The Obesity Conundrum

Practical Approaches for Patients Who Are Obese and "Well", Obese with Risk Factors, and Obese and "Sick"

THURSDAY, NOVEMBER 14, 2013

COURSE CHAIR

Ken Fujioka, MD

This continuing medical education activity is sponsored by VINDICO medical education

This activity is supported by an educational grant from novo nordisk®

Held in conjunction with obesityweek 2013
Where Science and Treatment Meet
November 11-16, 2013 • Atlanta, GA

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Welcome

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Correlation Between Gut and Weight in the Obese Patient: How the Human Body Regulates Body Weight in the Obese

Ken Fujioka, MD
Director, Nutrition and Metabolic Research
Division of Diabetes and Endocrinology
Scripps Clinic
San Diego, CA

Regulation of Energy Intake

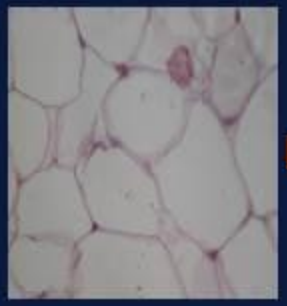
Peripheral Signals

Hypothalamic Pathways

Higher Cortical Centers

Arcuate Nucleus

PVN, LHA, DMN



LEPTIN

GHRELIN

CCK

GLP-1

PEPTIDE YY

AMYLIN

INSULIN

LepR

GSHR

Y2R

LepR

GLPR1

μ-OR

5HT2c

NPY
AgRP

POMC

Orexigenic Pathway

NPY

Y1R
Y5R

AGRP

MC4R

αMSH

MCH1R

MCH

BDNF

NTRK2

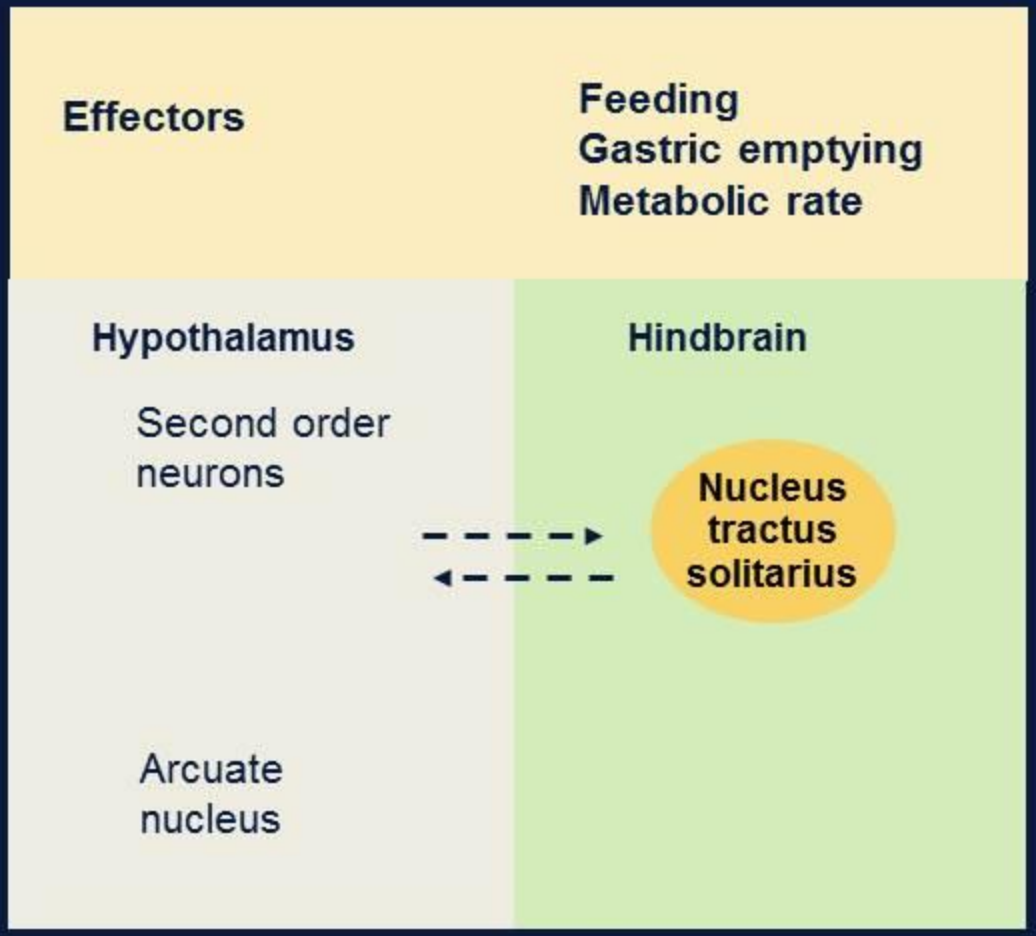
Anorexigenic Pathway

Courtesy of WT Garvey, 2013.

Patient A: Back Injury

- Was 155 pounds and doing well
  - Exercises regularly
  - Eats a reasonably healthy diet
- Has a back injury
  - Cannot exercise
  - Sleep is disrupted
  - Eating habits change for the worse
  - Stays at home while recovering from back surgery
- Gains 45 pounds

Two Pathways That Direct Obesity



Leptin Insulin
Adiposity Signals

PPY GLP-1
PP OXM
Satiety Peptides

Ghrelin
Hunger Signals

Vagal Afferents

Adapted from Badman MK, et al. *Science*. 2005;307(5717):1909-1914.

Patient A: Back Injury

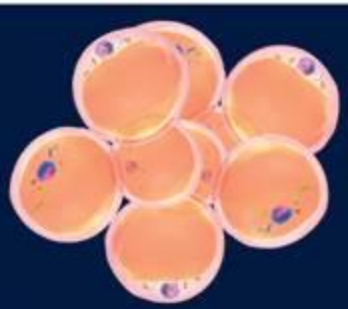
- 45-year-old man
- Height is 5 feet 9 inches
- Weight went from 155 lbs to 200 lbs
- BMI changed from 23.5 kg/m^2 to 31 kg/m^2

- Is the patient going to go on to diabetes and be metabolically sick?
  - What predicts this?

Obese Healthy

- Not all individuals who gain weight and become obese will go on to have metabolic abnormalities such as diabetes or metabolic syndrome
  - MHO = Metabolically Healthy Obese
  - OMH = Obese Metabolically Healthy
  - Obese well
  - Obese without cardiometabolic risk factors
- Remember this is a minority of obese patients

Pathophysiology



Inflammatory State
↑ Free Fatty Acids
Insulin Resistance

Low Number of Larger
Hypertrophic Adipocytes

Chronic Nutrition Overload

Increase in Adipocyte Mass

No Inflammation
No ↑ Free Fatty Acids
No Insulin Resistance

High Number of
Small Adipocytes

NHANES 1999-2004

- Evaluated 6 parameters for metabolic disease
  - Blood pressure
  - Triglycerides
  - Fasting glucose
  - C-reactive protein
  - Low HDL-C
  - Insulin resistance
    - Fasting insulin x FBS/22.5

Wildman RP, et al. *Arch Int Med*. 2008;168:1617-1624.

NHANES Study: 31.7% Metabolically Healthy Obese

- Metabolically healthy: 1 or fewer cardiometabolic abnormalities
- Metabolically unhealthy: 2 or more cardiometabolic abnormalities
- 5440 participants 20 years or older
- Excluded if they had known CV disease

- 31.7% of the obese (BMI > 30 kg/m^2) were metabolically healthy
  - 71% white, 11% African American, 18% other

Wildman RP, et al. *Arch Int Med*. 2008;168:1617-1624.

Metabolically Healthy but Obese: Phenotype in African Americans

- 126 obese (BMI ≥ 30 kg/m^2) with no known CV disease
- Definition of Metabolically Healthy and Obese
  - HDL-C ≥ 40 mg/dL
  - Absence of diabetes (random < 200 mg/dL and fasting < 126 mg/dL)
  - Blood pressure 140/90 mm Hg or better
- 28.5% Metabolically Healthy and Obese
  - Average BMI 44 kg/m^2 for both Healthy and Unhealthy

Cherqaoui R, et al. *J Clin Hypertens* (Greenwich). 2012;14(2)92-96.

Discordant Risk: Overweight and Cardiometabolic Risk in Chinese

- 2009 China Health and Nutrition Survey
- 8,233 adults (age 18 to 98)
- BMI ≥ 23 kg/m^2 ("Asian cut point")
  - Prediabetes or diabetes (A1C > 5.7%)
  - High C-reactive protein ≥ 3mg/L
  - Blood pressure ≥ 130/85 mm Hg
  - Triglycerides ≥ 150 mg/dL
  - Low HDL-C < 40 mg/dL for men and < 50 mg/dL for women
- 21.7% were metabolically healthy
  - Could not have any of the above
  - 66.8% of BMI < 23 kg/m^2 metabolically healthy

Gordon-Larsen P, et al. *Obesity*. 2013;21(1)166-174.

Metabolic Obesity and Phenotypic Obesity in Asian Indians

- 2350 Asian Indian adults
- BMI ≥ 25 kg/m^2
- Metabolically healthy was not having metabolic syndrome (any 3 of the following):
  - FBS ≥ 100 mg/dL
  - Blood pressure ≥ 130/85 mm Hg
  - Triglycerides ≥ 150 mg/dL
  - Low HDL-C < 40 mg/dL for men and < 50 mg/dL for women
  - Waist ≥ 90 cm for men; ≥ 80 cm for women
- 13.3% metabolically healthy
  - These patients could have had 1 or 2 of the above

Geetha L, et al. *J Diabetes Sci Technol*. 2011;1;5(2)439-446.

Metabolically Healthy Obese Phenotype in Hispanic Participants (IRAS Family Study)

- 1054 Hispanic adults (38% obese)
- Metabolically Healthy BMI ≥ 30 kg/m^2
  - One or fewer cardiometabolic risk factors
  - (BS ≥ 100 mg/dL, BP ≥ 130/85 mm Hg, Low HDL-C (< 40 mg/dL and <50 mg/dL), TG ≥ 150 mg/dL, CRP ≥ 3, HOMA-IR > 5.13
- 19% of the Obese met the criteria of Metabolically Healthy
  - When you looked at the % of lean and fat tissue between MHO and metabolically unhealthy they were the same

Samaropoulos XF, et al. A metabolically healthy obese phenotype in Hispanic participants in the IRAS family study. *Obesity* (Silver Spring). 2013 Feb 18. [Epub ahead of print]

Summary

- There is good fat and bad fat
- Large fat cells are not good for metabolic health
- Small fat cells are a good thing for metabolic health
- There is a large variation in how different races will handle weight gain
  - Increase in number of fat cells
  - Some races do not have the ability to expand the fat mass and end up with large hypertrophied adipocytes

Characterizing the Obesity Population

- **Obese and "Well"**: Individuals who carry excess weight, but who do not have any comorbidities or risk factors for comorbid conditions and who do not experience any impairments in their daily feeling or functioning.

- **Obese with Risk Factors**: Individuals who carry excess weight who do not yet have any comorbidities, but who have measurable risk factors for comorbid conditions and/or impairments to their daily feeling or functioning.

- **Obese and "Sick"**: Individuals who carry excess weight and who have one or more obesity-attributable comorbidities and impairments to their daily feeling or functioning.

The George Washington University School of Public Health and Health Services. Obesity Drug Outcome Measures. 2012.

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MEDICINE & DENTISTRY
UNIVERSITY OF ALBERTA

Across the Spectrum: Characterizing the Obesity Population to Help Guide Treatment

Arya M Sharma, MD, PhD, FRCPC

Research Chair for Obesity Research & Management

University of Alberta

Medical Director

Alberta Provincial Obesity Program

Edmonton, AB, Canada

www.drsharma.ca

“Ideal Weight”

Synonymous with “desirable weight”

First introduced in 1943 by the Metropolitan Life Insurance Company (MLIC) standard height-weight tables for men and women

Metropolitan Life Insurance Company (MLIC) Standard Height-Weight Tables for Women

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HEIGHT AND WEIGHT GOALS			
Women			
Height	Small frame	Medium frame	Large frame
4'10"	102-111 lbs	109-121 lbs	113-131 lbs
4'11"	103-113	111-123	120-134
5'0"	104-115	113-126	112-137
5'1"	106-116	115-129	125-140
5'2"	108-121	118-132	128-143
5'3"	-124	121-135	14
5'4"	-127	124-141	13
5'5"	17-130	127-141	137-1
5'6"	120-133	130-144	140-1 9
5'7"	123-135	133-147	143-163
5'8"	126-139	136-150	146-167
5'9"	129-142	139-158	149-170
5'10"	132-145	142-156	152-176
5'11"	135-148	145-159	155-176
6'0"	138-151	148-162	158-179

BMI=19.3 kg/m^2

BMI=25.6 kg/m^2

Anatomical Terms Used to Describe Obesity (Historical)

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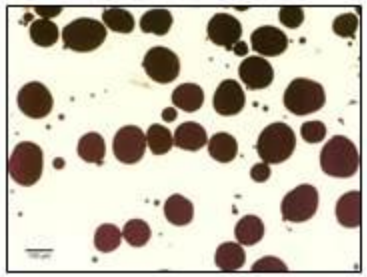
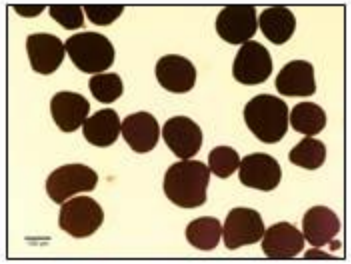
- Cellular
  - hyperplastic
  - hypertrophic





Sharma AM, Kushner RF. *Int J Obes* (Lond). 2009;33(3):289-295.

