New Frontiers in CVD
Dilemmas of Obesity & Diabetes

The Four Challenging “Hot Spots”
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

1. Dietary risks
2. High systolic blood pressure
3. Child and maternal malnutrition
4. Tobacco smoke
5. Air pollution
6. High body-mass index
7. Alcohol and drug use
8. High fasting plasma glucose

DALYS (%)

HIV/AIDS and tuberculosis
Diarrhoea, lower respiratory, and other common infectious diseases
Maternal disorders
Nutritional deficiencies
Other communicable, maternal, neonatal, and nutritional diseases
Neoplasms
Cardiovascular diseases
Chronic respiratory diseases
Cirrhosis
Digestive diseases
Neurological disorders
Mental and substance use disorders
Musculoskeletal disorders
Other non-communicable diseases
Transport injuries
Unintentional injuries
Self-harm and interpersonal violence

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

Excessive Adipose Accumulation

↓ Systemic Vascular Resistance

↑ Fat-Free Mass

↑ Total and Central Blood Volume

↓ LV Stroke Volume

No Change or a Mild Increase in Heart Rate

↑ Cardiac Output in Most

LV Dilatation in Some

Hypertension

LV Hypertrophy

Neurohormonal and Metabolic Alterations

Inadequate

Adequate

LV Systolic Dysfunction

LV Diastolic Dysfunction

LV Failure

CJ Lavie et. al. J Am Coll Cardiol 2017;70:2022
Adipose Tissue Depots Occur Throughout The Body

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

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

- Adiposity
  - Lipid production
  - Activity of the sympathetic nervous system
  - Activity of the renin-angiotensin-aldosterone system
  - Mechanical stress

- Hydrolysis of triglycerides
- Release of free fatty acids

- Adipose tissue macrophages and other inflammatory cells
- Proinflammatory cytokines
- Impaired insulin signaling and insulin resistance

- Insulin
- Nonalcoholic fatty liver disease
  - Steatohepatitis
  - Cirrhosis
- Type 2 diabetes

- Lipotoxicity
- Dyslipidemia

- Renal compression
- Pharyngeal soft tissue
- Mechanical load on joints
- Intraabdominal pressure

- Systemic and pulmonary hypertension

- Congestive heart failure
- Stroke
- Chronic kidney disease
- Coronary artery disease
- Obstructive sleep apnea
- Osteoarthritis
- Gastroesophageal reflux disease
  - Barrett’s esophagus
  - Esophageal adenocarcinoma

Four Hyperglycemia-induced Pathogenic Mechanisms Are Activated By Overproduction Of ROS Species
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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5. Bariatric Surgery
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
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/m²), 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

A. Men
   Index age, 45 years

B. Women
   Index age, 45 years

C. White Participants
   Index age, 45 years

D. Black Participants
   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

Healthy overweight men (n=209) and women (n=710), mean age 44.7 years, BMI 32.4 kg/m², 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

Body Weight (kg)  BMI (kg/m²)  Waist (cm)

Control  Advice Only  Food Only  Food and Advice

Control  Advice Only  Food Only  Food and Advice

Control  Advice Only  Food Only  Food and Advice

DJA Jenkins et. al. J Am Coll Cardiol 2017;69:1103
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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4. Novel Diabetes Drugs
5. Bariatric Surgery
Randomized, controlled, cardiovascular outcome trials of glucose-lowering drugs or strategies in people with type 2 diabetes mellitus

