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#HID2021

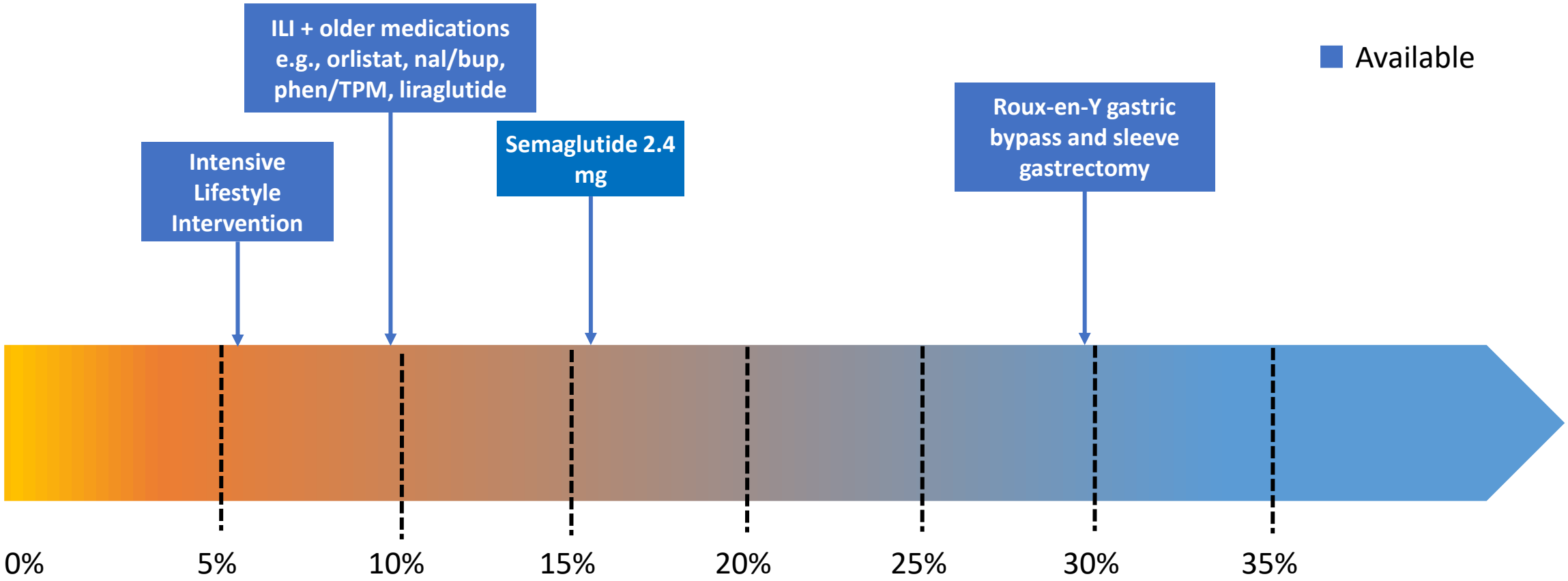
Pharmacologic Strategies in Obesity: Effect on Metabolic & CV Risk

Donna H. Ryan, MD
Professor Emerita
Pennington Biomedical Research Center
ryandh@pbrc.edu

Disclosures

- Honoraria or consultation fees received: Boeringer Ingelheim, Epitomee, Gila Therapeutics, ifa Celtic, Janssen, Lilly, Naturally Slim, Novo Nordisk, Phenomix, real appeal (United Health), ReDesign Health (Calibrate), Sanofi, and Ysopia
- Participation in a company sponsored speaker's bureau: Novo Nordisk
- Stock or equity: Gila Therapeutics, Phenomix, Xeno Bioscience, Epitomee, ReDesign Health and Scientific Intake

