



National Institute of
Diabetes and Digestive
and Kidney Diseases

Treatment of Overweight and Obesity in Adults: What Works?

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Roundtable on Obesity Solutions

Health and Medicine Division, NASEM

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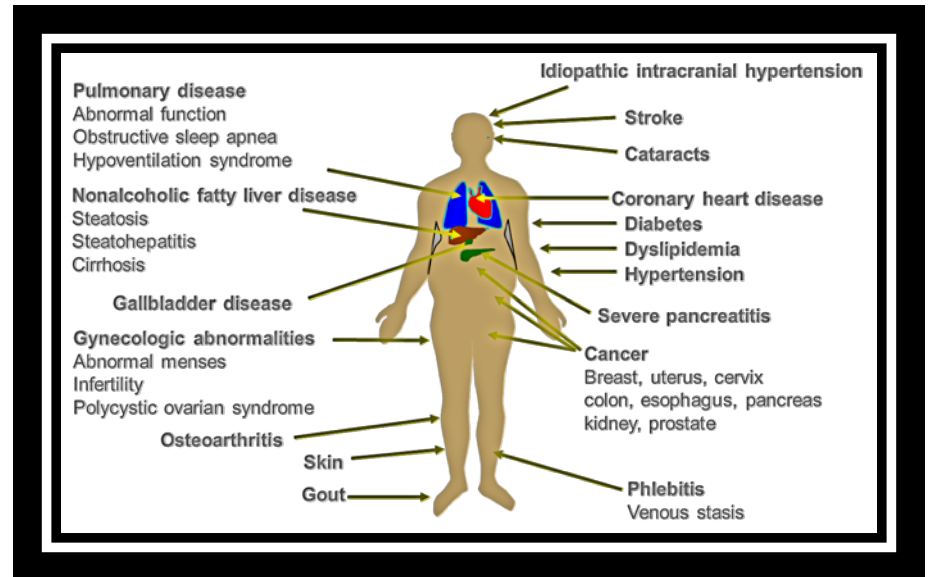
Disclosure: Spouse receives research project support from Rhythm Pharmaceuticals



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Why Do We Encourage Our Patients With Obesity to Lose Weight?

- To prevent or ameliorate obesity-related diseases and conditions
- To improve the way they feel and function



How Do We Help Our Patients with Obesity Lose Weight and Maintain Weight Loss?

- **Three Major Modalities**

- Lifestyle Interventions
- Pharmacotherapy
- Bariatric Surgery

- **Focus of this Talk– Efficacy of Adult Obesity Treatments for Weight Outcomes**

- Guidelines from Professional Societies
- Systematic Reviews/Meta-analyses
- Large RCTs and Observational Studies

AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults

- Evidence-based guidelines, focusing on RCTs
- Addressed a limited number of “Critical Questions”
 - What is the efficacy of lifestyle intervention?
 - What are the benefits and risks of bariatric surgical procedures?
- No critical question on pharmacotherapy
 - Recent SR/MA and Clinical Practice Guidelines that address pharmacotherapy

*AHA/ACC/TOS Guideline for the
Management of Overweight and Obesity in
Adults: Circulation. Nov 12 2013*

AHA/ACC/TOS Guideline: Lifestyle Intervention

- Patients who need to lose weight should receive a comprehensive program (diet, physical activity and behavior modification) of 6 mo or longer (SOE: High)
- The gold standard is on site, high intensity (≥ 14 sessions in 6 mo) comprehensive intervention delivered in group or individual sessions by a trained interventionist and persisting for a year or more. —Mean weight loss 5-10% Initial Weight (SOE: High)
- Low- to-moderate intensity primary-care based interventions have not been shown to be effective SOE: High
- Other approaches (i.e., web-based) are secondary because the amount of weight loss, and thus the health benefits, is less (up to 5 kg at 6-12 months) SOE: Moderate



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AHA/ACC/TOS Guideline for the Management of
Overweight and Obesity in Adults: Circulation. Nov 12
2013



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What is behavioral obesity treatment?

“...an approach used to help individuals develop a set of skills to achieve a healthier weight. It is more than helping people to decide *what* to change; it is helping them identify *how* to change.”

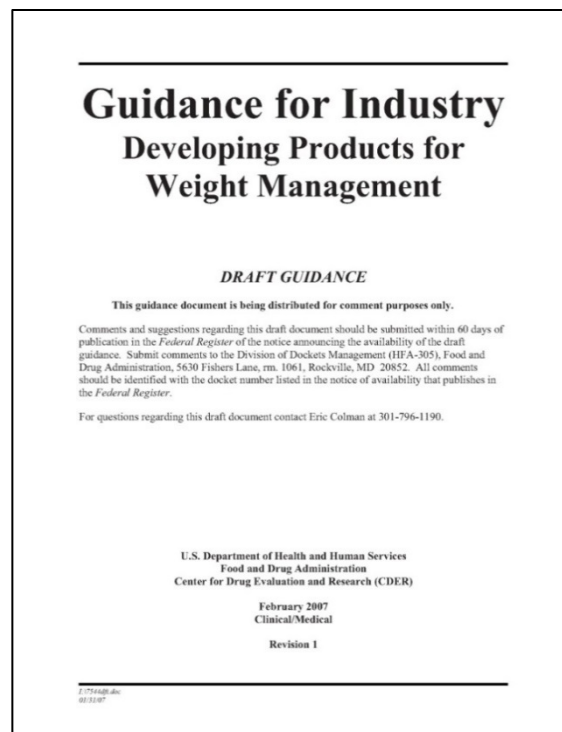
--Gary Foster, 2005

Components of Behavioral Treatment

- Self-monitoring
- Stimulus control
- Goal setting
- Problem solving
- Stress Reduction
- Relapse Prevention

If behavioral treatment were a drug, it would be approvable.....

