New Frontiers in CVD
Dilemmas of Obesity & Diabetes

The Four Challenging "Hot Spots"

ACC New York, Dec 8, 2017

No Disclosures

New Frontiers in CVD
Dilemmas of Obesity & Diabetes

1. Obesity. Diabetes and CV Disease

2. Mechanisms of Obesity and Diabetes

3. Obesity and Dietary Approach

4. Novel Diabetes Drugs

5. Bariatric Surgery

Obesity, Diabetes & Cardiovascular Diseases

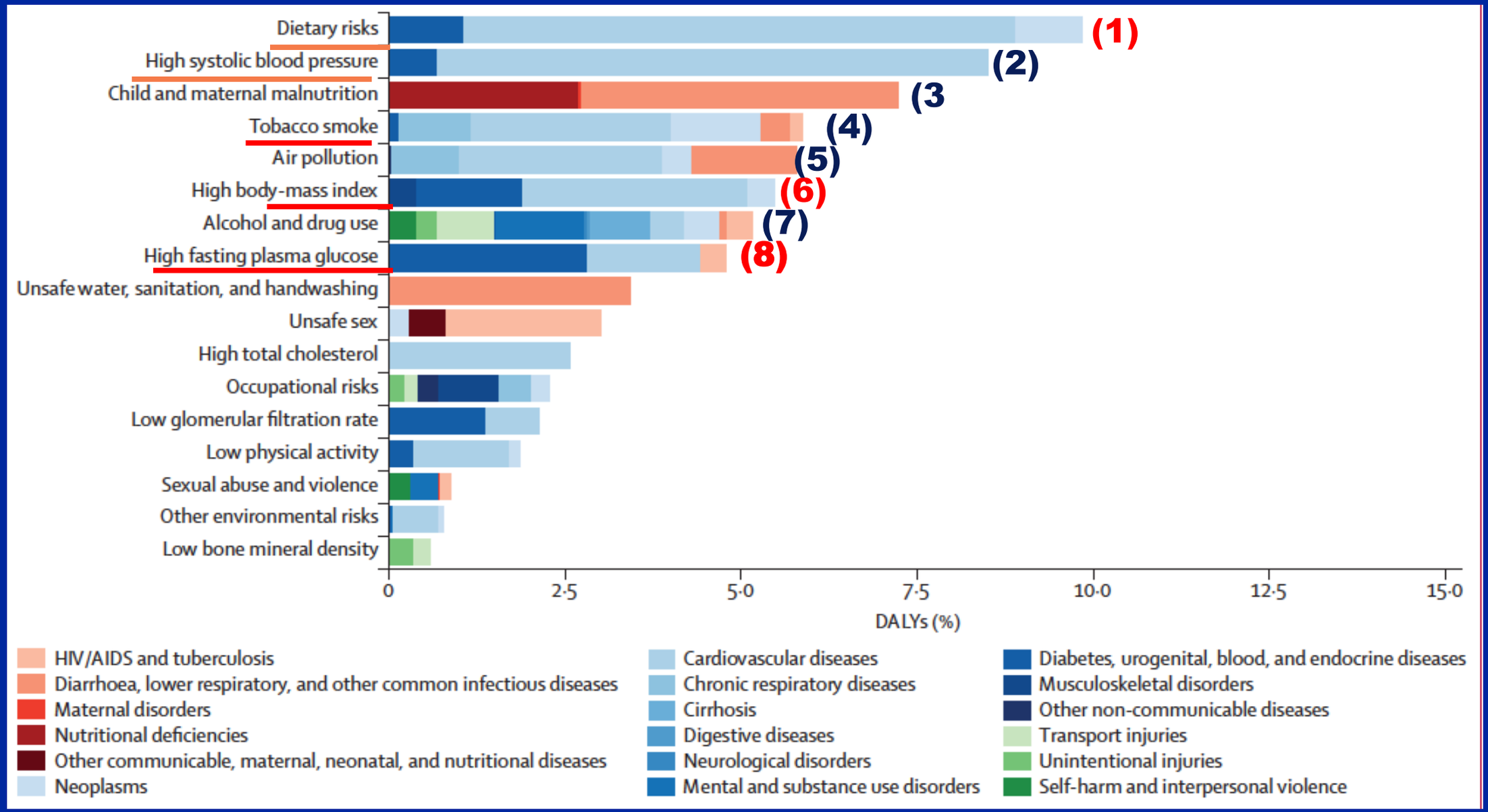
1. **Eight of the top 10 leading causes of death and disability in the United States today are chronic diseases (e.g., obesity and diabetes), each of them with a closely linked.**

2. **People who are overweight or obese account for more than two thirds of the U.S. population. Some professional organizations now classify obesity, defined as a BMI of 30 or higher, as a disease.**

3. **Excess body weight, is a major RF for CVD, associated with a proinflammatory state, a systemic adrenergic activity, dyslipidemia, hyperglycemia & with circulating levels of a variety of perturbed bioactive molecules. Clearly, the pathophysiology is complex.**

PE Scherer, JA Hill. Circ Res 2016; 118:1703
SB Heymsfield et al., N Engl J Med 2017; 376:254

Global DALYs & Mortality – Risk Factors



GBD 2013 Risk Factors Collaborators (MH Forouzanfat et. al.) Lancet. 2015;386:2287

Obesity, Diabetes & Cardiovascular Diseases

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2. People who are overweight or obese account for more than two thirds of the U.S. population. Some professional organizations now classify obesity, defined as a BMI of 30 or higher, as a disease.

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Obesity, Diabetes & Cardiovascular Diseases

4. Diabetes affects >180 million people around the world, and the number of patients is anticipated to increase to 300 million by 2025.

5. Obesity-associated type 2 diabetes accounts for 90% to 95% of all diagnosed diabetes cases in adults.

6. Diabetes is a powerful predictor of CV morbidity and mortality, and an independent RF for death in heart failure.

7. The complex mechanisms underlying the deleterious impact of diabetes on the heart and the vasculature are poorly characterized.

PE Scherer, JA Hill. Circ Res 2016; 118:1703
SB Heymsfield et al., N Engl J Med 2017; 376:254

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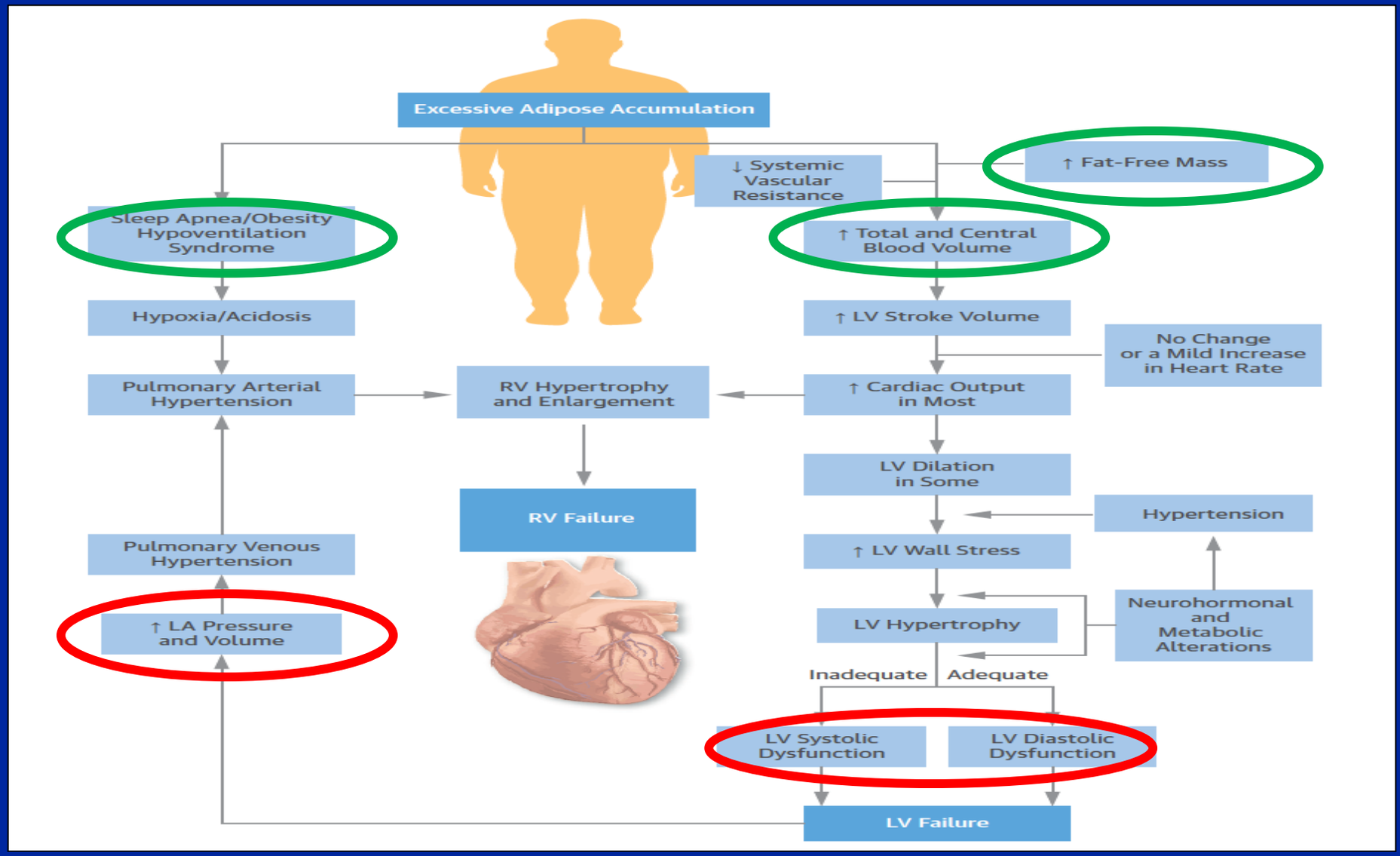
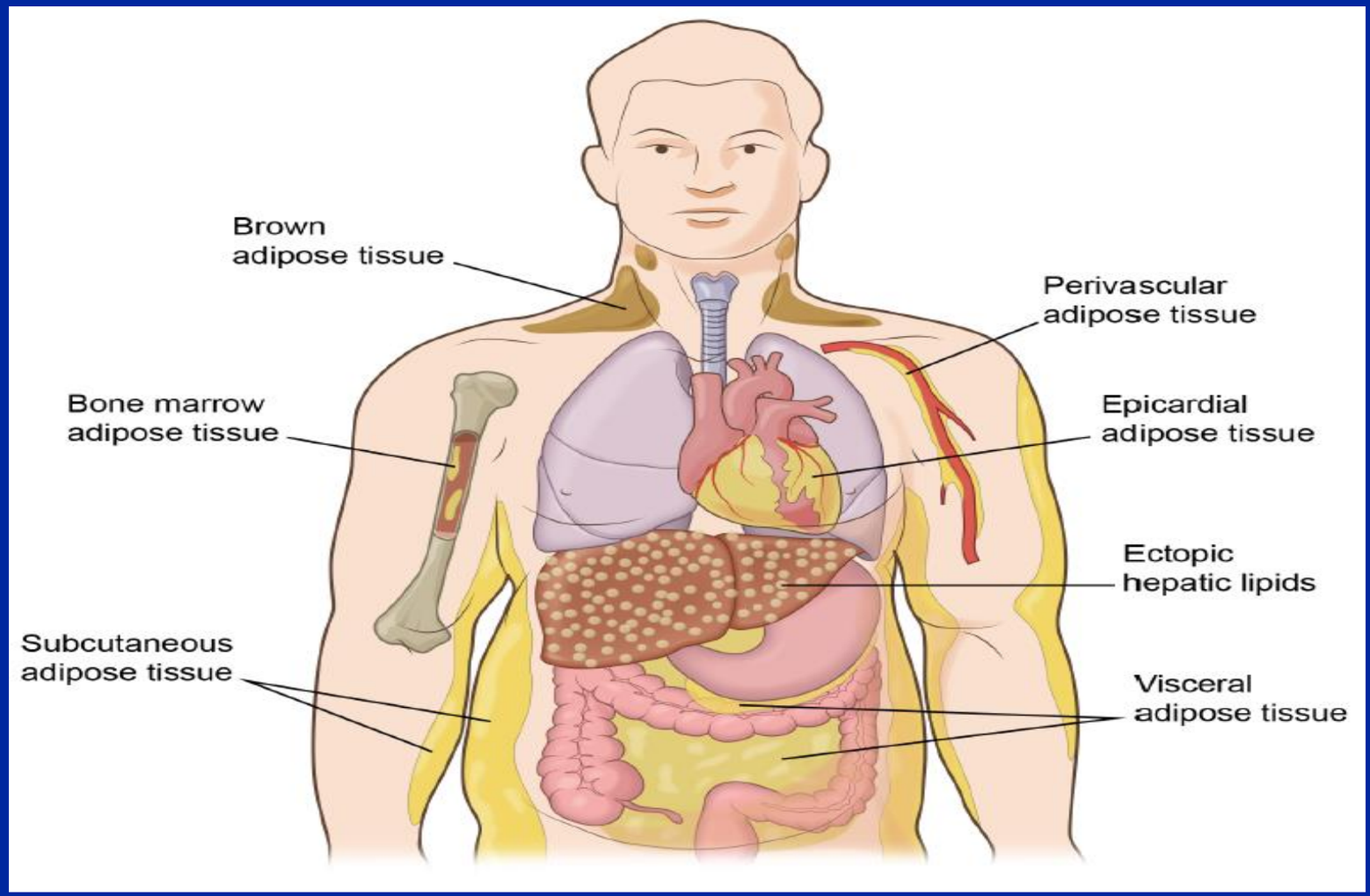
Obesity and CVD