Available Treatments for Obesity



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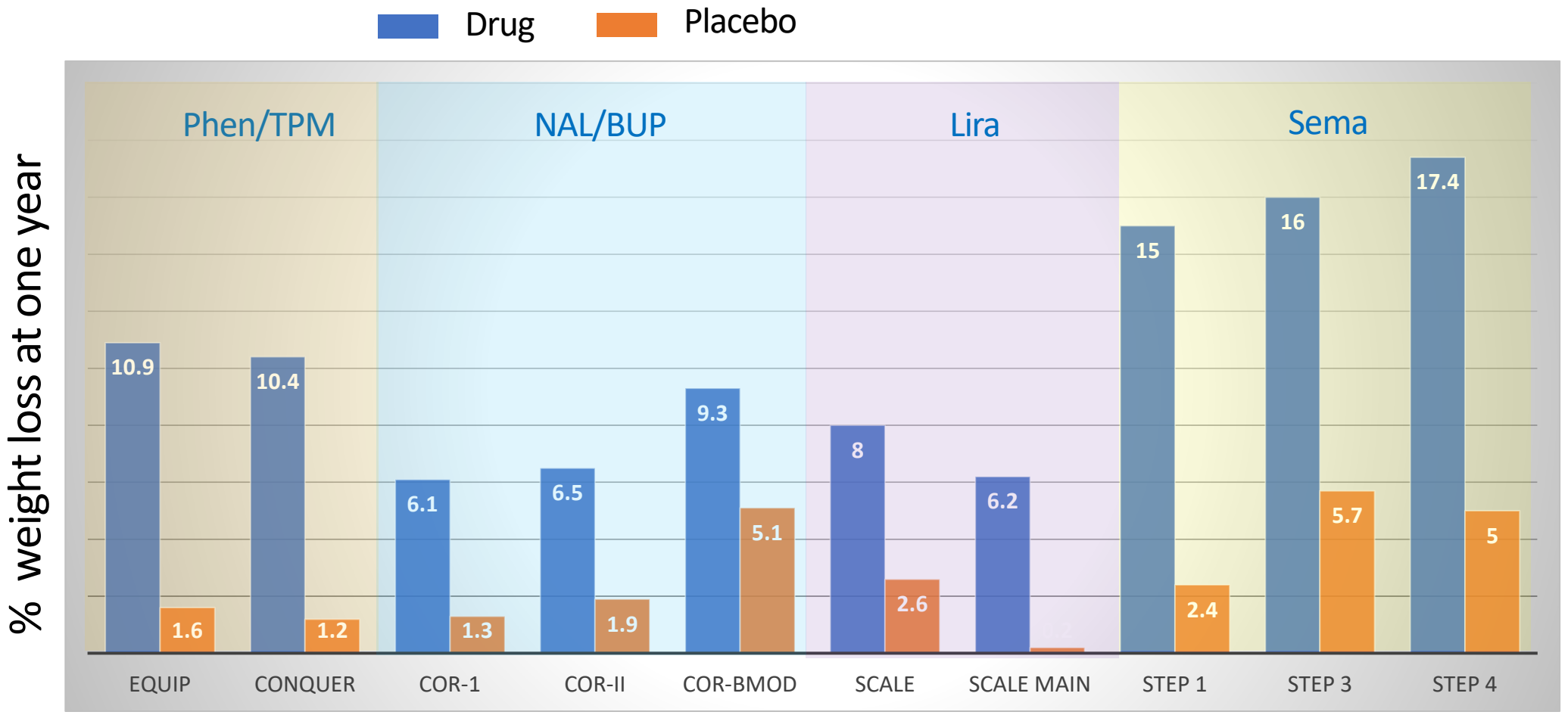
Percent Weight Loss (Drug versus Placebo) for Appetite Regulation Medications



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Wadden TA, et al. JAMA. 2021 Apr 13;325(14):1403-1413. [STEP 3]
Rubino D, et al. JAMA. 2021 Apr 13;325(14):1414-1425. [STEP 4]

Why have antiobesity medications been underprescribed?

- Only 1.3% of eligible persons are given a prescription.[1]
- Eligible: BMI $\geq$30 kg/m^2 or $\geq$27 kg/m^2 with comorbidity and unable to lose weight and keep it off with lifestyle alone. (42% of US adults have BMI $\geq$30 kg/m^2)
- Efficacy less than desirable; side effect profiles less than desirable
- REMS required for phentermine/topiramate
- Residual stigma associated with phen/fen, rimonabant, sibutramine, lorcaserin
- Barriers to prescription
  - Prior authorization
  - High tiers and high co-pays

1. Saxon DR, et al. Obesity 2019. 27: 1975-1981.

Why might semaglutide 2.4 mg change this paradigm?

- The mean weight loss is 15%-17%
  - Desirable to patients
  - Desirable to providers because of impact on comorbidities
- Familiarity and confidence in safety of GLP-1 analog class among those who treat diabetes
- Cardiovascular outcome trial (SELECT) may prove pivotal[1]

1. Ryan DH et al. Am Heart J 2020;229:61-69.

Cardiovascular Outcomes with Anti-Obesity Medications

Phen/TPM[1,2]

The AQCLAIM CVOT trial
Ongoing

- Global RCT, 16,000 participants
- Primary objective: evaluate effect of long-term treatment on incidence of nonfatal MI, nonfatal stroke, or CV death in overweight and obese subjects with documented CVD

Nal/Bup[1,3,4]

The Light Study
Unblinded early and prematurely terminated

- Global RCT, 8910 participants
- Primary outcome (3-point MACE) with nal/bup vs placebo (n, %):* 90 (2.0) vs 102 (2.3) [HR, 0.88; adjusted 99.7% CI, 0.57-1.34]

Liraglutide 3.0 mg[4,5]

***Post hoc* analysis**

- Pooled data from a 2-year Phase 2 dose-finding trial and 4 Phase 3a RCTs (SCALE) trials, 5908 participants
- Primary outcome (3-point MACE) with liraglutide 3.0 mg vs placebo (n, %): 8 (0.002) vs 10 (0.04) [HR, 0.42; 95% CI, 0.17-1.08]

* After 50% of planned events.