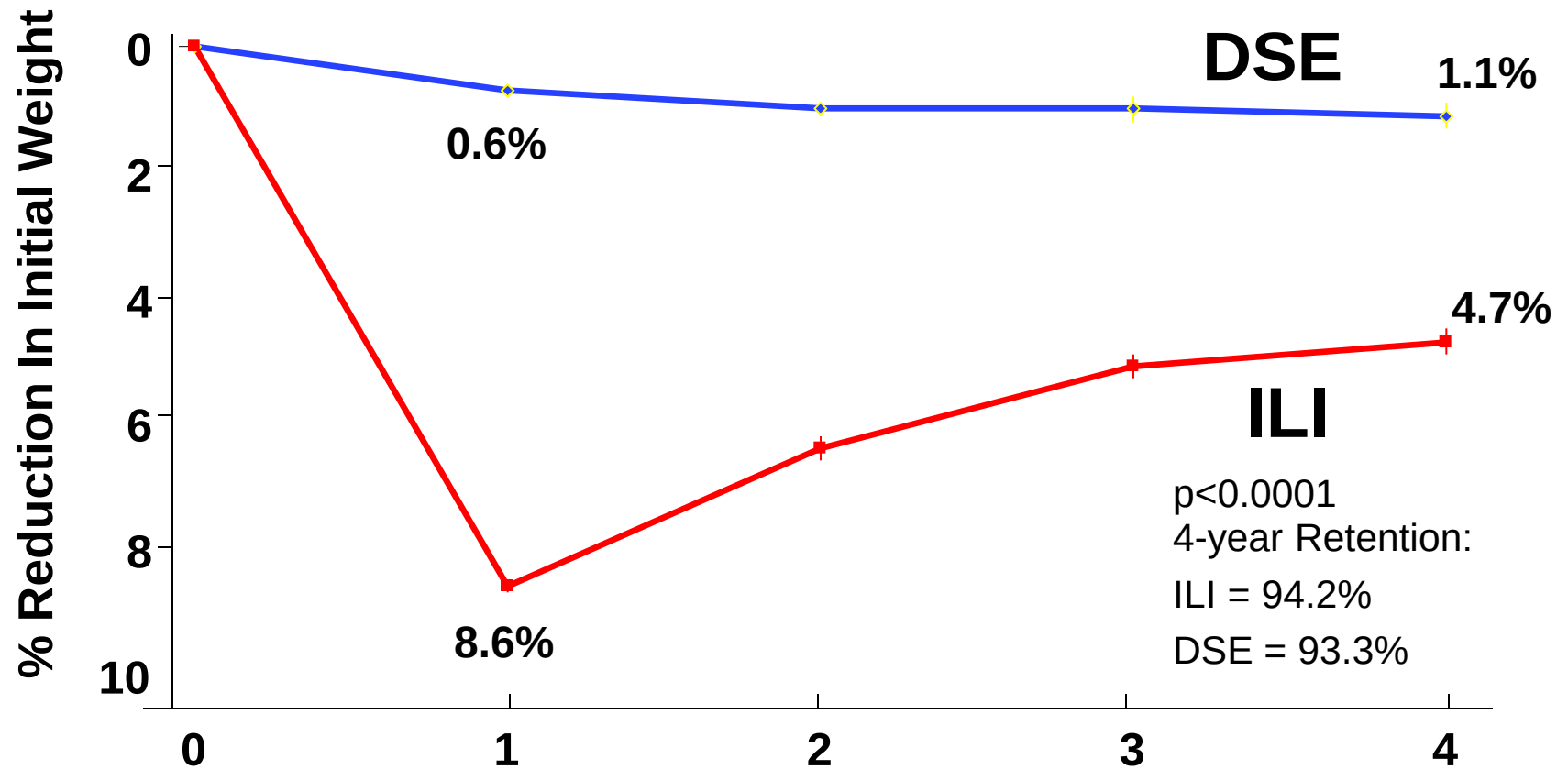
- In general, a product can be considered effective for weight management if **after 1 year of treatment either** of the following occurs:
 - The difference in mean weight loss between the active-product and placebo-treated groups is **at least 5 percent** and the difference is statistically significant **OR**
 - The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant



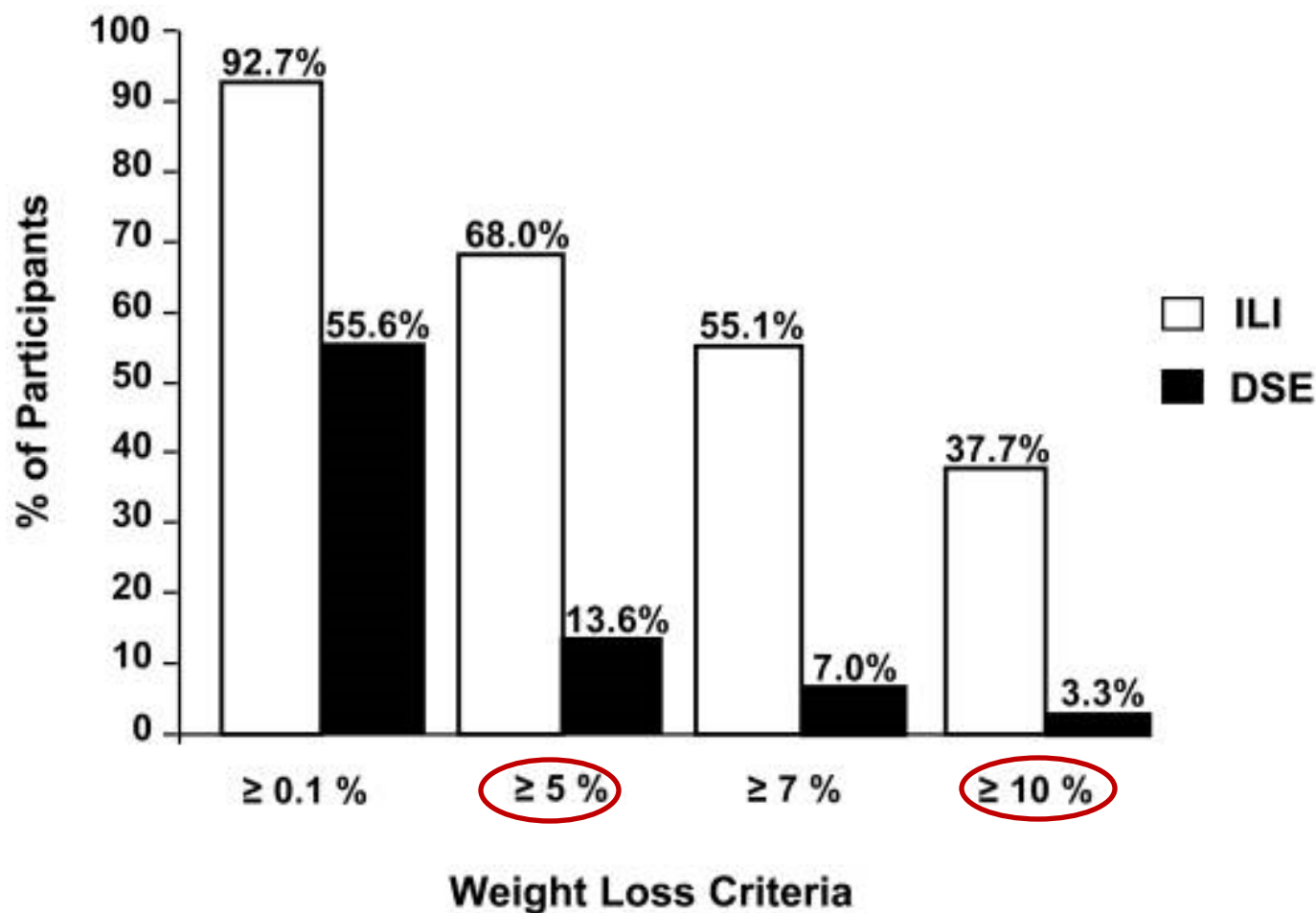


- ▶ Multicenter RCT comparing an Intensive Lifestyle Intervention (ILI) program vs. Diabetes Support and Education (control group) in over 5,000 participants with type 2 diabetes with overweight or obesity
- ▶ Participants were followed for up to 11 years; primary outcome was cardiovascular morbidity and mortality
- ▶ ILI Intervention:
 - ▶ Diet, physical activity and behavioral strategies
 - ▶ Group plus individual sessions
 - ▶ Frequency: Weekly for 6 months; 3x/month for 6 months

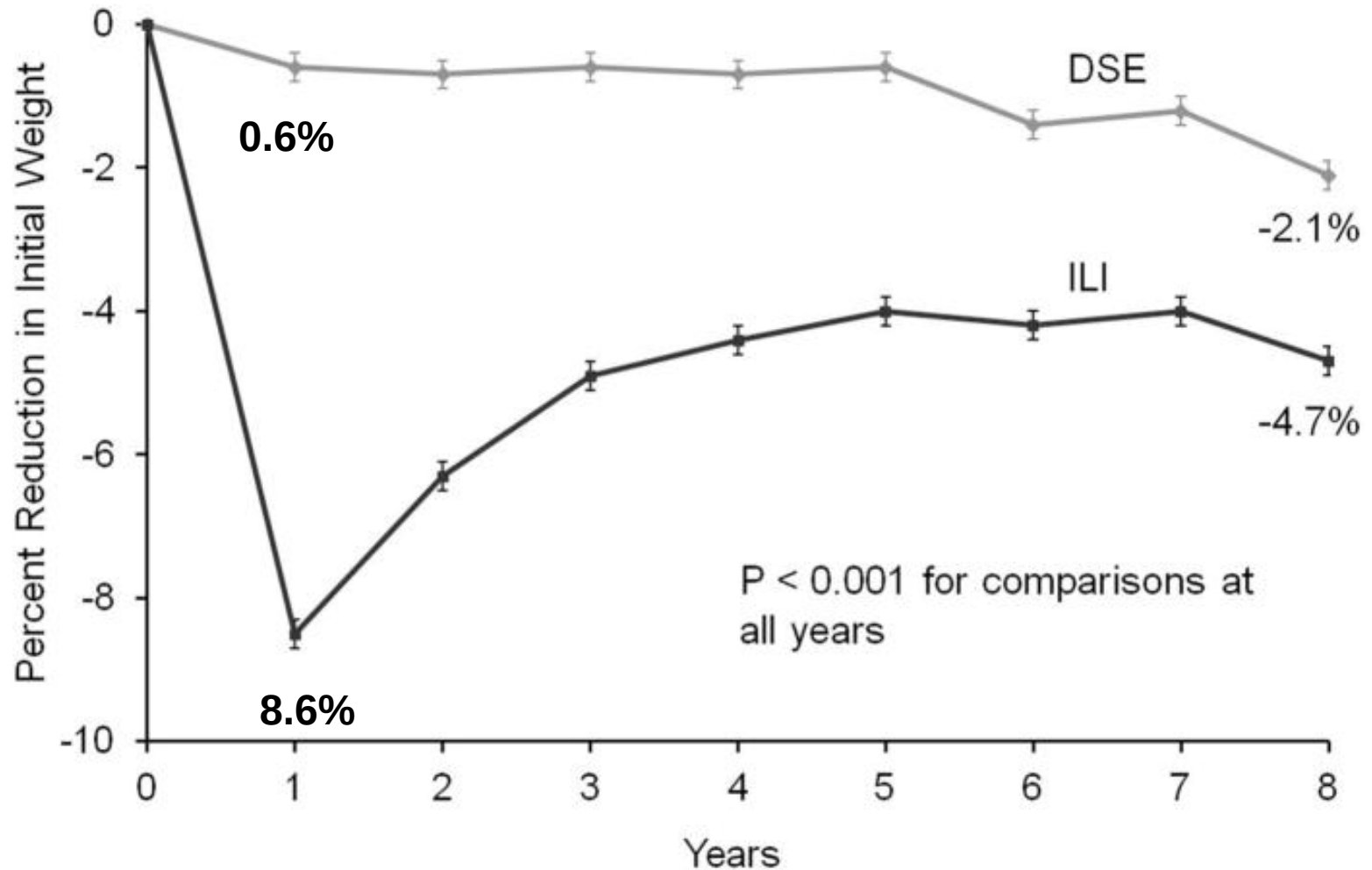
Intensive Lifestyle Intervention had Greater Percentage Reduction in Body Weight at Each of 4 Years