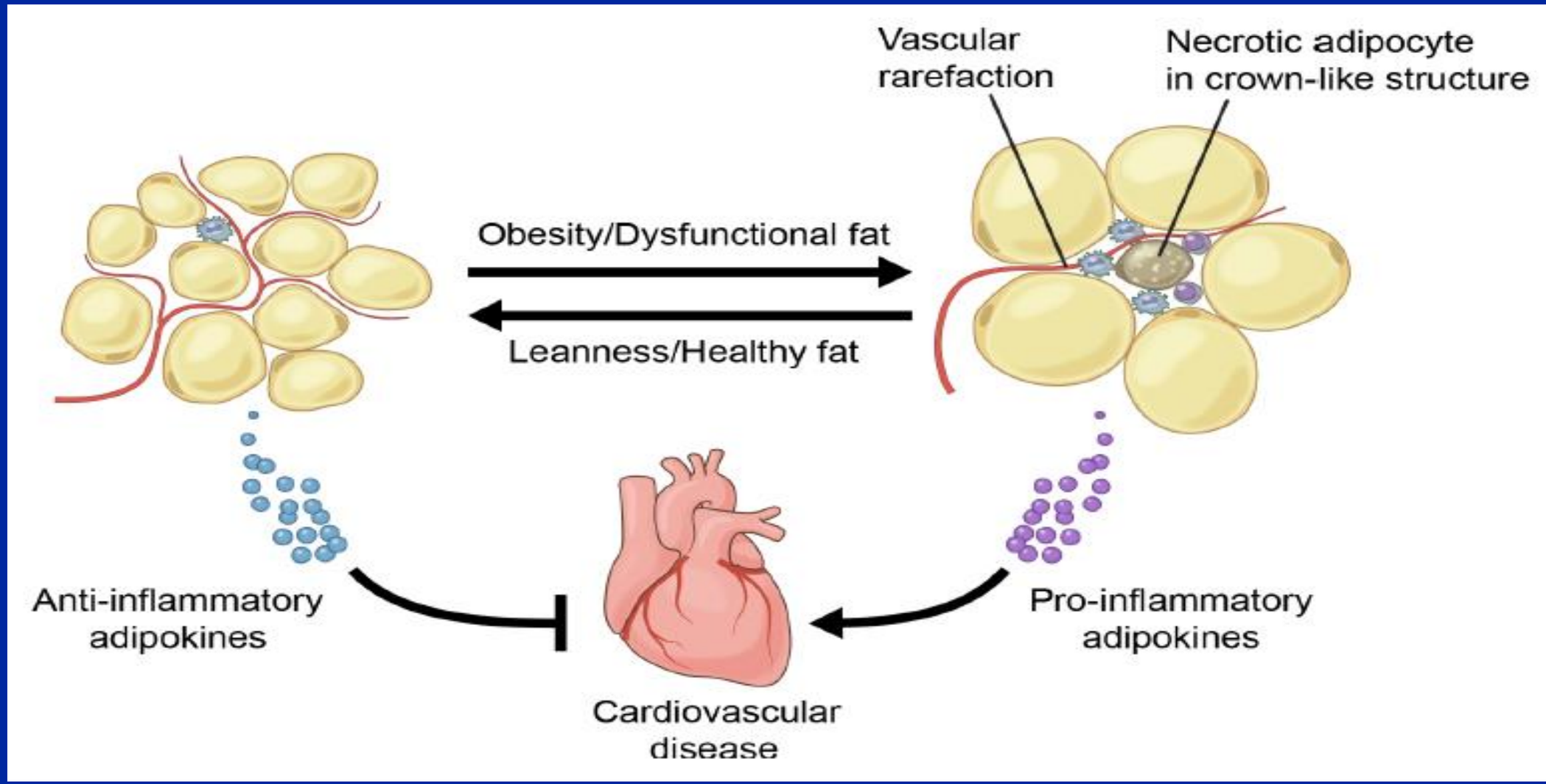
CJ Lavie et. al. J Am Coll Cardiol 2017;70:2022

Adipose Tissue Depots Occur Throughout The Body



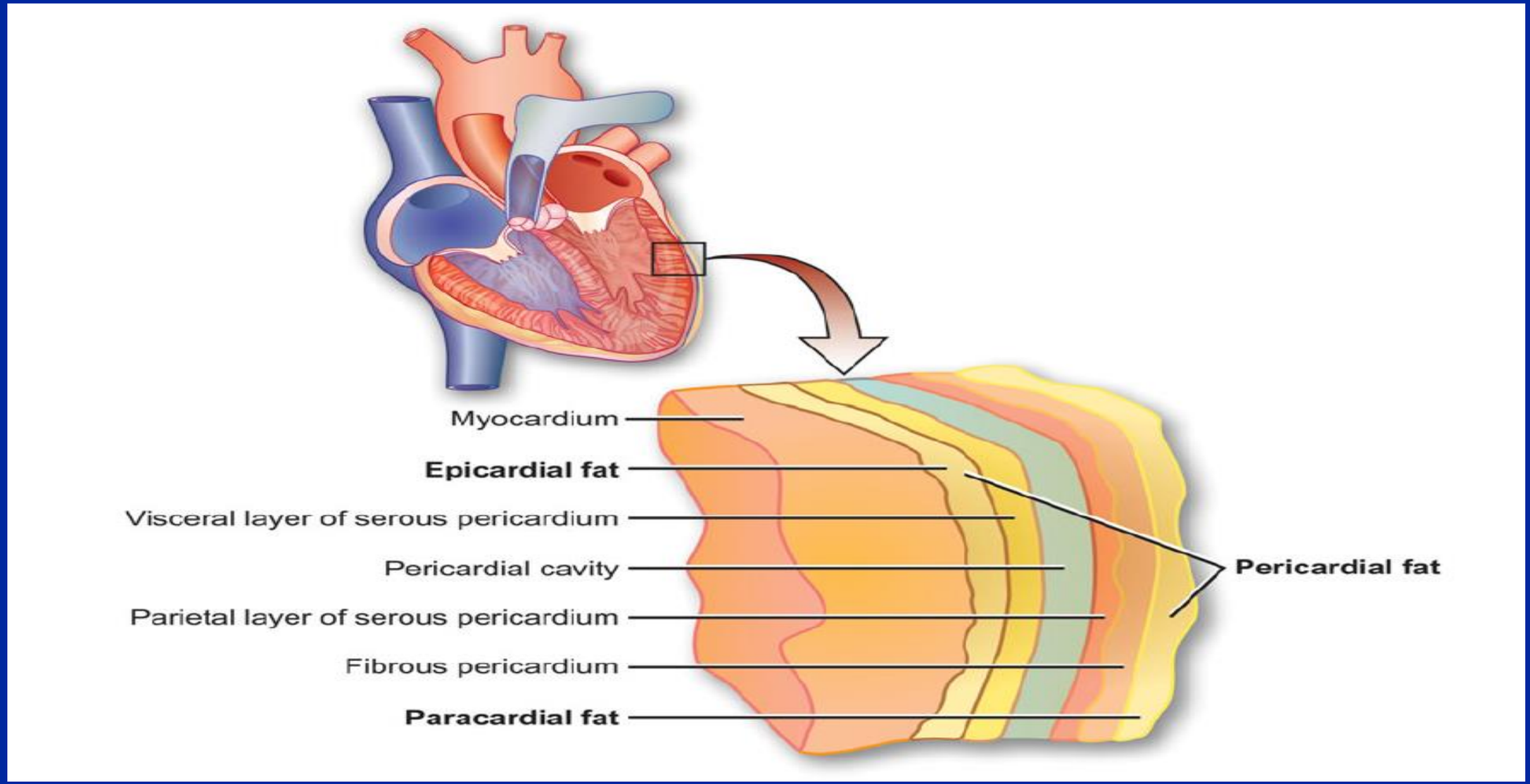
JJ Fuster et. al. Circ Res. 2016;118:1786

Lean Adipose Tissue & Protective Anti-adipokines VS Obesity Detrimental Pro-Adipokines



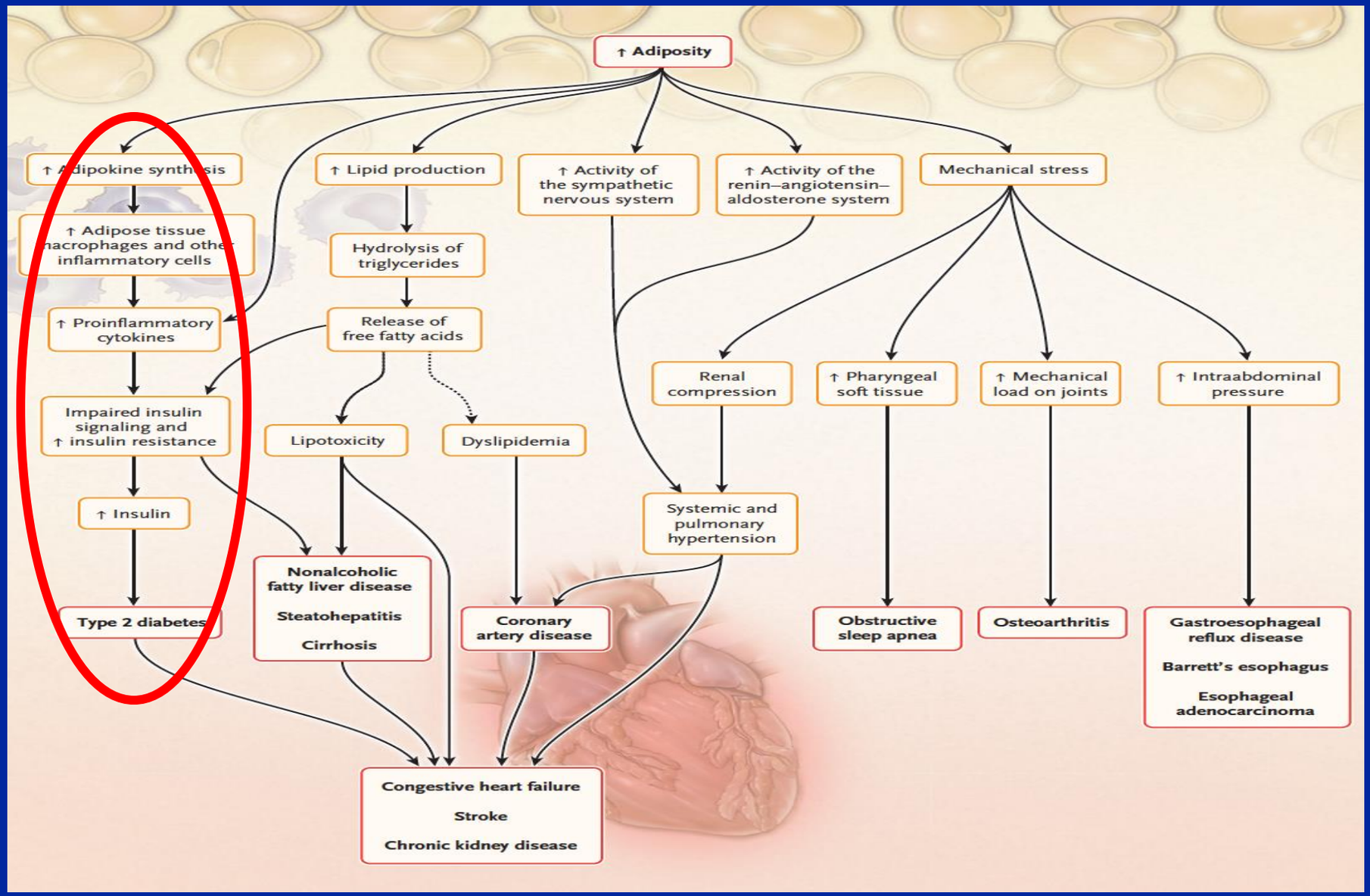
JJ Fuster et. al. Circ Res. 2016;118:1786

Definition of Epicardial Fat And Related Adipose Tissues



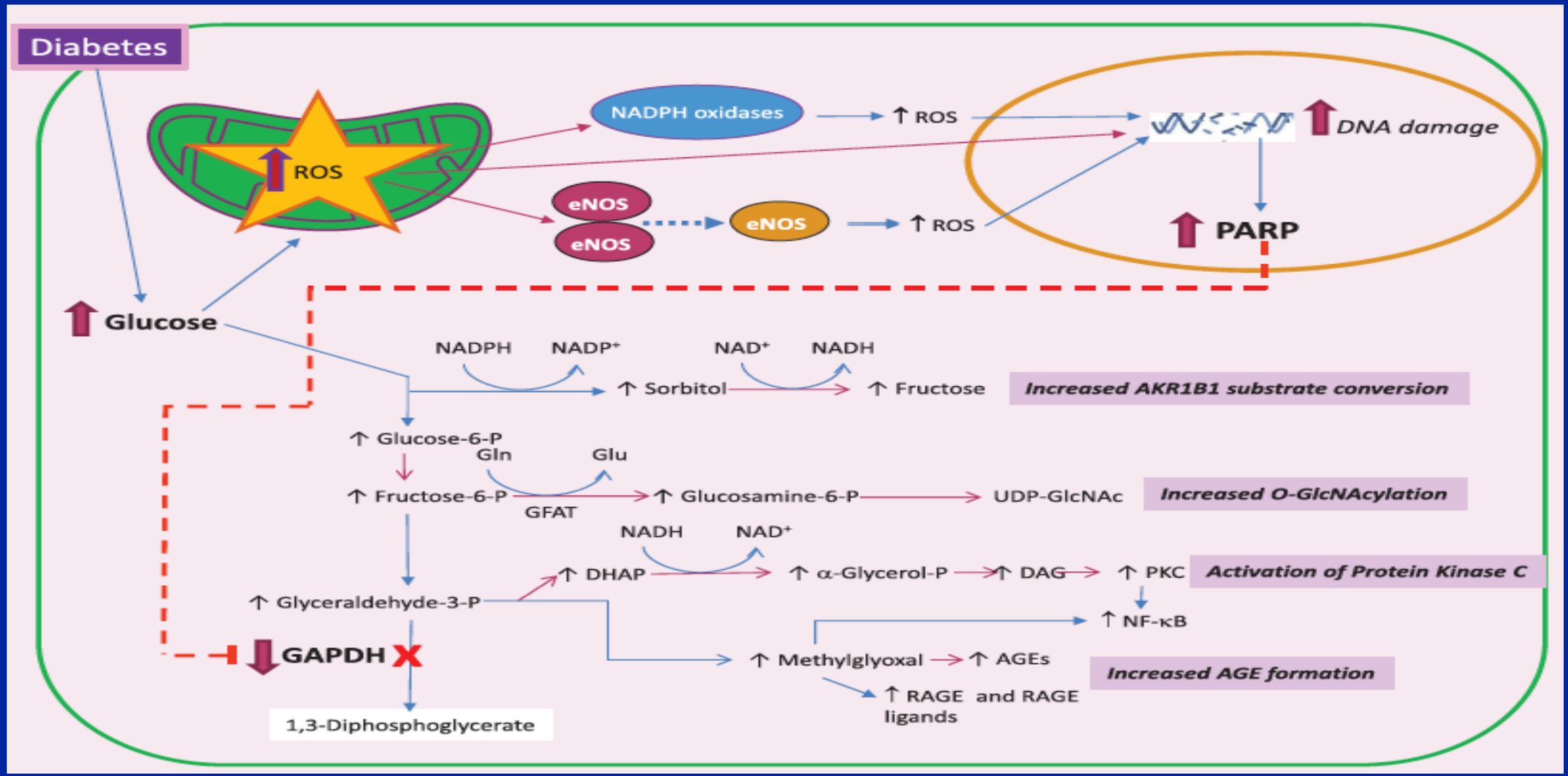
CX Wong et. al. Eur Heart J. 2017;38:1294