Anatomical Terms Used to Describe Obesity (Historical)

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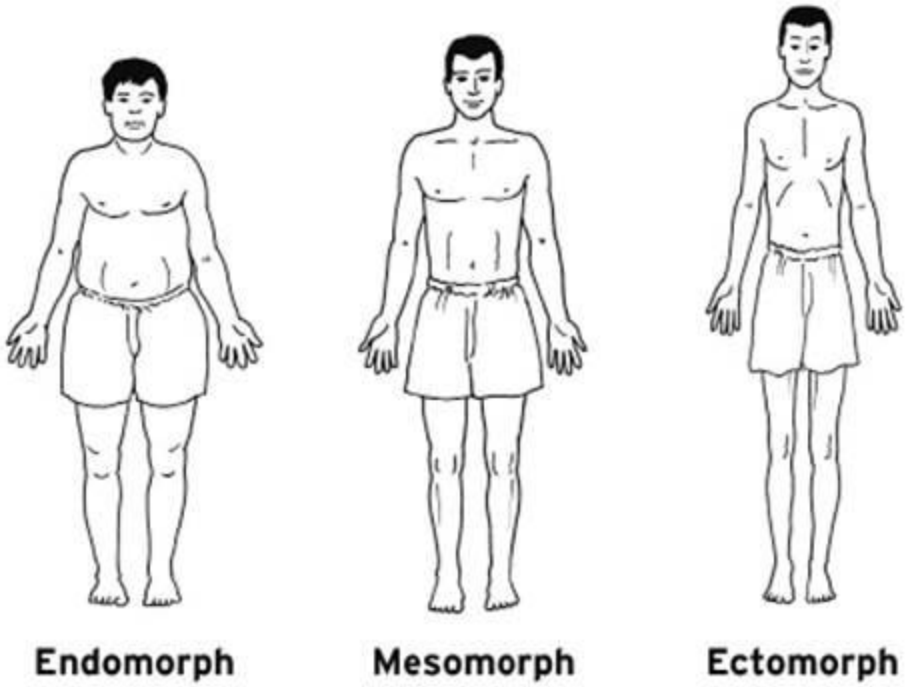
University of Alberta

- Cellular
  - hyperplastic
  - hypertrophic
- Somatotypes
  - ectomorphic,
  - mesomorphic
  - endomorphic

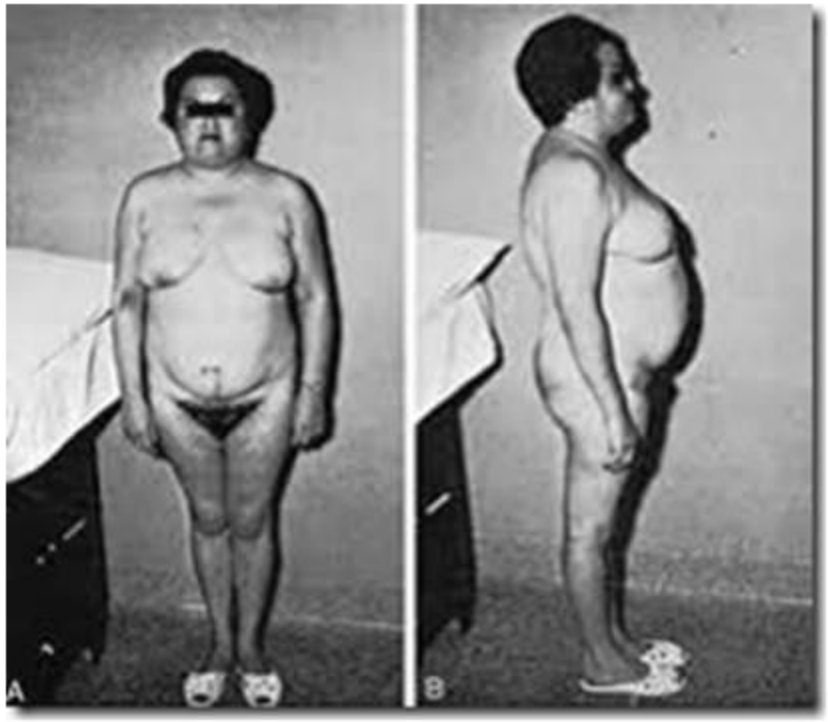


Sharma AM, Kushner RF. *Int J Obes* (Lond). 2009;33(3):289-295.

Anatomical Terms Used to Describe Obesity (Historical)

Faculty of Medicine & Dentistry
University of Alberta

- Cellular
  - hyperplastic
  - hypertrophic
- Somatotypes
  - ectomorphic,
  - mesomorphic
  - endomorphic
- Body segment
  - central
  - peripheral



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Anatomical Terms Used to Describe Obesity (Historical)

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University of Alberta

- Cellular
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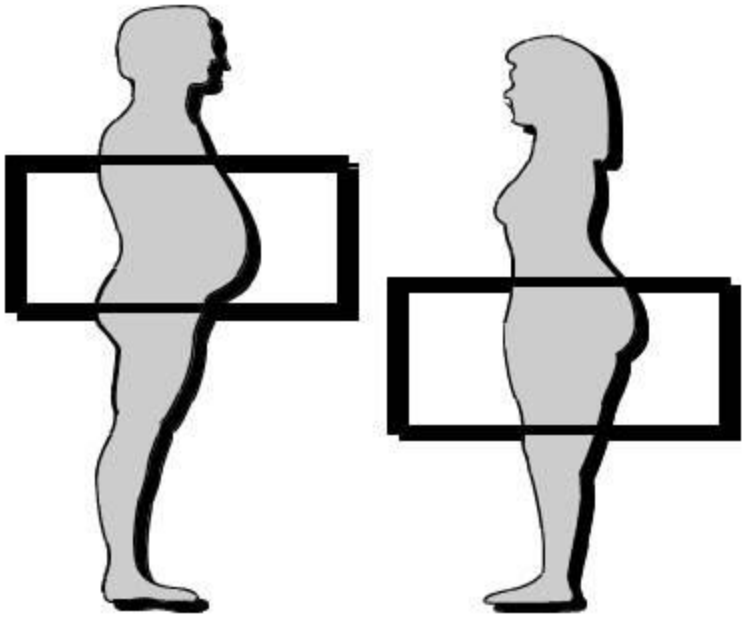
- Somatotypes
  - ectomorphic,
  - mesomorphic
  - endomorphic
- Body segment
  - central
  - peripheral
- Distribution pattern
  - android
  - gynoid



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Anatomical Terms Used to Describe Obesity (Historical)

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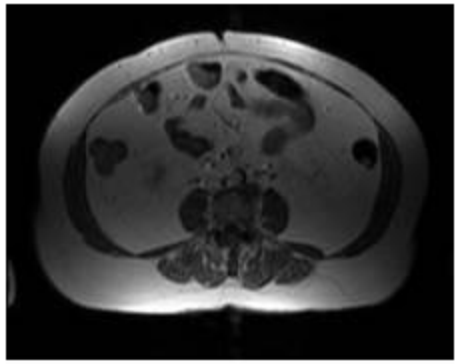
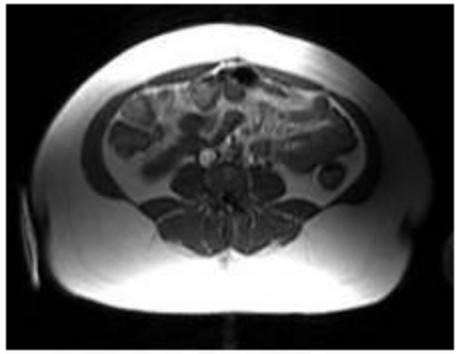
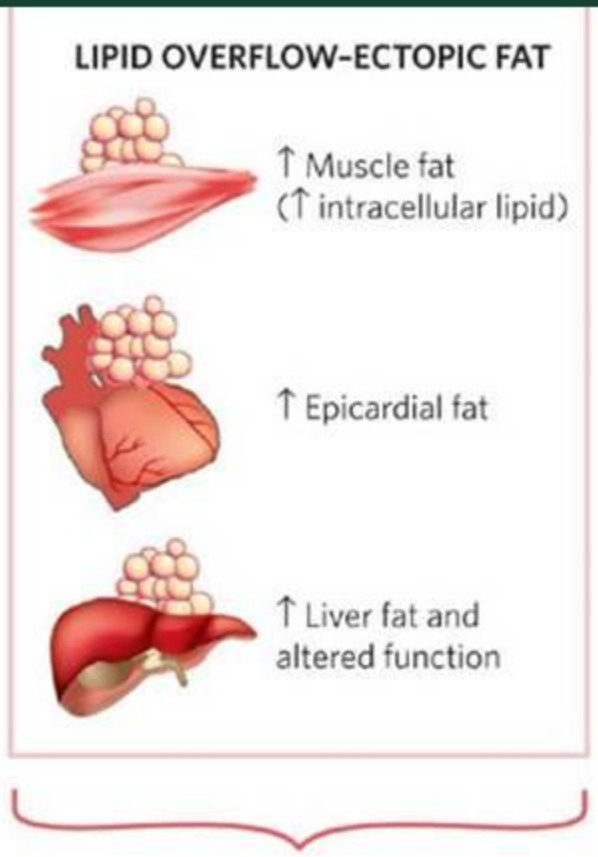
- Cellular
  - hyperplastic
  - hypertrophic
- Somatotypes
  - ectomorphic,
  - mesomorphic
  - endomorphic
- Body segment
  - central
  - peripheral
- Distribution pattern
  - android
  - gynoid
- Depot
  - visceral
  - subcutaneous
  - ectopic (visceral, subcutaneous, ectopic)







Sharma AM, Kushner RF. *Int J Obes* (Lond). 2009;33(3):289-295.

Quetelet Index (1832)

$$\frac{\text{body weight (kg)}}{\text{height (m)}^2}$$

Renamed “Body Mass Index” by Ancel Keys in 1972

Adolphe Quetelet (1796–1874)

BMI and Body Fat

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DXA scan of two individuals with the same BMI but markedly different percent body fat

Yajnik CS, et al. *Lancet*. 2004;363(9403):163.

Relationship Between BMI and Percent Body Fat in Men and Women

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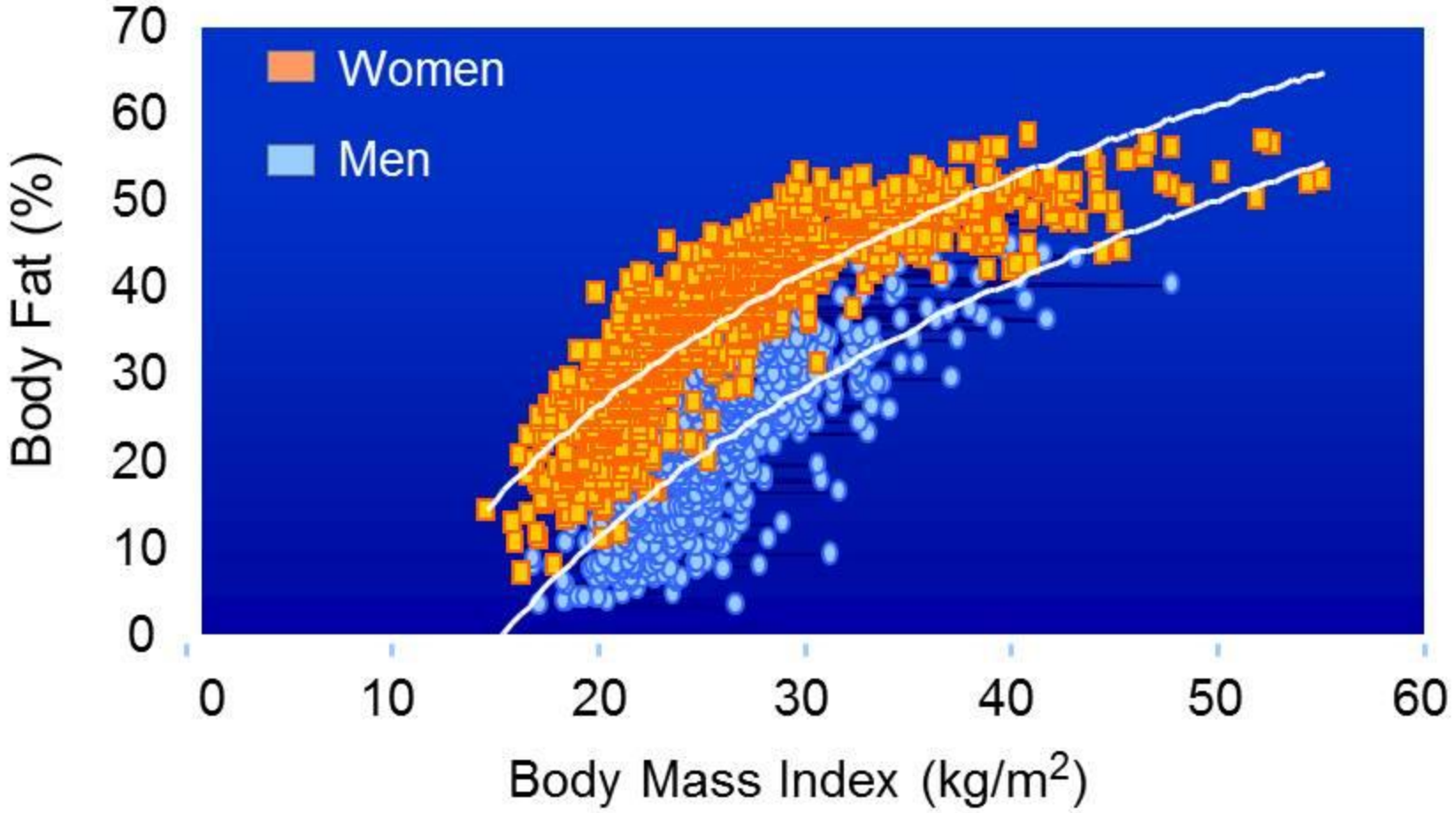

Adapted from Gallagher D, et al. *Am J Clin Nutr.* 2000;72:694-701.

