Endocrinologic and Metabolic Drugs Advisory Committee Meeting
Silver Spring, MD
March 28, 2012

FDA 2007 Draft Guidance for Industry: Developing Products for Weight Management

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Development of FDA's Obesity Drug Guidance

- January 1995 Advisory Committee meeting
- "Biggest change we are hoping to bring about is the approval of [obesity] drugs for long-term use"
- Major considerations:
  - Duration and size of Phase 3 trials
  - Patient population
  - Criteria to define efficacy

1996 FDA Draft Guidance

- Duration and size of Phase 3 trials
  - One year of placebo-controlled exposure in 1500 patients
  - Second year of open-label exposure in 200 to 500 patients
- Patient population
  - BMI $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 with co-morbidities
- Efficacy criteria
  - Mean weight loss is 5% greater in drug- vs. placebo-treated patients OR
  - Proportion of patients losing 5% is greater in drug- vs. placebo-treated group

Obesity Drugs Approved Since 1996

- Dexfenfluramine (Redux)
  - Approved 1996
  - Withdrawn 1997
- Sibutramine (Meridia)
  - Approved 1997
  - Withdrawn 2010
- Orlistat (Xenical)
  - Approved 1999

Revising FDA's Obesity Drug Guidance

- 1998/2000 NIH Clinical Guidelines on the Identification and Treatment of Overweight and Obesity
- September 2004 Advisory Committee meeting
- Major considerations:
  - Size and duration of studies
  - Patient population
  - Efficacy criteria

- Current DRAFT version (2007): *Developing Products for Weight Management*

2007 FDA Draft Guidance for Industry:

Developing Products for Weight Management

Purpose of Guidance

- Provides recommendations regarding the development of drug products intended to be used for *medical weight loss*
  - A long-term reduction in fat mass with a goal of reduced morbidity and mortality
  - Quantifiable improvements in biomarkers such as blood pressure, lipids, and HbA1c

Benefits of Weight Loss

- Weight loss ≥ 5% is associated with improvement in various metabolic and cardiovascular risk factors
- Modest degrees of intentional weight loss with lifestyle intervention may reduce the incidence of obesity-related morbidity and mortality
- Effects of drug-induced weight loss on clinical outcomes: mixed

Weight Loss vs. Weight Maintenance

- Weight loss and maintenance must be demonstrated over at least *one year* before a product will be considered effective

- No specific weight maintenance/prevention of weight regain indication

Lifestyle Modification and Benefit-Risk Considerations

- Dietary intake, exercise, and other behaviors
- Weight-loss drug should only be considered:
  - After sufficient trial of lifestyle modification has "failed"
  - Benefits of weight loss expected to outweigh risks of treatment
- Lifestyle modification programs should be applicable to the use of the product post-approval

Patient Population: Adults

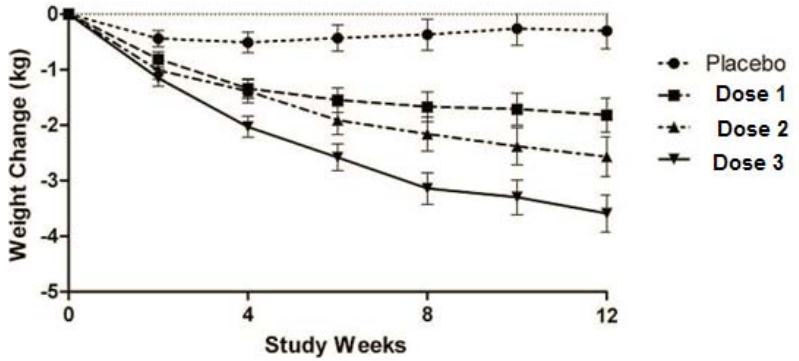
- BMI $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 with co-morbidities
  - Type 2 diabetes
  - Hypertension
  - Dyslipidemia
  - Sleep apnea
  - Cardiovascular disease

- Representation from variety of demographic, ethnic, racial groups

- Include patients with BMI > 40 kg/m^2

Phase 1 and 2 Trials

- Pharmacokinetics
  - Broad range of BMIs
- Dose-response

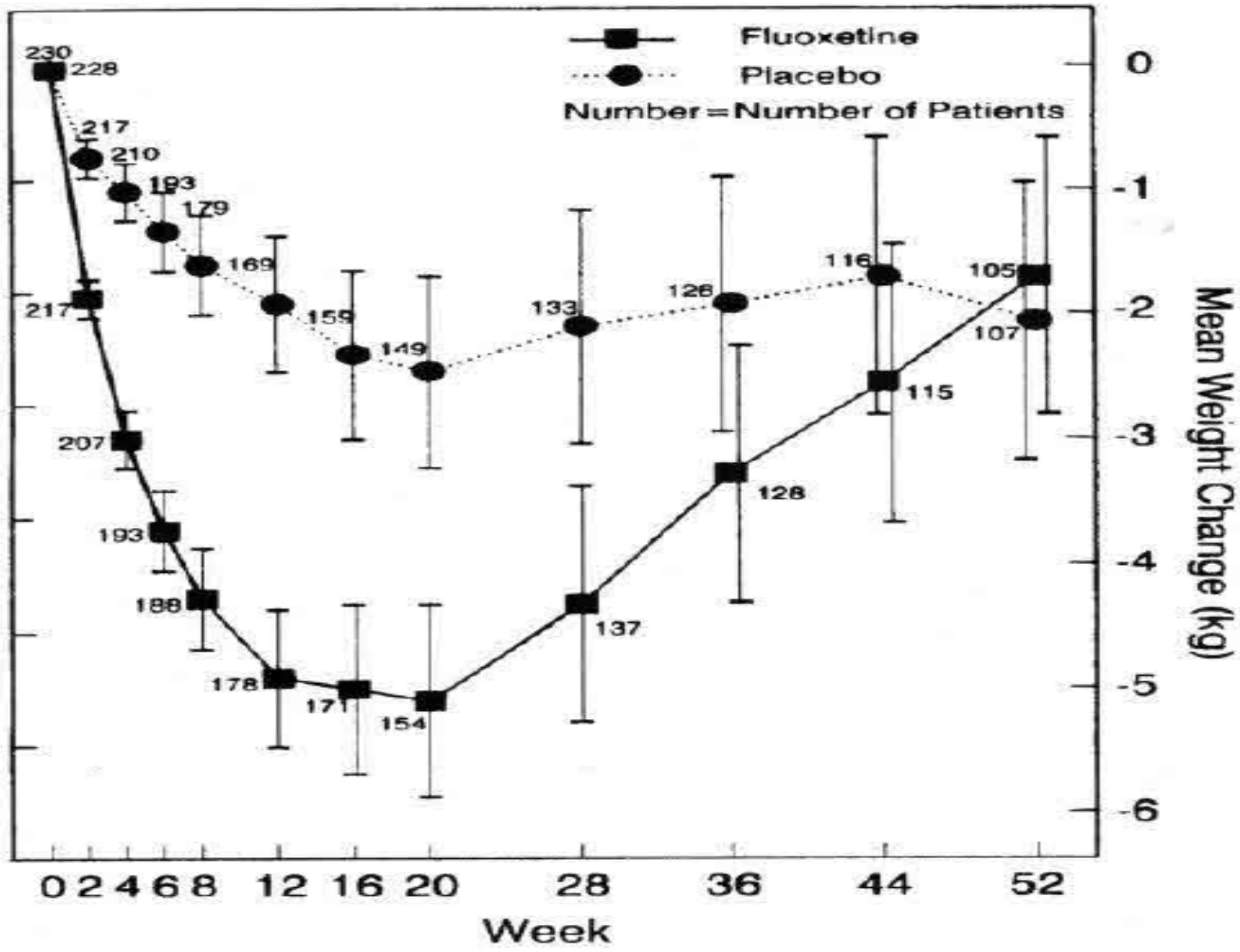


- No-effect and maximally-tolerated doses
- Duration sufficient to capture maximal or near-maximal weight loss effects
- How will drug be used

Phase 3 Trials: Design

- Placebo RCT
- Size driven by safety: N=3000 active, 1500 placebo
  - Rules out ~ 50% increase in adverse event when placebo ≥ 3% (i.e., 4.5% vs. 3%)
  - Subgroup analyses
- Duration: 1 year

Why 1 Year?



Goldstein DJ Int J Obes 1994

Phase 3 Trials: Weight Loss Efficacy Benchmarks

- Mean: The difference in mean weight loss between the drug and placebo groups is at least 5% and statistically significant

- Categorical: The proportion of subjects who lose greater than or equal to 5% of baseline body weight in the active-product group is at least 35%, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant

Xenical (orlistat)

- Approved 1999
- Mean placebo-subtracted weight loss: ~ 3%
- Categorical weight loss (proportion who lost 5%):

Study	Xenical	Placebo	P value
1	36%	21%	0.021
2	55%	27%	<0.001
3	51%	26%	<0.001
4	37%	16%	<0.001
5	43%	22%	<0.001

Phase 3 Trials: Statistical Considerations

- LOCF analysis in the modified ITT population
- Sensitivity analyses
  - e.g., body weight measurements in *all* patients near calendar date when scheduled to complete trial

Phase 3 Trials: Secondary Efficacy Endpoints

- Blood pressure
- Heart rate
- Lipids
- Fasting glucose and insulin
- HbA1c (in patients with Type 2 diabetes)
- Waist circumference
- Adjustment of concomitant medication(s)
- Quality of life

Phase 3 Trials: Safety

- Body composition
- 5HT2 receptor agonists
  - Valvulopathy assessment: echocardiography
- Centrally-acting drugs
  - Neuropsychiatric function, suicidality assessment
  - Abuse liability

Combination Therapy

- Drug-drug interaction studies
- Phase 2: Efficacy and safety of combo vs. components
- Phase 3: Efficacy and safety combo vs. placebo (longer-term)
- Special category: drugs associated with weight gain

Summary: Phase 3 Program

- Size
  - 3000 active / 1500 placebo randomized
- Duration
  - 1 year
- Patient population
  - BMI $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 with co-morbidities
- Efficacy criteria: 5% weight loss
  - Mean
  - Categorical

Example Phase 3 Program: Contrave (Naltrexone/Bupropion)

	Placebo N=1515	Dose 1 (low) N=633	Dose 2 (proposed) N=2545
n (%) completed one year	828 (55%)	322 (51%)	1401 (55%)
Mean age	45 yrs	44 yrs	46 yrs
Female sex	82%	85%	82%
Race/Ethnicity			
White	79%	74%	78%
Black	17%	22%	18%
Hispanic	11%	12%	9%
Asian	1%	1%	1%
Mean BMI	36 kg/m^2	36 kg/m^2	36 kg/m^2
Mean weight	100 kg	99 kg	101 kg
Co-morbidities			
Hypertension	24%	20%	25%
Dyslipidemia	53%	50%	56%
Prior MI	<1%	0	<1%
Diabetes	11%	0	13%