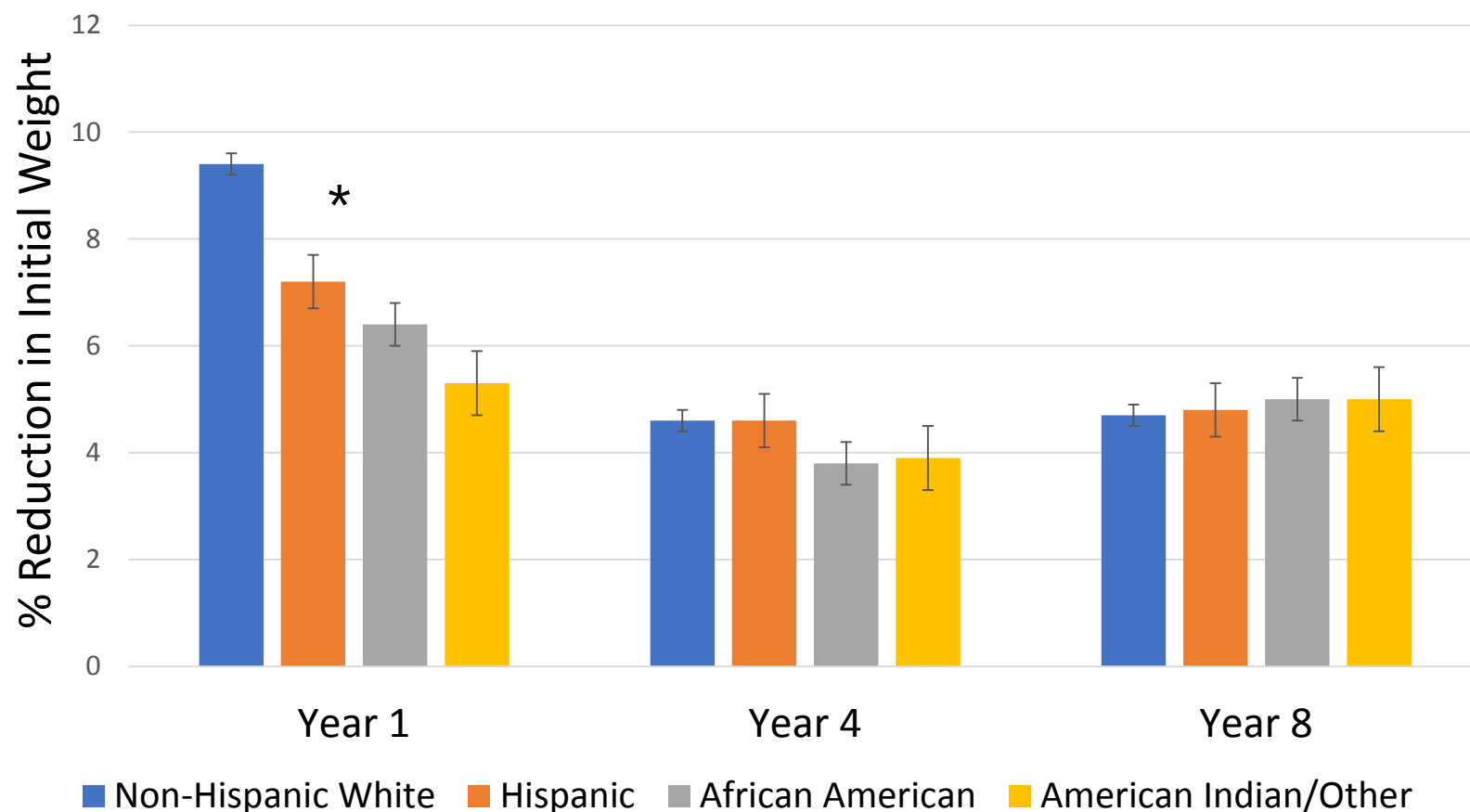
Percent Achieving 5% and 10% Weight Losses at 1 Year



Intensive Lifestyle Intervention had Greater Percentage Reduction in Body Weight Over Eight Years



Weight Loss in the Lifestyle Arm of the Look AHEAD Study by Race/Ethnicity



P<0.008

Obesity 2014, 22:5-13

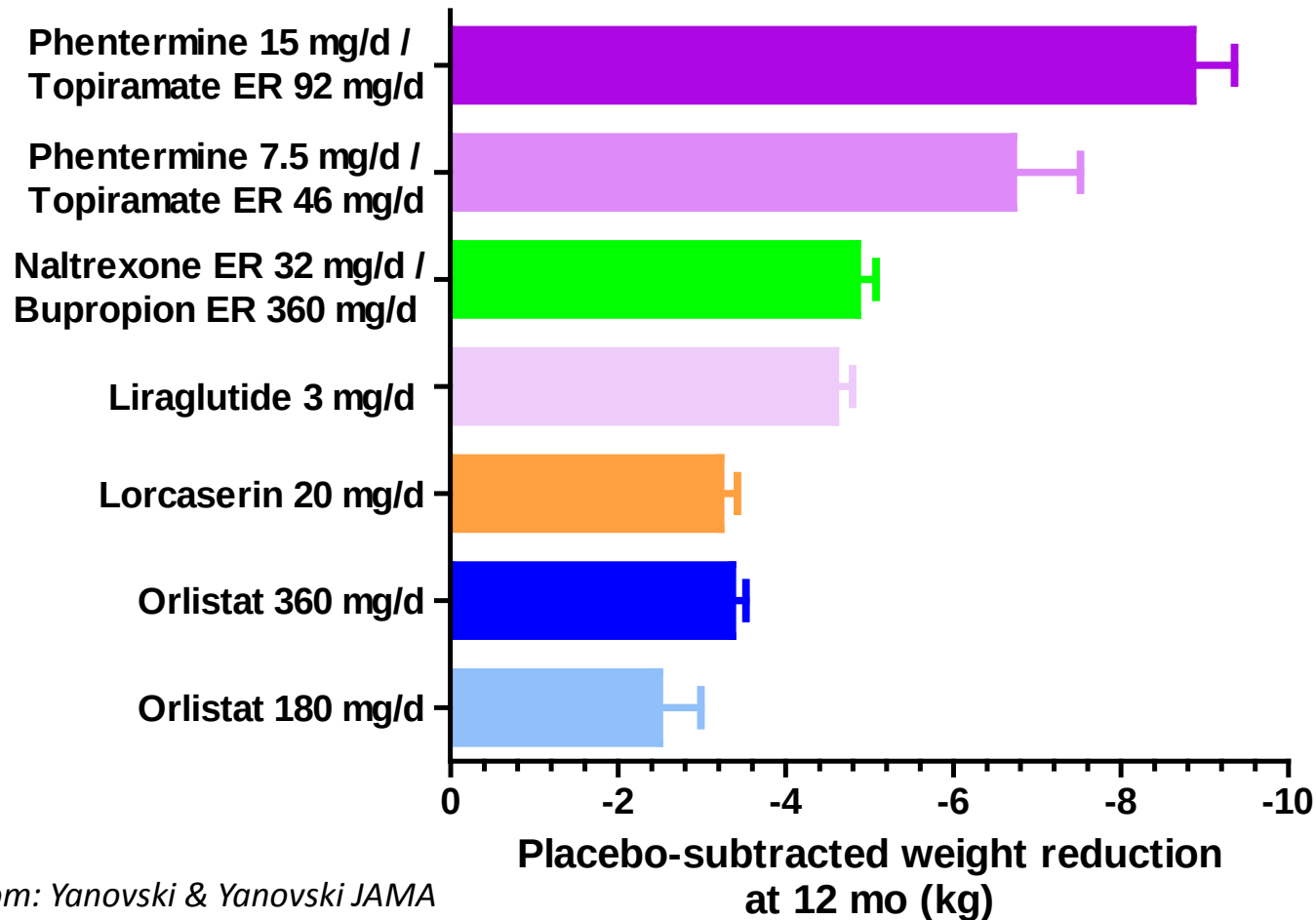
The Challenges:

- How can we enhance initial weight loss for those who may not respond to behavioral treatment with sufficient weight loss to improve health?
- How can we enhance longer-term weight maintenance and minimize regain?

Drugs Approved by the FDA for Obesity

Generic Name	Trade Names	DEA Schedule	Approved Use	Year Approved	Price per month
Benzphetamine	Didrex	III	Short-term	1960	\$20 -\$50
Phendimetrazine	Bontril, Prelu-2	III	Short-term	1961	\$6 - \$20
Diethylpropion	Tenuate	IV	Short-term	1973	\$47 - \$120
Phentermine	Adipex, Ionamin	IV	Short-term	1973	\$6 - \$45
Orlistat	Xenical, Alli	None	Long-term	1999	\$45 - \$520
Lorcaserin	Belviq	IV	Long-term	2012	\$240
Phentermine + Topiramate-ER	Qsymia	IV	Long-term	2012	\$140 - \$195
Bupropion-ER +Naltrexone-ER	Contrave	None	Long-term	2014	\$180 - \$210
Liraglutide	Saxenda	None	Long-term	2014	\$900-\$1000

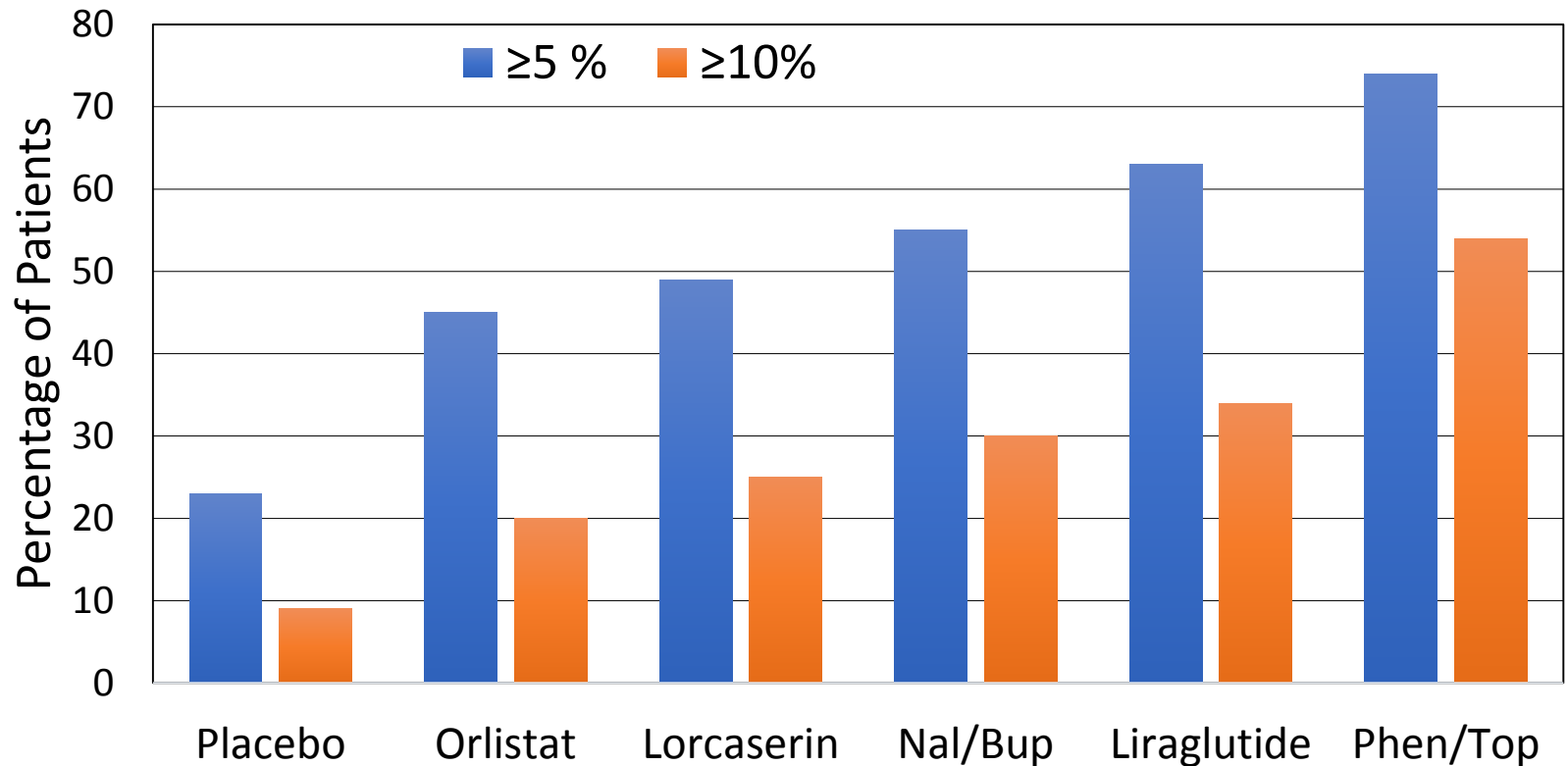
Efficacy of Obesity Medications FDA Approved for Long-term Use