CI, confidence interval; CV, cardiovascular; CVD cardiovascular disease; CVOT, cardiovascular outcomes trial; HR, hazard ratio; Lira, liraglutide; MACE, major adverse cardiovascular events; MI, myocardial infarction; nal/bup, naltrexone/bupropion; phen/TPM, phentermine/topiramate; RCT, randomized controlled trial.

1. Wilding JPH and Jacob S. *Obes Rev*. 2021;22:e13112; 2. EU Clinical Trials Register. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=AQCLAIM. Accessed July 2021; 3. Nissen SE, et al. *JAMA*. 2016;315:990-1004; 4. Cataldi M, et al. *International Journal of Obesity Supplements.* 2020;10:14-26; 5. Davies M, et al. *Diabetes Obes Metab*. 2018;20:734-739.

SELECT TRIAL: SEMAGLUTIDE 2.4 MG WEEKLY CARDIOVASCULAR OUTCOME TRIAL POWERED FOR SUPERIORITY

- 17,500 participants age ≥45, BMI ≥27, with prior cardiovascular disease (myocardial infarction, stroke, symptomatic peripheral artery disease) but without established type 2 diabetes or A1c ≥6.5%[1]
- Semaglutide 0.5 mg and 1 mg reduced MACE in individual with type 2 diabetes (SUSTAIN 6)[2]
- The exclusion of patients with diabetes in SELECT avoids the argument that improved glycemic control is the mechanism by which semaglutide reduces risk

1. Ryan DH et al. Am Heart J 2020;229:61-69.
2. Marso SP, et al. N Engl J Med 2016; 375:1834-1844.

GLP-1 has pleiotropic effects

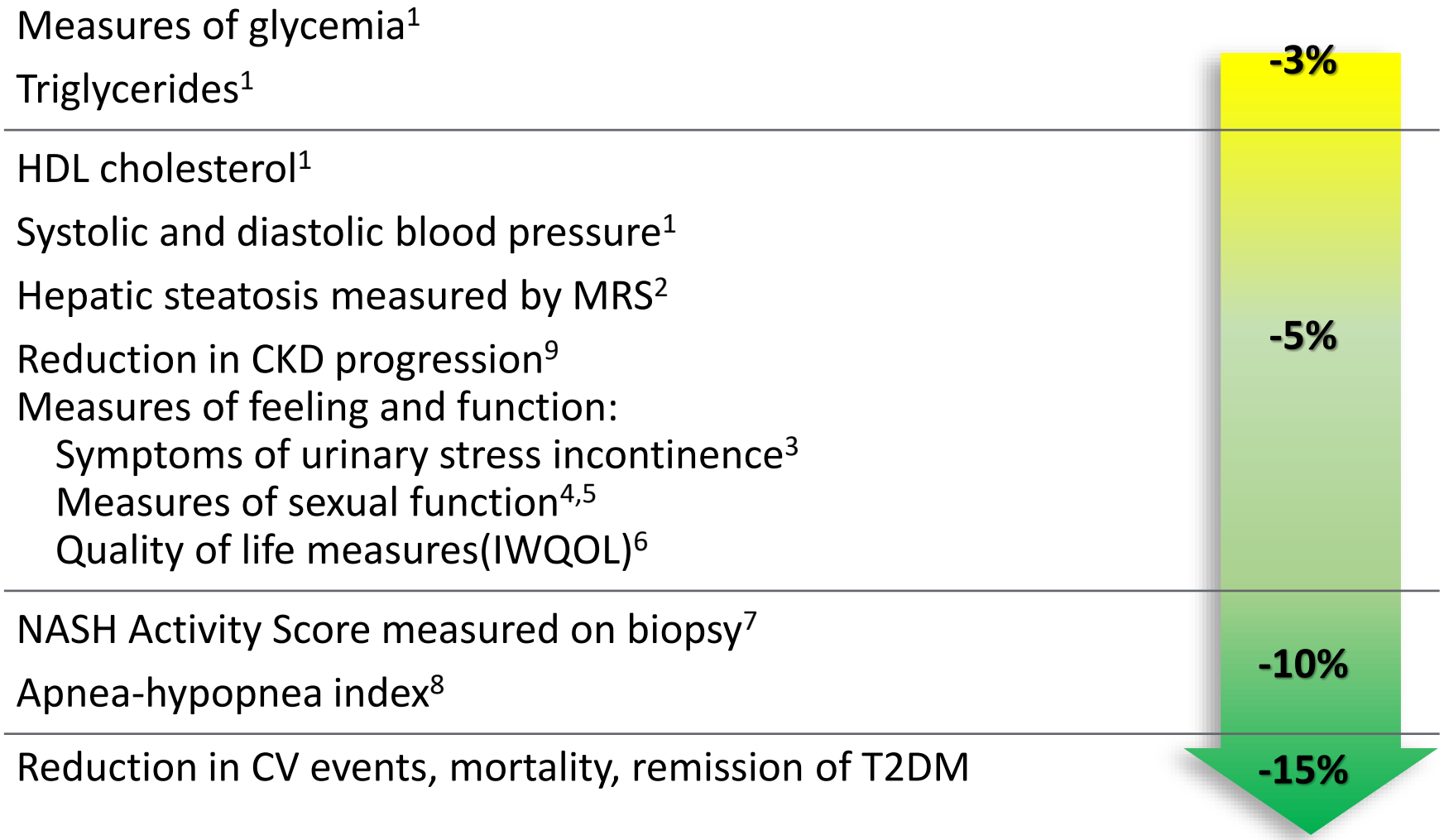
1. Ryan DH et al. Am Heart J 2020;229:61-69.