Source: EMDAC meeting on Contrave (Dec 2010); Dr. Eileen Craig's Clinical Presentation

Drug Utilization Trends of Anti-Obesity Products in the Outpatient Setting Y1991 - Y2011

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OUTLINE

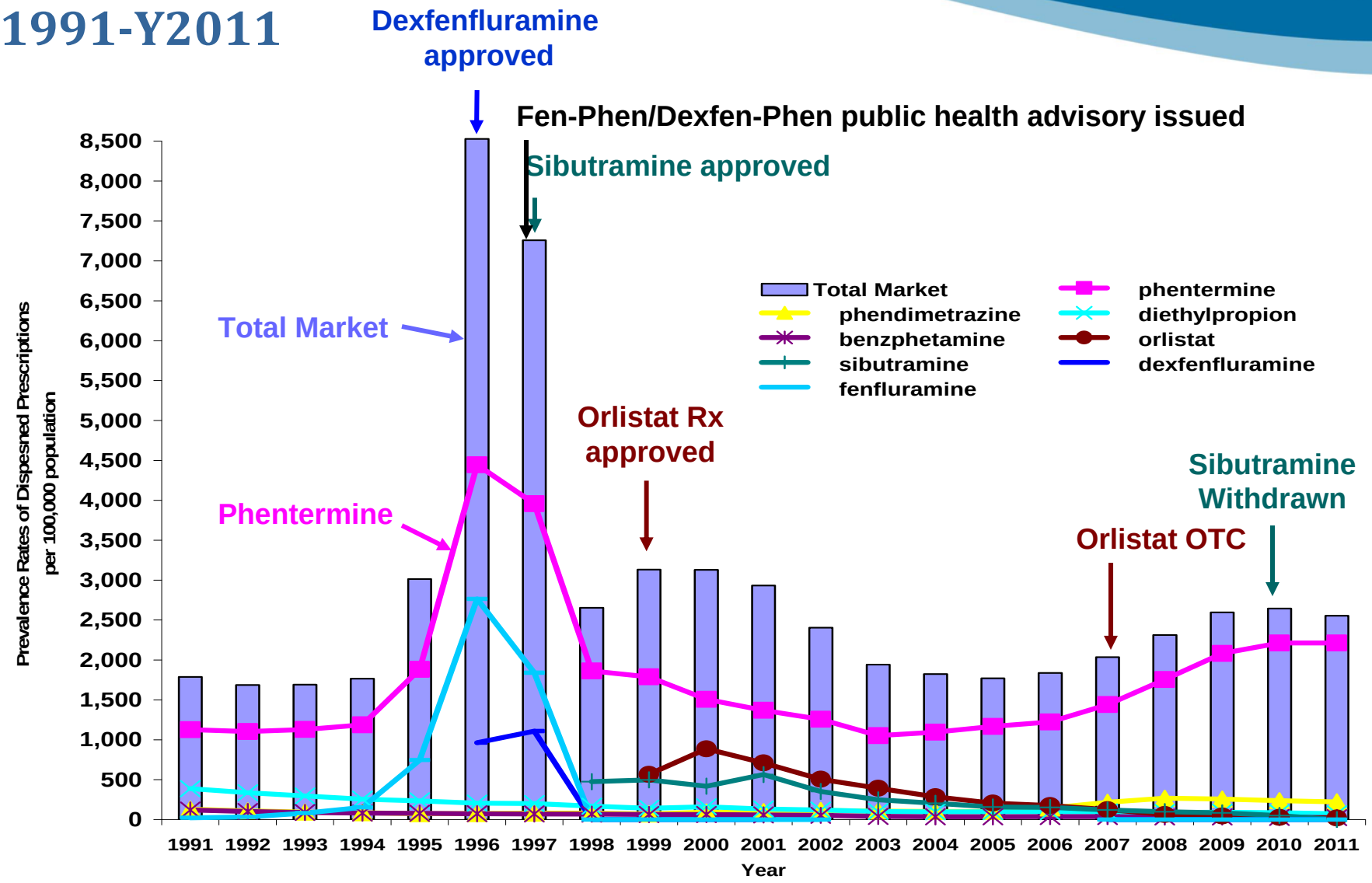
- Anti-obesity prescription utilization trends, Y1991-Y2011
- Payment methods and Prescriber specialties
- BMI, Y1991-Y2011 cumulative
- Patient demographics - age and sex, Y2008-Y2011 cumulative
- Concurrency analysis, Y2008-Y2011 cumulative
  - Concurrent Drugs
  - Concurrent Diagnoses
- Limitations
- Summary

Outpatient Utilization Data Sources

- The IMS Health, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions.
- Source: The Vector One® database
  - Over 1.9 billion prescription claims per year, representing over 158 million unique patients.
  - Payers including Commercial plans, Medicare Part D plans, Cash and Medicaid claims

Anti-Obesity Prescription Utilization Trends, Y1991-Y2011

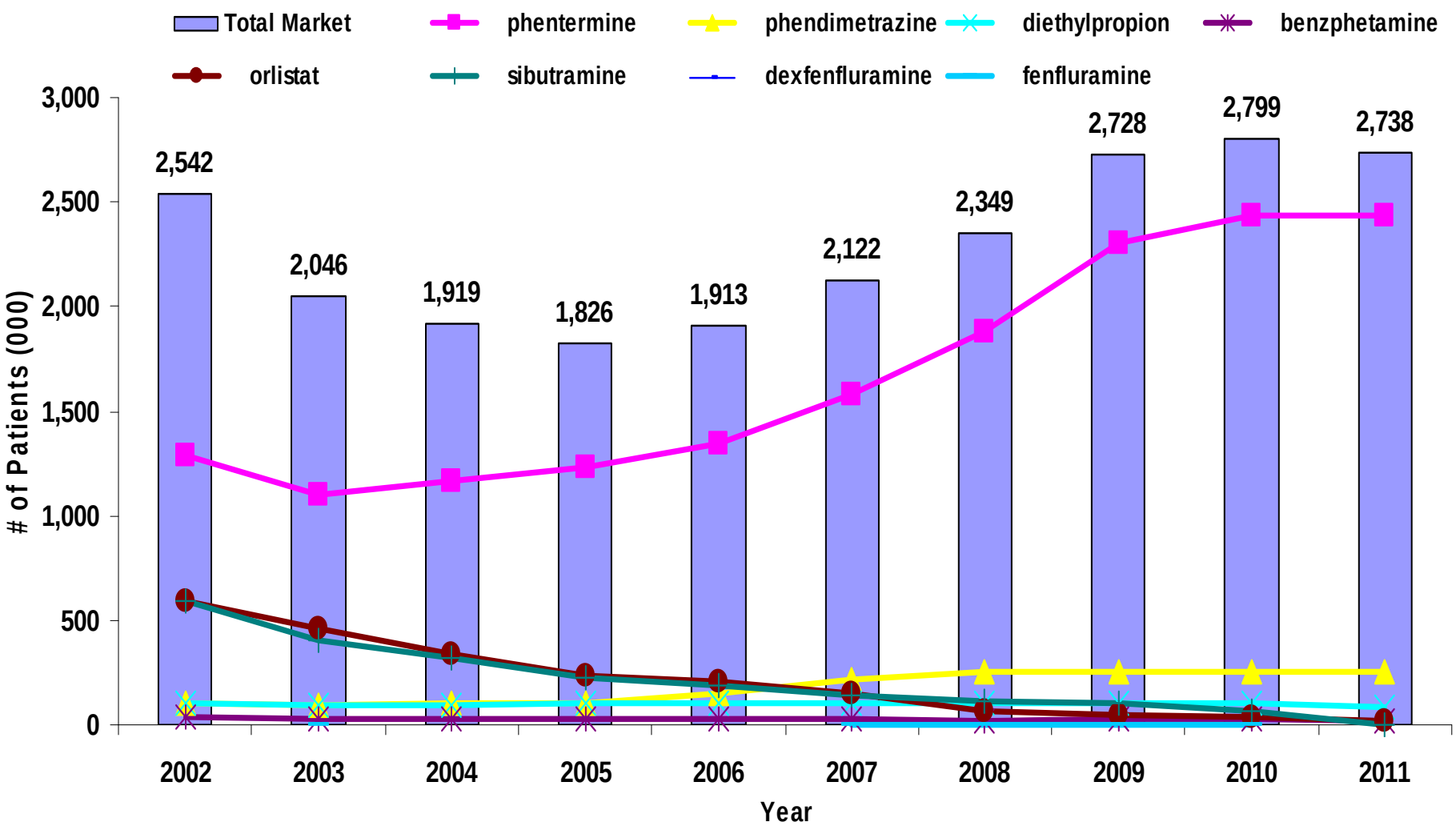
Outpatient Prescription Utilization, Y1991-Y2011



IMS, Vector One®: National (VONA). Data extracted 1-24-12. Files:VONA 2012-153 select Anti-obesity products 1991-2011 (2).xls

Source: U.S. Census Bureau, Population Division Annual Estimates of the Resident Population by Sex and Selected Age Groups for the United States: April 1, 1990 to July 1, 1999, and April 1, 2000 to July 1, 2009 (NC-EST2009-02), and April 1, 2010 to July 1, 2011 (NST-EST2011-01). Accessed 3-15-12

