비만치료의 최신 지견

인제의대 해운대백병원 내분비대사내과

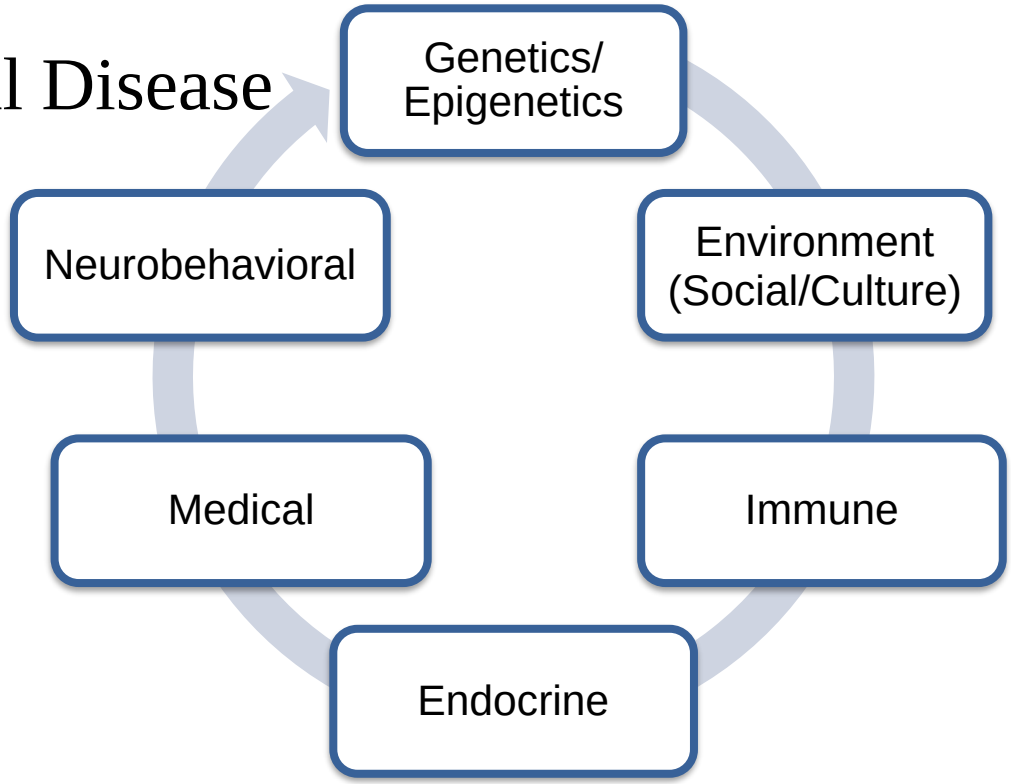
김 태 년

Obesity Defined as a Disease

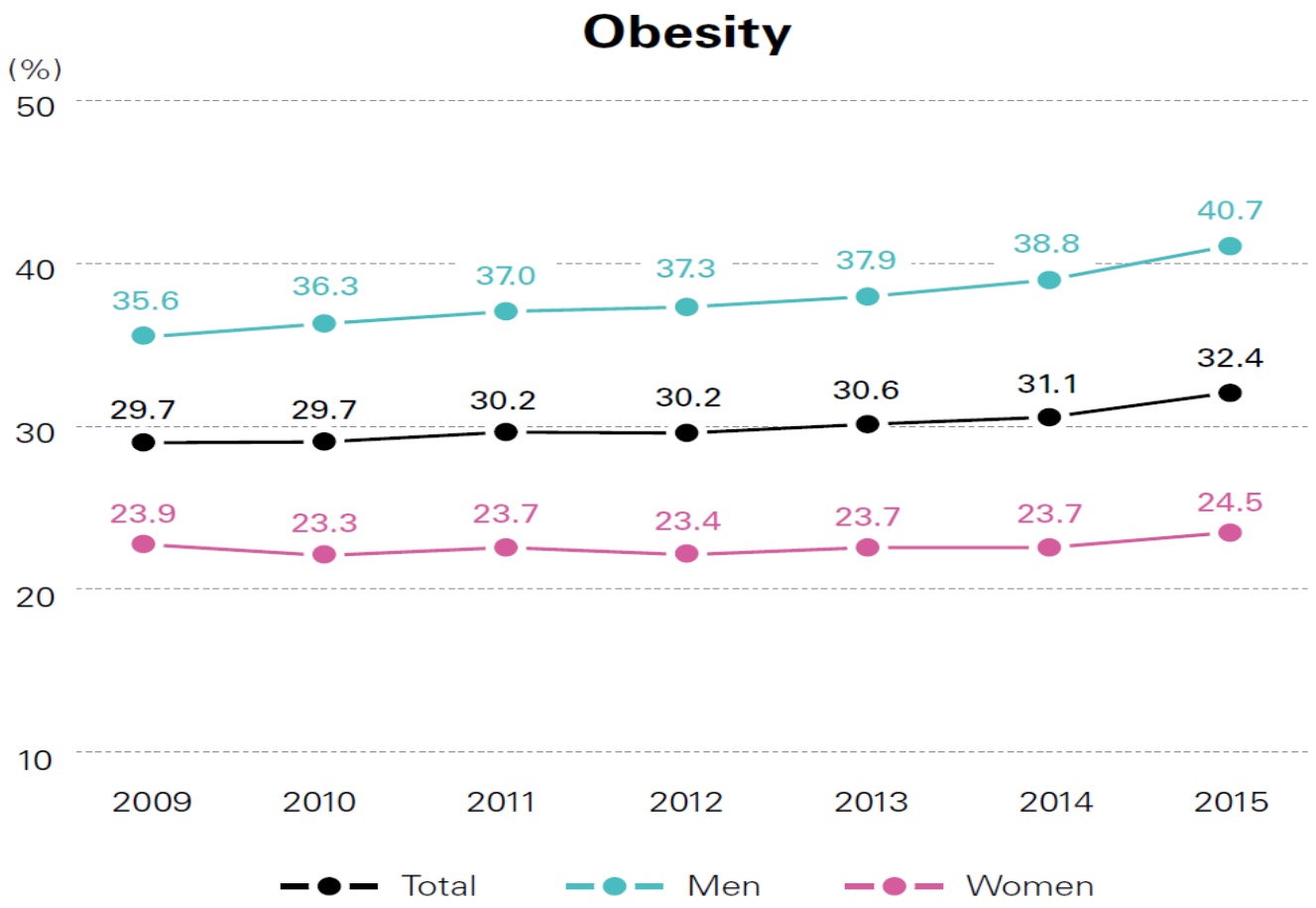
- Abnormal or excessive fat accumulation that may impair health

World Health Organization

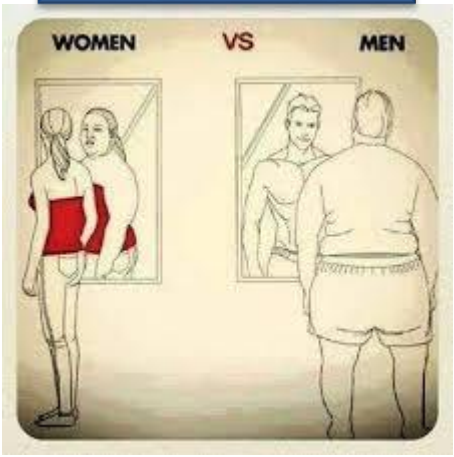
- Obesity as a Multifactorial Disease



The prevalence of obesity



See themselves in mirror



- Data derived from the NHIS data set: 2009-2015
- Data was presented by age and sex standardization using the 2010 Census Korean population.
- The definition of obesity is a BMI ≥ 25 kg/m^2

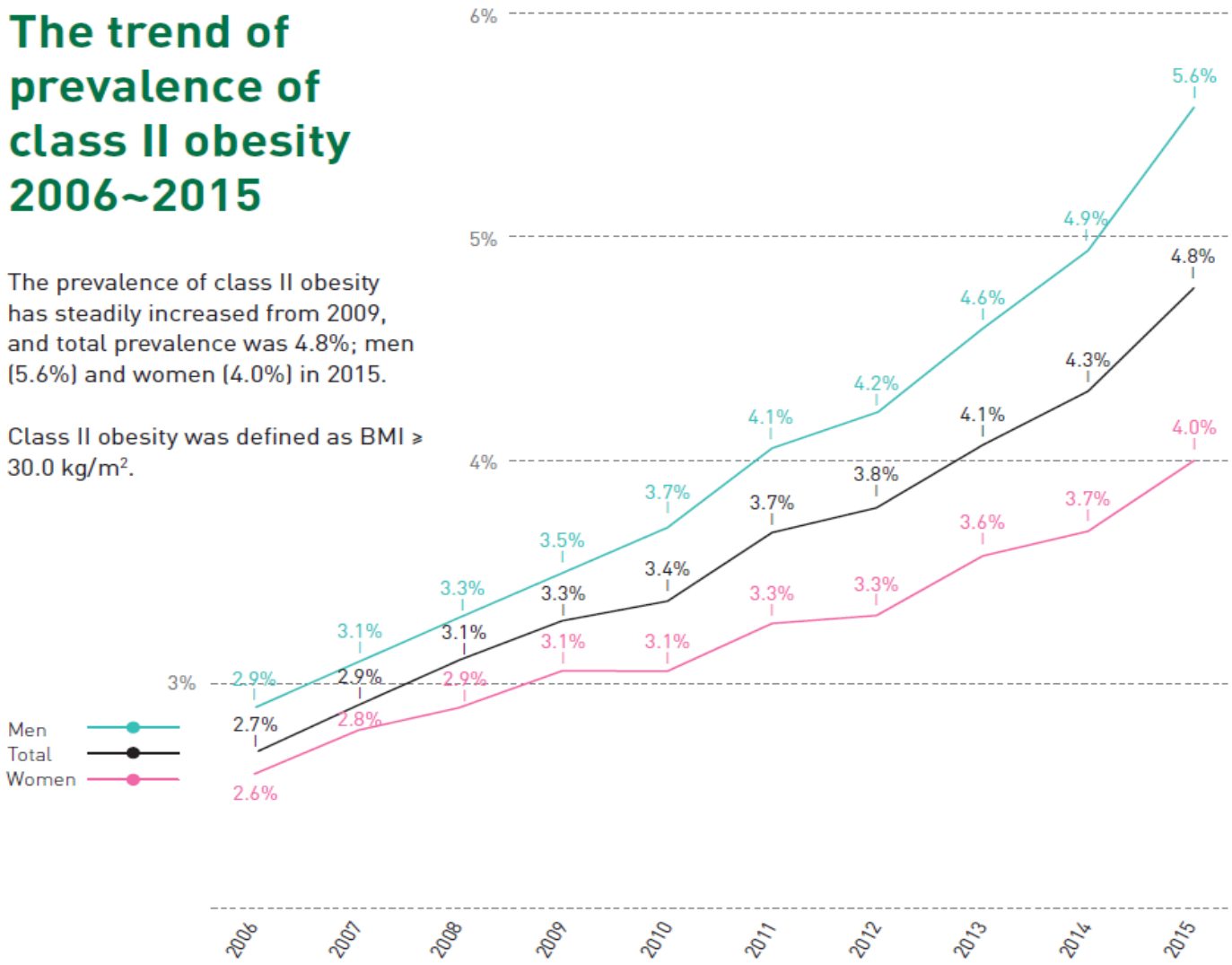
2017 Obesity fact sheet

The prevalence of class II obesity

The trend of prevalence of class II obesity 2006~2015

The prevalence of class II obesity has steadily increased from 2009, and total prevalence was 4.8%; men (5.6%) and women (4.0%) in 2015.

Class II obesity was defined as BMI ≥ 30.0 kg/m².



2016 Obesity fact sheet

Objectives

- 왜 비만치료제를 사용해야 하는가?
- 가이드라인
- 약물치료 방법
- 얼마 동안 사용해야 하는가?
- 비만대사수술은?

Case

- 36세 여자(체중증가에 대한 우려 & 체중감소가 소원)
- 10년간 꾸준히 체중증가(2번의 출산)
- 현재는 BMI 32 kg/m^2
- 부모 모두 비만
- 현재는 만성질환(-), 약물치료(-)
- 살이 찌는 이유를 도대체 알 수 없다.
- “내 몸의 대사가 느린 것 같아 병원을 찾았다”
- 난 간식도 하지 않고 음료수도 마시지 않는다.
- 일주일에 3회이상 운동
- **“What else can I do?” she asks in frustration**

What would you recommend regarding weight management?

1. Initiate lifestyle counseling
2. Refer to a commercial weight loss program
3. Consider pharmacotherapy
4. Lifestyle modification + pharmacotherapy
5. Refer for a bariatric procedure
6. None of the above

Within Subsets of Patients with Overweight ~ Obesity

Deranged endocrine and immune responses ↓

Sick Fat Disease (SFD) (Adiposopathy)

Endocrine/metabolic:
- Elevated blood glucose
- Elevated blood pressure
- Dyslipidemia
- Other metabolic diseases
- Cancer

Abnormal and pathologic physical forces ↓

Fat Mass Disease (FMD)

Biomechanical/structural:
- Stress on weight-bearing joints
- Immobility
- Tissue compression (i.e., sleep apnea, gastrointestinal reflux, etc.)
- Tissue friction (i.e., intertrigo, etc.)

