CAROLINAS CHAPTER/AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS

# 2016 Annual Meeting

## HILTON HEAD ISLAND

# SUNDAY PRESENTATIONS

September 9-11, 2016 ~ Sonesta Resort ~ Hilton Head Island, SC

This continuing medical education activity is jointly provided by the
Carolinas Chapter, AACE and Southern Regional Area Health Education Center

## 8.25 CME Credits!

# Bariatric Surgery Update

Hilary Blackwood, MSN, RN, ACNP-BC
WakeMed Physician Practices
Bariatric Surgery Program
Cary, North Carolina

# Obesity: more than just pounds

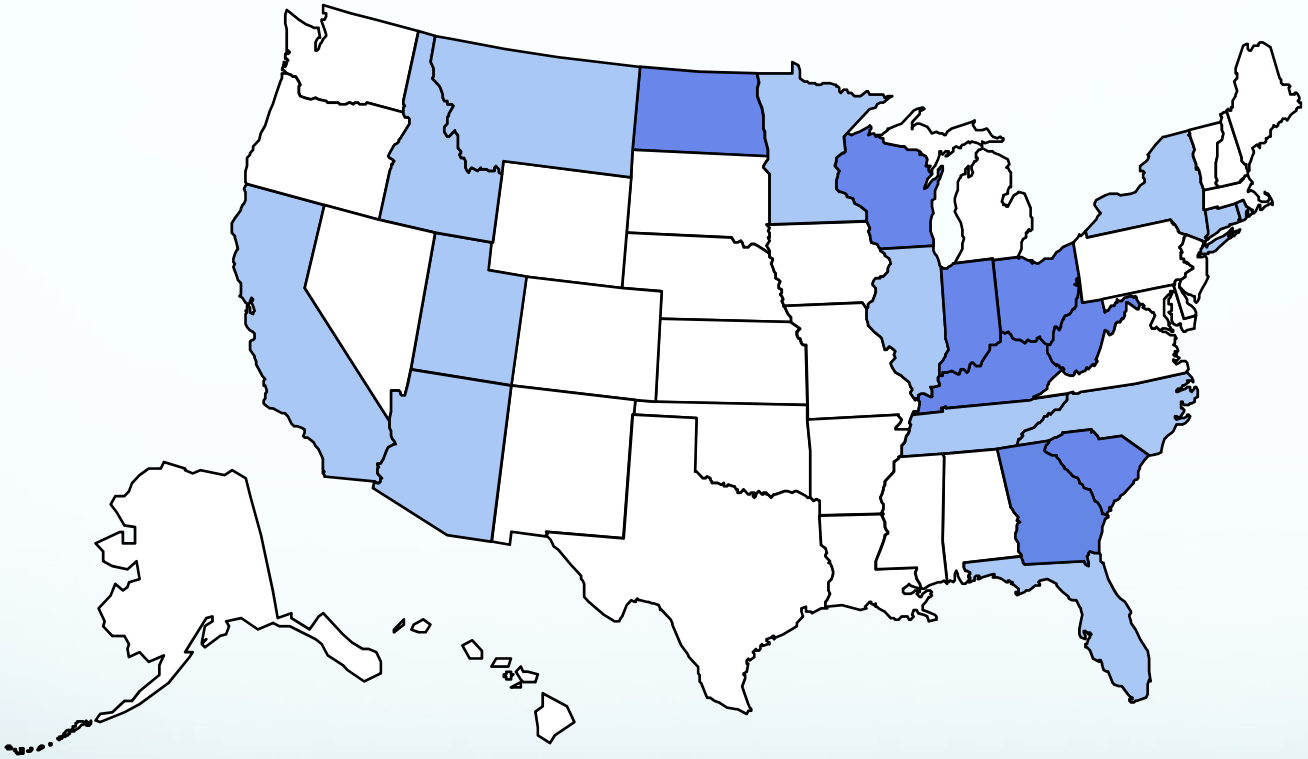
## BMI = Weight kg/Height $m^2$

| | |
|---|---|
| Underweight | ≤ 19 |
| Normal | 19 - 25 |
| Overweight | 26 - 29 |
| Obese Class I | 30 - 35 |
| **Obese Class II** | **35 - 39.9** |
| **Morbid Obesity** | **≥ 40** |
| **Super Obesity** | **≥ 50** |

# Obesity Trends* Among U.S. Adults

## BRFSS, 1985

**(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)**

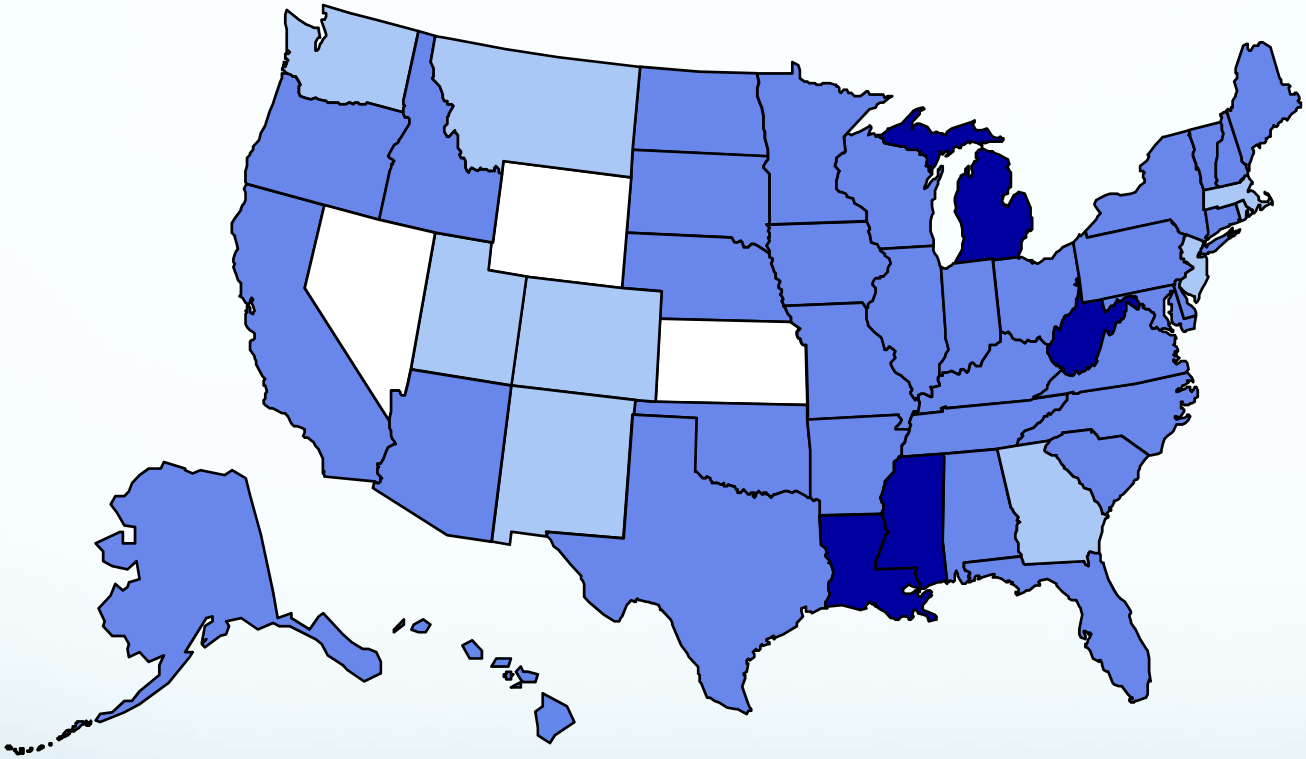


No Data | <10% | 10%–14%

# Obesity Trends* Among U.S. Adults

## BRFSS, 1991

**(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)**

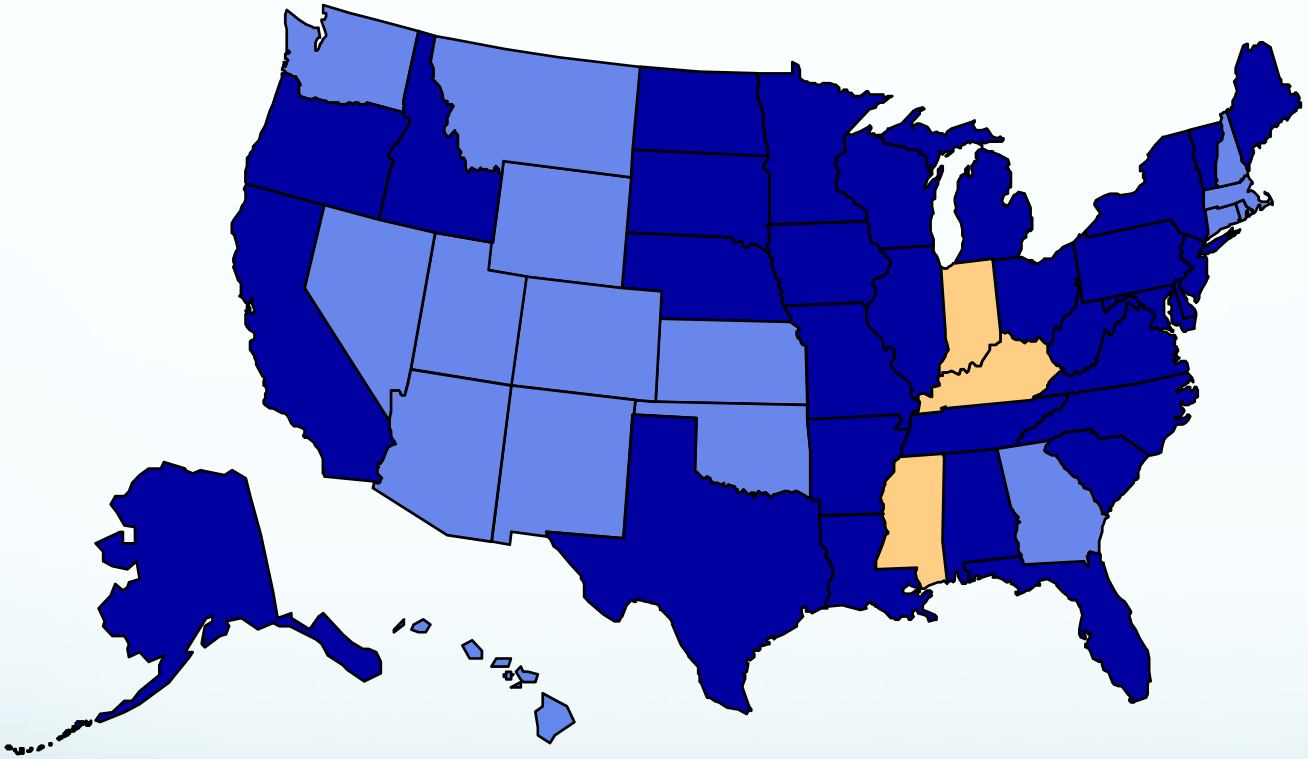


No Data | <10% | 10%–14% | 15%–19%

# Obesity Trends* Among U.S. Adults

## BRFSS, 1997

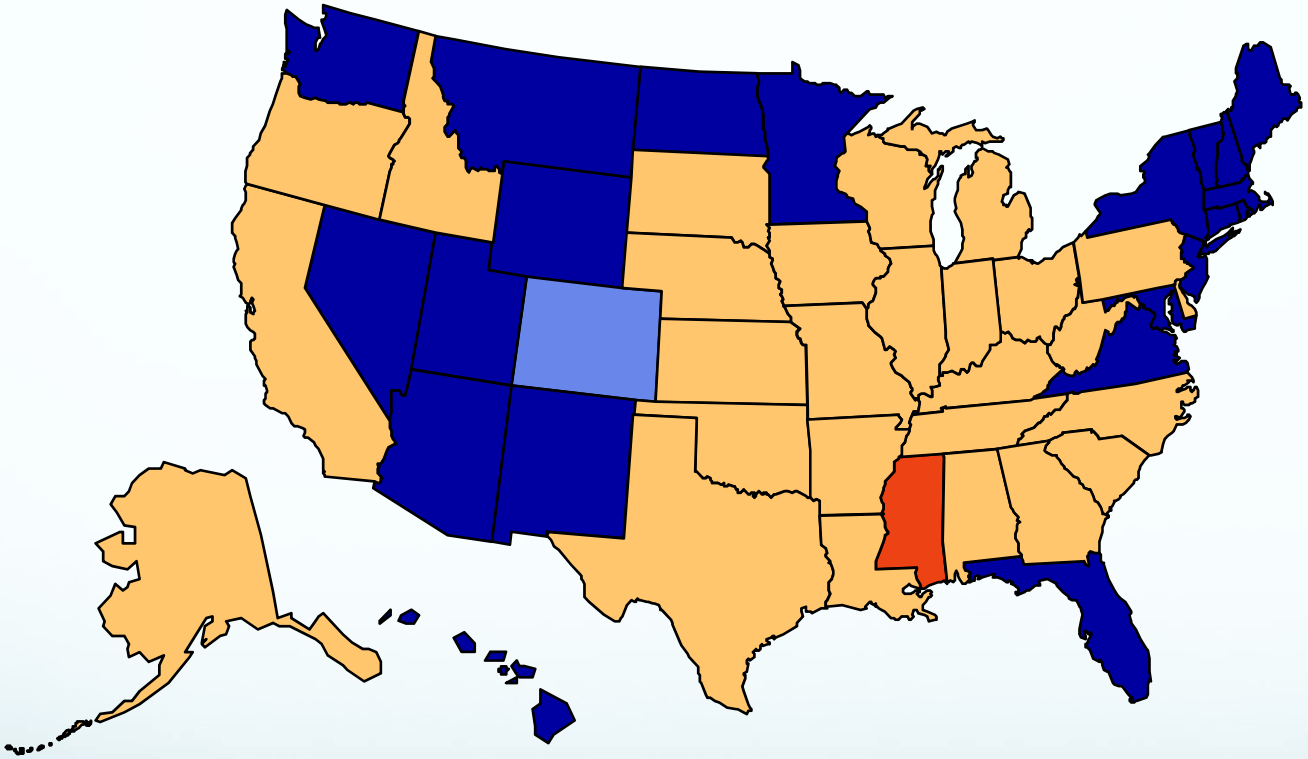
**(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)**



# Obesity Trends* Among U.S. Adults

## BRFSS, 2001

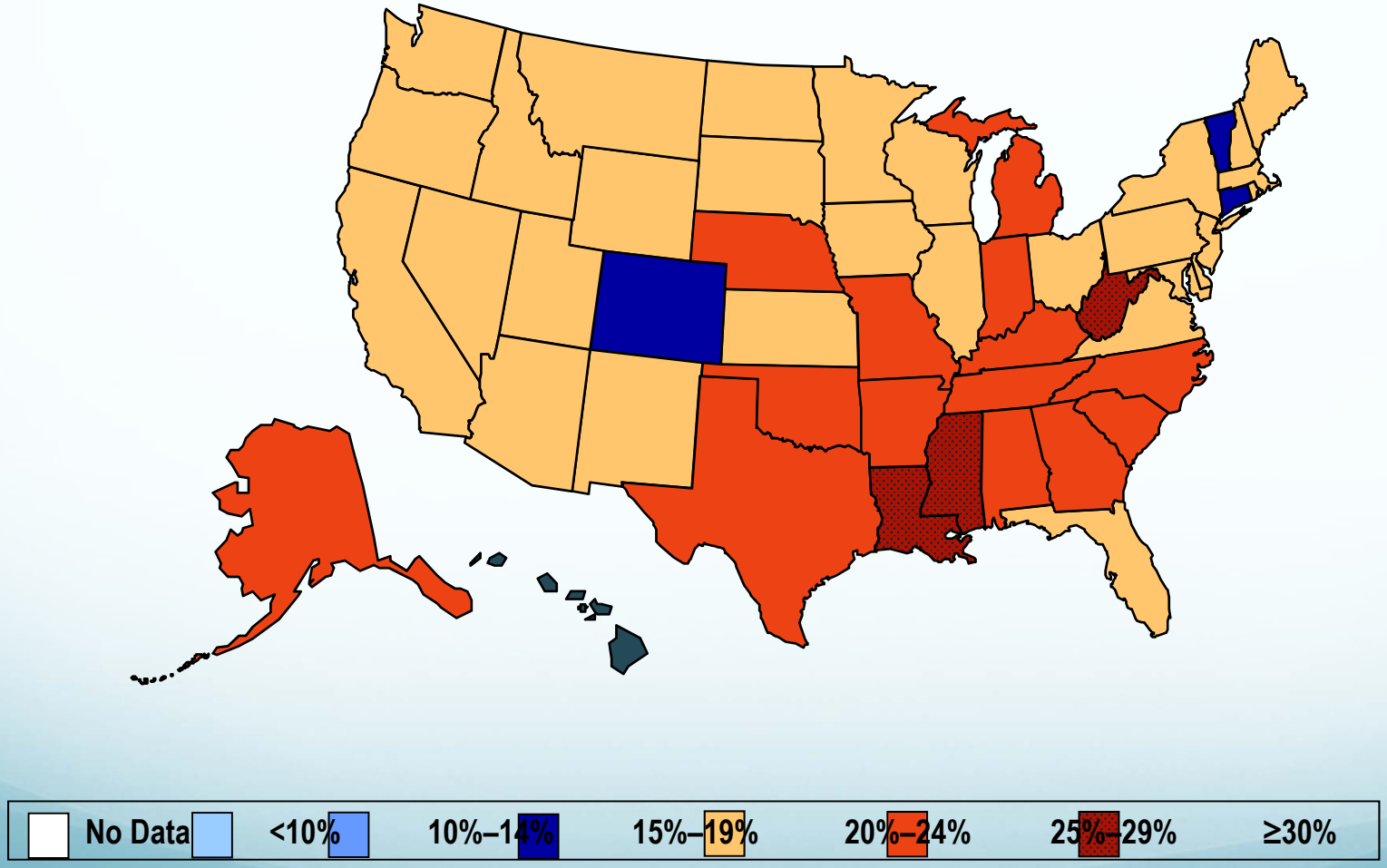
**(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)**



# Obesity Trends* Among U.S. Adults

## BRFSS, 2005

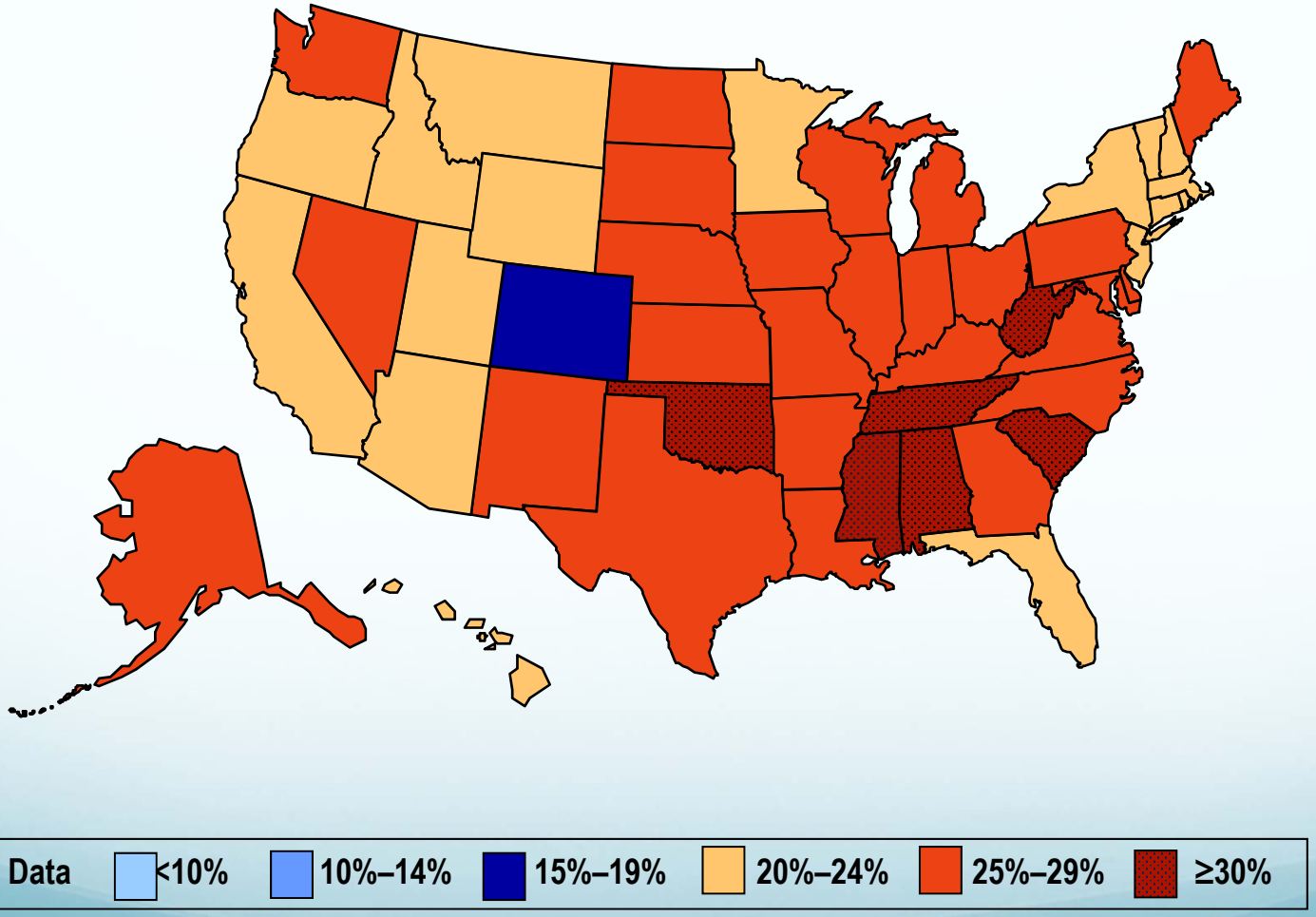
**(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)**



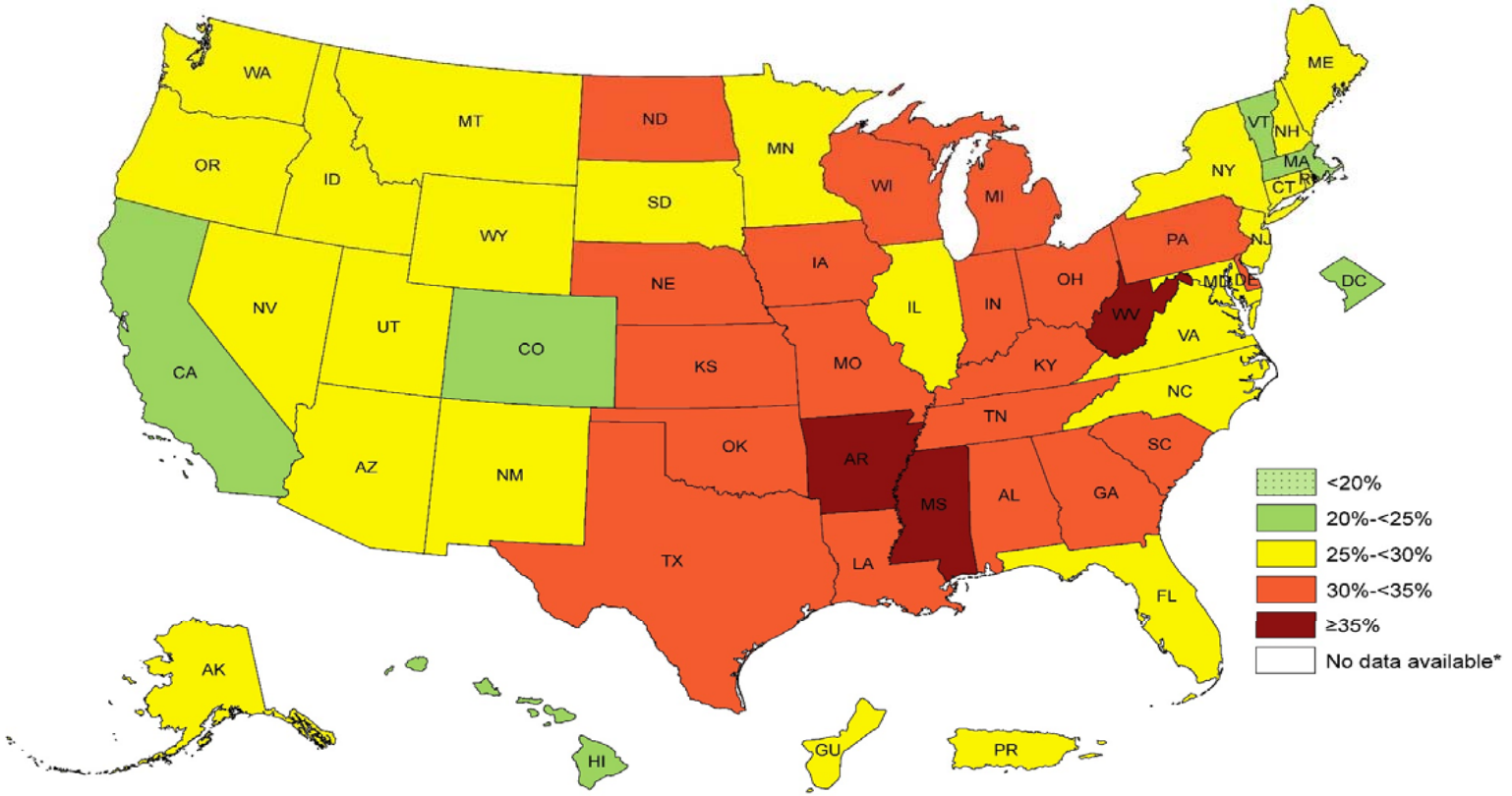
# Obesity Trends* Among U.S. Adults

## BRFSS, 2008

**(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)**



# Prevalence¶ of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2014




***Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%.**

# Prevalence¶ of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2014

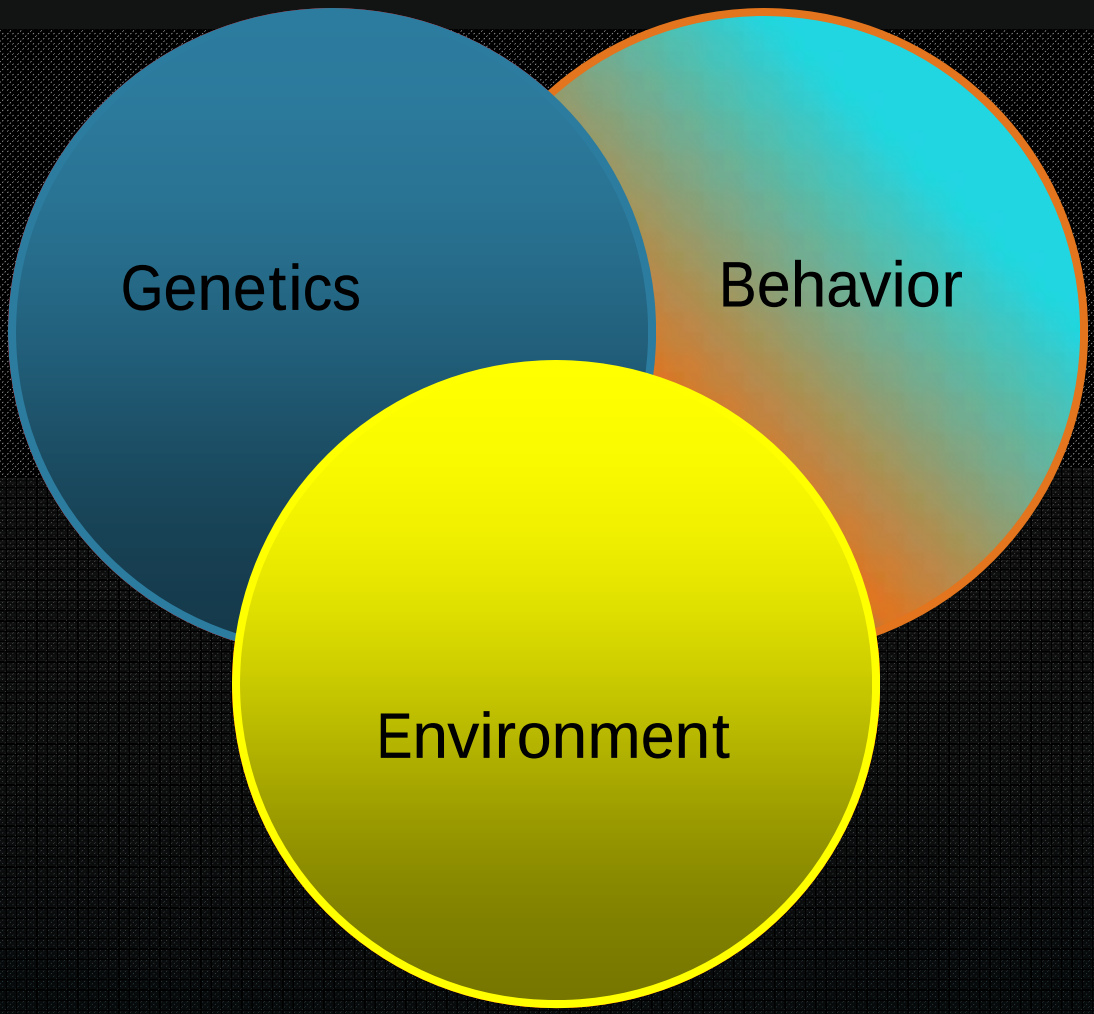
## Summary

- No state had a prevalence of obesity less than 20%.
- 5 states and the District of Columbia had a prevalence of obesity between 20% and <25%.
- 23 states, Puerto Rico, and Guam had a prevalence of obesity between 25% and <30%.
- 19 states had a prevalence of obesity between 30% and <35%.
- 3 states (Arkansas, Mississippi and West Virginia) had a prevalence of obesity of 35% or greater.

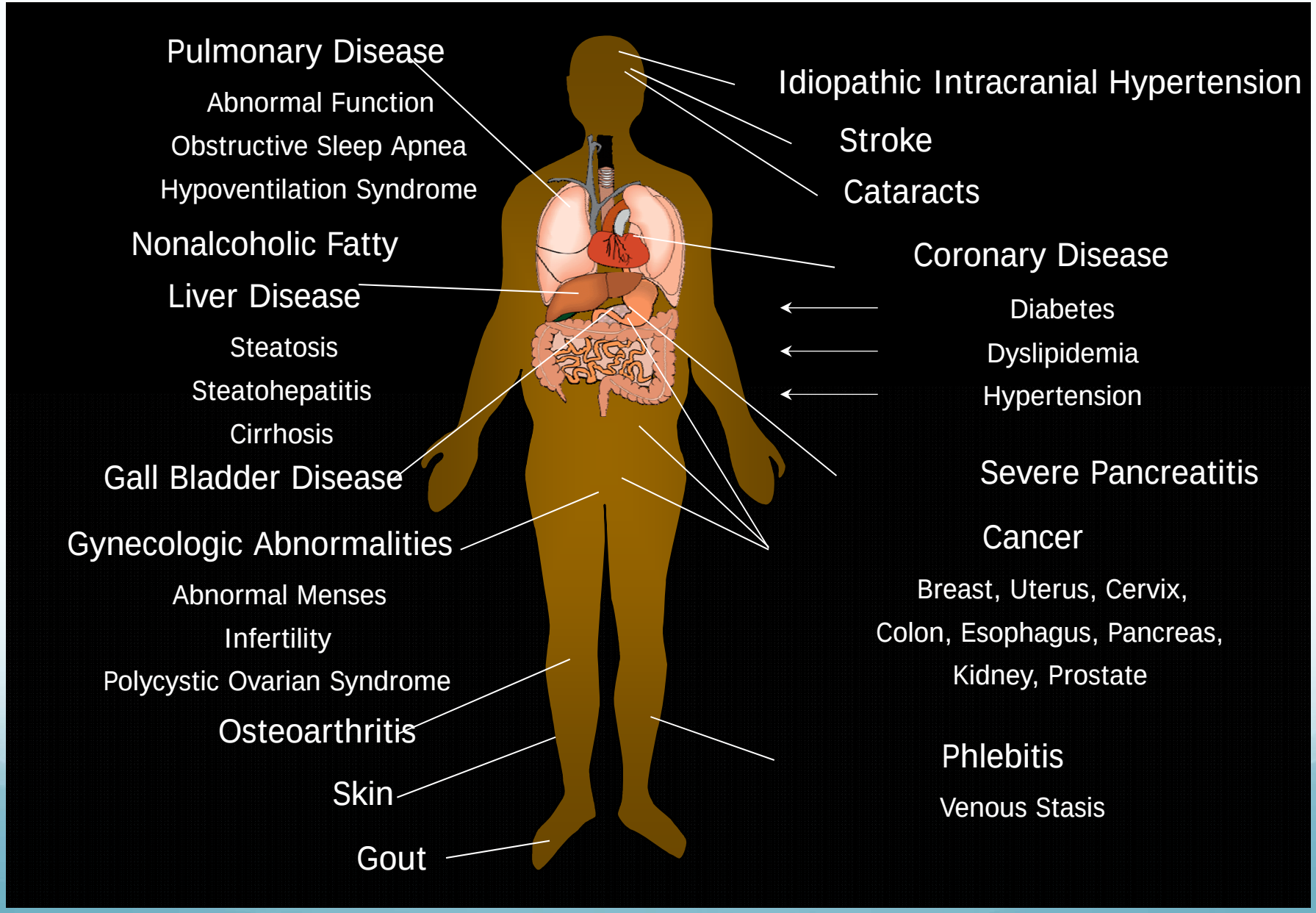
¶ Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.

http://www.cdc.gov/obesity/data/prevalence-maps.html

# Causes of Obesity



# Obesity


Pulmonary Disease
Abnormal Function
Obstructive Sleep Apnea
Hypoventilation Syndrome
Nonalcoholic Fatty
Liver Disease
Steatosis
Steatohepatitis
Cirrhosis
Gall Bladder Disease
Gynecologic Abnormalities
Abnormal Menses
Infertility
Polycystic Ovarian Syndrome
Osteoarthritis
Skin
Gout
Idiopathic Intracranial Hypertension
Stroke
Cataracts
Coronary Disease
Diabetes
Dyslipidemia
Hypertension
Severe Pancreatitis
Cancer
Breast, Uterus, Cervix,
Colon, Esophagus, Pancreas,
Kidney, Prostate
Phlebitis
Venous Stasis

# Illnesses secondary to Obesity

- Type 2 Diabetes – 25% of our patients
- Hypertension – 54 % of our patients
- Elevated Lipids – 64% of our patients
- Pulmonary Compromise
  - Shortness of Breath – nearly all patients
  - Sleep Apnea Syndrome – 23 % of our patients
  - Hypoventilation – 16% of our patients

# Non-Surgical Weight Loss Approaches

- Diet
- Behavior modification
- Exercise
- Medications
- Psychological counseling

# 1991 NIH Consensus Conference on Surgery for Obesity

For patients with morbid obesity:

- Surgical intervention is the only method proven to have a significant long-term impact on the disease.
- Medical interventions have failed.