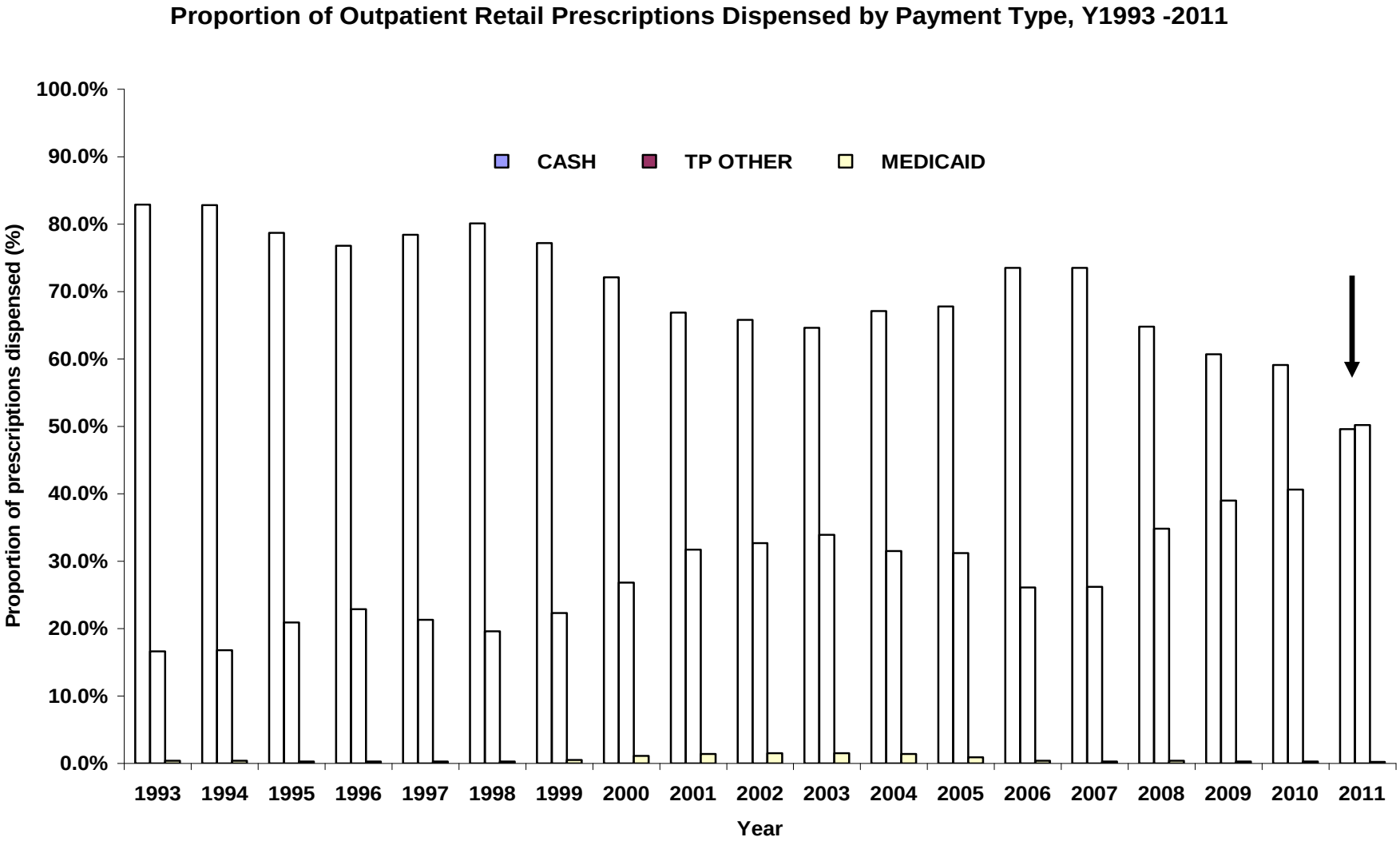
Patient Counts, Y2002-Y2011



IMS, Vector One®: Total Patient Tracker. Data extracted 3-22-12. Files:TPT_2011-153_anti-obesity products_2002-2011_3-22-12 WORKING file. xls

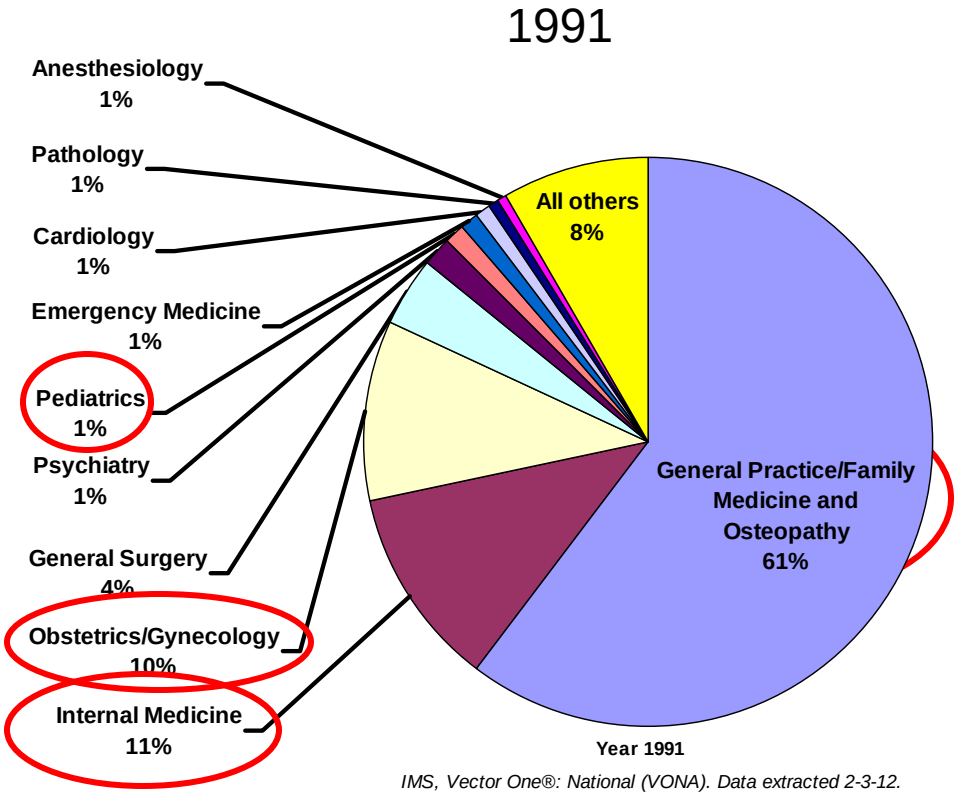
Payment Methods and Prescriber Specialties

Outpatient Prescription Utilization by Payment Method, Y1993-Y2011



IMS, Vector One®: National (VONA). Data extracted 1-24-12.
Files: VONA_2012-153_select_Anti-obesity_products_by_payor_1991-2011(1).xls

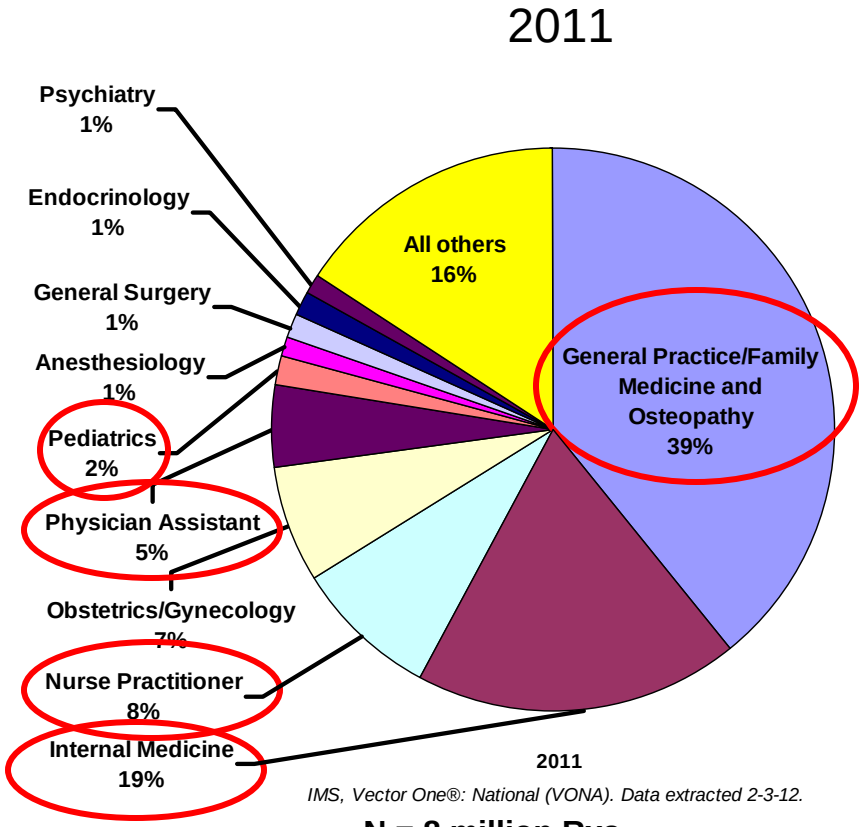
Outpatient Anti-Obesity Drug Utilization: Prescriptions by Specialty, Y1991 and Y2011



IMS, Vector One®: National (VONA). Data extracted 2-3-12.

N = 4.5 million Rxs

(1,789 Rxs/100,000 US pop)



IMS, Vector One®: National (VONA). Data extracted 2-3-12.

N = 8 million Rxs

(2,554 Rxs/100,000 US pop)

Products included:
benzphetamine, dexfenfluramine, diethylpropion, fenfluramine, phendimetrazine, phentermine, orlistat, sibutramine

Outpatient Utilization Data Sources

- SDI Physician Drug and Diagnosis Audit (PDDA)
  - Monthly survey that monitors disease states and physician intended prescribing habits on a national-level
  - 3,200 panelists, 30 specialties
  - Includes diagnoses, patients characteristics, and treatment patterns

Issuance of Anti-Obesity Agent Intended Prescription or Sample by Patient Body Mass Index (BMI), Cumulative Y1991-Y2011

Physician Reports of the Number Of Drug Ocurrences for Anti-Obesity Products and associated Patient Body Mass Index (BMI)

	01/1991-12/2011 Occur (000)	95% CI (000)	01/1991-12/2011 Share% (000)
Total Market	**84,945**	(83,568, 86,322)	*100.0%*
BMI 0-18	**112**	(62, 162)	*0.1%*
BMI 19-24	**3,553**	(3,271, 3,835)	*4.2%*
BMI 25-29	**13,938**	(13,380, 14,495)	*16.4%*
BMI 30+	**50,326**	(49,266, 51,386)	*59.3%*
BMI UNSPEC	**17,017**	(16,401, 17,633)	*20.0%*

SDI, Physician Drug and Diagnosis Audit. File: PDDA 2012-153 obesity prods BMI drug iss 1991-2011 2-21-12.xls

Products include: benzphetamine, dexfenfluramine, diethylpropion, fenfluramine, phendimetrazine, phentermine, orlistat, sibutramine