BMI and Risk of Cardiovascular Mortality

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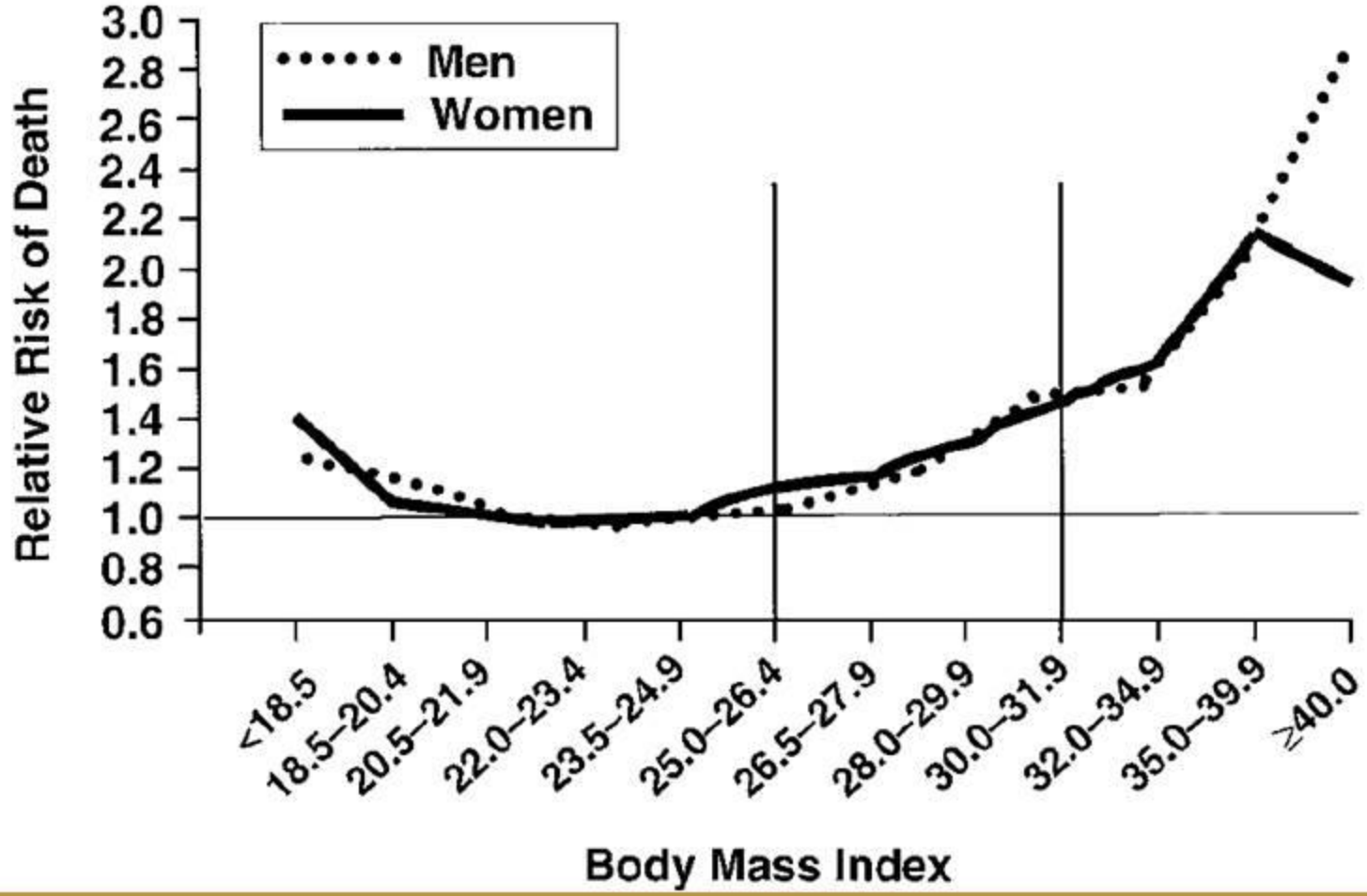

Adapted from Calle EE, et al. *N Engl J Med*. 1999;341(15):1097-1105.

INTERHEART Study

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University of Alberta

Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: a case-control study

Salim Yusuf, Steven Hawken, Stephanie Ôunpuu, Leonelo Bautista, Maria Grazia Franzosi, Patrick Commerford, Chim C Lang, Zvonko Rumboldt, Churchill L Onen, Liu Lisheng, Supachai Tanomsup, Paul Wangai Jr, Fahad Razak, Arya M Sharma, Sonia S Anand, on behalf of the INTERHEART Study Investigators*

Lancet 2005; 366: 1640–49

See Comment page 1589

*See Lancet Online for webappendix and a full list of investigators

Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Canada (Prof S Yusuf DPhil, S Hawken MSc, S Ôunpuu PhD, Prof A M Sharma MD, S Anand MD, F Razak MSc); University of Wisconsin Medical School, Wisconsin, USA (L Bautista MD); Istituto Mario Negri, Milano, Italy (M Grazia Franzosi PhD); University of Cape

Summary

Background Obesity is a major risk factor for cardiovascular disease, but the most predictive measure for different ethnic populations is not clear. We aimed to assess whether markers of obesity, especially waist-to-hip ratio, would be stronger indicators of myocardial infarction than body-mass index (BMI), the conventional measure.

Methods We did a standardised case-control study of acute myocardial infarction with 27 098 participants in 52 countries (12 461 cases and 14 637 controls) representing several major ethnic groups. We assessed the relation between BMI, waist and hip circumferences, and waist-to-hip ratio to myocardial infarction overall and for each group.

Findings BMI showed a modest and graded association with myocardial infarction (OR 1·44, 95% CI 1·32–1·57 top quintile vs bottom quintile before adjustment), which was substantially reduced after adjustment for waist-to-hip ratio (1·12, 1·03–1·22), and non-significant after adjustment for other risk factors (0·98, 0·88–1·09). For waist-to-hip ratio, the odds ratios for every successive quintile were significantly greater than that of the previous one (2nd quintile: 1·15, 1·05–1·26; 3rd quintile: 1·39; 1·28–1·52; 4th quintile: 1·90, 1·74–2·07; and 5th quintiles: 2·52, 2·31–2·74 [adjusted for age, sex, region, and smoking]). Waist (adjusted OR 1·77; 1·59–1·97) and hip (0·73; 0·66–0·80) circumferences were both highly significant after adjustment for BMI ($p<0·0001$ top *vs* bottom

Yusuf S, et al. *Lancet.* 2005;366:1640-1649.

Association of Waist-to-Hip Ratio Within BMI Categories with Myocardial Infarction Risk

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University of Alberta

- It does not matter what your BMI is. Even if your BMI is as low, 23 range, the people who have a high waist-to-hip ratio, have a BMI of 23.
- You have got the exact same risk for having a myocardial infarct as the person with a BMI of 30 who has a high waist-to-hip ratio.
- A lot of this depends on where the fat is actually located.

Yusuf S, et al. *Lancet.* 2005;366:1640-1649.

Relationship Between Visceral Adipose Tissue and Waist

Faculty of Medicine & Dentistry
University of Alberta

- The people with the greater waist circumference on average are going to have more visceral fat than those with the lower waist circumference on average.

Pouliot MC, et al. *Am J Cardiol*. 1994;73:460-468.

International Journal of Obesity (2009) 1–7

0307-0565/09 $32.00
www.nature.com/ijo

REVIEW

A proposed clinical staging system for obesity

AM Sharma[1] and RF Kushner[2]

[1]*Division of Endocrinology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada and* [2]*Division of General Internal Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA*

Current classifications of obesity based on body mass index, waist circumference and other anthropometric measures, although useful for population studies, have important limitations when applied to individuals in clinical practice. Thus, these measures do not provide information on presence or extent of comorbidities or functional limitations that would guide decision making in individuals. In this paper we review historical and current classification systems for obesity and propose a new simple clinical and functional staging system that allows clinicians to describe the morbidity and functional limitations associated with excess weight. It is anticipated that this system, when used together with the present anthropometric classification, will provide a simple framework to aid decision making in clinical practice.
International Journal of Obesity advance online publication, 3 February 2009; doi:10.1038/ijo.2009.2

Keywords: body mass index; obesity staging; obesity diagnosis; obesity treatment

Edmonton Obesity Staging System (EOSS)

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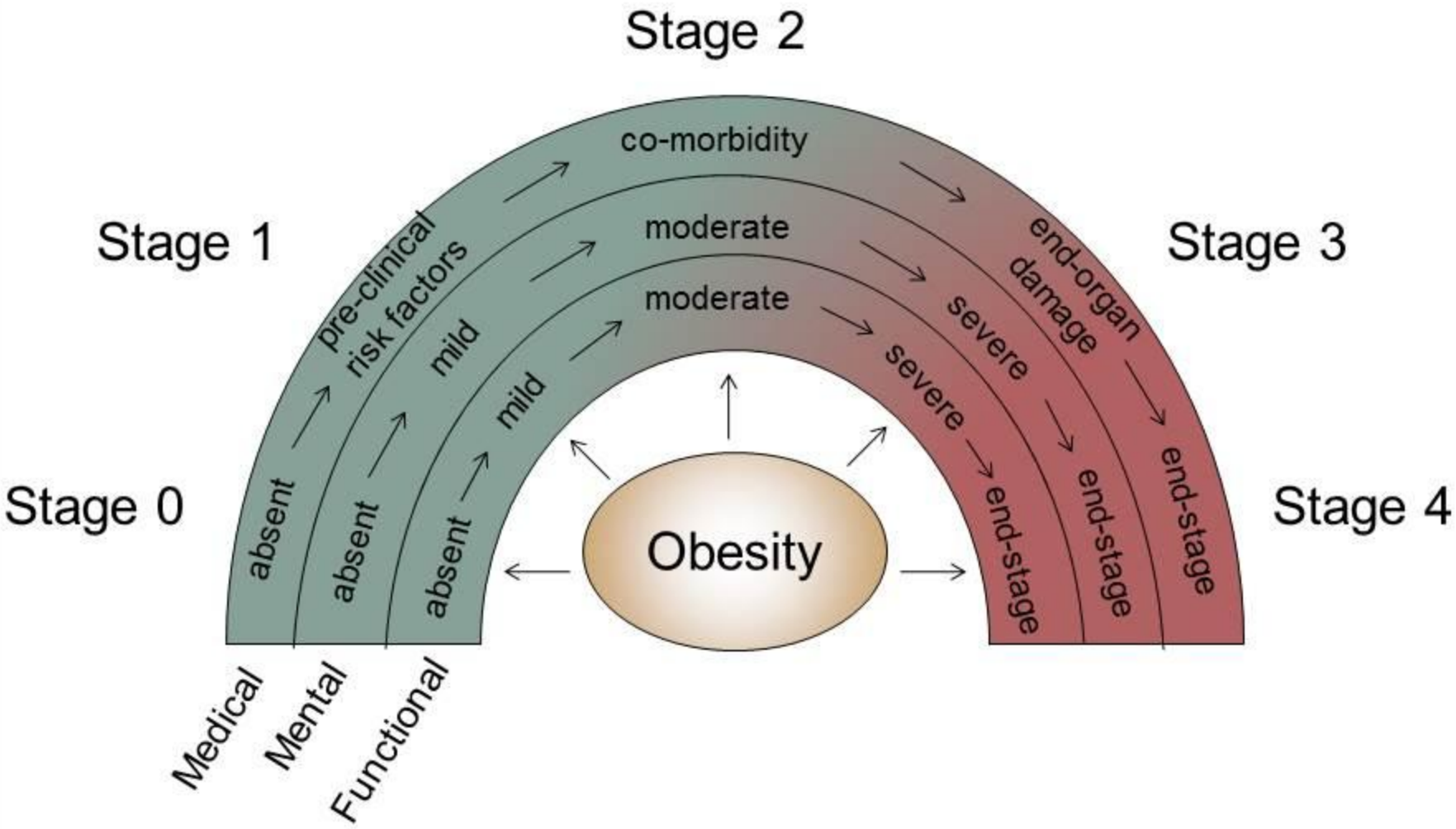

Sharma AM, Kushner RF. *Int J Obes* (Lond). 2009;33(3):289-295.

CMAJ RESEARCH

Using the Edmonton obesity staging system to predict mortality in a population-representative cohort of people with overweight and obesity

Raj S. Padwal MSc MD, Nicholas M. Pajewski PhD, David B. Allison PhD, Arya M. Sharma MD PhD

Abstract

Background: Anthropometric-based classification schemes for excess adiposity do not include direct assessment of obesity-related comorbidity and functional status and thus have limited clinical utility. We examined the ability of the Edmonton obesity staging system, a 5-point ordinal classification system that considers comorbidity and functional status, in predicting mortality in a nationally representative US sample.

Methods: We analyzed data from the National Health and Human Nutrition Examination Surveys (NHANES) III (1988–1994) and the NHANES 1999–2004, with mortality follow-up through to the end of 2006. Adults (age ≥ 20 yr) with overweight or obesity who had been randomized to the morning session at the mobile examination centre were scored according to the Edmonton obesity staging system. We examined the relationship between staging system scores and mortality, and Cox proportional hazards models were adjusted for the presence of the metabolic syndrome or hypertriglyceridemic waist.

Results: Over 75% of the cohort with overweight or obesity were given scores of 1 or 2. Scores of 4 could not be reliably assigned because specific data elements were lacking. Survival curves clearly diverged when stratified by scores of 0–3, but not when stratified by obesity class alone. Within the data from the NHANES 1988–1994, scores of 2 (hazard ratio [HR] 1.57; 95% confidence interval [CI] 1.16 to 2.13) and 3 (HR 2.69; 95% CI 1.98 to 3.67) were associated with increased mortality compared with scores of 0 or 1, even after adjustment for body mass index and the metabolic syndrome. We found similar results after adjusting for hypertriglyceridemic waist (i.e., waist circumference ≥ 90 cm and a triglyceride level ≥ 2 mmol/L for men; the corresponding values for women were ≥ 85 cm and ≥ 1.5 mmol/L), as well as in a cohort eligible for bariatric surgery.

Interpretation: The Edmonton obesity staging system independently predicted increased mortality even after adjustment for contemporary methods of classifying adiposity. The Edmonton obesity staging system may offer improved clinical utility in assessing obesity-related risk and prioritizing treatment.

Competing interests: Raj Padwal and Arya Sharma are supported by an alternative funding plan from the Government of Alberta and the University of Alberta. David Allison has received grants, honoraria, donations, and consulting fees from numerous other commercial and nonprofit entities with interests in obesity. No other competing interests were declared.

This article has been peer reviewed.