Key Strategy

We want to achieve health benefits of weight loss.

And we want our antiobesity medications to provide additional benefits

Weight Loss Benefits Begin with Modest Weight Loss, but Greater Weight Loss Produces Greater Benefits

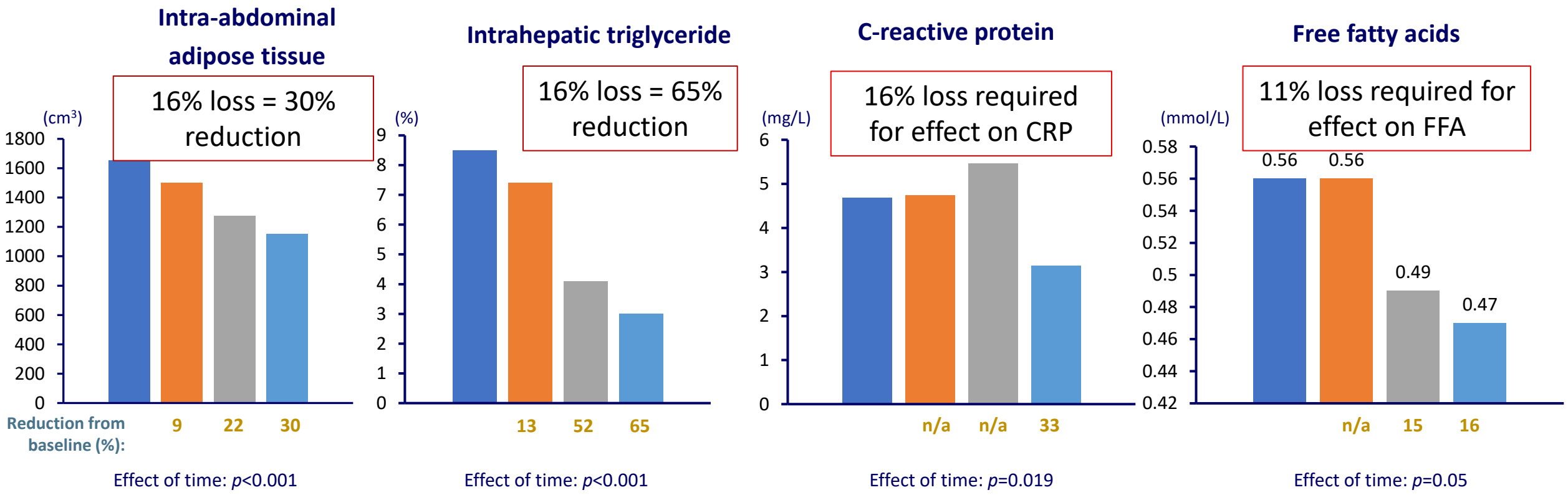


1. Wing et al. Diabetes Care 2011;34:81-1486. **2.** Lazo et al. Diabetes Care 2010;33:2156–63.**3.** Phelan et al. Urol. 2012;187:939-44. **4.** Wing et al. Diab Care 2013;36:2937-44. **5.** Wing et al. Journal of Sexual Medicine 2010 ; 7:156-65. **6.** Crosby, Manual for the IWQOL-LITE Measure. **7.** Promrat et al. Hepatology 2010;51:121–29. **8.** Foster et al. Arch Intern Med 2009;169:1619–26. **9**. Look AHEAD Research Group. Lancet Diabetes Endocrinol. 2014 Oct;2(10):801-9.

Why we don’t need to normalize body weight

- The goal of weight loss is reduction of excess abnormal body fat.
- Excess abnormal body fat is cleared first.

Why does modest weight loss produce health benefit? Effect of weight loss on metabolic function and adipose tissue biology