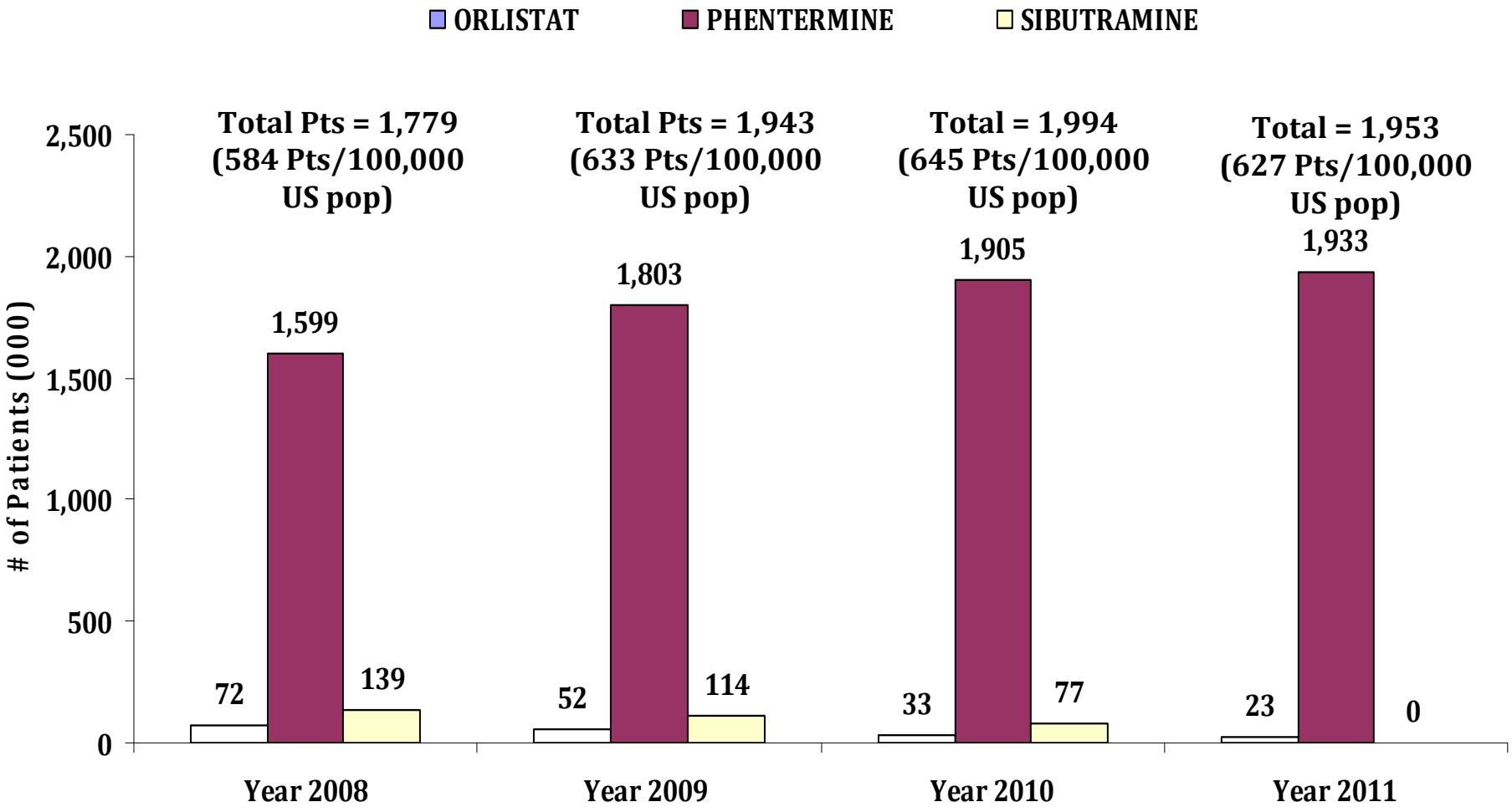
Underweight BMI: < 18.5
Normal weight BMI:18.5 - 24.9
Overweight BMI:25 - 29.9
Obesity BMI: 30+

Patient Demographics and Concurrency Analysis, Y2008-Y2011 Annually and Cumulative

Data Source:
Patient Demographics and Concurrency Analyses

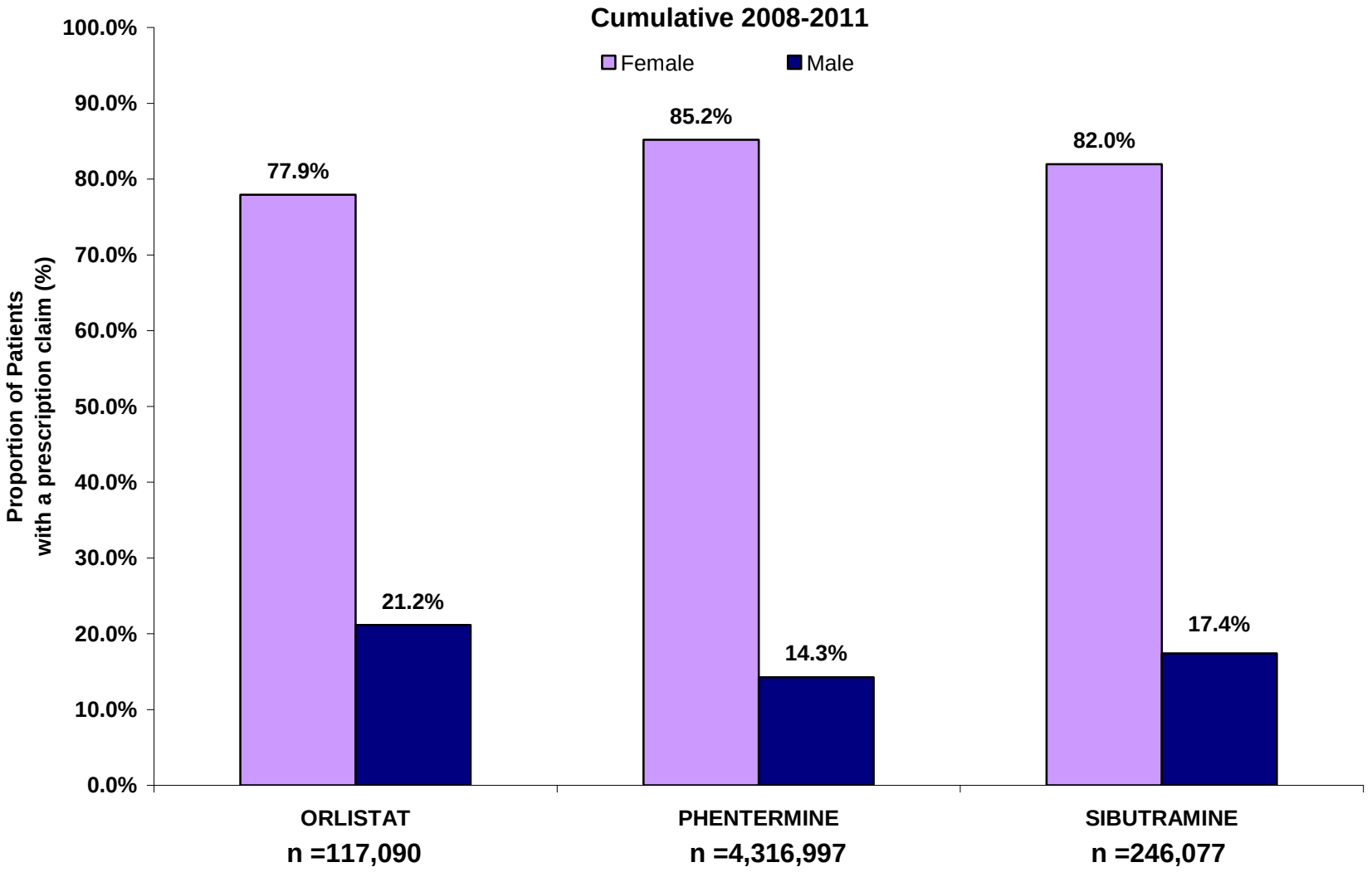
- ***Wolters Kluwer SOURCE Lx® database***
  - Longitudinal patient data source
  - U.S. adjudicated medical and prescription claims
    - Commercial plans, Medicare Part D plans, Cash and Medicaid claims.
    - 4.8 billion paid, non-reversed prescriptions claims linked to over 172 million unique prescription patients
    - ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis

Outpatient Utilization: Number of Patient with Claims (in thousands)



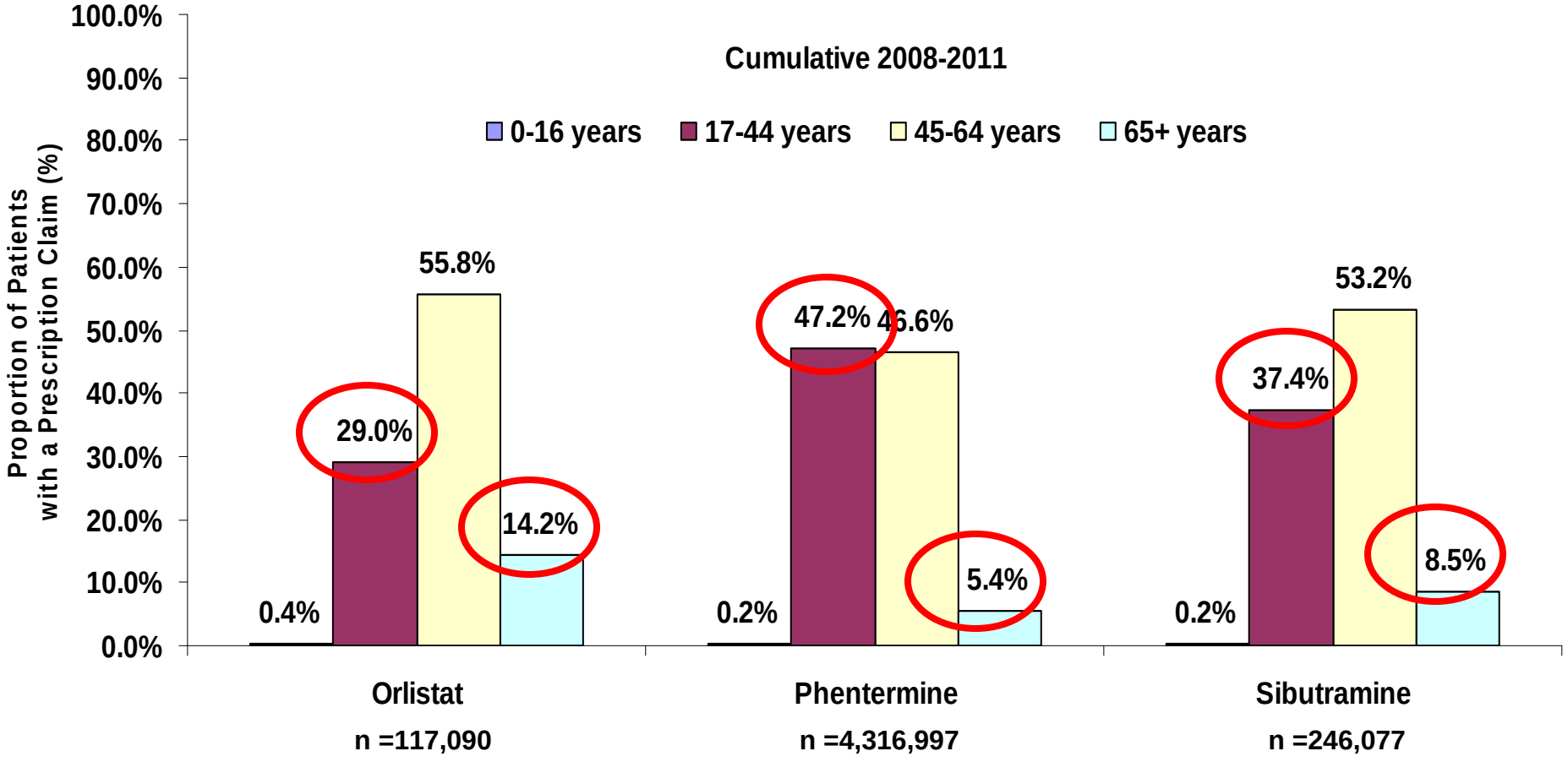
Wolters Kluwer Health's Source® Lx. CPA tool. Years 2008-2011. Extracted February 2012.