Some Pathways through Which Excess Adiposity Leads to Major Risk Factors and Common Chronic Diseases



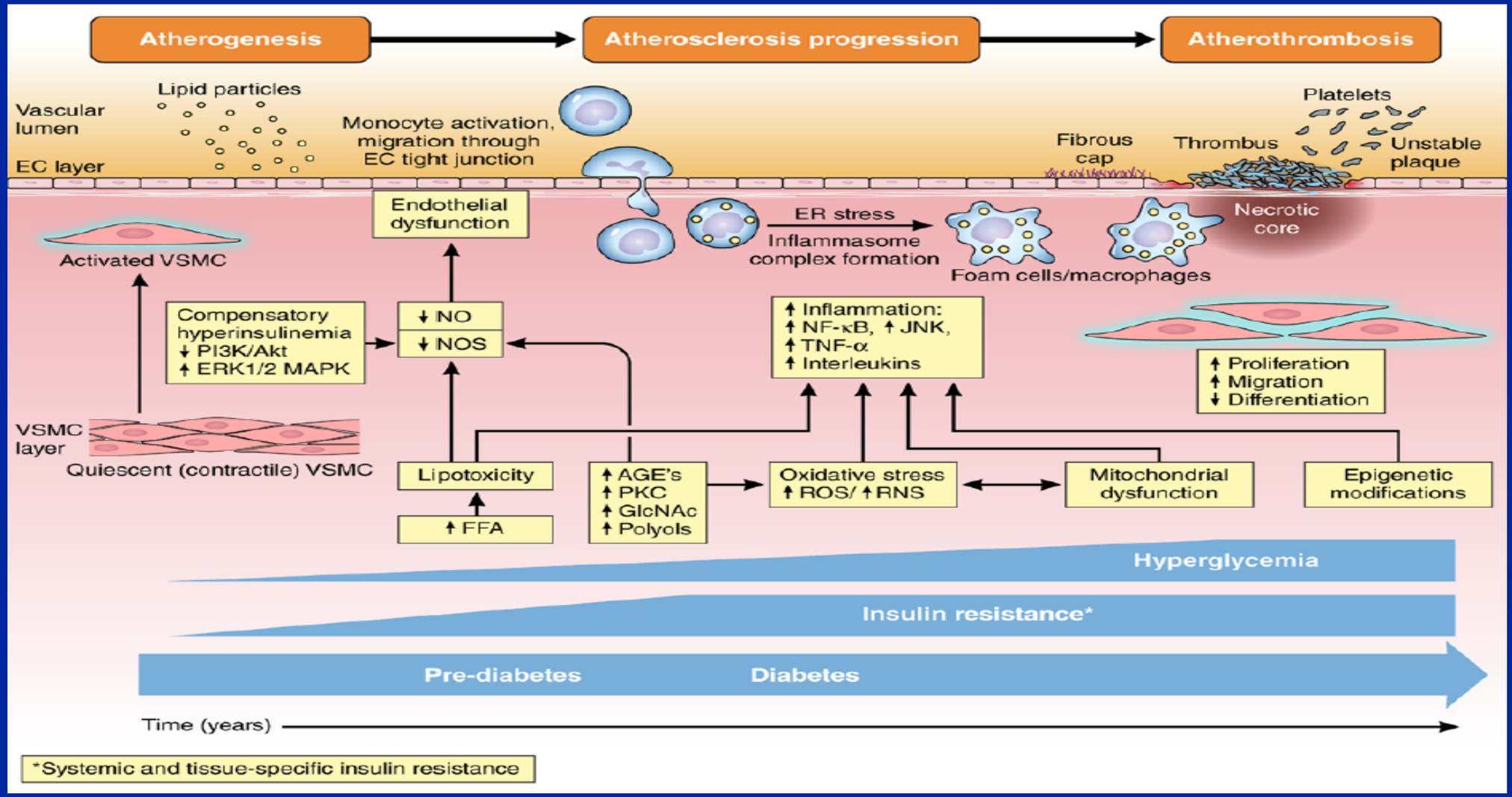
SB Heymsfield et. al. N Engl J Med 2017;376:254

Four Hyperglycemia-induced Pathogenic Mechanisms Are Activated By Overproduction Of ROS Species



MS Shah et. al. Circ Res. 2016;118:1808

Progression Of Atherosclerosis In Diabetes Mellitus



CC Low Wang et. al. Circulation. 2016;133:2459

Potential Reasons for the Obesity Paradox in AF

1. Nonpurposeful weight loss
2. Greater metabolic reserves
3. Less cachexia
4. Protective cytokines
5. Earlier presentation*
6. Attenuated response to renin-angiotensin-aldosterone system
7. Higher blood pressure leading to more cardiac medications
8. Different cause of CVD and AF
9. Increase muscle mass and muscular strength
10. Implications related to cardiorespiratory fitness
11. Confounders and collider bias

CJ Lavie et. al. J Am Coll Cardiol 2017;70:2022

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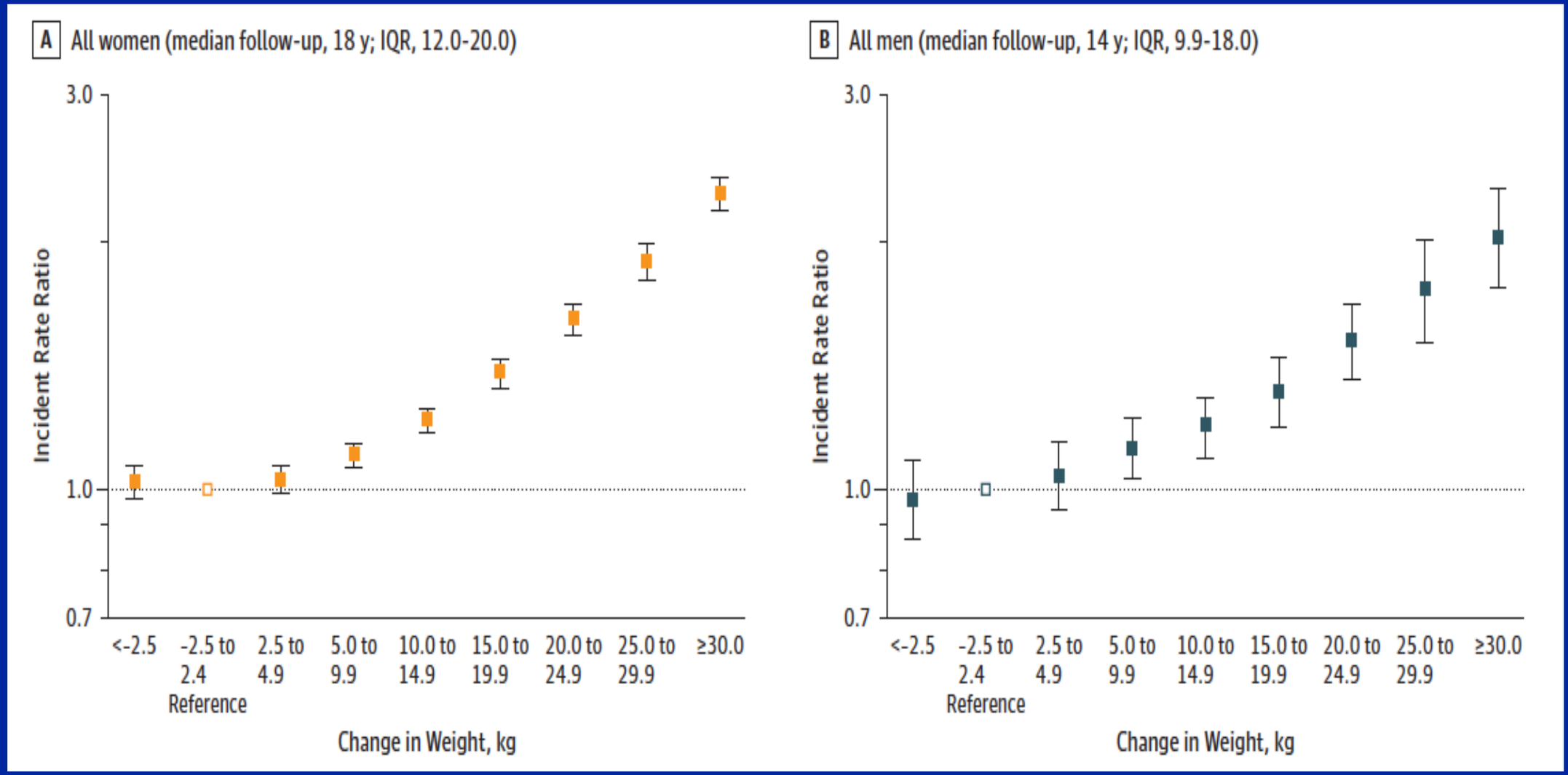
Associations of Weight Gain From Early / Middle Adulthood With Major Health Outcomes Later in Life

Cohort analysis of US women from the Nurses' Health Study (1976-June 30, 2012) and US men from the Health Professionals Follow-Up Study (1986-January 31, 2012) who recalled weight during early adulthood, at age of 18 years in women; 21 years in men, and reported current weight during middle adulthood, at age of 55 years. Beginning at the age of 55 years, participants were followed up to the incident disease outcomes. CVD, cancer, and death were confirmed by medical records or the National Death Index. A composite healthy aging outcome was defined as being free of 11 chronic diseases and major cognitive or physical impairment. In these cohorts of health professionals, weight gain during adulthood was associated with significantly increased risk of major chronic diseases and decreased odds of healthy aging. These findings may help counsel patients regarding the risks of weight gain.

Y Zheng et al., JAMA 2017; 318:255

Associations of Weight Gain From Early to Middle Adulthood With the Risk of a Major Chronic Diseases



Y Zheng et al., JAMA 2017; 318:255

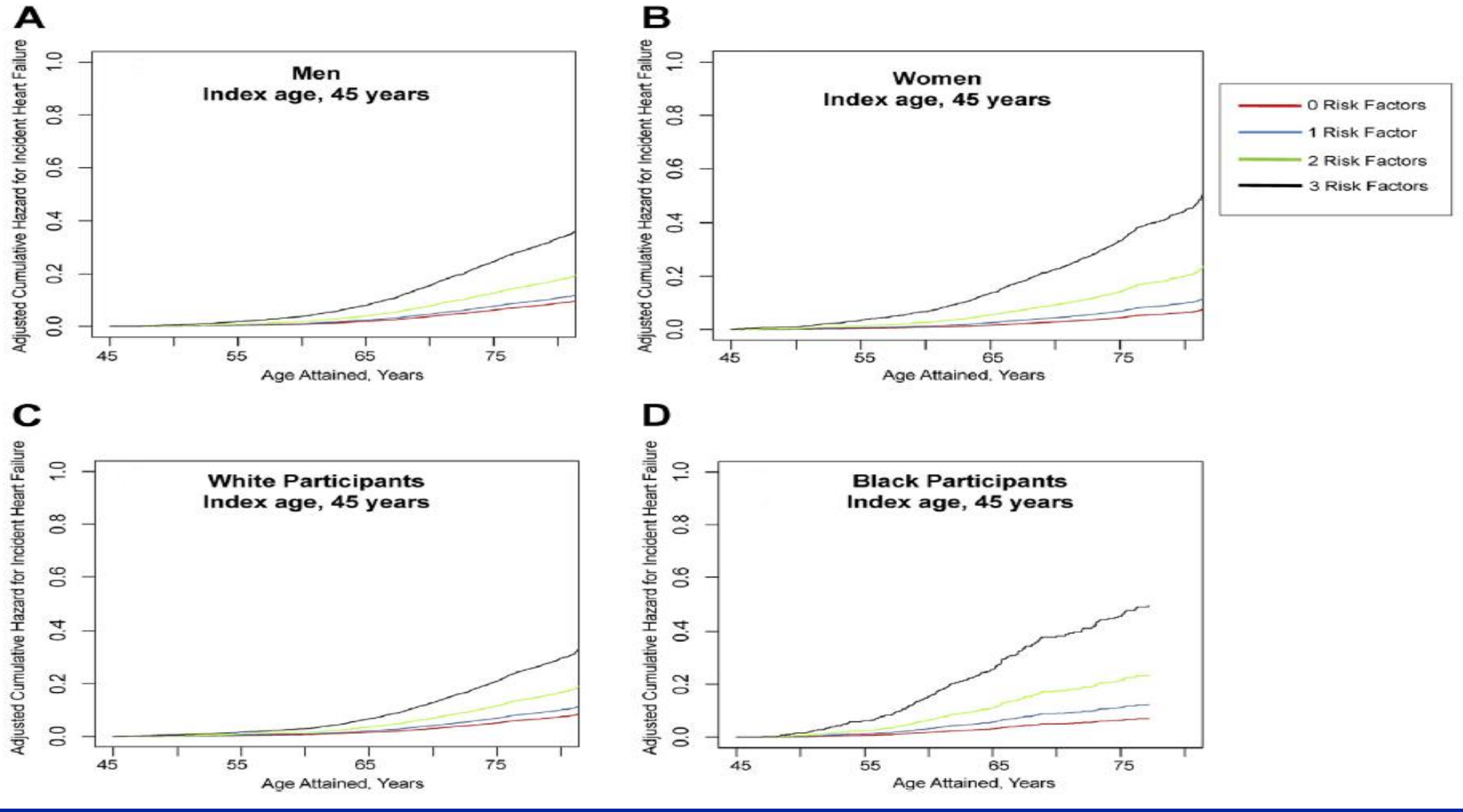
Hypertension, Obesity, Diabetes - Heart Failure

The Cardiovascular Disease Lifetime Risk Pooling Project

We conducted a pooled, individual-level analysis sampling from communities across the United States as part of 4 cohort studies: the Framingham Heart, Framingham Offspring, Chicago Heart Association Detection Project in Industry, and ARIC. Participants with and without hypertension (blood pressure ≥140/90 mm Hg or treatment), obesity (body mass index ≥30 kg/m^2), or diabetes (fasting glucose ≥126 mg/dL or treatment), and combinations of these factors, at index ages of 45 years and 55 years through 95 years. Estimate the association between risk factors at mid-life and incident heart failure, heart failure-free survival, and overall survival

