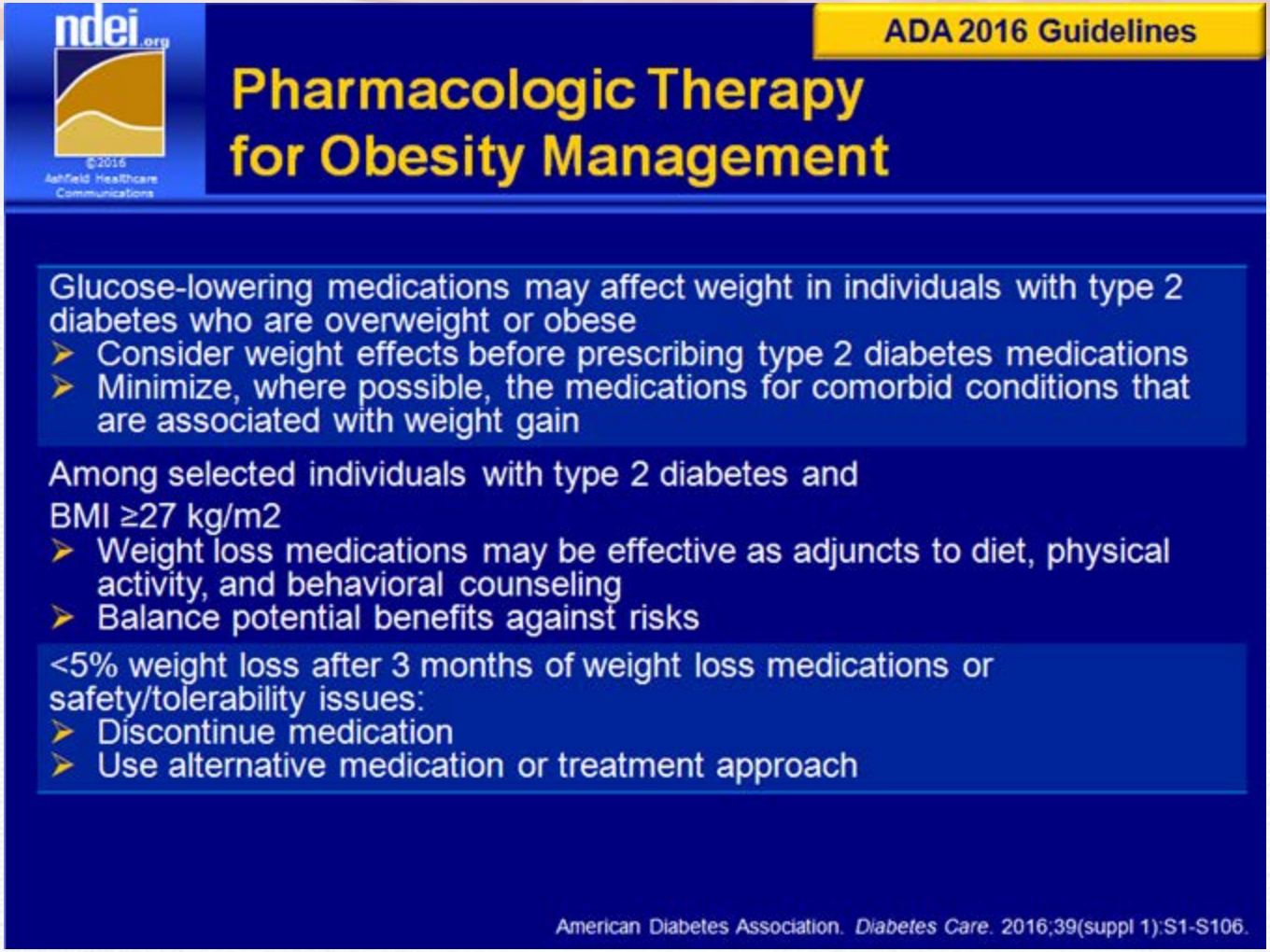


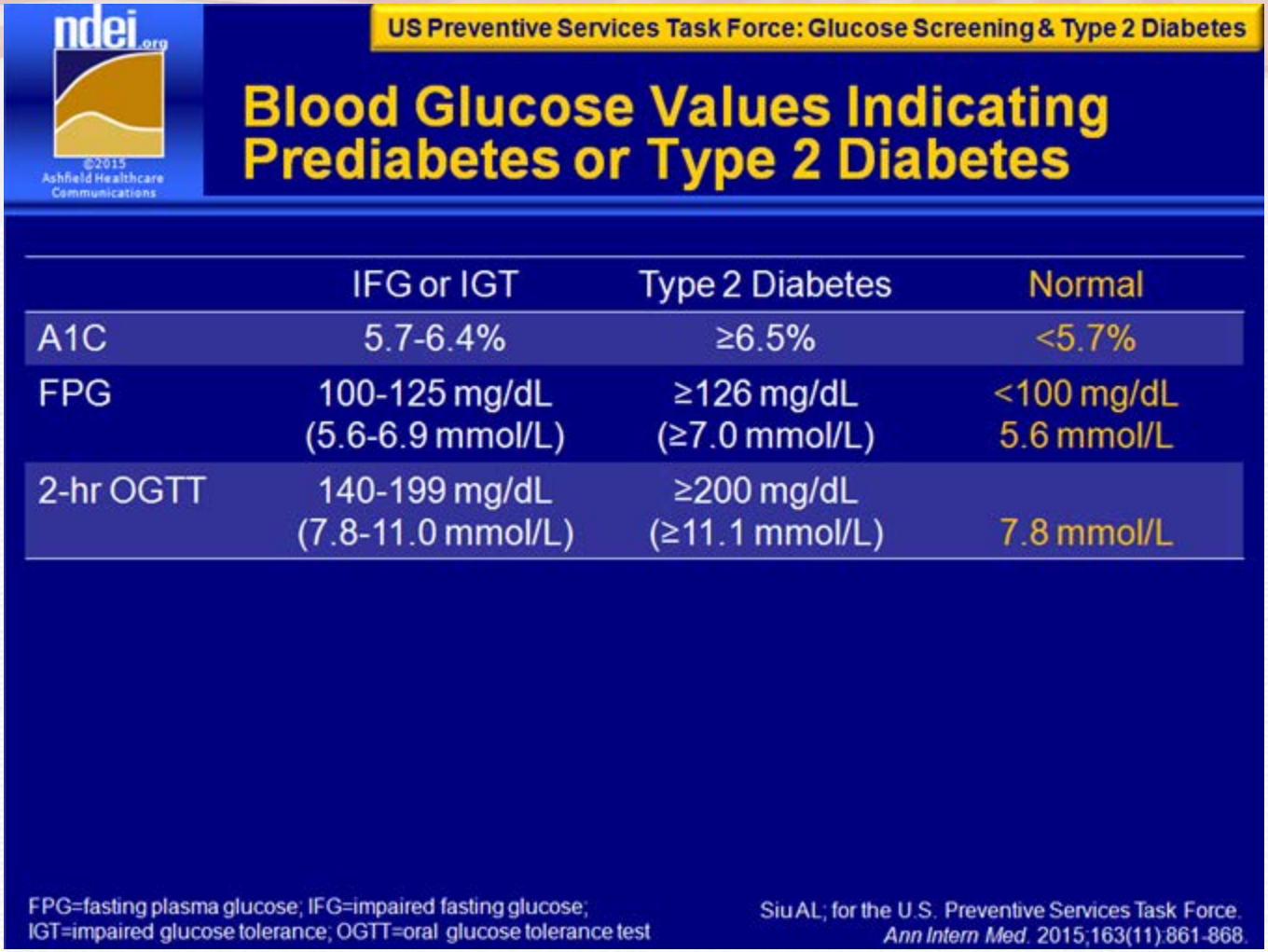


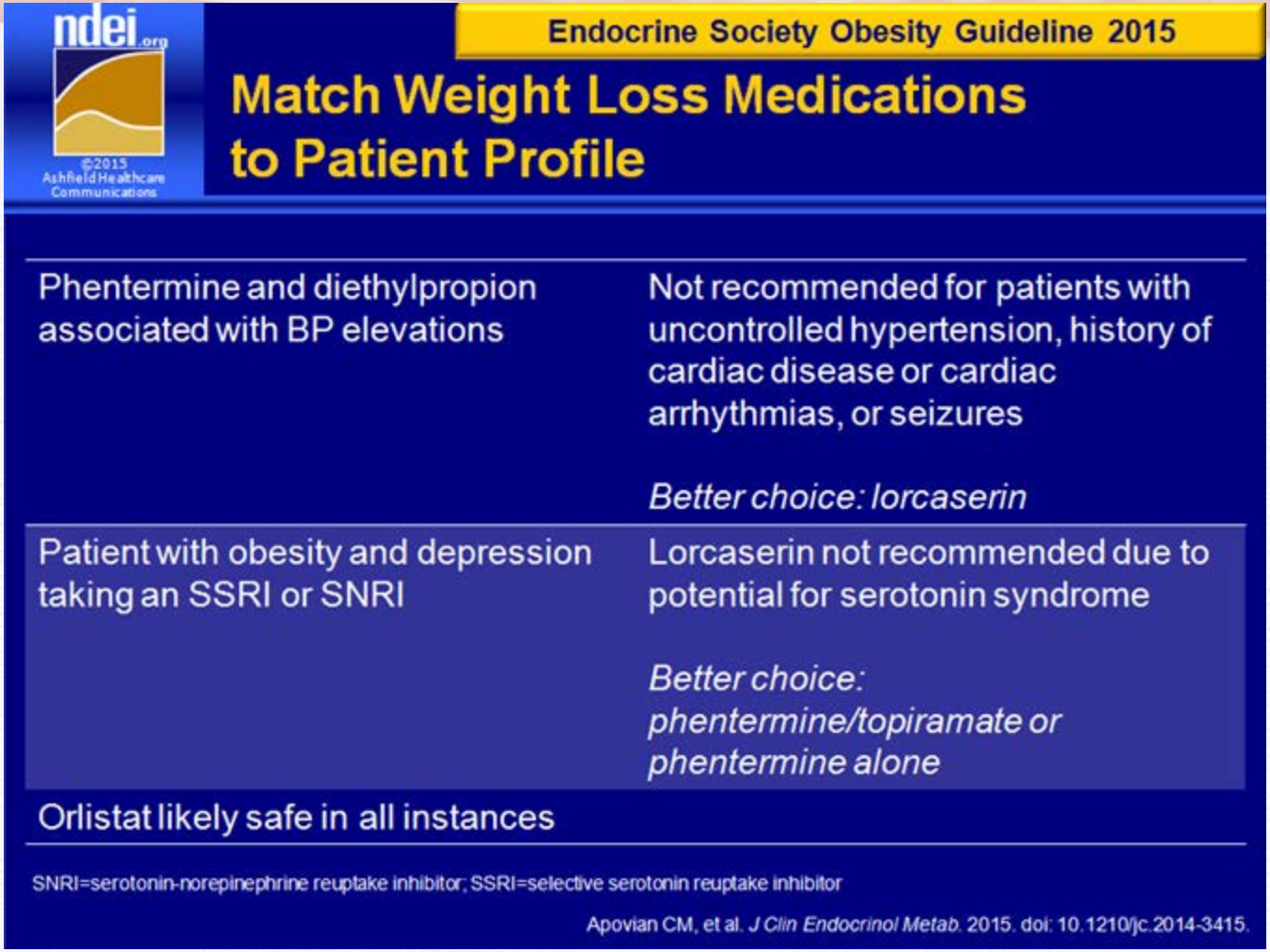


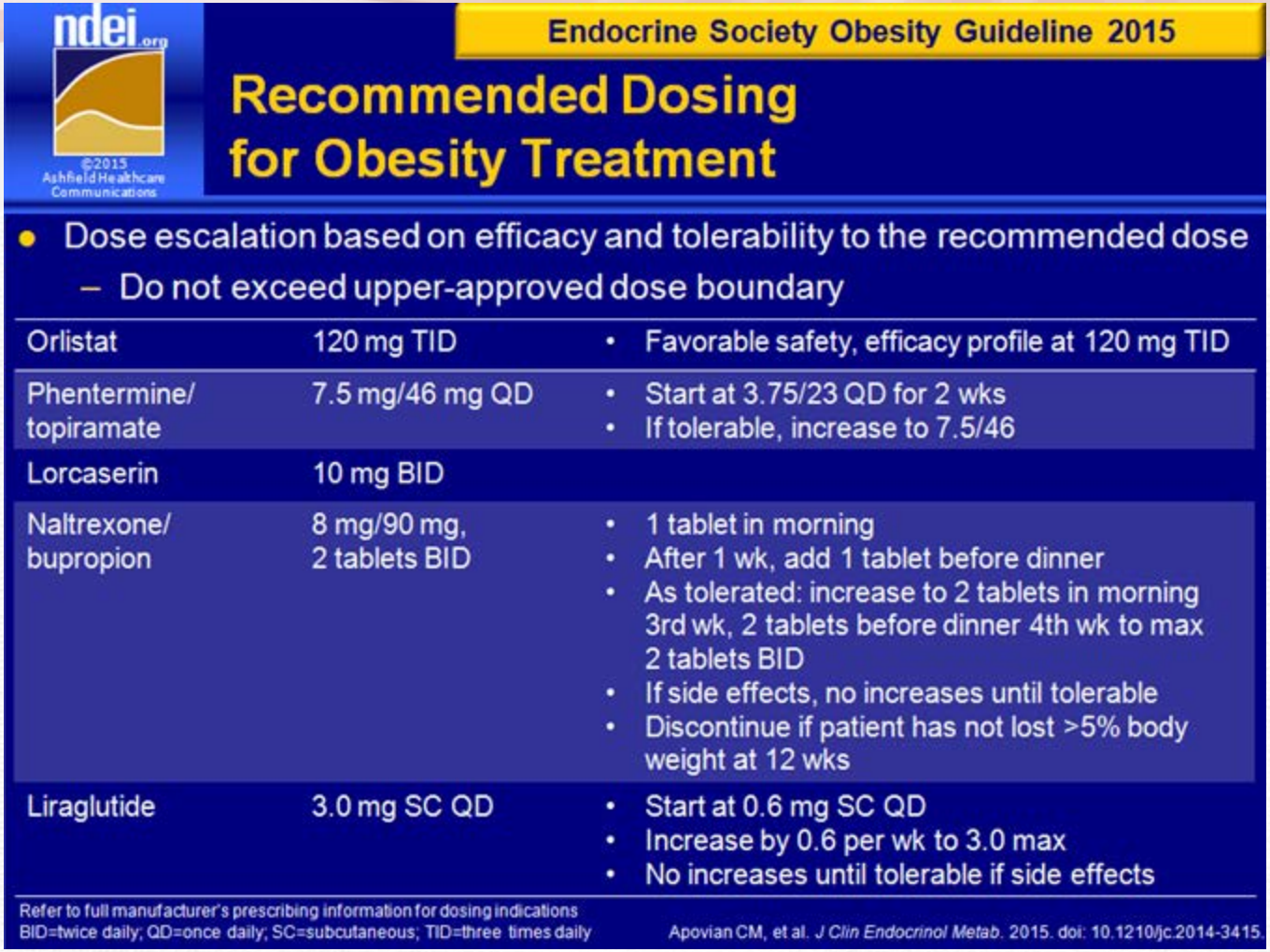












Off-Label Long-Term Use of Phentermine

- Phentermine is the most widely prescribed weight loss medication
  - It is not approved for long-term use
  - No long-term controlled safety and efficacy data
- Reasonable for clinicians to prescribe phentermine long term providing the patient:
  1. Has no evidence of serious CVD