*Obesity Research* 1998; 6 (suppl 2):51S–209S

# Indications for surgery – Per major insurance carriers

- BMI > 40 with or without a significant co-morbidity
- BMI > 35 and 2 significant medical problems

- Failure of non surgical attempts to lose weight.

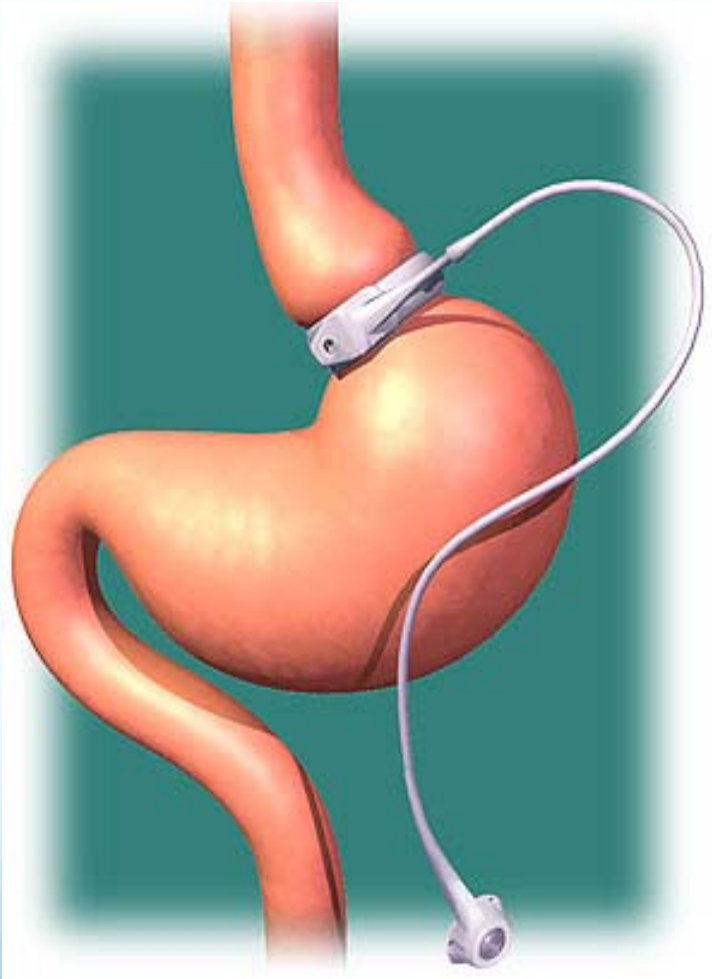
# SURGICAL TREATMENT OPTIONS

# Types of Obesity Surgery

- Gastric Restrictive
  - Adjustable Gastric Band
  - Sleeve Gastrectomy
- Combined Restriction and Malabsorption
  - Roux en Y Gastric Bypass
  - Biliopancreatic Diversion with Duodenal Switch
  - Single-Anastomosis Duodenal Switch or Stomach Intestinal Pylorus Sparing Surgery (SIPS)

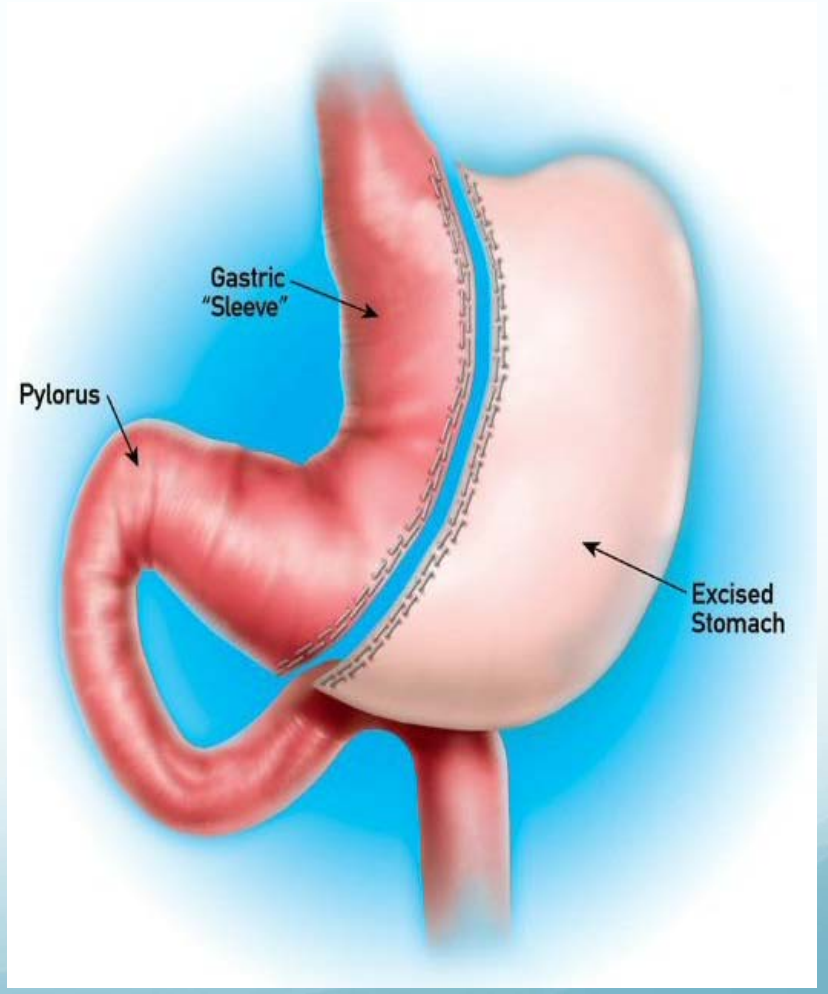
# Adjustable Gastric Band

- Creates a small gastric pouch from the proximal stomach
- Pouch drains via narrow opening, resulting in resistance to passage of solids
- Feeling of satiety when pouch above band is full.
- No bowel resection

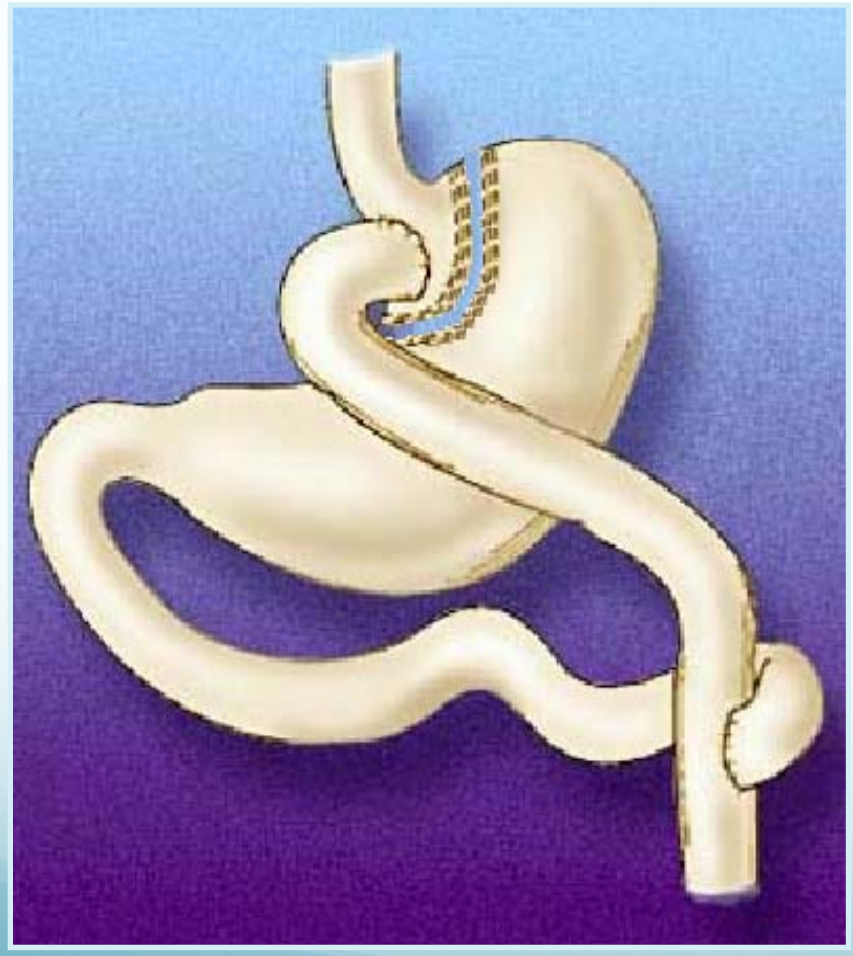


# Sleeve Gastrectomy

- 70-80% gastrectomy, leaving a cylindrical or ‘sleeve’ shaped stomach
- No foreign body
- Feeling of fullness is achieved when small stomach is full.

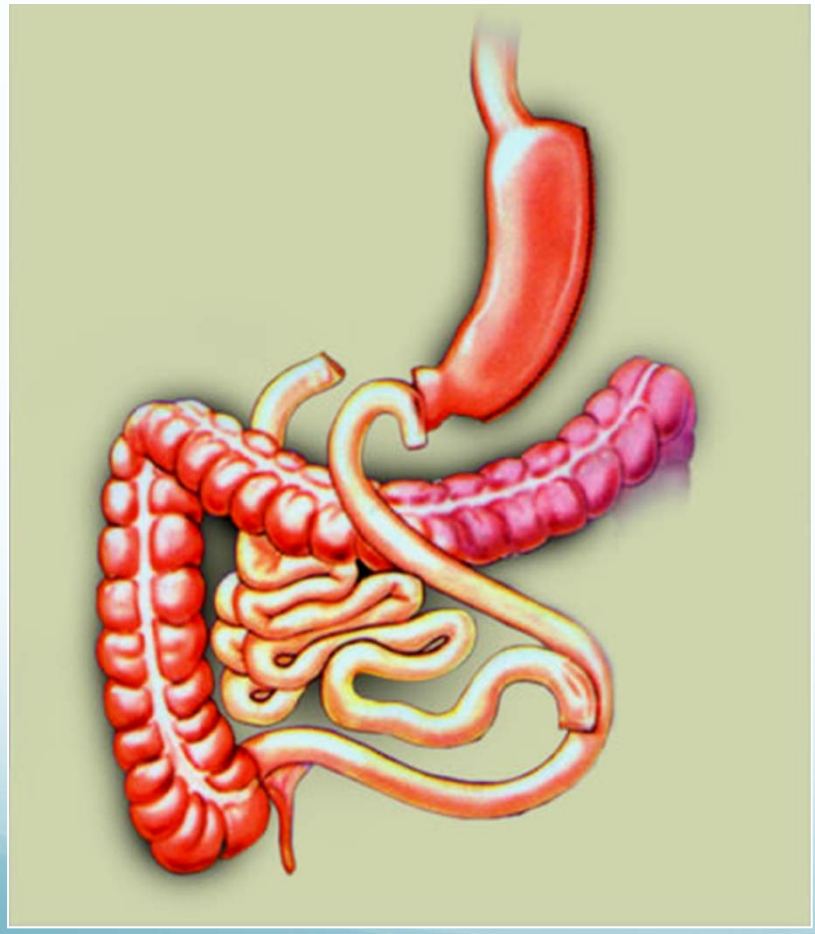


# Roux-en-Y Gastric Bypass



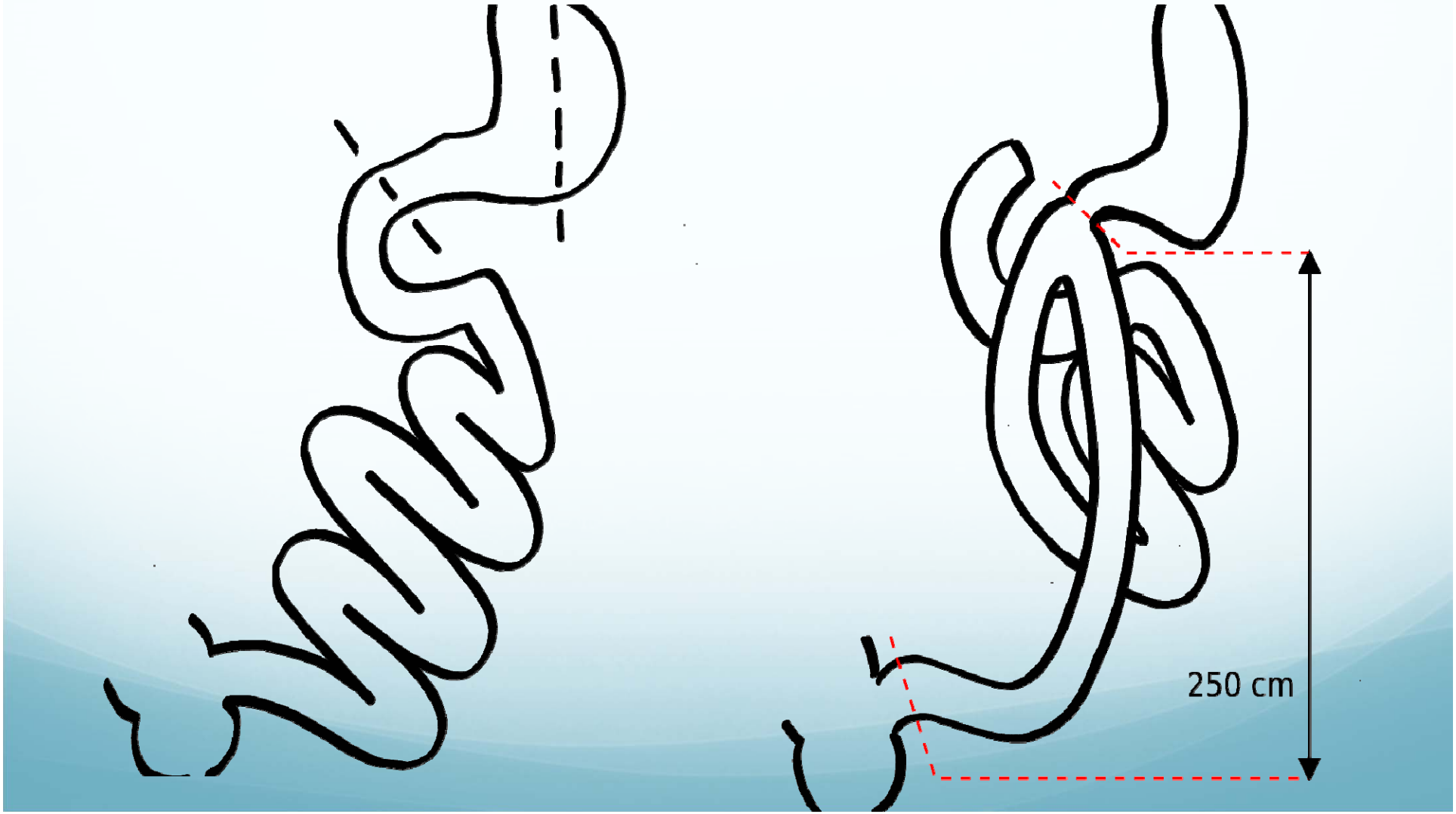
- Reduced gastric capacity
- Malabsorptive limb (100-150 cm)
- Food bypasses duodenum and first portion of the jejunum

# Biliopancreatic Diversion / Duodenal Switch



- Weight loss from both restriction and malabsorption
- Restriction – partial gastrectomy
- Malabsorption – division / separation of flow of food from flow of bile and digestive enzymes

# Single-Anastomosis Duodenal Switch or Stomach Intestinal Pylorus Sparing Surgery (SIPS)



# Single-Anastomosis Duodenal Switch or Stomach Intestinal Pylorus Sparing Surgery (SIPS)

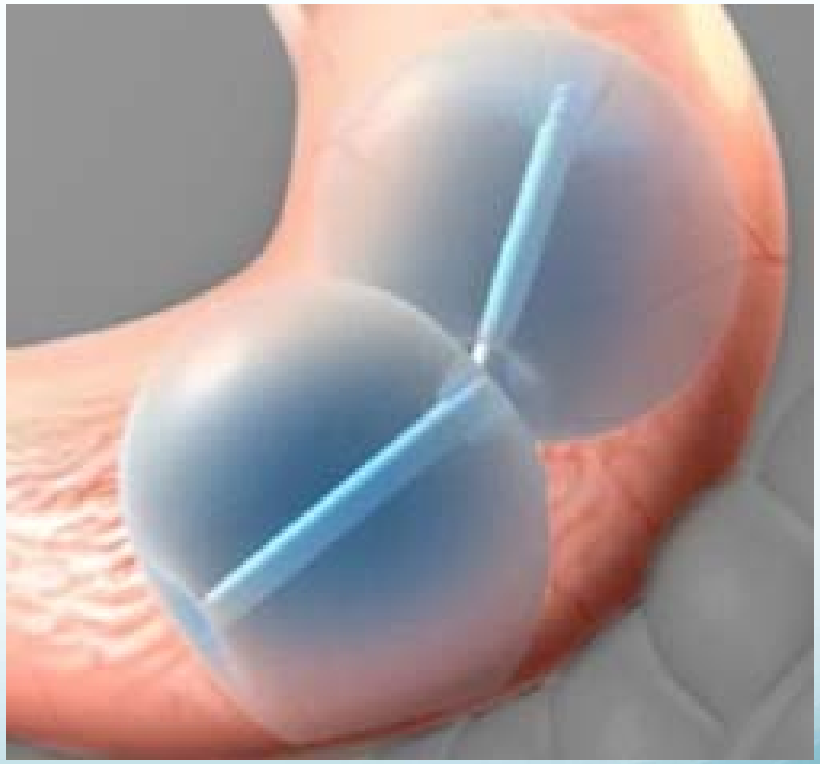
- Modification of the Duodenal Switch
- Single anastomosis (less risk of complications)
- Pylorus sparing
- Longer common channel resulting in les frequent bowel movements and less vitamin deficiencies
- Up to 70% EWL
- Not yet covered by major insurance carriers

# NON-SURGICAL TREATMENT OPTIONS

# Gastric Balloon

## Orbera GastricBalloon

## ReShape Dual Gastric Balloon



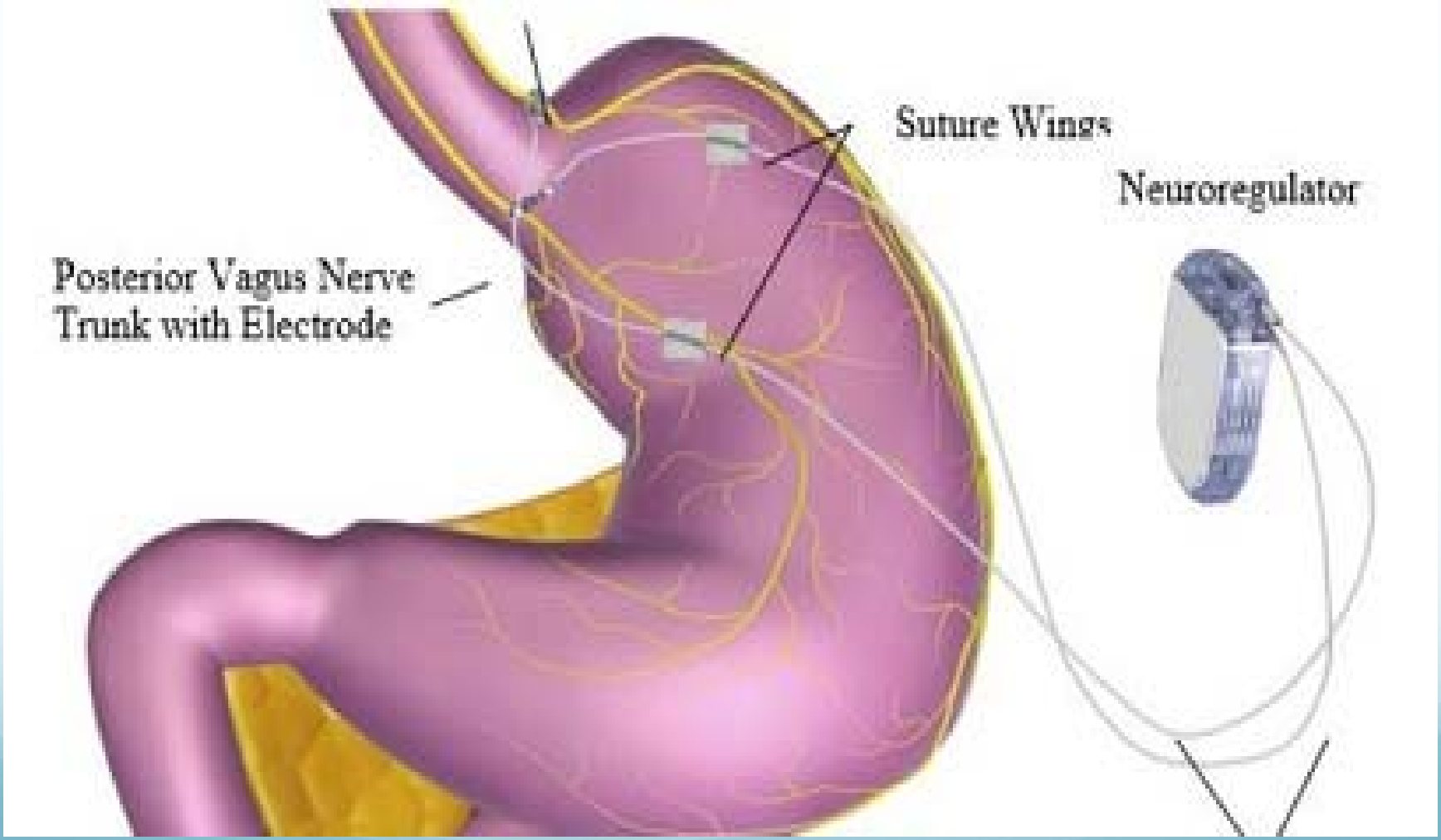
# Gastric Balloon

- FDA approved 2015, BMI >30
- BMI 30-40 with at least 1 co-morbidity, or BMI >50 needing to lose weight prior to bariatric surgery
- Outpatient, endoscopic placement, silicone balloon filled with 450-700 ml saline (Orbera) or 450 ml saline each balloon (ReShape) to match body structure
- Early satiety
- Removed endoscopically after 6 months
- 25-30% EWL
- Side effects – intolerance, postoperative nausea, gastric ulcer, rare gastric perforation (0.1%)
- Self pay $7,000-10,000

# Gastric Pacing – Maestro Rechargeable System

- FDA approved 2015
- BMI 40-45, or 35-39.9 with at least 1 co-morbidity
- Rechargeable electrical pulse generator, wire leads and electrodes implanted surgically into the abdomen.
- Sends intermittent electrical pulses to the trunks in the abdominal vagus nerve, to signal the brain that the stomach feels empty or full.
- Specific mechanisms for weight loss due to use of the device are unknown.

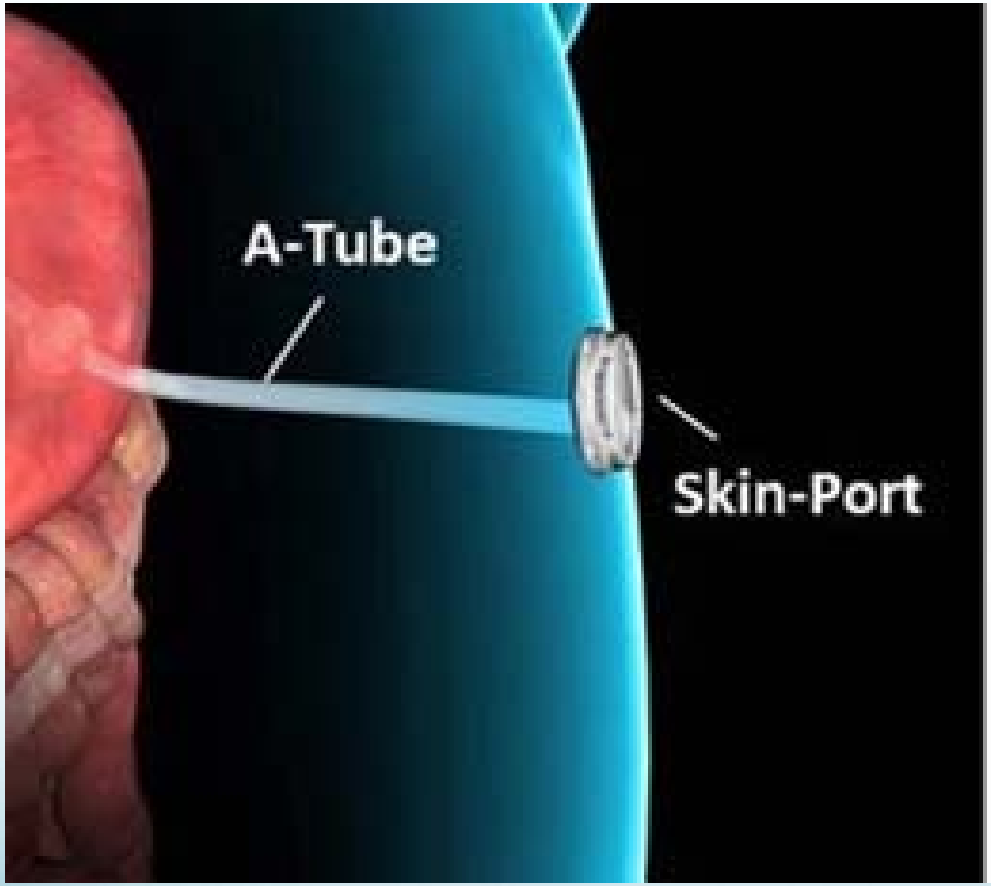
# Gastric Pacing – Maestro Rechargeable System



# Gastric Emptying System

- FDA approved 2016
- Endoscopic placement
- G-tube drains gastric contents 20-30 minutes after meals

# Gastric Emptying System –




# PRE-OPERATIVE EVALUATION

# Pre-operative Evaluation

- Multi-Disciplinary approach to bariatric care
  - Medical
  - Nutrition
  - Psychology

# Medical Evaluation

- History and Physical Exam
  - Medical Co-morbidities
    - Optimize status of co-morbidities
- Smoking Cessation
- Clinical Testing
- Birth Control

# Medical Evaluation – Clinical Testing

- Blood work - baseline testing
  - CMP, CBC, HBA1c, TSH, Lipid Panel
  - B12, 25-hydroxy Vitamin D
  - Thiamine, A, E, K
- EKG, Chest x-ray, Urinalysis
- Barium Swallow or EGD
- Polysomnography testing / update
- Operative note: any type of stomach or bowel surgery, hernia repair, cardiac surgery or oncology surgery with path
- Colonoscopy over 50
- Mammogram over 40

# Medical Evaluation (cont).

- Operative note: any type of stomach or bowel surgery, hernia repair, cardiac surgery or oncology surgery with path
- Specialist Consult / Clearance:
  - Cardiology, Pulmonary, Endocrinology, Hematology, Oncology, Gastroenterology

# Nutrition Evaluation

- Identification of  barriers to optimal postoperative dietary adherence
- Determine pre-existing nutrition and bariatric surgery knowledge deficits
- Begin diet education process and implementation of gastric bypass meal planning principles to enhance likelihood of post operative success
- Socioeconomic considerations – finances and transportation

# Nutrition Education

## Education for successful post op transition begins at the initial evaluation

Diet advancement

Meal planning guidelines

Supplementation

Potential food and fluid intolerance

Volume

- Initial and long term restriction

# Psychological Evaluation

- Evaluate presence / status of psychopathologies
  - Depression, Bipolar disorder, Schizophrenia
  - Suicidal / Homicidal Ideations
- Evaluate coping skills / competency
- Determine support systems
- Evaluate knowledge base regarding bariatric surgery
- Identify barriers to success
  - Eating disorders (binge eating disorder, purging), Substance abuse

# Post-operative Care: Short-term Concerns

# The Honeymooon Period

- Lasts for approximately 12 months after bariatric surgery
- Initially, like a “New Mom”
- Hyper-vigilance may wane over time

# Patient Accountability and Self Monitoring

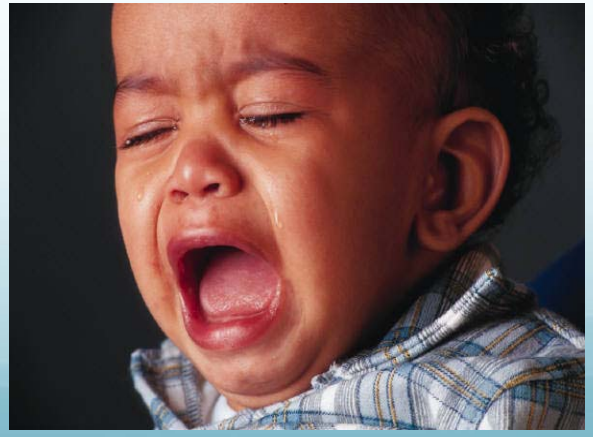
- ***"Surgery is only a Tool"….***
- ***Using* the tool:**
  - **Help the patient to recognize that they are ultimately responsible for their long-term success**
  - **Interconnectedness of lifestyle choices**
  - **Take responsibility for choices made**

# Patient Accountability and Self-Monitoring

- **Clinic follow-up**
- **Regular weigh-ins**
- **Blood work**

# REALITIES:
# AKA: The Difficult Truths

- THE MORE WEIGHT YOU HAVE TO LOSE, THE LONGER IT WILL TAKE
- THE WEIGHT ‘DROPS OFF” AT FIRST
- SOME PEOPLE LOSE STEADILY, BUT MOST HAVE WEIGHT LOSS PLATEAUS



# Nutrition

- Full liquid diet for 2 weeks
- Pureed diet 3rd week
- Soft solid diet until 3 months postop
- Regular diet
  - 6 small meals / day
  - 60-80 gms protein / day
  - 20 / 10 guideline
  - ~1200 calories / day
  - 64 oz noncaloric, noncaffeinated fluids / day

# Nutrition:
# Re-learning how to eat

- **Transition from liquid to soft solid diet**
  - **Q 3-4 hour meal times**
  - **2-4 oz meal volume (initial)**
  - **Protein first -> vegetables -> fruits**
  - **Separate fluid from food**
  - **Chew well/small bite size**
  - **20-30 minute meal times**
  - **Caffeine, carbonation, extreme temperature, sugar, fat**

# Short-term Care: Nutrition

- **Food and Fluid Intolerance**
  - **N/V, Abdominal Pain/Cramping**
    - **Short term (first three months)**
      - **Eating behaviors**
        - **Too much**
        - **Too fast**
        - **Temperature**
        - **Inadequate chewing**
        - **Drinking with meals**
        - **Bite size**

# Short-term Care: Physical Activity

- **The Key to the "Calories in - Calories out" Balance**
- **Regular, moderate physical activity**
  - **Motivating Factors**
  - **Health Benefits**
- **Aerobic exercise - long duration, low intensity**
- **Strength training - short duration, high intensity**

# Short-term Care: Social Support

- **No man is an island**
- **Need positive social support for good eating habits and exercise**
- **Family Members, Friends, Co-Workers**
- **Program Personnel, Primary Care Providers**
- **Support Groups, Psych Groups, Personal Counseling**
- **Fellow patients, “Angels”**

# Post-operative care: Long-term Concerns

# Long-term care: On the road to success?

- Is the weight loss as expected?
- Coming to post-op visits

  and following program recommendations?