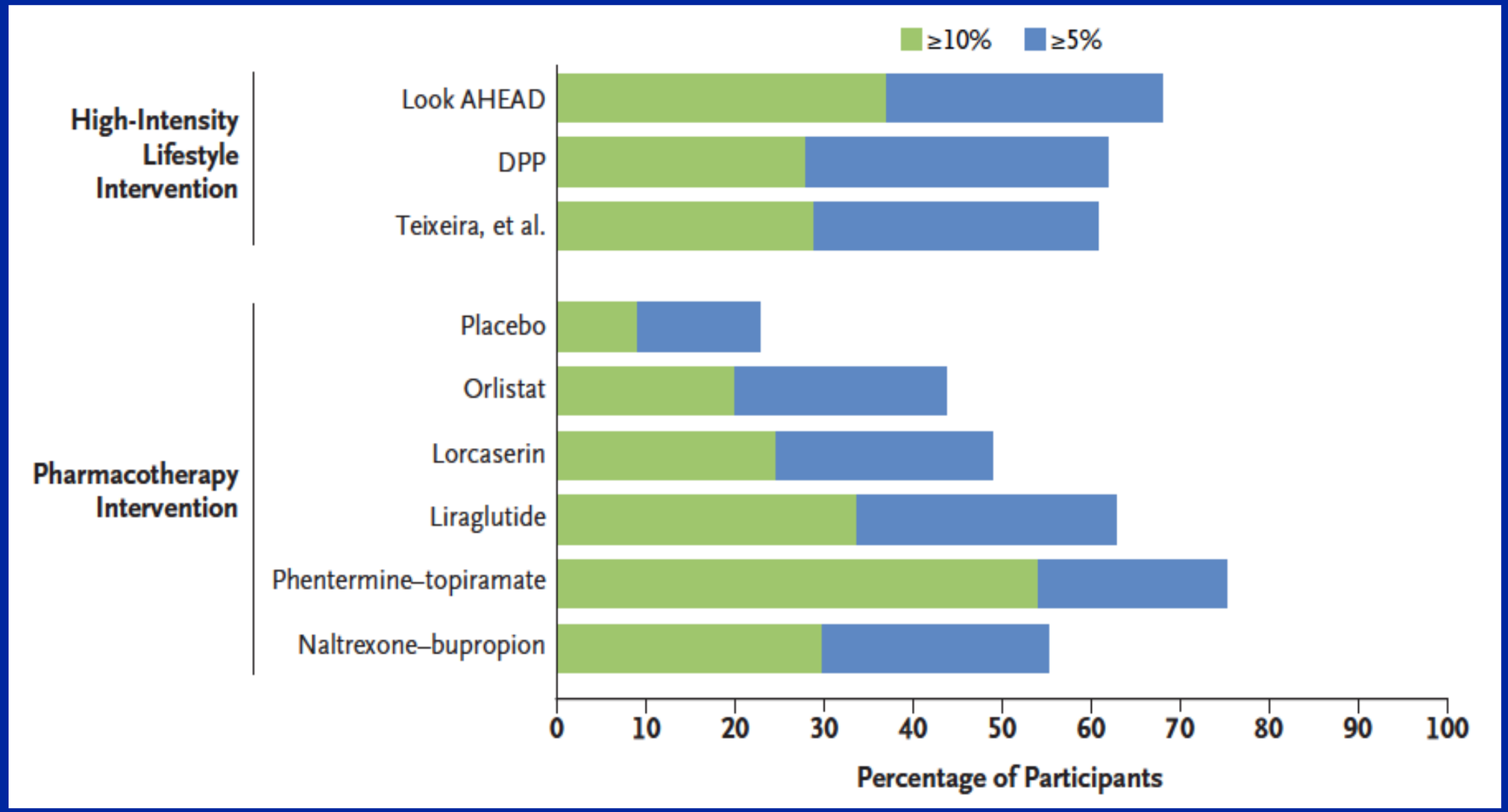
FS Ahmad et al., J Am Coll Cardiol HF 2016; 4:911

Cumulative Hazard for Incident Heart Failure for Index Age 45 Years



FS Ahmad et. al. J Am Coll Cardiol HF 2016;4:911

Weight Loss at 1 Year with High Lifestyle Interventions or Pharmacotherapy Combined with Moderate Lifestyle Counseling



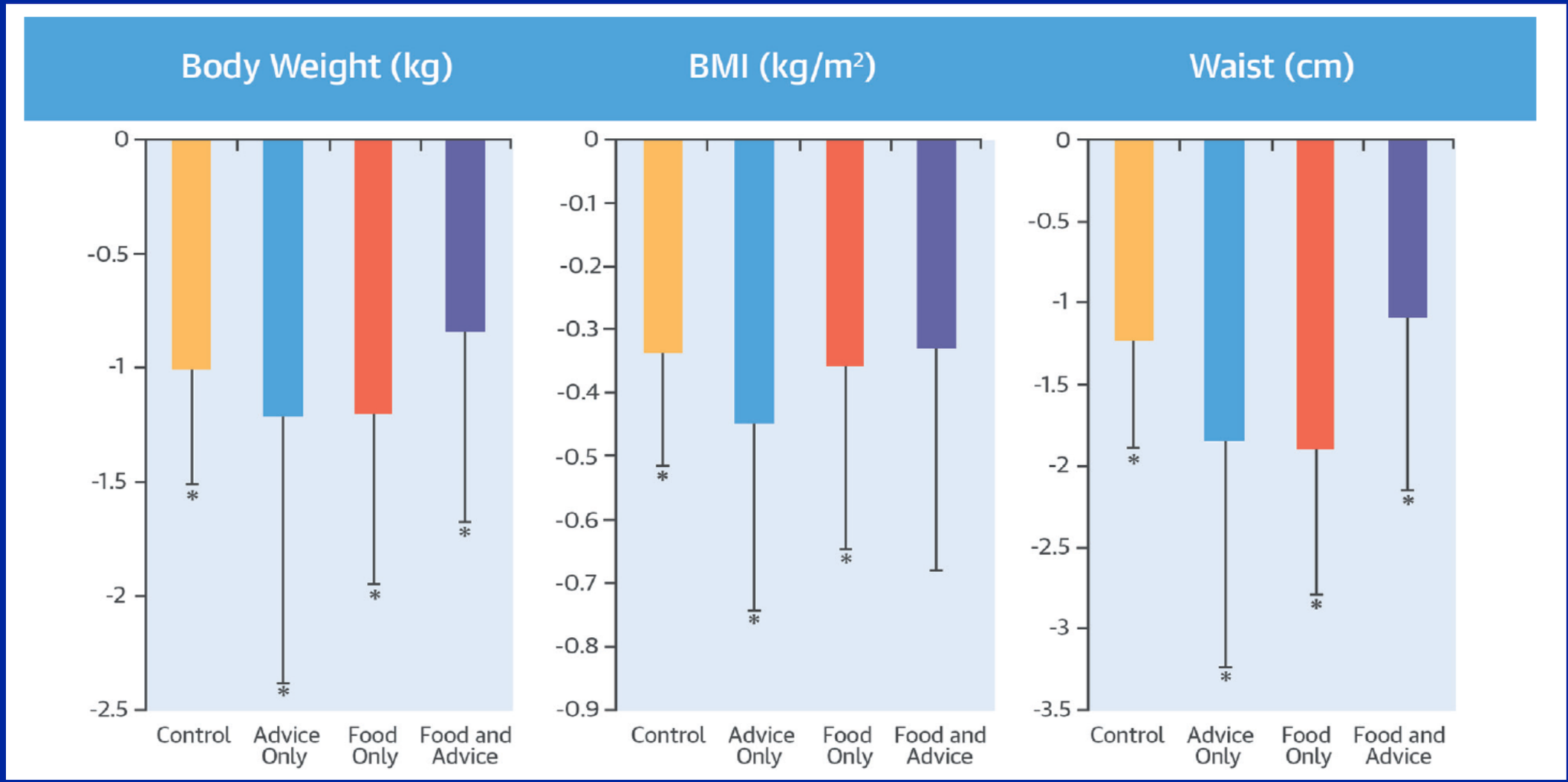
SB Heymsfield et. al. N Engl J Med 2017;376:254

Effect of Current Dietary Recommendations on Weight Loss and CV Risk Factors

Healthy overweight men (n=209) and women (n=710), mean age 44.7 years, BMI 32.4 kg/m^2, were randomized between November 2005 and August 2009 to receive Health Canada's food guide (control, n=486) or 1 of 3 interventions: advice (DASH); weekly food provision reflecting this advice; or food delivery plus advice. Interventions lasted 6 months with 12-month follow-up. Provision of foods increased retention but only modestly increased intake of recommended foods. Current dietary recommendations showed small overall benefits in coronary heart disease risk factors.

DJA Jenkins et al., J Am Coll Cardiol 2017; 69:1103

Current Dietary Recommendations on Weight Loss and Cardiovascular Risk Factors



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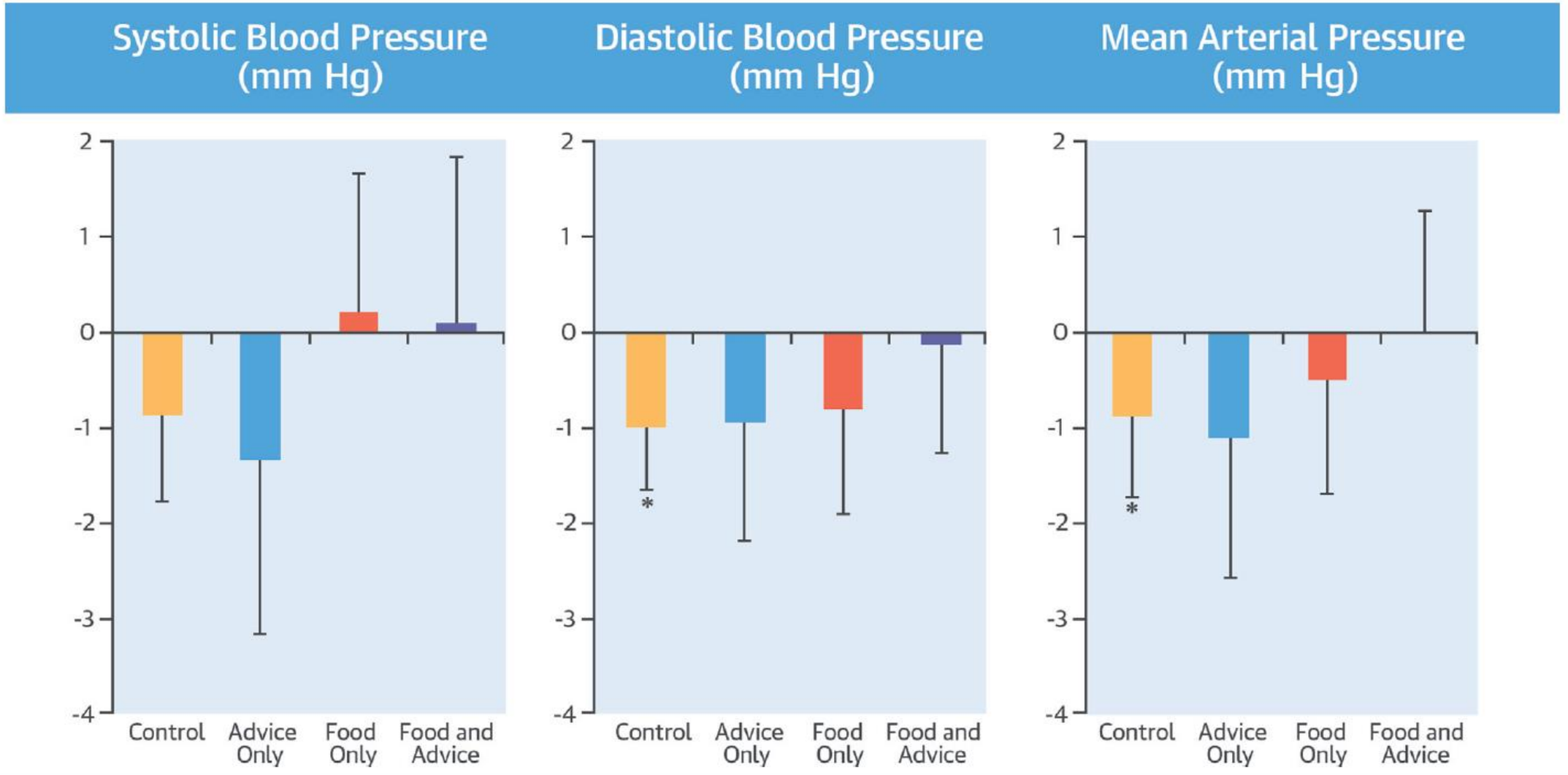
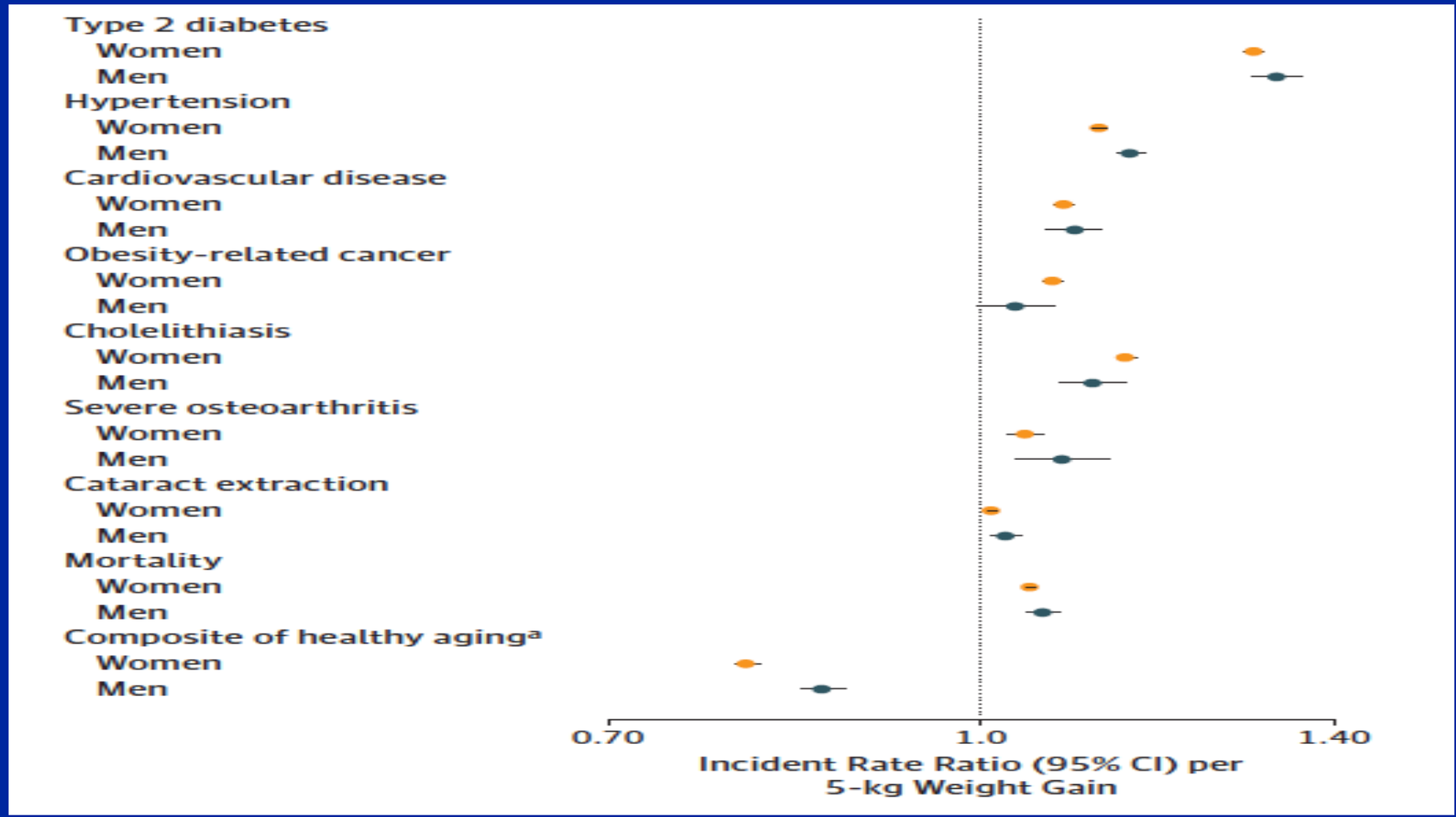
Current Dietary Recommendations on Weight Loss and Cardiovascular Risk Factors