Magkos F et al. Cell Metabolism 2016;23:591–601

PROGRESSIVE WEIGHT LOSS HAS DOSE-DEPENDENT AND TISSUE-DEPENDENT BIOLOGIC EFFECTS

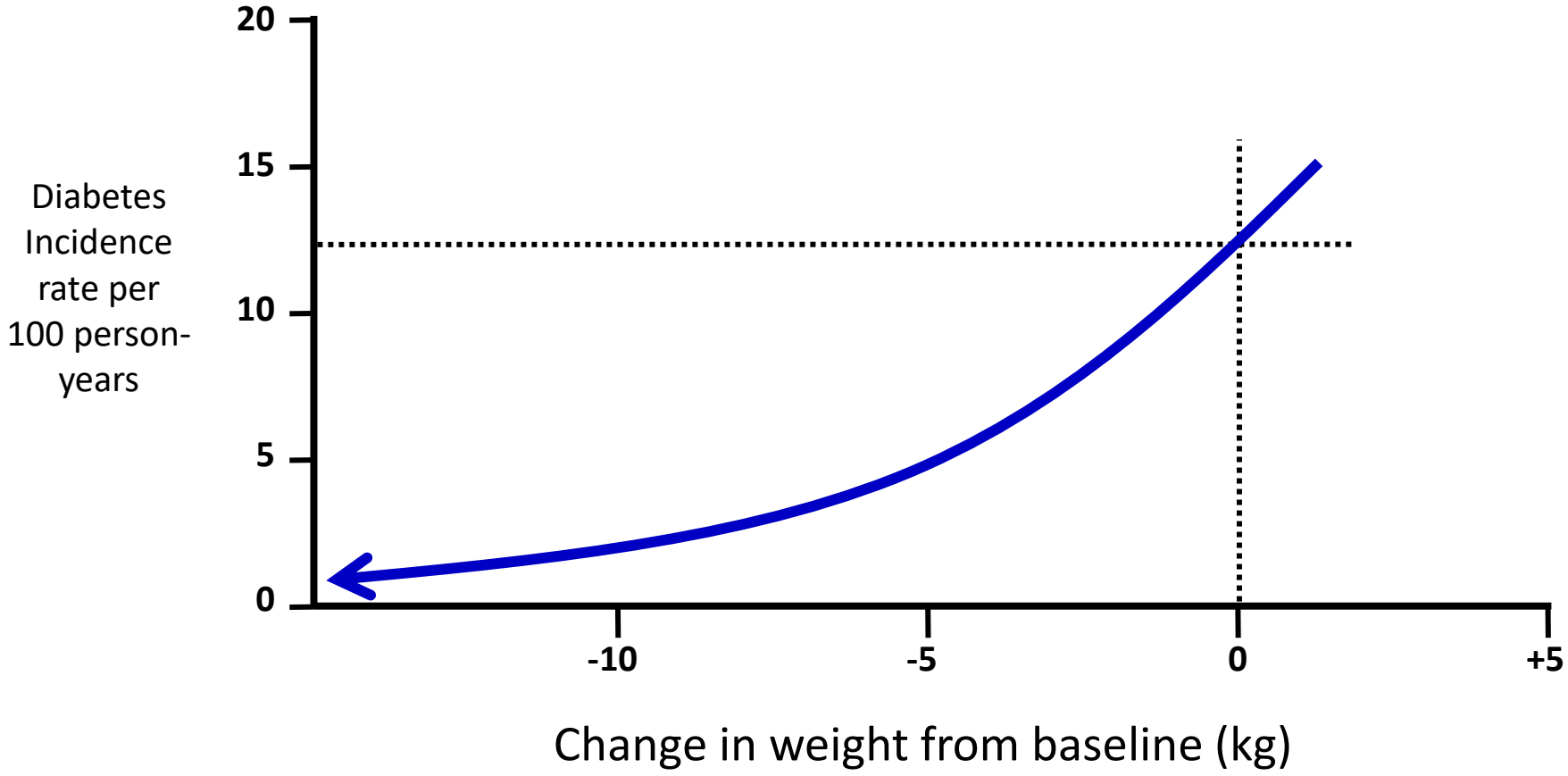
	5% weight loss	11% weight loss	16% weight loss
Improvement in glucose, insulin, triglycerides, alanine transaminase	+	++	+++
Improvement LDL & HDL cholesterol, adiponectin, free fatty acids		+	++
Improvement in C-Reactive Protein			+
Adipose tissue insulin sensitivity	+++	+++	+++
Liver insulin sensitivity	+++	+++	+++
Muscle insulin sensitivity	+	++	+++
Beta Cell function	+	++	+++
Adipose tissue biology*		+	++

*Upregulation of genes involved in cholesterol flux downregulation of genes involved in lipid synthesis, extracellular matrix remodeling and oxidative stress