# Long-term Care

- Weight Status – loss / regain
- Psychological Concerns
- Lab work and Vitamin Supplementation
- Status of Co-Morbidities
- Complications

# Long-term Care: Weight Regain

- **Expect It.. and Manage It**

- **Look at Diet Patterns**
- **Look for Exercise**
- **Look at Psychological Issues**
- **Consider Anatomic Problems**

# Long-term Care: Weight Regain - Diet Changes

- **Excesses and Inadequacies**
- **How many meals per day?**
- **Grazing**
- **“Drinking and Driving”**
- **Lack of meal planning**
- **Empty calories**
- **Alcohol**
- **Vitamin Supplements still in the routine?**
- **Soft Calorie Syndrome**

# Long-term Care: Weight Regain - Diet Changes

- **Soft Calorie Syndrome:**
  - **Frequent consumption of soft or liquid, calorie dense foods**
  - **Pass through the pouch quickly, creating rapid return of hunger**
  - **Examples may include ice cream, sugar sweetened beverages, juices, candy, chips pretzels, crackers, cookies**
  - **** Foods that dissolve in water*****

# Long-term Care: Weight Regain

- **Addiction Transfer**
  - **No longer able to use food as a coping mechanism**
  - **Transfer addiction of overeating to another compulsive behavior, ex gambling, shopping, sex, smoking, alcohol**
  - **Alcohol - “less is more”**

# Long-term Care: Weight Regain

- **Medication side effect**
  - **Anti-depressants - SSRIs, Tricyclic antidepressants, MAOIs (does not include Buproprion)**
  - **Anti-psychotics**
  - **Anti-hypertensives - Beta Blockers**
  - **Steroids**
  - **Diabetes Medications - Insulin, Sulfonylureas (Glipizide, Glyburide,Amaryl), TZDs (Avandia)**

# Long-term Care: Weight Regain – Anatomic Evaluation

- **Pouch Size Small? Anastomosis 8-15mm?**
  - **Evaluate with EGD / Barium Swallow**
- **Gastro - Gastric Fistula -**
  - **Evaluate with EGD / Barium Swallow**
- **Revision Possibilities -**
  - **Lengthen the Roux Limb of RNY Bypass or cinch the anastomosis**
  - **Conversion of Gastric Band to Sleeve Gastrectomy, RNY Bypass, BPD – DS, SIPS**
  - **Conversion of Sleeve Gastrectomy to RNY Bypass or BPD – DS**
- **Previous trial – Band over bypass**

# Long-term Care: Excessive Weight Loss

- **Diet Changes**
  - **Skipping meals**
  - **Lack of structured meal times**
  - **Lack of meal planning**
  - **Grazing on “Junk foods”**
  - **Leaving major food groups out of diet**
- **Look at Psychological Issues**
  - **Fear of weight regain**
  - **Excessive exercise**
  - **Self-induced vomiting**

# Long-term Care: Psychological Management

- **Antidepressants**
- **Anxiolytics**
- **Sleep Aids**
- **Support Groups**
- **Counseling / Therapy**

# Post-operative Care: Lab work

- Gastric Band - lower risk for vitamin deficiencies unless food intolerance or excessive vomiting, folate, B12, thiamine, calcium
- Gastric Bypass – bypass of duodenum (folate, iron, calcium, thiamine) and distal stomach (B12)
- Gastric Sleeve – Iron, B12, calcium, thiamine
- Biliopancreatic diversion / DS or SIPS – iron, calcium and A,D,E,K

# Long-term Care: Labwork

- Screen preoperatively, 3 and 6 months postop and then at least annually for restrictive procedures, every 3 months for mal-absorptive procedures
  - Comprehensive Chemistry Panel
  - CBC, Ferritin,
  - Folate
  - B12
  - Thiamine (B1)
  - 25 hydroxy Vit D
  - PTH
  - Vitamins A, E, K

# Post-operative Supplementation: Multivitamin

- Chewable Multivitamin
  - Begin on DC from hospital
  - Daily
    - Choose complete formula, 100% daily value (band)200% daily value (all others)
      - 800 mcg folate
      - 15mg Zn
      - 18 mg iron

- Considerations:

- Start wth chewable or liquid and progress to tablet at 10-14 days post op
- Time release = decreased effectiveness
- Take with food or milk
- Separate from calcium supplements by at least 2 hours

# Post-operative Supplementation: Vitamin B12

- Begin Supplementation when starting solid food
  - Daily
    - Sublingual (500 mcg) or chewable tablets (1000mcg)
  - Weekly
    - Nasal spray: 500 mcg
  - Monthly
    - Intramuscular injection 1000 mcg

# Post-operative Supplementation: Calcium

- Calcium (citrate) with Vitamin D
  - 1500-2000 mg daily in divided doses, DS and SIPS 1800-2400 mg daily
- Initiate calcium supplementation when starting solid foods
- Absorbed in duodenum and proximal jejunum; deficiencies occur secondary to decreased intake of calcium rich foods
- Separate calcium supplementation from iron containing supplements by 2 hours for optimal absorption
- Long-term deficiency increases risk of osteoporosis

# Post-operative Supplementation: Iron

- **Required for RNY, BPD/DS and SIPS patients**
- **18-27 mg QD (in multivitamin) plus OTC supplement to achieve a total of 45-60 mg**
  - **Chewable, liquid, or tablet**
- **Additional supplementation also recommended for menstruating women and patients with history of anemia**
- **Best absorbed ferrous fumarate, sulfate or gluconate**
- **Absorption enhanced if taken with Vitamin C**

# Post-operative Supplementation: Fat Soluble Vitamins

- **Required for all DS and SIPS patients**
  - Vitamin A 10,000 IU daily
  - Vitamin D 2,000 IU daily
  - Vitamin K 300 ug daily
- **Water soluble preparations of fat soluble vitamins are available**
- **Intake of vitamin supplementation may be achieved with combination of multivitamin and calcium supplementation**
- **Caution with Vitamin K for patients on anticoagulation therapy**
- **Vitamin E deficiency not prevalent, but should be monitored**

# Long-term Care: Co-Morbidities

- **Diabetes**
- **Hypothyroidism**
- **Sleep Apnea**
- **Hypertension**
- **Hyperlipidemia**

# POSTOPERATIVE COMPLICATIONS

# Adjustable Gastric Band

- Reflux:
  - Band Slip - UGI
  - Erosion into stomach wall - EGD
  - Tubing kink, port flip – fluoroscopy or UGI
- Postprandial pain:
  - Cholelithiasis – abdominal ultrasound
  - Eating patterns - UGI
- Incisional Hernia:
  - Physical exam / CT Scan

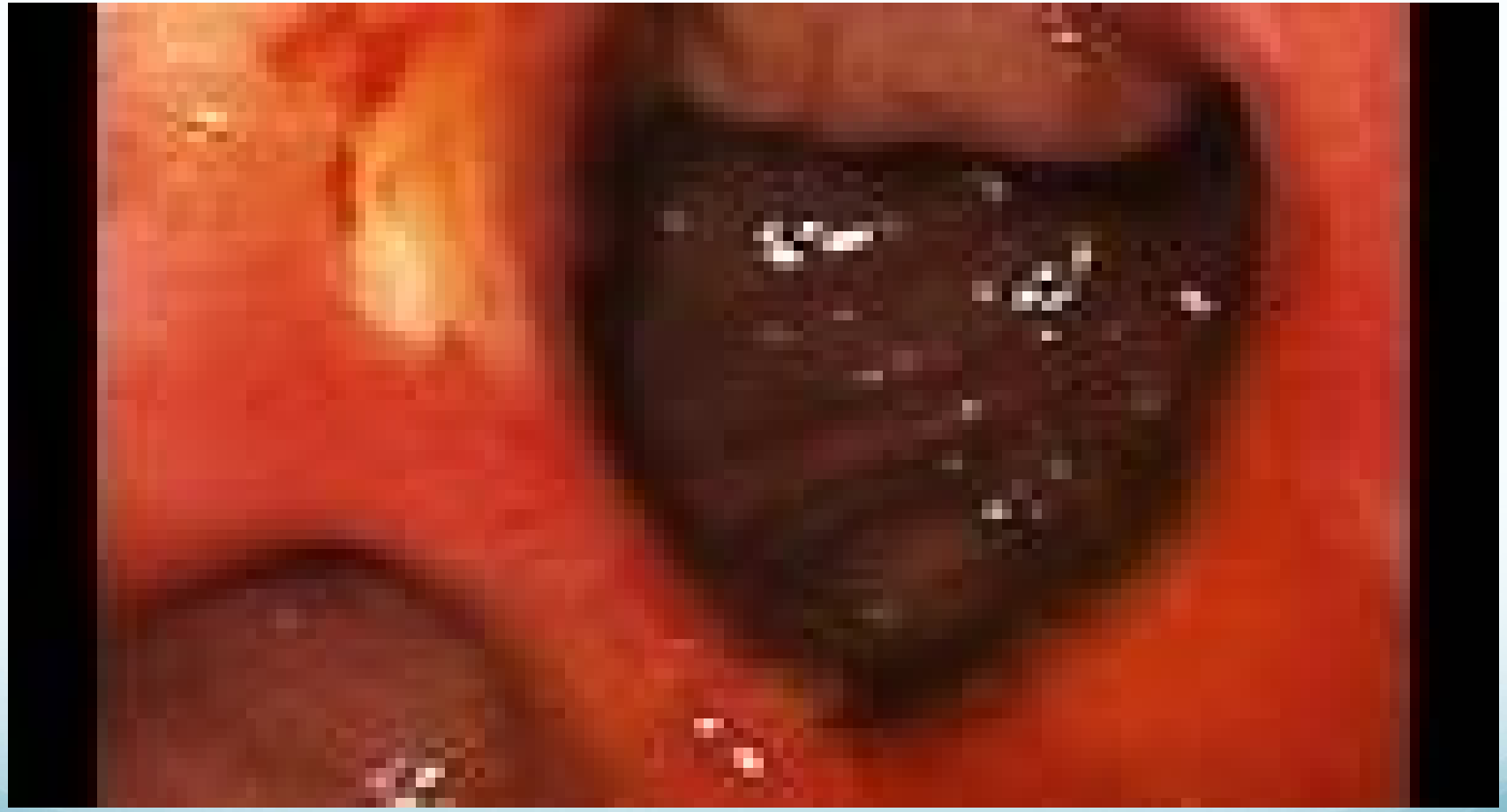
# Abdominal Pain

- RUQ or Midabdominal, postprandial – RNY, Sleeve, BPD / DS, SIPS
  - Gallstones / Biliary dyskinesia - Abdominal Ultrasound, HIDA scan
  - Incisional Hernia - Physical exam / CT Scan
  - Bowel obstruction – CT scan / laparoscopy
  - Internal hernia – specific to RNY – CT scan / laparoscopy
- LUQ – RNY
  - CT scan / Laparoscopy
- Postprandial - RNY, Sleeve
  - Anastomotic Stricture – UGI / endoscopy

# Marginal Ulcer

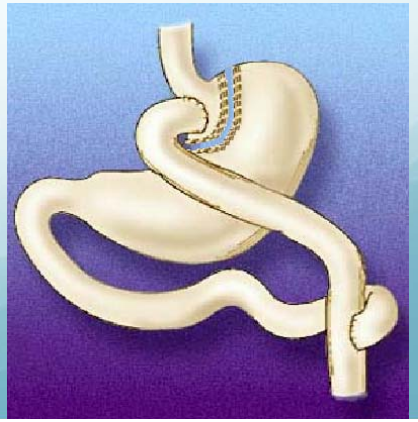
- **Ulcer at the margin between gastric pouch and the jejunal anastomosis – unique to Gastric Bypass**
- **Assess via Barium Swallow or EGD**
  - **Treat with PPI therapy bid +/- Sucralfate or Misoprostil**
  - **Absolutely *NO* NSAIDs, ASA for postoperative patients**
  - **Smoking cessation is a must!!**

# Marginal Ulcer



# Dumping Syndrome

- **Non-pyloric sparing**
- **Typically due to rapid emptying or "Dumping" of gastric contents into the jejunum 10-15 minutes after ingestion.**
- **Calorie dense foods – refined sugars and fat, leading to the release of gut hormones and rapid entry of water into the intestinal lumen**



# Dumping Syndrome (Gastrointestinal and Vasomotor)

- **Immediate Symptoms**
  - Nausea +/- vomiting
  - Abdominal cramping
  - Diarrhea
- **Delayed symptoms**
  - Hypoglycemia
  - Hot flashes
  - Diaphoresis
  - Dizzy, weak, faint
  - Hypotension

# Postprandial Hyperinsulinemic Hypoglycemia

- **Neuroglycopenic and autonomic symptoms occuring 1-3 hours after intake of a mixed (carbohydrate rich) meal**
- **Diagnosis –**
  - Symptoms occurring >1 year after surgery
  - Normal fasting glucose and insulin levels
  - Symptomatic hypoglycemia followed by spontaneous resolution of hypoglycemia
  - Positive provocative test

# Postprandial Hyperinsulinemic Hypoglycemia

- **Treatment**
  - Dietary Modification – Small frequent meals, high protein and fiber, low in simple carbohydrate content
  - Pharmacotherapy – Nifedipine, Acarbose, Octreotide
  - Gastrostomy tube placement into remnant stomach
  - Gastric outlet restriction
  - Reversal of bypass
  - Conversion of bypass to Sleeve Gastrectomy
  - Distal pancreatectomy not recommended

# In Conclusion,

**Optimal long-term patient care for bariatric surgery patients is a careful balance best achieved by helping the patient to assume responsibility for self-care activities, and partnership between the Bariatric team and the patient's Primary Care Physician and Specialty Team(s).**

# PITUITARY UPDATE

## Carolinas AACE
## September 11, 2016

**Mary Lee Vance, M.D.**
**Professor of Medicine and Neurosurgery**
**University of Virginia**

# Disorders of the Anterior and Posterior Pituitary

- Financial disclosures: None

# Disorders of the Anterior and Posterior Pituitary

- Prevalence – Pituitary lesion: 10% of normal population; most commonly found as incidental finding on MRI for headache, trauma, C-spine disease, stroke, seizure
- Needs evaluation

# Pituitary Update

- Diagnostic Issues: Acromegaly, Cushing's disease
- "Incidentaloma"

# Disorders of the Anterior and Posterior Pituitary

- Diagnostic Issues: MRI findings
- Caveat: “over-read” of study; inadequate precise imaging of pituitary

# PITUITARY DISEASE

- DxD: MRI lesion:
- Pituitary adenoma; pars intermedia cyst; Rathke's cleft cyst; craniopharyngioma; chordoma; arachnoid cyst; epidermoid cyst; lymphocytic hypophysitis; metastatic tumor

# Acromegaly – Diagnostic Issues

- Common Situation
- Young patient: incidental MRI finding of adenoma; no obvious clinical features of Acromegaly
- Needs IGF-1
- Early Dx so important

# Acromegaly: Diagnostic Issues

- Screening: random GH (not definitive; pulsatile secretion); IGF-1
- Lab: still seeing false elevations: LabCorp; ARUP; other labs
- Quest: best lab for IGF1: (assay I & data base for normal range) – must request (I have no association with Quest Lab)

# Acromegaly: Diagnostic Issues

- OGTT: must be done properly: indwelling venous catheter: measure simultaneous glucose & GH ) 0”, 30”, 60”, 90” 120”
- Some patients: DECREASE in glucose: a stimulus for GH release
- Normal GH response: GH < 0.4 mg/dl

# Cushing's - Diagnostic Issues

- PCOS or Cushing's?
- Identical clinical features: obesity, acne, hirsutism, menstrual disturbance, infertility
- Common clinical features: insulin resistance/diabetes, hypertension, depression
- Specific features: supraclavicular fat pads (Cushing's); not post cervical fat pad

# Cushing's - Diagnostic Issues

- PCOS or Cushing's?
- Cannot distinguish between PCOS and Cushing's clinically or with routine biochemical tests: needs evaluation for Cushing's
- Every young woman I've seen with Cushing's has been diagnosed with PCOS

# Cushing's - Diagnostic Issues

- Screening tests: all equally reliable: 92% accurate: 24 h UFC, 1 mg dex test, late night salivary cortisol – ~ 8% false positive tests
- Multiple tests necessary to confirm ***CONSISTENT*** overproduction of cortisol (Lab important – avoid ARUP for salivary cortisols)
- TIME is the best test if not clear results

# Cushing's - Diagnostic Issues "Water Bottle" People

- 24 hour UFC: fluid intake, urine volume:
- 30 normal subjects: normal intake vs. 5 L/day
- High fluid intake: urine volume > 2,000 cc/d; UFC: 23/30 (77%): UFC above normal
- Normal intake: 6/30 (20%) UFC above normal

Mericq, MV, Cutler, GB, J Clin Endocrinol Metab, 1998

# Cushing's - Diagnostic Issues

- 11 p.m., midnight salivary cortisol: appropriate collection important
- 92% accurate: may be increased in patients with depression, variable work/sleep schedule
- Laboratory reliability is an issue

# Cushing's - Diagnostic Issues

- Case: 55 yo woman, weight gain, depression, stressful job (IRS-computer security), random serum cortisol elevated.
- Multiple 11 p.m. salivary cortisols – extremely elevated; UFCs normal; normal serum cortisol after 1 mg dex
- No clinical features of Cushing's

# Cushing's - Diagnostic Issues

- IPSS: Differential Dx (source of ACTH); not for Dx Cushing's
- Experienced interventional radiologist required
- CRH: required (now available) for accurate study
- Must have active Cushing's for the test

# Hypophysitis - Diagnostic Issues

- Immunotherapy: Ipilimumab (melanoma)
- Presentation: Headache, fatigue
- MRI: diffuse pituitary enlargement, no discrete adenoma/cyst
- Diabetes insipidus: none reported (428 patients; 4 series)
- More common in men than women

**Faje, A, 2015, Pituitary**

# Hypophysitis - Diagnostic Issues

- Immunotherapy: Ipilimumab (melanoma)
- Deficiencies: thyroid, adrenal, gonadal, growth hormone (descending order of frequency)
- Resolution of pituitary enlargement: all patients
- Persistent deficiencies: majority

Faje, A, 2015, Pituitary

# Diabetes Insipidus - Diagnosis

- Occurrence: most commonly after pituitary surgery
- Post op incidence: 15%: 3% permanent, 12% transient
- Diagnosis: frequent urination, especially nocturia (every 30 minutes)

# Diabetes Insipidus

- High risk patients:
  Craniopharyngioma; Rathke's cleft cyst; large tumor with damage to pituitary stalk during surgery
- Lymphocytic hypophysitis: most commonly women with pituitary stalk thickening

# Diabetes Insipidus

- Lab: serum sodium, osmolality: normal if no fluid restriction; urine S.G., osmolality: low. (Never fluid restrict post op)
- Rx: desmopressin: NO fixed dose; monitor I & O until pattern firmly established

# SIADH

- Occurrence: post op, day 10 - 13: patient calls, feels unwell, symptoms similar to adrenal insufficiency
- Low serum sodium - transient
- Rx: Fluid restriction: 500 cc/day for 3-4 days: repeat serum sodium
- NO IV SALINE – a WATER, not a sodium problem

# PITUITARY UPDATE

- Treatments

# Pituitary Lesions

## Goals of Treatment(s)

- Shrinkage/complete removal of tumor
- Remission from hormone hypersecretion
- Persistent tumor: control of tumor growth
- Identify & replace deficient hormone(s)
- Address fertility issues
- Document & treat complications

# Acromegaly Treatments

- Transsphenoidal surgery: 1st line: Remission: overall: 60%; microadenoma: ~ 90% (U Va outcomes)
- Residual disease: Radiation therapy; medical therapy (No medical therapy cures Acromegaly)

# Pharmacologic Treatments
## Acromegaly

- Current treatments: Somatostatin analogs; GH receptor blocker; dopamine agonists
- How effective?
- Somatostatin analogs (Octreotide LAR, Lanreotide): ↓ IGF-1: ~ 90% of patients; Normal IGF-1: 40% - 60% of patients
- GH receptor antagonist: Normal IGF-1: ~ 87% of patients

# Acromegaly: Somatostatin Analogs – Meta-Analysis: 44 Clinical Trials

## Normal IGF-1

| | Unselected | Pre - Selected | All |
|---|---|---|---|
| Octreotide LAR | 63%<br>n=126 | 68%<br>n=486 | 67%<br>n=612 |
| Lanreotide SR | 42%<br>n=609 | 56%<br>n=305 | 47%<br>n=914 |
| Octreotide s.c. | | | 54%<br>n=266 |

***Freda et al JCE&M 2005***

# Pharmacologic Treatments
## Acromegaly

- Cabergoline: Normal IGF-1 < 10% of patients
- Cabergoline suppresses prolactin in patients with co-secretion of GH and prolactin (20% of patients with acomegaly)
- May augment effect of somatostatin analog: some studies suggestivr; not proven

# Pharmacologic Treatments
## Acromegaly – Pasrieotide LAR

- 1 yr Rx: Normal IGF-1: 38.6% in 136 patients
- Hyperglycemia: 28.7% of patients
- No assessment of tumor volume
- Expensive: $152,000/year

Colao, et al, JCE&M, 2014

# Pharmacologic Treatments
## Acromegaly - Costs

- Sandostatin LAR: 20 mg/month: $ 40,414/year
- Pasireotide LAR: $ 152,000/year
- Pegvisomant: 20 mg/day: $92,207/year
- Patient assistance programs available

# U Va Approach - Acromegaly

- Transsphenoidal surgery; Gamma knife treatment; medical therapy
- 6 weeks after Gamma knife: Medical Rx: Somatostatin analog; if not effective, pegvisomant; if not effective: combination Somatostatin analog + pegvisomant (very expensive)
- Stop drug(s) every 6 mos to assess effect of Gamma knife; new pituitary deficiency

# ACROMEGALY - Fractionated Stereotactic Radiotherapy (LINAC)

- 34 patients, 27 XRT sessions; mean f/u: 12.7 yr.
- Remission: 38%, @ mean of 12.7 yr.; 50% remission @ 15 yrs.
- New pituitary deficiency: 39% of patients
- Tumor growth: none observed
- Complications: no visual impairment, stroke, necrosis, brain tumor

Diallo, A, et, al, 2015, Endocrine

# ACROMEGALY
## Gamma Knife (U Va Series)

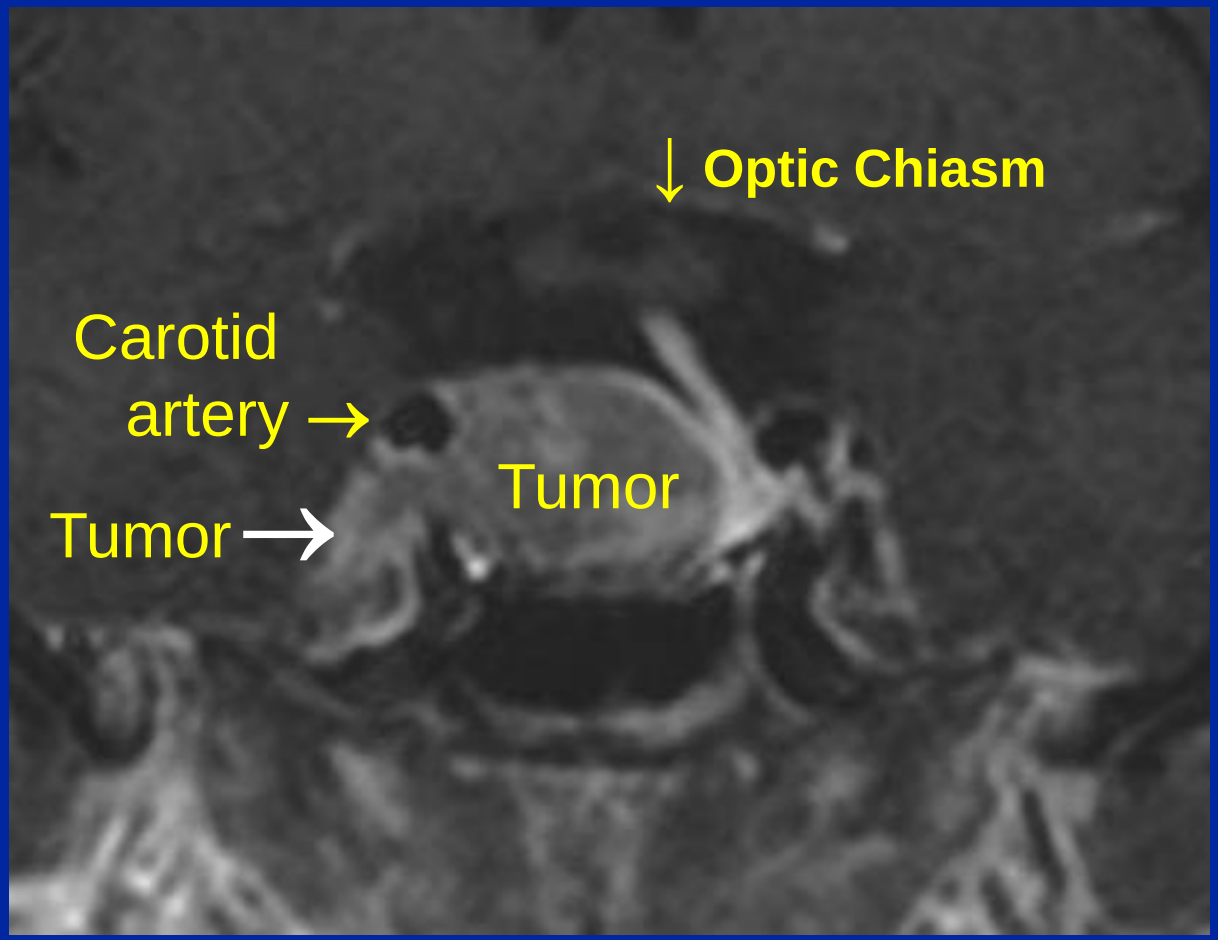
- 136 patients; median F/U: 61.5 months
- Remission: normal IGF-1 or GH < 1 [OGTT] – off of medication
- Remission: 65% of pts; Mean time to remission: 27.5 mos.
- New pituitary hormone deficiency: 31.6% of patients

Lee, et al, 2014, J Clin Endocrinol Metab

# Radiation/Radiosurgery
## Typical Case

- Patient with a macroadenoma, cavernous sinus invasion
- Transsphenoidal surgery: remove as much of tumor as possible (intrasellar portion)
- Residual tumor: continues to grow over time
- Cushing's, Acromegaly, Prolactinoma: no curative medical treatments. Drugs: EXPENSIVE; often only partial control

# Tumor Invading Right Cavernous Sinus




22 yo woman with Cushing's - desires fertility

# Cushing's Disease Medical Therapies

- Ketoconazole: blocks cortisol synthesis
- Very effective; dose titration necessary
- Monitor liver enzymes regularly

# Pharmacologic Treatments
## Cushing's Disease

- Mefipristone: Glucocorticoid receptor blocker

- No hormone measurements; clinical features (BP, weight, glucose, symptoms) only way to assess response/side effects

# Pharmacologic Treatments
## Cushing's

- Mifepristone: 50 patients; 6 mo Rx: ↓ glucose AUC in 60% pts.
- ↓ HbA1c: 7.4% to 6.3%
- ↓ diastolic BP: 38% pts.
- Clinical improvement: 87% pts.
- Side effects: fatigue, nausea, headache, ↓ K+, arthralgia, endometrial thickening

Fleseriu, et al, 2012, JCE&M

# Cushing's Disease – Medical Therapies

- ↓ ACTH production:
- Cabergoline: normal UFC: 37%; high doses required

- Long term effect of high dose cabergoline worrisome (cardiac valves)

# Cushing's Disease – Medical Therapies

- ↓ ACTH production: Pasireotide
- 12 mos Rx: 39 patients; 600 ug bid; nl UFC: 13%; 900 ug bid nl UFC: 25%
- :Diabetes: 18%; Hyperglycemia: 40% of patients

Colao, et al, NEJM, 2012

# Pharmacologic Treatments
## Cushing's Disease - Costs

- Pasireotide: 600 mg bid: $150,000/year
- Mefipristone: $200,000/year
- Patient assistance available

# Refractory Tumors – Medical Therapies

- Temozolamide (Temodar) – oral alkylating chemotherapy, crosses blood-brain barrier
- Use: aggressive, refractory tumors; pituitary carcinoma

- Limited experience

# Refractory Tumors - Temodar

- 7 patients: refractory after surgery, radiation, medical treatments
- Tumor regression: 2 patients (~ 20%)
- Stable: 4 patients
- Progression: 1 patient - carcinoma

Bush, et al, JCE&M, 2010

# CUSHING'S DISEASE
## Gamma Knife (U Va)

- Adjunctive therapy
- 96 patients
- Remission: 70% of patients (nl 24h UFC)
- Median time to remission: Medical treatment at time of Gamma knife
  No ketoconazole 12.6 mo
  On ketoconazole 21.8 mo
- Tumor control: 98% of patients

Sheehan et al, J. Neurosurgery, August, 2013

# GAMMA KNIFE TREATMENT Cushing's Disease (U Va)

- Relapse of Cushing's: 15/96 patients (15.6%)
- New pituitary hormone deficiency: 36% - higher risk (p = 0.01) if entire sella treated
- Visual complications: 5/96 (5.2%): cranial nerve deficit (transient in most)
- No stroke or neoplasia

Sheehan, et al, J Neurosurgery, 2013

# CUSHING'S DISEASE
# Conventional Radiotherapy

- 30 adults, conventional XRT
- 25/30 (83%) remission; 6 - 60 mos; 22/25 within 2 yrs
- Deficiencies: GH: 57%, gonadotropin: 33%, TSH:13%, ACTH: 3%

Estrada, et al, NEJM, 1997

# CUSHING'S DISEASE
# Conventional Radiotherapy

- 24 patients (11-67 yrs): “low dose” (20 Gy):
  Remission: 11/24 (46%), 4 - 36 mo
- Relapse: 5/11 (45%), mean: 50 mo (2 eventually became normal)
- New deficiency: GH: 66%, Gonadotropins: 14%, ACTH: 13%, no TSH deficiency
- Tumor growth: not assessed
- Complications: no new tumor formation, optic nerve damage, brain necrosis

Littley, et al. Clin Endocrinol. 1990

# Fertility – Medical Therapies

- Fertility is possible – must discuss with all patients
- LH (HCG) + FSH: restoration of gonadal function (men & women)
- Takes time; expensive

# Pituitary Disease

- More common than appreciated
- Requires coordinated care
- Long term follow up necessary
- Thank you and…
- Questions?

# *"Update on Management of Lipid Disorders: 2016"*

## Carolinas Chapter AACE Annual Meeting Sept 9-11, 2016


Robert H. Eckel, M.D.

Professor of Medicine

Division of Endocrinology, Metabolism and Diabetes

Division of Cardiology

Professor of Physiology and Biophysics

Charles A. Boettcher II Chair in Atherosclerosis

Director Lipid Clinic, University Hospital

# Duality of Interests

– ***Consultant/Advisory Boards***

- Merck
- Novo Nordisk
- Regeneron/Sanofi aventis

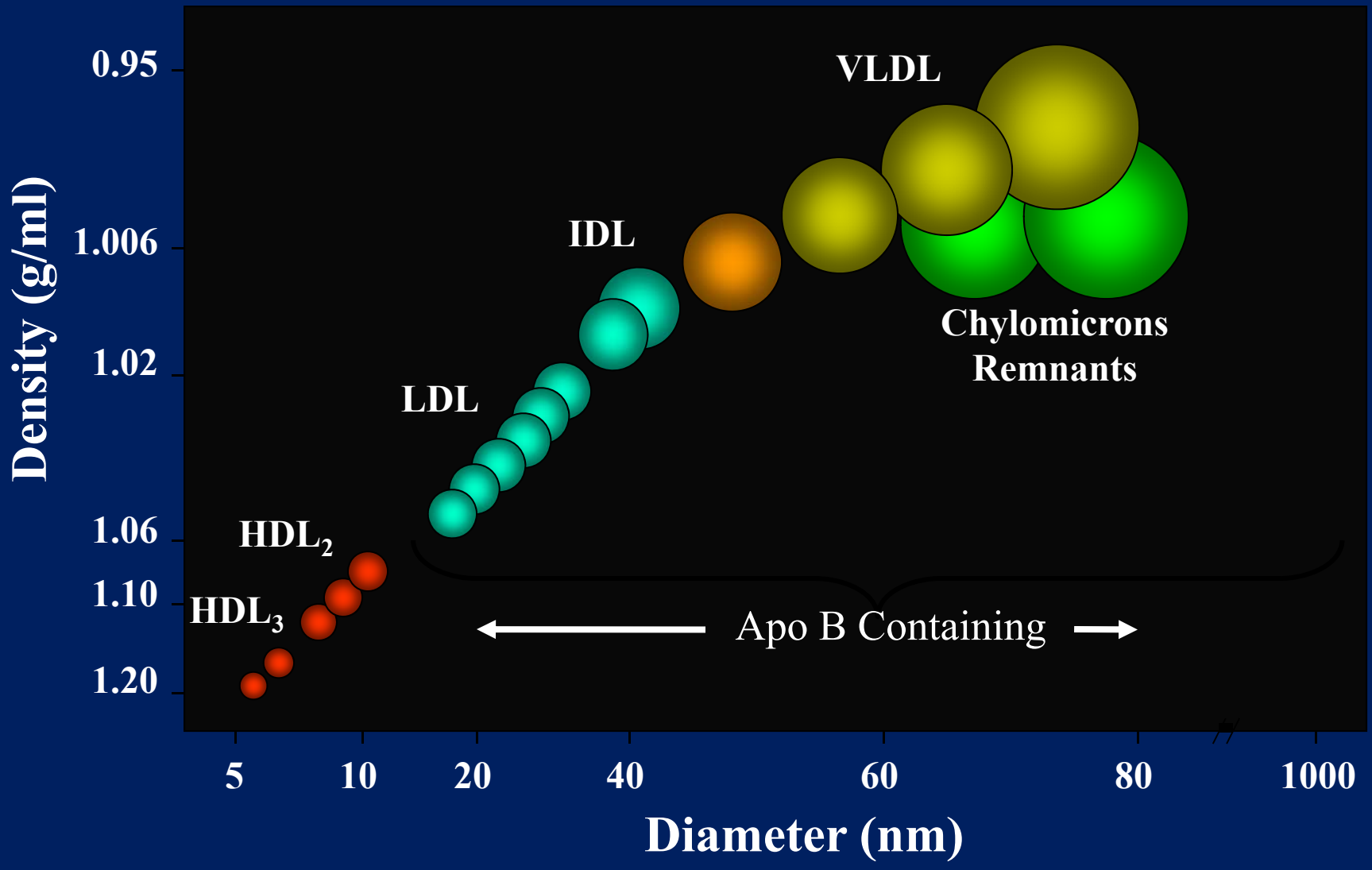
– ***Grants/Research Fellowships***

- Ionis Pharmaceuticals
- UniQure, Inc.