DJA Jenkins et. al. J Am Coll Cardiol 2017;69:1103

Associations of Weight Gain From Early to Middle Adulthood With Risk of Individual Health Outcomes



Y Zheng et al., JAMA 2017; 318:255

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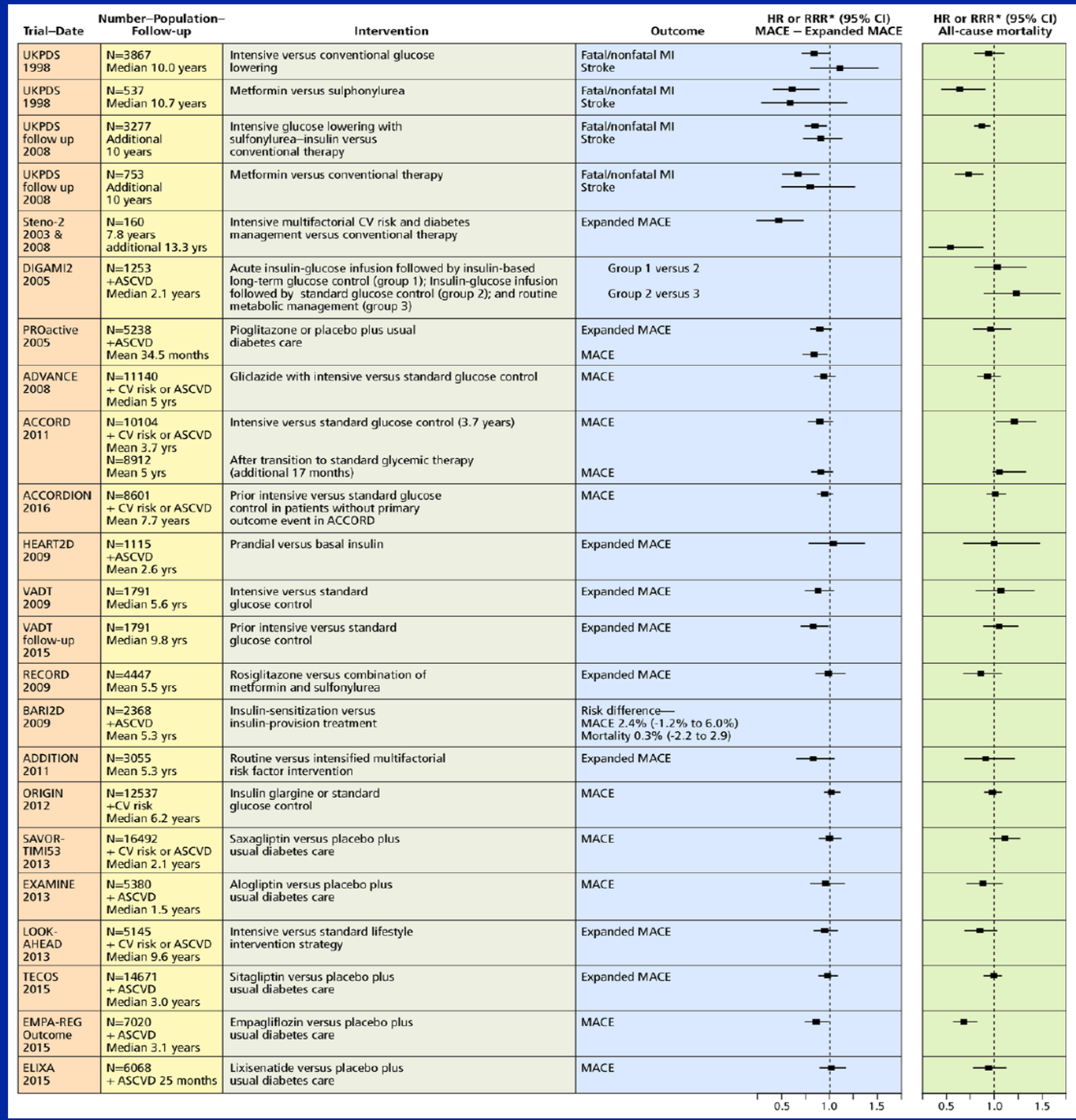
Randomized, controlled,cardiovascular outcome trials of glucose-lowering drugs or strategies in people with type 2 diabetes mellitus



Trial–Date	Number–Population–Follow-up	Intervention	Outcome
UKPDS 1998	N=3867 Median 10.0 years	Intensive versus conventional glucose lowering	Fatal/nonfatal MI Stroke
UKPDS 1998	N=537 Median 10.7 years	Metformin versus sulphonylurea	Fatal/nonfatal MI Stroke
UKPDS follow up 2008	N=3277 Additional 10 years	Intensive glucose lowering with sulfonylurea–insulin versus conventional therapy	Fatal/nonfatal MI Stroke
UKPDS follow up 2008	N=753 Additional 10 years	Metformin versus conventional therapy	Fatal/nonfatal MI Stroke
Steno-2 2003 & 2008	N=160 7.8 years additional 13.3 yrs	Intensive multifactorial CV risk and diabetes management versus conventional therapy	Expanded MACE
DIGAMI2 2005	N=1253 +ASCVD Median 2.1 years	Acute insulin-glucose infusion followed by insulin-based long-term glucose control (group 1); Insulin-glucose infusion followed by standard glucose control (group 2); and routine metabolic management (group 3)	Group 1 versus 2 Group 2 versus 3
PROactive 2005	N=5238 +ASCVD Mean 34.5 months	Pioglitazone or placebo plus usual diabetes care	Expanded MACE MACE
ADVANCE 2008	N=11140 + CV risk or ASCVD Median 5 yrs	Gliclazide with intensive versus standard glucose control	MACE
ACCORD 2011	N=10104 + CV risk or ASCVD Mean 3.7 yrs N=8912 Mean 5 yrs	Intensive versus standard glucose control (3.7 years) After transition to standard glycemic therapy (additional 17 months)	MACE MACE
ACCORDION 2016	N=8601 + CV risk or ASCVD Mean 7.7 years	Prior intensive versus standard glucose control in patients without primary outcome event in ACCORD	MACE
HEART2D 2009	N=1115 +ASCVD Mean 2.6 yrs	Prandial versus basal insulin	Expanded MACE
VADT 2009	N=1791 Median 5.6 yrs	Intensive versus standard glucose control	Expanded MACE
VADT follow-up 2015	N=1791 Median 9.8 yrs	Prior intensive versus standard glucose control	Expanded MACE
RECORD 2009	N=4447 Mean 5.5 yrs	Rosiglitazone versus combination of metformin and sulfonylurea	Expanded MACE
BARI2D 2009	N=2368 +ASCVD Mean 5.3 yrs	Insulin-sensitization versus insulin-provision treatment	Risk difference— MACE 2.4% (-1.2% to 6.0%) Mortality 0.3% (-2.2 to 2.9)
ADDITION 2011	N=3055 Mean 5.3 yrs	Routine versus intensified multifactorial risk factor intervention	Expanded MACE
ORIGIN 2012	N=12537 +CV risk Median 6.2 years	Insulin glargine or standard glucose control	MACE
SAVOR-TIMI53 2013	N=16492 + CV risk or ASCVD Median 2.1 years	Saxagliptin versus placebo plus usual diabetes care	MACE
EXAMINE 2013	N=5380 + ASCVD Median 1.5 years	Alogliptin versus placebo plus usual diabetes care	MACE
LOOK-AHEAD 2013	N=5145 + CV risk or ASCVD Median 9.6 years	Intensive versus standard lifestyle intervention strategy	Expanded MACE
TECOS 2015	N=14671 + ASCVD Median 3.0 years	Sitagliptin versus placebo plus usual diabetes care	Expanded MACE
EMPA-REG Outcome 2015	N=7020 + ASCVD Median 3.1 years	Empagliflozin versus placebo plus usual diabetes care	MACE
ELIXA 2015	N=6068 + ASCVD 25 months	Lixisenatide versus placebo plus usual diabetes care	MACE

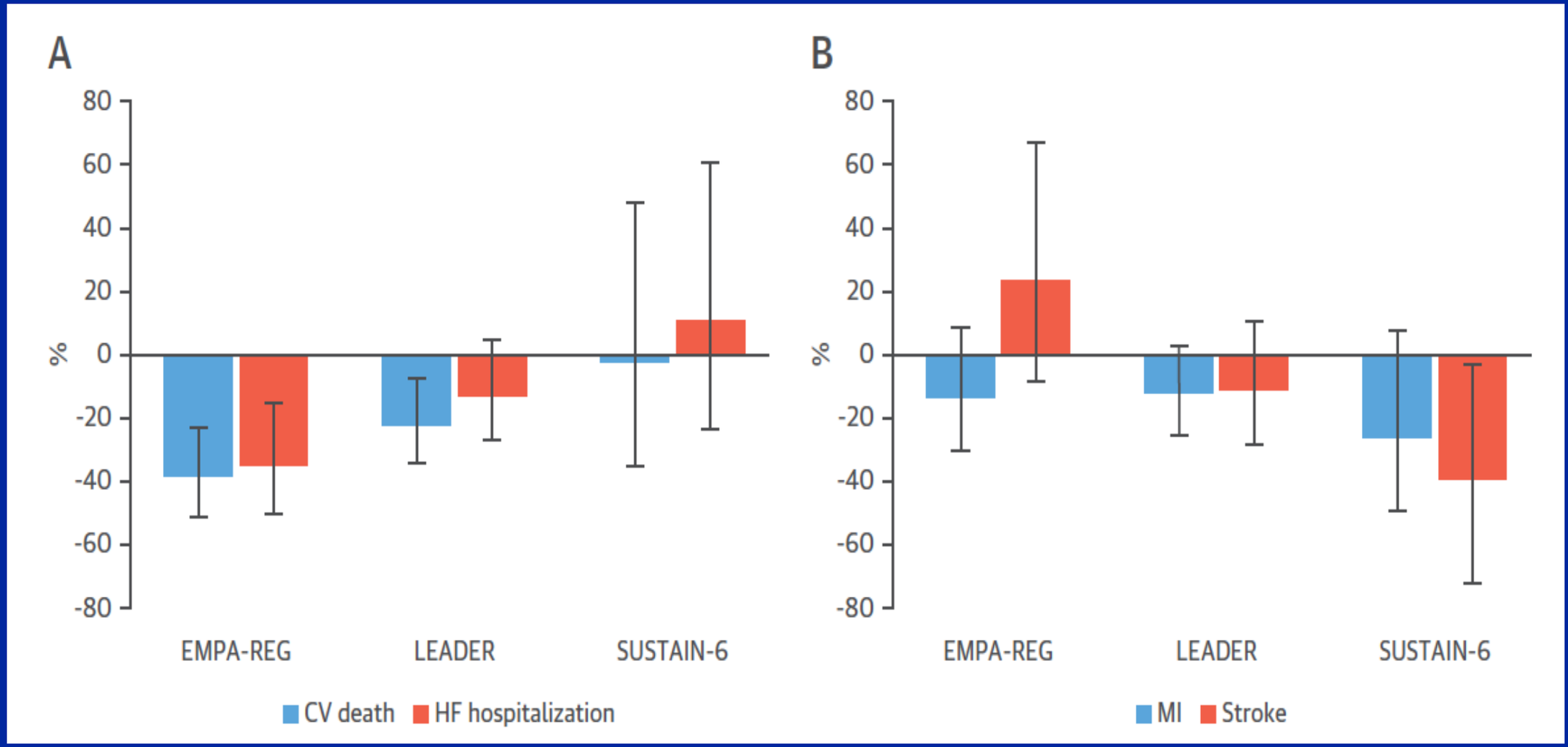
CC Low Wang et. al. Circulation. 2016;133:2459

Novel Diabetes Drugs and the CV Specialist

Recently, treatment with 2 newer classes of type 2 diabetes drugs were found to reduce events in patients with diabetes and CVD. The sodium-glucose cotransporter 2 inhibitor, empagliflozin, markedly and rapidly reduced CV death and heart failure hospitalization. More recently, the glucagon-like peptide-1 receptor agonists liraglutide and semaglutide also reduced CV death and/or major adverse CV events, but did so more slowly and did not influence heart failure risks, suggesting alternative mechanisms of benefit.

N Sattar et al., J Am Coll Cardiol 2017; 69:2646

Outcome Benefits
in the EMPA-REG OUTCOME, LEADER & SUSTAIN-6 Trials



N Sattar et. al. J Am Coll Cardiol 2017;69:2646

Incretin-Based Therapy for Diabetes

Incretin-based therapies are effective glucose-lowering drugs that have an increasing role in the treatment of type 2 diabetes because of their efficacy, safety, and ease of use. Both glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors are commonly used for glycemic control as adjuncts to metformin, other oral antiglycemic agents, or insulin. Glucagon-like peptide-1 receptor agonists may have additional effects, such as weight loss, that may be advantageous in obese patients. There is a large body of evidence from randomized controlled clinical trials supporting their CV safety However, concerns have been raised, particularly regarding their safety in heart failure.