Magkos F et al. Cell Metabolism 2016;23:591–601

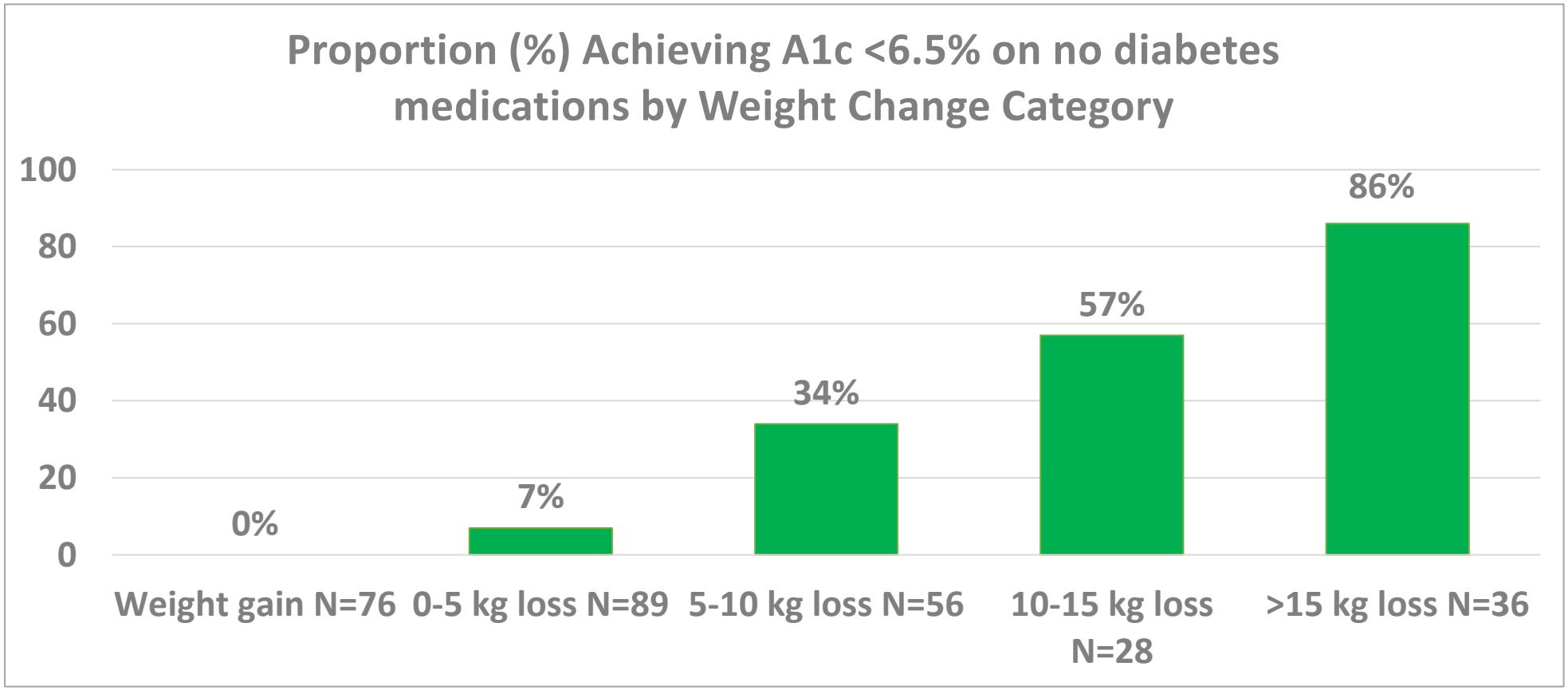
The DPP Experience: Every Kilogram Lost Reduced Risk of Diabetes by 16%

After 10 Kg (~10%) weight loss, there was no additional benefit in diabetes prevention in persons with TGY.



Adapted from Hamman et al., *Diabetes Care (2006)* 29: 2102-2107.

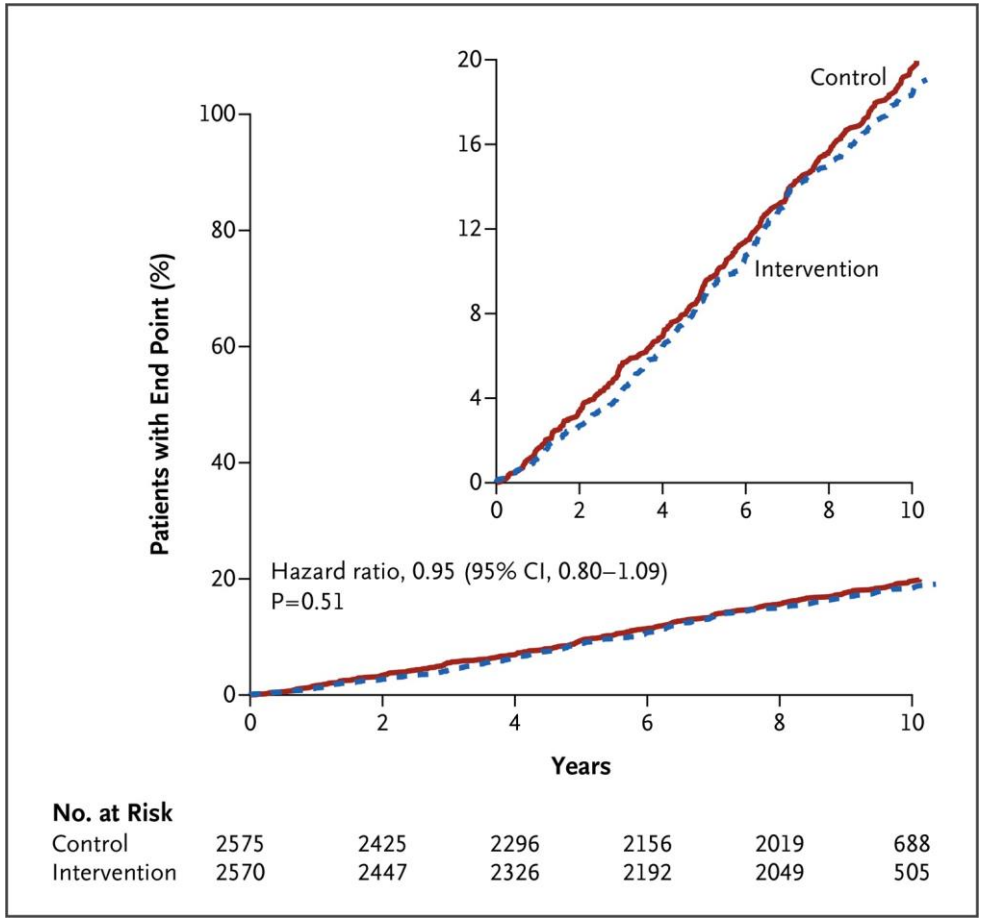
DIRECT: Percentage Achieving Diabetes Remission by Weight Change Category