1. Bays HE: "Sick fat," metabolic disease, and atherosclerosis. Am J Med 2009 122:S26-37
2. Bays HE: Adiposopathy is "sick fat" a cardiovascular disease? J Am Coll Cardiol 2011 57:2461-2473
3. Bays HE: Adiposopathy, diabetes mellitus, and primary prevention of atherosclerotic coronary artery disease: treating "sick fat" th rough improving fat function with antidiabetes therapies. Am J Cardiol 2012 110:4B-12B

살을 얼마나 빼면 될까?

2016 AACE

	DIAGNOSIS			TREATMENT GOALS	
	Anthropometric Component	Clinical Component		Intervention/ Weight-Loss Goal	Clinical Goals
TERTIARY PREVENTION					
Overweight or Obesity	BMI ≥25 (≥23 in certain ethnicities)	Metabolic syndrome		10%	Prevention of T2DM
		Prediabetes		10%	Prevention of T2DM
		T2DM		5% to ≥15%	• Reduction in A1C • Reduction in number and/or doses of glucose lowering medications • Diabetes remission especially when diabetes duration is short
		Dyslipidemia		5% to ≥15%	• Lower triglycerides • Raise HDL-c • Lower non-HDL-c
		Hypertension		5% to ≥15%	• Lower systolic and diastolic BP • Reductions in number and/or doses of antihypertensive medications
		Nonalcoholic fatty liver disease	Steatosis	5% or more	Reduction in intrahepatocellular lipid
			Steatohepatitis	10% to 40%	Reduction in inflammation and fibrosis

The Look AHEAD Study

Intensive lifestyle intervention (ILI) vs. usual care (diabetes support and education (DSE))

Published in final edited form as:
Obesity (Silver Spring). 2014 January ; 22(1): 5–13. doi:10.1002/oby.20662.

Eight-Year Weight Losses with an Intensive Lifestyle Intervention: The Look AHEAD Study

The Look AHEAD Research Group

Abstract

Objective—To evaluate 8-year weight losses achieved with intensive lifestyle intervention (ILI) in the Look AHEAD (Action for Health in Diabetes) study.

Design and Methods—Look AHEAD assessed the effects of intentional weight loss on cardiovascular morbidity and mortality in 5,145 overweight/obese adults with type 2 diabetes, randomly assigned to ILI or usual care (i.e., diabetes support and education [DSE]). The ILI provided comprehensive behavioral weight loss counseling over 8 years; DSE participants received periodic group education only.

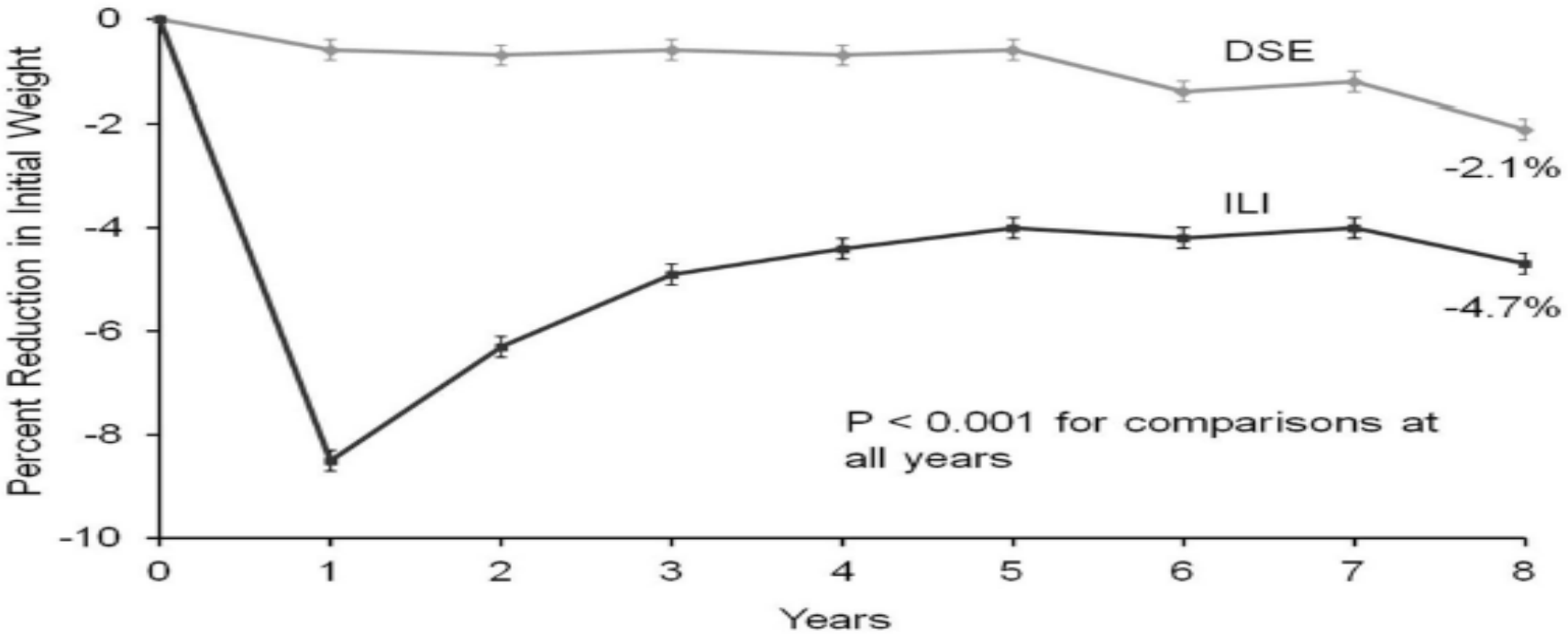
Results—All participants had the opportunity to complete 8 years of intervention before Look AHEAD was halted in September 2012; ≥88% of both groups completed the 8-year outcomes assessment. ILI and DSE participants lost (mean±SE) 4.7±0.2% and 2.1±0.2% of initial weight, respectively ($p<0.001$) at year 8; 50.3% and 35.7%, respectively, lost ≥5% ($p<0.001$), and 26.9% and 17.2%, respectively, lost ≥10% ($p<0.001$). Across the 8 years ILI participants, compared with DSE, reported greater practice of several key weight-control behaviors. These behaviors also distinguished ILI participants who lost ≥10% and kept it off from those who lost but regained.

Conclusions—Look AHEAD's ILI produced clinically meaningful weight loss (≥5%) at year 8 in 50% of patients with type 2 diabetes and can be used to manage other obesity-related co-morbid conditions.

Trial Registration—clinicaltrials.gov Identifier: NCT00017953

Obesity. 2014;22(1):5–13

Percent reduction in initial weight



고강도 생활 수정 요법군(ILI)와 일반 관리군(DSE)에 따른 8년간 체중 변화

Baseline 대비 8년간의 체중 변화
일반 관리군(DSE) < 고강도 생활 수정 요법군(ILI)

체중 변화 비율(-4.7% vs -2.1%) / 5% 이상 체중 감소 비율 (50.3% vs 35.7%)
10% 이상 체중 감소 비율 (26.9% vs 17.2%)

intensive lifestyle intervention (ILI), diabetes support and education (DSE; usual care group).

Obesity. 2014;22(1):5–13

Rationale for Pharmacotherapy

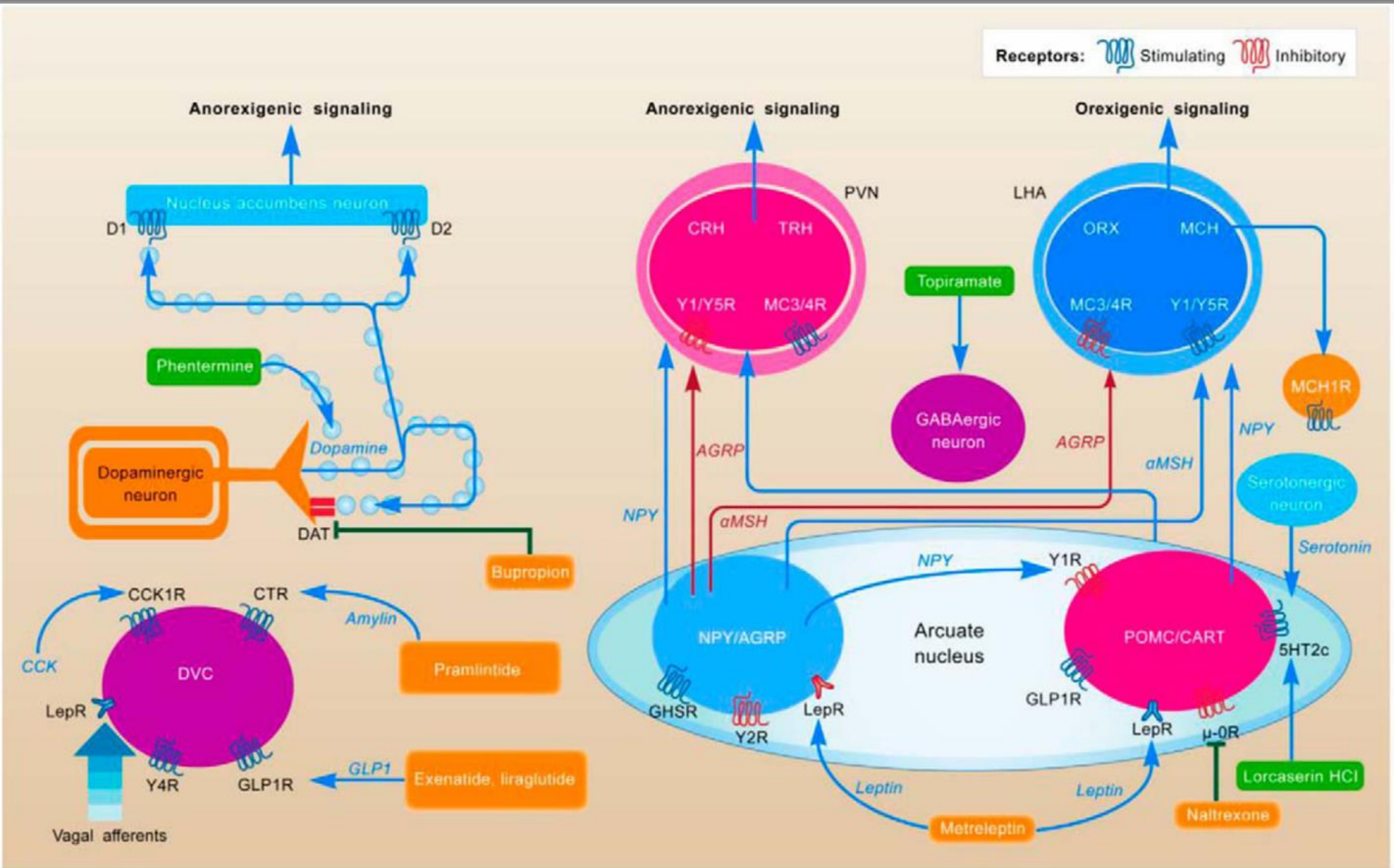
1. Obesity is a chronic disease that requires long-term Tx

2. Weight loss and weight-loss maintenance are very difficult for many patients

3. Weight loss pharmacotherapy should be considered as an “adjunct” therapy

4. The primary function of most medications are to assist with weight loss by impacting appetite, allowing patients to more easily follow a diet

Antiobesity agents and their mechanism of action



Guildelines say: Key Recommendations

1. **Diet, exercise and behavior modification** are fundamental to all form of weight management

2. Consider changing medications for other chronic disease that may cause weight gain

3. Consideration should be given to adding an **FDA approved weight loss medication** to a lifestyle program

4. Only continue a weight loss medications if **patients lose 5% of baseline weight at 3 months**. If so, continue indefinitely (vs considering intermittent therapy).