Outpatient Utilization: Patient Demographics - Sex



Wolters Kluwer Health's Source® Lx. CPA tool. Years 2008-2011. Extracted March 2012

Outpatient Utilization: Patient Demographics - Age



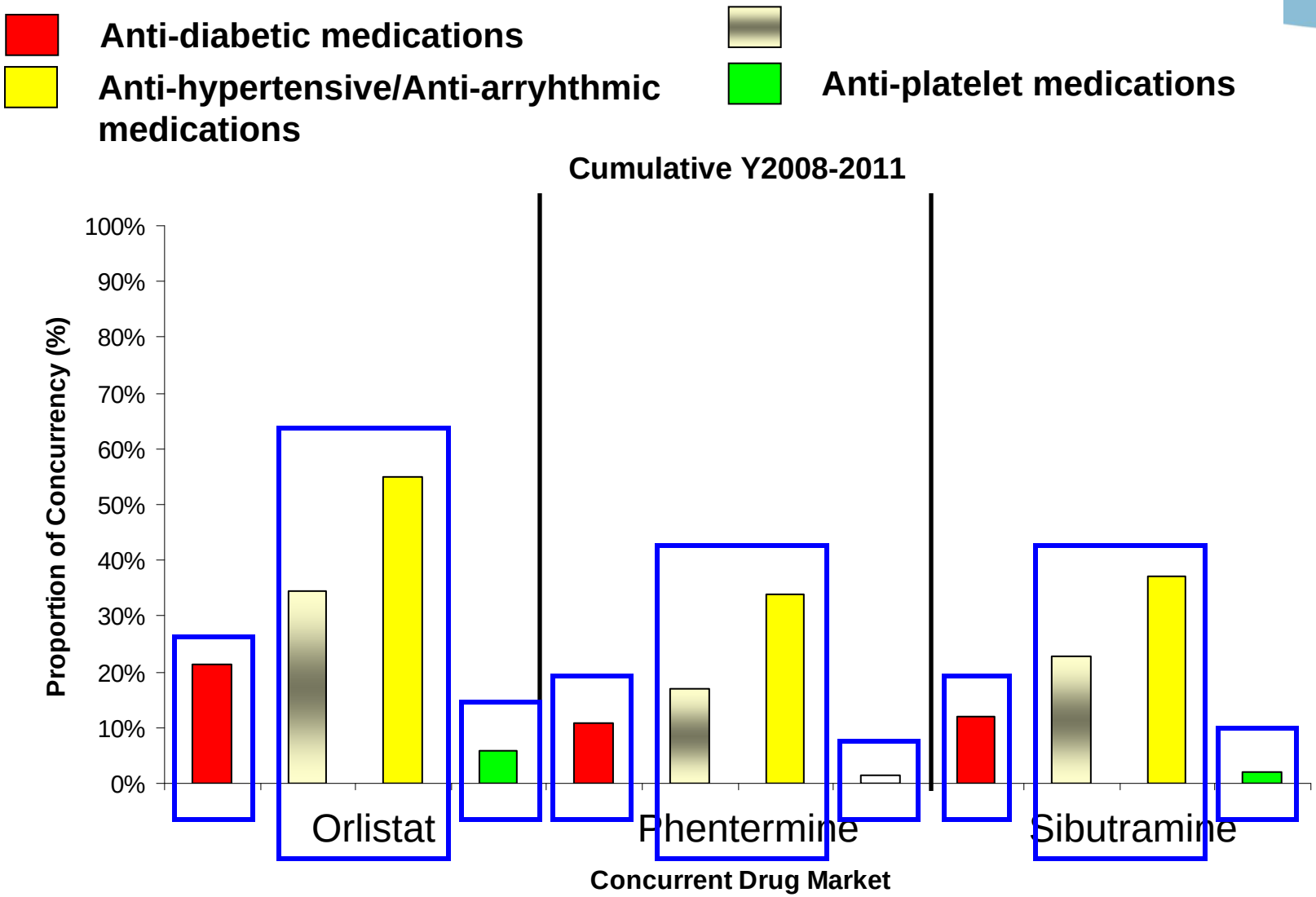
Wolters Kluwer Health's Source® Lx. CPA tool. Years 2008-2011. Extracted February 2012.

Concurrency Analyses, Y2008-Y2011 Cumulative

Concurrency Analyses

- Concurrent drugs by overlapping days supply for dispensed prescriptions for the following drug groups:
  - **Anti-hypertensive and Anti-arrhythmic medications**
  - **Anti-platelet medications**
  - **Anti-diabetic medications**
  - **Lipid disorder medications**
- Concurrent diagnoses using ICD-9 codes for one or more of the following ICD-9 groups:
  - **Diabetes**
  - **Lipid disorders**
  - **Stroke**
  - **Hypertension**
  - **Ischemic heart disease**
  - **Congestive heart failure**
  - **Arrhythmia**

Analysis of Anti-Obesity Agent Claim Concurrent with a Drug in Selected Markets

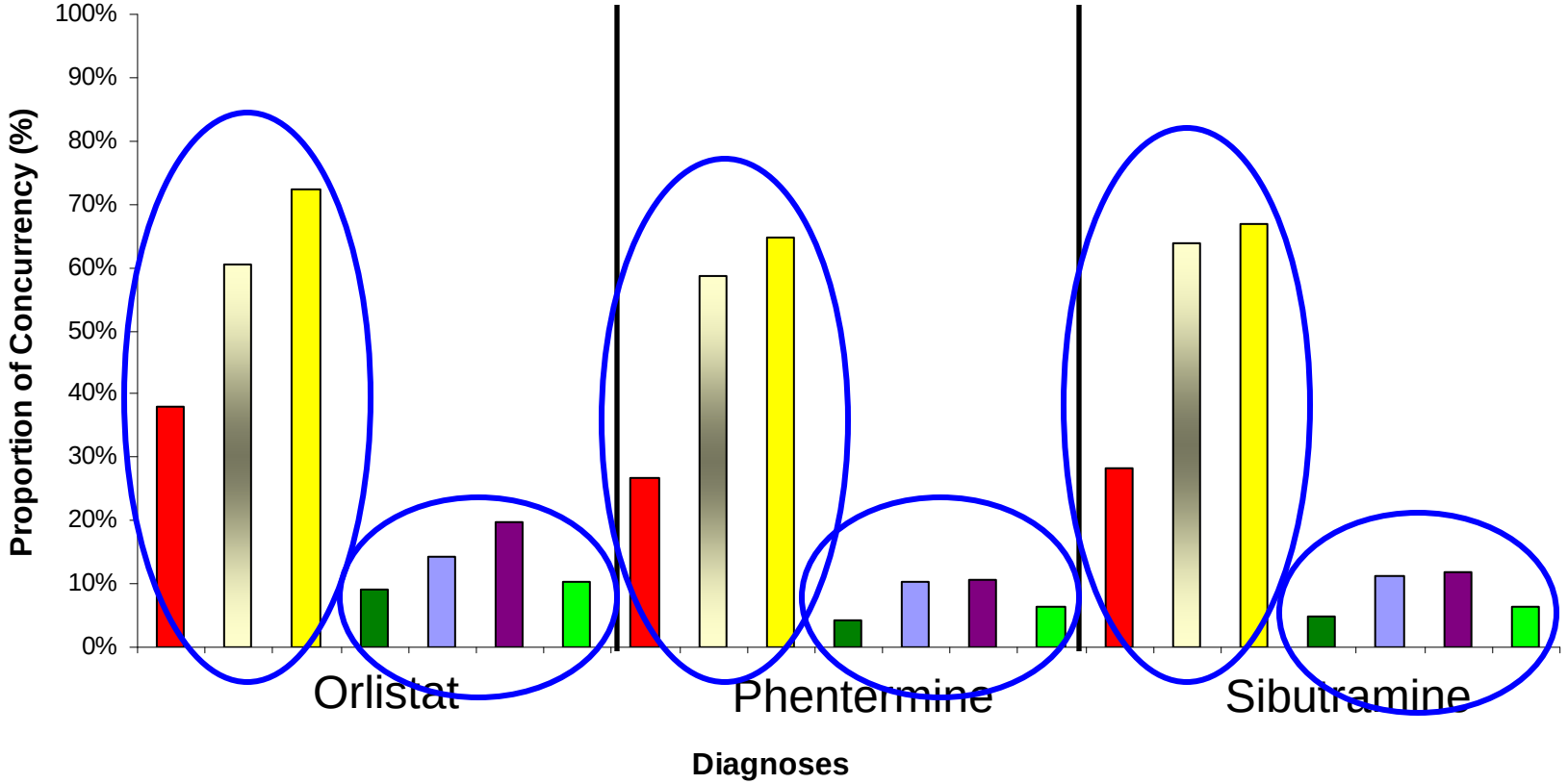


Wolters Kluwer Health's Source® Lx. CPA tool. Years 2008-2011. Extracted February 2012.

Analysis of Anti-Obesity Agent Claim with Selected Concurrent Diagnoses

Diabetes
Hypertension
Arrhythmia
Stroke
Lipid Disorder
Congestive HF
Ischemic HD

Cumulative Y2008-2011



Wolters Kluwer Health's Source® Lx. CPA tool. Years 2008-2011. Extracted February 2012.

Limitations

- Concurrent drug analysis:
  - Medication use was used a proxy for disease states
  - Indications for use not known
  - Levels of other uses or off-label use were not available
- Concurrent diagnosis analysis:
  - ~ 34% of patients with an anti-obesity prescription claim had a medical claim with one or more selected diagnoses
  - Documented diagnoses may be "rule out" diagnoses
- Disease severity was not delineated with medication usage
- No statistical tests were performed to determine statistically significant changes over time

Overall Summary

- Prevalence of dispensed anti-obesity prescriptions per U.S. population increased by 43% from Y1991-Y2011
- Approximately 2.7 million patients received an anti-obesity medication in year 2011
- Phentermine had the market lead
- Females accounted for the majority of use
- Orlistat: older population; Phentermine: younger population
- Prescribed by primary care providers
- Most drug use mentions for anti-obesity agents were associated with overweight and obese patients

Summary

	Diabetes	Lipid disorder	Hypertension	Arryhthmia	Ischemic Heart Disease	Congestive Heart Failure	Stroke	Antiplatelet Medications
Concurrent Drug	11% - 21%	17% - 34%	34% - 55%					2% - 6%
Concurrent Diagnosis	27% - 38%	59% - 64%	65% - 72%	10% - 14%	11% - 20%	4% - 9%	6% - 10%	

- **High to Moderate rates**:
  - Diabetes diagnosis
  - Lipid disorder diagnosis/medications
  - Hypertension diagnoses
  - Anti-hypertensive/Anti-arrhythmic medications
- **Moderate to Low rates:**
  - Arrhythmia diagnoses
  - Ischemic heart disease diagnoses
  - CHF diagnoses
  - Stroke diagnoses
  - Diabetes medications and anti-platelet medications

Duration of Use – Anti-Obesity Drugs

Endocrinologic and Metabolic Drugs
Advisory Committee Meeting

March 28-29, 2012

Christian Hampp, Ph.D.