Lean MEJ et al. *Lancet.* 2018; 391: 541-551

Lifestyle Intervention - a Challenging Method for Cardiovascular Risk Reduction

- Look AHEAD CV Morbidity and Mortality (10 years)
  Look AHEAD Research Group. N Engl J Med 2013; 369:145-154
- >5000 participants with type 2 diabetes randomized to intensive lifestyle intervention or support and education
- No difference in reduction in death from cardiovascular causes, non-fatal acute myocardial infarction or stroke, or admission to hospital for angina



The Look AHEAD Research Group. N Engl J Med 2013; 369:145-54.

Secondary Analysis of Look AHEAD shows CV Morbidity and Mortality Improvement for those who lost ≥10%

Lancet Diabetes Endocrinol. 2016 Nov;4(11):913-921. doi: 10.1016/S2213-8587(16)30162-0. Epub 2016 Aug 30.

Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial.

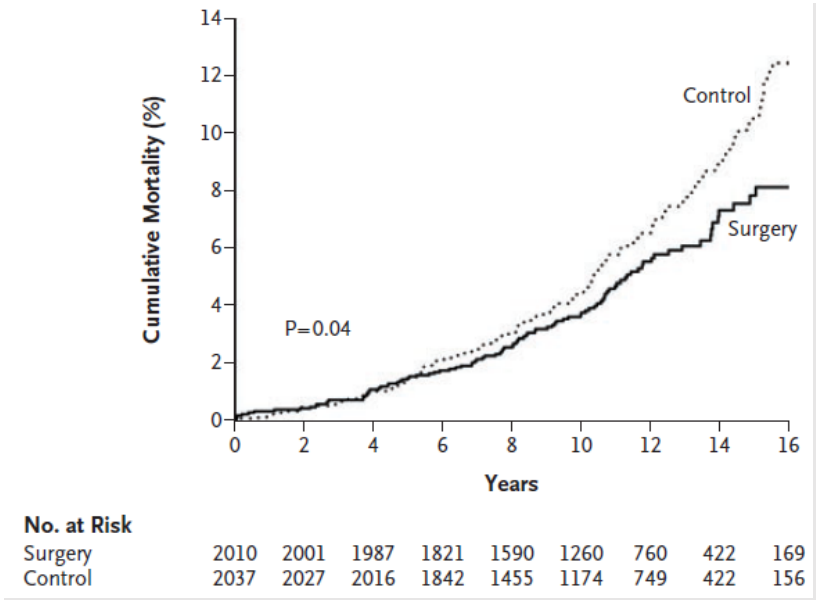
Look AHEAD Research Group.

- **Primary outcome**: composite of death from cardiovascular causes, non-fatal acute myocardial infarction, non-fatal stroke, or admission to hospital for angina.
- **Secondary outcome** included the same indices plus coronary artery bypass grafting, carotid endartectomy, percutaneous coronary intervention, hospitalisation for congestive heart failure, peripheral vascular disease, or total mortality
- "…participants in the intensive lifestyle intervention group who lost at least 10% of their bodyweight had a 20% lower risk of the primary outcome (adjusted HR 0·80, 95% CI 0·65-0·99; p=0·039), and a 21% lower risk of the secondary outcome (adjusted HR 0·79, 95% CI 0·66-0·95; p=0·011)…"

Look AHEAD
Action for Health in Diabetes

Lancet Diabetes Endocrinol. 2016 11: 913-921.