Treatment options for overweight and obesity

Treatment	25.0–26.9 (or 23.0–24.9*)	27.0–29.9 (or 25.0–29.9*)	30.0–34.9	≥35.0
Diet, physical activity, and behavioral therapy	+	+	+	+
Pharmacotherapy	With comorbidities	+	+	+
Metabolic surgery			Uncontrolled comorbidities	+

Modified ADA/AHA/ACC treatment options

1. 2018 ADA guideline for obesity management for the treatment of type 2 diabetes: stanards of medical care in diabetes-2018
2. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults. J Am Coll Cardiol. 2013

Pharmacotherapy (Available for chronic use)

- **Orlistat (Xenical®)**

  : approval by FDA (1999)

- **Lorcaserin (Belviq®)**

  : approval by FDA (2012)

- **Phentermine/Topiramate (Qsymia®)**

  : approval by FDA (2012)

- **Naltrexone/Bupropion (Contrave® , Mysimba®)**

  : approval by FDA(2014.9), EMA (2015)

- **Liraglutide 3.0mg (Saxenda®)**

  : approval by FDA (2014), EMA (2015)

Short-term anti-obesity drugs

Phentermine

- Approved by the FDA in 1959 for **short-term (≤12 wk)** weight management

- **NE transporter inhibitor**

→ **Appetite suppression** mediated by activation of POMC neurons in the arcuate nucleus

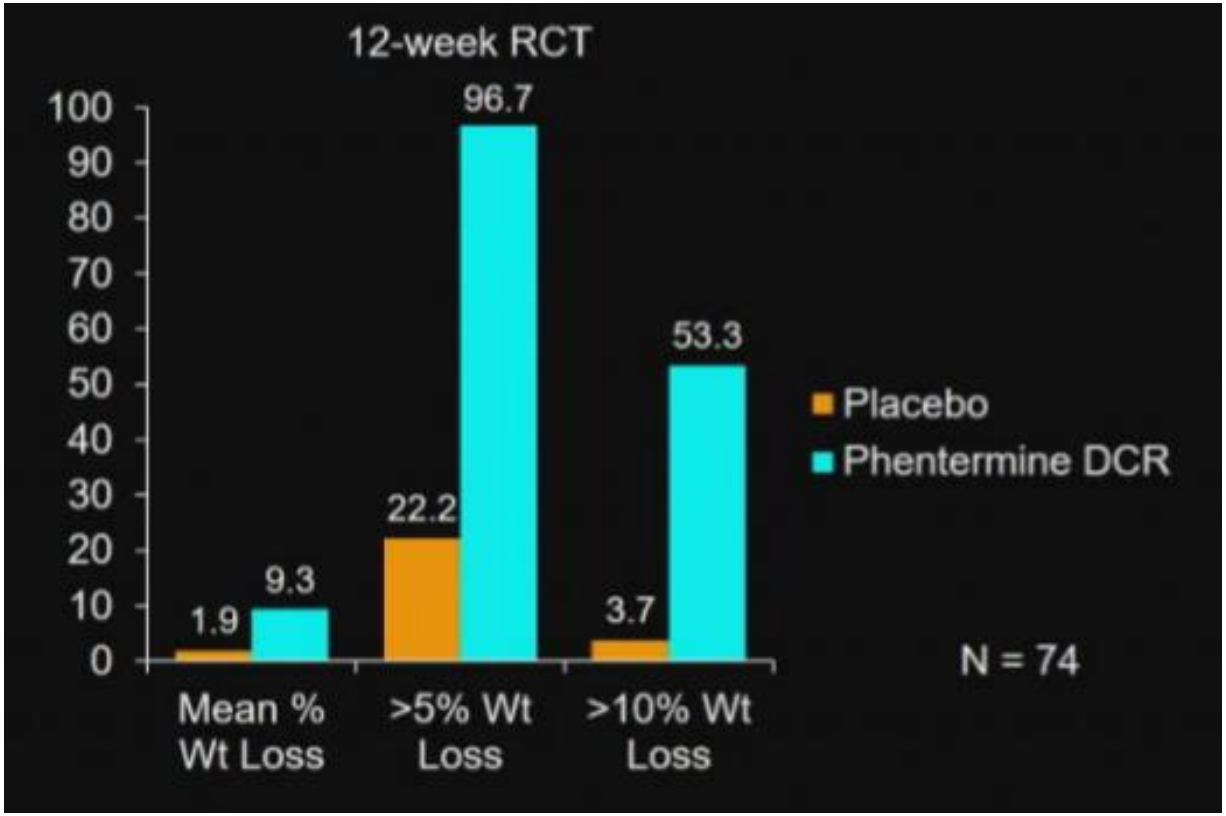
- The most commonly prescribed medication for obesity in the US

- Administered orally once or twice daily with dosing ranging from 15 to 37.5 mg daily

Short-term anti-obesity drugs

Phentermine

- Efficacy: More weight loss than placebo by "5-10%"
- Side effects: Increased BP and HR, insomnia, agitation, dry mouth, headache, tremor



Kang et al. Diabetes Obes Metab 2010;12:876-882

Orlistat (Xenical®)

- Approved by the FDA in 1999 for the treatment of obesity

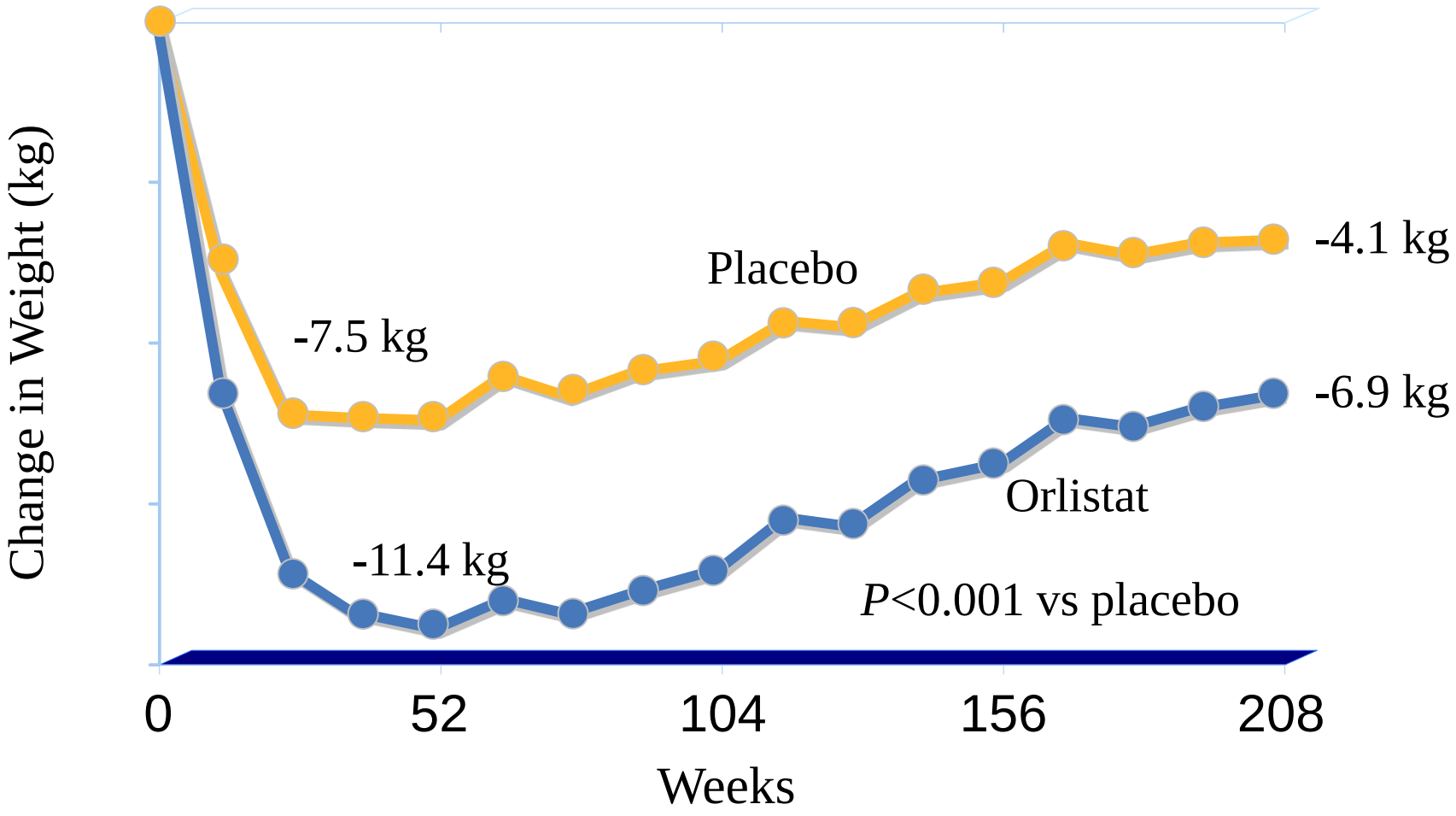
- Mechanism: **Gastric- and pancreatic-lipase inhibitor**
→ inactivates gastrointestinal lipase, **reducing the absorption of dietary fat**

- Dose: 60-**120 mg** with meals

- Commonly experienced gastrointestinal side-effects : diarrhea, flatulence, bloating, abdominal pain and dyspepsia

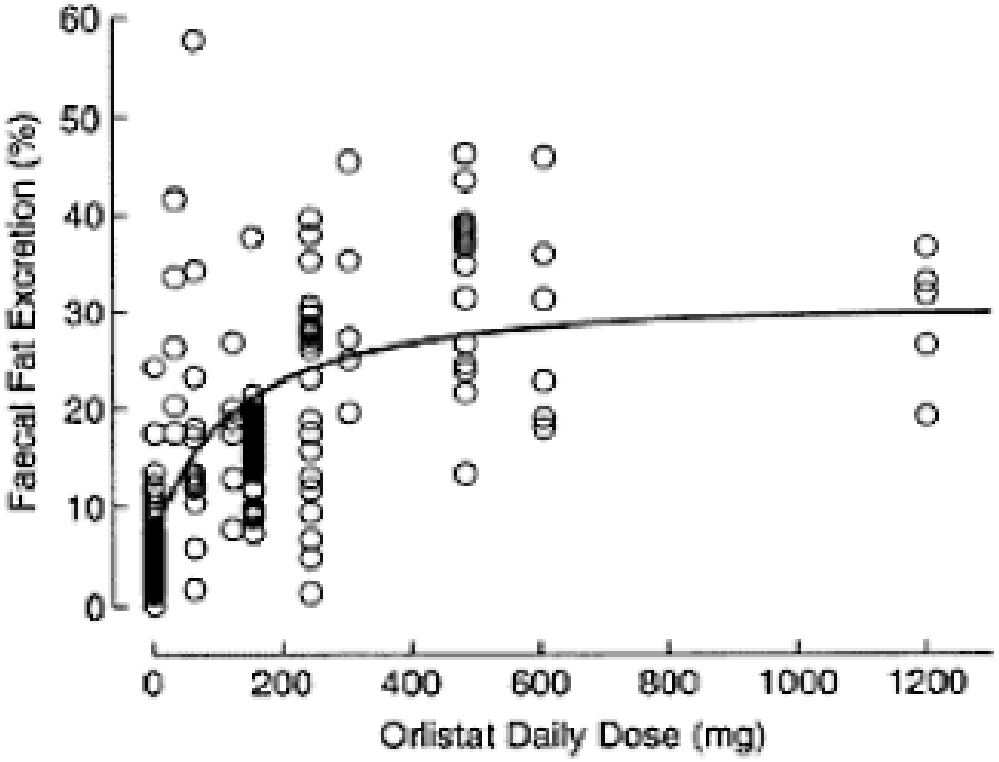
Patel D. et al. Metabolism. 2015;64(11):1376-1385
Narayanaswami V. et al. Pharmacol Ther. 2017 Feb;170:116-147

Effect of Long-term Orlistat Therapy on Body Weight



Torgenson et al. Diabetes Care 2004;27:155

How much dietary fat is expected to be excreted stool with orlistat treatment?