– ***Medical Education***

- CMHC
- HealthTeamWorks
- Medscape
- Medical Education Resources
- MedIelligence
- VOX Media

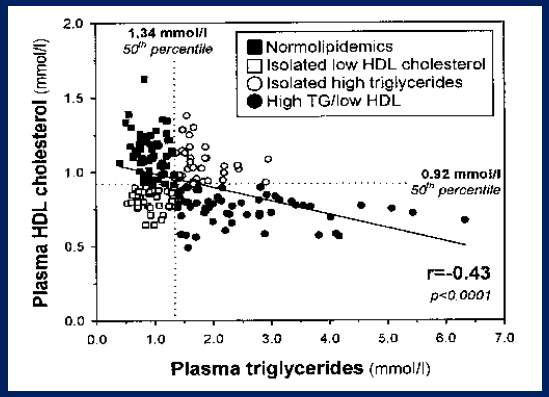
# Lipoprotein Classes



# The Lipid Patient

## Five Groups, Rule of 30s

- ↑ LDL cholesterol – 160, 130, 100, 70 mg/dL
- ↑ TG (↓ HDL cholesterol) – 150, 200 mg/dL



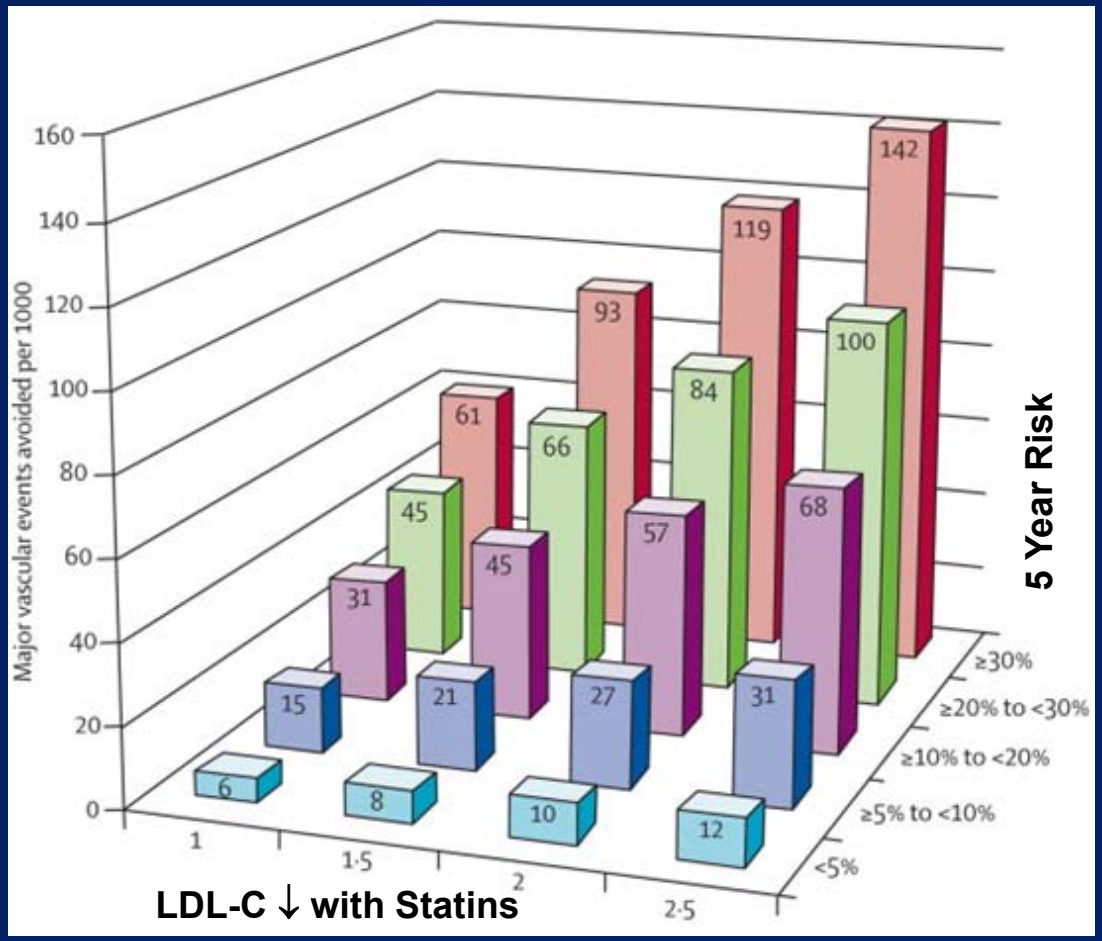

- ↑ LDL cholesterol + ↑ TG - >160 + >200 mg/dL
- ↓ HDL cholesterol - <30 mg/dL
- ↑ Lipoprotein (a) - >30 mg/dL

# Assessing Acquired Causes of Dyslipidemia

- Lifestyle
  - Diet, inactivity, alcohol, tobacco
- Medications
  - Steroids, diuretics, β-blockers, PIs, cis-RA
- Insulin resistance, metabolic syndrome
- Thyroid disease
- Liver disease
- Kidney disease
  - Proteinuria
  - ↓ GFR

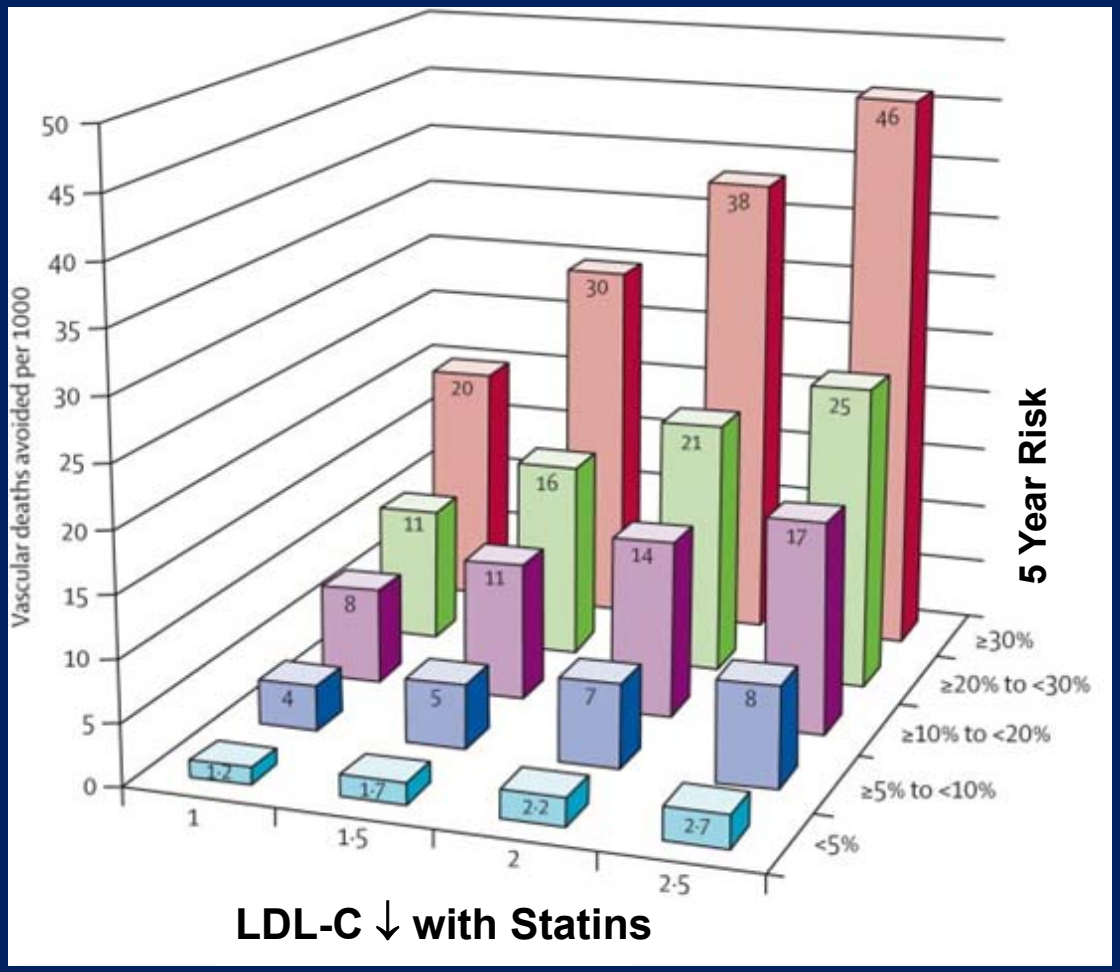
# 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

# Predicted 5-Year Benefit on Major CVD Events of LDL-C Reductions with Statins: Meta-Analysis of 27 RCTs




Cholesterol Treatment Trialists (CTT), *Lancet* 380:581, 2012

# Predicted 5-Year Benefit on CVD Deaths of LDL-C Reductions with Statins: Meta-Analysis of 27 RCTs




Cholesterol Treatment Trialists (CTT), *Lancet* 380:581, 2012

## ACC/AHA Prevention Guideline

# 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

## A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

*Endorsed by the American Academy of Physician Assistants, American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women With Heart Disease*

EXPERT PANEL MEMBERS

Neil J. Stone, MD, MACP, FAHA, FACC, Chair; Jennifer G. Robinson, MD, MPH, FAHA, Vice Chair; Alice H. Lichtenstein, DSc, FAHA, Vice Chair; C. Noel Bairey Merz, MD, FAHA, FACC; Conrad B. Blum, MD, FAHA; Robert H. Eckel, MD, FAHA; Anne C. Goldberg, MD, FACP, FAHA; David Gordon, MD*; Daniel Levy, MD*; Donald M. Lloyd-Jones, MD, SCM, FACC, FAHA; Patrick McBride, MD, MPH, FAHA; J. Sanford Schwartz, MD; Susan T. Shero, MS, RN*; Sidney C. Smith, Jr, MD, FACC, FAHA; Karol Watson, MD, PhD, FACC, FAHA; Peter W. F. Wilson, MD, FAHA

*Circulation* 129(25 Suppl 2):S1-45, 2014

# 4 Statin Benefit Groups

**1. Secondary Prevention**

**2. Diabetes**
**40 to 75 yrs**
**LDL-C 70-189 mg/dl**

**3. LDL-C**
**≥ 190 mg/dL**

Rx: Optimal benefit with high intensity fixed dose statins → lower LDL-C ≥ 50%
Use moderate intensity if age >75 or can't tolerate high intensity

4. Primary Prevention –
40 to 75 yrs
LDL-C 70-189 mg/dl
ASCVD Risk ≥ 7.5 %

Rx: Moderate intensity
or high intensity fixed dose statin

Statin Rx not automatic,
requires clinician-patient discussion

# Intensity of Statin Therapy

**Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)***

| High-Intensity Statin Therapy | Moderate-Intensity Statin Therapy | Low-Intensity Statin Therapy |
|---|---|---|
| Daily dose lowers LDL–C on average, by approximately ≥50% | Daily dose lowers LDL–C on average, by approximately 30% to <50% | Daily dose lowers LDL–C on average, by <30% |
| **Atorvastatin (40†)–80 mg**<br>**Rosuvastatin 20** *(40)* **mg** | **Atorvastatin 10** *(20)* **mg**<br>**Rosuvastatin** *(5)* **10 mg**<br>**Simvastatin 20–40 mg‡**<br>**Pravastatin 40** *(80)* **mg**<br>**Lovastatin 40 mg**<br>*Fluvastatin XL 80 mg*<br>**Fluvastatin 40 mg bid**<br>*Pitavastatin 2–4 mg* | *Simvastatin 10 mg*<br>**Pravastatin 10–20 mg**<br>**Lovastatin 20 mg**<br>*Fluvastatin 20–40 mg*<br>*Pitavastatin 1 mg* |

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

# Statins:

# Don’t forget the 6% rule!

# Important to Note

- '**No Evidence**' could be
  - There is no evidence, or
  - The existing evidence is inconclusive
- We treat people not populations.
- Goal-setting and the use of other lipid modifying Rx is not precluded;
  - It's just not evidence-based.

# AHA/ACC Prevention Guideline

## 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk

### A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

*Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Nutrition, American Society for Preventive Cardiology, American Society of Hypertension, Association of Black Cardiologists, National Lipid Association, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women With Heart Disease*

EXPERT WORK GROUP MEMBERS

Robert H. Eckel, MD, FAHA, Co-Chair; John M. Jakicic, PhD, Co-Chair; Jamy D. Ard, MD; Janet M. de Jesus, MS, RD*; Nancy Houston Miller, RN, BSN, FAHA; Van S. Hubbard, MD, PhD*; I-Min Lee, MD, ScD; Alice H. Lichtenstein, DSc, FAHA; Catherine M. Loria, PhD, FAHA*; Barbara E. Millen, DrPH, RD, FADA; Cathy A. Nonas, MS, RD; Frank M. Sacks, MD, FAHA; Sidney C. Smith, Jr, MD, FACC, FAHA; Laura P. Svetkey, MD, MHS; Thomas A. Wadden, PhD; Susan Z. Yanovski, MD*

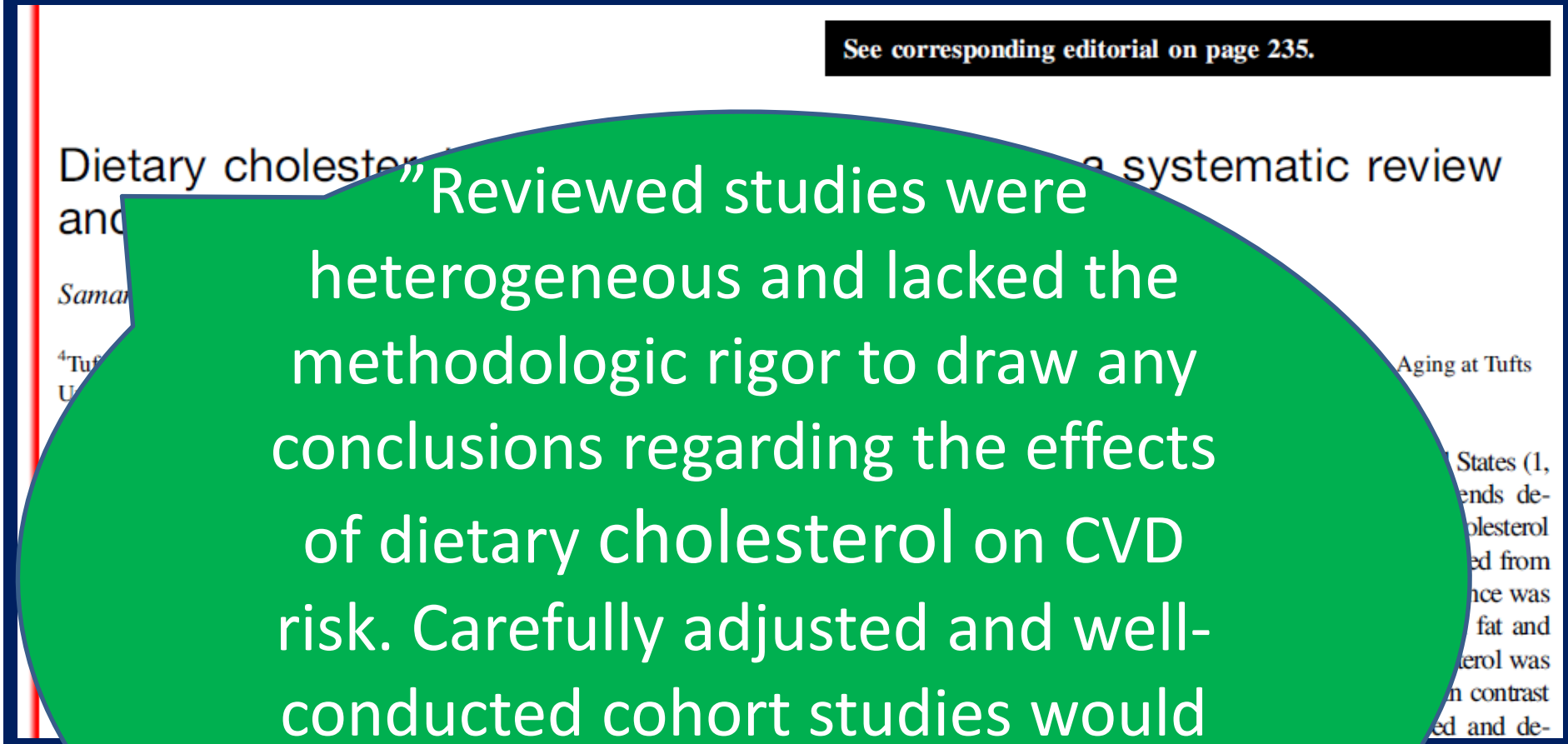
*Circulation*, 129(25 Suppl 2):S1-45, 2014

# Maintain an Overall Healthy Diet!


# Nutrition Lifestyle Recommendations: Lipids and BP

- **Dietary patterns emphasis-based:**
  - DASH and Mediterranean-style eating plans
- Fruits, vegetables, and whole grains
- 30 – 35% fat intake
  - <6% saturated fats, no *trans* fats
- Low sodium (<2400 mg/day)
- Cut out processed or pre-prepared food
- Healthy eating for a lifetime

Eckel RH et al, *Circulation* 129 (25 Suppl 2):S76-99, 2014




"Reviewed studies were heterogeneous and lacked the methodologic rigor to draw any conclusions regarding the effects of dietary cholesterol on CVD risk. Carefully adjusted and well-conducted cohort studies would be useful to identify the relative effects of dietary cholesterol on CVD risk."

Berger S et al, *AJCN* 102:276, 2015

# Physical Activity Guidelines: Lipids and BP

- Advise adults to engage in aerobic physical activity
  - 3 to 4 sessions a week
  - lasting on average 40 min per session
  - involving moderate-to-vigorous intensity physical activity.

Eckel RH et al, *Circulation* 129 (25 Suppl 2):S76-99, 2014

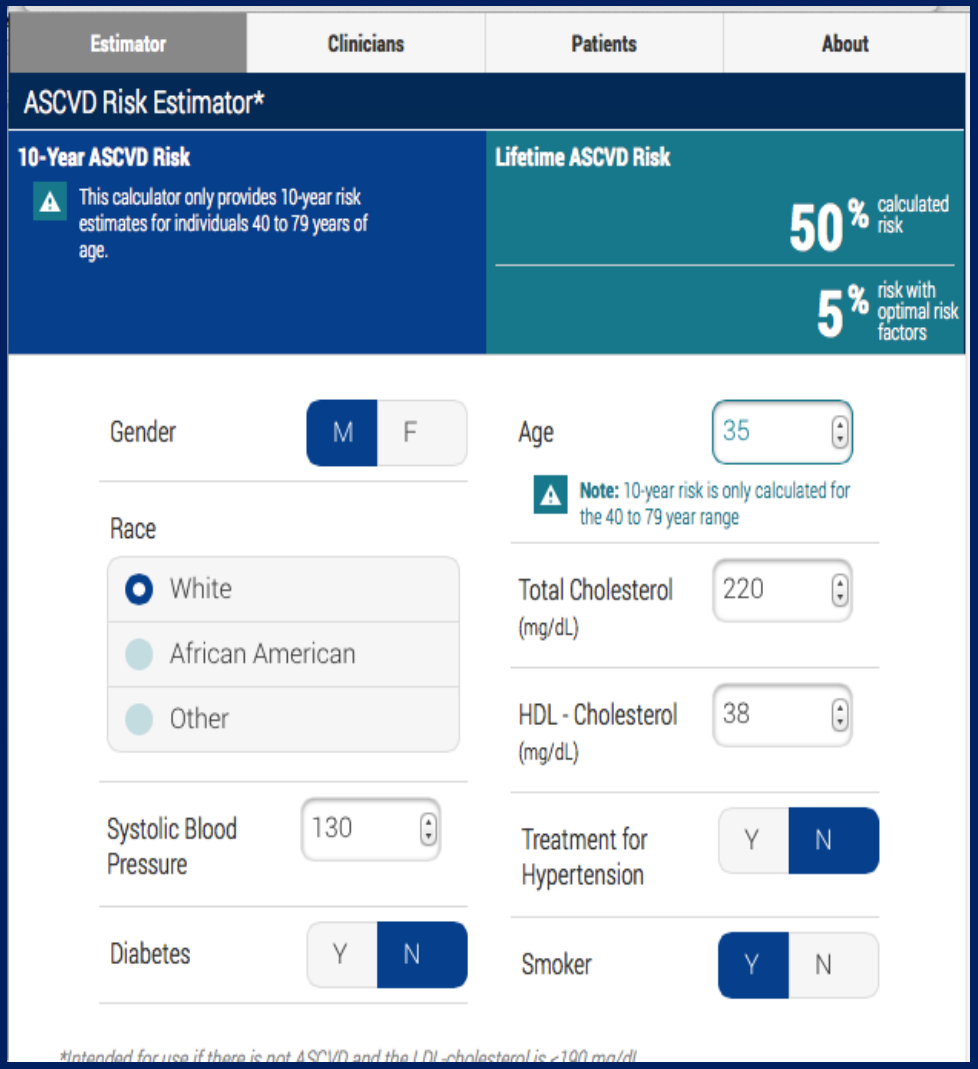
# Risk Estimator

- Includes:
  - Race
  - Gender
  - Age
  - Total cholesterol
  - HDL cholesterol
  - Blood pressure / Use of BP medicines
  - Diabetes status
  - Smoking status

http://my.americanheart.org/professional/StatementsGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp

# Emphasis on Healthy Lifestyle

- For those 20-59 risk estimator provides lifetime risk estimate
  - Better in women?
- This is intended to drive discussions of greater adherence to heart-healthy lifestyle
- Part of risk discussion



# Individuals Not in a Statin Benefit Group

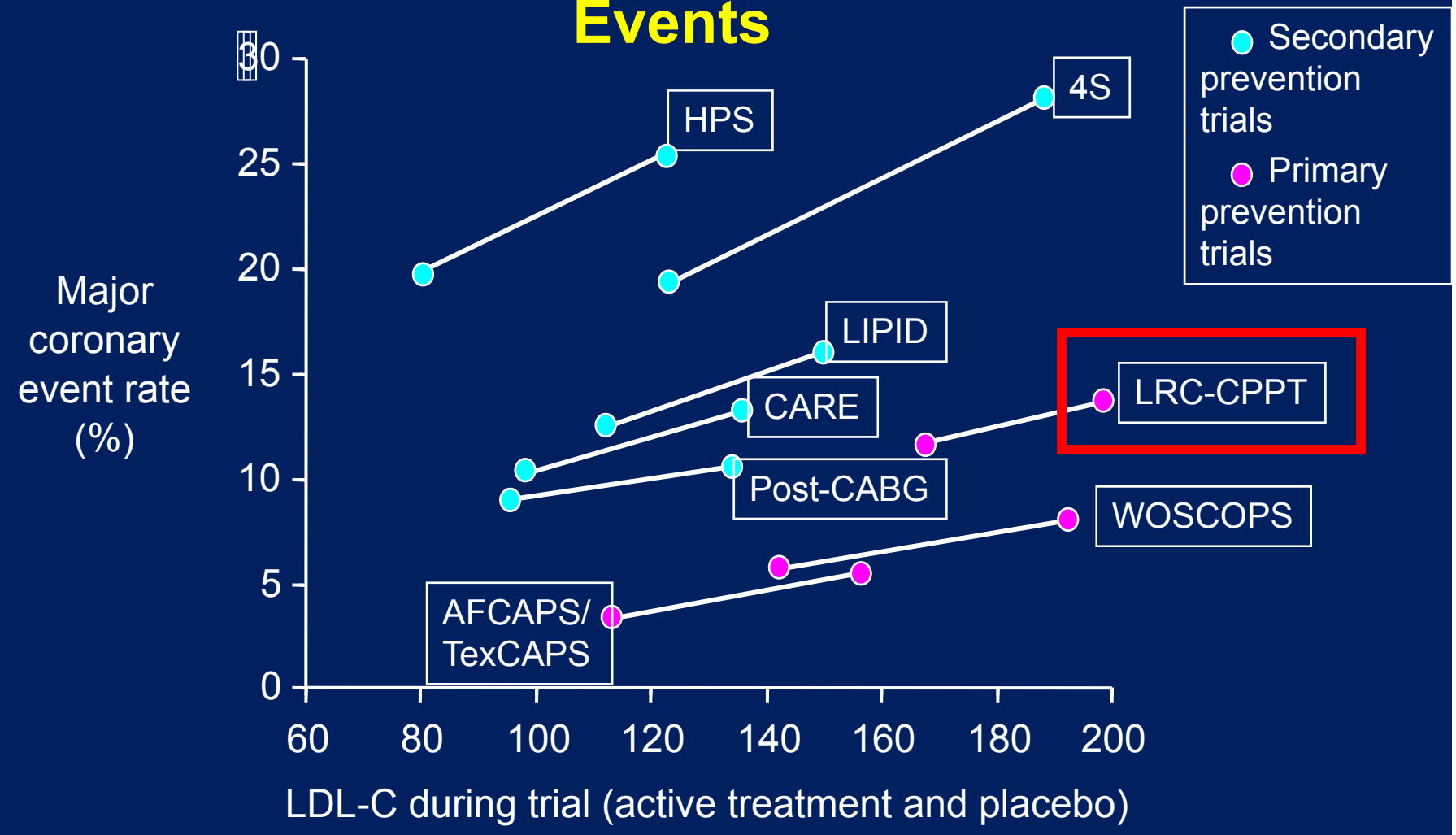
- In those not clearly in 1 of 4 statin benefit groups, additional factors may inform treatment decision-making:
  - *Family history of premature ASCVD*
  - *Elevated lifetime risk of ASCVD*
  - *LDL–C ≥160 mg/dL*
  - *hs-CRP ≥2.0 mg/L*
  - *Subclinical atherosclerosis*
    - *CAC score ≥300 or ABI<0.9*
- Discussion of potential for ASCVD risk reduction benefit, potential for adverse effects, drug-drug interactions, and patient preferences

# Now let’s focus on LDL-C

# Range of LDL Cholesterol Lowering with Drugs

- PCSK9 inhibitors 35-65%
- Statins 15-60%
- Bile Acid Sequestrants 5-35%
- Ezetimibe 15-20%
- Fibrates (TG normal) 10-20%
- Nicotinic acid 0-25%

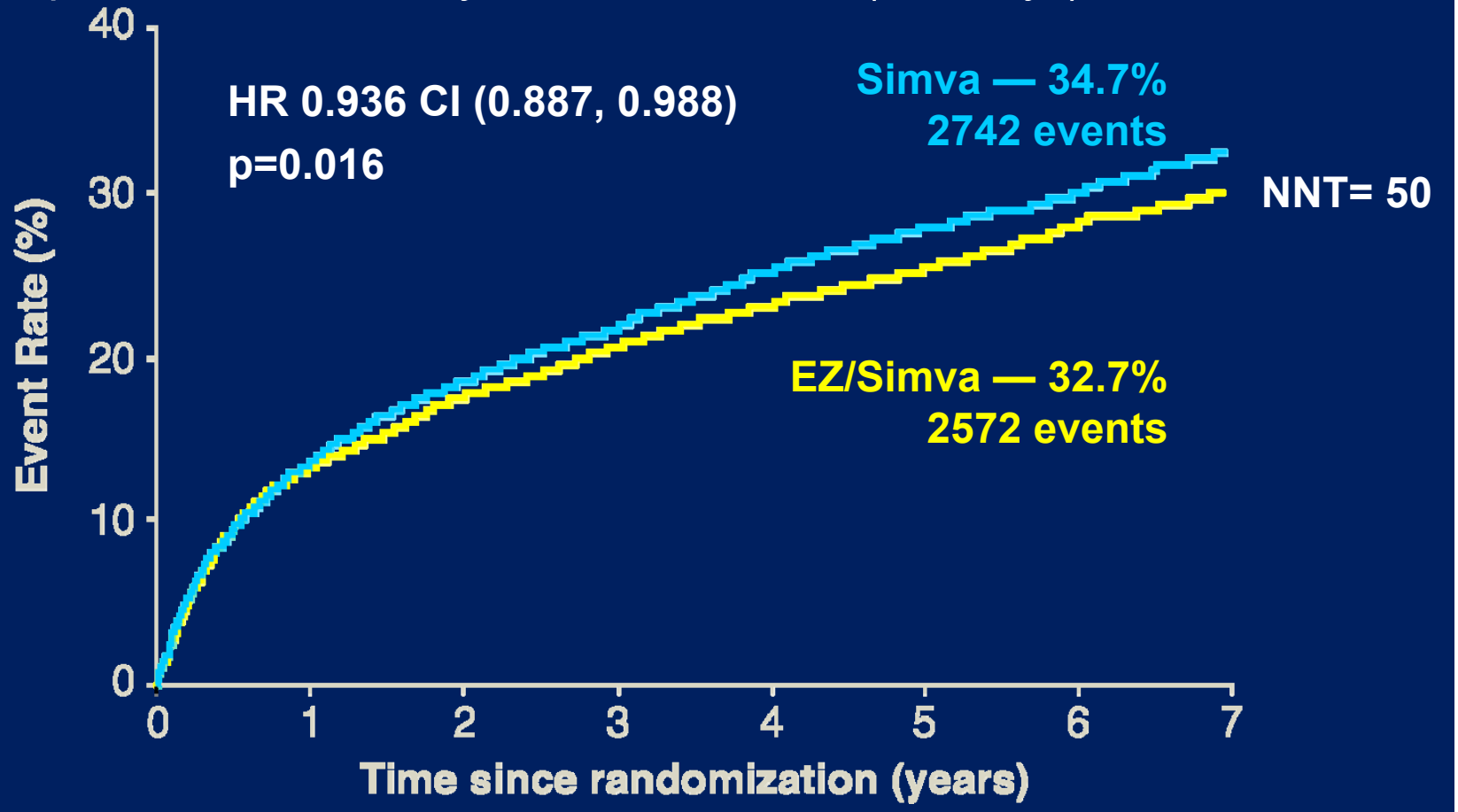
# Randomized Intervention Trials: Relationship Between LDL-C Reduction and Major Coronary Events




Modified from Waters DD and Azar RR. *Am J Cardiol*. 86:35J-43J, 2000.
Fox R. *Circulation*. 2001;104:e9051; Schwartz GG et al. *JAMA*. 285:1711, 2001

# IMRPOVE-IT:Primary Endpoint — ITT

*Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke*




*7-year event rates*

Cannon CP, et. al. *N Engl J Med 372:2387, 2015*

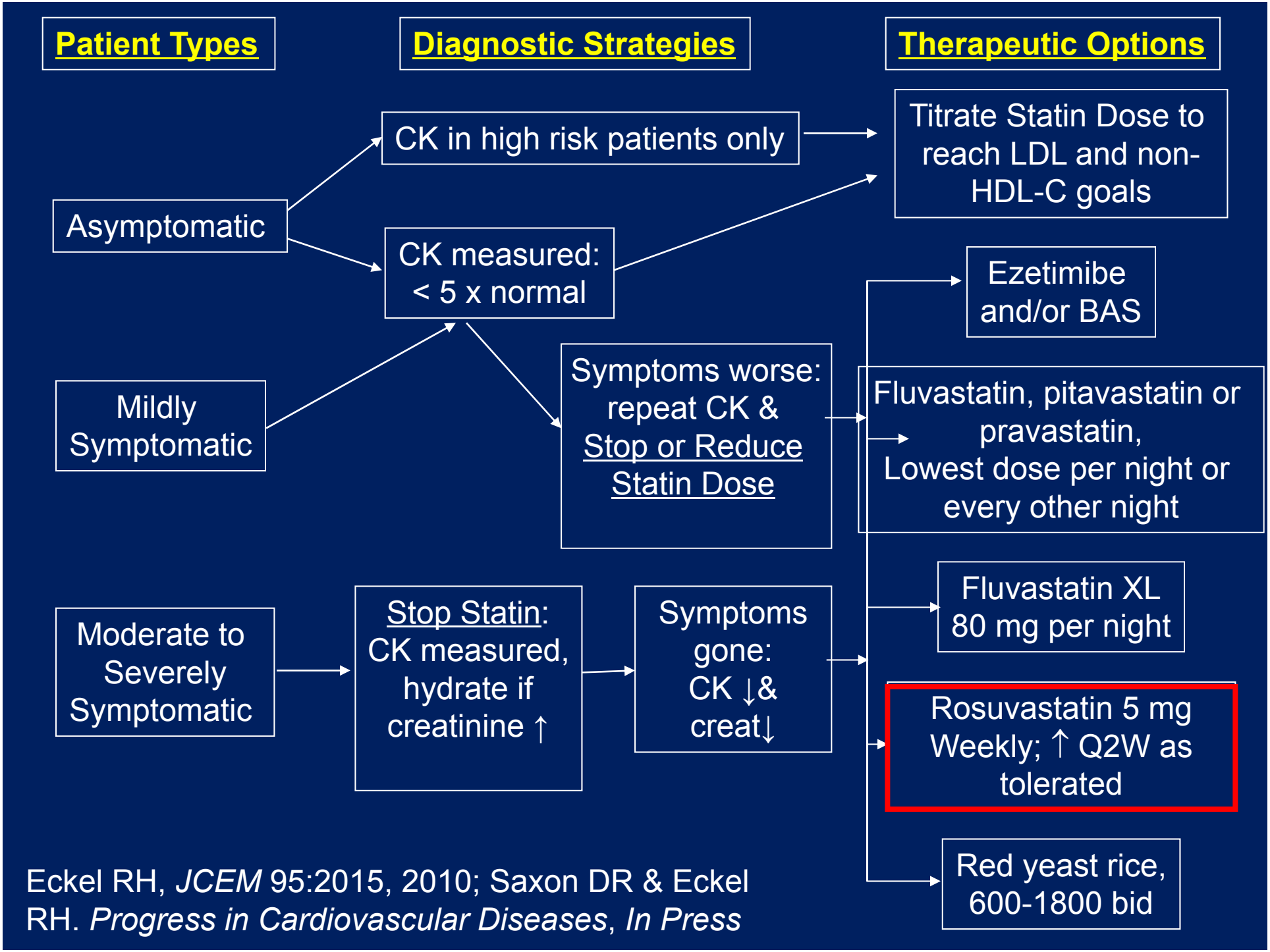
# Statins: The Down Side

- Abnormal AST and ALT
  - < 3X ULN: ~1.3%
  - > 3X ULN: <1.0%
    - Dose related
- Myopathy: Any disease of muscles
  - Myalgias: pain in a muscle of group of muscles
    - ~10%
  - Myositis: muscle symptoms with ↑ CK
    - ~2.5%
  - Rhabdomyolysis: > 50 fold ↑ in CK + renal impairment
    - <0.1%
- New onset T2DM

Bruckert E et al, *Cardiov Drugs* 19:403, 2005
Brown WV, *Curr Opin Lipid* 19:558, 2008
Onusko E, *J Fam Pract* 57:449, 2008
Preiss D et al, *JAMA* 305:2556, 2011

# What the Clinician Needs to Consider

- Hypothyroidism
- Vitamin D deficiency
- Other drugs
  - Fibrates, azole anti-fungals, cyclosporine, macrolides, diltiazem, HIV protease inhibitors
- Genetic differences in drug-metabolizing enzymes, e.g. OATP1B1
  - SLCO1B1, CYP2D2, 3A4
- Neuromuscular diseases
  - Mitochondrial myopathy, McArdles disease, myotonic dystrophy, polymyositis




Eckel RH, *JCEM* 95:2015, 2010; Saxon DR & Eckel RH. *Progress in Cardiovascular Diseases*, *In Press*