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<table>
<thead>
<tr>
<th>Trial/Date</th>
<th>Number/Population</th>
<th>Follow-up</th>
<th>Intervention</th>
<th>Outcome</th>
<th>HR or IRR* (95% CI)</th>
<th>MACE - Expanded MACE</th>
<th>HR or IRR* (95% CI)</th>
<th>All-cause mortality</th>
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<tbody>
<tr>
<td>UKPDS 1998</td>
<td>N=3228</td>
<td>Median 10.0 years</td>
<td>Intensive versus conventional glucose lowering</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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<tr>
<td>UKPDS 1998</td>
<td>N=3228</td>
<td>Median 10.0 years</td>
<td>Metformin versus placebo</td>
<td>Fasting/Non-fasting MI</td>
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<td>UKPDS Follow up 2008</td>
<td>N=3228</td>
<td>Median 10 years</td>
<td>Intensive versus conventional therapy</td>
<td>Fasting/Non-fasting MI</td>
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<td>Stop-2</td>
<td>N=160</td>
<td>Median 7.8 years</td>
<td>Intensive versus conventional therapy</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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<tr>
<td>OASIS</td>
<td>N=1253</td>
<td>Median 2.1 years</td>
<td>Acute insulin-glucose infusion followed by insulin-based, long-term glucose control</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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<tr>
<td>ACCORD 2011</td>
<td>N=10012</td>
<td>Median 3.7 years</td>
<td>Intensive versus standard glucose control</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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<td>Intensive versus standard glucose control</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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<tr>
<td>CAFOD 2009</td>
<td>N=5689</td>
<td>Median 5.6 years</td>
<td>Intensive versus standard glucose control</td>
<td>Fasting/Non-fasting MI</td>
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<td>VADT 2015</td>
<td>N=1751</td>
<td>Median 9.8 years</td>
<td>Intensive versus standard glucose control</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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<td>RECORD 2009</td>
<td>N=4477</td>
<td>Median 5.5 years</td>
<td>Roaglucose versus combination of metformin and sulfonylurea</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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<td>ERADO 2009</td>
<td>N=238</td>
<td>Median 5.5 years</td>
<td>Insulin-sensitization vs insulin-provision treatment</td>
<td>Fasting/Non-fasting MI</td>
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<td>ADDITION 2011</td>
<td>N=1055</td>
<td>Median 5.5 years</td>
<td>Routine versus intensified multifactorial risk factor intervention</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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<td>CHARM 2012</td>
<td>N=2757</td>
<td>Median 5.2 years</td>
<td>Insulin-glimepiride vs standard glucose control</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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<td>SAVVY- ERBOS 2013</td>
<td>N=1649</td>
<td>Median 2.1 years</td>
<td>Sitagliptin versus placebo plus usual diabetes care</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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<tr>
<td>EXAMINE 2013</td>
<td>N=2300</td>
<td>Median 1.5 years</td>
<td>Albiglutide versus placebo plus usual diabetes care</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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<tr>
<td>LOOK- AHEAD 2013</td>
<td>N=1785</td>
<td>Median 9.8 years</td>
<td>Intensive versus standard lifestyle intervention strategy</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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<tr>
<td>LEADER 2015</td>
<td>N=17871</td>
<td>Median 1.0 years</td>
<td>Sitagliptin versus placebo plus usual diabetes care</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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<tr>
<td>EMPA-REG OUTCOME 2013</td>
<td>N=7020</td>
<td>Median 2.1 years</td>
<td>Empagliflozin versus placebo plus usual diabetes care</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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<tr>
<td>ELISA 2013</td>
<td>N=6088</td>
<td>Median 2.5 months</td>
<td>Linagliptin versus placebo plus usual diabetes care</td>
<td>Fasting/Non-fasting MI</td>
<td>Stroke</td>
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</tr>
</tbody>
</table>

*HR (Hazard Ratio) or IRR (Incidence Rate Ratio)
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 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 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
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**
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 Primary Prevention Of ASCVD In Diabetes Mellitus

**Table:**

<table>
<thead>
<tr>
<th>Trial and Event</th>
<th>Ischemic events</th>
<th>Hazard ratio</th>
<th>HR estimate</th>
<th>HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>POPADAD trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from CHD or stroke</td>
<td>78</td>
<td>1.23</td>
<td>(0.79, 1.93)</td>
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</tr>
<tr>
<td>Non-fatal MI</td>
<td>111</td>
<td>0.98</td>
<td>(0.68, 1.43)</td>
<td></td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>70</td>
<td>0.71</td>
<td>(0.44, 1.14)</td>
<td></td>
</tr>
<tr>
<td>JPAD trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD (fatal and non-fatal)</td>
<td>63</td>
<td>0.81</td>
<td>(0.49, 1.33)</td>
<td></td>
</tr>
<tr>
<td>Stroke (fatal and non-fatal)</td>
<td>60</td>
<td>0.84</td>
<td>(0.53, 1.32)</td>
<td></td>
</tr>
</tbody>
</table>

**Graph:**

- Favors aspirin vs Favors placebo
- Hazard ratio plot for different events

**References:**

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

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The Three Most Commonly Performed Bariatric Surgical Procedures

- **Laparoscopic Gastric Band**
- **Laparoscopic Sleeve Gastrectomy**
- **Roux-en-Y Gastric Bypass**

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
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

Changes in Body Weight at 5 Years

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Absolute Reduction (kg)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>RYGB</td>
<td>-37.0 ±13.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BPD</td>
<td>-44.7 ±22.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SG</td>
<td>-23.2 ±9.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Medical Therapy</td>
<td>-5.3 ±10.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

M Pareek, DL Bhatt et al. 2018 (Subm)
Five-year Rates Of Diabetes Remission In RCT Of Patients With Obesity And Type 2 DM

M Pareek, DL Bhatt et. al. 2018 (Subm)
Five-year Changes In Glycated Hemoglobin In RCT Of Patients With Obesity And Type 2 DM

Changes in Glycated Hemoglobin at 5 Years

- RYGB
- BPD
- SG
- Medical Therapy

Mingrone et al.

Schauer et al.

M Pareek, DL Bhatt et. al. 2018 (Subm)
General Complications of Metabolic Surgery

- Death: 0.1-0.3
- Cardiopulmonary: 0.3-1.3
- Bleeding: 1.0-4.0
- Sepsis: 0.1-5.6

M Pareek, DL Bhatt et. al. 2018 (Subm)
Algorithm For The Treatment Of Type 2 DM As Suggested By The International Diabetes Organizations

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
Entitled 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
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The Four Challenging “Hot Spots”