Elizabeth Kang, MPH

Division of Epidemiology I

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Recommended Duration of Use

	Anti-Obesity Drugs	Comparator Drugs
Recommended for **short-term** use ("a few weeks")	phentermine	
No limitation in duration	orlistat sibutramine	captopril repaglinide

- Comparator drugs: selected to demonstrate ability to detect long-term use in the database, when present
- Captopril and repaglinide: similar dosing schedule and total amount of utilization in study period

Methods - Database

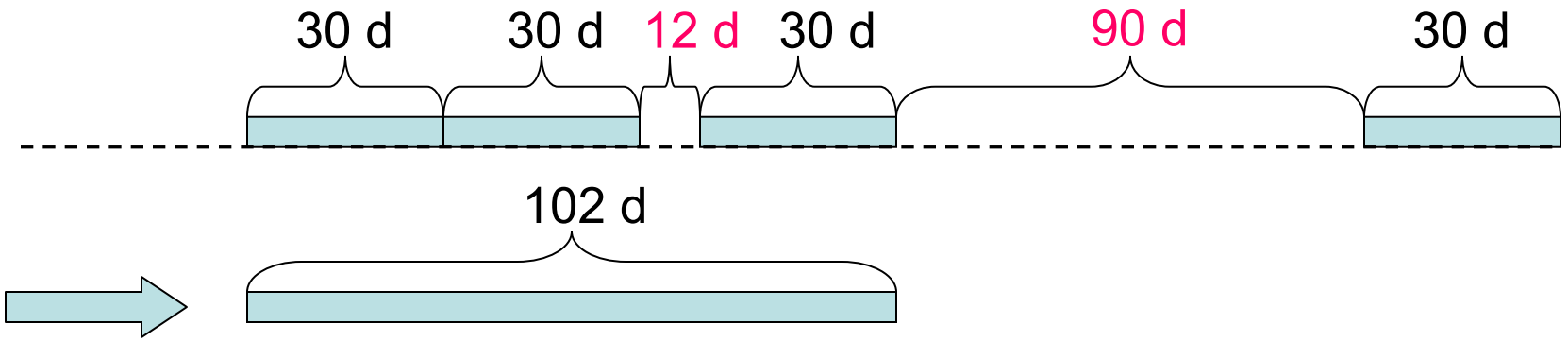
Wolters Kluwer Pharma Solutions Source® Lx database, 2002-2011:

- Prescription claims from commercial plans, Medicare Part D plans, cash, and Medicaid claims
- Represents 172 million unique patients, 27,000 pharmacies (2011)
- Not nationally projected

Exclusions:

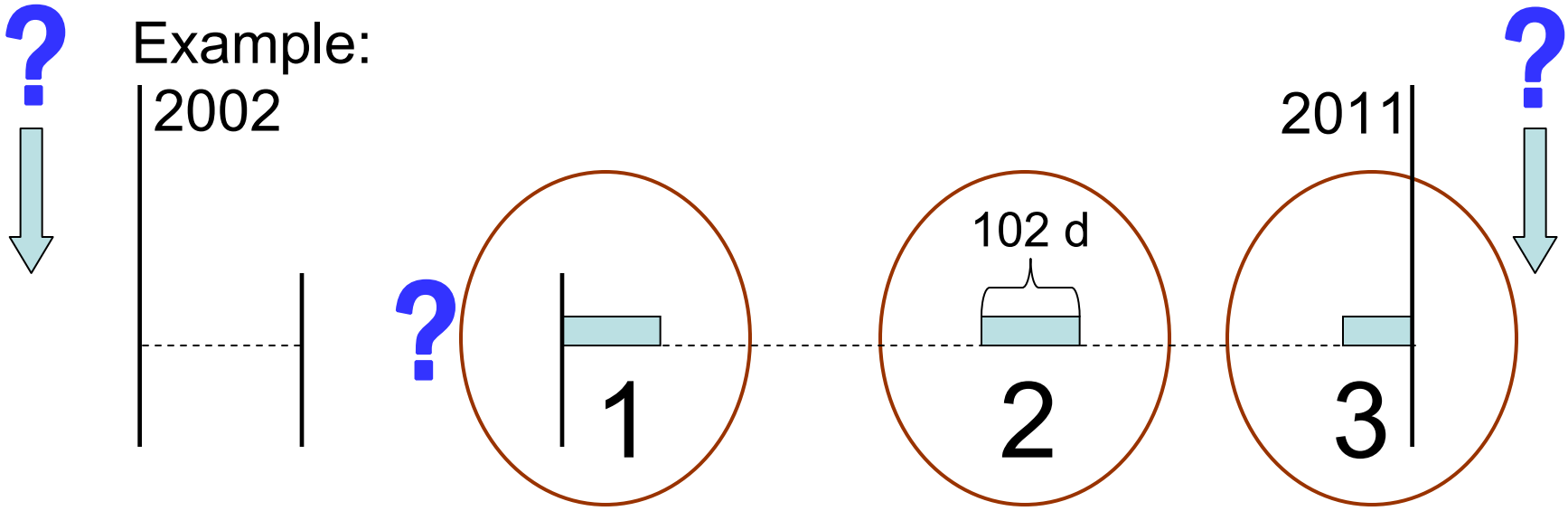
- Removed entire patient record (7.2% of subjects) with:
  - Unknown gender (1.7%)
  - Unknown year of birth (1.4%)
  - Duplicate claims for drug of interest (5.0%)
  - Dispensing with 0 (0.1%) or >90 days of supply (0.8%)

Duration of Use: Episodes



- Episode: string of dispensings not interrupted by gaps in supply of >15 days between two dispensings
- Fully observed episode: dispensing for **any** drug 180 days before and after episode
- Duration of episode =
  last day of supply of last dispensing – fill date of first dispensing +1
- Sensitivity analysis: gap ≤ 30 days, stockpiling considered

What We Counted



- Duration of use: only fully observed episodes (range: 64%, phentermine to 79%, repaglinide)
- Number of episodes: all available episodes

Results - Demographics

	orlistat	phentermine	sibutramine	captopril	repaglinide
Number of patients (x1000)	233	1,363	234	604	281
% female	77.8	85.5	81.2	56.5	52.2
Mean age at 1st Rx (years)	47	41	44	63	64

Results – Dispensings

	orlistat	phentermine	sibutramine	captopril	repaglinide
Mean disp. per pt	3.4	3.6	3.0	9.5	7.9
Median disp. per pt	2	2	2	4	3
Mode days of supply per disp. (%)	30 (77%)	30 (87%)	30 (90%)	30 (83%)	30 (76%)
Source (%)					
Retail	95	99	97	88	90
Mail order	3	0.4	2	4	7
Payment type (%)					
Cash	13	45	15	4	2
Commercial Ins.	70	47	81	68	67
Medicaid	10	1	2	9	10
Medicare	2	1	1	16	18

Number of Episodes

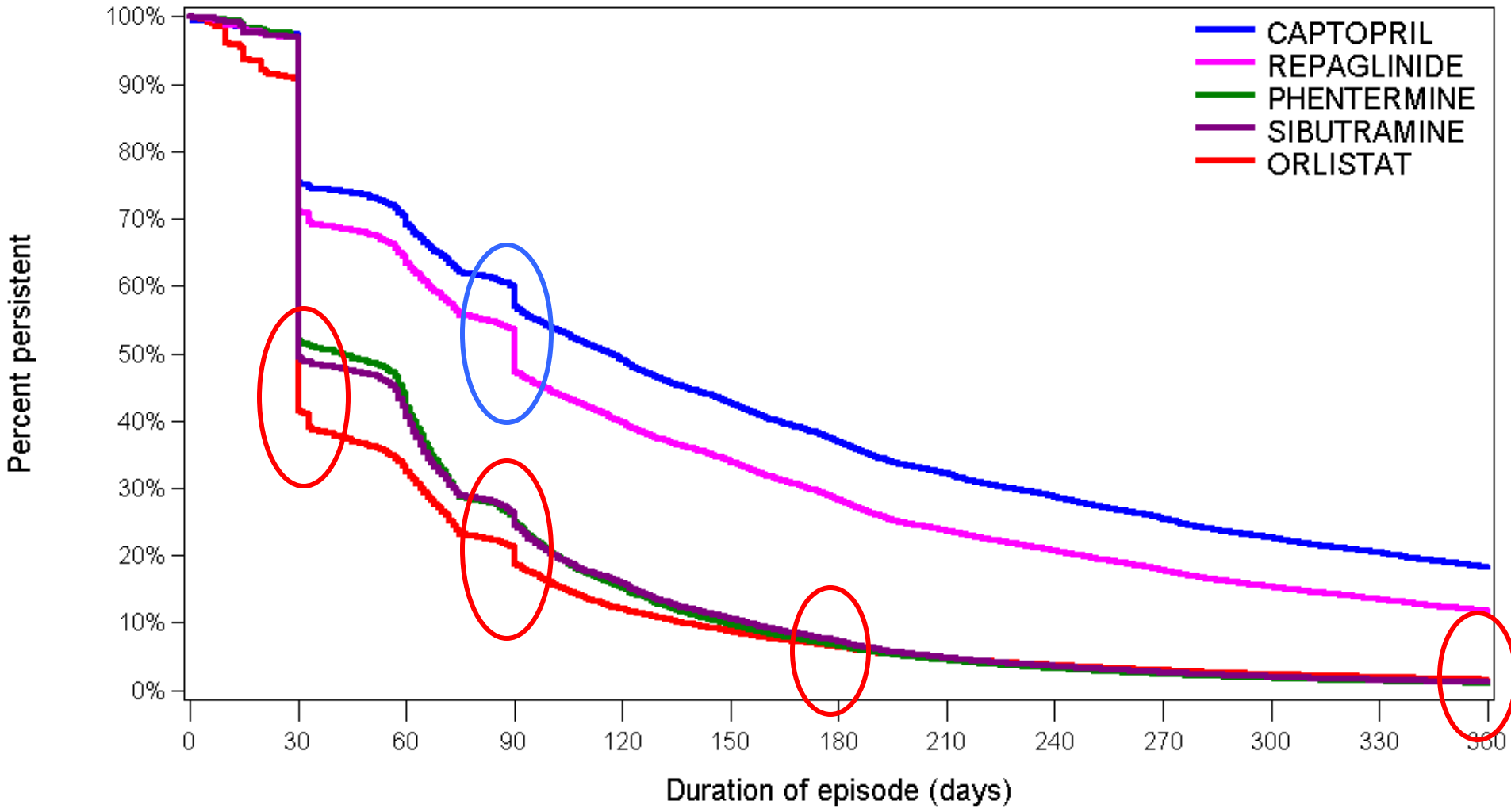
	orlistat	phentermine	sibutramine	captopril	repaglinide
% with one episode	61	55	68	48	47
Mean # episodes	2.1	2.1	1.7	2.9	3.0
Median # episodes	1	1	1	2	2
Upper quartile	2	2	2	3	3