1회 120 mg, 1일 3회

- Dose-response relationship for the effect of orlistat on fecal fat excretion (percent of fat intake)

From Zhi. J et al. Clin. Pharmacol/ Ther. 56,82-85,1994

Lorcaserin (Belviq®)

- Approved by FDA in 2012, about 13 years after the approval of orlistat

- **Selective 5-HT_{2C} agonist**
→ activates 5-HT_{2C} receptors that are expressed on POMC neurons of arcuate nucleus resulting in **increased satiety**

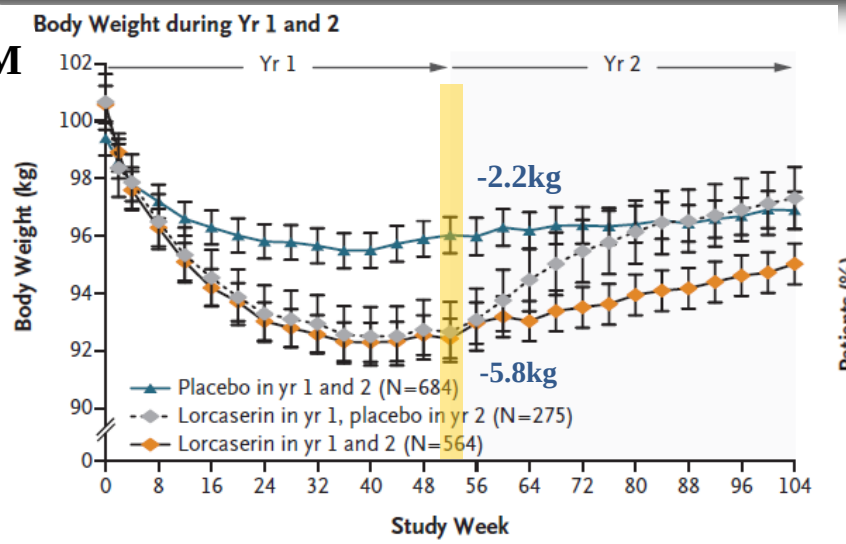
- No increase in rate of cardiac valvulopathy found after 2 years of lorcaserin treatment

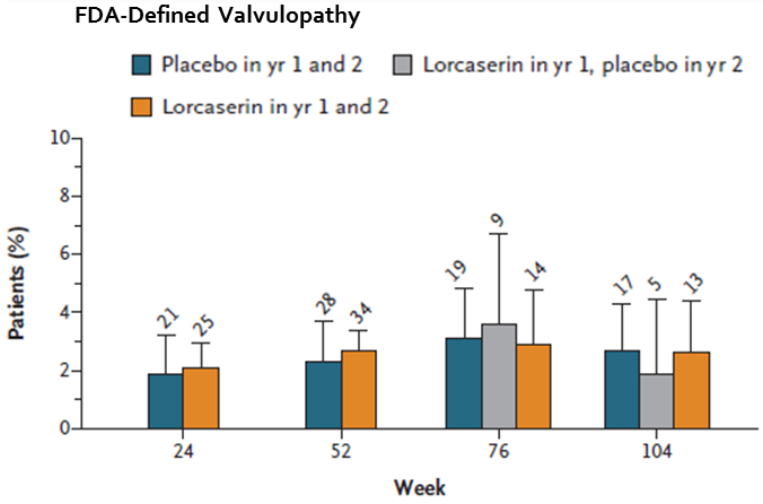
- Most common adverse reactions (≥5%): minimal, headache, dizziness, fatigue, nausea, dry mouth, and constipation

- Efficacy: More weight loss than placebo by ~4%

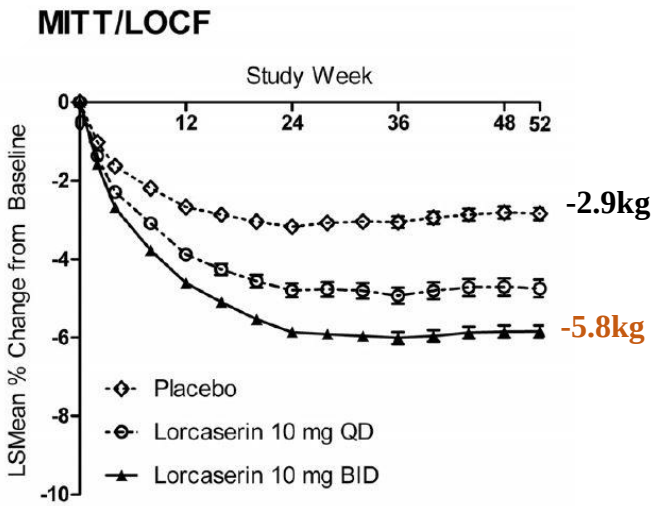
Lorcaserin: Phase 3 Trials

BLOOM

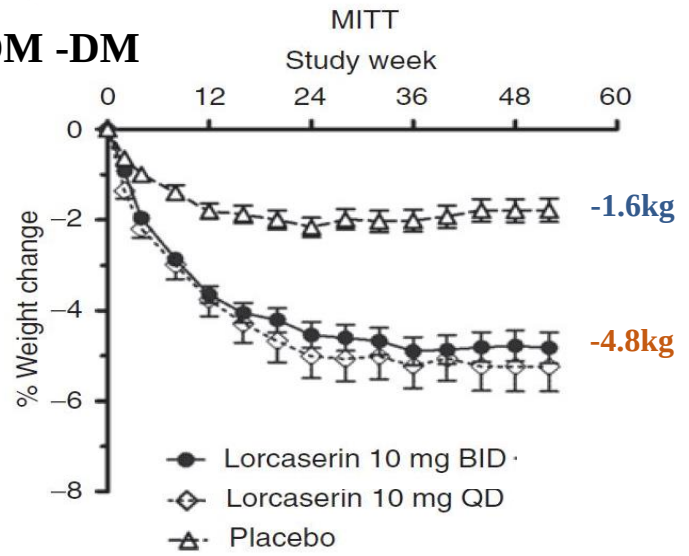




BLOSSOM

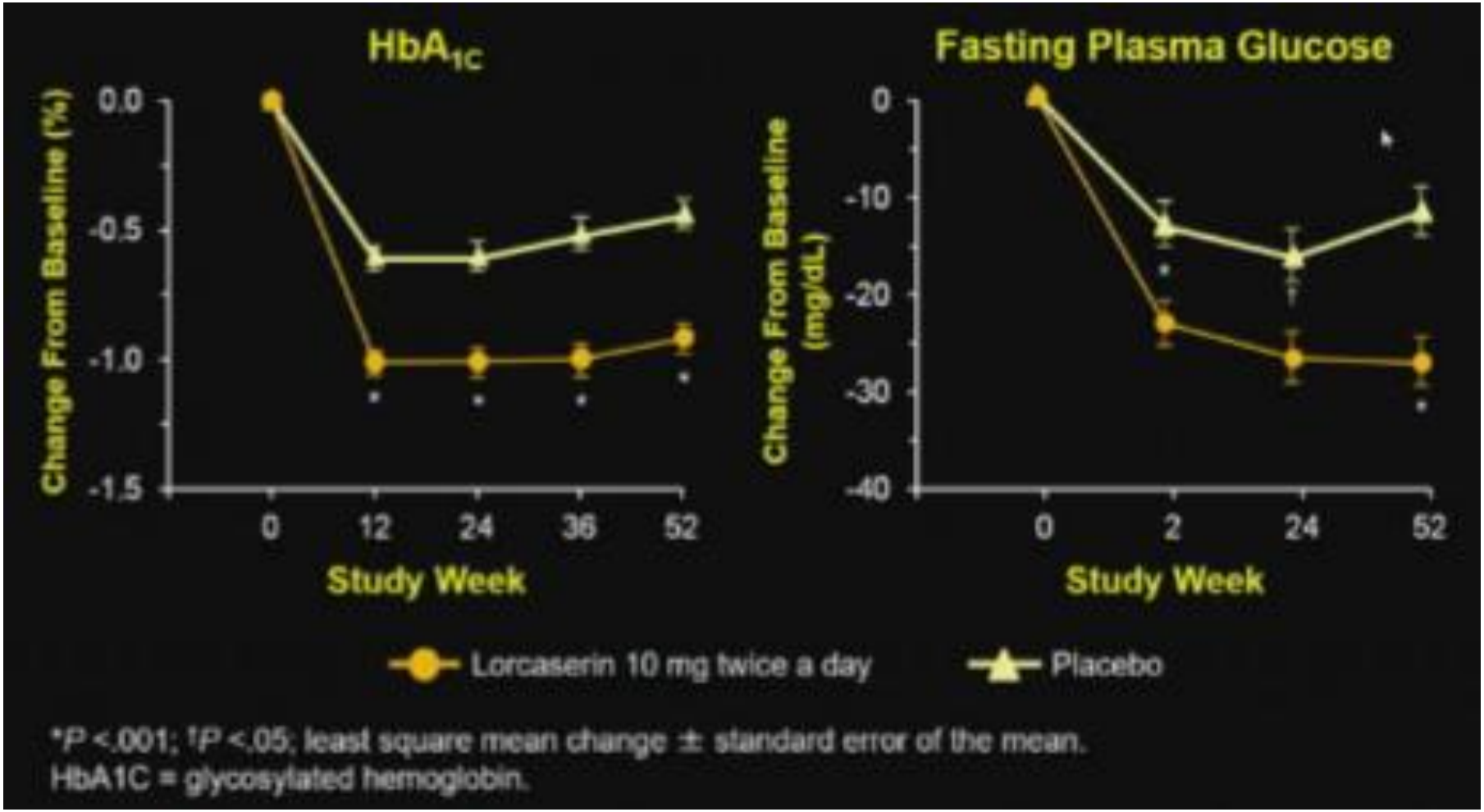


BLOOM -DM



N Engl J Med 2010;363:245-56. J Clin Endocrinol Metab, October 2011, 96(10):3067–3077 . Obesity (16 March 2012) | doi:10.1038/oby.2012.66

Lorcaserin: BLOOM *Diabetes Study*



O'Nell et al. Obesity 2012;20:1426-1436

Naltrexone/Bupropion (Contrave®)

- Mechanism:
  - Naltrexone: opioid antagonist
  - Bupropion: reuptake inhibitor of dopamine and norepinephrine
    suppress appetite and reward

- 1일 1정 (naltrexone 8mg + bupropion 90mg) 복용부터 시작
- 4주에 걸쳐 다음과 같이 증량

	Morning	Evening
제 1주 : 오전 1정		-
제 2주 : 오전 1정, 오후 1정		
제 3주 : 오전 2정, 오후 1정		
제 4주 및 이후 : 오전 2정, 오후 2정		

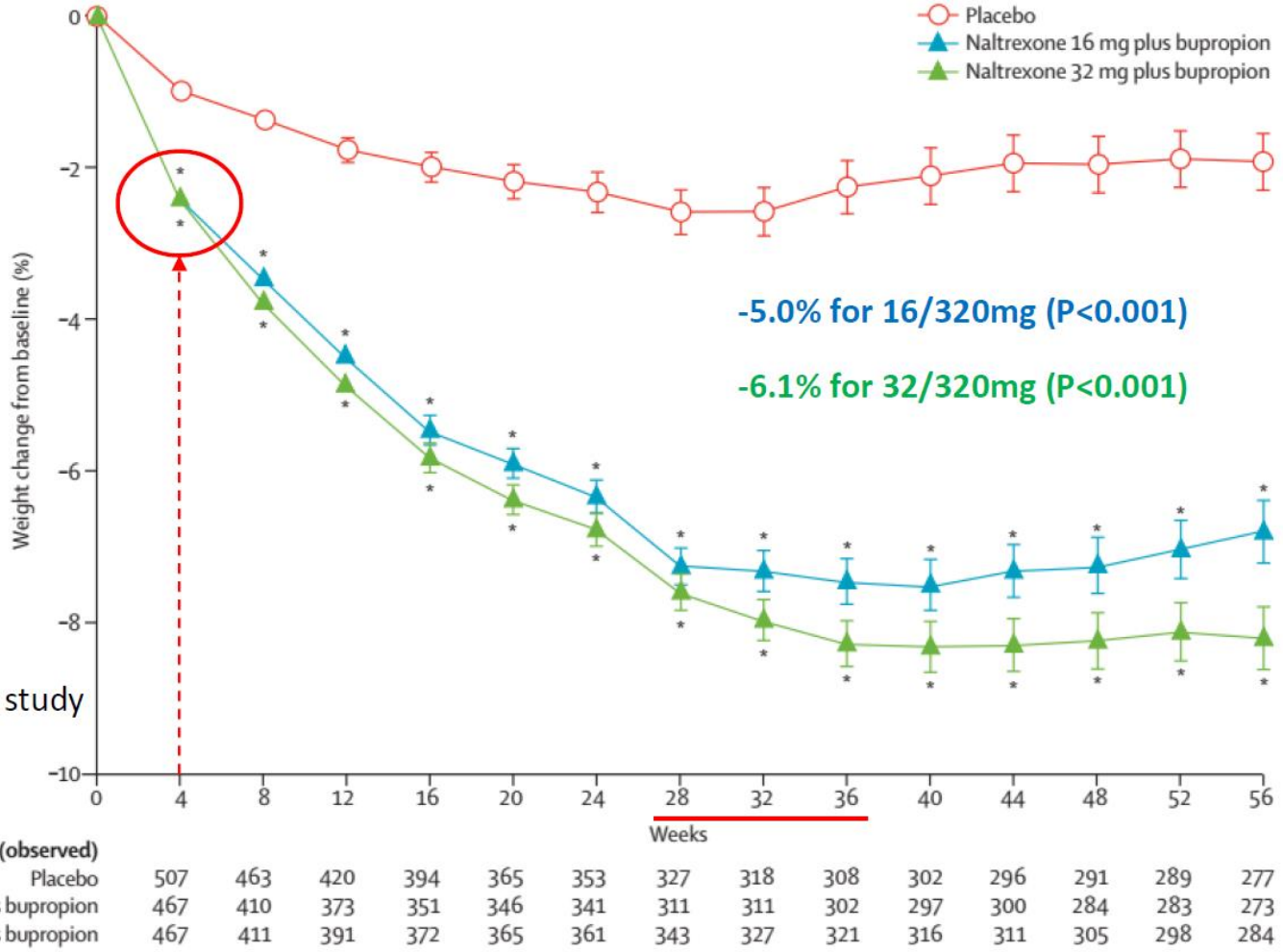
- 음식물과 함께 복용 권장 (고지방식이 제외)
- 유지용량 도달 후 12주 이내에 투여시점 대비 체중감량이 5% 미만인 경우 복용 중단

- Efficacy: More weight loss than placebo by 5~6%

Contrave Obesity Research I (COR-I)

N=1,742

Efficacy, safety, and tolerability of two doses of NB over 1yr



50% completed
Discontinuation early in the study
(by weeks 4 and 8)