Adapted from: Yanovski & Yanovski JAMA
311:74-86, 2014

Yanovski & Yanovski JAMA 313:1213-14, 2015

Proportion of Patients Achieving $\geq 5\%$ and $\geq 10\%$ Weight Loss at 1y



Khera R, Murad MH, Chandar AK, et al..
JAMA. doi:10.1001/jama.2016.7602

Weight Loss at 12 Weeks Predicts Treatment Response at One Year

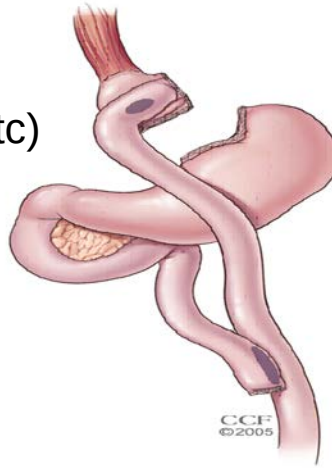
- Depending on medication used and intensity of lifestyle intervention from 25% to more than 50% of drug treated patients may NOT achieve a 5% weight reduction after 12 weeks of therapy
- Exposed to risks and costs of drug, with little prospect of benefit
 - Consider discontinuing and re-evaluate treatment options
 - Intensification of behavioral strategies
 - Referral to dietician or lifestyle interventionist, more intensive program
 - Consider medication with different mechanism of action
 - Reassess and manage medical or other contributory factors
 - Consider referral for bariatric surgery in appropriate patients

*-AHA/ACC/TOS Guideline for the Management of Overweight
-Endocrine Society Clinical Practice Guidelines on
Pharmacological Management of Obesity*

Bariatric Surgical Procedures

Roux-en-Y Gastric Bypass (RYGB)

- Restrictive and malabsorptive
- Metabolic effects (bile acids, gut hormones, microbiome, etc)
- Greatest improvement in medical comorbidities



Laparoscopic Adjustable Gastric Band (LAGB)

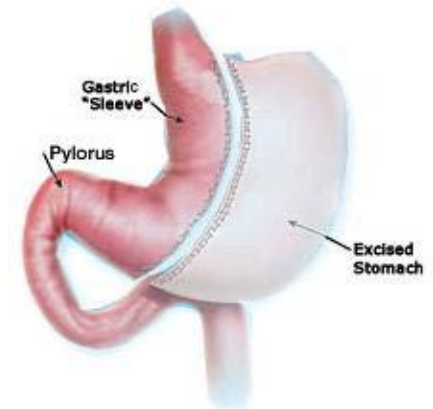
Restrictive only: an inflatable silicone device is placed around the top portion of the stomach

- Slows and limits food consumption
- Lesser weight loss
- Reversible



Sleeve Gastrectomy

- AKA “gastric sleeve”
- Theoretically restrictive only (80% of stomach excised)
- May also have metabolic effects
- Increasing in popularity
 - From 18% to >50% of procedures between 2011-2016



AHA/ACC/TOS Guideline :

Bariatric Surgery

- Advise your patients with BMI ≥ 35 and a co-morbidity or ≥ 40 that bariatric surgery may be an appropriate option to improve health and offer referral to an experienced bariatric surgeon for consultation and evaluation.
- Mean weight loss 2-3y 20-35% of initial weight depending on procedures (SOE: High)
- Some regain --about 7% initial weight over 10y (SOE Low) –caveat—older procedures



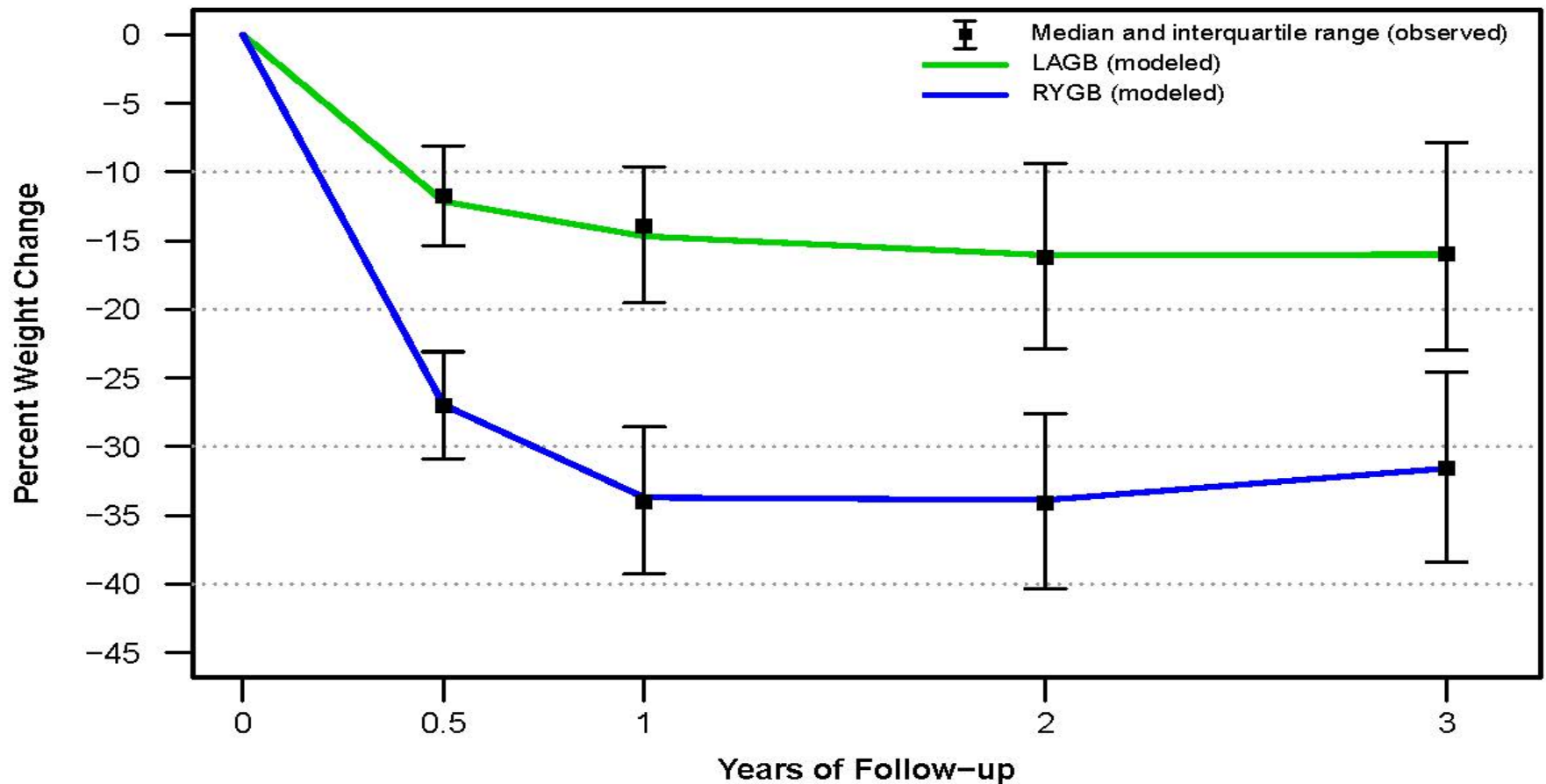
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Longitudinal Assessment of Bariatric Surgery (LABS)