Number of Episodes

Sensitivity analysis: gaps ≤ 30 days, stockpiling

	orlistat		phentermine		sibutramine		captopril		repaglinide	
% with one episode	61	68	55	61	68	74	48	58	47	56
Mean # episodes	2.1	1.7	2.1	1.8	1.7	1.4	2.9	2.1	3.0	2.2
Median # episodes	1	1	1	1	1	1	2	1	2	1
Upper quartile	2	2	2	2	2	2	3	2	3	2

Duration of Longest Episode



Duration of Longest Episode

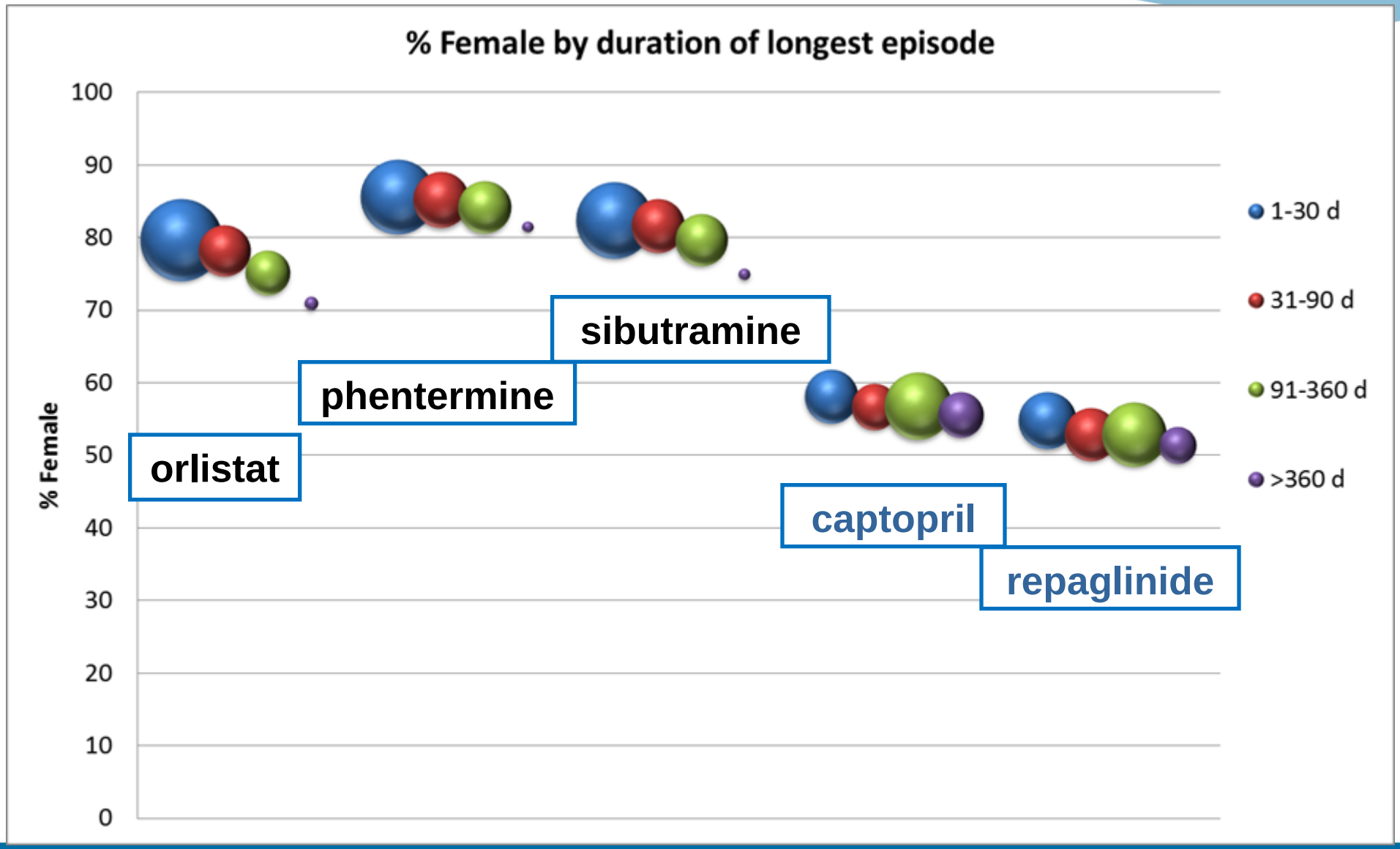
Duration	orlistat	phentermine	sibutramine	captopril	repaglinide
Mean (days)	66	73	73	219	164
Median (days)	30	42	30	117	90
1-30 d (%)	58	48	51	25	29
31-90 d (%)	23	27	25	19	24
91-360 d (%)	17	24	23	39	36
>360 d (%)	2	1	1	18	12

Duration of Longest Episode

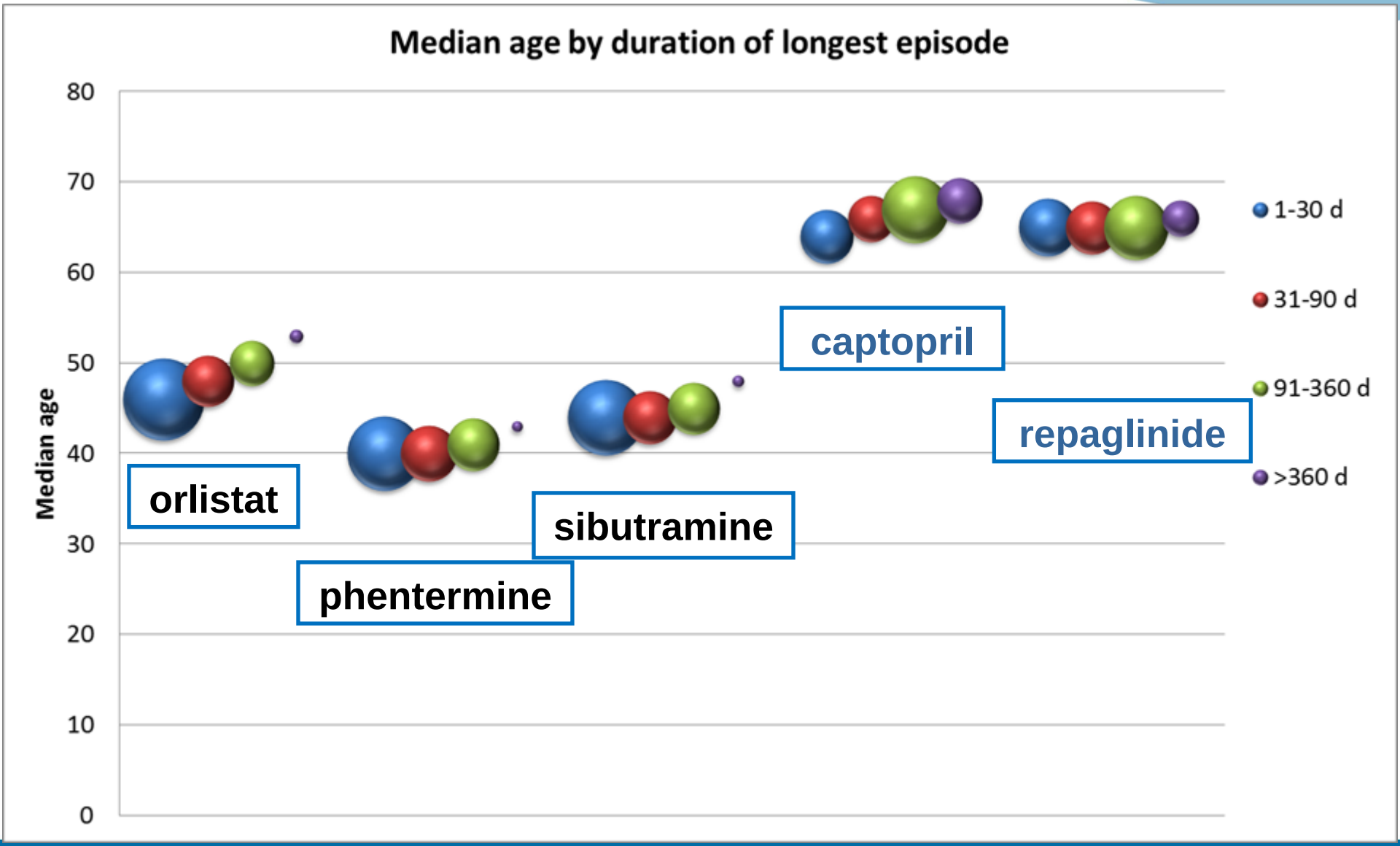
Sensitivity analysis: gaps ≤ 30 days, stockpiling

Duration	orlistat		phentermine		sibutramine		captopril		repaglinide	
Mean (days)	66	88	73	91	73	89	219	280	164	218
Median (days)	30	30	42	60	30	60	117	152	90	112
1-30 d (%)	58	52	48	43	51	47	25	22	29	26
31-90 d (%)	23	22	27	25	25	23	19	15	24	20
91-360 d (%)	17	23	24	30	23	28	39	38	36	35
>360 d (%)	2	4	1	2	1	2	18	24	12	18