Number of participants by visit (observed)	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56
Placebo	507	463	420	394	365	353	327	318	308	302	296	291	289	277
Naltrexone 16 mg plus bupropion	467	410	373	351	346	341	311	311	302	297	300	284	283	273
Naltrexone 32 mg plus bupropion	467	411	391	372	365	361	343	327	321	316	311	305	298	284

Lancet 2010;376:595-605

Naltrexone/Bupropion: side effects

- >10% : Nausea, constipation, headache, dizziness, vomiting
- 5-10%: Dry mouth, hot flush, insomnia, tremor, abdominal pain, tinnitus

- Contraindication
  - 조절되지 않는 고혈압, 발작 병력, 양극성장애, 섭식장애, MAO 억제제 투여중인 자(투여 중지 후 최소 14일 경과 후 복용), 폐쇄각녹내장, 마약 사용자, 알코올 금단, 신장애, 중증 간장애, 임신부, 수유부, 75세 이상 고령자
  - 18세 미만, 65세 초과: 안정성 미확립
  - 뇌혈관질환 기왕력자에서 주의, 자살충동 모니터링

Phentermine/Topiramate ER

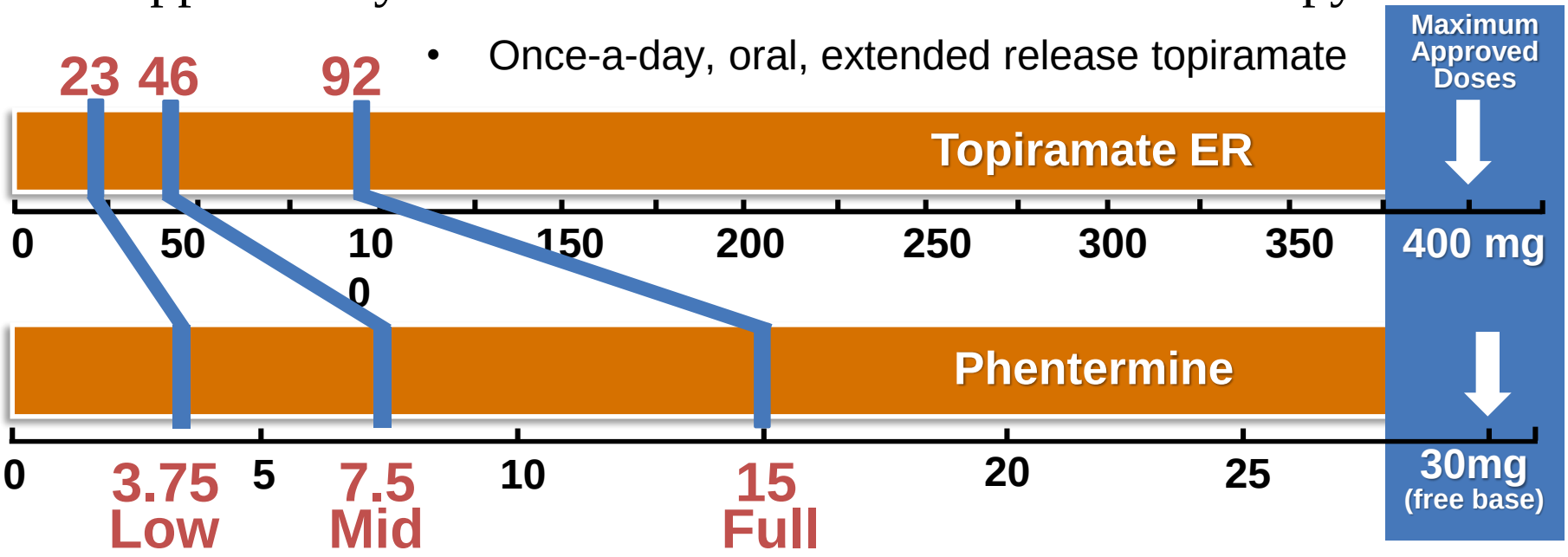
- Mechanism:
  - Appetite suppressant
  - Phentermine: Inhibit NE and Dopamine release
  - Topiramate: mechanism on weight loss is not known

- Side effects: SE of Phentermine plus: suicidal thoughts, acute glaucoma, mood/sleep disorders, cognitive impairment, paresthesia, metabolic acidosis, nephrolithiasis, Cr ↑

- Efficacy: More weight loss than placebo by 8-10%

Phentermine/Topiramate ER

- Approved by the FDA in 2012 as a combination therapy
  - Once-a-day, oral, extended release topiramate



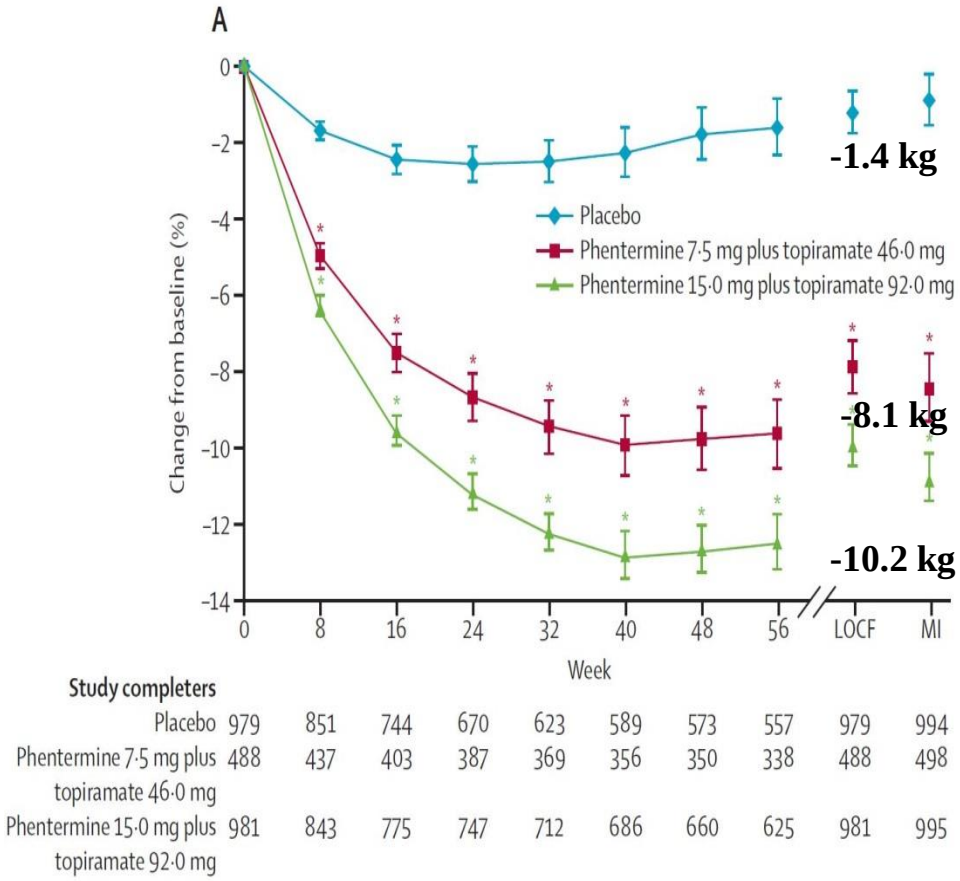
DOSING

- Begin with low dose for 2 wks phentermine 3.75/ topiramate ER 23
- Advance to treatment dose phentermine 7.5/ topiramate ER 46
- If <3% weight loss after 12 wks, either discontinue or advance to full dose phentermine 15/ topiramate ER 92 (transition dose phentermine 11.25/ topiramate ER 69 for 2 wks)
- If <5% weight loss after 12 wks on full dose, discontinue (take every other day for one wk)

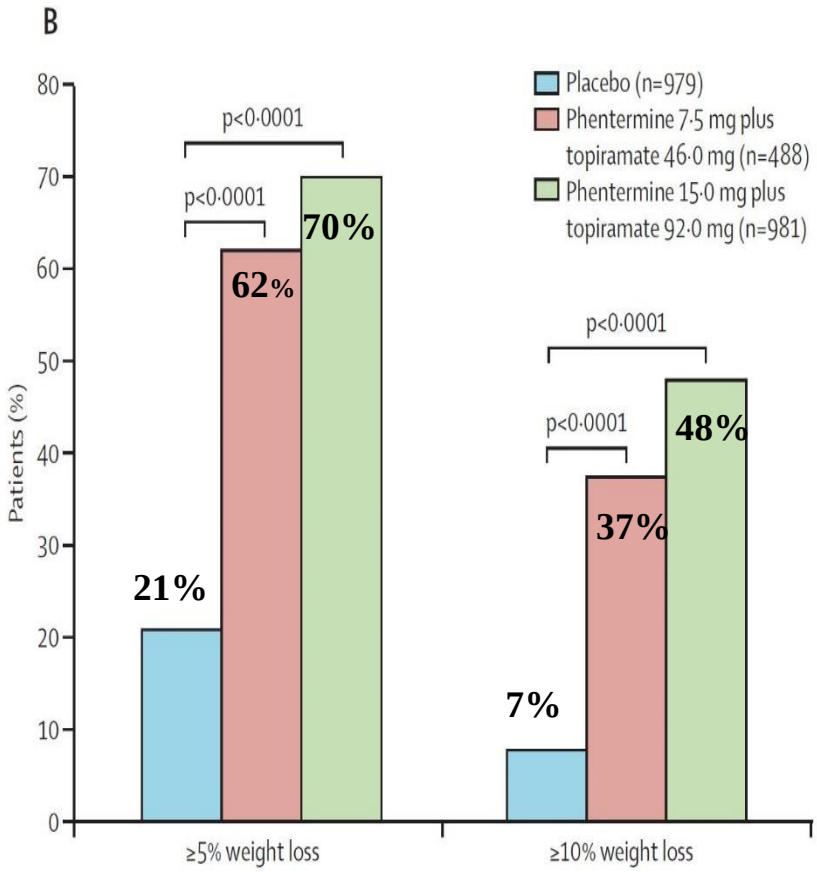
Phentermine and topiramate extended-release [package insert]. Mountain View, CA: Vivus; 2012.

Phentermine/Topiramate ER: efficacy & SE

CONQUER: **Effects of phentermine/topiramate ER on bodyweight over 56weeks**



Study completers										
Placebo	979	851	744	670	623	589	573	557	979	994
Phentermine 7·5 mg plus topiramate 46·0 mg	488	437	403	387	369	356	350	338	488	498
Phentermine 15·0 mg plus topiramate 92·0 mg	981	843	775	747	712	686	660	625	981	995

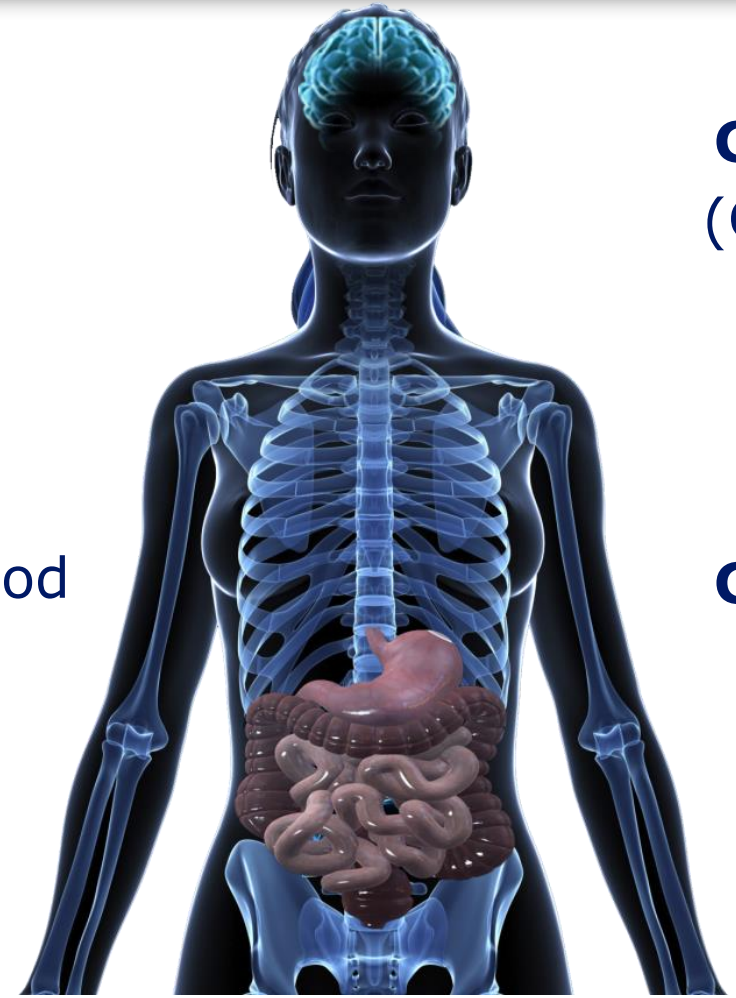


Lancet 2011; 377: 1341–52

Liraglutide 3.0mg (Saxenda®)
:Metabolic effects of GLP-1

Appetite[1]