- Observational cohort study of adults who underwent a first bariatric surgery at 10 U.S. hospitals between 2006 and 2009
 - (70% RYGB, 25% LAGB 5% Other)
- Assessments completed prior to surgery and 6 months, 12 months, and annually thereafter up to 7 years follow up

Weight Change Following Bariatric Surgery

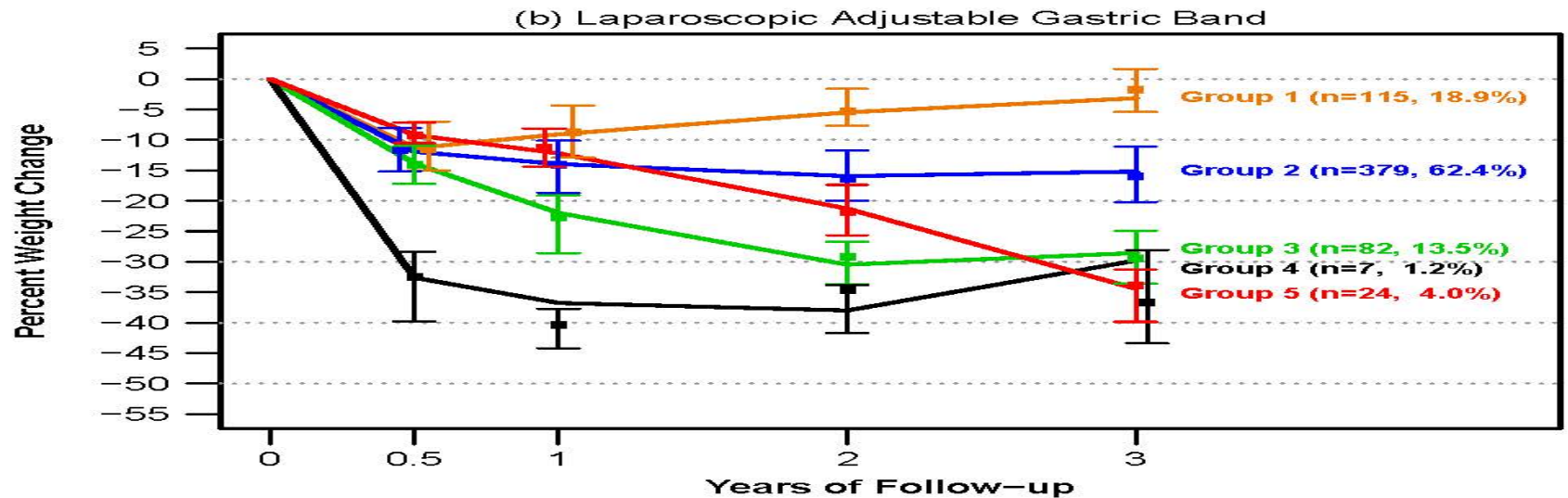
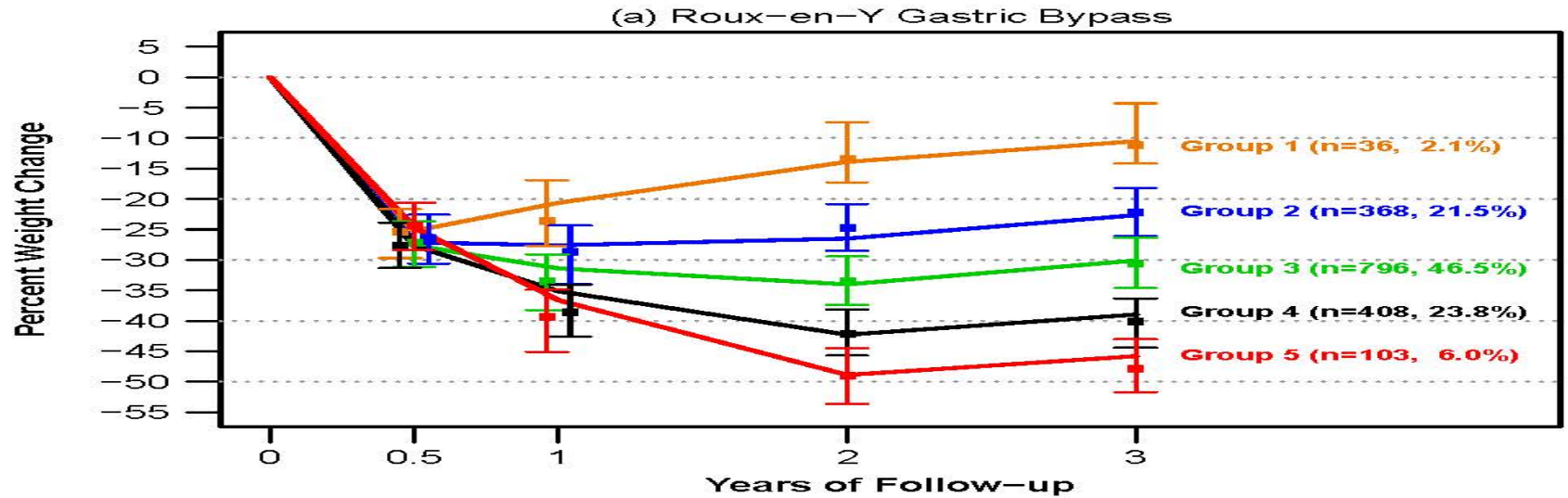