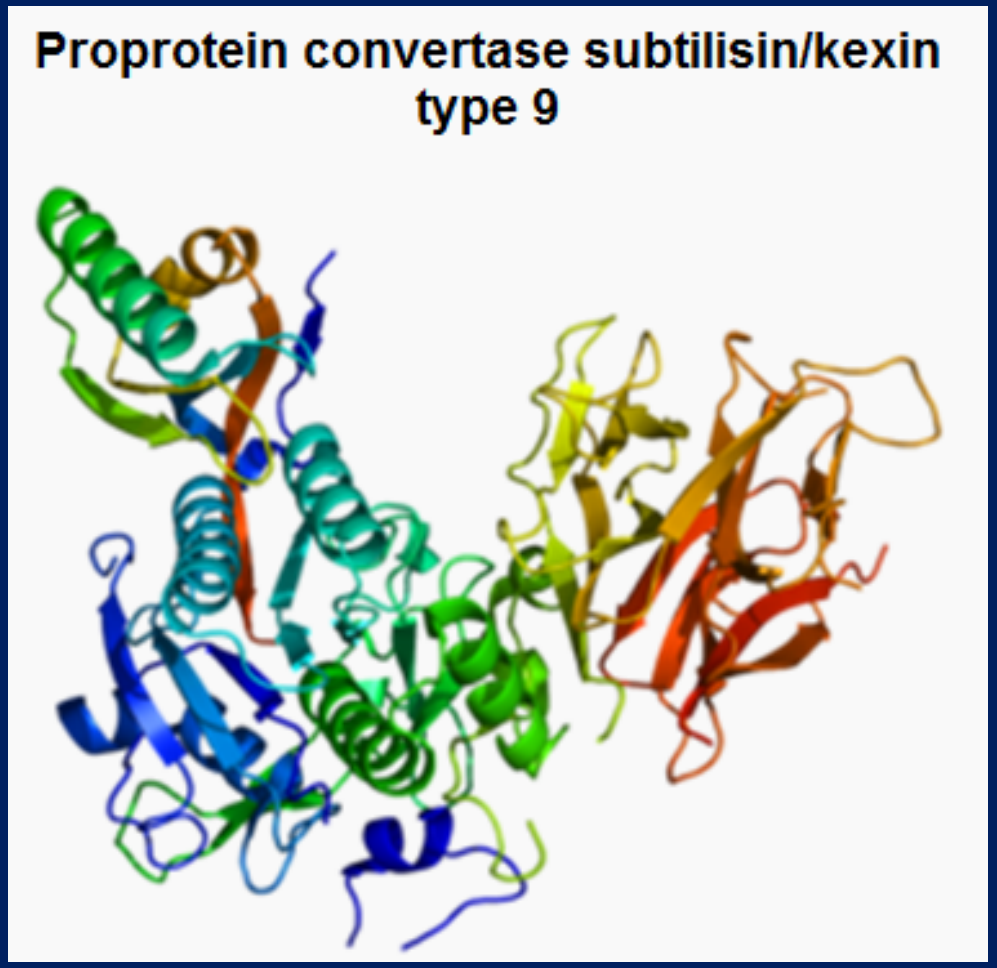
**But the need for adiditonal cholesterol lowering remains for some patients!**

# Patient Populations with an Unmet Need for Additional LDL-C Lowering

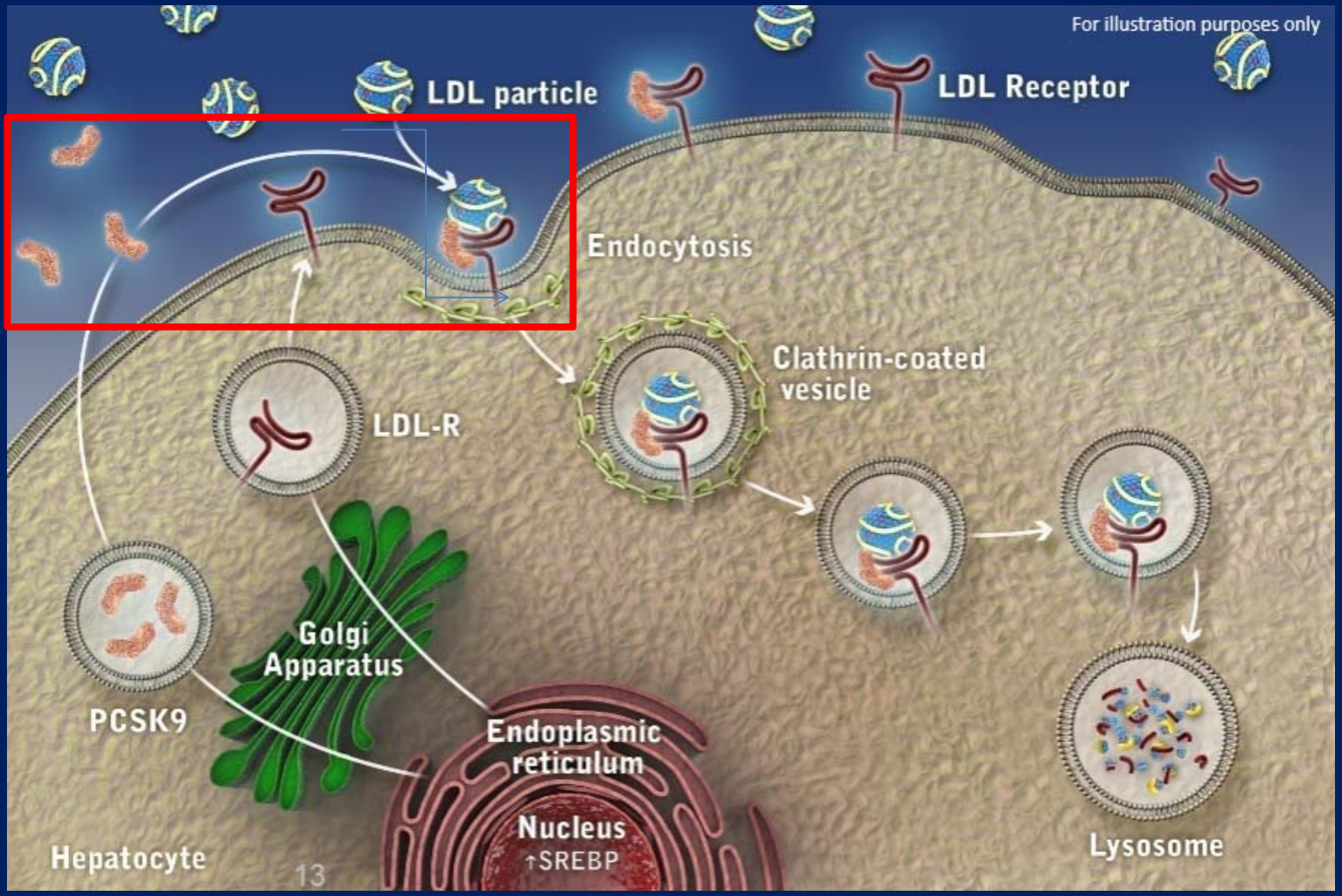
| FH Population | High / Very High CV Risk Population | Statin-Intolerant Population |
|---|---|---|
| • Genetic disorder<br>• High risk of early CHD<br>• HeFH prevalence 1:200 to 1:250 [1,2]<br>• Untreated LDL-C of 200-400 mg/dL [3] | • Previous MI /stroke / CVD or multiple CV risk factors incl. T2DM<br>• Difficult to achieve LDL-C goals, despite current therapies [5] | • 10-15% on high-intensity statins show intolerance [6]<br>• Many discontinue due to muscle pain and/or weakness |
| **79% with HeFH not at goal (<100 mg/dL) [4]** | **• 20% with CHD not at goal (<100 mg/dL)**<br>**• 59% at very high CV risk not at goal (<70 mg/dL)** | **Nearly all patients who need considerable LDL-C reductions will not reach goal** |

[1] Nordestgaard et al. *Eur Heart J* 2013;34:3478-90. [2] Sjouke et al. *Eur Heart J* (in press).
[3] 2011 ESC/EAS Guidelines for the management of dyslipidaemias. [4] Pijlman et al. *Atherosclerosis* 2010;209:189-94.
[5] Virani et al. *Am Heart J* 2011;161:1140-6. [6] Arca et al. *Diabetes Metab Syndr Obes* 2011;4:155-66.

**PCSK9 is proprotein convertase subtilisin/kexin type 9 (PCSK9)**

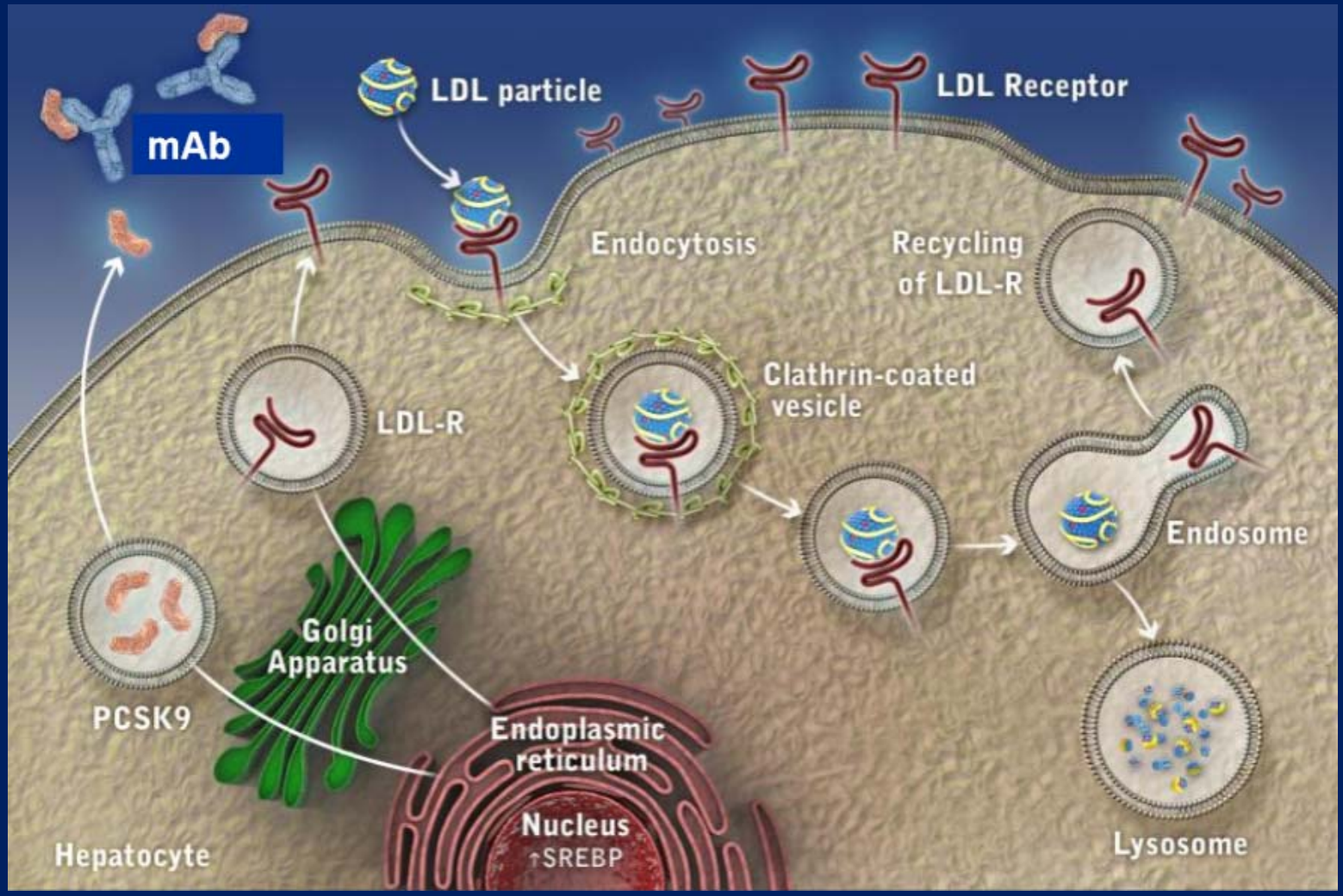


# PCSK9-Mediated Degradation of the LDL Receptor



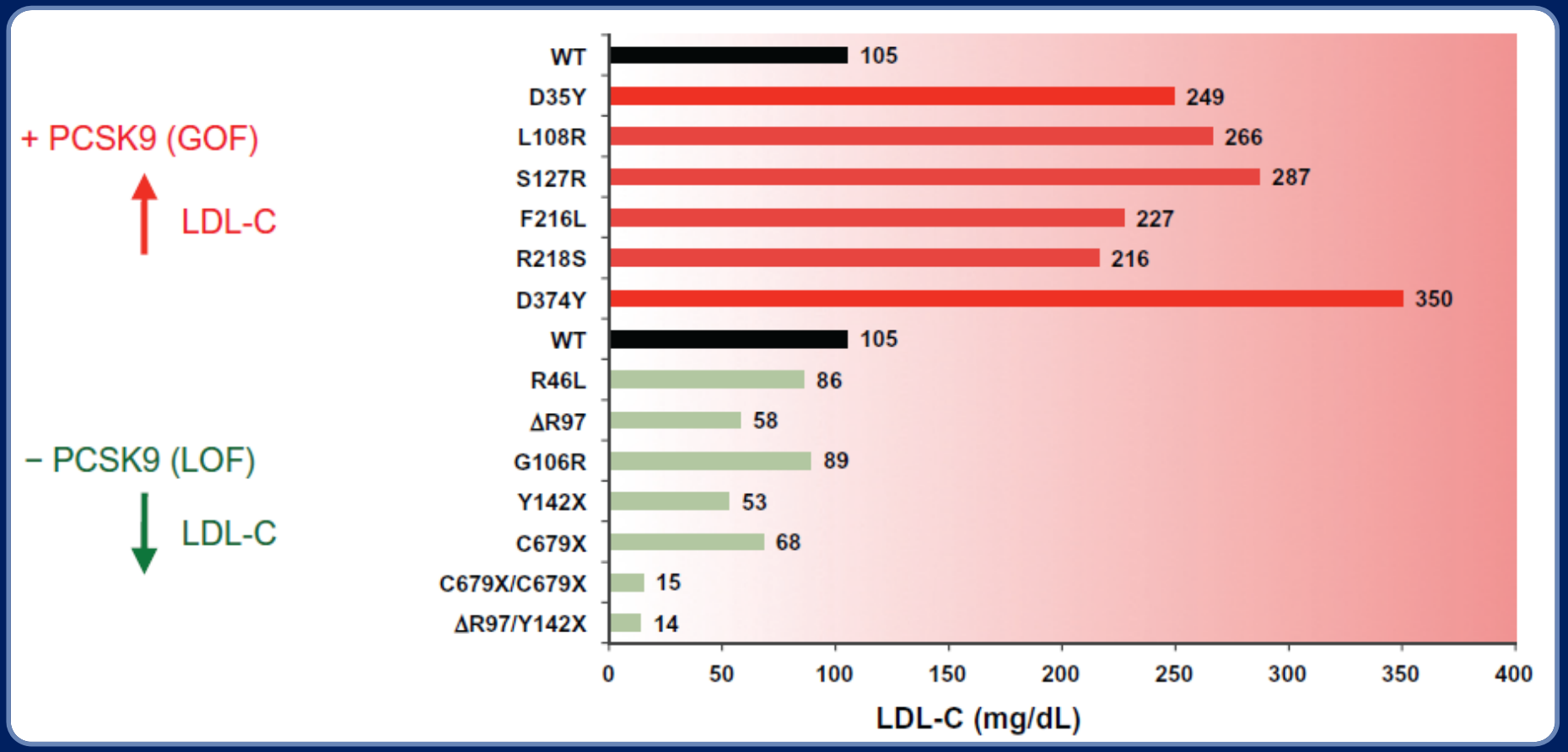

Stein EA. PCSK9 Forum.

# How PCSK9 Monoclonal Antibodies Restore LDL Receptor Function



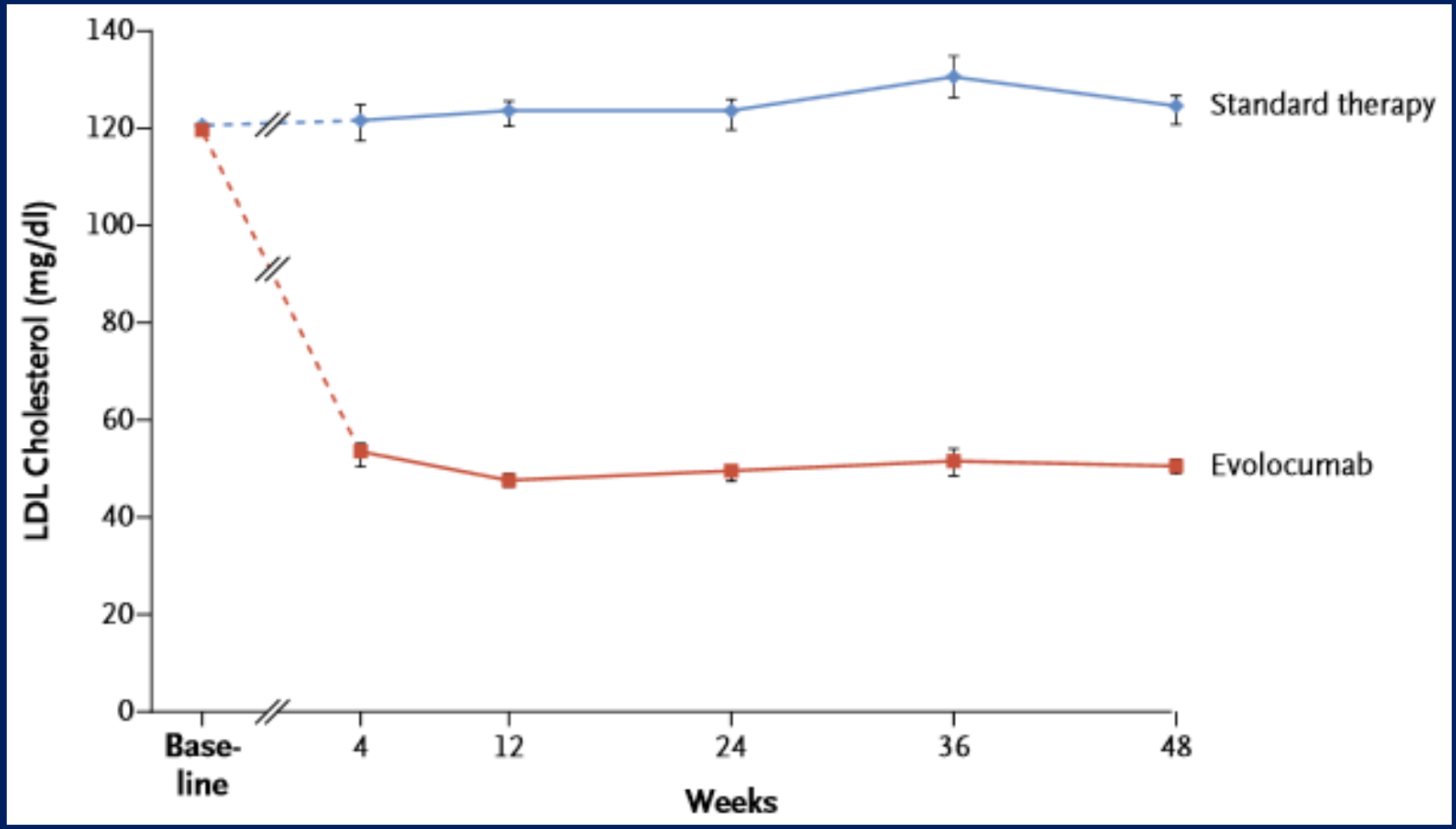

Stein EA. PCSK9 Forum.

# Effect of Human Mutations in PCSK9 on Plasma LDL-C



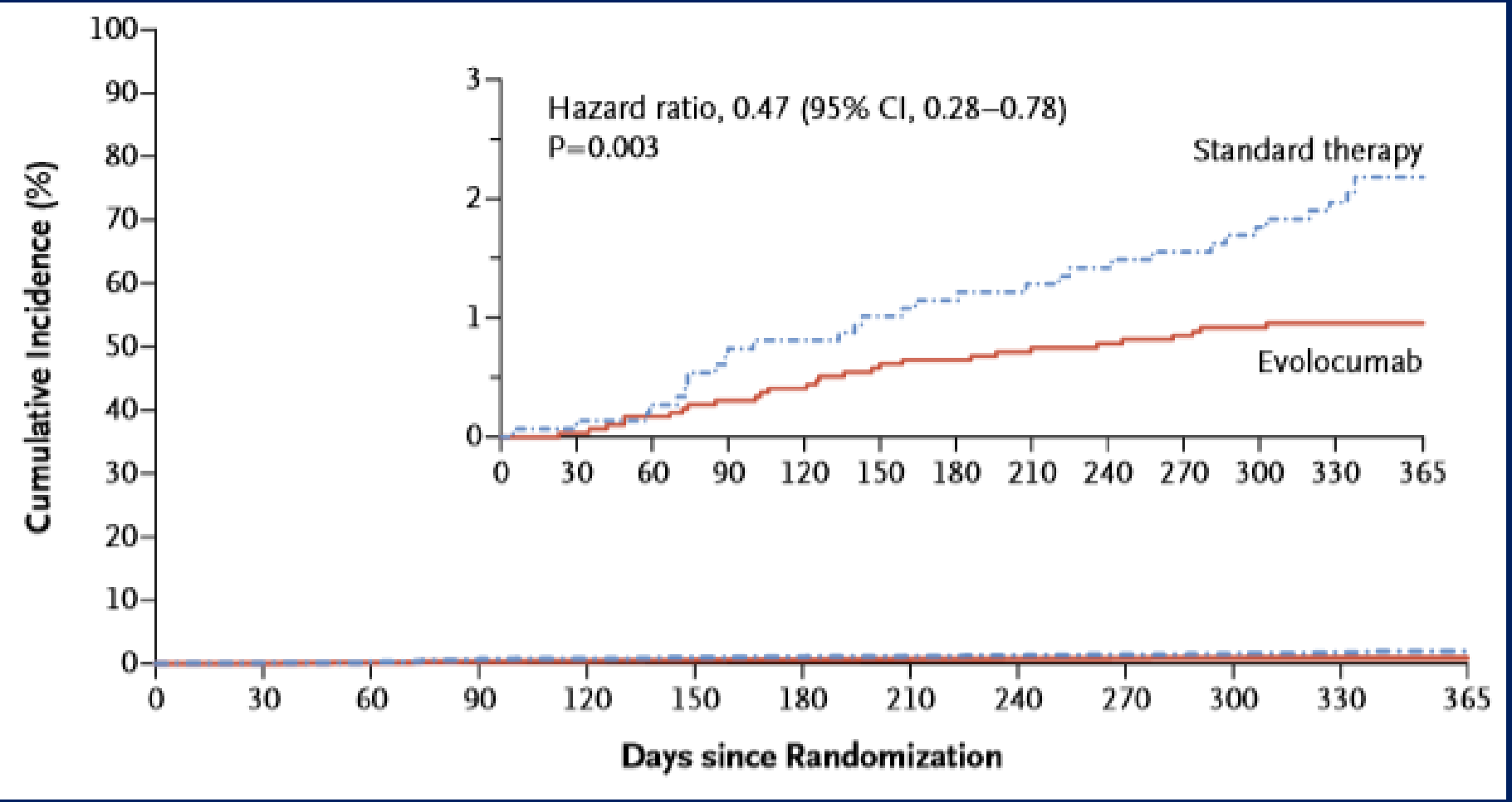

Poirier S and Mayer G. *Drug Des Dev Ther*. 2015;7:1135-1148.

# OSLER-1 & OSLER-2: Evolocumab Effect on LDL-C




Sabatine MS et al, *NEJM* 372:1500, 2015

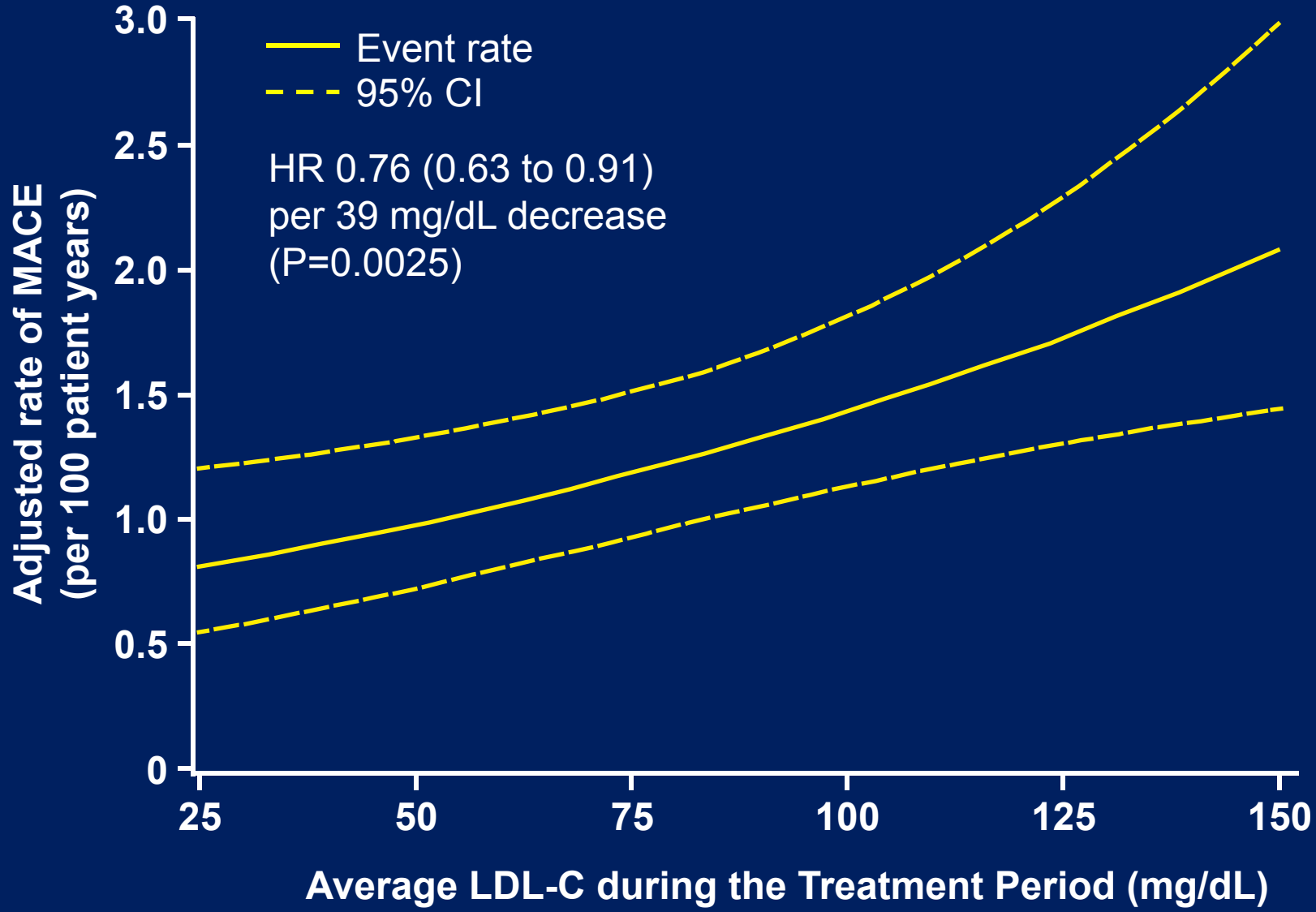
# OSLER-1 & OSLER-2: Cumulative Incidence of CVD Events



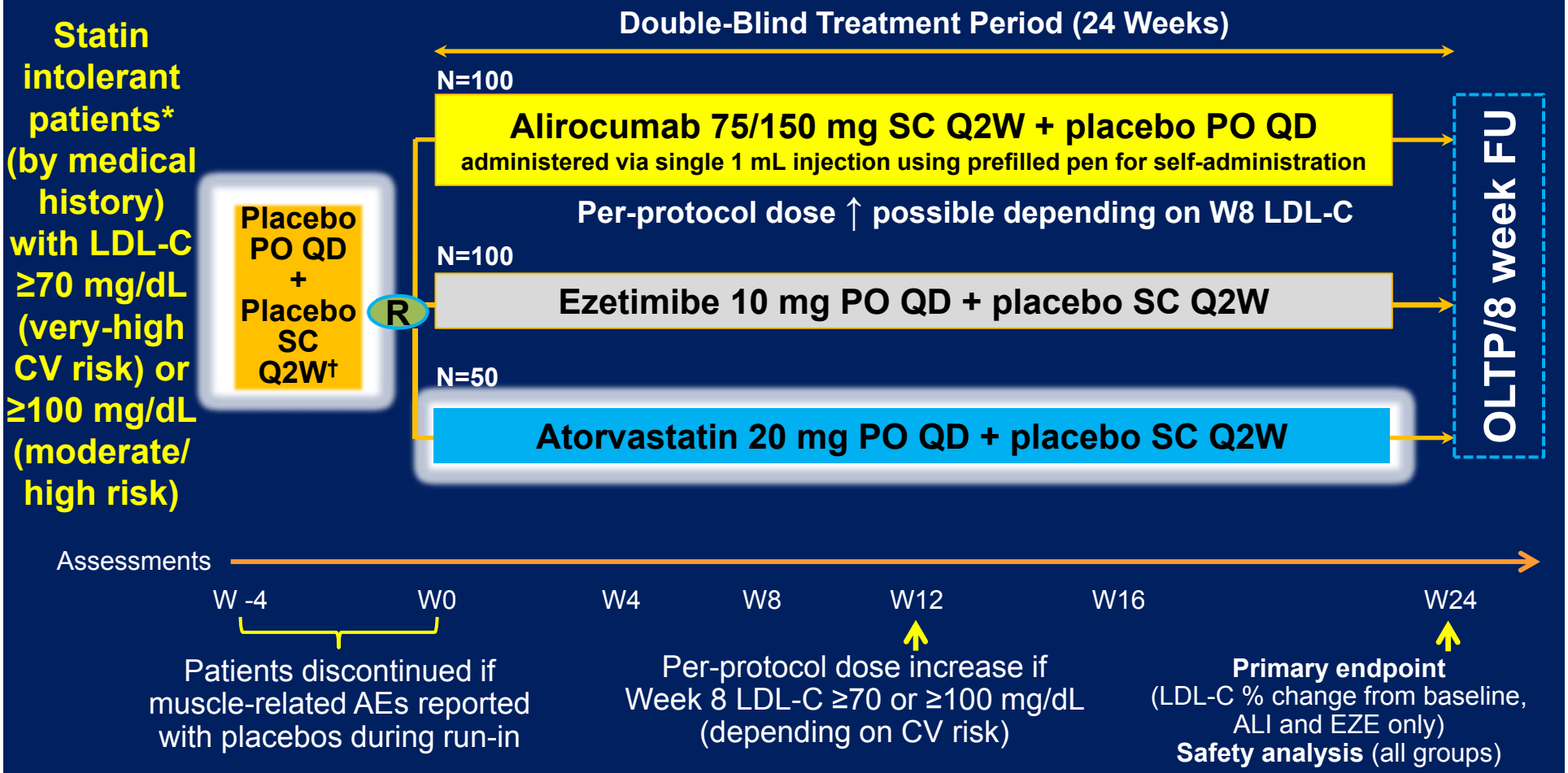

Sabatine MS et al, *NEJM* 372:1500, 2015

# Adjusted MACE Rate by Average Achieved LDL-C During Alirocumab Treatment

*Multivariate Analysis Adjusted on Baseline Characteristics; Pool of 10 Phase 3 trials*



# ODYSSEY ALTERNATIVE Study Design

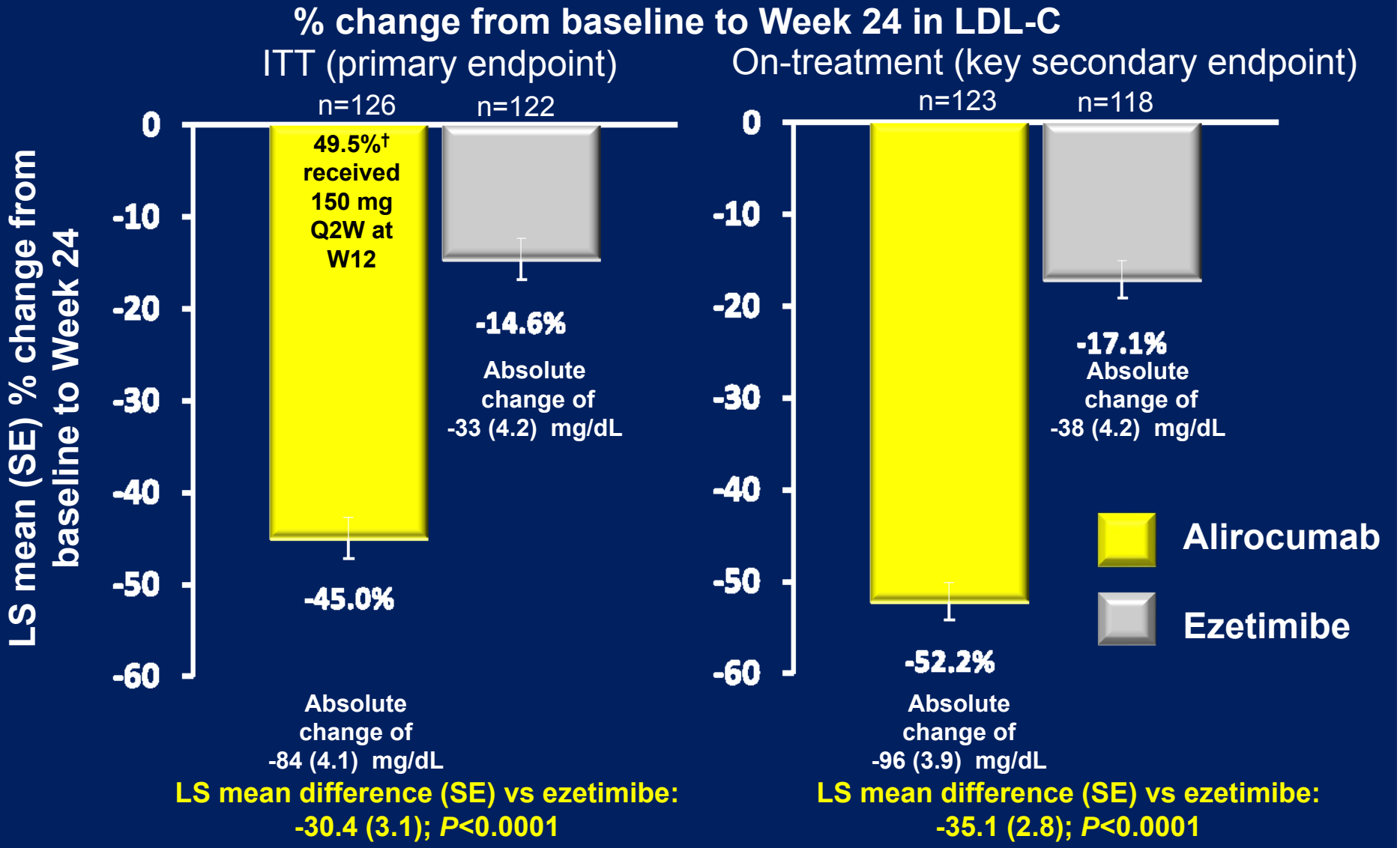



*Unable to tolerate at least two different statins, including one at the lowest dose, due to muscle-related symptoms

†4-week single-blind placebo run-in follows 2-week washout of statins, ezetimibe and red yeast rice.