- ↑ Satiety
- ↑ Fullness
- ↓ Hunger
- ↓ Prospective food consumption
- ↓ Energy intake



Glucose regulation[2]

(Glucose-dependent)

- ↑ Insulin secretion
- ↓ Glucagon secretion

Gastric effects[3,4]

- ↓ Gastric acid
- ↓ Gastric emptying

GLP-1, glucagon-like peptide-1

1. Flint *et al. J Clin Invest* 1998;101:515–20;
2. Nauck *et al. Diabetologia* 1993;36:741–4;
3. O'Halloran *et al. J Endocrinol* 1990;126:169–73;
4. Nauck *et al. Am J Physiol* 1997;273:E981–8

Liraglutide

- Approved by the FDA in 2014 for chronic weight management

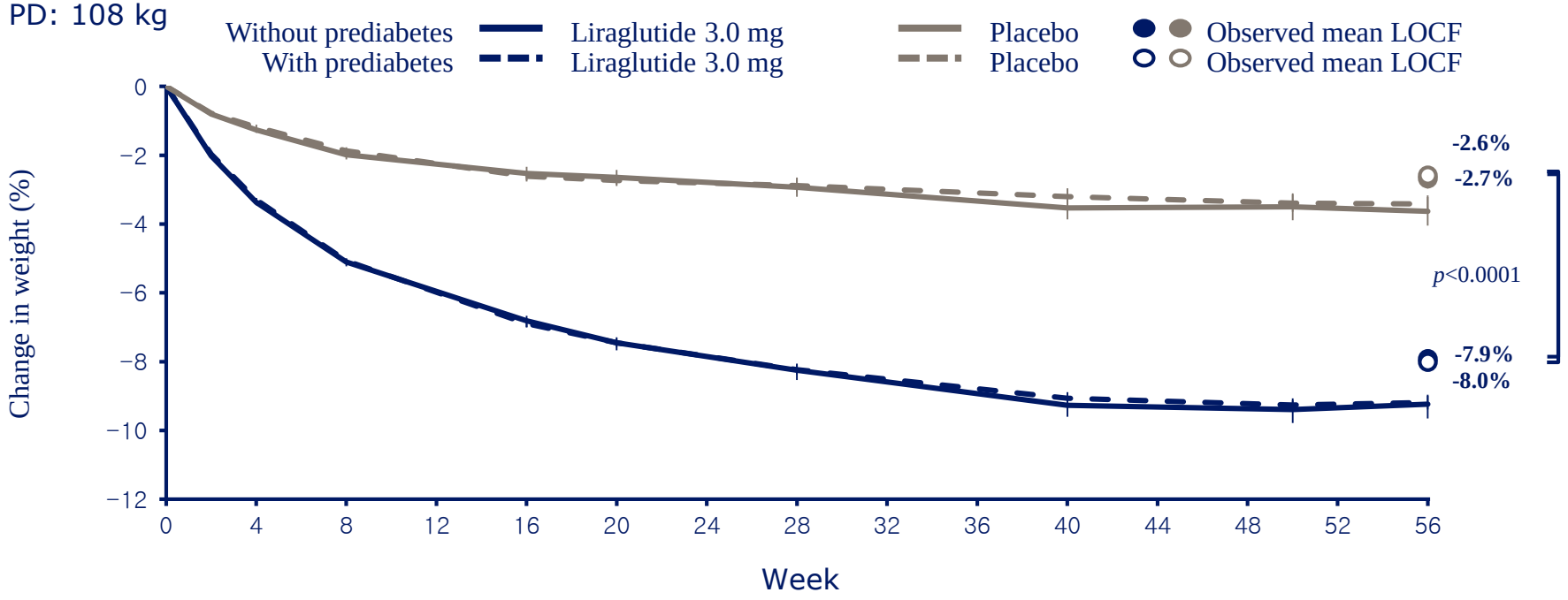
- **Long acting GLP-1 agonist**; **decreases appetite**

- Adverse reactions (≥5%) : **nausea, hypoglycemia, diarrhea**, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain and increased lipase activity.

- **Efficacy: More weight loss than placebo by ~7%**

Weight Loss with Liraglutide 3.0 mg

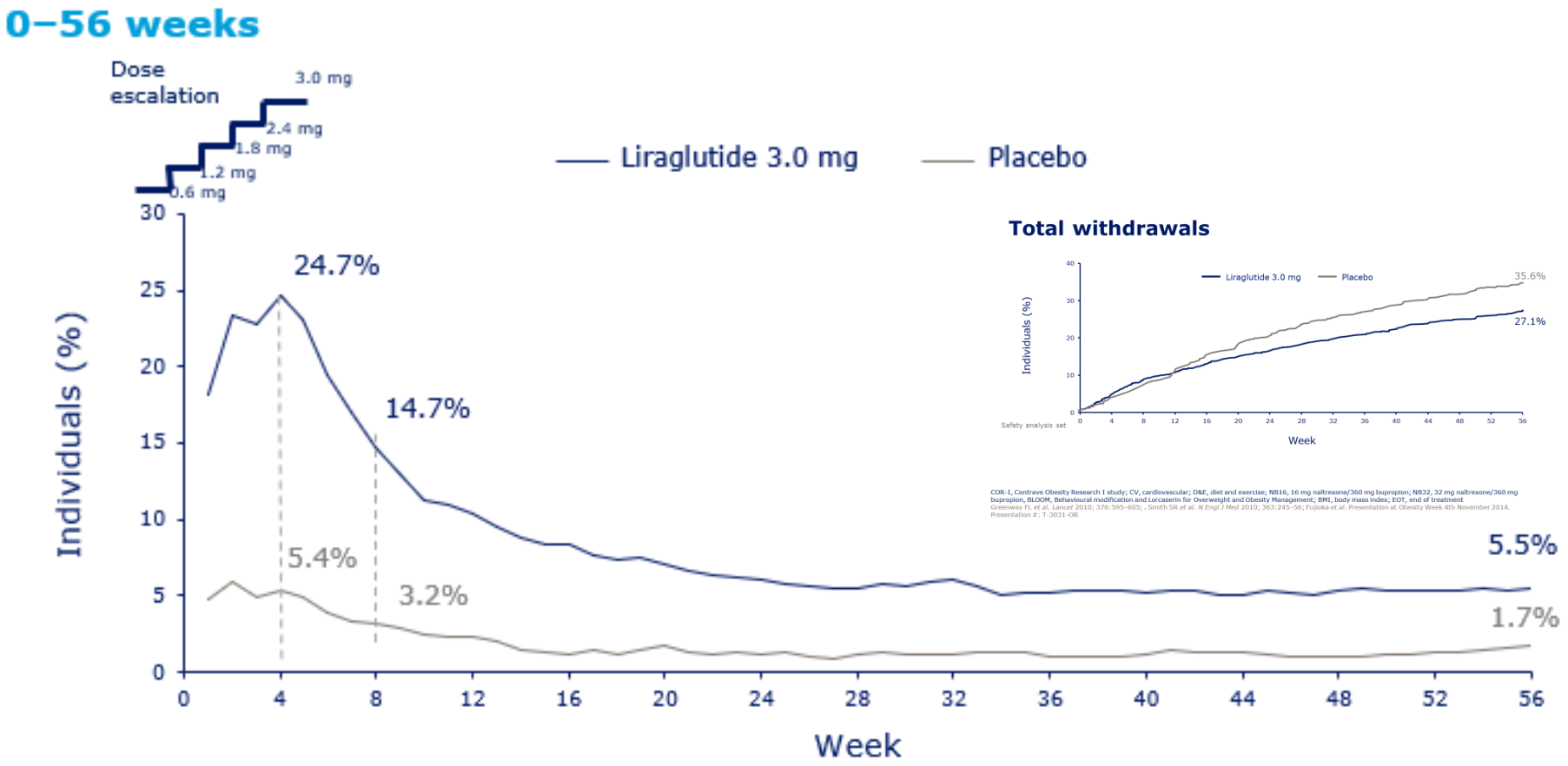
Mean baseline weight:
Without PD: 104 kg
With PD: 108 kg



FAS, fasting visit data only. Line graphs are observed means (±SE). Circles are observed means LOCF. Statistical analysis is ANCOVA.
FAS, full analysis set; LOCF, last observation carried forward; PD, prediabetes; SE, standard error

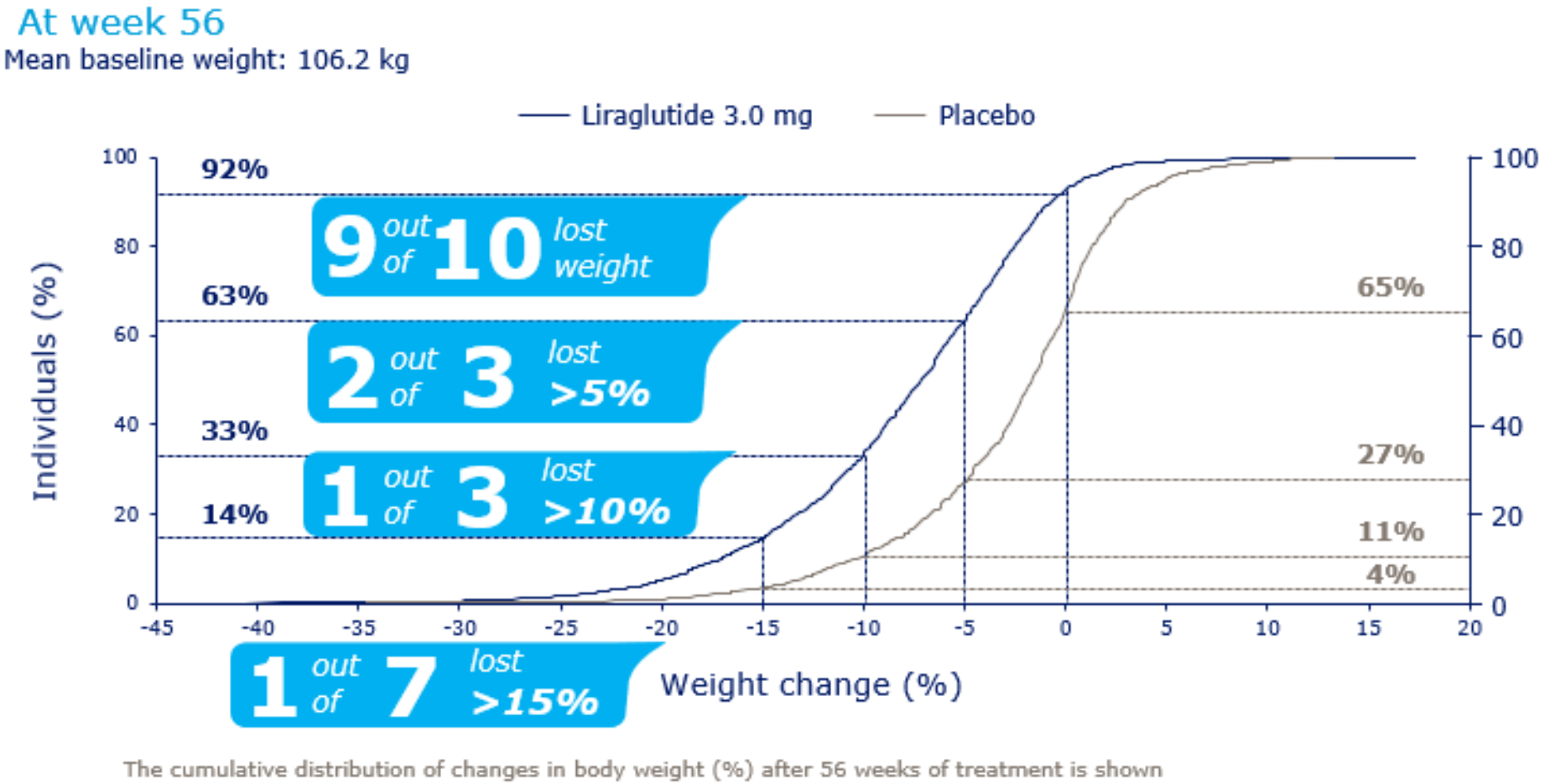
Greenway *et al*. Presentation at Obesity Week 4th November 2014. Presentation:T-3027-OR

Nausea diminishes after 8 – 12 weeks



Pi-Sunyer et al. N Engl J Med 2015;373:11–22

9 out of 10 lost weight with Saxenda®, with the majority losing ≥5%



The cumulative distribution of changes in body weight (%) after 56 weeks of treatment is shown