Number of Participants

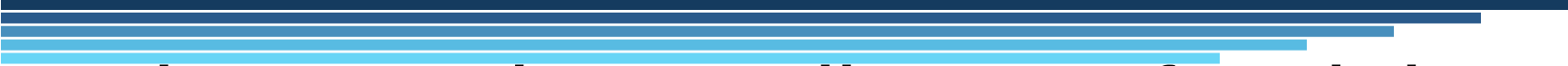
LAGB	610	596	579	559	543
RYGB	1738	1636	1621	1548	1515

JAMA. 2013 Dec 11;310(22)

Trajectories of Weight Change Following Bariatric Surgery



Median and interquartile range (observed)
Group trajectory (modeled)



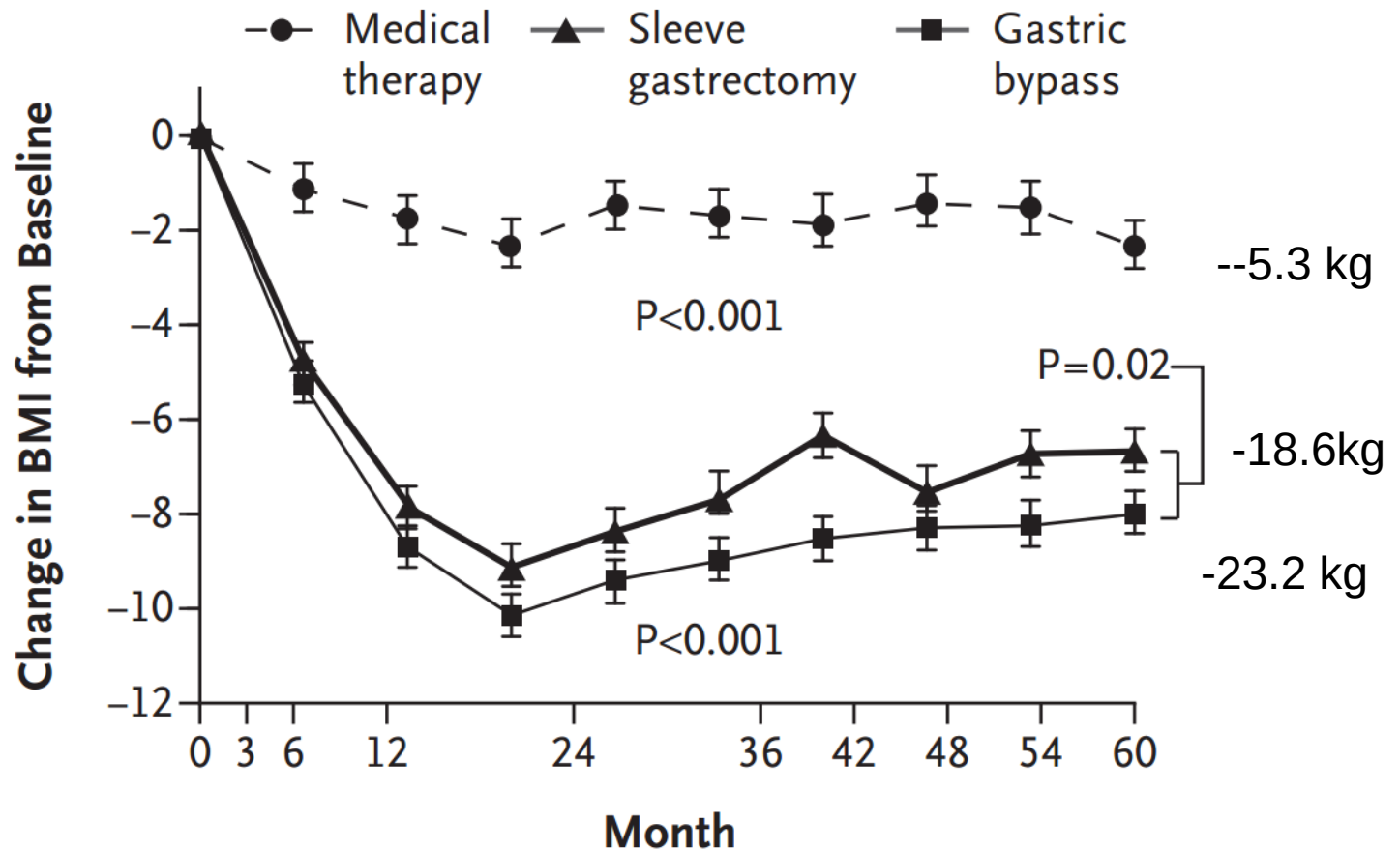
What are the predictors of weight and health outcomes in patients undergoing bariatric surgery?

“Few baseline variables were associated with 3-year weight change and the effects were small. These results indicate that baseline variables have limited predictive value for an individual's chance of a successful weight loss outcome after bariatric surgery”

Courcoulas et al, SOARD, 2014

Change in BMI over 5 Years in Patients with Diabetes Sleeve Gastrectomy vs. Gastric Bypass

Body-Mass Index



N=134

Schauer: NEJM. 2017;376(7):641.

Conclusions

- Intensive lifestyle interventions using behavioral treatment can lead to mean weight loss of 5-10% at one year
 - Less intensive treatments –in person or electronically– lead to smaller weight losses
 - Over time, some regain can be expected-even with continued treatment
 - In RCTs of intensive lifestyle interventions, there are initial differences in weight loss by race/ethnicity, but these diminish over time

Conclusions

- Adjunctive treatment with obesity medications or surgery can be considered in appropriate patients
- Adding drug treatment can increase weight loss from 3-9 percent more than lifestyle treatment alone
 - More likely to respond with clinically meaningful weight loss
 - Initial weight loss predicts later treatment response
- Bariatric Surgery leads to the largest and most sustained weight reduction
 - Differences by procedure: RYGB>SG>LAGB
 - Within each procedure, there is some variability in weight loss and maintenance
 - Few predictors of treatment response

Knowledge Gaps for Efficacy of Obesity Treatments

- Efficacy of drug and surgical treatments in racial/ethnic minority and other health disparities populations (low SES, rural, etc)
- Effectiveness of newer modes of delivery for lifestyle intervention in large and diverse populations
- Predictors of response, beyond initial weight loss for all obesity treatments
 - Genetic and phenotypic (including behavioral and metabolic) characteristics to allow more targeted treatment recommendations
- Long-term safety and efficacy of Sleeve Gastrectomy and other newer procedures and devices for obesity treatment