OLTP: Alirocumab open-label treatment period; W, Week.

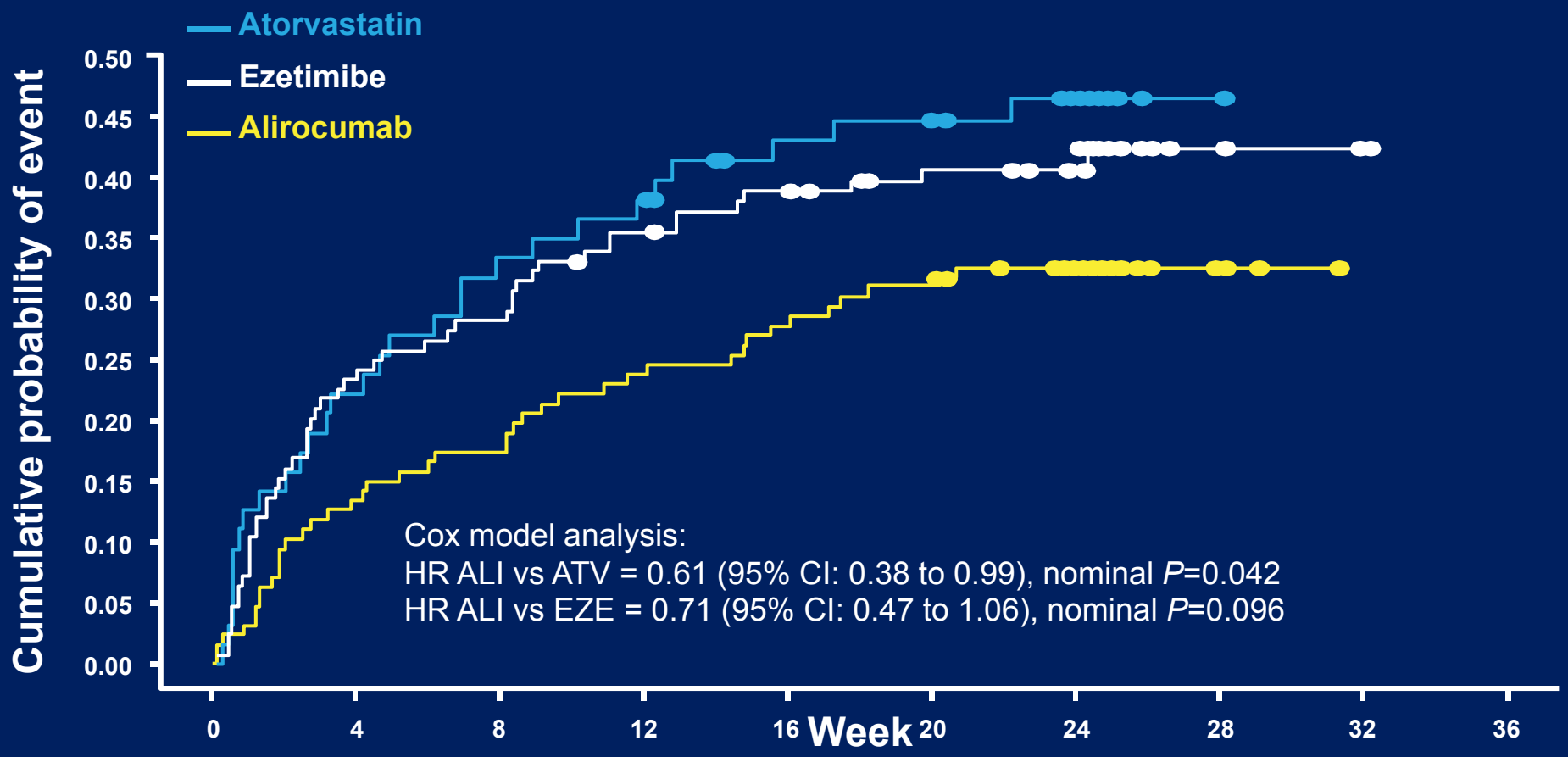
# Alirocumab Significantly Reduced LDL-C from Baseline to Week 24 vs. Ezetimibe




†49.5% of 109 patients who received at least one injection after Week 12 had dose increase.

# Fewer Skeletal Muscle AEs with Alirocumab than with Atorvastatin

## Kaplan-Meier estimates for time to first skeletal muscle event†



# AAlirocumab FDA Approved July 24, 2015

"PRALUENT(alirocumab) is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C."

# Evolocumab FDA Approved August 27, 2015

"Repatha (evolocumab) is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). Repatha is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C."

# PCSK9 Phase 3 Trials for CVD Events Reduction

## (Statin Treated)

| Trial | Drug | LDL-C Criterion | Sample Size | Completion Date |
|---|---|---|---|---|
| FOURIER | Evolocumab | ≥ 70 mg/dL | 27,500 | Jan 2018 |
| ODYSSEY Outcomes | Alirocumab | ≥ 70 mg/dL | 18,000 | Jan 2018 |
| SPIRE-1 | Bococizumab | ≥ 70 mg/dL | 17,000 | June 2018 |
| SPIRE-2 | Bococizumab | ≥ 100 mg/dL | 9,000 | Jan 2018 |

**There are two other relatively new FDA-approved drugs for 'homozygous FH' –**

**lomitapide and mipomersen**

# LIPOSORBER® SYSTEM

# Comparison of Approved Aggressive Therapies for FH

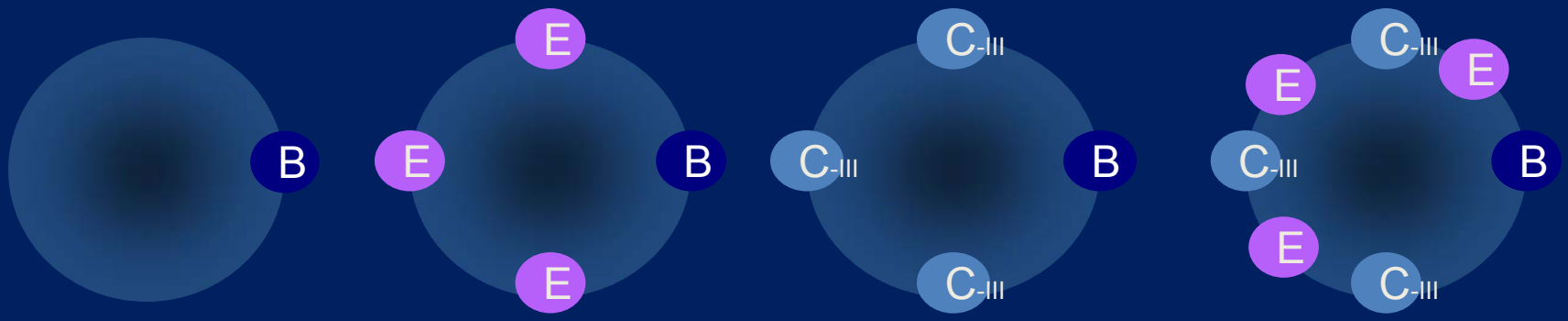
| | Apheresis | Mipomersen | Lomitapide |
|---|---|---|---|
| LDL-C Reduction | ~70-80% | ~25-38%<br>(higher in Women) | ~40-50% |
| Lp(a) Reduction | ~70-80% | ~20-30% | ~1-19% |
| Short Term Safety | Good | Hepatic Fat (5%) | Hepatic Fat (8-9%)<br>Diarrhea common |
| Compliance | Good | 90% | 90% |
| Long Term Safety | 37 yrs | Unknown | Unknown |
| Availability | Limited | Yes | Yes |
| Cost | +++ | ++++ | ++++ |
| Cardiac Benefit | Yes | Unknown | Unknown |
| Quality of Life | Yes | Unknown | Unknown |

# What about hypertriglyceridemia?

# Range of Triglyceride Lowering with Drugs

- Fibrates 20-45%
- Nicotinic acid 10-30%
- Omega-3 fatty acids 15-35%
- Statins 0-35%
  - Low end – minimal or no effect
  - High end – mod to high dose

# VLDL Defined by Apolipoprotein Content




Lp B | Lp B:E | Lp B:C-III | Lp B:C-III:E

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Antisense Inhibition of Apolipoprotein C-III in Patients with Hypertriglyceridemia

Daniel Gaudet, M.D., Ph.D., Veronica J. Alexander, Ph.D., Brenda F. Baker, Ph.D., Diane Brisson, Ph.D., Karine Tremblay, Ph.D., Walter Singleton, M.D., Richard S. Geary, Ph.D., Steven G. Hughes, M.B., B.S., Nicholas J. Viney, B.Sc., Mark J. Graham, M.S., Rosanne M. Crooke, Ph.D., Joseph L. Witztum, M.D., John D. Brunzell, M.D.,* and John J.P. Kastelein, M.D., Ph.D.

ABSTRACT

BACKGROUND

Apolipoprotein C-III (APOC3) is a key regulator of plasma triglyceride levels. Elevated triglyceride levels are associated with a risk of adverse cardiovascular events and pancreatitis. ISIS 304801 is a second-generation antisense inhibitor of APOC3 synthesis.

or ischemic cardiovascular disease. Whether lifelong low levels of nonfasting triglycerides owing to mutations in the gene encoding apolipoprotein C3 (*APOC3*) are associated with a reduced risk of ischemic cardiovascular disease in the general population is unknown.

METHODS

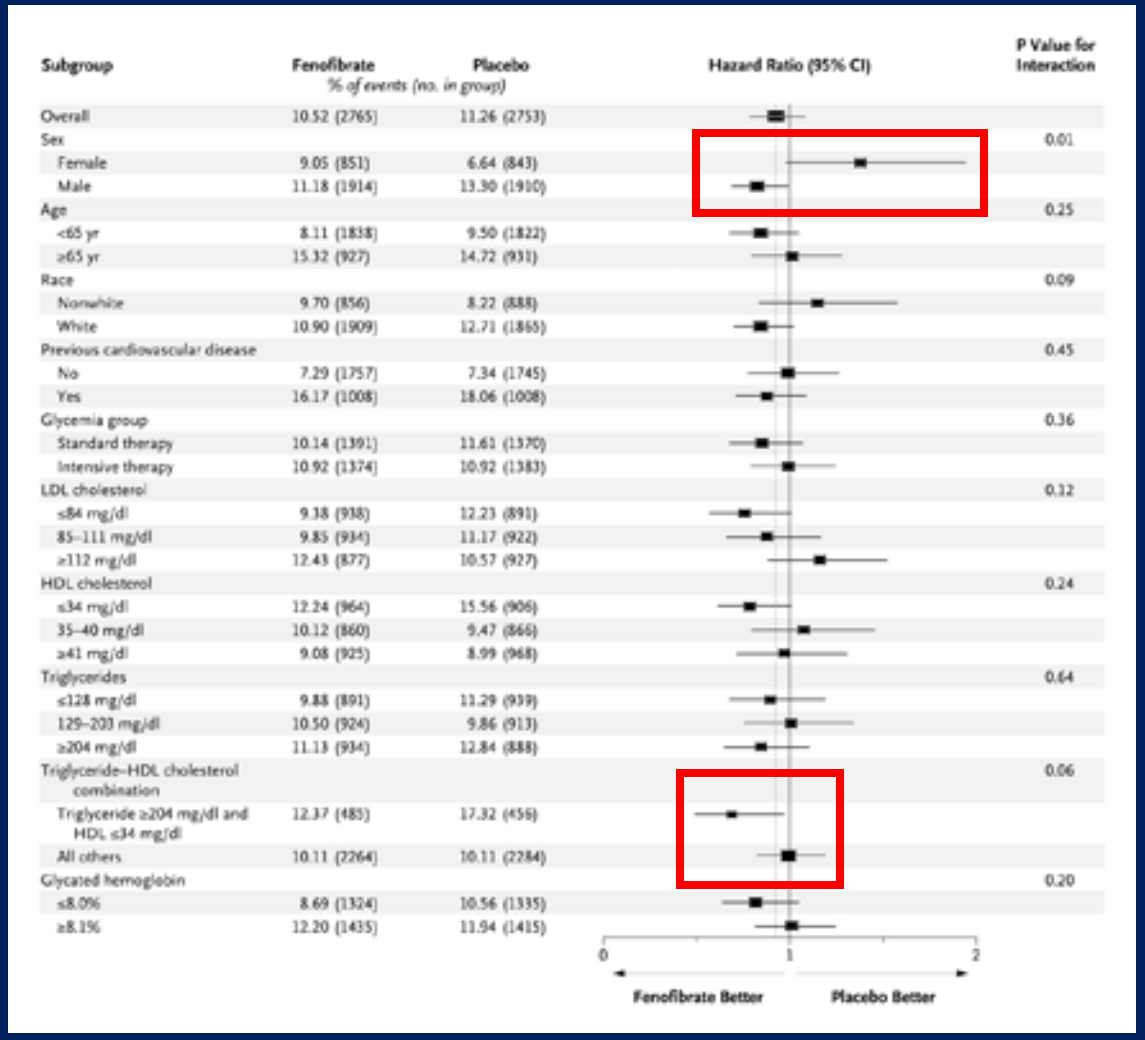
From the Department of Medicine, Université de Montréal and Ecogene-21 Clinical Research Centre, Chicoutimi, QC, Canada (D.G., D.B., K.T.); Isis Pharma-

ty Hospital and
Faculty of Health and Medical Sciences, University of Copenhagen (A.B.J., R.F.-S., B.G.N., A.T.-H.), the Department of Clinical Biochemistry, Rigshospitalet (A.B.J., R.F.-S., A.T.-H.), the Department of Clinical Biochemistry (B.G.N.) and the Copenhagen General Population Study (R.F.-S., B.G.N., A.T.-H.), Herlev Hospital, and the Copen-

# Fibrate Monotherapy Trials

| TRIAL | Year Reported | Drug | CHD Risk Reduction (primary endpoint) |
|---|---|---|---|
| Coronary Drug Project (CDP) | 1975 | Clofibrate | 9% (NS) |
| World Health Organization | 1978 | Clofibrate | 20% (P<0.05) |
| Helsinki Heart Study (HHS) | 1987 | Gemfibrozil | 34% (P <0.02) |
| VA-HDL Intervention Trial (VA-HIT) | 1999 | Gemfibrozil | 22% (P <0.006) |
| Bezafibrate Infarction Prevention (BIP) | 2000 | Bezafibrate | 7.3% (P =0.26) |
| Fenofibrate Diabetes (FIELD) | 2005 | Fenofibrate | 11% (P=0.16) |

# ACCORD LIPID: Hazard Ratios for Primary Outcome in Subgroups in Patients with Diabetes



| Subgroup | Fenofibrate (% of events (no. in group)) | Placebo (% of events (no. in group)) | P Value for Interaction |
|---|---|---|---|
| Overall | 10.52 (2765) | 11.26 (2753) | |
| Sex | | | 0.01 |
| Female | 9.05 (851) | 6.64 (843) | |
| Male | 11.18 (1914) | 13.30 (1910) | |
| Age | | | 0.25 |
| <65 yr | 8.11 (1838) | 9.50 (1822) | |
| ≥65 yr | 15.32 (927) | 14.72 (931) | |
| Race | | | 0.09 |
| Nonwhite | 9.70 (856) | 8.22 (888) | |
| White | 10.90 (1909) | 12.71 (1865) | |
| Previous cardiovascular disease | | | 0.45 |
| No | 7.29 (1757) | 7.34 (1745) | |
| Yes | 16.17 (1008) | 18.06 (1008) | |
| Glycemia group | | | 0.36 |
| Standard therapy | 10.14 (1391) | 11.61 (1370) | |
| Intensive therapy | 10.92 (1374) | 10.92 (1383) | |
| LDL cholesterol | | | 0.32 |
| ≤84 mg/dl | 9.38 (938) | 12.23 (891) | |
| 85–111 mg/dl | 9.85 (934) | 11.17 (922) | |
| ≥112 mg/dl | 12.43 (877) | 10.57 (927) | |
| HDL cholesterol | | | 0.24 |
| ≤34 mg/dl | 12.24 (964) | 15.56 (906) | |
| 35–40 mg/dl | 10.12 (860) | 9.47 (866) | |
| ≥41 mg/dl | 9.08 (925) | 8.99 (968) | |
| Triglycerides | | | 0.64 |
| ≤128 mg/dl | 9.88 (891) | 11.29 (939) | |
| 129–203 mg/dl | 10.50 (924) | 9.86 (913) | |
| ≥204 mg/dl | 11.13 (934) | 12.84 (888) | |
| Triglyceride–HDL cholesterol combination | | | 0.06 |
| Triglyceride ≥204 mg/dl and HDL ≤34 mg/dl | 12.37 (485) | 17.32 (456) | |
| All others | 10.11 (2264) | 10.11 (2284) | |
| Glycated hemoglobin | | | 0.20 |
| ≤8.0% | 8.69 (1324) | 10.56 (1335) | |
| ≥8.1% | 12.20 (1435) | 11.94 (1415) | |



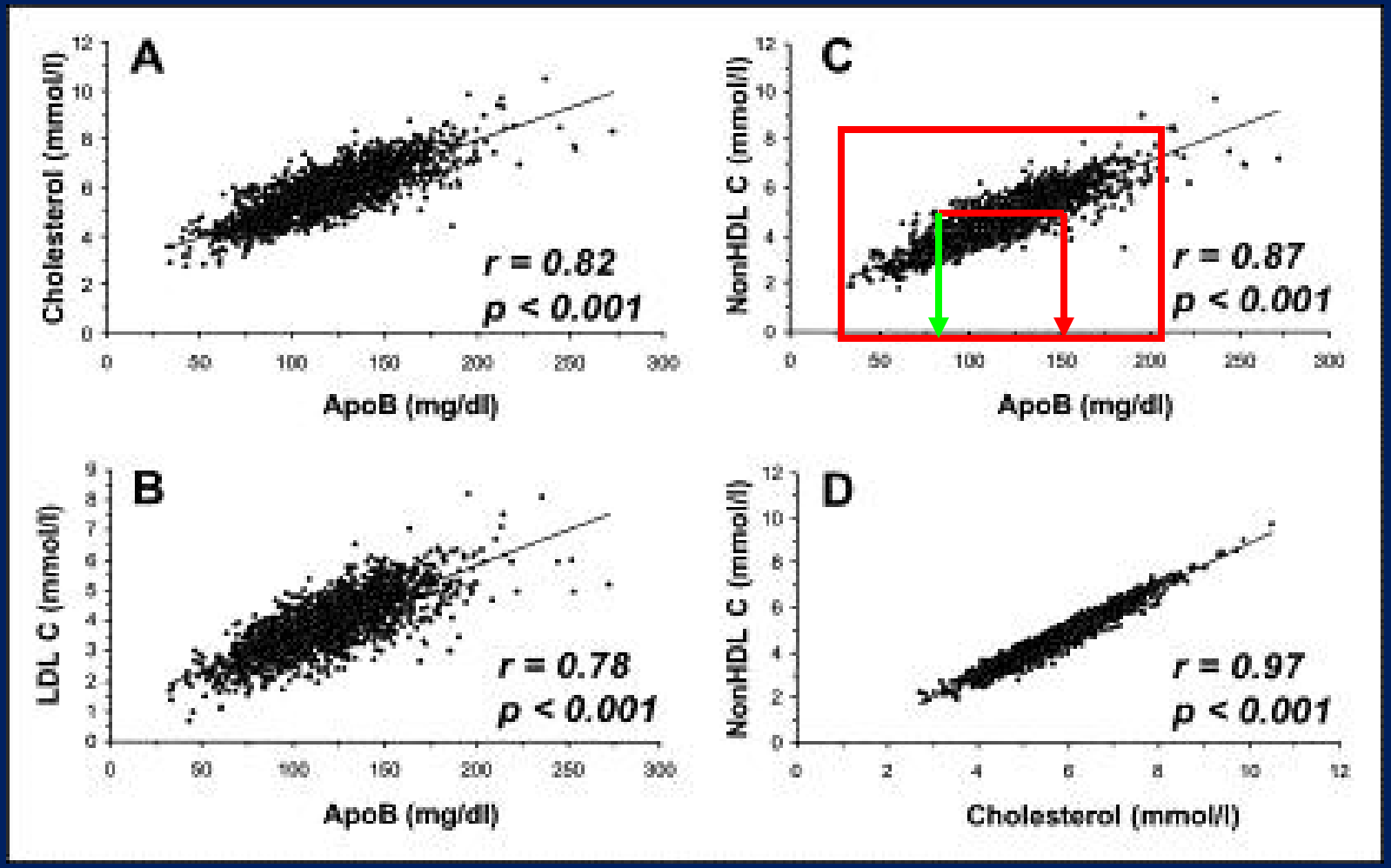
ACCORD Study Group. *NEJM*, Mar 14, 2010

# So Let's See What We Can Conclude Here

- Fibrates do not reduce CHD events in high risk patient groups
- The impact of hypertriglyceridemia on CHD outcomes remains unclear
  - Post-hoc analysis indicates that high risk patients with TGs > 200 mg/dl may be more likely to benefit.
  - The amount of TG lowering may not predict benefit, but VLDL-C may be better.
- Do you treat patients with fibrates who are not hypertriglyceridemic?
- The optimal trial awaits us!
  - VAFIT – doubtful
  - K-877, a selective PPAR alpha modulator?

# Is apo B useful in predicting risk in patients with hypertriglyceridemia?

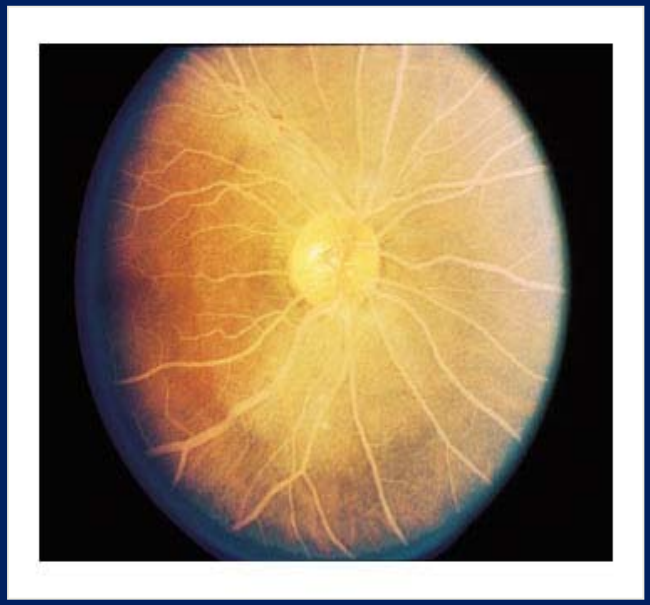
# Correlations Between Apo B, Cholesterol, LDL Cholesterol and Non-HDL Cholesterol



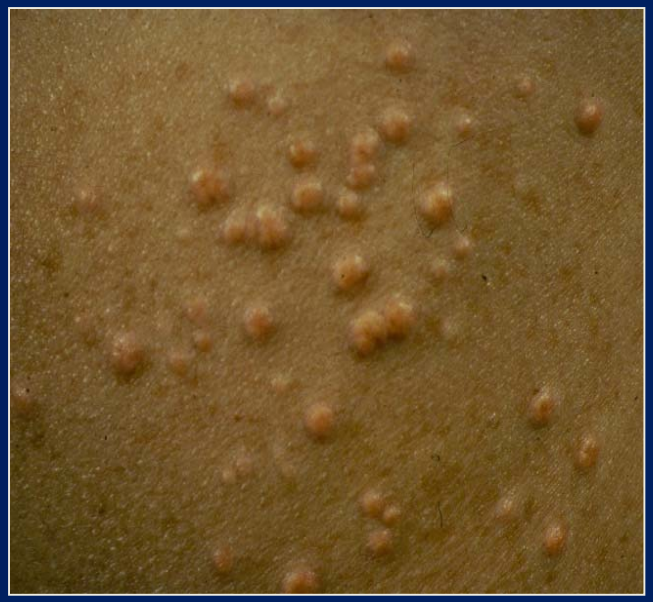

Sniderman AS et al, *Am J. Card* 91:1173, 2003

# Exam Findings Associated with Severe Hypertriglyceridemia

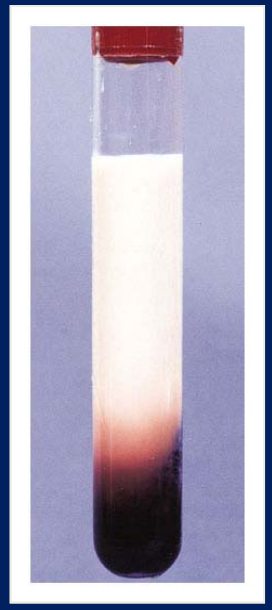
Lipemia Retinalis



Eruptive Xanthomas

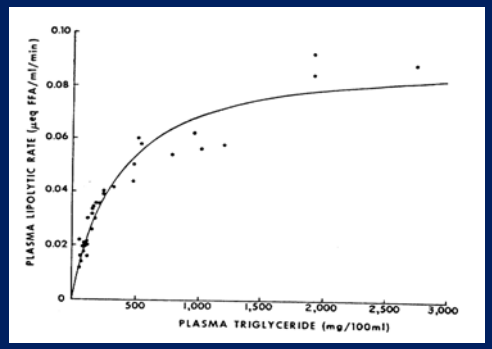


Lipemic Serum



# Dietary Treatment of Severe Hypertriglyceridemia

- **TG > 1000 mg/dl:** < 5% fat; no ETOH
  - ? D/C all TG-lowering Rx
    - < 5% fat → ~25% TG ↓ qd in saturation kinetics



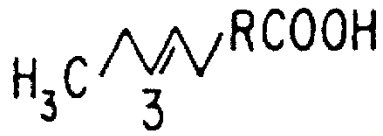
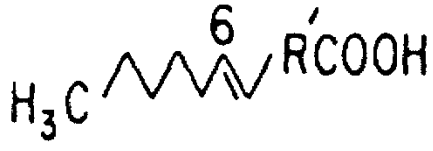
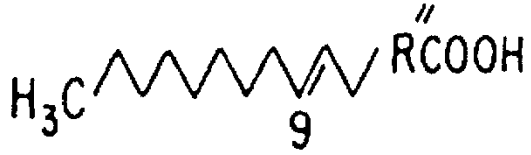

    - Fasting TG q 3 days until <1000 mg/dl
    - Restart Rx when TG <1000 mg/dl
    - If TG do not reach <1000 mg/dl, hospitalize & control diet

# Dietary Treatment of Moderate Hypertriglyceridemia

- **TG = 500-1000 mg/dl:**
  - 20-35% fat
    If TG ↑, ↓ CHO, ↑ PUFA & MUFA
    ± ETOH when <400 mg/dl
- Fiber: > 25 g daily
- Sucrose in moderation

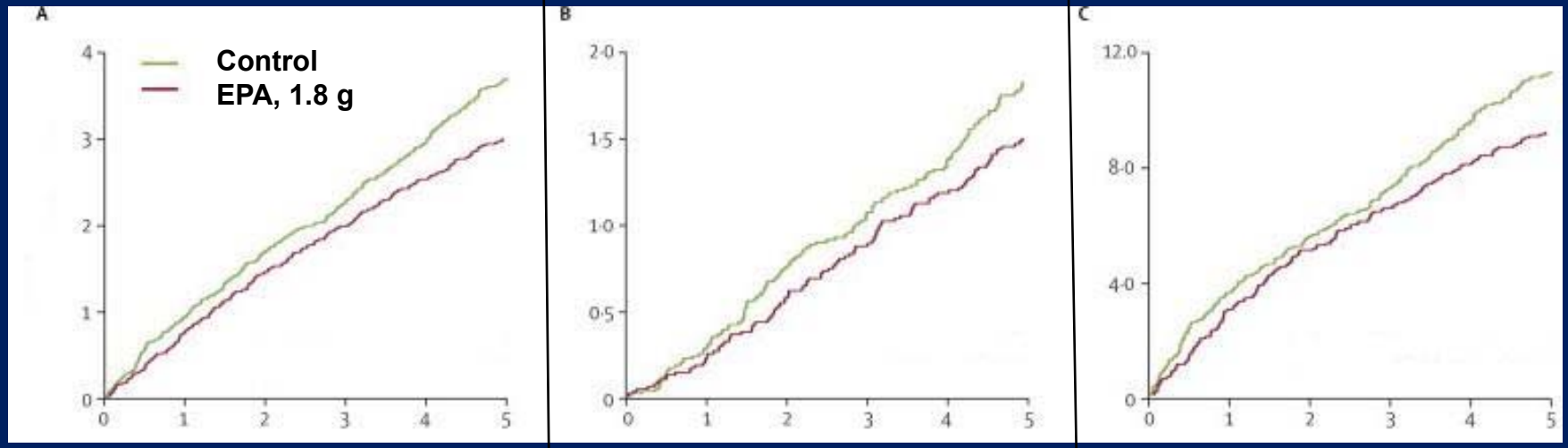
# FATTY ACID NOMENCLATURE

# DIETARY SOURCES

| FAMILY | FATTY ACID | STRUCTURE | DIETARY SOURCES |
|---|---|---|---|
| ω3 | Eicosapentaenoic Acid (C20:5 ω3) |  | Marine Oils, Fish |
| ω6 | Linoleic Acid (C18:2 ω6) |  | Vegetable Oils |
| ω9 | Oleic Acid (C18:1 ω9) |  | Vegetable Oils; Animal Fats |

# JELIS Study: Major Coronary Events

**Total population** | **Primary prevention** | **Secondary prevention**




**Numbers at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Control | 9319 | 8931 | 8671 | 8433 | 8192 | 7958 |
| Treatment | 9326 | 8929 | 8658 | 8389 | 8153 | 7924 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 7478 | 7204 | 7103 | 6841 | 6678 | 6508 |
| 7503 | 7210 | 7020 | 6823 | 6649 | 6482 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 1841 | 1727 | 1658 | 1592 | 1514 | 1450 |
| 1823 | 1719 | 1638 | 1566 | 1504 | 1442 |

**N= 18,645 ; baseline total cholesterol >250 mg/dl**
(with a total cholesterol > vs. placebo)

Yokoyama M, et al. *Lancet*. 369:1090, 2007

**Several CVD outcome trials using omega-3 fatty acids in patients with TG of 200-500 mg/dL have been initiated:**

1. **Strength (EPA + DHA)**
2. **REDUCE-IT (EPA)**

# What about HDL?

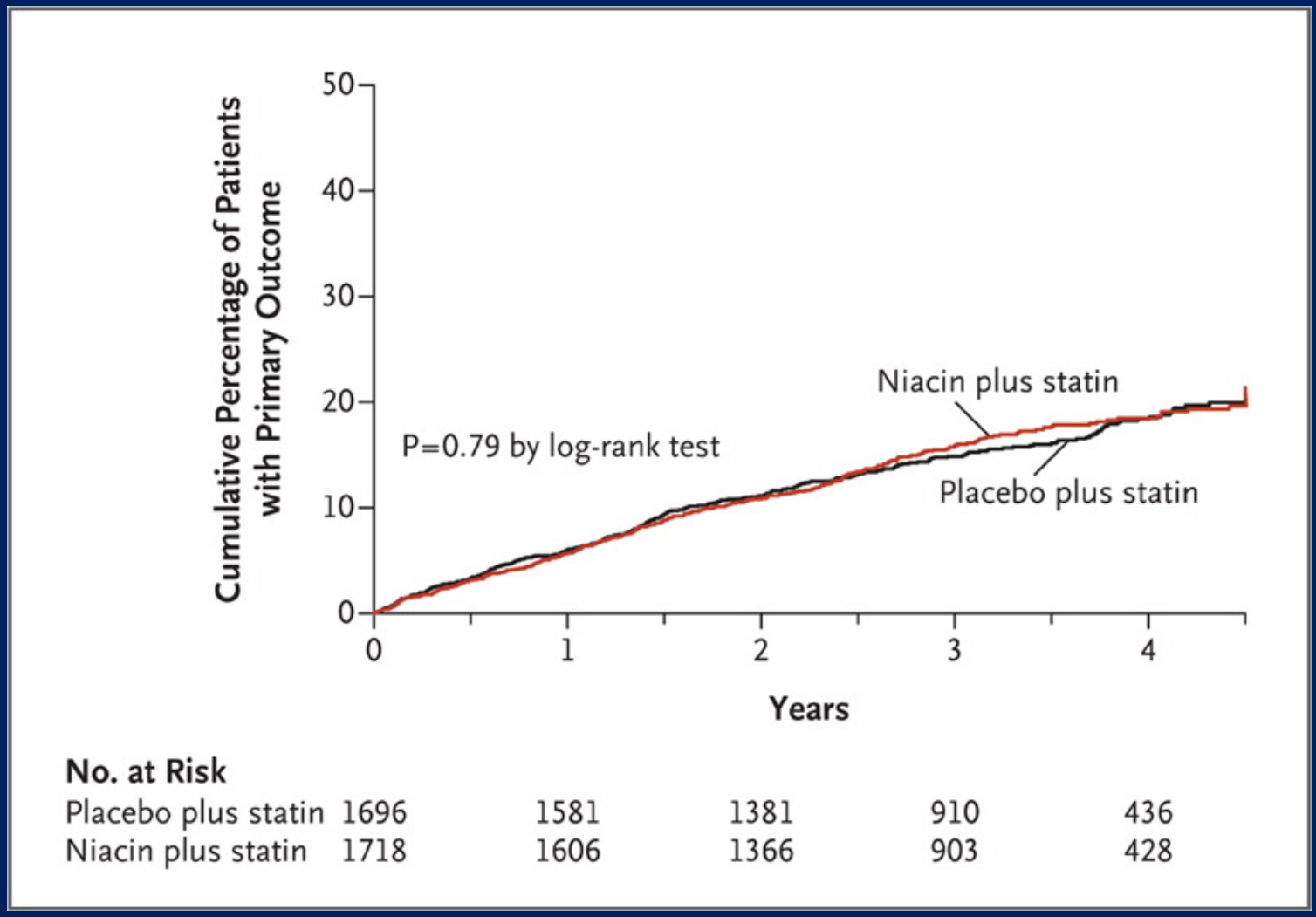
# Effects of Drugs on HDL-C Levels

- Niacin 15-35%
- Fibrates 5-15%
- Statins 5-10%
- Resins 5-10%
- Estrogens – p.o. 10-15%
- PCSK9 inhibitors 5-10%
- CETP inhibitors 25–60%
  - Torcetrapib - ↑ mortality; abandoned
  - Dalcetrapib (JTT-705): Phase 3 trial stopped
  - Anacetrapib (MK-0859): Phase 3 trial ongoing
  - Evacetrapib (Lilly): Phase 3 ongoing