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Dr. Raj S. Padwal,
rpadwal@ualberta.ca

CMAJ 2011. DOI:10.1503/cmaj.110387

EOSS Predicts Mortality in NHANES III

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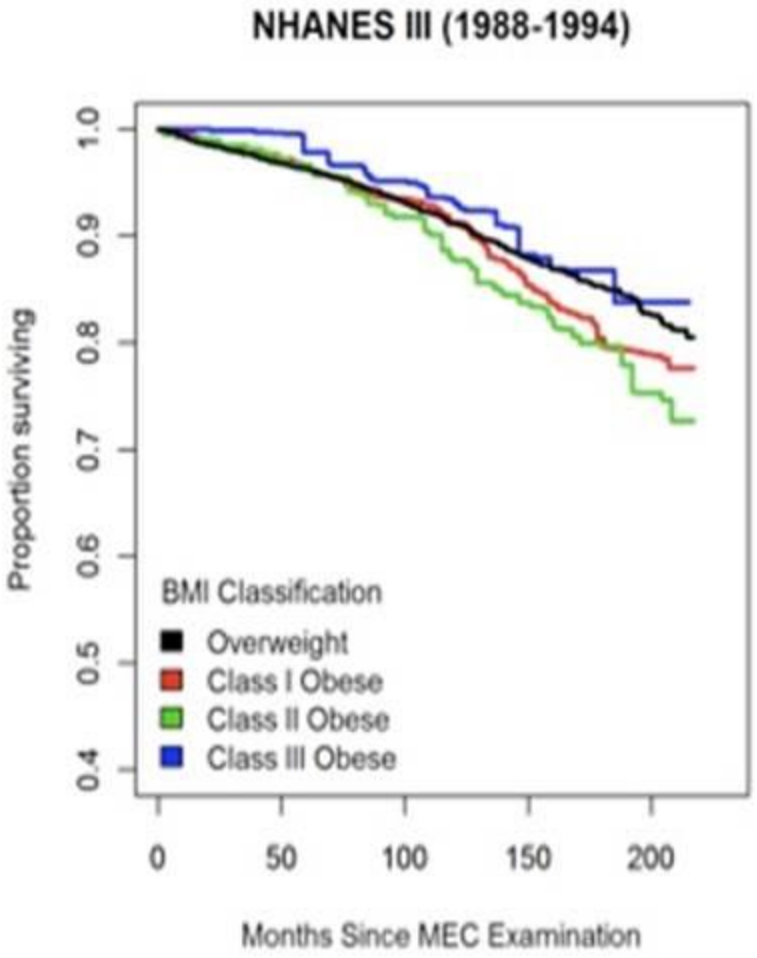
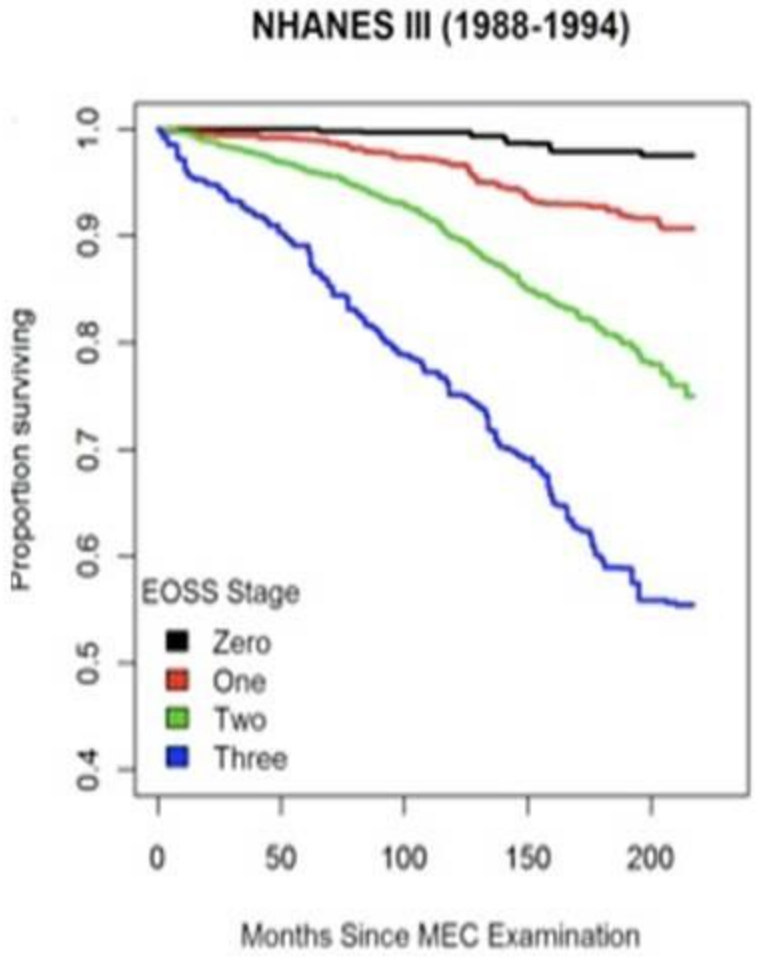
University of Alberta





Reprinted with permission from Padwal R, et al. *CMAJ*. 2011; 183(14):E1059-66.

EOSS Predicts Mortality at Every Level of BMI NHANES III

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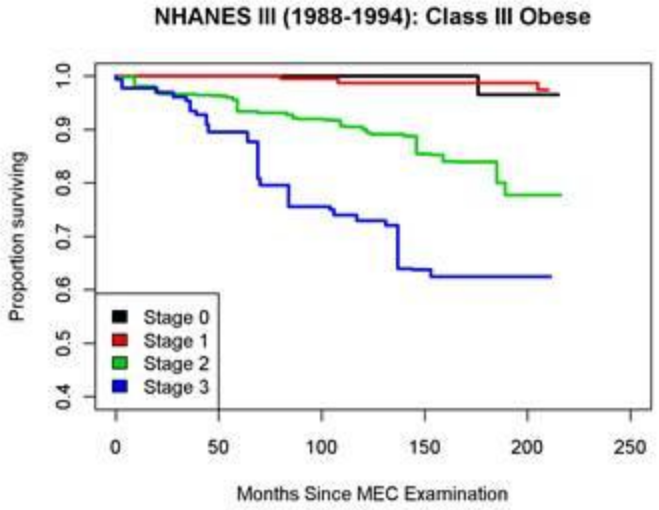
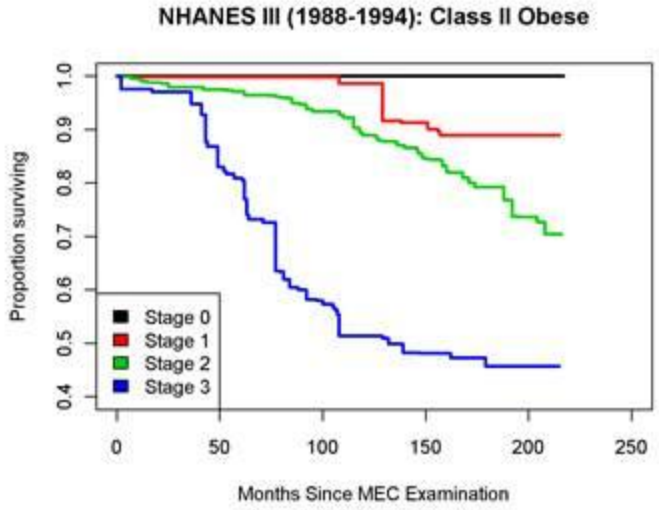
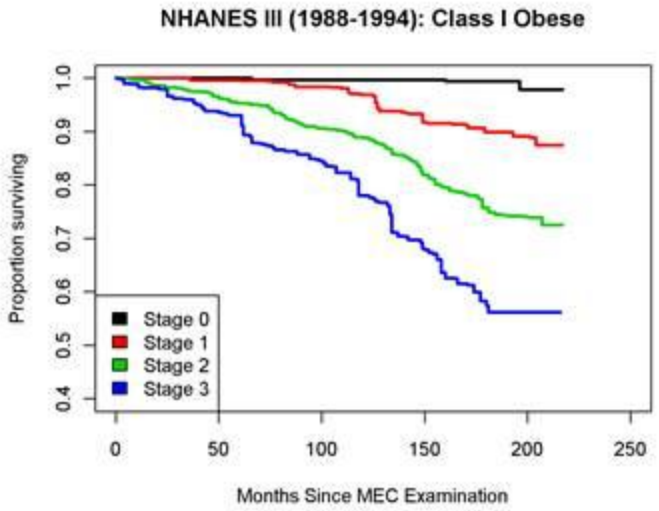
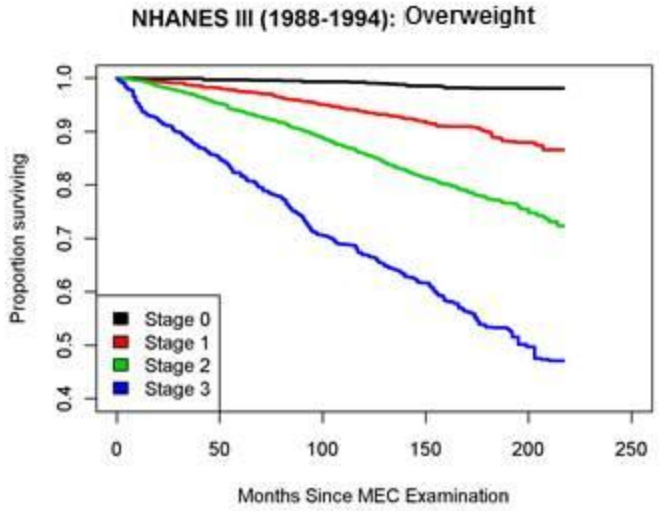
University of Alberta



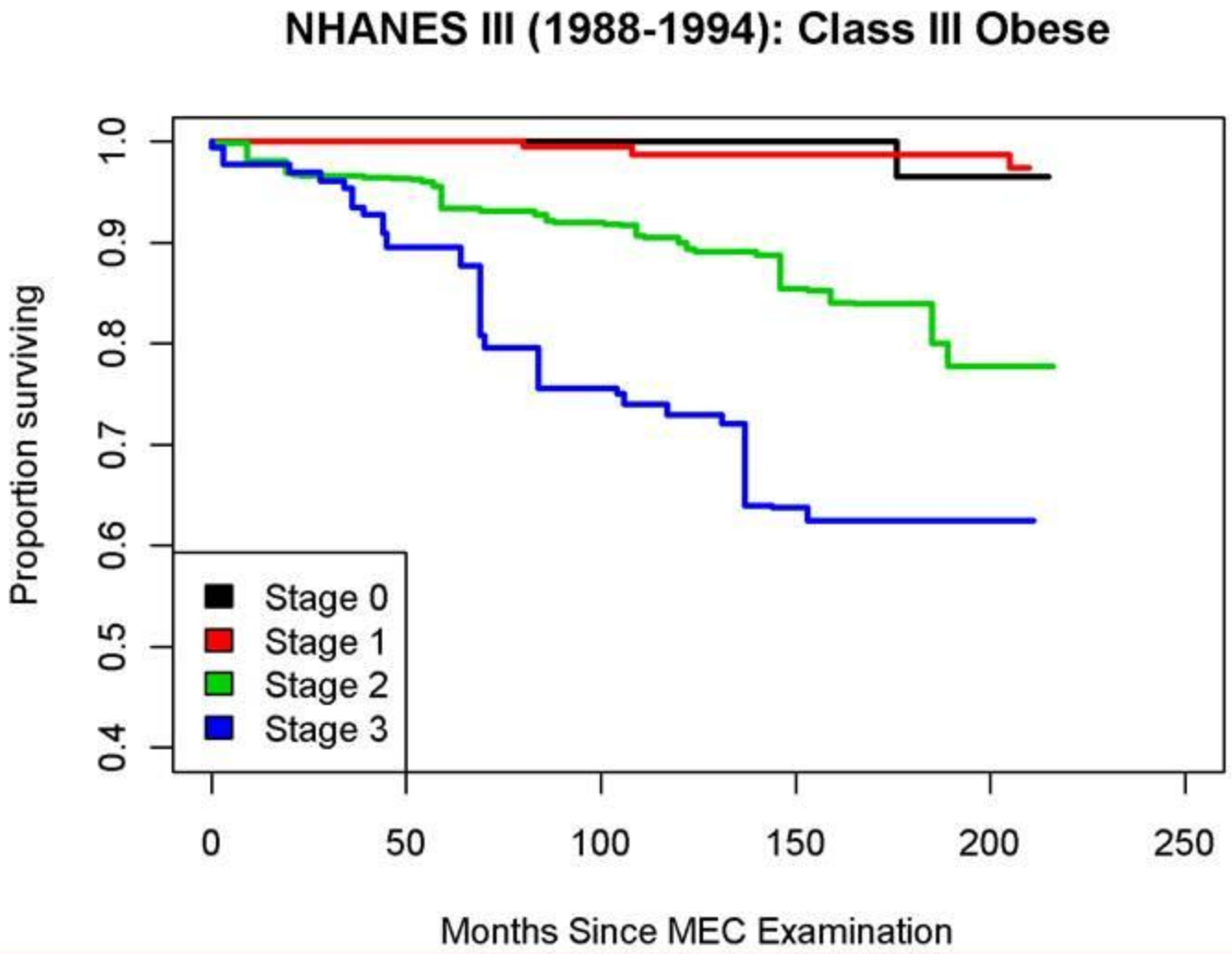






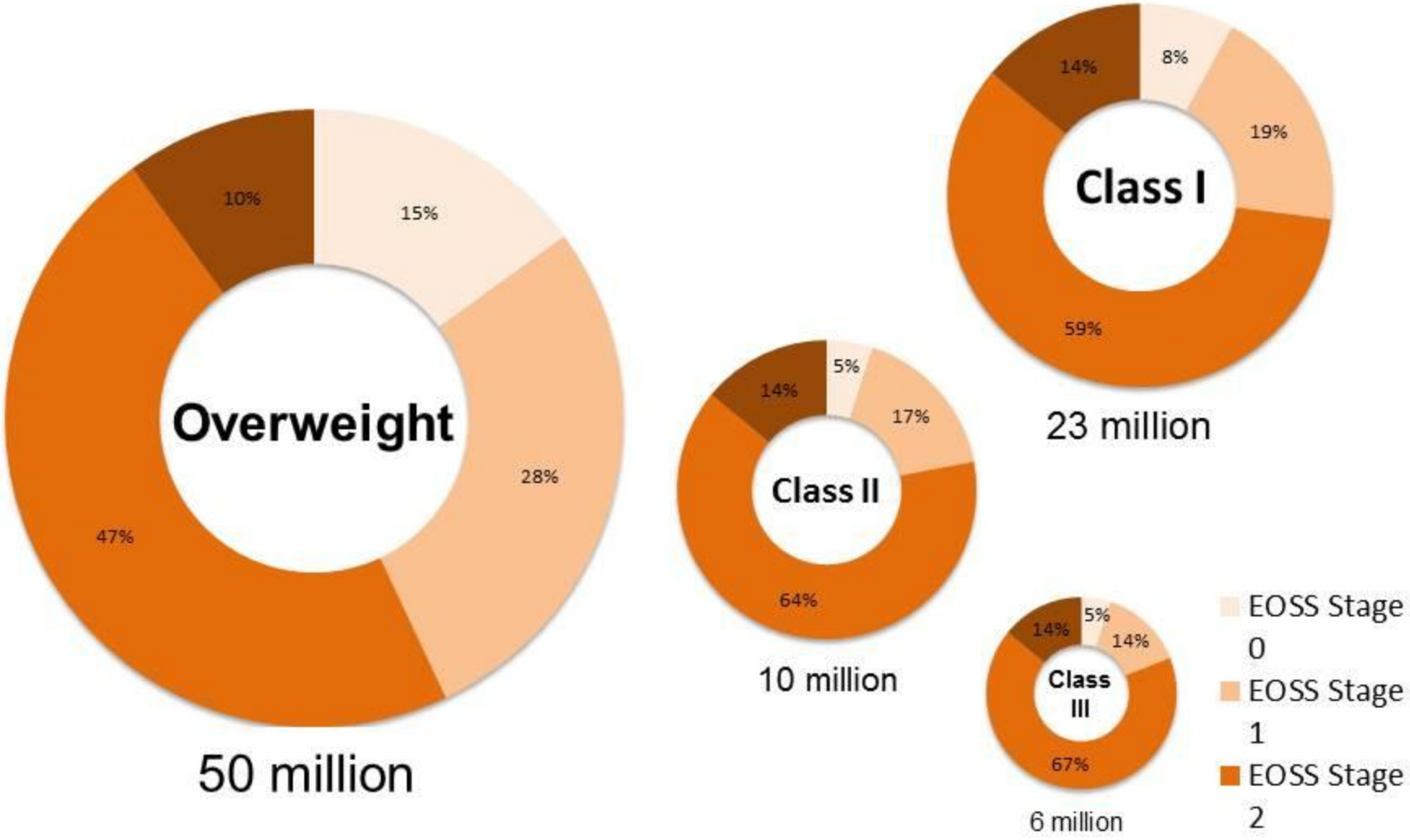
EOSS Predicts Mortality at Every Level of BMI NHANES III

Faculty of Medicine & Dentistry
University of Alberta



EOSS Distribution Across BMI Categories NHANES III (1988-1994)

Faculty of Medicine & Dentistry
University of Alberta



Padwal R, et al. *CMAJ*. 2011; 183(14):E1059-66.