G Waldrop et al., J Am Coll Cardiol 2016; 67:1488

Canagliflozin for 1ary and 2ary Prevention of CV Events

Canagliflozin is a sodium glucose cotransporter 2 inhibitor that significantly reduces the composite of CV death, nonfatal MI, or nonfatal stroke in patients with type 2 diabetes mellitus and elevated CV risk. The CANVAS Program randomly assigned 10,142 participants with type 2 diabetes mellitus to canagliflozin or placebo. The primary prevention cohort comprised individuals ≥50 years of age with ≥2 risk factors for CV events but with no prior CV event, and the secondary prevention cohort comprised individuals ≥30 years of age with a prior CV event. The primary end point was a composite of CV death, nonfatal myocardial infarction, or nonfatal stroke

CANVAS (KW Mahaffey et al.) Circulation 2017; 137:1

Canagliflozin for 1ary and 2ary Prevention of CV Events

1) In the total cohort, the 1ary end point was reduced with canagliflozin compared with placebo (26.9 versus 31.5/1000 patient-years; *P*<0.001 for noninferiority, *P*=0.02 for superiority).

2) The 1ary end point event rate was higher in the 2ary prevention group compared with the 1ary prevention group (36.9 versus 15.7/1000 patient-years, *P*<0.001).

3) Renal outcomes and heart failure hospitalization were similarly reduced in the secondary and primary prevention cohorts. Lower extremity amputations were similarly increased in the secondary and primary prevention cohorts (HR, 2.07; HR, 1.52)

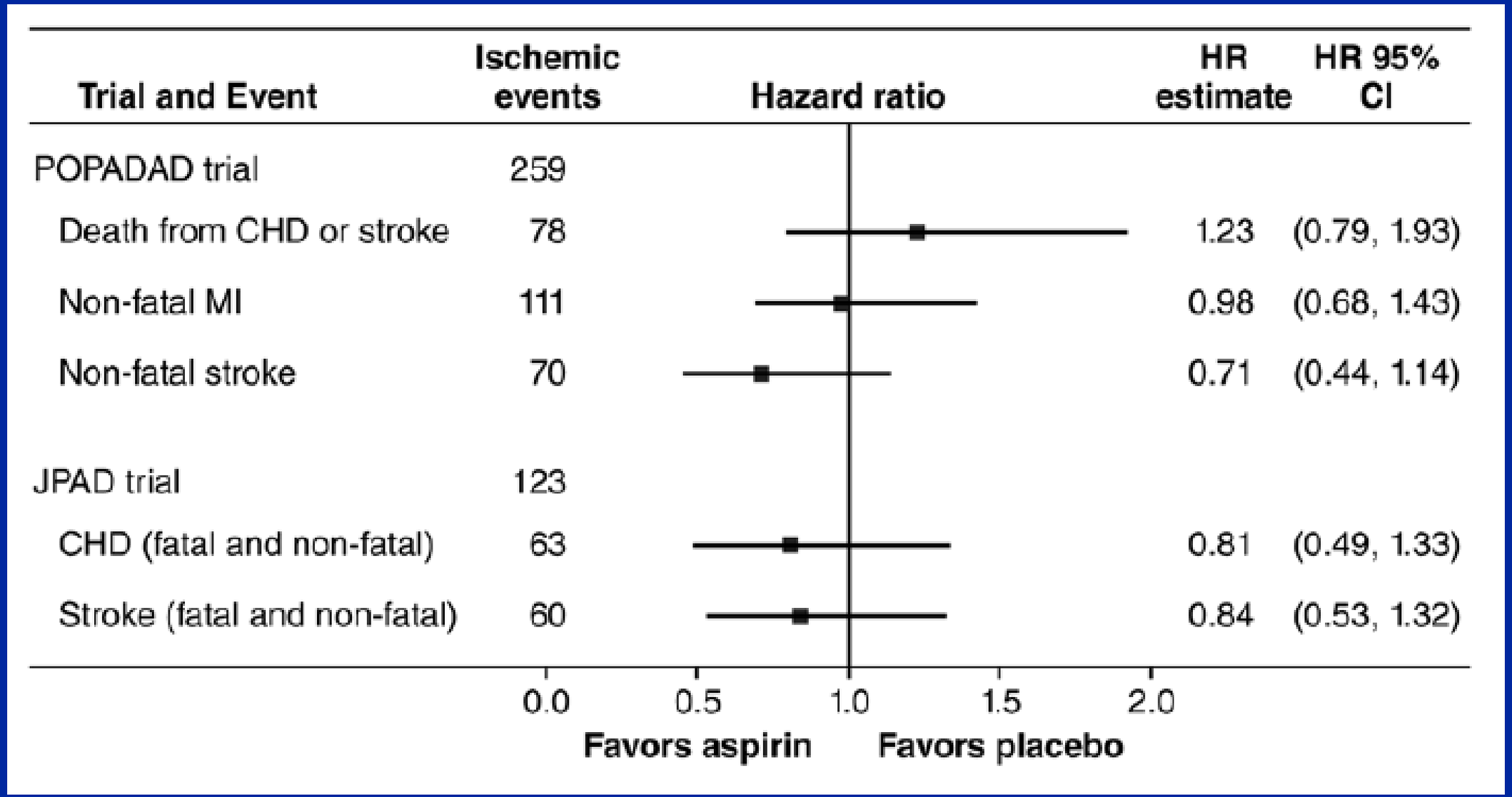
CANVAS (KW Mahaffey et al.) Circulation 2017; 137:1

Effects of Canagliflozin on CV Biomarkers in Older Adults With Type 2 Diabetes

In 666 T2DM patients randomized to receive canagliflozin 100 or 300 mg or placebo, the study assessed the median percent change in serum N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin I (hsTnI), soluble (s)ST2, and galectin-3 from baseline to 26, 52, and 104 weeks. Compared with placebo, treatment with canagliflozin delayed the rise in serum NT-proBNP and hsTnI for over 2 years in older T2DM patients. These cardiac biomarker data provide support for the beneficial cardiovascular effect of sodium glucose co-transporter 2 inhibitors in T2DM.

JL Januzzi et al., J Am Coll Cardiol 2017; 70:704

Comparison Of Data From Contemporary Trials For Aspirin In 1ary Prevention Of ASCVD In Diabetes Mellitus



CC Low Wang et. al. Circulation. 2016;133:2459

Low-Dose Aspirin for 1ary Prevention of CV Events in Patients with Type 2 DM

The JPAD trial examined whether low-dose aspirin affected CV events in 2539 Japanese patients with type 2 diabetes mellitus and without preexisting CVD. Patients received aspirin (81 or 100 mg daily; aspirin group) or no aspirin (no-aspirin group). After that trial ended in 2008, we followed up with the patients until 2015, with no attempt to change the previously assigned therapy. Primary end points were CV events For the safety analysis, hemorrhagic events, consisting of GI bleeding, hemorrhagic stroke, and bleeding from any other sites. The median follow-up period was 10.3 years. Aspirin did not affect the risk for CV events, but increased risk for GI bleeding

Y Saito et al., Circulation 2017; 135:659

Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections

The GOLD Randomized Clinical Trial

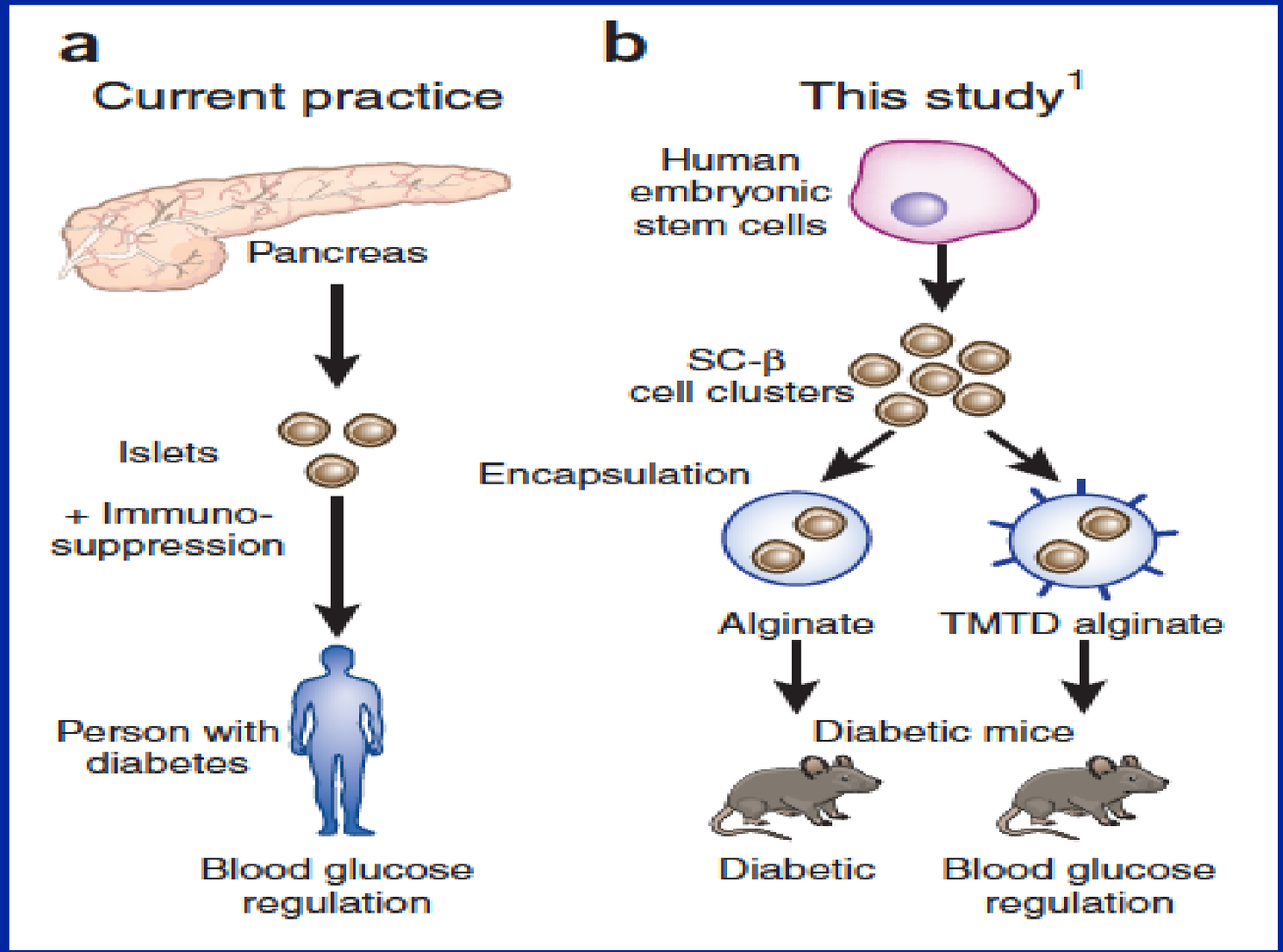
M Lind et al., JAMA 2017; 317:379

Effects of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections

The DIAMOND Randomized Clinical Trial

RW Beck et al., JAMA 2017; 317:371

Curing Diabetes With Encapsulated Stem Cell-derived Beta Cells



Q Tang et. al. Nature Med 2016;22:236

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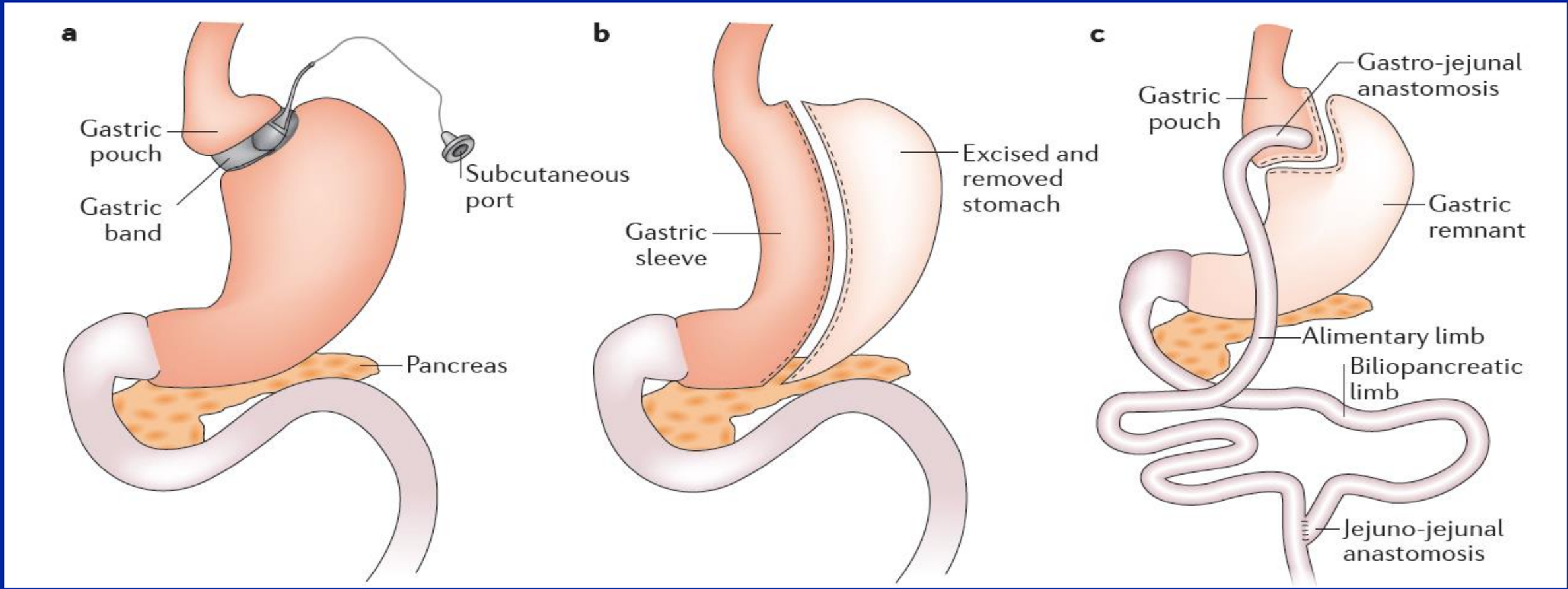
The Three Most Commonly Performed Bariatric Surgical Procedures

Laparascopic Gastric Band | **Laparascopic Sleeve Gastrectomy** | **Roux-en-Y Gastric Bypass**



AJ Beamish et. al. Nature Review 2016;13:730

Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 5-Year Outcomes

We assessed outcomes 5 years after 150 patients who had type 2 diabetes and a BMI of 27 to 43 were randomly assigned to receive intensive medical therapy alone or intensive medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. The primary outcome was a glycated hemoglobin level of 6.0% or less with or without the use of diabetes medications. At 5 years, the criterion for the primary end point was met by 5% of who received medical therapy alone, as compared to 29% who underwent gastric bypass, adjusted P=0.03, and 11 of 47 patients 23% who underwent sleeve gastrectomy, adjusted P=0.07.