# HDL and Atherosclerosis

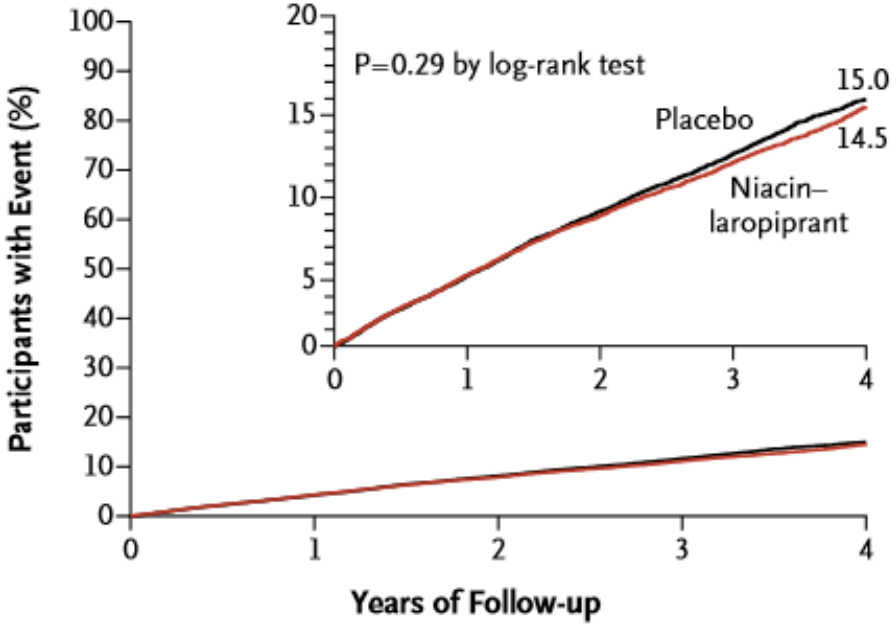
- Anti-oxidant
- Anti-inflammatory
- Anti-thrombotic
  - ↑ prostacyclin
- Promotes vascular reactivity
  - ↑ NOS
- Decreases myeloproliferative cell development
- Reverse cholesterol transport

# AIM HIGH:
# Niaicn + Statin Fails to Reduce CVD Events




Boden WE et al *NEJM* 2011, 365(24):2255-67

# HPS2 Thrive and CVD Risk: Another Niacin Failure




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Niacin–laropiprant | 12,838 | 12,232 | 11,517 | 7672 | 4978 |
| Placebo | 12,835 | 12,247 | 11,523 | 7643 | 5036 |
| Benefit per 1000 participants assigned to niacin–laropiprant | | 0±3 | 3±3 | 5±5 | 5±7 |

The HPS2-THRIVE Collaborative Group, *NEJM* 371:203, 2014

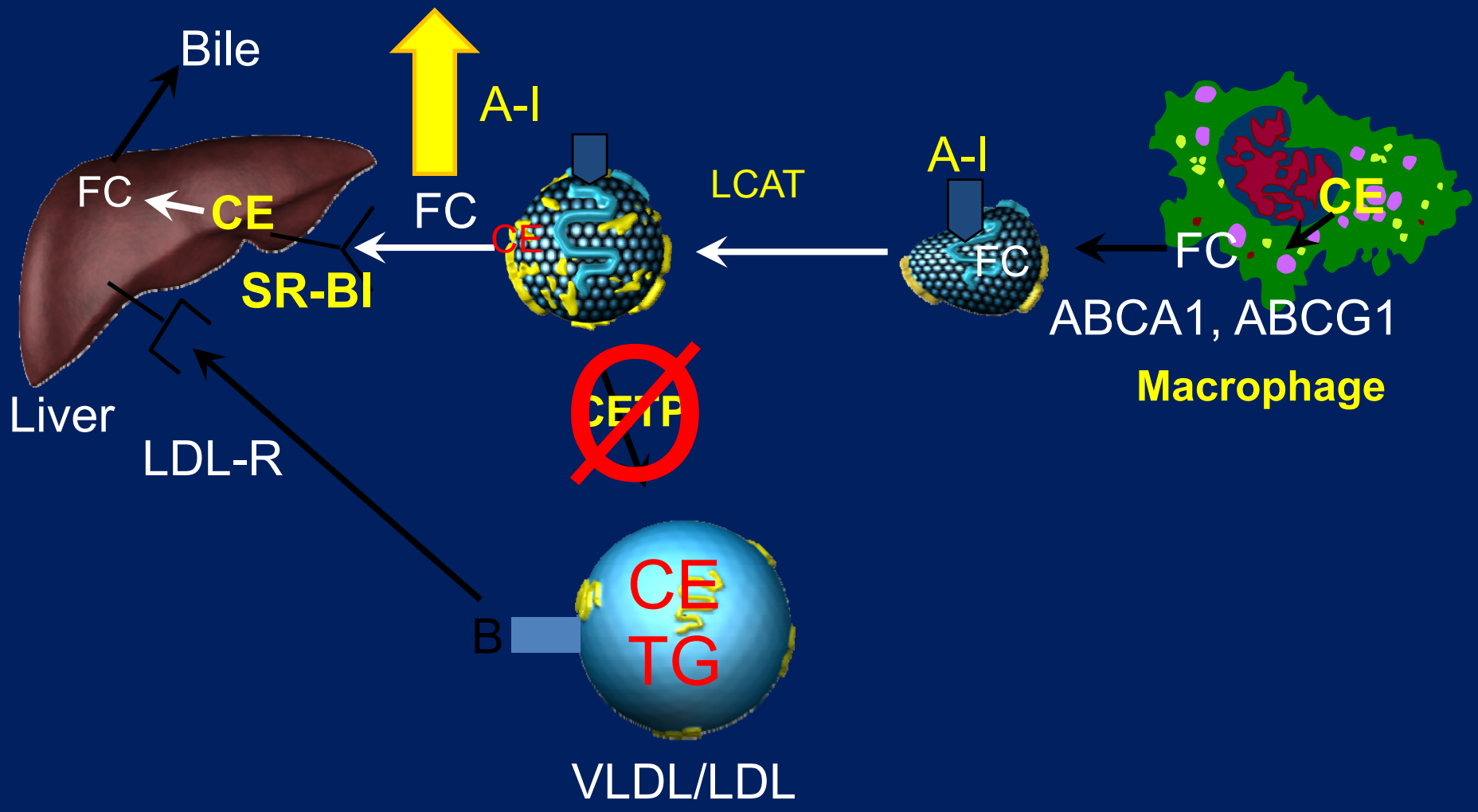
# HPS2 Thrive and CVD Risk: Niacin/Laropiprant Adverse Effects

- Gastrointestinal
- Musculoskeletal
- Skin-related
- Infection
- Bleeding
- New-onset T2DM
- In T2DM – ↑ glycemia

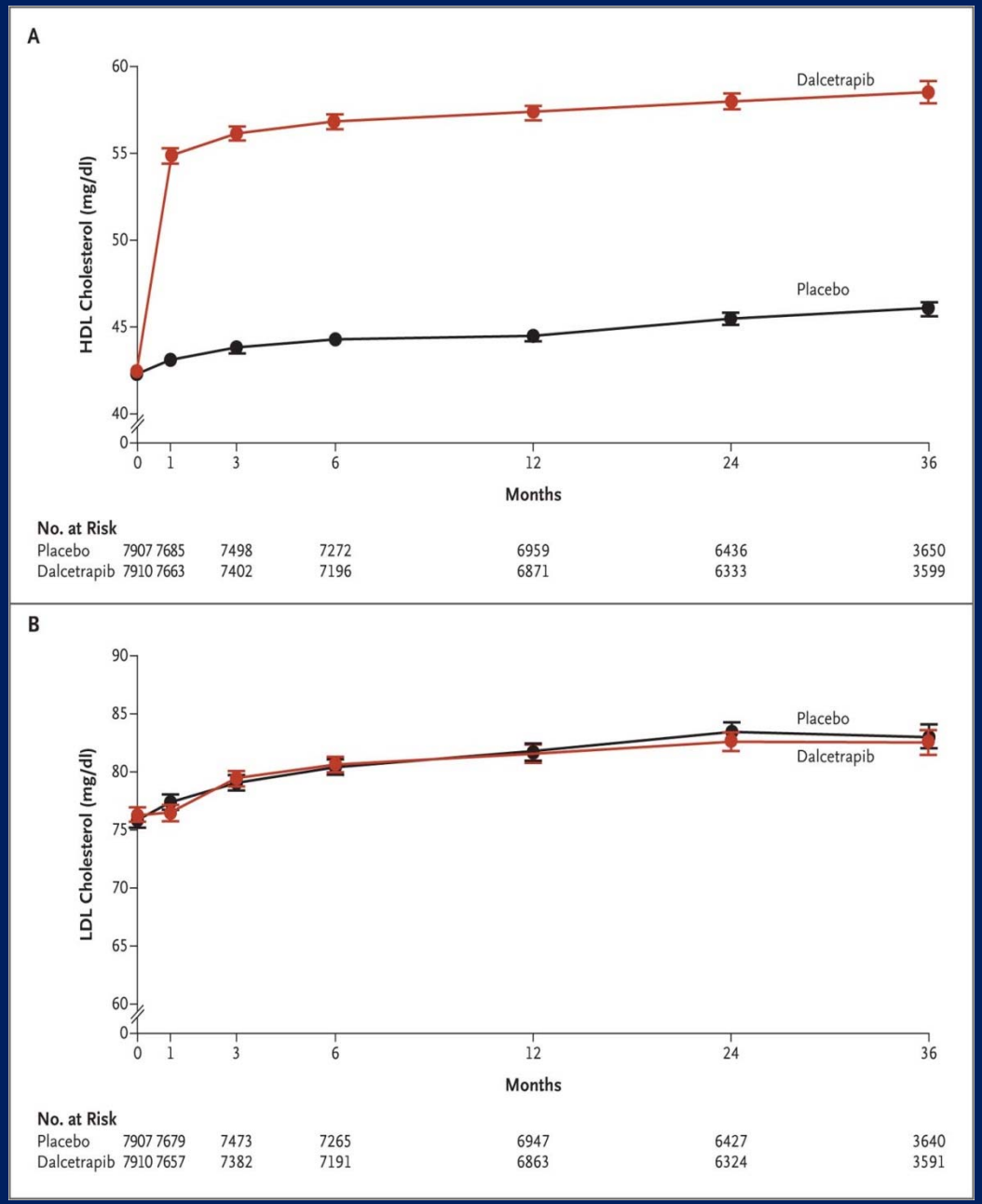
All p<0.001 vs. placebo

The HPS2-THRIVE Collaborative Group, *NEJM* 371:203, 2014

# CETP Inhibitors Markedly Increase HDL-C Levels

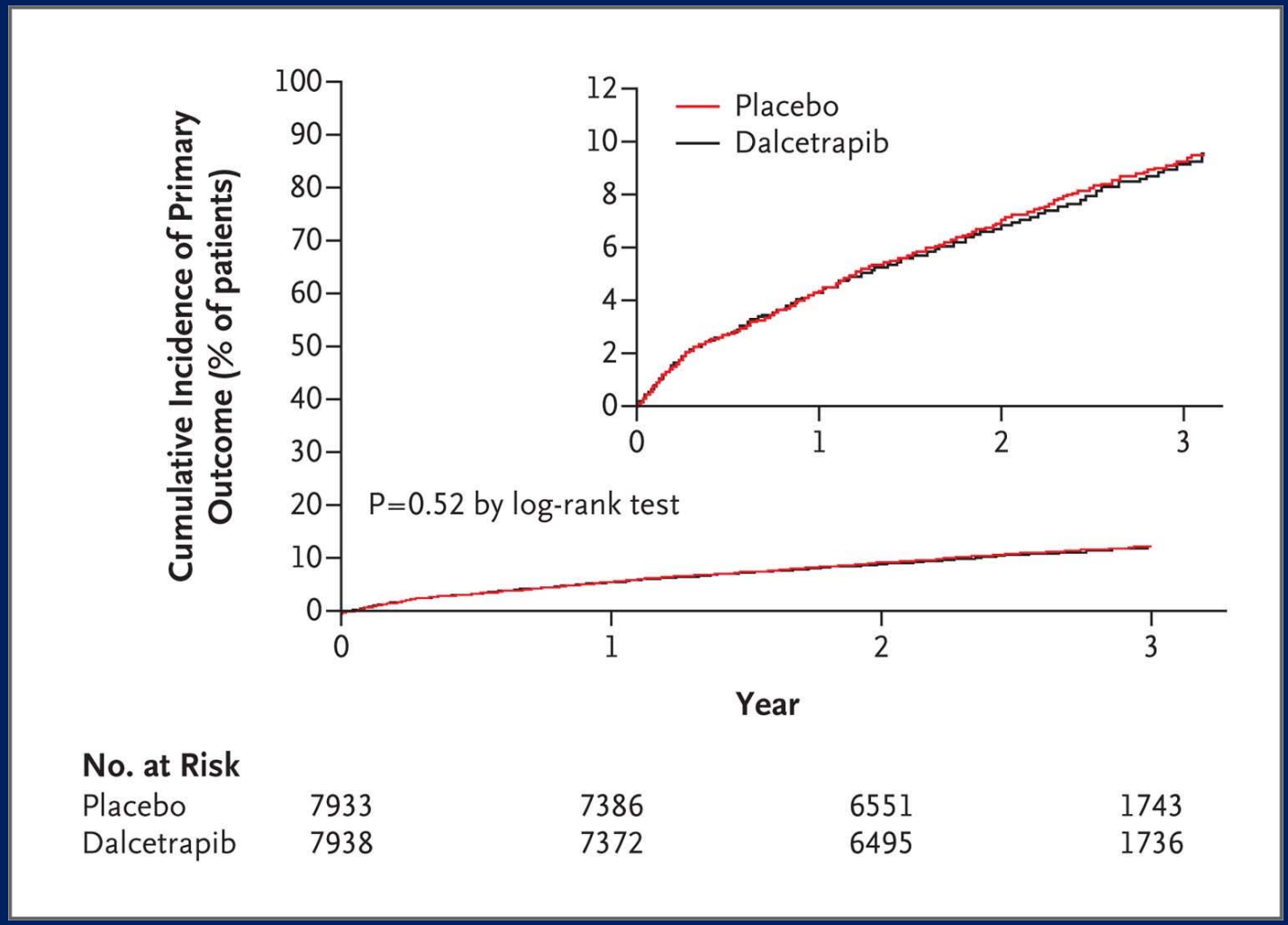


# Dal-OUTCOMES: Lipid Effects




Schwartz GG et al. *NEJM* 367:208, 2012

# Dal-OUTCOMES: Incidence of the Primary Efficacy End Point




**No. at Risk**

| | | | | |
|---|---|---|---|---|
| Placebo | 7933 | 7386 | 6551 | 1743 |
| Dalcetrapib | 7938 | 7372 | 6495 | 1736 |

Schwartz GG et al. *NEJM* 367:208, 2012

**The evidence is now overwhelming that low levels of HDL-C do not cause CHD!**

# Cholesterol Efflux Capacity Beyond HDL Cholesterol Levels in Coronary Artery Disease (CAD)

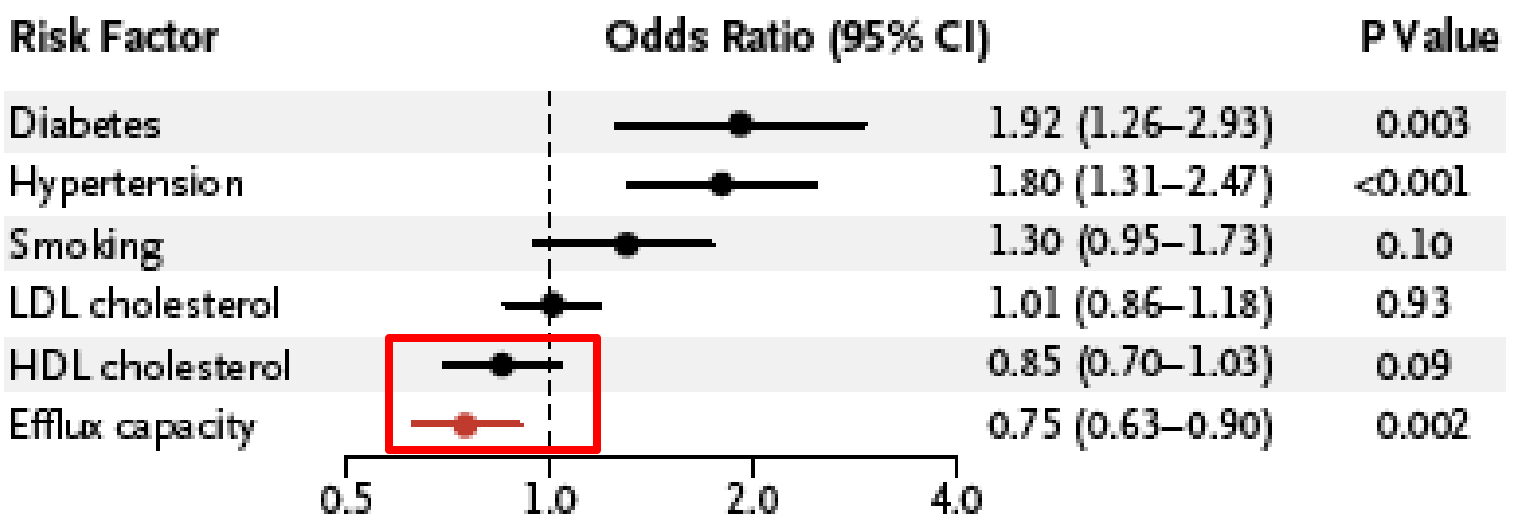
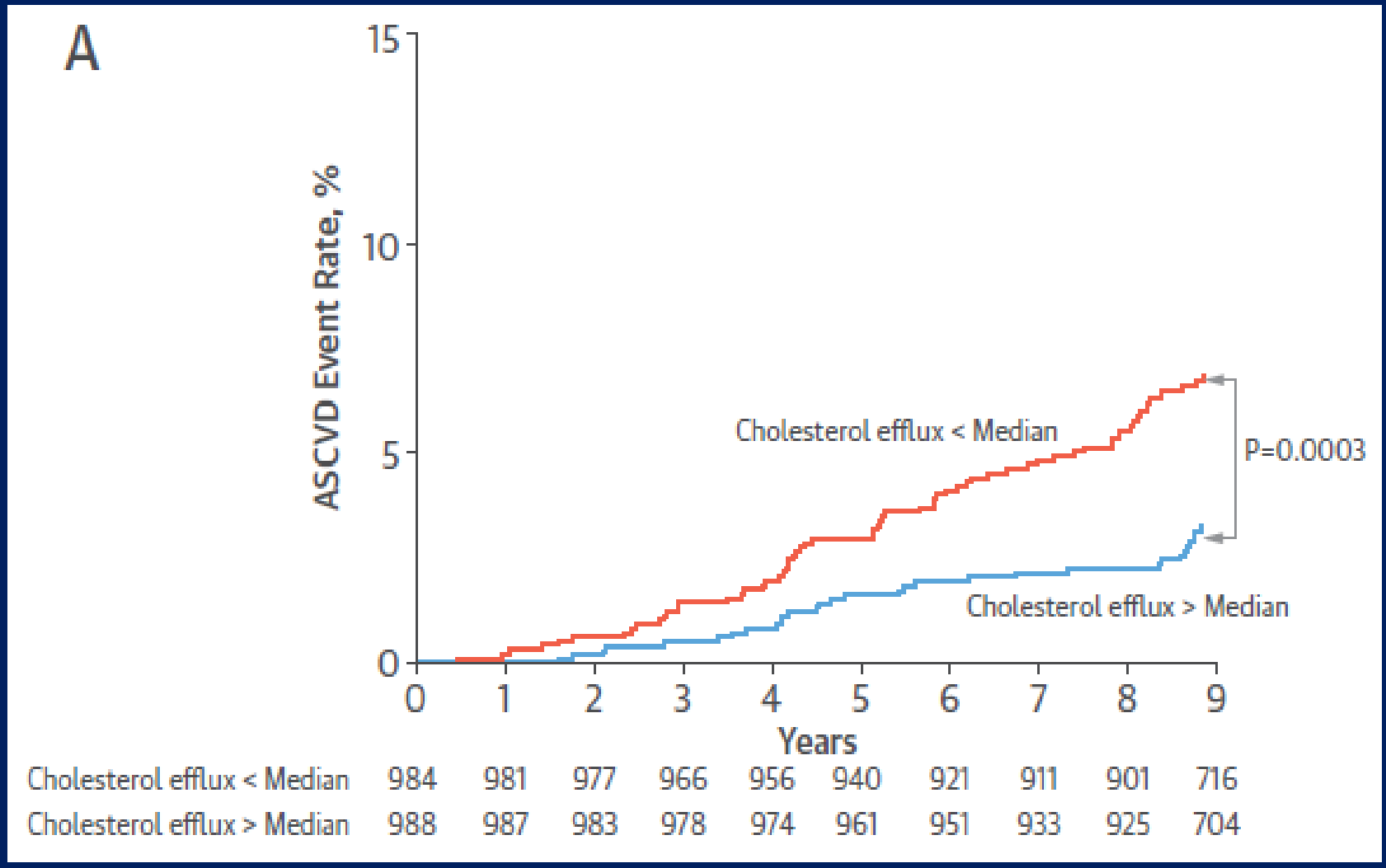



**Figure 1. Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors.**

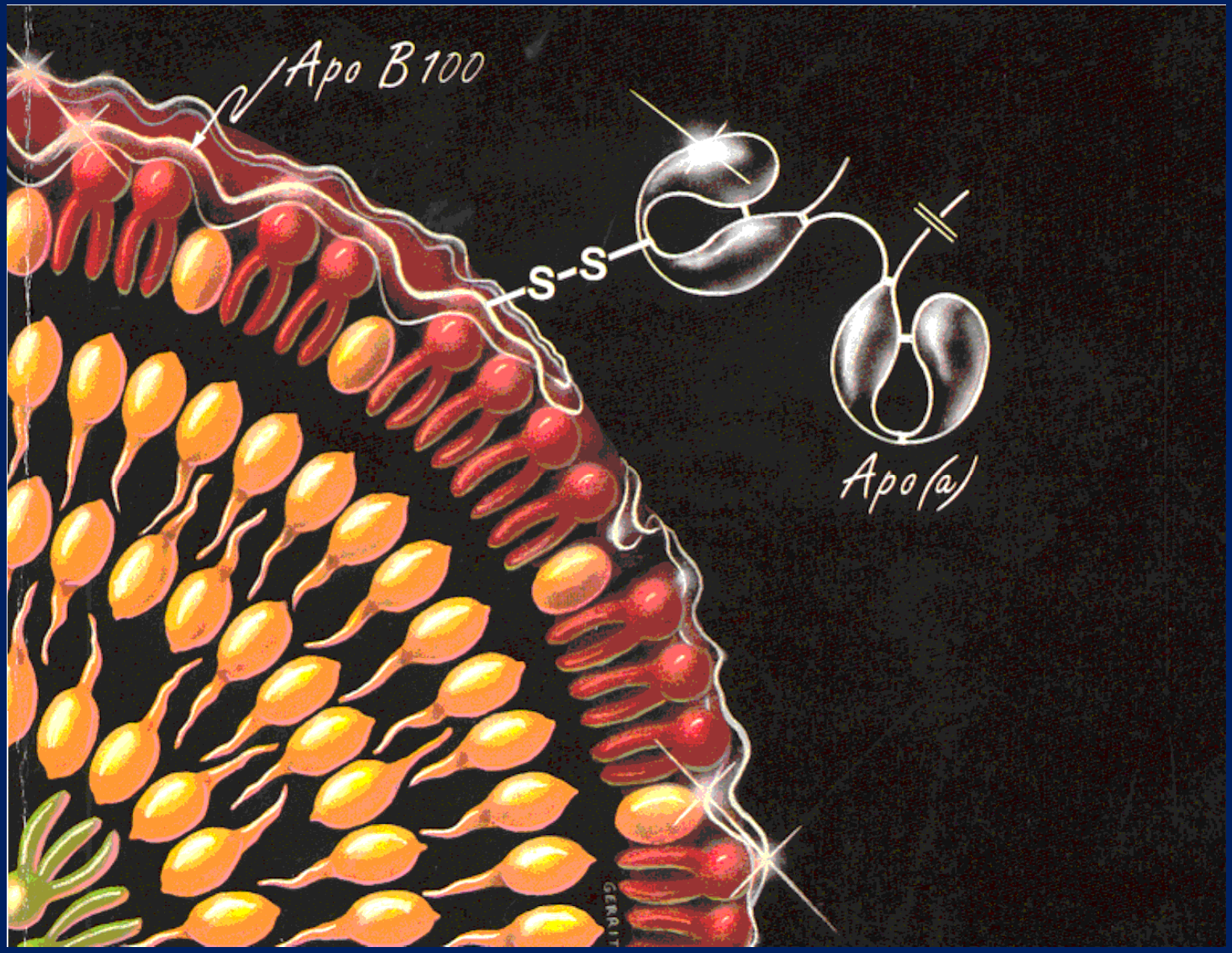
The logistic-regression model was also adjusted for age and sex. Odds ratios for continuous variables are per 1-SD increase.

Khera AV, et al. *N Engl J Med.* 2011;364(2):127-135.

# Cholesterol Efflux Capacity and ASCVD Events: Dallas Heart Study



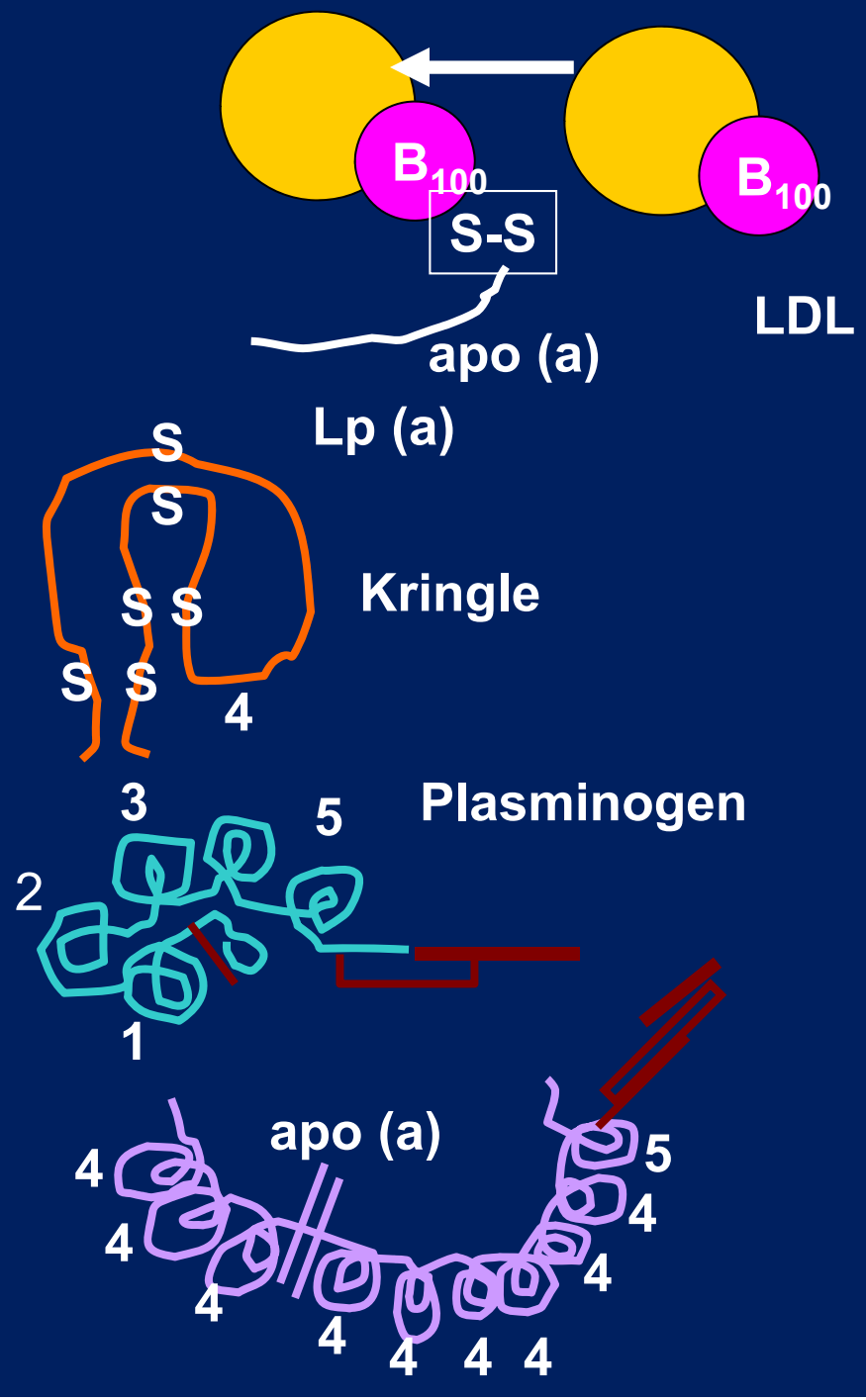

Mody P et al, *JACC* 67:2480, 2016


Apo B100
S-S
Apo(a)

# Lipoprotein (a) - a potential link between athero-thrombosis and atherosclerosis?

-Present at very low to very high levels –
(<0.1 → >250 mg/dL)

-Concentration is strongly influenced by hereditary



# Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study

*Sotirios Tsimikas, Nicholas J Viney, Steven G Hughes, Walter Singleton, Mark J Graham, Brenda F Baker, Jennifer L Burkey, Qingqing Yang, Santica M Marcovina, Richard S Geary, Rosanne M Crooke, Joseph L Witztum*

## Summary

**Background** Lipoprotein(a) (Lp[a]) is a risk factor for cardiovascular disease and calcific aortic valve stenosis. No effective therapies to lower plasma Lp(a) concentrations exist. We have assessed the safety, pharmacokinetics, and pharmacodynamics of ISIS-APO(a)$_{Rx}$, a second-generation antisense drug designed to reduce the synthesis of apolipoprotein(a) (apo[a]) in the liver.

**Methods** In this randomised, double-blind, placebo-controlled, phase 1 study at the PAREXEL Clinical Pharmacology Research Unit (Harrow, Middlesex, UK), we screened for healthy adults aged 18–65 years, with a body-mass index less than 32·0 kg/m², and Lp(a) concentration of 25 nmol/L (100 mg/L) or more. Via a randomisation technique, we randomly assigned participants to receive a single subcutaneous injection of ISIS-APO(a)$_{Rx}$ (50 mg, 100 mg, 200 mg, or 400 mg) or placebo (3:1) in the single-dose part of the study or to receive six subcutaneous injections of ISIS-APO(a)$_{Rx}$ (100 mg, 200 mg, or 300 mg, for a total dose exposure of 600 mg, 1200 mg, or 1800 mg) or placebo (4:1) during a 4 week period in the multi-dose part of the study. Participants, investigators, and study staff were masked to the

Published **Online**
July 23, 2015
http://dx.doi.org/10.1016/S0140-6736(15)61252-1

See **Online/Comment**
http://dx.doi.org/10.1016/S0140-6736(15)60638-9

**University of California San Diego, La Jolla, CA, USA** (Prof S Tsimikas MD, Prof J L Witztum MD); **Isis Pharmaceuticals, Carlsbad, CA, USA** (Prof S Tsimikas, N J Viney BSc, S G Hughes MBBS,

*Lancet* July 22, 2015

# Lipid Rx and ↓ ASCVD: 2016

| | |
|---|---|
| • Statins | Yes |
| • Ezetimibe | Yes |
| • Cholestyramine | Yes |
| • PCSK9 inhibitors | Probable |
| • Fibrates | ± |
| • Omega-3 fatty acids | ± |
| • Niacin | No |
| • CETP inhibitors | No, ? |


Thank You!