EOSS: EDMONTON OBESITY STAGING SYSTEM - *Staging Tool*

STAGE 0

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

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

Class I, Stage 0 Obesity

EOSS Score

WHO Obesity Classfication

STAGE 1

- Patient has obesity-related **SUBCLINICAL** risk factors (borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc)

- OR -

- **MILD** physical symptoms - patient currently not requiring medical treatment for comorbidities (dyspnea on moderate exertion, occasional aches/pains, fatigue, etc.)

- OR -

- **MILD** obesity-related psychological symptoms and/or mild impairment of well-being (quality of life not impacted)

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

Class III, Stage 1 Obesity

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

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

Stage 0 / Stage 1 Obesity

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

STAGE 2

- Patient has an **ESTABLISHED** obesity-related comorbidities requiring medical intervention (HTN, Type II Diabetes, sleep apnea, PCOS, osteoarthritis, reflux disease)

- OR -

- **MODERATE** obesity-related psychological symptoms (depression, eating disorders, anxiety disorder)

- OR -

- **MODERATE** functional limitations in daily activities (Quality of life is beginning to be impacted)

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

Class II, Stage 2 Obesity

STAGE 3

- Patient has **significant** obesity-related end-organ damage (myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis)

- OR -

- **SIGNIFICANT** obesity-realted psychological symptoms (major depression, suicide ideation)

- OR -

- **SIGNIFICANT** functional limitations (eg: unable to work or complete routine activities, reduced mobility)
- **SIGNIFICANT** impairment of well-being (quality of life is significantly impacted)

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

Class III, Stage 3 Obesity

STAGE 4

- **SEVERE** (potential end stage) from obesity related comorbidities

- OR -

- **SEVERELY** disabling psychological symptoms

- OR -

- **SEVERE** functional limitations

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

Class III, Stage 4 Obesity

Alberta Health Services

UNIVERSITY OF ALBERTA

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

Management Recommendations by Obesity Stage

Faculty of Medicine & Dentistry
University of Alberta

Stage 0: Identification of factors contributing to increased body weight. Counseling to prevent further weight gain through lifestyle measures including healthy eating and increased physical activity.

Stage 1: Investigation for other (non-weight related) contributors to risk factors. More intense lifestyle interventions, including diet and exercise to prevent further weight gain. Monitoring of risk factors and health status.

Stage 2: Initiation of obesity treatments including considerations of all behavioral, pharmacological and surgical treatment options. Close monitoring and management of comorbidities as indicated.

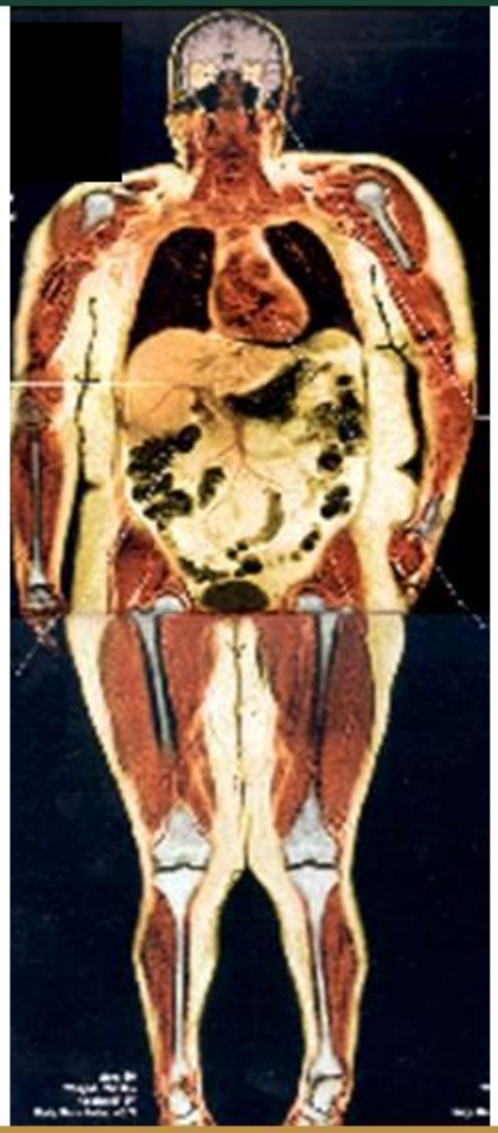
Stage 3: More intensive obesity treatment including consideration of all behavioral, pharmacological and surgical treatment options. Aggressive management of comorbidities as indicated.

Stage 4: Aggressive obesity management as deemed feasible. Palliative measures including pain management, occupational therapy and psychosocial support.

Sharma AM, Kushner RF. *Int J Obes* (Lond). 2009;33(3):289-295.

Obesities are heterogeneous complex disorders of multiple etiologies characterized by excess body fat that threatens or affects socioeconomic, mental or physical health

Sharma 2007



The Obesity Conundrum

Practical Approaches for Patients Who Are Obese and "Well", Obese with Risk Factors, and Obese and "Sick"

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Treatment Options for Obesity: When and How Do They Fit?

Louis J. Aronne, MD, FACP

Professor of Clinical Medicine

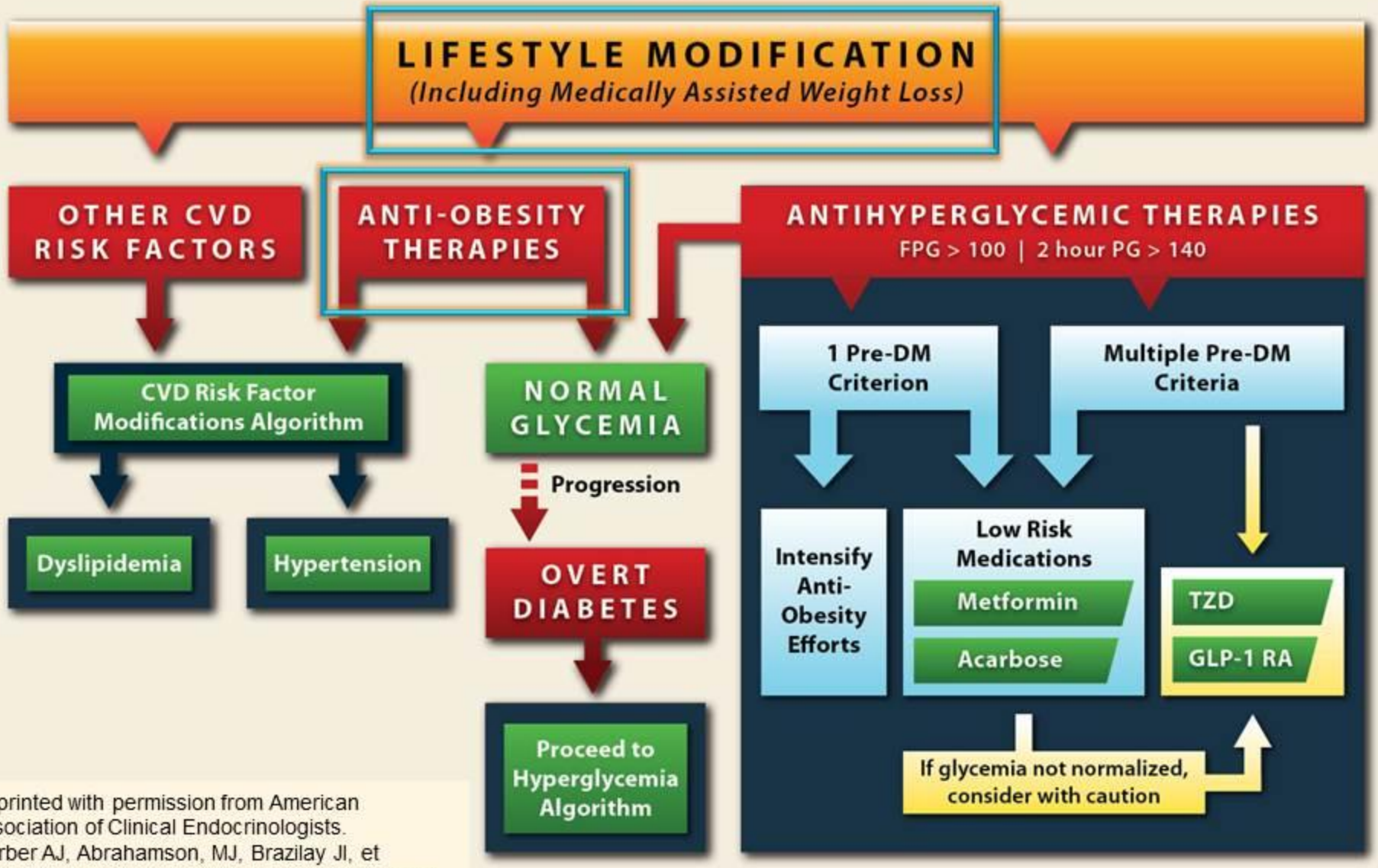
Weill Cornell Medical College

Director, Comprehensive Weight Control Program

New York, NY

Prediabetes Algorithm

IGF (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)



Garber AJ, Abrahamson, MJ, Brazilay JI, et al. AACE Comprehensive Diabetes Management Algorithm. *Endocr Pract*. 2013;19:327-336.

Glycemic Control Algorithm

LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

ENTRY A1c < 7.5%

MONOTHERAPY*

- Metformin
- GLP-1 RA
- DPP4-i
- AG-i
- SGLT-2 **
- TZD
- SU/GLN

If A1c > 6.5% in 3 months add second drug (Dual Therapy)

ENTRY A1c ≥ 7.5%

DUAL THERAPY*

MET or other first-line agent +

- GLP-1 RA
- DPP4-i
- TZD
- ** SGLT-2
- Basal insulin
- Colesevelam
- Bromocriptine QR
- AG-i
- SU/GLN

If not at goal in 3 months proceed to triple therapy

TRIPLE THERAPY*

MET or other first-line agent + 2ND LINE AGENT

- GLP-1 RA
- TZD
- ** SGLT-2
- Basal insulin
- DPP4-i
- Colesevelam
- Bromocriptine QR
- AG-i
- SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

ENTRY A1c > 9.0%

NO SYMPTOMS	SYMPTOMS
DUAL THERAPY OR TRIPLE THERAPY	INSULIN ± OTHER AGENTS

ADD OR INTENSIFY INSULIN

LEGEND

✓ = Few adverse events or possible benefits

⚠ = Use with caution

Reprinted with permission from American Association of Clinical Endocrinologists. Garber AJ, Abrahamson, MJ, Brazilay JI, et al. AACE Comprehensive Diabetes Management Algorithm. *Endocr Pract.* 2013;19:327-336.