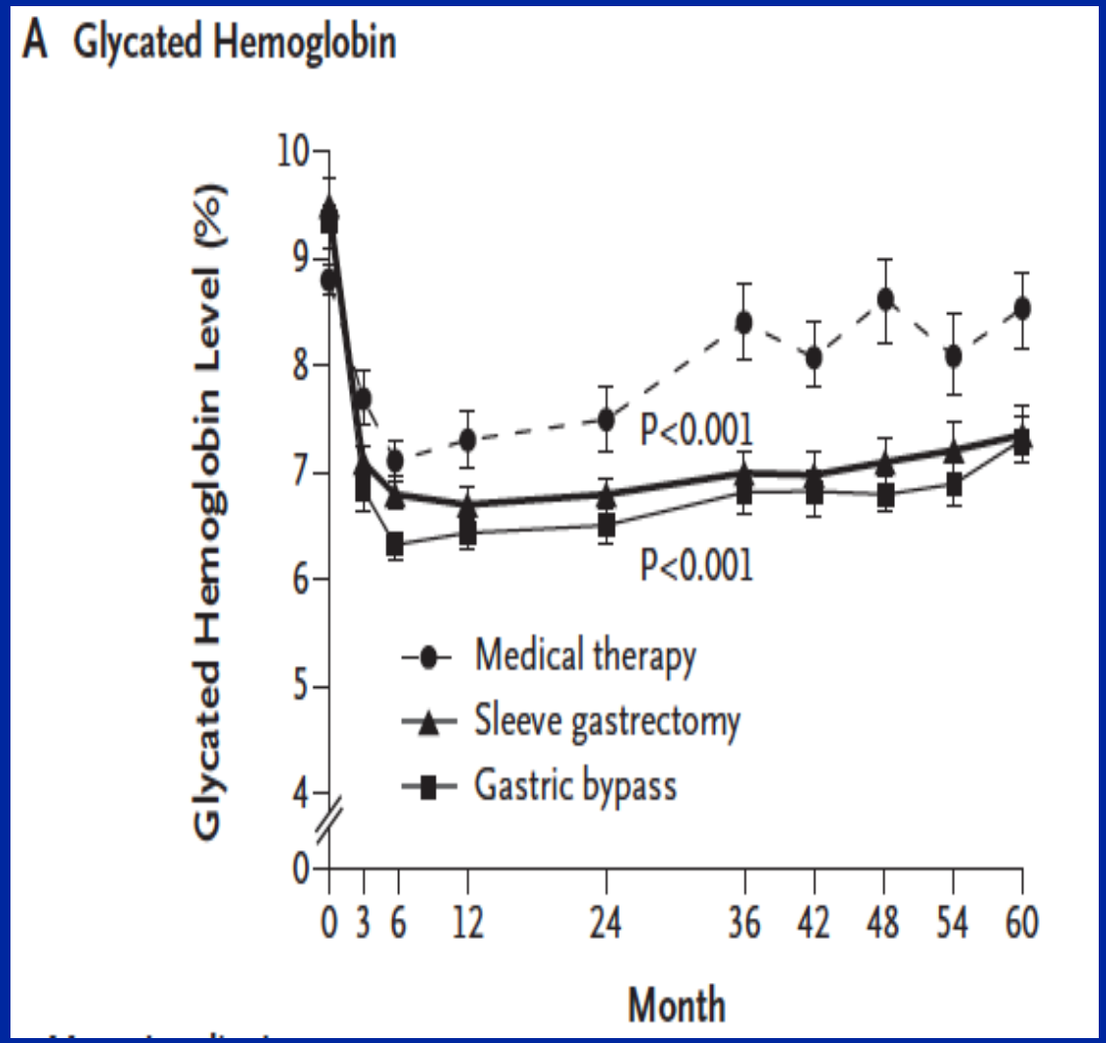
STAMPEDE (PR Schauer et al.) N Engl J Med 2017; 376:641

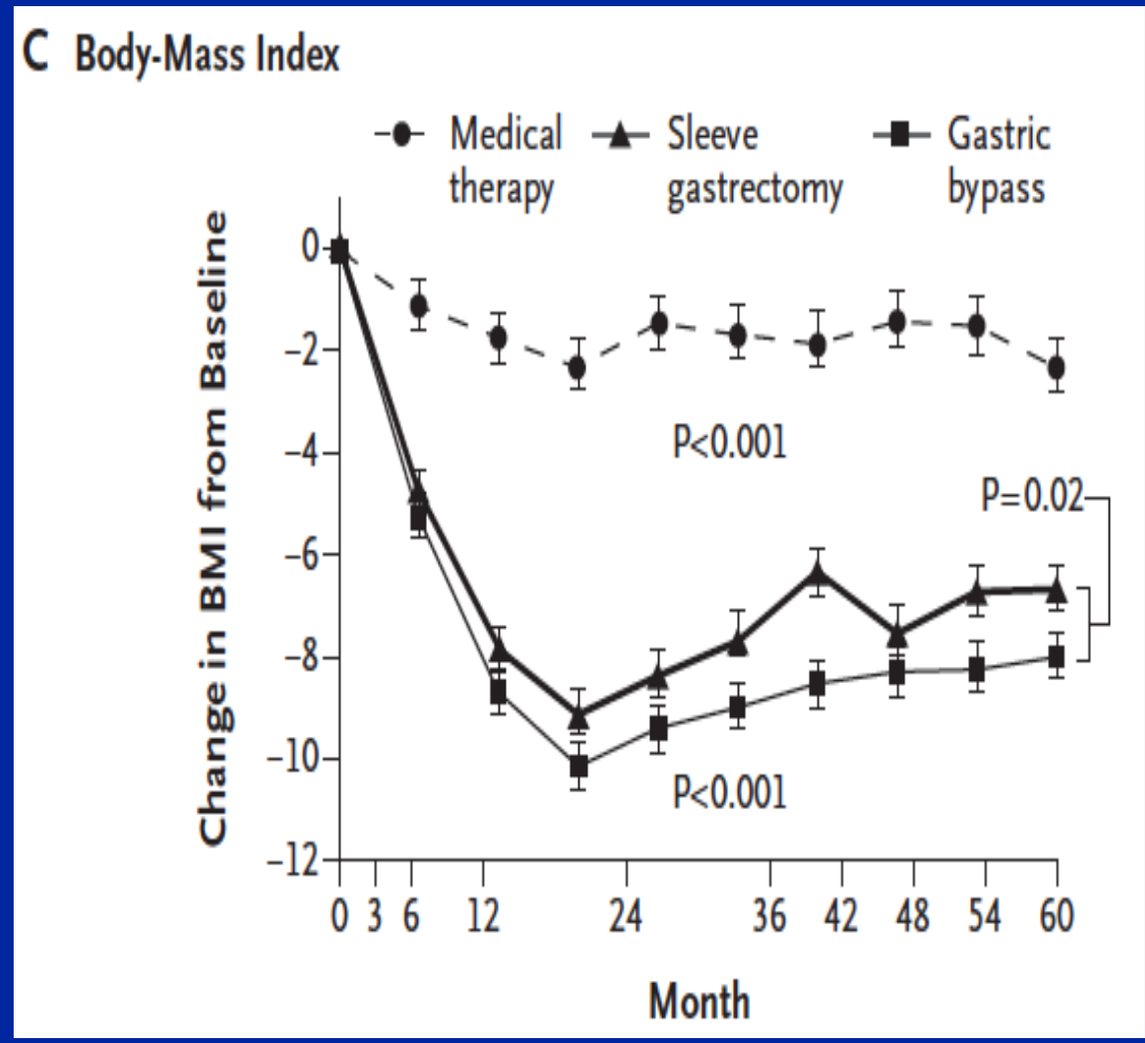
Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 5-Year Outcomes

At 5 years, changes from baseline observed in the gastric-bypass and sleeve-gastrectomy groups were superior to the changes seen in the medical-therapy group with respect to body weight: -23%, -19%, and -5% in the gastric-bypass, sleeve-gastrectomy, and medical-therapy groups; triglyceride level: -40%, -29%, and -8%; HDL-C level: 32%, 30%, and 7; use of insulin: -35%, -34%, and -13%; and quality-of-life measures: general health score increases of 17, 16, and 0.3; No major late surgical complications were reported except for one reoperation.

***STAMPEDE** (PR Schauer et al.) N Engl J Med 2017; 376:641*

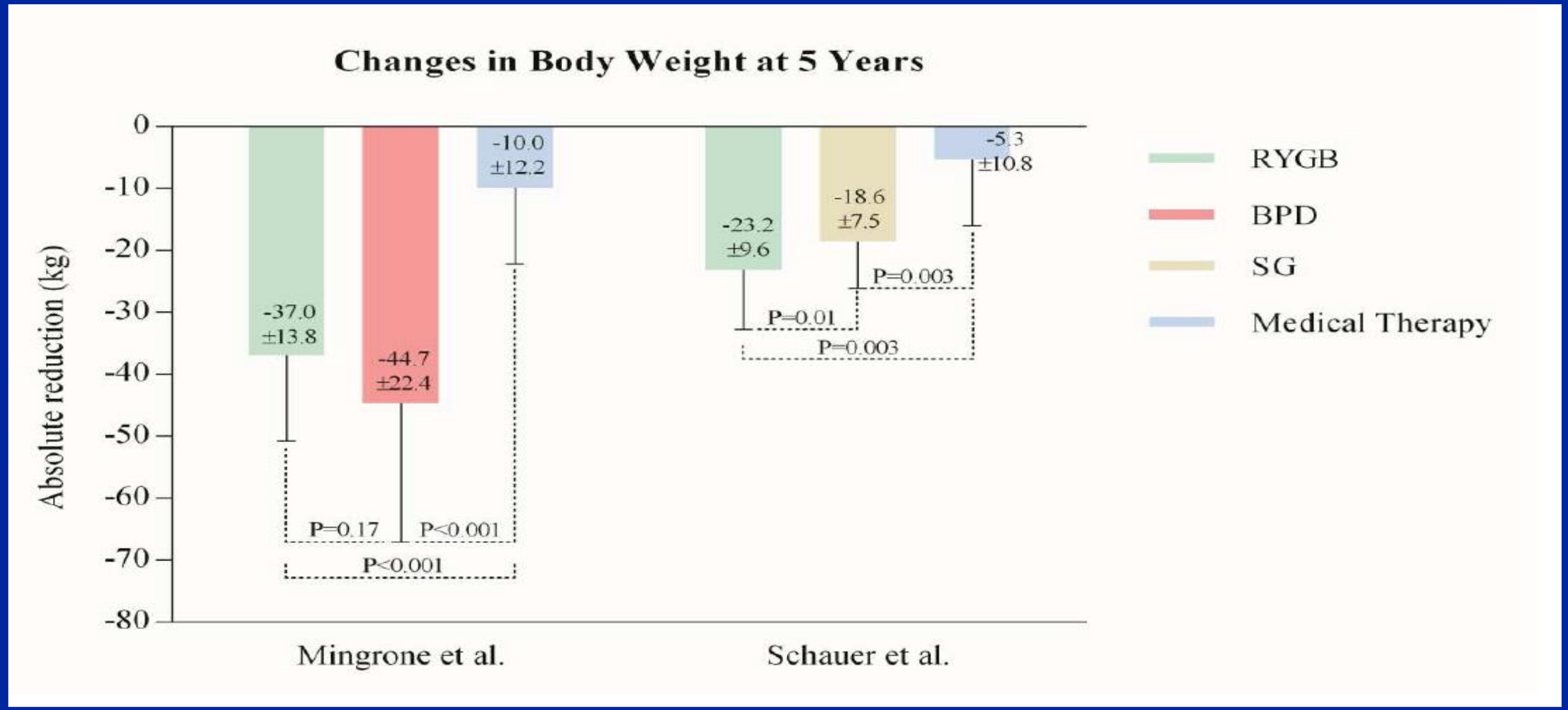
Mean Changes in Measures of Diabetes Control from Baseline to 5 Years





STAMPEDE (PR Schauer et. al.) N Engl J Med 2017;376:641

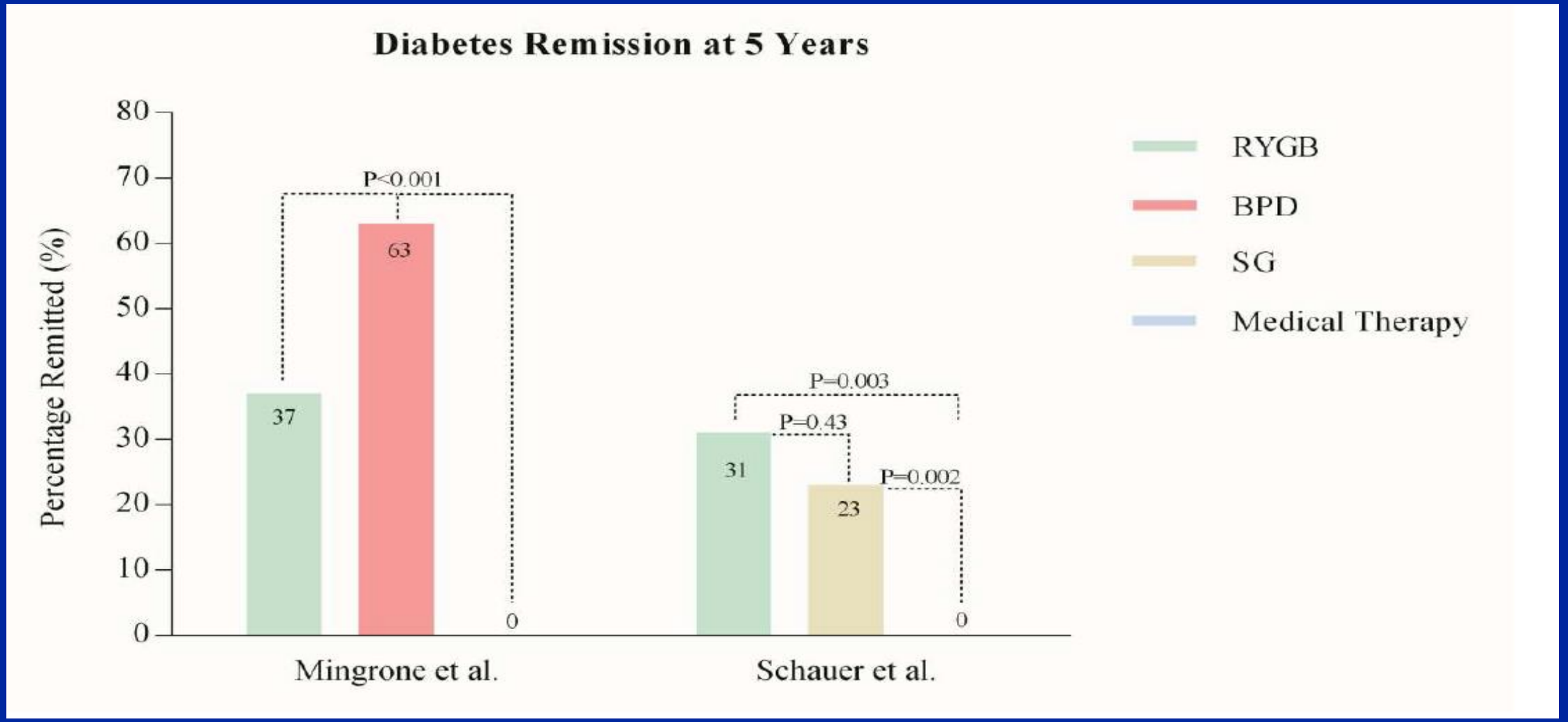
Five-year Changes In Body Weight In RCT Of Patients With Obesity and Type 2 DM