  2. Does not have serious psychiatric disease or history of substance abuse
  3. Knows that other weight-loss medications have documented efficacy and safety for long-term treatment and phentermine does not
  4. Does not demonstrate a clinically significant increase in pulse or BP while on phentermine
  5. Demonstrates significant weight loss while on phentermine
- Start at 7.5 or 15 mg QD
  - Increase only if no clinically significant weight loss
  - Follow patient at least monthly during escalation, at least every 3 months when on stable dose

Apovian CM, et al. *J Clin Endocrinol Metab*. 2015. doi: 10.1210/jc.2014-3415.

Guidelines for Children and Adolescents With Type 2 Diabetes: Lifestyle Changes, Metformin for All

In all instances except ketosis, diabetic ketoacidosis, unclear distinction between types 1 and 2

- At type 2 diabetes diagnosis, initiate
  - Lifestyle changes
    - Nutrition interventions
    - Physical activity
  - Metformin
    - Confirm type 2 diabetes diagnosis prior to initiation
    - Start at low dose (500 mg/d) due to possible GI effects
    - Monitor for glycemic deterioration
    - Add insulin, other antihyperglycemic therapy if needed

GI=gastrointestinal

Metformin and insulin are the only antihyperglycemic agents approved for use in children/adolescents by the US Food and Drug Administration.

Copeland KC et al. *Pediatrics*. 2013;131:364-382.

Guidelines for Children and Adolescents With Type 2 Diabetes: Weight Loss, Diet (2 of 2)

- Refer patients to registered dietician
- Provide nutrition education
  - Consume 3 planned meals with snacks/day
  - No eating while watching TV, using computer
  - Use smaller plates to make portions seem larger
  - Leave small amounts of food on plate

General Recommendations

- Eat regular meals and snacks
- Reduce portion size
- Choose calorie-free drinks (except milk)
- Increase fruit, vegetable intake
- Consume 3-4 servings low-fat dairy/day
- Limit
  - Juice to 1 cup/day
  - High-fat food intake
  - Frequency, size of snacks
- Reduce calories from fast-food meals