* Order of medications listed are a suggested hierarchy of usage

** Based upon phase 3 clinical trials data

PROGRESSION OF DISEASE

Our Typical Patient

- BMI 37 kg/m^2
- Multiple diagnoses, several usually unrecognized
  - T2DM and proteinuria
- 7 - 8 medications
- Sleep apnea > 50%
- Stage 3

- Treating obesity is a way to treat multiple comorbidities
- You may want to focus on treating people with comorbid illnesses

Treatment Guidelines are Based on BMI and Comorbid Conditions

Treatment	Body Mass Index (BMI) (kg/m^2)				
	25–26.9	27–29.9	30–34.9	35–39.9	≥40
Diet, physical activity, behavior therapy	Yes with comorbidities →	Yes with comorbidities →	Yes →	Yes →	Yes →
Pharmaco-therapy	- - - - - - - - - - - -	Yes with comorbidities →	Yes →	Yes →	Yes →
Weight-loss surgery	- - - - - - - - - - - -	- - - - - - - - - - - -	Lap band with DM ←	Yes with comorbidities →	Yes →

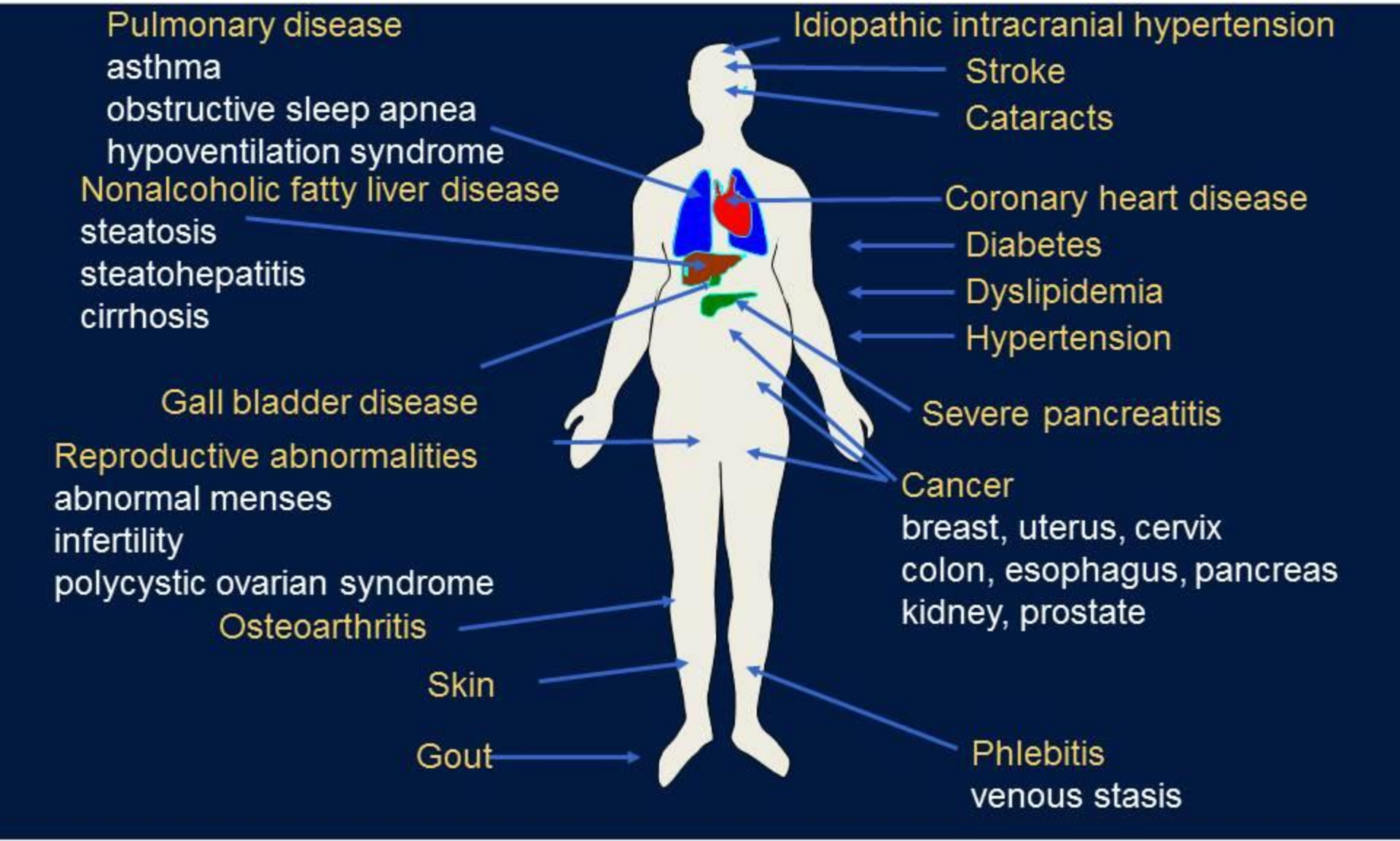
*Yes alone indicates that the treatment is indicated regardless of the presence or absence of comorbidities. The solid arrow signifies the point at which therapy is initiated.

NIH/NHLBI, NAASO. The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Bethesda, Md: NIH; 2000.

Do We Stick to Guidelines for Weight Management?

- Yes, with exceptions: Does not apply to surgery
- Examples
  - Severe documented weight gain referred by a health care provider
  - Hormone sensitive tumors like breast or prostate referred by oncology
  - Comorbidity like sleep apnea or T2DM which may respond to weight loss

Medical Complications of Obesity: Almost Every Organ System is Affected, and May Benefit from Weight Loss



Bariatric Surgery: Long-Term Weight Loss and Decreased Mortality

- **Swedish Obese Subjects (SOS) Study**
- Up to 16 years follow-up
- Hazard ratio*=0.76 (95% CI: 0.59–0.99), *P*=0.04

*Surgical group vs control group at 16 years

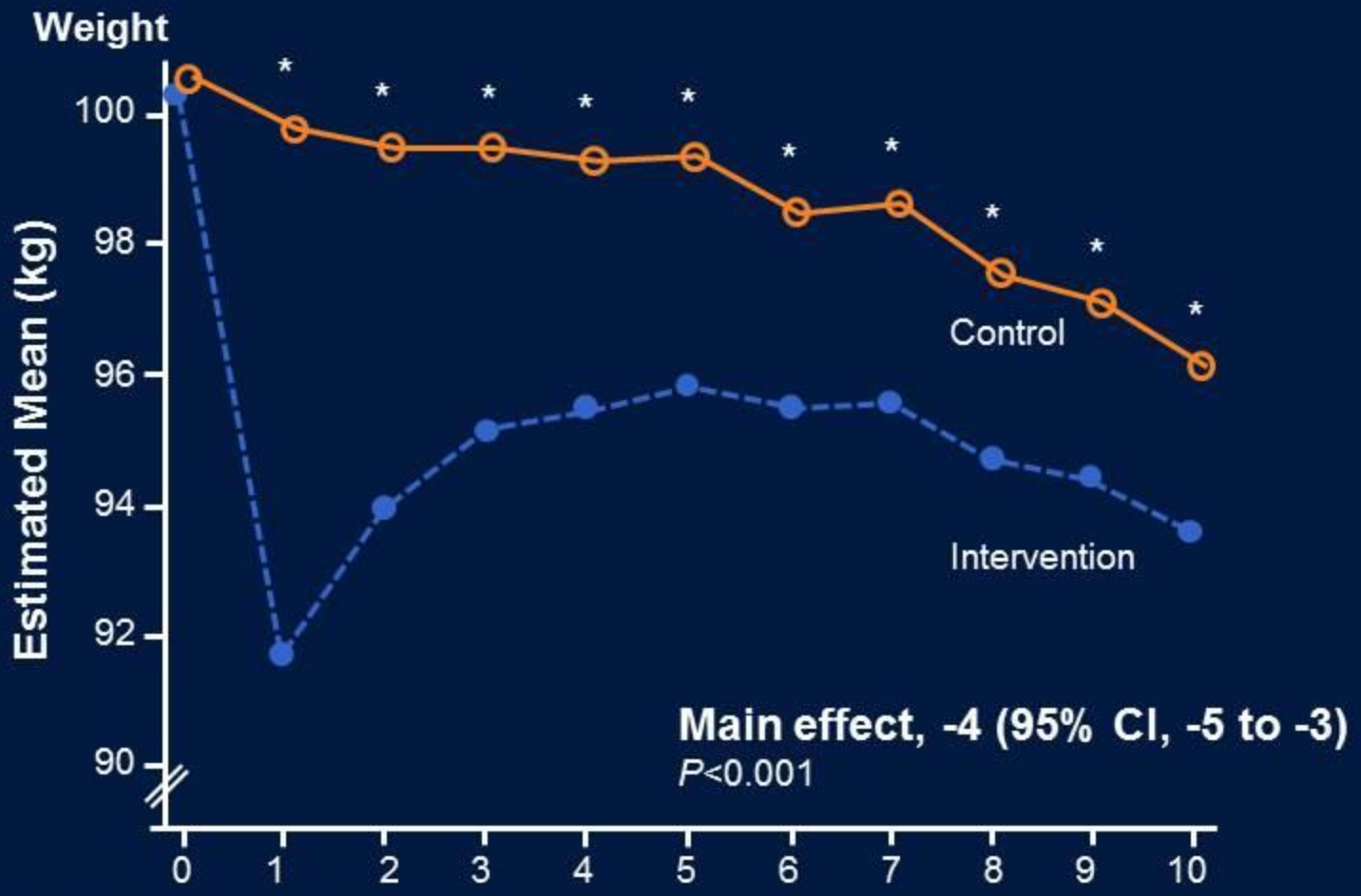
Sjostrom L, et al. *N Engl J Med*. 2007;357:741-752.

Bariatric Surgery Reduces Diabetes, Cancer, and CV Mortality

	Matched Subjects				
	Surgery Group (n=7925)		Control Group (n=7925)		
	No	No./10,000 person-yr	No	No./10,000 person-yr	
All causes of death	213	37.6	321	57.1	-34%
All deaths caused by disease	150	26.5	285	50.7	-48%
Cardiovascular diseases	55	9.7	104	18.5	-48%
Diabetes	2	0.4	19	3.4	-88%
Cancer	31	5.5	73	13.3	-59%
Other diseases	62	11	89	15.5	-29%
All non-disease causes	63	11.1	36	6.4	+73%
Accident unrelated to drugs	21	3.7	17	3.0	
Poisoning of undetermined intent	9	1.6	4	0.7	
Suicide	15	2.6	5	0.9	
Other non-disease causes	18	3.2	10	1.8	

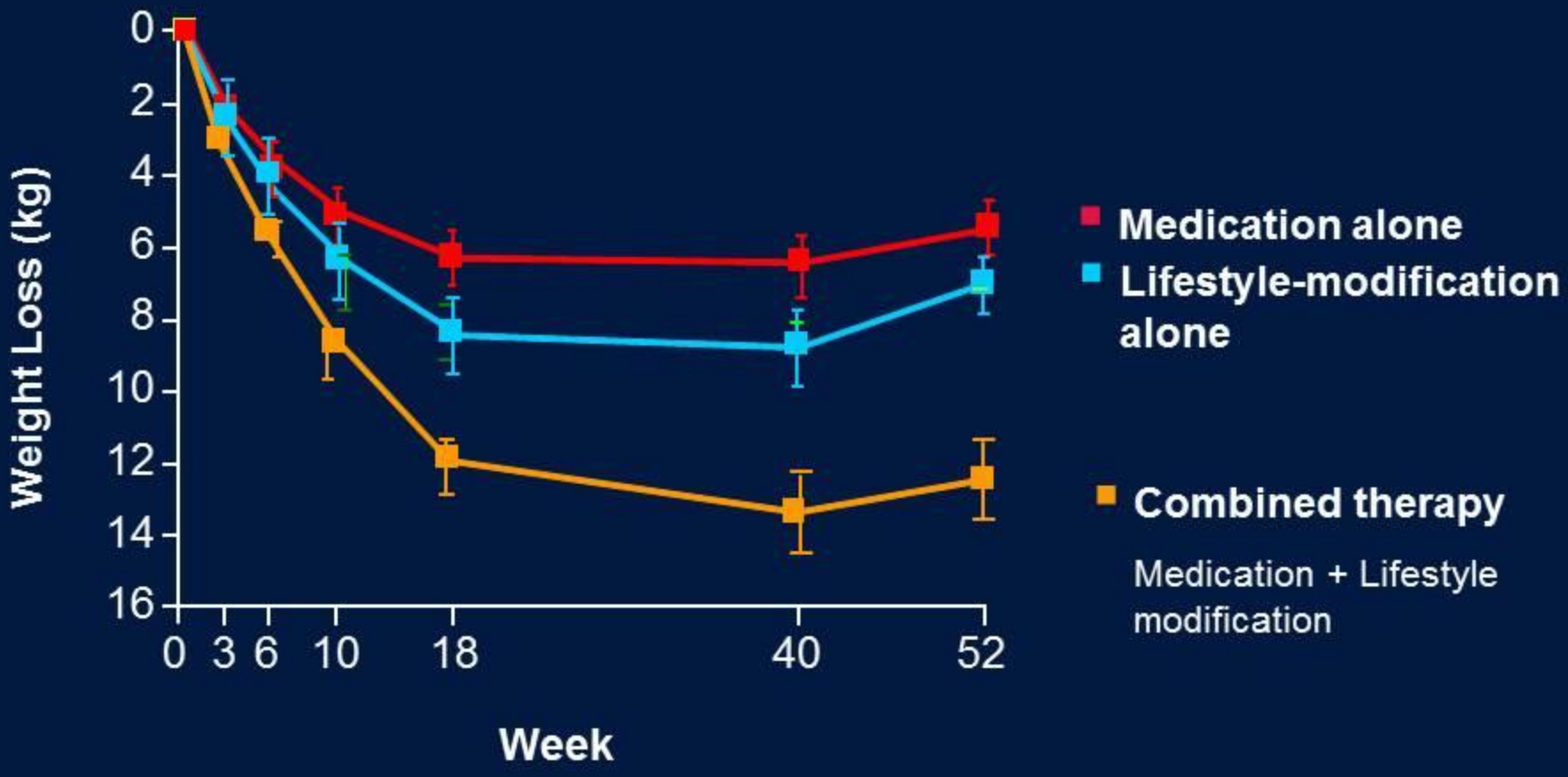
Adams TD, et al. *N Engl J Med.* 2007;357(8):753-761.

Look AHEAD Trial – Diet and Lifestyle Did Not Reduce CV Endpoints but Did Improve Other Comorbidities



Reprinted with permission from Look AHEAD trial. *Diabetes Care*. 2007;30(6):1374-1383.National institutes of Health. Weight loss does not lower heart disease risk from type 2 diabetes. NIH News; October 2012.

Look AHEAD — Was it Enough Weight Loss? Improved Efficacy of Combined Lifestyle Intervention and Pharmacotherapy



Adapted from
Wadden TA, et al. *NEJM*. 2005;353:2111-2120.

In this trial the Lifestyle Modification was delivered by the MD

*Study was with Sibutramine, which is no longer available in the U.S

Recent Additions to Obesity Pharmacotherapy

Agents	Action	Approval
Lorcaserin	• 5-HT_{2C} serotonin agonist • Little affinity for other serotonergic receptors	• Approved, Summer 2012
Phentermine/ Topiramate ER	• Sympathomimetic • Anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)	• Approved, Summer 2012

Kushner RF. *Expert Opin Pharmacother*. 2008;9:1339-1350.
Phentermine and topiramate extended-release [package insert]. Mountain View, CA :Vivus; 2012.
Lorcaserin hydrochloride [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2012.