# Spells

**William F. Young, Jr., MD, MSc**
**Mayo Clinic, Rochester, MN**

# DISCLOSURE*

## Relevant Financial Relationship(s)

## None

## Off Label Usage

## *Perhaps*

*A provider must disclose the above information to learners prior to beginning of the educational activity (ACCME)

# Disclosure of ABIM Service

- I chair the Endocrine Specialty Board (July 2014 – present)
- I am a member of the Endocrine Exam Committee (July 2013 – present)
- I am a member of the ABIM Council (July 2014 – present)
- As is true for any ABIM candidate who has taken the certification exam, I have signed a Pledge of Honesty in which I have agreed to keep the ABIM exam confidential
- No exam questions will be disclosed in my presentation

# Spells:  Finding a Cause is . . .

**Truly A Medical Detective Story**

# Spells

**The most famous spell of all**

**Definition**

**Historical Perspectives**

**Personal Perspectives**

**Case Presentations**

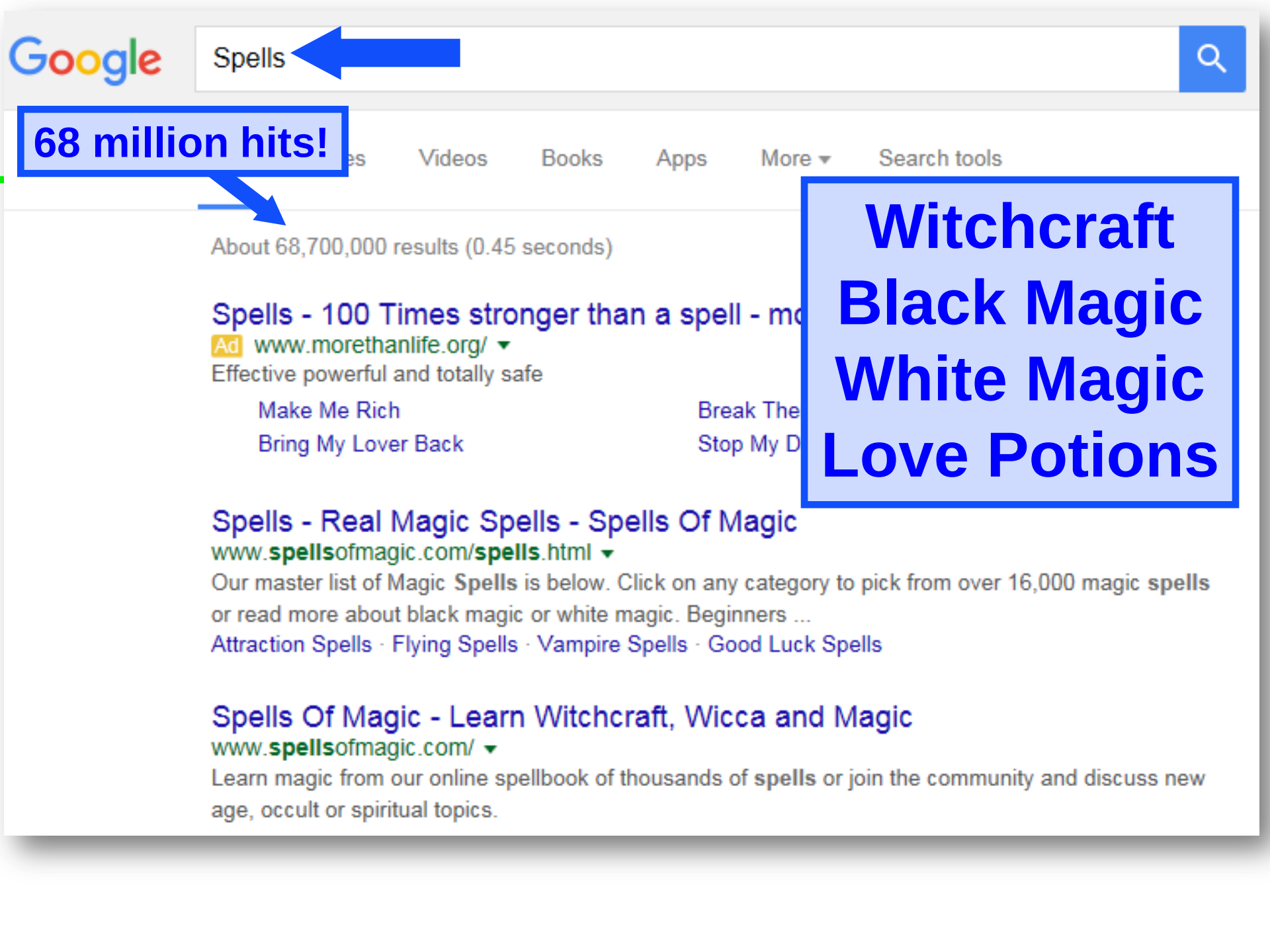
- Differential Diagnosis
- Diagnostic Approach

**Summary**

# Spells

## Definition:

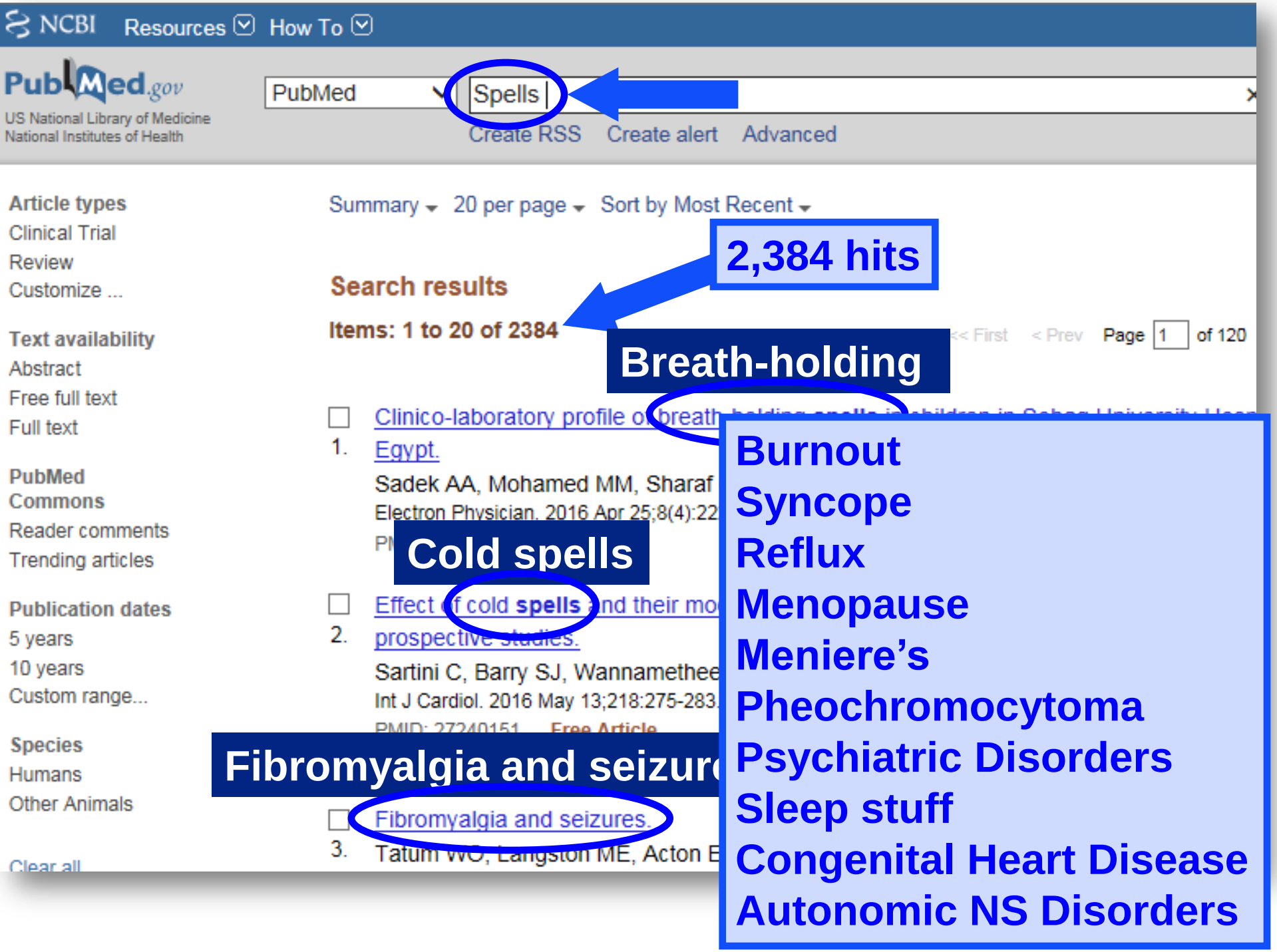
- Witch-dependent spells
- Witch-independent spells:
  - ✓ Stedman's medical dictionary
  - ✓ Google search


Google
Spells
68 million hits!
Videos
Books
Apps
More
Search tools
About 68,700,000 results (0.45 seconds)
Witchcraft
Black Magic
White Magic
Love Potions
Spells - 100 Times stronger than a spell - mo
Ad www.morethanlife.org/
Effective powerful and totally safe
Make Me Rich
Break The
Bring My Lover Back
Stop My D
Spells - Real Magic Spells - Spells Of Magic
www.spellsofmagic.com/spells.html
Our master list of Magic Spells is below. Click on any category to pick from over 16,000 magic spells or read more about black magic or white magic. Beginners ...
Attraction Spells · Flying Spells · Vampire Spells · Good Luck Spells
Spells Of Magic - Learn Witchcraft, Wicca and Magic
www.spellsofmagic.com/
Learn magic from our online spellbook of thousands of spells or join the community and discuss new age, occult or spiritual topics.

# Spells

## Definition:

- Witch-dependent spells
- Witch-independent spells:
  - ✓ Stedman's medical dictionary
  - ✓ Google
  - ✓ **PubMed search**


NCBI Resources How To
PubMed.gov
US National Library of Medicine
National Institutes of Health
PubMed
Spells
Create RSS
Create alert
Advanced
Article types
Clinical Trial
Review
Customize ...
Text availability
Abstract
Free full text
Full text
PubMed Commons
Reader comments
Trending articles
Publication dates
5 years
10 years
Custom range...
Species
Humans
Other Animals
Clear all
Summary
20 per page
Sort by Most Recent
Search results
Items: 1 to 20 of 2384
2,384 hits
<< First
< Prev
Page 1 of 120
Breath-holding
Clinico-laboratory profile of breath
1. Egypt.
Sadek AA, Mohamed MM, Sharaf
Electron Physician. 2016 Apr 25;8(4):22
Cold spells
Effect of cold spells and their mo
2. prospective studies.
Sartini C, Barry SJ, Wannamethee
Int J Cardiol. 2016 May 13;218:275-283.
Free Article
Fibromyalgia and seizur
Fibromyalgia and seizures.
3. Tatum WO, Langston ME, Acton E
Burnout
Syncope
Reflux
Menopause
Meniere's
Pheochromocytoma
Psychiatric Disorders
Sleep stuff
Congenital Heart Disease
Autonomic NS Disorders

# Spells – Definition*

**“a sudden onset of a symptom or symptoms that are recurrent, self-limited, and stereotypic in nature”**

*WF Young and DE Maddox, 1995

# Spells -- Historical Perspective

## 1700s: Vapors

"Sophia stood trembling all this while. Her face was whiter than snow, and her heart was throbbing through her stays."

From *Tom Jones*
by Henry Fielding (1749)

# Spells -- Historical Perspective

## 1800s: Hysteria

"Rapid action of the heart . . . is often a source of great distress. Pains about the heart may simulate angina. Flushes in various parts are among the most common symptoms, and may be seen in the head, back, hands, or feet. Sweating occasionally occurs."

From The Principles and Practice of Medicine by Sir William Osler M.D.; Chapter on Hysteria (1892)

# Spells -- Historical Perspective

## Adrenal Medulla -- Genesis of Pheochromocytoma

- ". . . and the two kidneys, and the fat that is on them, which is by the flanks . . ." From the *Bible*, Leviticus 3:4
- *Glandulae Renibus Incumbentes* -- Bartholomeus Eustachius (1520-1574)
- 1886: "Fraulein Minna Roll, aged 18, suffered with intermittent attacks of palpitation, anxiety, vertigo, headache, chest pain, cold sweats, and vomiting. Pulse was rapid and arteries tense." Died despite champagne therapy and injections of ether. Bilateral adrenal tumors thought to be angiosarcomas -- but in retrospect a + chromaffin reaction. *Dr. Felix Frankel, Freiburg, 1886*
- **1926** -- Cesar Roux in Lusanne & Charles Mayo in Rochester – **the spell was born.**

# Spells

**And 2 major career errors**

Definition

Historical Perspectives

**Personal Perspectives**

Case Presentations

- Differential Diagnosis
- Diagnostic Approach

Summary

# Subspecialty Clinics: Hypertension

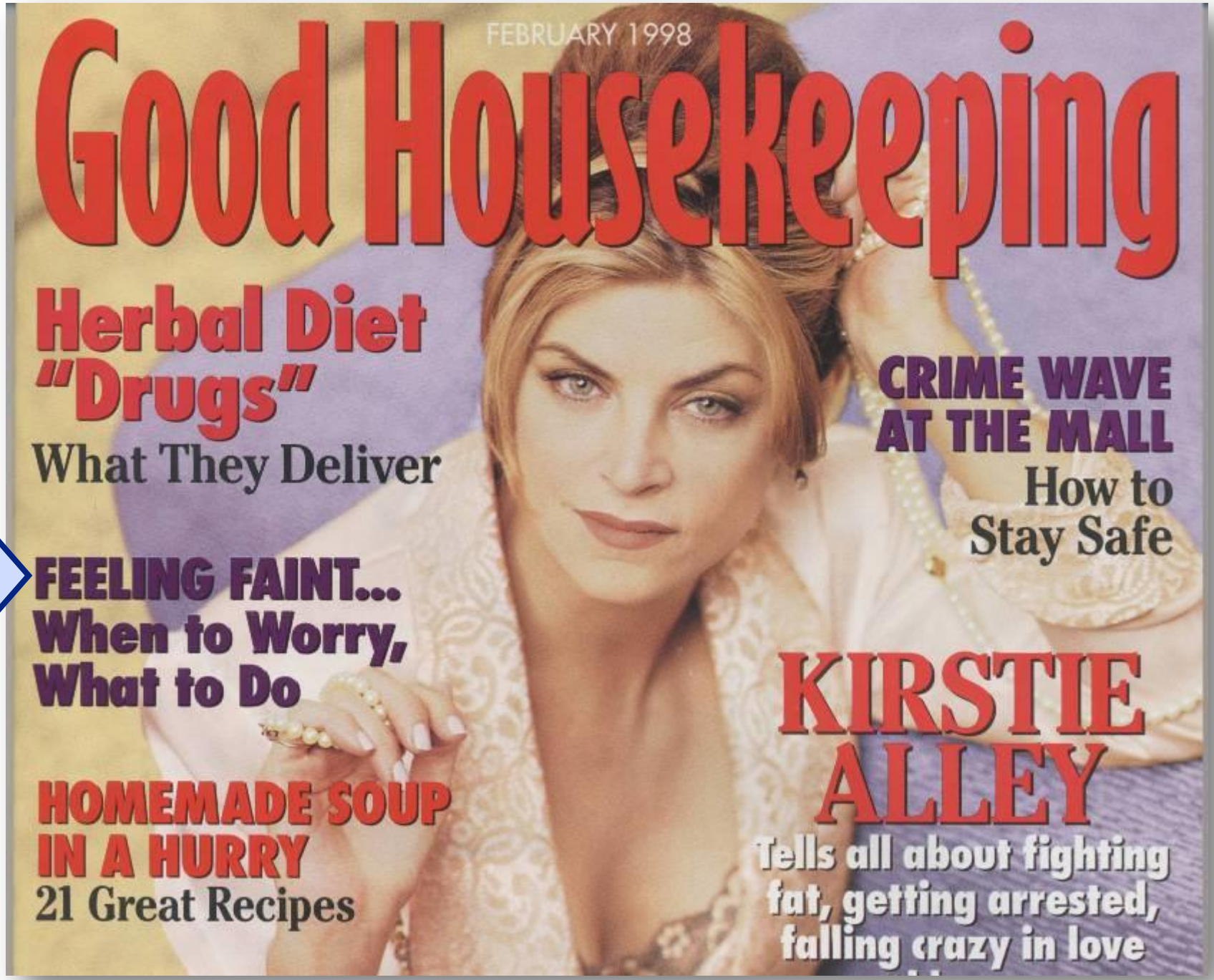
## Spells: In Search of a Cause

WILLIAM F. YOUNG, JR., M.D., AND DANIEL E. MADDOX, M.D.


- *Objective*: To determine the cause of spells, present clinical features, and discuss diagnostic approaches.
- *Design*: Relevant medical literature is reviewed, and three illustrative cases are presented.
- *Results*: Spells are a sudden onset of a symptom or symptoms that are stereotypic, self-limited, and recurrent. A spell involves both subjective perceptions and objective findings. In the assessment of patients who have spells, use of a systematic approach is important in determining the cause. The causes of spells include endocrine, cardiovascular, psychologic, pharmacologic, neurologic, and other miscellaneous disorders. A comprehensive history, physical examination, and basic laboratory studies are important in the initial assessment. Specialized testing is usually needed and directed by clinical suspicion based on the spell "phenotype" (for example, a pheochromocytoma, carcinoid syndrome, or mast cell disease) and the type of facial flush or pallor.
- *Conclusion*: In the assessment of the patient who has spells, the clinician should cast a wide but defensible diagnostic net. Initial studies should be directed by the clues obtained from the history and physical examination.


(*Mayo Clin Proc 1995; 70:757-765*)

BMI = body mass index; CT = computed tomography; 5-HIAA = 5-hydroxyindoleacetic acid; $PGD_2$ = prostaglandin $D_2$; PGD-M = prostaglandin $D_2$ metabolite; VMA = vanillylmandelic acid


FEBRUARY 1998
Good Housekeeping
Herbal Diet "Drugs"
What They Deliver
CRIME WAVE AT THE MALL
How to Stay Safe
FEELING FAINT... When to Worry, What to Do
KIRSTIE ALLEY
Tells all about fighting fat, getting arrested, falling crazy in love
HOMEMADE SOUP IN A HURRY
21 Great Recipes

# Spells

Definition

Historical Perspectives

Personal Perspectives

**Case Presentations**

- Differential Diagnosis
- Diagnostic Approach

Summary

# 32 Causes of Spells

**Endocrine**

- pheochromocytoma
- thyrotoxicosis
- **primary hypogonadism (menopause)**
- medullary thyroid carcinoma
- pancreatic tumors (e.g., insulinoma)
- "**hyperadrenergic spells**"

**Cardiovascular**

- **labile essential hypertension**
- angina & cardiovascular deconditioning
- pulmonary edema
- syncope
- orthostatic hypotension
- paroxysmal cardiac arrhythmia
- renovascular disease

**Psychological**

- **anxiety and panic attacks**
- somatization disorder
- hyperventilation
- factitious (e.g., drugs, valsalva)

**Pharmacologic**

- withdrawal of adrenergic-inhibitor
- MAO-inhibitor RX + decongestant
- sympathomimetic ingestion
- illegal drug ingestion (cocaine, PCP, LSD)

**Neurologic**

- postural orthostatic tachycardia (POTS)
- autonomic neuropathy
- migraine headache
- diencephalic epilepsy (autonomic seizures)
- stroke
- cerebrovascular insufficiency

**Other**

- mast cell disease - systemic vs. activation
- carcinoid syndrome
- allergies & recurrent idiopathic anaphylaxis
- **"unexplained" flushing spells**

# 32 Causes of Spells

**Endocrine**

- pheochromocytoma
- thyrotoxicosis
- **primary hypogonadism (menopause)**

**Pharmacologic**

- withdrawal of adrenergic-inhibitor
- MAO-inhibitor RX + decongestant
- sympathomimetic ingestion

## 3 Spell Facts:

1. **Most medical providers think that nearly all patients with spells must have an endocrine disorder**
2. **Most patients with spells do NOT have an endocrine disorder**
3. **<0.1% of patients with spells have pheochromocytoma!**

# So . . . Just What is a Typical Pheochromocytoma Spell?

## I Interviewed 4 Patients with spells on 1 day (. . . a typical week):

- Goal—To answer the question: What is a typical pheochromocytoma spell?

# Spell History -- Key Components

- Detail spell symptom sequence
- Characterize symptoms
- Precipitating and alleviating factors
- Determine flush or pallor
- **Identify type of flush (“wet” or “dry”)**

# Flushing

## Neurogenic Flushing -- “Wet Flush”:

- Sympathetic cholinergic neurons
- Perspiration
- Post-menopausal hot flash

## Direct Vasodilatation -- “Dry Flush”:

- Histamine, polypeptides, and PGS
- Exogenous agents
  (e.g., nicotinic acid, and amyl nitrate)
- Not associated with perspiration

# Spell History -- Key Components

- Detail spell symptom sequence
- Characterize symptoms
- Circumstances before 1st spell (e.g., abd trauma)
- Precipitating and alleviating factors
- Determine flush or pallor
- Identify type of flush (“wet” or “dry”)
- **Investigate blood pressure change**
- Timing, frequency, and duration
- Determine status following the spell
- **Look for atypical features**
- **List medications -- prescription and OTC**
- Identify stress factors

# Spells du Monde Test Menu

- Clinical assessment
- 24-hr urine fx METs & CATs
- Plasma fx metanephrines
- TSH, FT4
- Chromogranin A , VIP, HPP, sub P
- Testosterone, estradiol, LH/FSH
- Calcitonin
- Glucose & Insulin / 72-hr fast
- PAC/PRA ratio
- 24-hr urine 5-HIAA
- Tryptase, 24-hr U $PGF_{2\alpha}$, M-His
- 24-hr BP & Holter/Event monitor
- Echocardiogram/CV testing
- Hyperventilation test
- Bone marrow biopsy
- 24-hr urinary aldo
- Drug screen
- Autonomic testing
- EEG
- Carotid US
- CT/MRI abdomen
- MRI -- head/neck
- $^{123}$I-MIBG scan
- Octreotide scan
- Renal artery eval
- Allergy Consult
- Psych Consult
- Card Consult
- Neurology Consult
- Endocrine Consult

# Adrenal Medulla, Catecholamines, and Pheochromocytoma

**228**

William F. Young Jr.

**Chapter Updated:** April 22, 2016



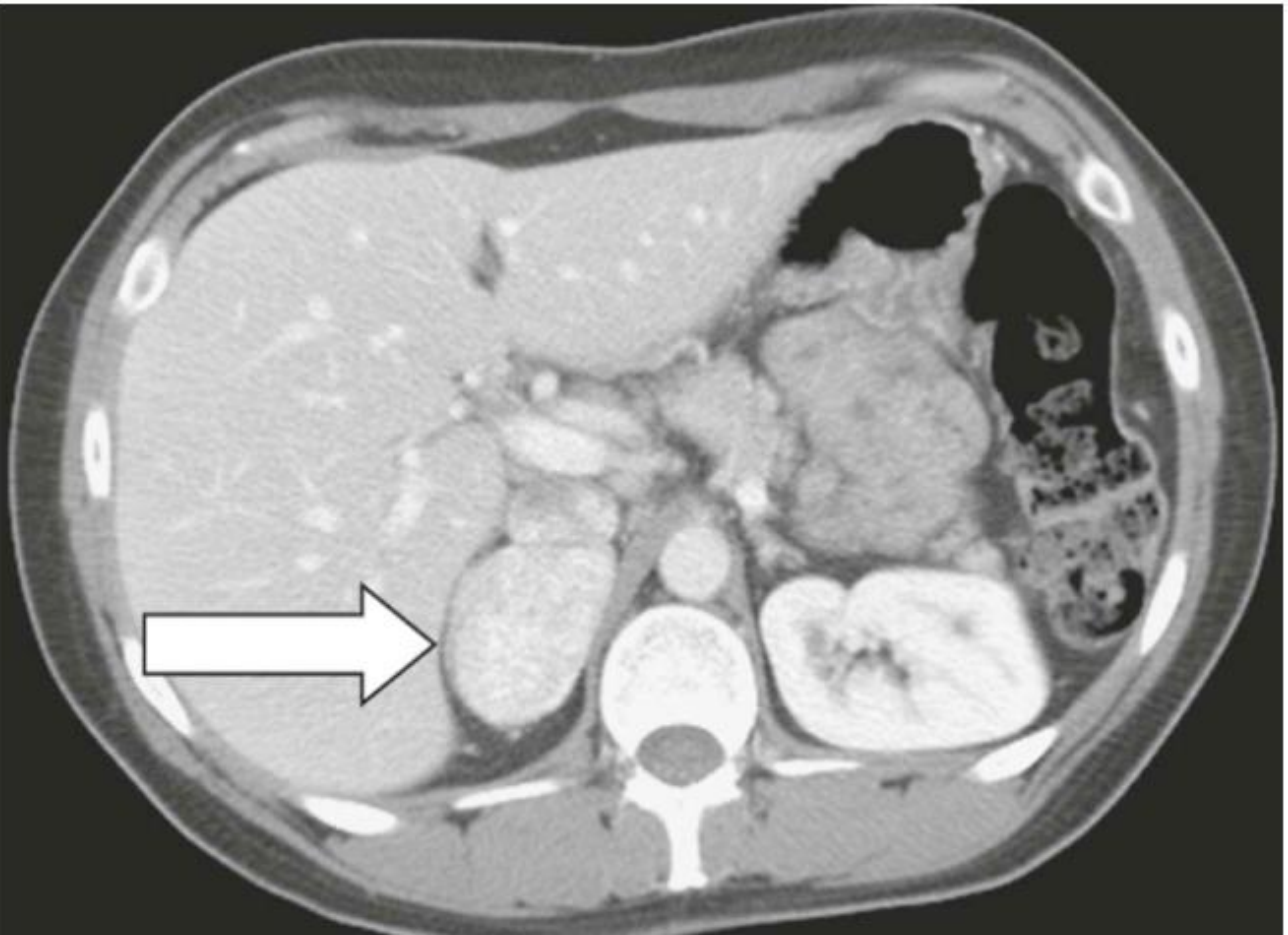


Figure 228-2

Contrast-enhanced computed tomography of the abdomen in a 32-year-old second-year medical student with the peripartum discovery of a pheochromocytoma. The plasma fractionated metanephrines were abnormal: metanephrine, 0.19 nmol/L (normal, <0.5 nmol/L); normetanephrine, 28.6 nmol/L (normal, <0.9 nmol/L). The 24-hour urine values were abnormal: norepinephrine, 781 µg (normal, <170 µg); epinephrine, 2.4 µg (normal, <35 µg); dopamine, 197 µg (normal, <700 µg); metanephrine, 117 µg (normal, <400 µg); normetanephrine, 8760 µg (normal, <900 µg). The axial image shows a typical 5-cm heterogeneously enhancing right adrenal mass, consistent with pheochromocytoma (arrow). After α- and β-adrenergic

# Common "Spelling" Errors

- Thinking that there is a "typical pheo spell" – up to 50% of pheos are found in asymptomatic patients – either because of an incidentally discovered adrenal mass or family testing
- Not recognizing that:
  - ✓ Most patients with "classic pheo spells" don't have a pheo!

# Common "Spelling" Errors

- Not recognizing that:
  - ✓In a patient with spells caused by pheo or PGL, the degree of ↑ of fx mets & cats should be markedly abnormal—in other words, if a pheo is responsible for "classic pheochromocytoma spells", then the biochemical tests are ALWAYS unequivocally abnormal (eg, >5-fold above the ULN)

# PHEO -- Diagnosis is Biochemical

**24-hr Urine metanephrines & catecholamines*:**

- Sensitivity 98% (sporadic); 90% (including

**Because of the:**

1. **Poor test specificity of plasma normetanephrine and**
2. **Rarity of ("I love rare") pheo,**

**97% of patients with + plasma normetanephrines at Mayo Clinic do NOT HAVE pheochromocytoma!**

# Medications That May ↑ Measured Levels of Catecholamines & Metanephrines

- ✓ Tricyclic antidepre
- ✓ Levodopa
- ✓ Drugs containing a
  (e.g., decongestar
- ✓ Amphetamines
- ✓ Buspirone and most psychoactive agents (except NOT selective serotonin reuptake inhibitors [SSRIs]; SNRIs may cause <2-fold increases above upper limit of reference range)
- ✓ Prochlorperazine
- ✓ Reserpine
- ✓ Withdrawal from clonidine and other drugs (eg, illicit drugs)
- ✓ Ethanol

NOTE: With current assay methodology, antihypertensive meds DO NOT interfere with testing!

# Spell Phenotypes -- Carcinoid Syndrome

## Flushing, Diarrhea, Cardiac Valvular Disease:

- **Marked flushing**
- **Severe diarrhea**
- Sx of pulmonic stenosis & tricuspid insufficiency
- Triggered by excitement, ETOH, eating

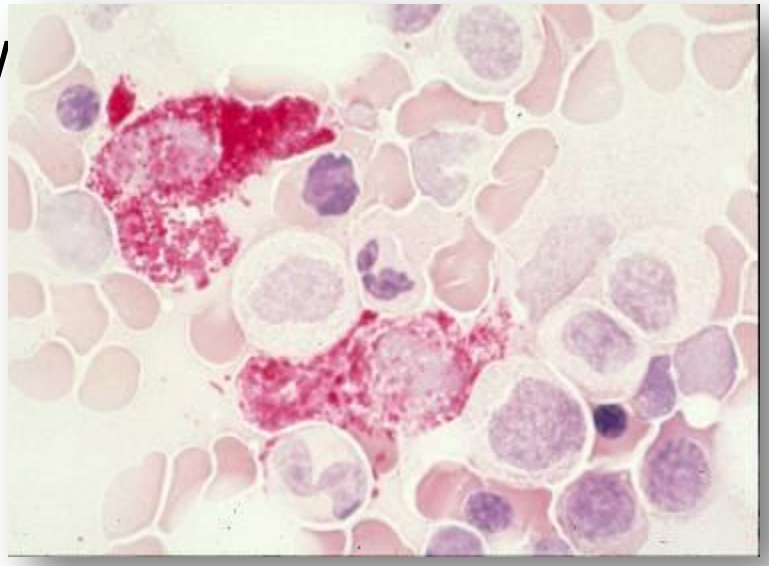
## First line test:

- >98% will have elevated 24h urine 5-HIAA
  - ✓**typically > 15 mg/24-h** (normal, 0 - 6)

# Spell Phenotypes – Mast Cell Disorders

## Sudden release of mast cell mediators:

- Flushing and facial warmth, pallor if abrupt drop in BP, palpitation
- **Lightheadedness, syncope**
- **Hypertensive subset ($PGF_2$)**
- **Fatigue and profound lethargy following spell**
- Biochemical dx -- baseline & w
  - ✓ blood studies: **tryptase**
  - ✓ 24h urine for:
    - ➢ methyl-histamine
    - ➢ **$PGF_{2\text{-alpha}}$**
- Histologic confirmation



# Unexplained Flushing Spells

## Considerations:

- Reassure, Reassure, Reassure!!!!!
- Empiric pharmacologic therapy:
  - ✓ wet flusher -- adrenergic inhibition (e.g., guanfacine [Tenex®])
  - ✓ dry flusher -- $H_1$ and $H_2$ blockade
  - ✓ antiserotonergic agent -- cyproheptadine
  - ✓ SSRI or TCA

# Some “Spelling” Pearls

## Diagnostic Approach:

- Take time -- “high complexity” CPT code
- Complete spell history
- Comprehensive physical examination
- Alert the patient on “day 1” of the challenge ahead

# MAYO CLINIC HEALTH LETTER

RELIABLE INFORMATION FOR A HEALTHIER LIFE

VOLUME 15 NUMBER 8 AUGUST 1997


## Inside this issue



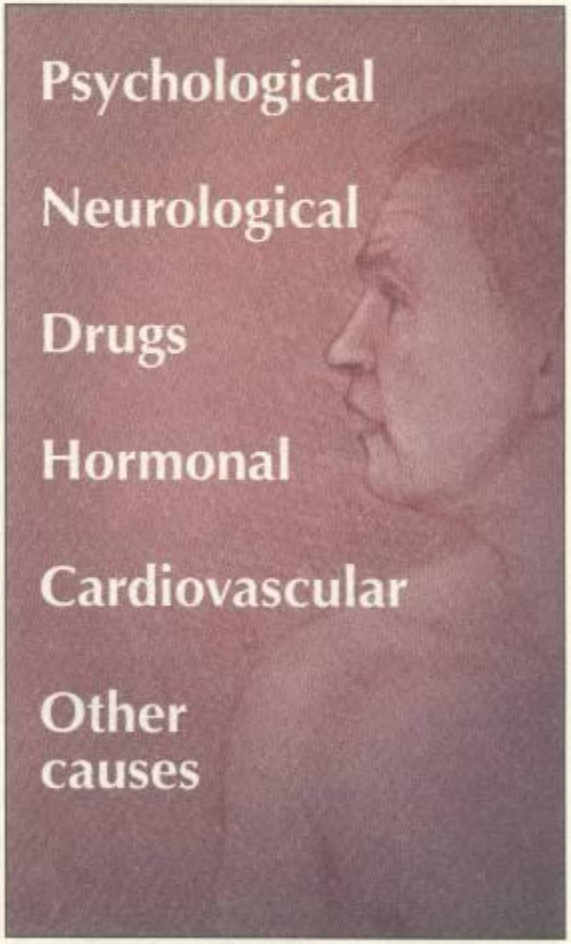
# Spells

## Finding the cause can be difficult

You're getting dressed when suddenly you start to perspire, your heart begins beating rapidly and you feel dizzy. After a few minutes, the symptoms disappear and you feel fine. But a couple of days later it happens again.

Years ago, your parents or grandparents may have called this a case of "the vapors." Today, many people refer to such episodes as "spells."

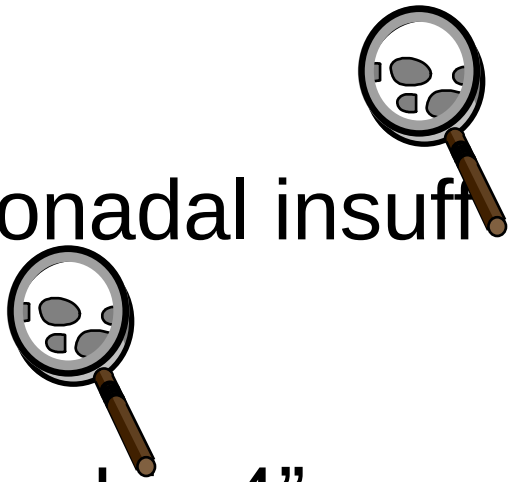
Because they often happen without warning and for unknown reasons, spells can be frightening and at times a bit embarrassing. But in most cases, they aren't life-threatening.



# Some “Spelling” Pearls

## Cast a wide but defensible diagnostic net:

- Direct toward clues found on history and physical:
  - ✓ Nocturnal spells = panic or gonadal insuff.
  - ✓ Flushing spells = rarely pheo



- Initial studies – e.g., exclude “the big 4” (pheo, carcinoid, insulinoma, mast cell)
- Case-directed studies