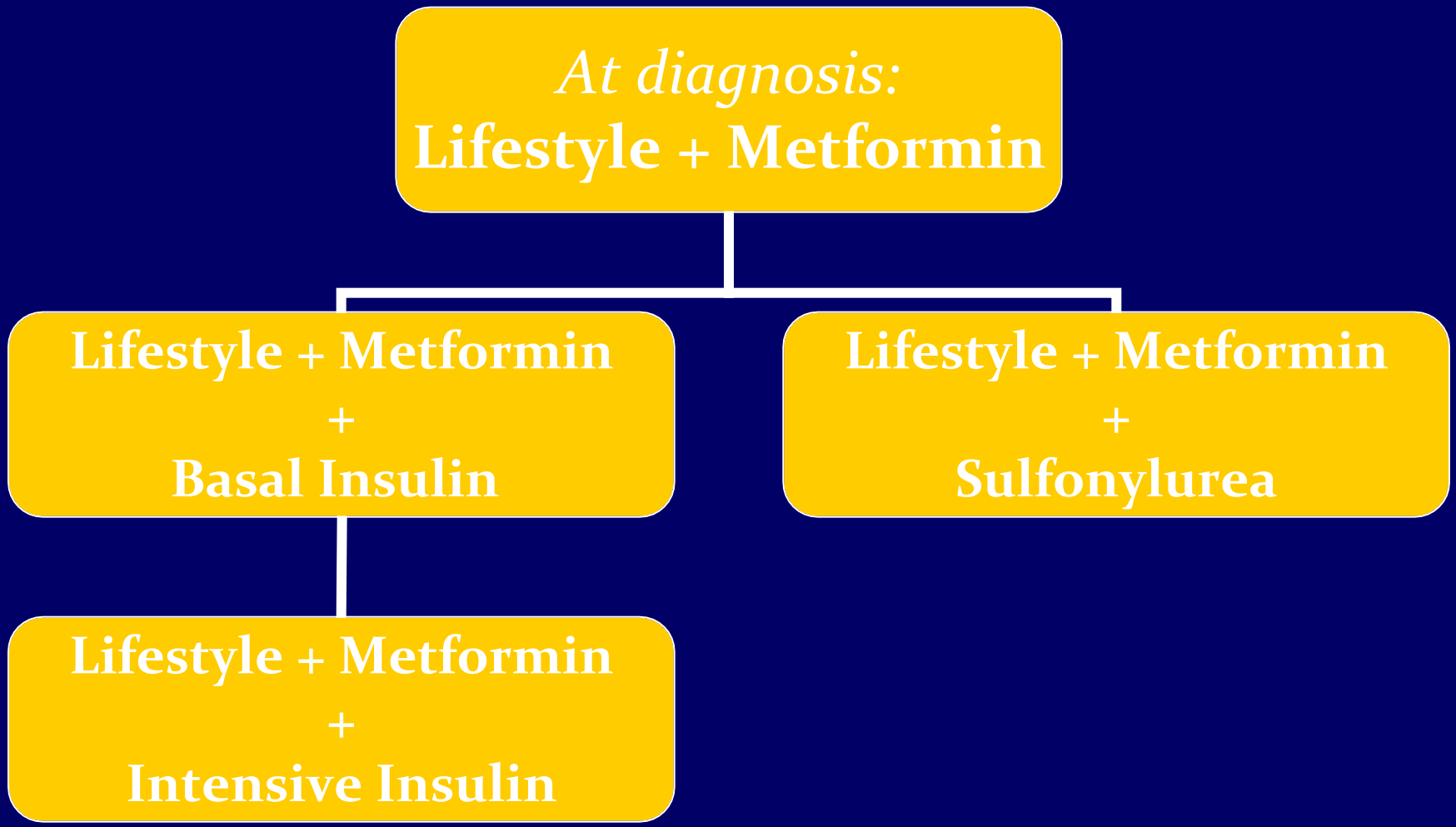
Copeland KC et al. *Pediatrics*. 2013;131:364-382.

Guidelines for Children and Adolescents With Type 2 Diabetes: Physical Activity

- Moderate-to-vigorous exercise: ≥60 min/day
  - Create individualized plan with patient and family
  - Provide written exercise "prescription" describing ideal duration, intensity, and frequency
  - Include activities that can be incorporated into daily routine
- Limit nonacademic screen time to <2 hrs/day
  - Discourage presence of video screens, TVs in bedroom

Copeland KC et al. *Pediatrics*. 2013;131:364-382.

Treatment to Fail Algorithm/ does not address physiology (Use of Insulin has gone up 500%)



After Metformin DZ modifying therapy

GLP 1 (wt loss, - hypo, beta cell fx, durability > 4 yr)

SGLT 2 (wt loss, - hypo)

DPP4 (wt neutral, - hypo)

TZD (IS, beta cell, - hypo, wt durability greater than SU and metformin)

Basal Insulin (wt gain, + hypo, BS monitoring * consider adding GLP 1 to basal prior to going to prandial insulin

Long-Term Mortality after Gastric Bypass

* 1984 to 2002
* 9949 Surgery
* 9628 Medical/Control
* 7925 matched for age, sex, and BMI

Adams TJ *et al* NEJM **Volume 357:753-761**

August 23, 2007 Number 8

SWEDISH

Major Obstacle in maintaining control is progressive beta cell failure and hypoglycemia

Hypoglycemia is associated with increased mortality and morbidity

Hyperglycemia is the major factor responsible for microvascular complx, 1% decrease A1c 35 % decrease risk of complx