Lorcaserin: Those Who Lost ≥ 4.5% Total Body Weight by Week 12 Went on to Lose 10%

Studies 009 and 011, MITT

-2.46%

-10.22%

MITT Lorcaserin BID	Week 12	Completed Week 12	Completed Week 52
N = 3097	≥4.5% wt loss	1369/3097 (44.2%)	1083/1369 (79.1%)
	<4.5% wt loss	1168/3097 (37.7%)	680/1168 (58.2%)

Slide courtesy Dr. Steve Smith

Lorcaserin: Key Secondary Endpoints

BLOOM Study

Endpoint		Lorcaserin	Placebo	*P* value
Waist circumference (cm)	↓	−6.8	−3.9	<0.001
SBP/DBP (mm Hg)	↓	−1.4 / −1.1	−0.8 / −0.6	0.04/0.01
Triglycerides (%)	↓	−6.15	−0.14	<0.001
Safety				
HR (beats/min)	↓	−2.0	−1.6	0.049
Beck depression II		−1.1	−0.9	0.26

Intention-to-Treat Analysis with LOCF Imputation

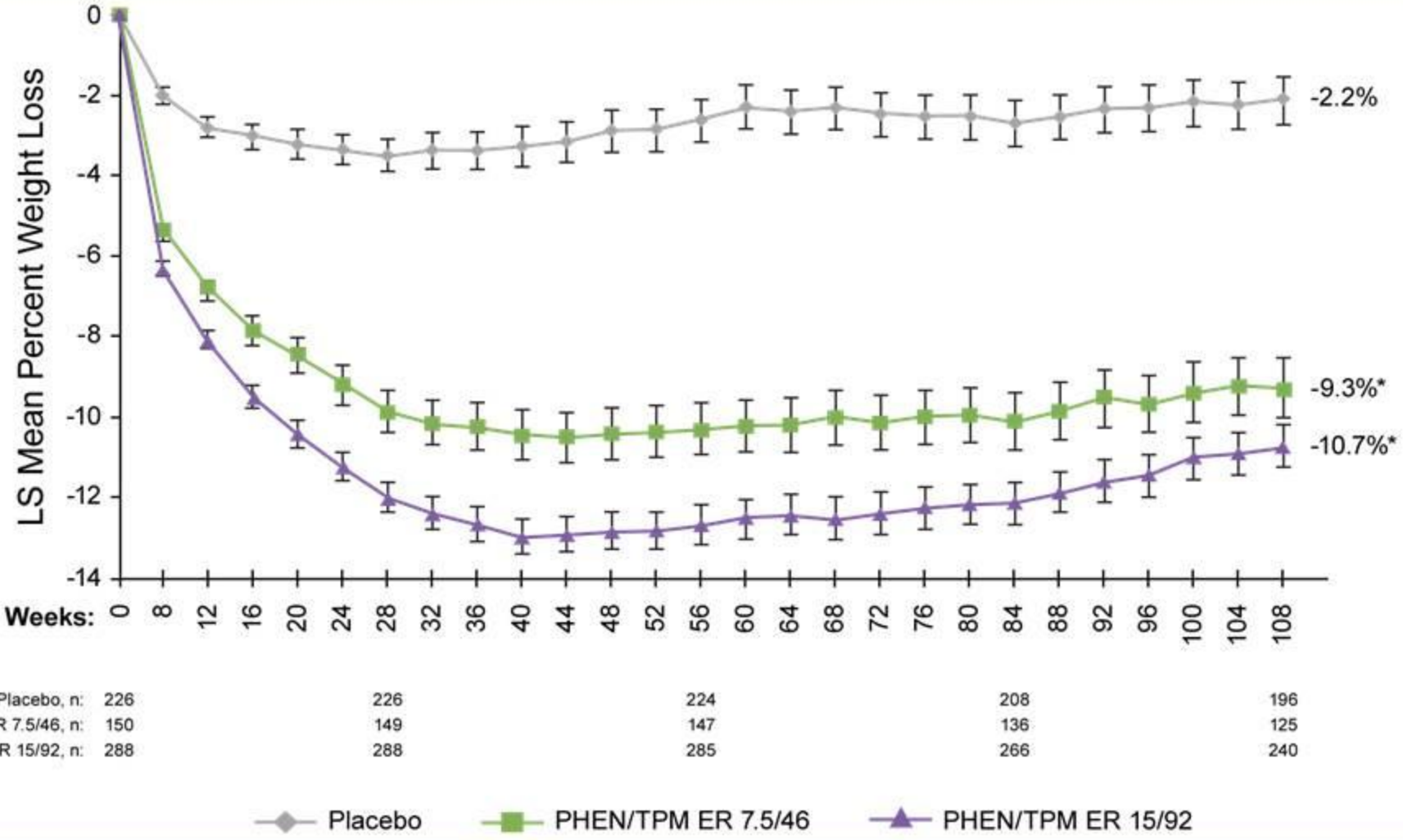
BLOOM-DM Study

Endpoint		Lorcaserin	Placebo	*P* value
Change in HbA1C (%)	↓	−0.9	−0.4	<0.001

Smith SR, et al. *NEJM*. 2010;363:245-256.
O'Neil PM, et al. *Obesity*. 2012;20:1426-1436.

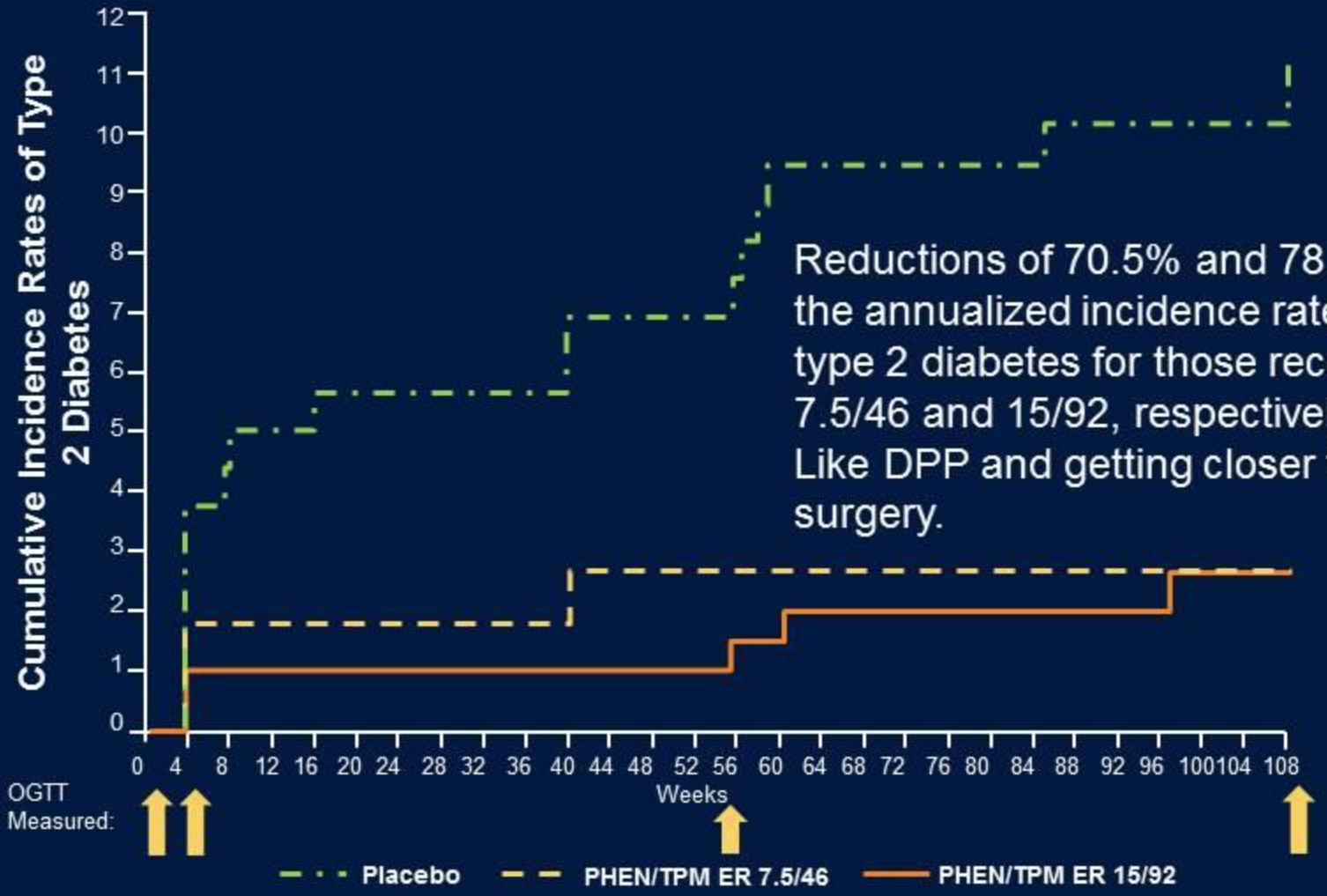
BLOOM-DM, Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus.

Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 2 Years: SEQUEL Study (completers)*



*Data from patients who completed 56 weeks on treatment (observed data, no imputation);
*P<.0001 vs placebo

Phentermine/Topiramate ER: Reductions in Rates of T2DM



Reprinted with permission from Garvey WT, et al. *Diabetes Care*. Published online before print, October 8, 2013.

Subanalysis of a Phase 3, randomized, placebo-controlled, double-blind study of overweight/obese subjects (BMI ≥27 to ≤45 kg/m^2) with ≥2 comorbidities.

Emerging Pharmacotherapies

Agents	Action	Approval/Phase
Liraglutide	• GLP-1 receptor agonist	• Phase 3 (3mg for obesity)
Naltrexone/ Bupropion SR	• Dopamine/noradrenaline reuptake inhibitor • Opioid receptor antagonist	• NDA submitted, FDA requested CV outcomes study

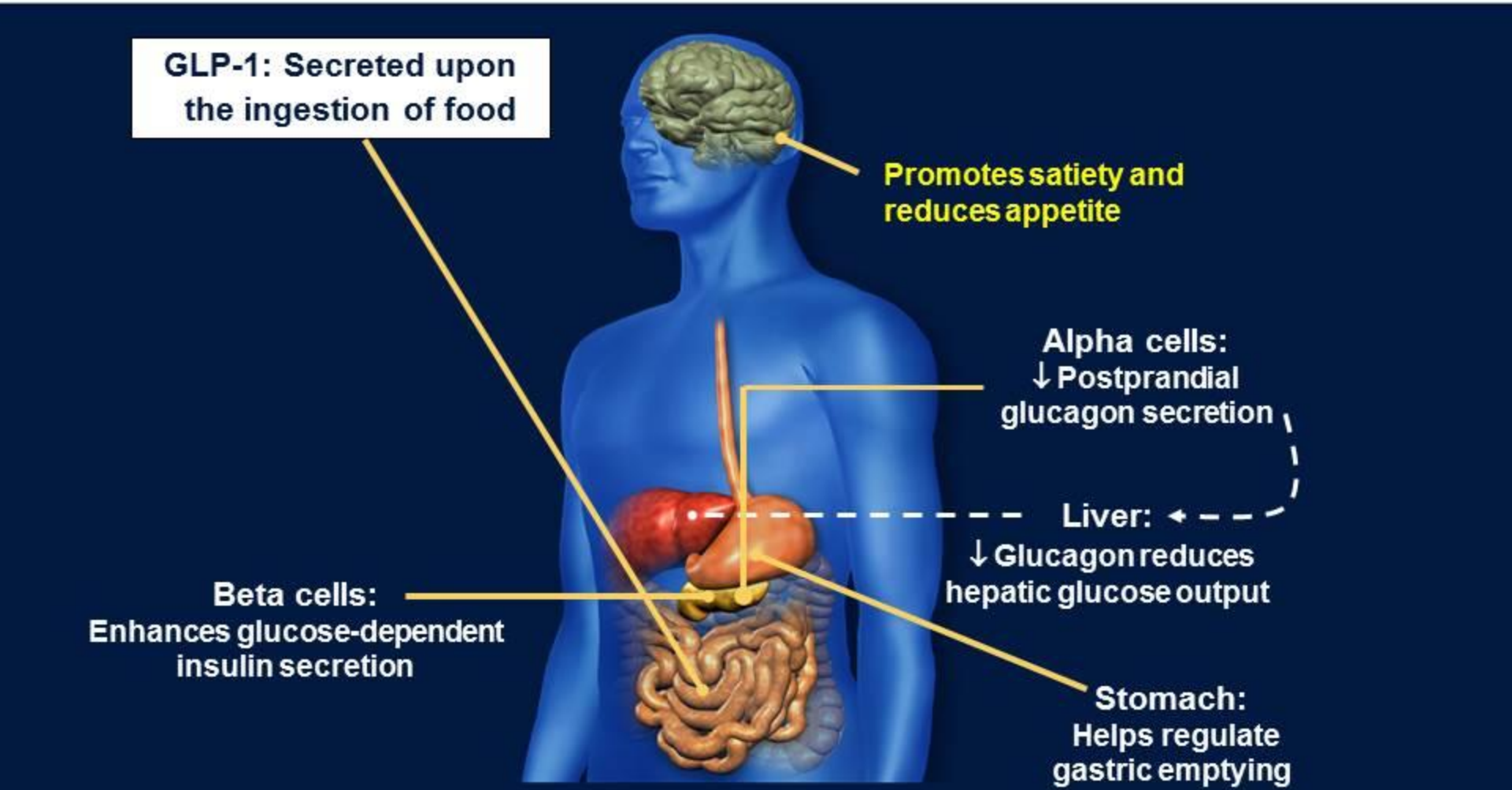
Clinicaltrials.gov. Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects With Cardiovascular Risk Factors (The Light Study). 2012.; Clinicaltrials.gov.
Effect of Liraglutide on Body Weight in Non-diabetic Obese Subjects or Overweight Subjects With Co-morbidities: SCALE - Obesity and Pre-diabetes. 2011.