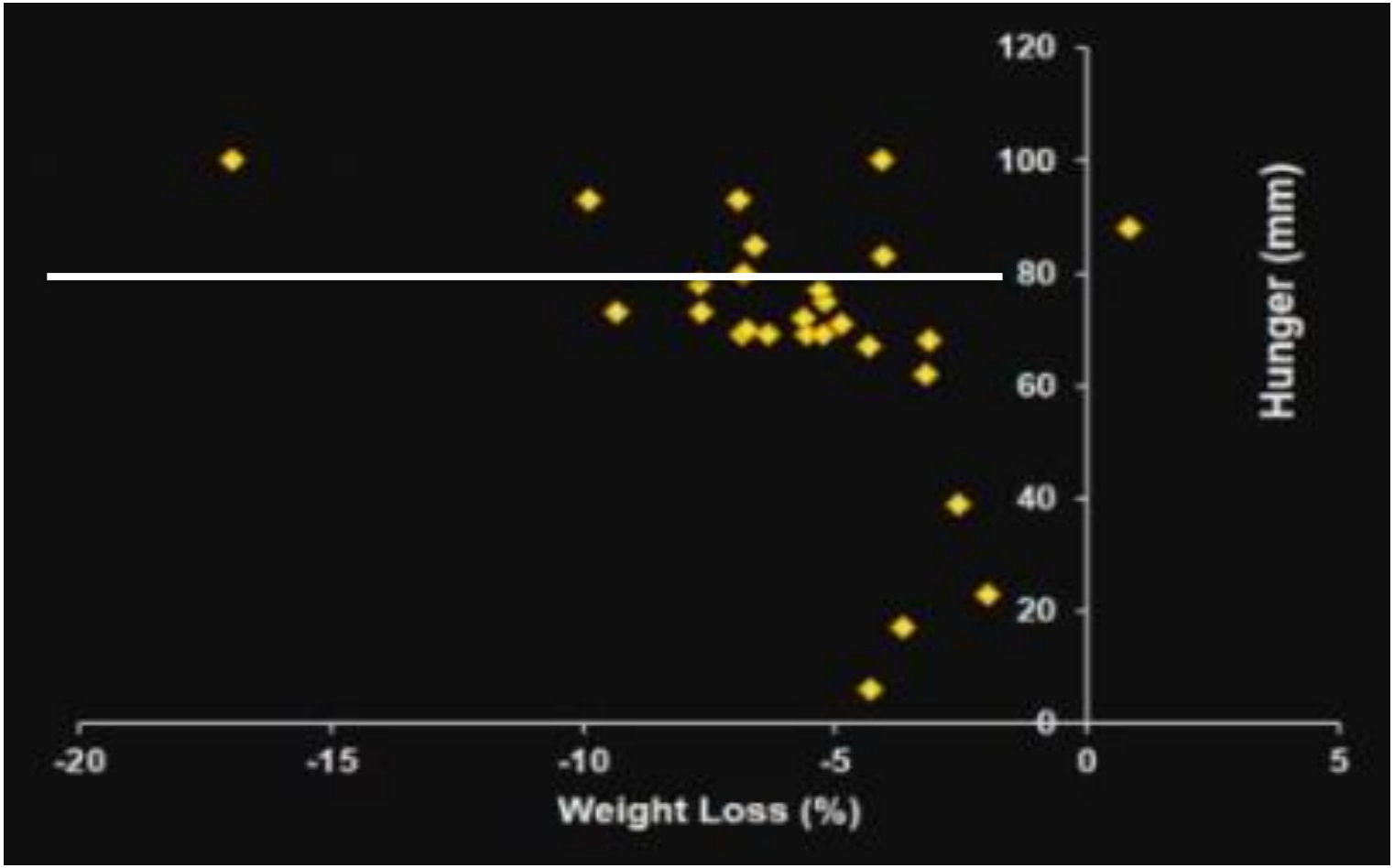
Pi-Sunyer et al. N Engl J Med 2015;373:11–22

Summary of Current Obesity Pharmacotherapy Options

Medication	Dosing	Long-term	Efficacy	Side effects	Cost
펜터민	Daily	No	~5%	++	1T; 800원 (1개월 24,000원)
제니칼	Meals	Yes	4-5%	++	1T: 1,000원 (1개월 90,000원)
큐시마	Daily	Yes	8-10%	+++	가격미정
벨빅	BID	Yes	4-5%	+	1T: 1,800원 (1개월 108,000원)
콘트라브	BID	Yes	5-7%	++	1T: 850원 (1개월 102,000원)
삭센다	Daily	Yes		++(+)	**1 pen: 10-14만원 (1개월 ~700,000원)**

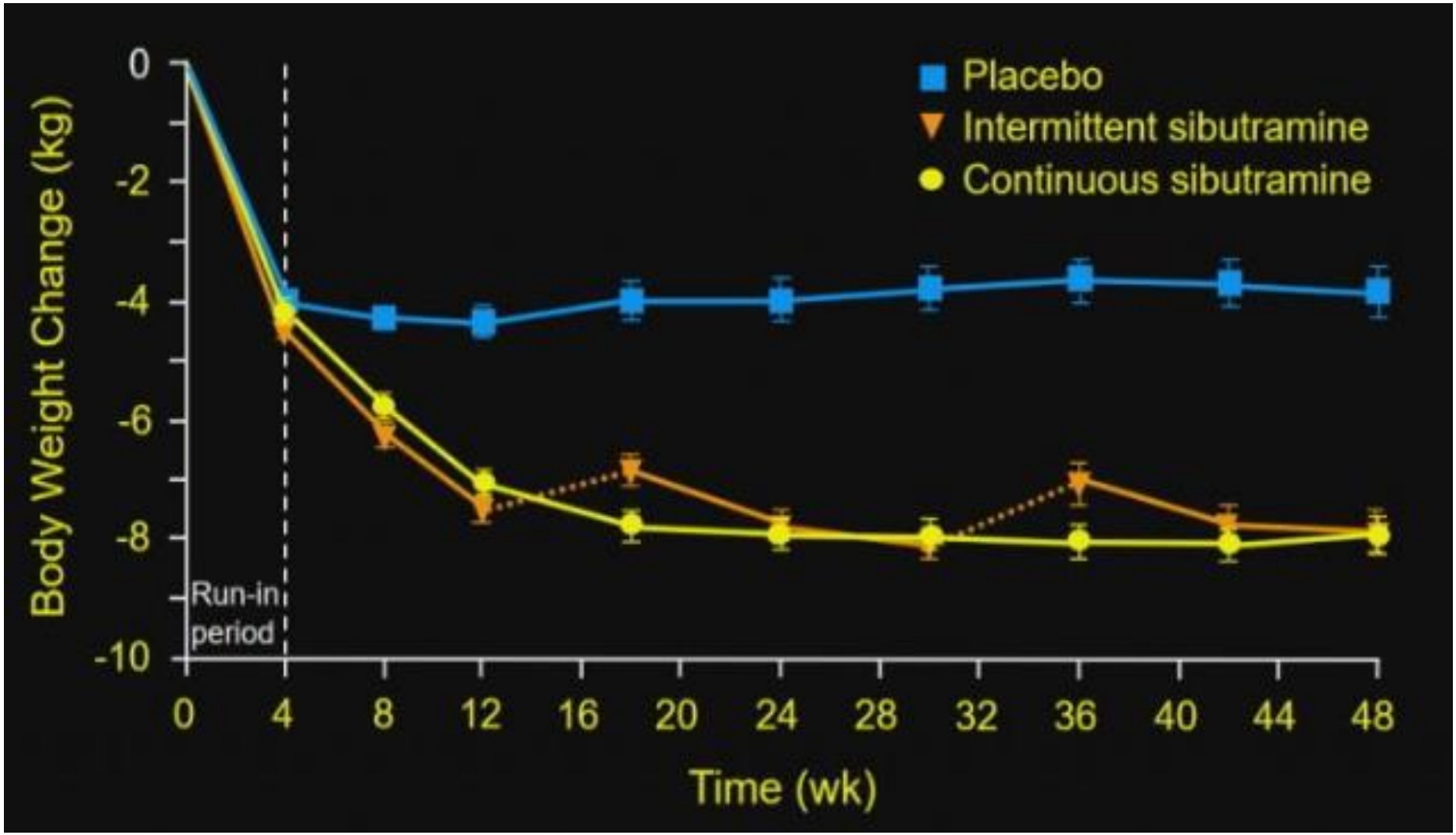
Variability in Response

Hunger predict weight loss response to Phentermine



Thomas et al. Obesity 2016;24:37-43

Continous vs Intermittent Therapy?

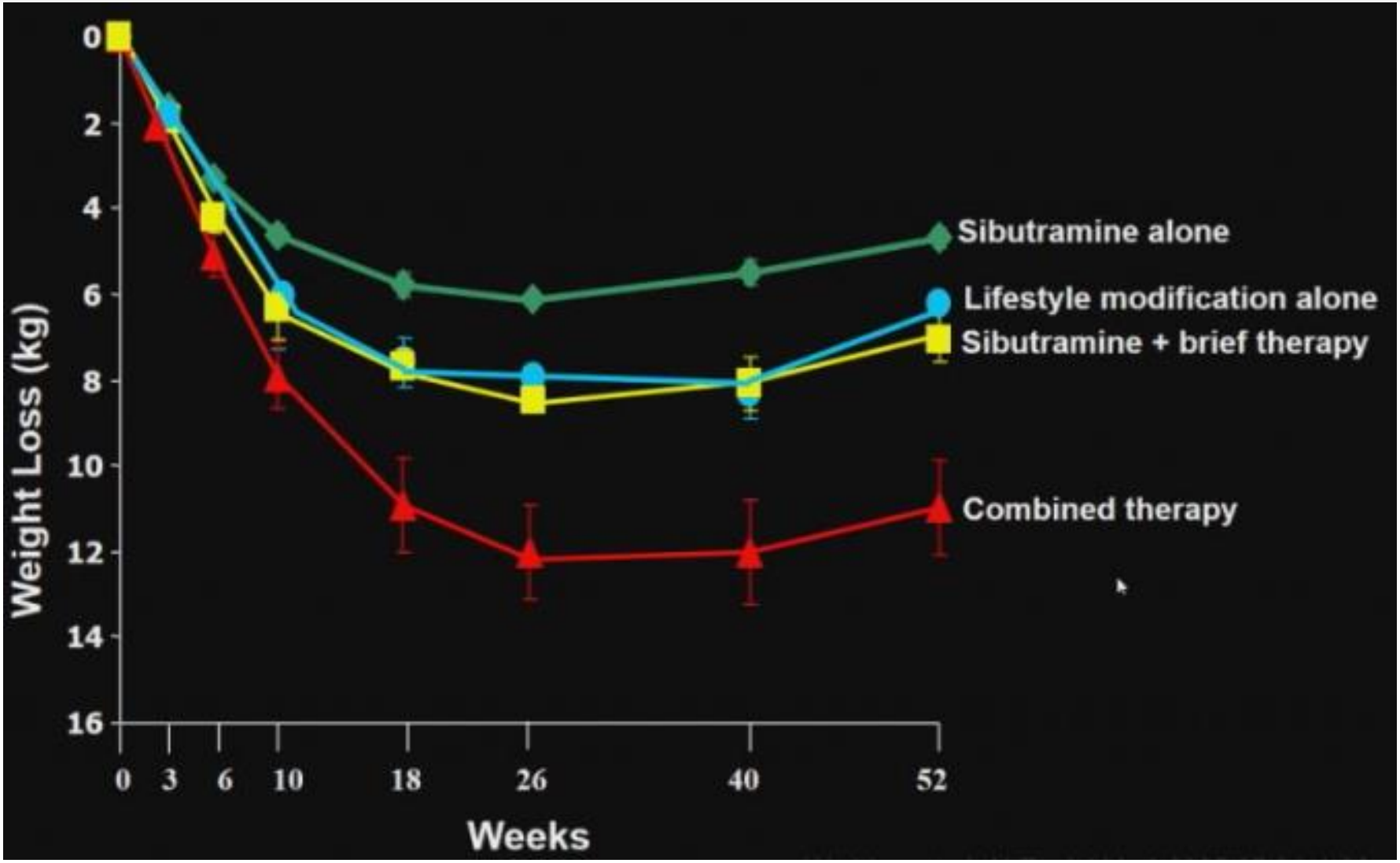


Wirth and Krause. JAMA 2001;286:1331

Medical Therapy Promotes Long-Term Weight Loss Maintenance

James WPT et al. Lancet. 2000;356:2119

Behavior + Medication



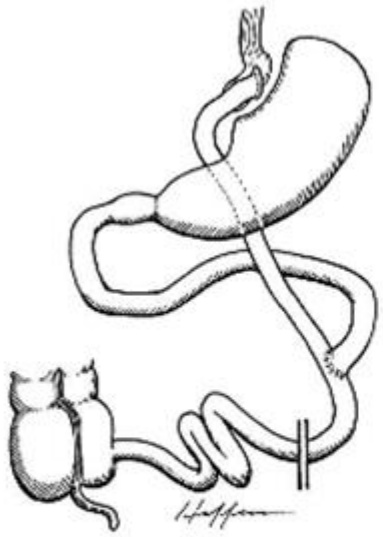
Wadden et al. N Engl J Med. 2005;35:2111-20

How Do I Use These Meds?