G Mingrone et. al. Lancet 2015;386:964 - PR Schauer et. al. N Engl J Med. 2017;376:641

M Pareek, DL Bhatt et. al. 2018 (Subm)

Five-year Rates Of Diabetes Remission In RCT Of Patients With Obesity And Type 2 DM



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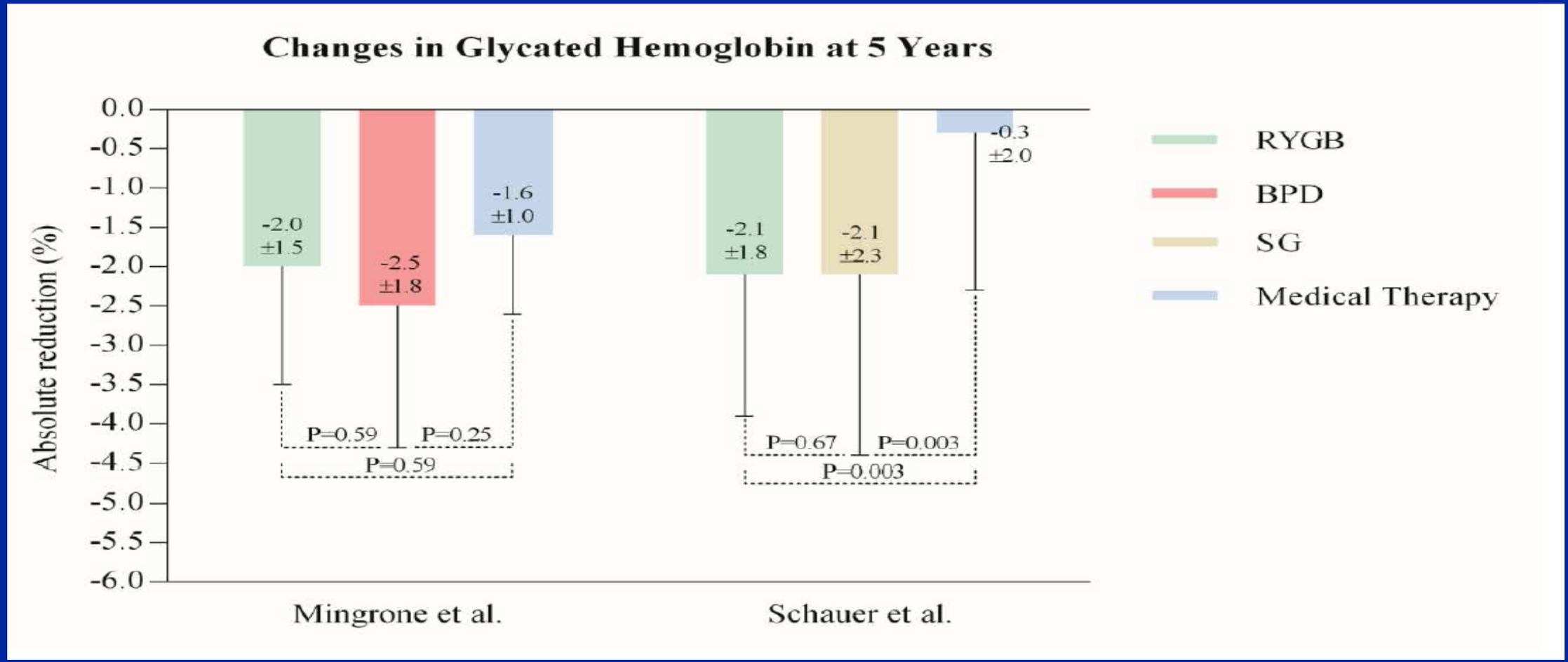
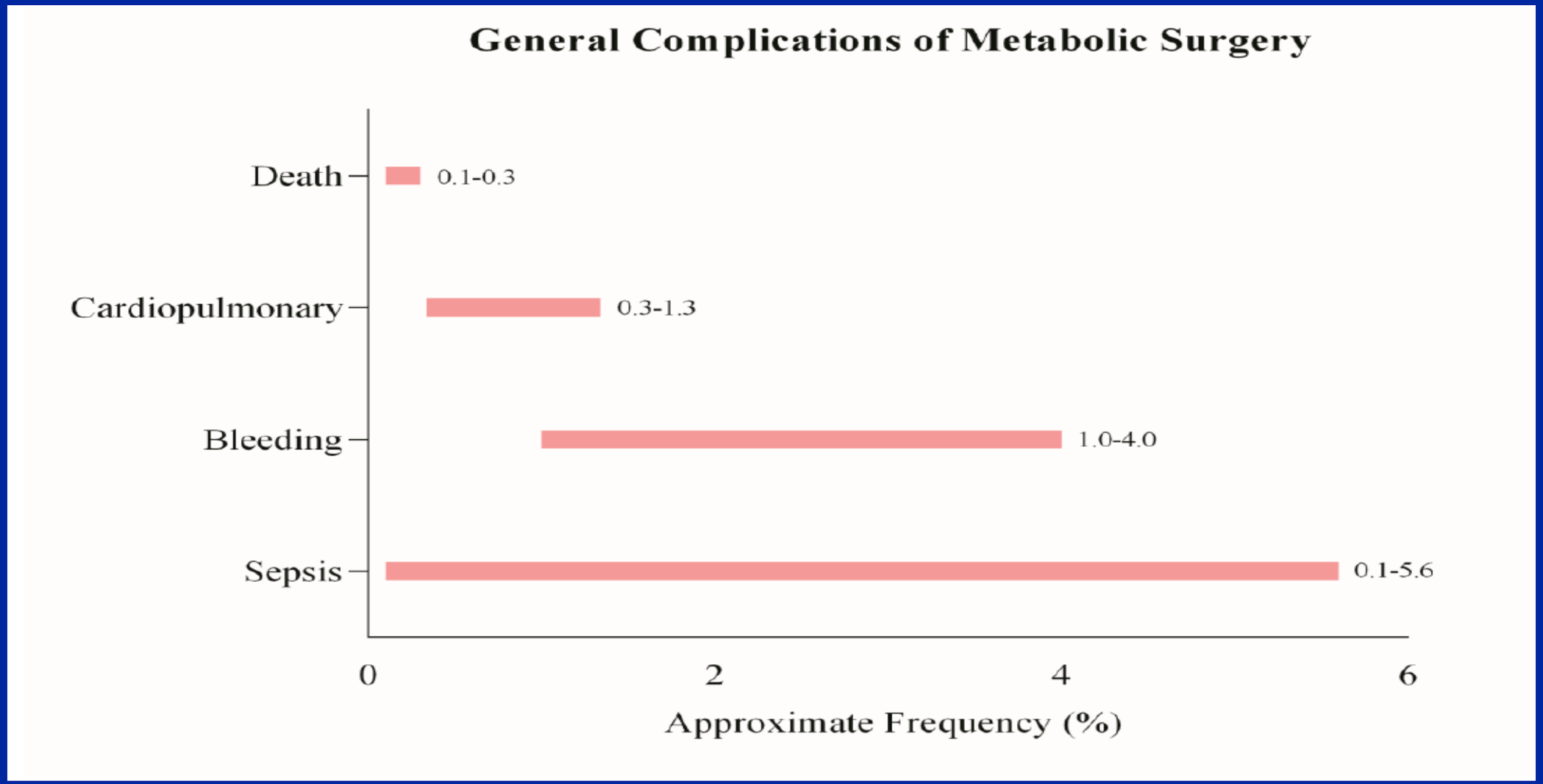
Five-year Changes In Glycated Hemoglobin In RCT Of Patients With Obesity And Type 2 DM



G Mingrone et. al. Lancet 2015;386:964 - PR Schauer et. al. N Engl J Med. 2017;376:641

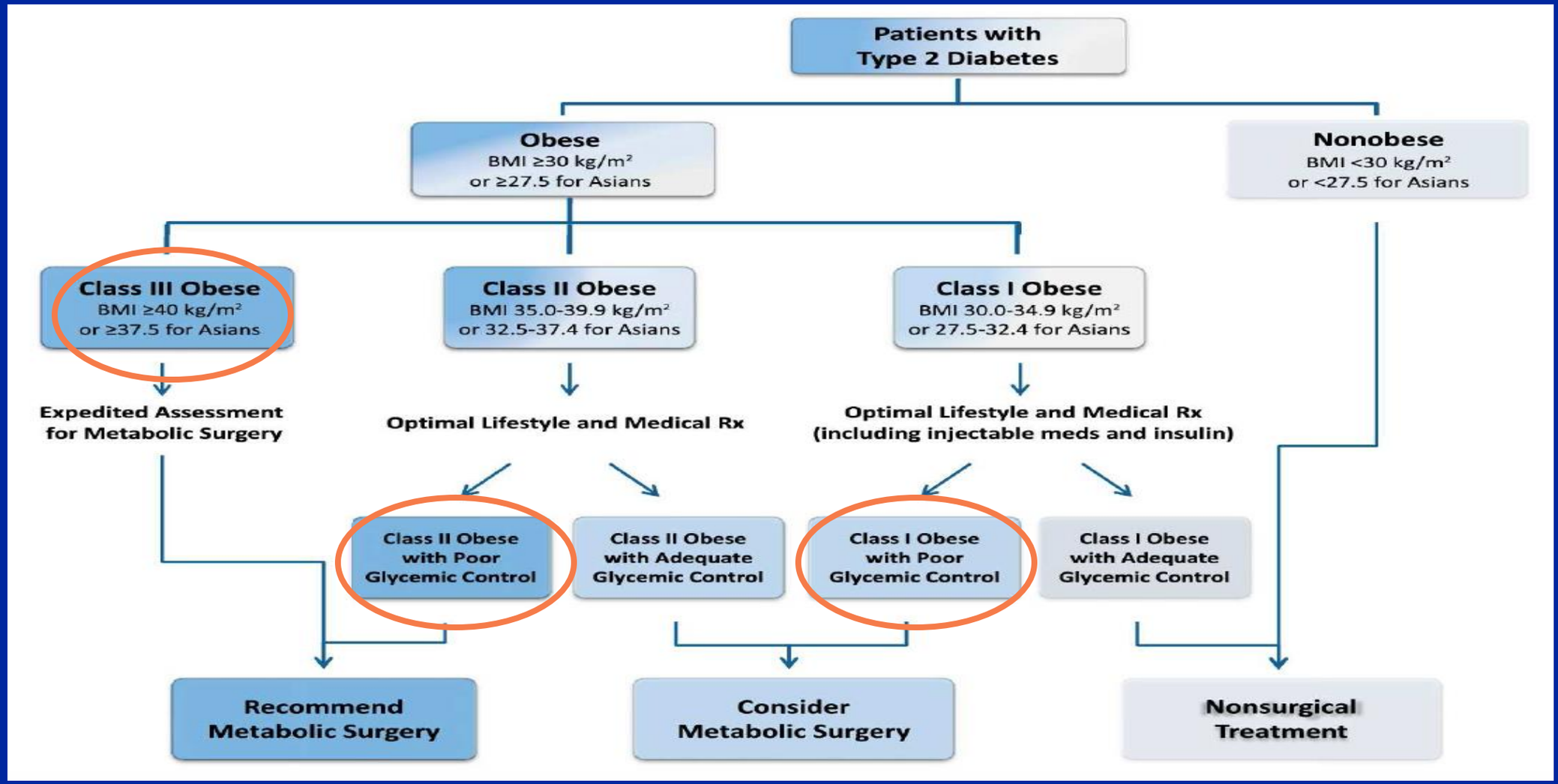
M Pareek, DL Bhatt et. al. 2018 (Subm)

General Complications of Metabolic Surgery



G Mingrone et. al. Lancet 2015;386:964 - PR Schauer et. al. N Engl J Med. 2017;376:641
M Pareek, DL Bhatt et. al. 2018 (Subm)

Algorithm For The Treatment Of Type 2 DM As Suggested By The International Diabetes Organizations



F Rubino et. al. Diabetes Care. 2016;39:861
M Pareek, DL Bhatt et. al. 2018 (Subm)

Bariatric Surgery and the Risk of New-Onset AF in Swedish Obese Subjects

SOS is a prospective matched cohort study conducted at 25 surgical departments and 480 primary healthcare centers in Sweden. The cohort was recruited between 1987 and 2001. Among 4,021 obese individuals with sinus rhythm and no history of AF, 2,000 underwent bariatric surgery (surgery group), and 2,021 matched obese control subjects received usual care (control group). During a median follow-up of 19 years, first AF occurred in 247 patients -12.4%- in the surgery group, and in 340 -16.8%- control subjects, 29% (p<0.001). Younger hypertensive individuals benefited the most.

S Jamaly et al., J Am Coll Cardiol 2016; 68:2497

Weight Loss and Heart Failure

A Nationwide Study of Gastric Bypass Surgery vs Intensive Lifestyle Treatment

Entiled obese people without previous HF from a Swedish nationwide registry of people treated with a structured intensive lifestyle program and the Scandinavian Obesity Surgery Registry. The 25,804 gastric bypass surgery patients had on average lost 18.8 kg more weight after 1 year and 22.6 kg more after 2 years than the 13,701 lifestyle modification patients. During a median of 4.1 years, Gastric bypass surgery was associated with one half the incidence of HF

J Sundström et al., Circulation 2017; 135:1577

New Frontiers in CVD
Dilemmas of Obesity & Diabetes

The Four Challenging "Hot Spots"

ACC New York, Dec 8, 2017

No Disclosures