Liraglutide

- Glucagon-Like Peptide 1 (GLP-1) receptor agonist approved in 2010 for treatment of type 2 diabetes (1.8 mg/day)
- Phase III trials assessing effects of high dose (3.0 mg/day) to promote weight loss (SCALE trials)

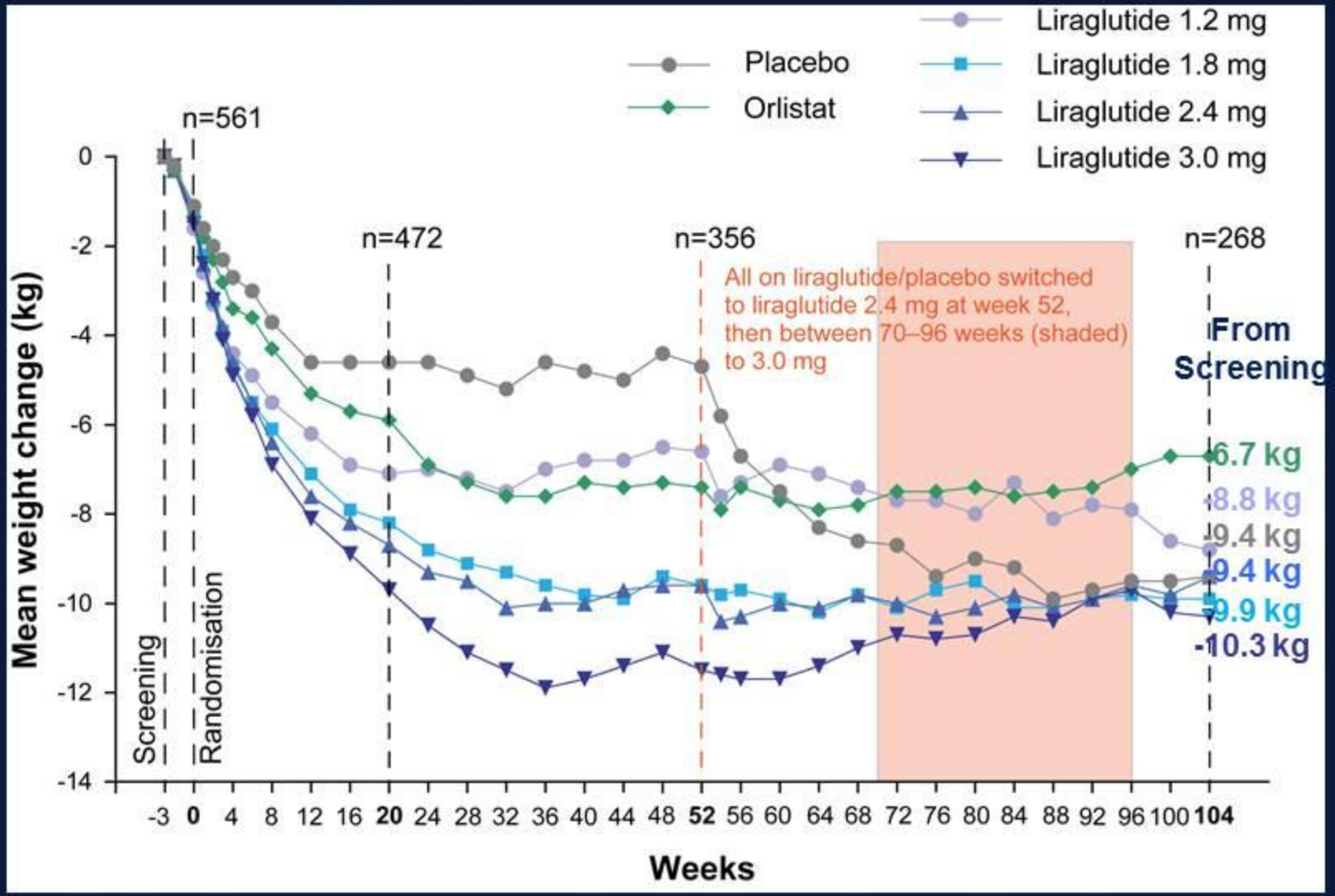
Inoue K, et al. *Cardiovasc Diabetol*. 2011,10:109. doi:10.1186/1475-2840-10-109.
Clinicaltrials.gov. Effect of Liraglutide on Body Weight in Non-diabetic Obese Subjects or Overweight Subjects With Co-morbidities: SCALE - Obesity and Pre-diabetes. 2011.
Effect of Liraglutide on Body Weight in Overweight or Obese Subjects With Type 2 Diabetes: SCALE - Diabetes. 2011.

GLP-1 Modulates Numerous Functions in Humans



Data from Flint A, et al. *J Clin Invest*. 1998;101:515-520; Data from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422. Data from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553; Data from Drucker DJ. *Diabetes*. 1998;47:159-169.

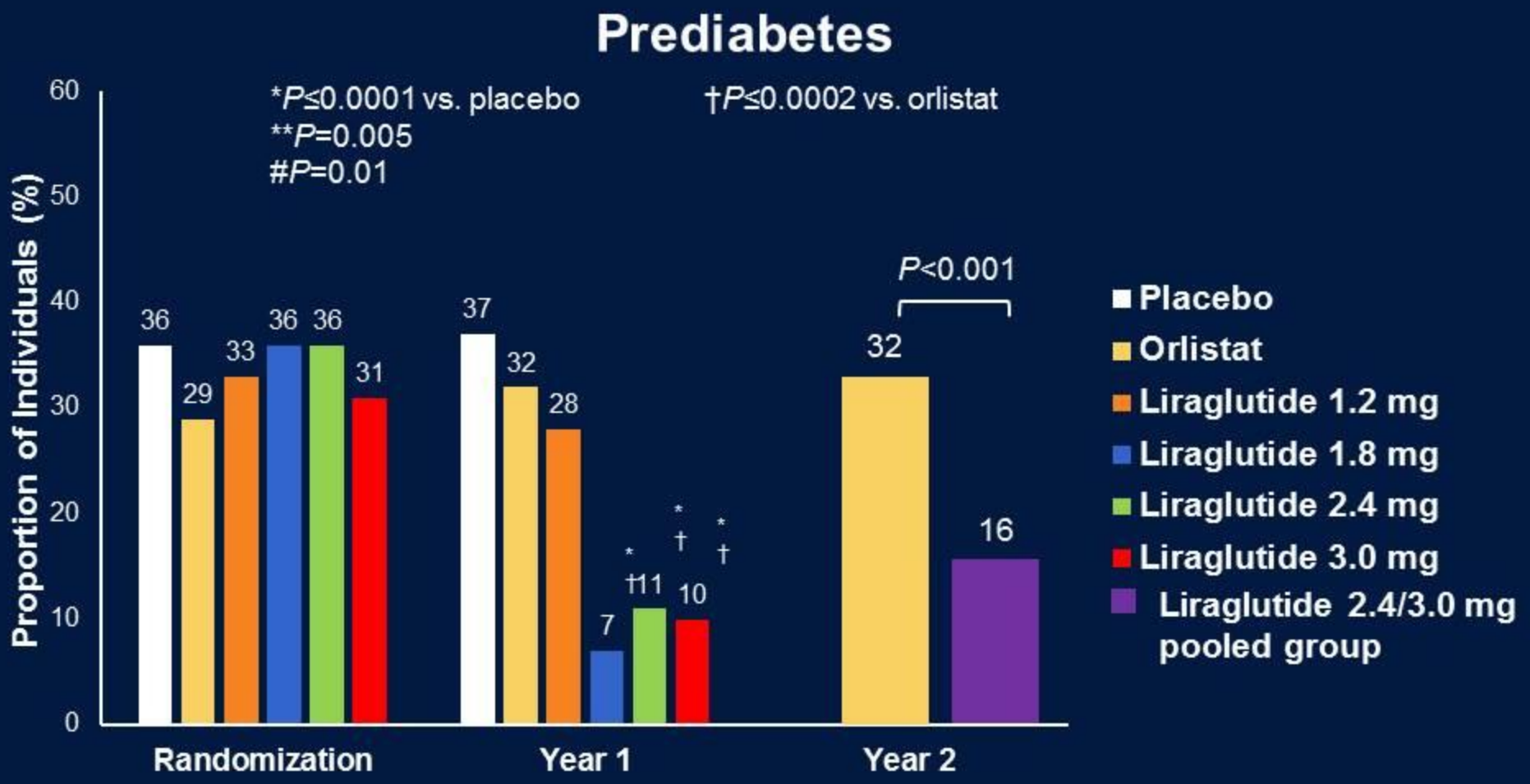
Liraglutide: Weight Loss Over 2 Years



Reprinted with permission from Astrup A, et al. *Int J Obes (Lond).* 2012;36(6):843-54.

ITT Observed Means
(ITT: intention to treat)

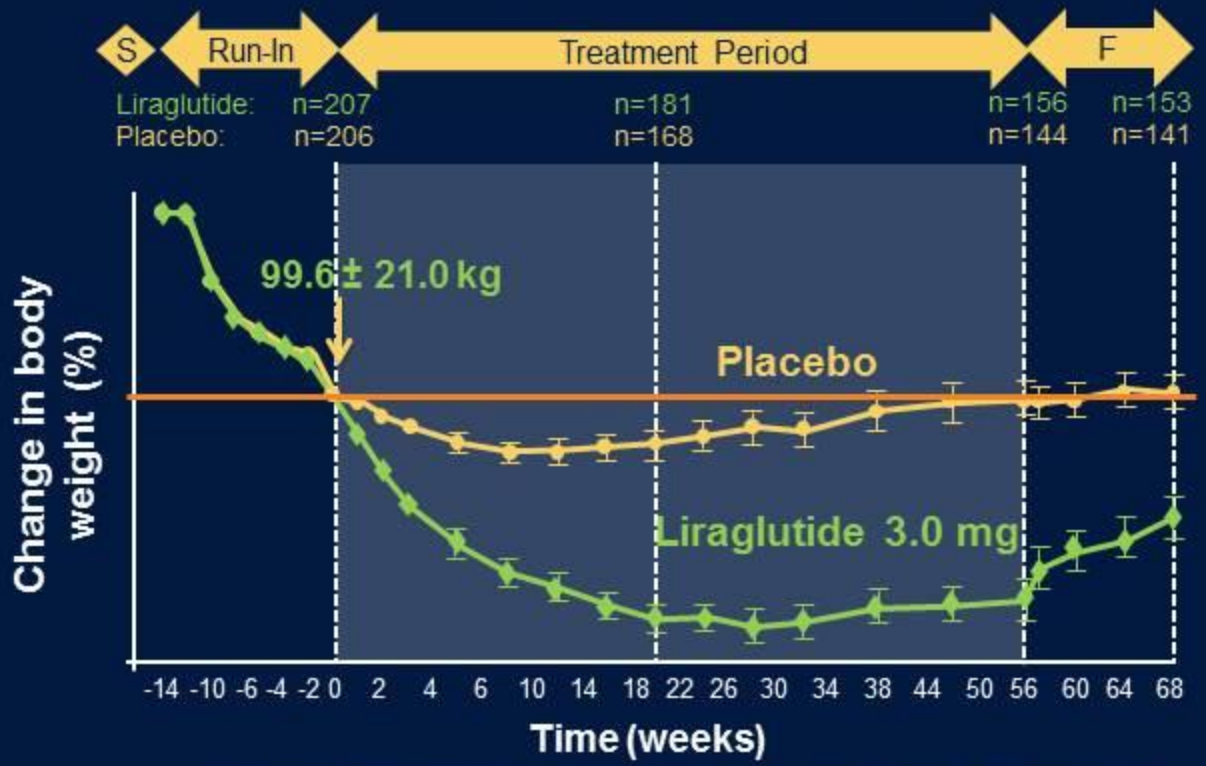
Liraglutide: Prevalence of Prediabetes at 1 and 2 years



Reprinted with permission from Astrup A, et al. *Int J Obes (Lond).* 2012;36(6):843-54.

Liraglutide 3 mg – Induced Weight Loss Following Hypocaloric Diet Run-In

Phase III: SCALE Maintenance Randomization Study



Mean ± SD weight at run-in (week – 12): 105.9 ± 22.1 kg

Mean percentage change in body weight and mean changes in vital signs from week –14 (screening) to week 68 (follow-up).

Reprinted with permission from Wadden, et al, *Int. J. Obesity (London)*, E-pub, 2013.

Summary

- Weight loss is now first line therapy for management of pre-diabetes and diabetes
- Weight loss improves multiple comorbid conditions
- Treatment selection depends upon BMI and is modified by patient's risk profile
- New antiobesity medications have been approved and others are in-development

The Obesity Conundrum

Practical Approaches for Patients Who Are Obese and "Well", Obese with Risk Factors, and Obese and "Sick"

THURSDAY, NOVEMBER 14, 2013

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Ken Fujioka, MD

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Case Presentations

Case 1

Case Description:

- Susan is a 52-year-old, newly single woman who comes in for weight management counseling. She gained her weight during a bad divorce several years ago. She is recently postmenopausal.
- She has two motivations: the first is to improve her tennis game (despite her size she plays doubles twice a week); the second is that she desires a better picture for her online dating profile. She tells you that she has always been a “big gal” with large hips and is a veteran of dieting.
- She takes no medications. Her mood is normal.

Case 1

Lab Data:

- BMI: 39 kg/m^2
- A1C: 5.4%
- BP: 132/84 mm Hg
- HR: 80 bpm
- LDL-C: 105 mg/dL
- HDL-C: 62 mg/dL
- Triglycerides: 147 mg/dL
- Total Cholesterol: 196 mg/dL

Case 2

Case Description:

- A 34-year-old, single woman with a history of major depression has noted rather significant weight gain since she was placed on antipsychotics along with her usual antidepressants.
- She is concerned about developing diabetes since her mother was just diagnosed with type 2 diabetes. She is not sexually active at this time.
- Her psychiatrist has just taken her off olanzapine (due to your advice), but the patient is still on a relatively high dose of an SSRI, which she needs to function.

Case 2

Lab Data:

- BMI: 33 kg/m^2
- Waist circumference: 39 inches (slightly flat)
- A1C: 6.2%
- FBS: 125 mg/dL
- BP: 136/82 mm Hg
- HR: 92 bpm
- LDL-C: 94 mg/dL
- Total cholesterol: 174 mg/dL
- HDL-C: 50 mg/dL
- Triglycerides: 151 mg/dL

Case 3

Case Description:

- A 55-year-old woman status post myocardial infarction 4 years ago comes in specifically asking if she can do anything about her weight.
- She is frustrated as she has tried multiple diets but struggles to stay on track. She gained most of her weight, which puts her in the obese category, after stopping cigarettes after her heart attack.
- She has had one episode of CHF 2 years ago and is starting to find mobility difficult with the increase in weight.
- She takes atorvastatin 20 mg daily, metoprolol 100 mg ER daily, lisinopril 20 mg daily, aspirin 81 mg daily.

Case 3

Lab Data:

- BMI: 36 kg/m^2
- BP: 130/77 mm Hg
- Total cholesterol: 186 mg/dL
- LDL-C: 102 mg/dL
- HDL-C: 47 mg/dL
- Triglycerides: 187 mg/dL
- A1C: 6.5%
- FBS: 126 mg/dL

The Obesity Conundrum

Practical Approaches for Patients Who Are Obese and "Well", Obese with Risk Factors, and Obese and "Sick"

Question & Answer

The Obesity Conundrum

Practical Approaches for Patients Who Are Obese and "Well", Obese with Risk Factors, and Obese and "Sick"

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