1. Use as an adjunct to **lifestyle modification**
2. Be Clear of **the goals**!
3. Use with the intention of using long-term but reassess **benefits** and **risks** regularly (**every 3 months**)
4. Consider **intermittent use**?
5. Consider **contraindications** or other comorbid conditions
6. Consider **eating-related behaviors** (hunger, cravings)?
7. What about combination therapies?

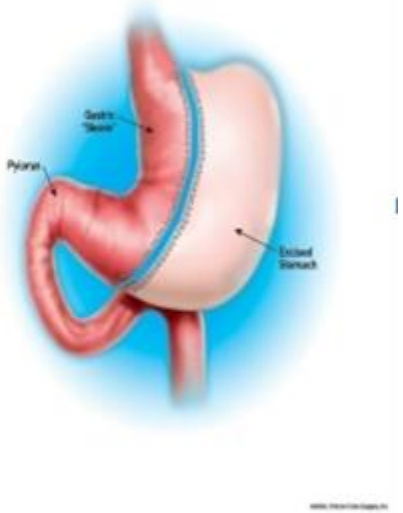
Cost is a major barrier !!!

Bariatric surgery: 현재의 수술 방법



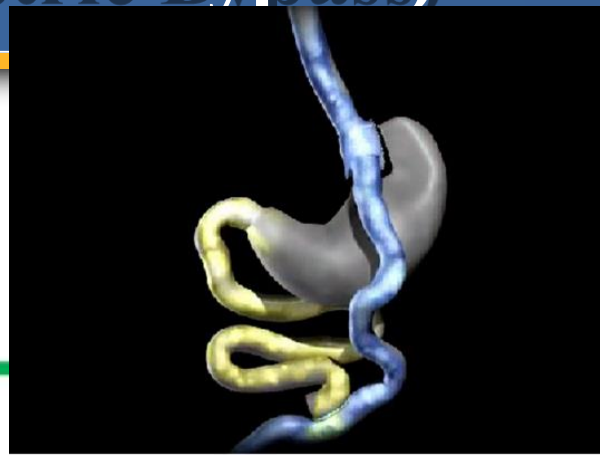
위 우회술

조절형 위밴드술

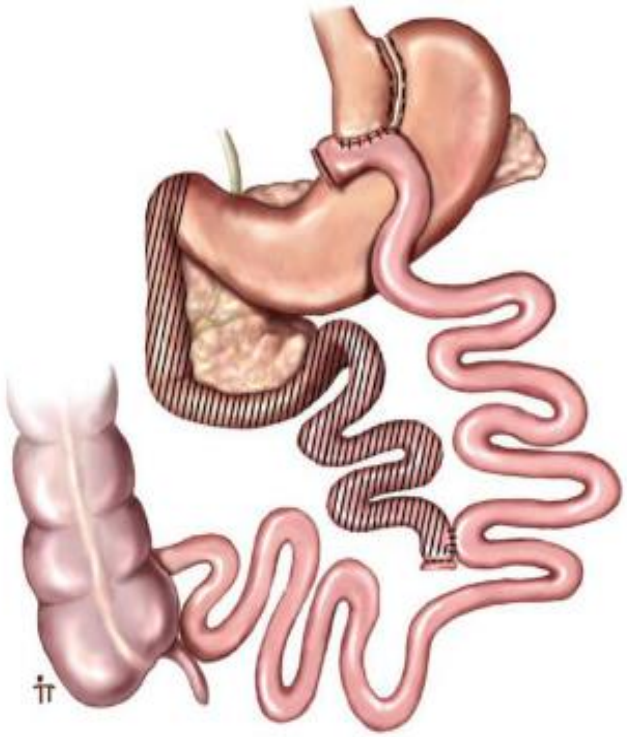


위소매절제술

복강경 위우회술 (Roux Y Gastric Bypass)



Three major components of Roux-en Y gastric bypass



- Restricted gastric volume/ excluding fundus
- Expedited access to distal jejunum and ileum
- Bypassing duodenum and upper jejunum

복강경 위우회술 (Roux Y Gastric Bypass)

- **Gold standard bariatric procedure**
- **Excellent long term weight loss**
- **Superior to purely restrictive procedures**
- **Multiple mechanisms**
  - Restriction-primary mechanism
  - Dumping (enteroglucagon)
  - Malabsorption?

Most common procedure in US

Difficult in gatric surveillance

조절형 위밴드술(Adjustable Gastric Banding)

- **Purely restrictive**
- **Adjustable stoma size via SQ port**
- **Simple, laparascopic**
- **Advantage**
  - Safe
  - Low short-term complication
- **Disadvantage**
  - Foreign body reaction
  - High long-term complication

위소매 절제술(Sleeve Gastrectomy)

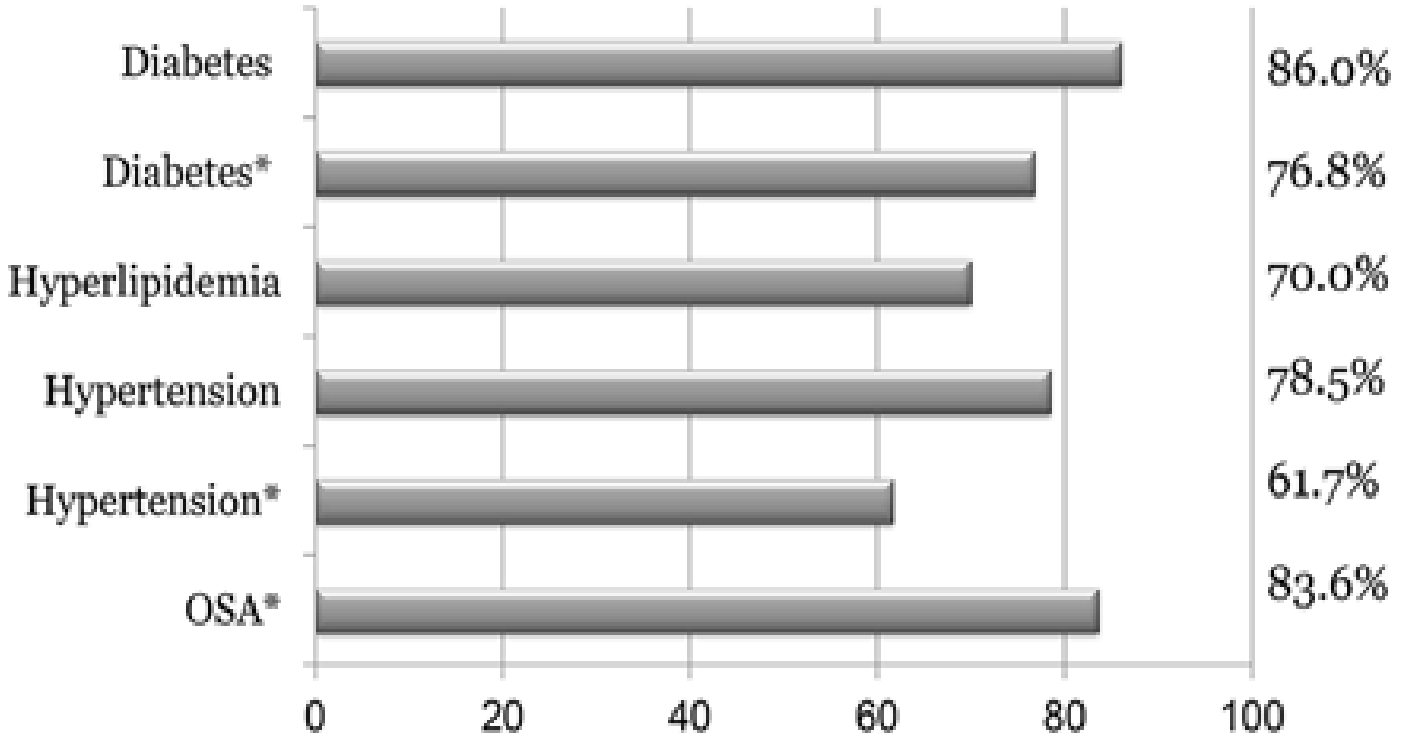
- **Primarily restrictive**
- **Additional Mechanism**
- **Less invasive than GBP**
- **More invasice than AGB**
- **Future definitive surgery**
- **Advantage**
  - Safe
  - Surveillance for gastric cancer
- **Disadvantage**
  - Permanent gastric resection
  - Gastroesophageal reflux

Typical Bariatric Surgery: Weight loss success rate

Operation name	Procedure type	Weight loss success rate (%)
Adjustible gastric banding	Pure Restrictive	50～60
Roux-en Y gastric bypass	Hybrid (restrictive & mal-absorptive)	70～80
Sleeve gastrectomy	Primarily Restrictive	60～70

The Korean Journal of Helicobacter and Upper Gastrointestinal Research, 2017;17(2):72-78
N Engl J Med 2007;357:741-52

Effects of Bariatric Surgery on Medical Complications of Obesity

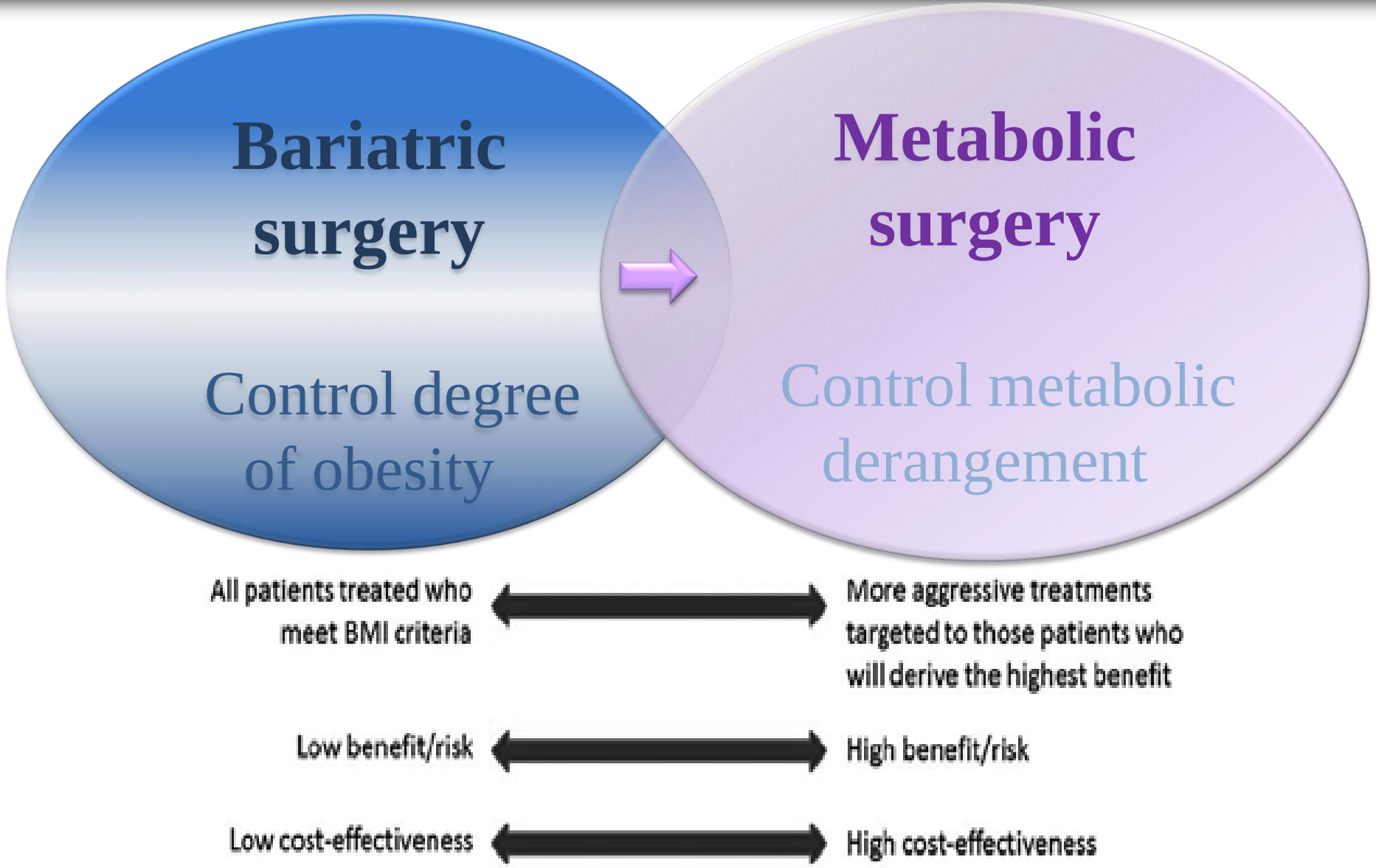


*, remission (otherwise improvement)
OSA, Obstructive sleep apnea

Bariatric surgery: a systematic review and meta-analysis

JAMA 2004;292:1724-1737

Paradigm shift: Bariatric surgery to Metabolic surgery



Conclusions

Overall Treatment Strategy

- Self-directed Lifestyle Change
- Professionally-directed Lifestyle Change
- Add Medications
- Weight Loss Surgery
- Post-surgical Combination Therapies

비만치료의 최신지견

감 사 합 니 다