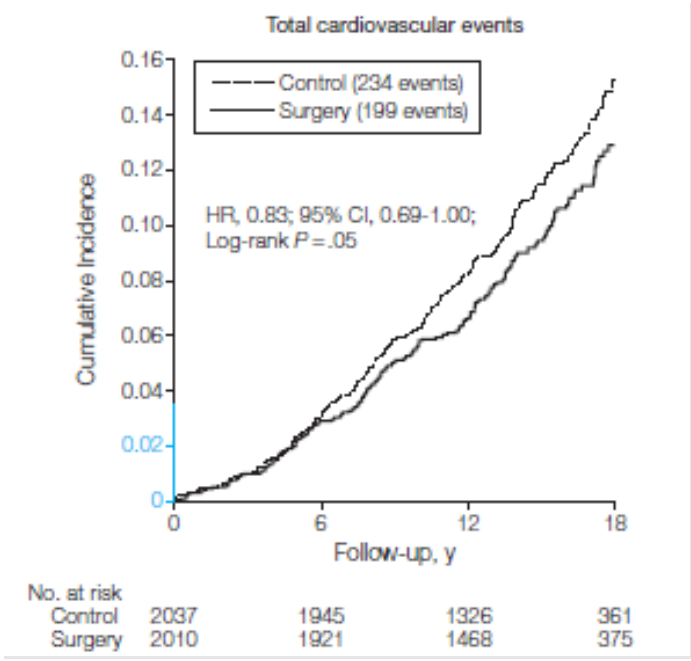
Non-randomized Comparisons of Bariatric Surgery vs. Matched Registry Controls Show Reduction in CV events and Mortality



ALL CAUSE MORTALITY

Surgery: 101 deaths; 13 MI; 29 cancer
Control: 129 deaths; 25 MI; 47 cancer
Unadjusted Hazard ratio 0.76; 95% CI 0.59-0.99 P=0.04

Sjostrom L, et al. NEJM 2007; 357:741-752.



CARDIOVASCULAR EVENTS

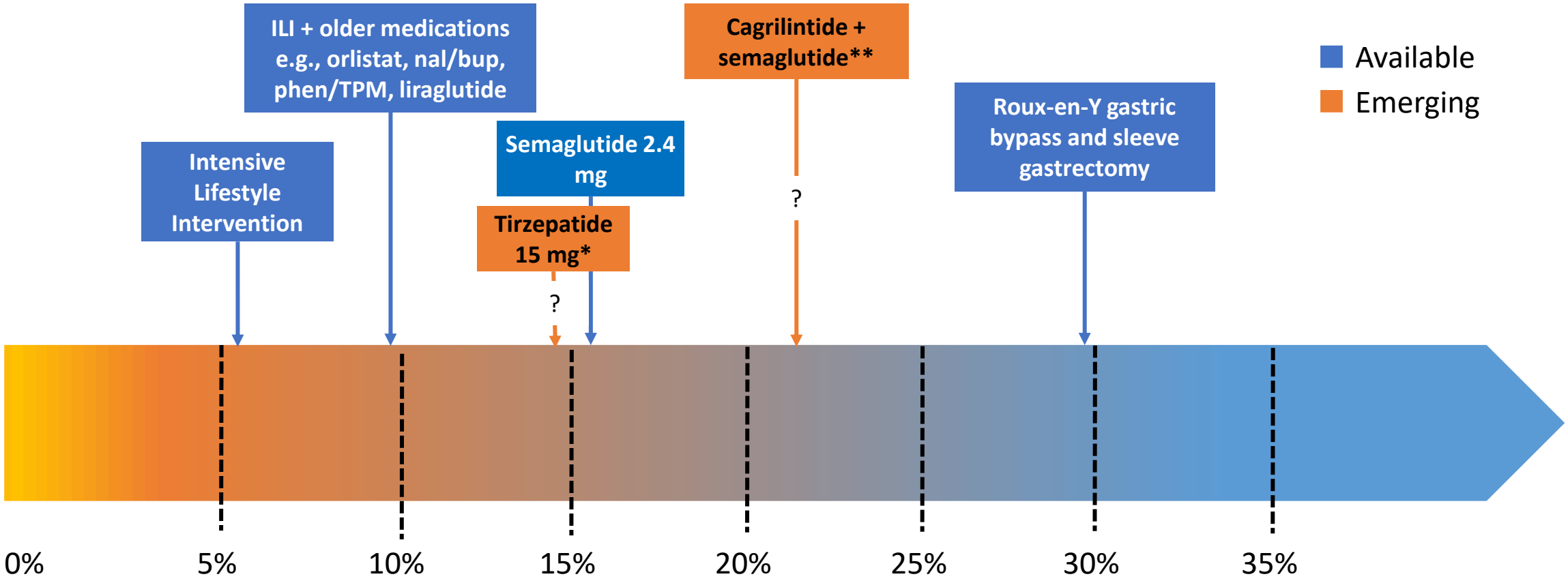
Surgery: 199 events (MI or stroke)
Control: 234 events
Unadjusted Hazard ratio 0.83; 95% CI 0.69-1.0; P<0.05

Sjostrom L, et al. JAMA 2012; 307 (1): 56-65.

What is needed for weight management to be the pathway to metabolic, CVD and NCD management?

- Positive CVOT for SELECT
- Recognition of health benefits in large real-world studies (progressive employers)
- More and better approaches to medicating for reduction of excess abnormal fat mass.

Available and Emerging Treatments for Obesity



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Thank you!