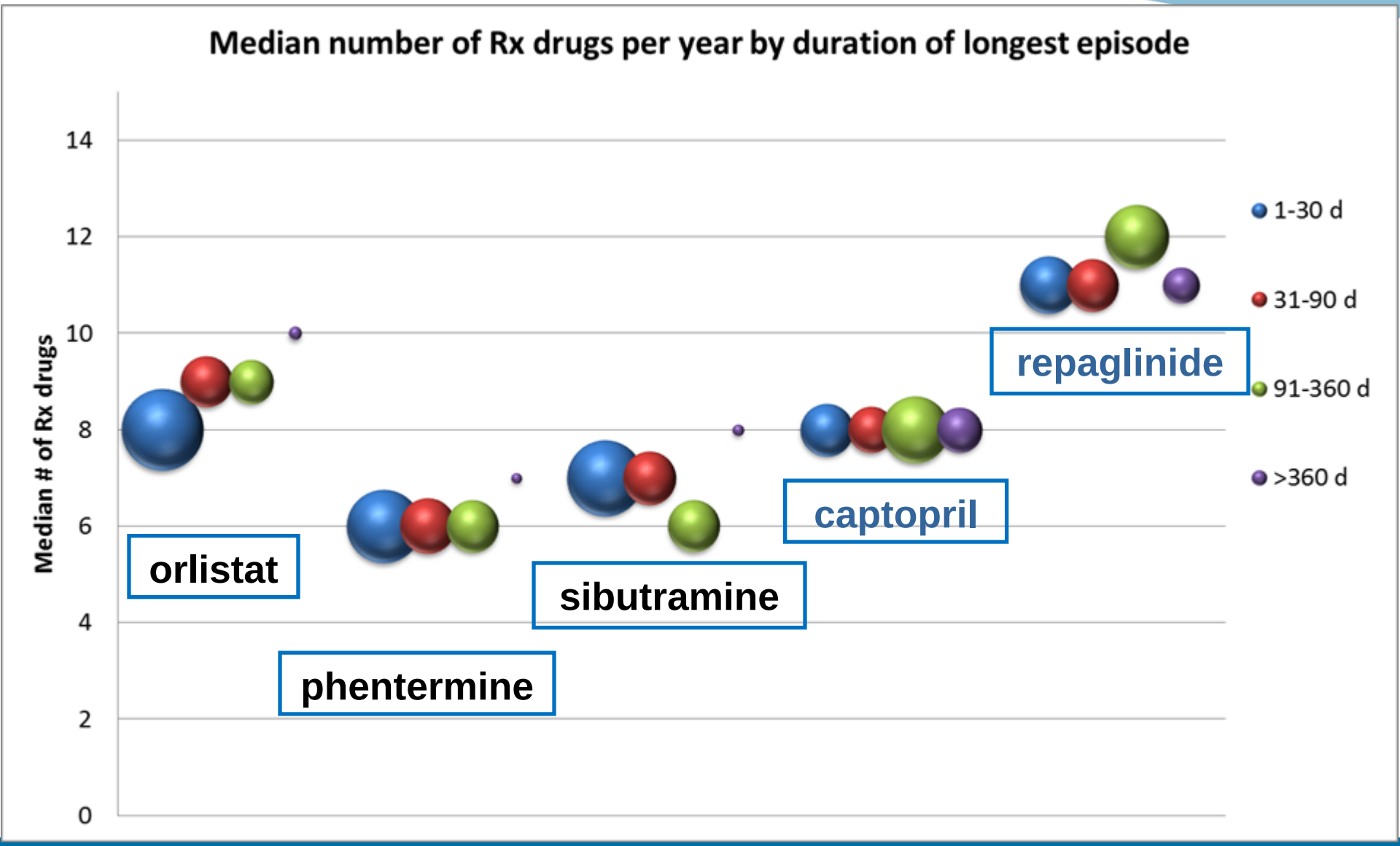
Proportion Female by Duration of Longest Episode



Median Age by Duration of Longest Episode



Median # of Rx Drugs per Year by Duration of Longest Episode



Limitations

- Only counted prescriptions dispensed in contributing pharmacies
- Duration of use:
  - Information only on days of continuous supply, not actual use
  - Especially relevant for episodes with only one dispensing
- Number of episodes:
  - Only snapshot, underestimation of lifetime use

Summary

Duration of anti-obesity drug use:

- Mostly short, few episodes
- Longest episode:
  - 30 days or shorter in about half of patients
  - Longer than 90 days only in about 25% of patients
  - 25-32% use phentermine longer than 90 days, despite limitation in label (“a few weeks”)
- Longer duration of use associated with fewer females, somewhat older age, no clear association with number of other Rx drugs

Statistical Considerations in the Design of Cardiovascular Safety Trials to Rule Out a Pre-specified Cardiovascular Risk

Implications in Trials to Treat Obesity

March 28, 2012

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Outline

- Background
- Trial Objectives
- Trial Size Implications
- Beyond Sample Size; Statistical Issues
- Conclusions

Event-Driven Trials

- Event-driven trials are a special case of information-based designs
  - The statistical information is fixed in advance rather than using the number of subjects to determine the trial size
  - Statistical information = number of events (*D*)
- The trial continues until *D* events are observed
- To observe *D* events, *N* subjects are followed for *t* years (i.e. *N*t* patient years)
  - *N*t* patient years can be anticipated, but actual value will depend on rate of events

Defining the Event

- In trials to assess cardiovascular safety, what is the primary safety endpoint?
- Commonly this is a composite endpoint, but components of the composite are debatable.
  - Major Adverse Cardiovascular Events (**MACE**) = cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke
  - **MACE+** = MACE plus other components such as hospitalization for unstable angina and revascularizations
- Definition of primary composite endpoint has implications

Event Definition Implications

- Event rate of MACE+ ≥ event rate of MACE
  - Fewer person years needed to observe *D* events for a fixed amount of risk to be ruled out
- If the additional components of MACE+ have the potential to add noise to event rates this can impact the trial results
  - The noise can favor active treatment in a non-excessive risk comparison
  - The noise can disfavor active treatment in a risk improvement comparison
- While trials are powered based upon the composite endpoint, individual components need to be assessed to ensure results are not driven by a single component

Measuring Association

- Association of the active and control can be expressed using various statistical measures
  - Risk Difference (RD) is the absolute difference in the probability of an event between the active and the control
    - $RD = r_A - r_C$
  - Relative Risk (RR) is the relative difference in the probability of an event between the active and the control
    - $RR = r_A / r_C$
  - Hazard Ratio ($H_z R$) is a ratio of the hazards of active and control
    - $H_z R = h_A(t)/h_C(t)$

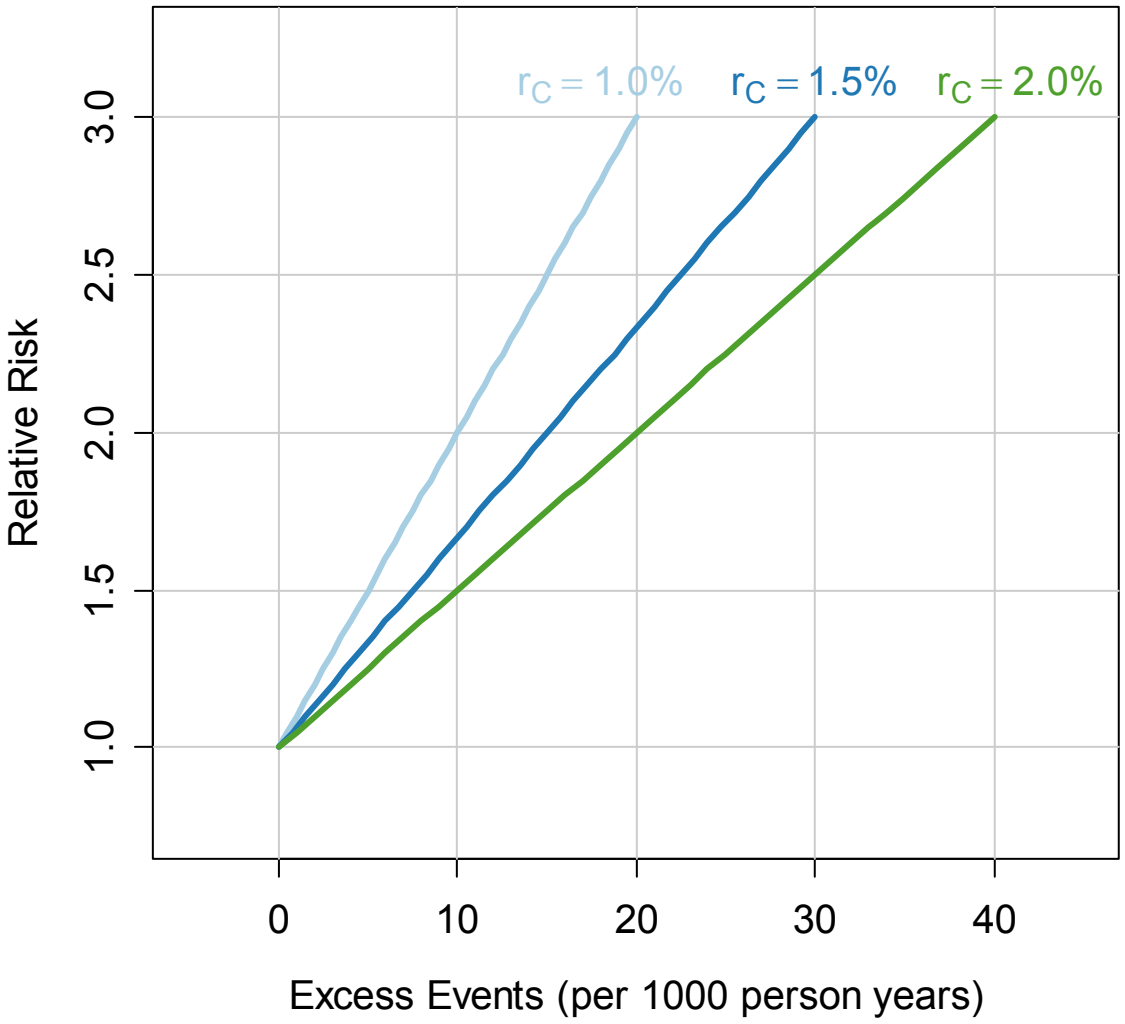
Absolute Risk or Relative Risk

- What is clinically more meaningful, RD or RR?

Illustration

	Relative Risk (RR)		
	1.3	**1.8**	**2.0**
Event Rate (r_c) = 10/1000 (1.0%)			
*RD = (RR-1)*1.0%*	.30%	.80%	1.0%
Event Rate (r_c) = 15/1000 (1.5%)			
*RD = (RR-1)*1.5%*	.45%	1.2%	1.5%

Absolute Risk or Relative Risk



Rule out 10 EE

r_C	RR	
1.0%	2.0	←
1.5%	1.67	
2.0%	1.5	←

Absolute Risk or Relative Risk

- If the annual event rate turns out to be ***higher*** than the planned event rate then the selected relative risk margin ***will not*** preserve the amount of excess risk (absolute risk difference) to exclude.
  - Planned rate = 1.0% implies ruling out a RD of 3.0/1000 excess events
  - Actual rate = 1.5% implies ruling out a RD of 4.5/1000 excess events
- If the annual event rate turns out to be ***lower*** than the planned event rate then the selected relative risk margin ***will*** rule out a smaller amount of excess risk (absolute risk difference) to be excluded.
  - Planned rate = 1.5% implies ruling out a RD of 4.5/1000 excess events
  - Actual rate = 1.0% implies ruling out a RD of 3.0/1000 excess events

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Trial Hypotheses

- **Risk Improvement**: CV risk of active is statistically better than the CV risk of control (similar to a *superiority* comparison)
  - H_0: $\rho \geq 1$
  - H_1: $\rho < 1$
- **Non-Excessive Risk**: CV risk of active is statistically no worse than CV risk of control by some value (define as risk margin; notated as Δ^*)
  - H_0: $\rho \geq \Delta^*$
  - H_1: $\rho < \Delta^*$

Illustration of Risk Improvement

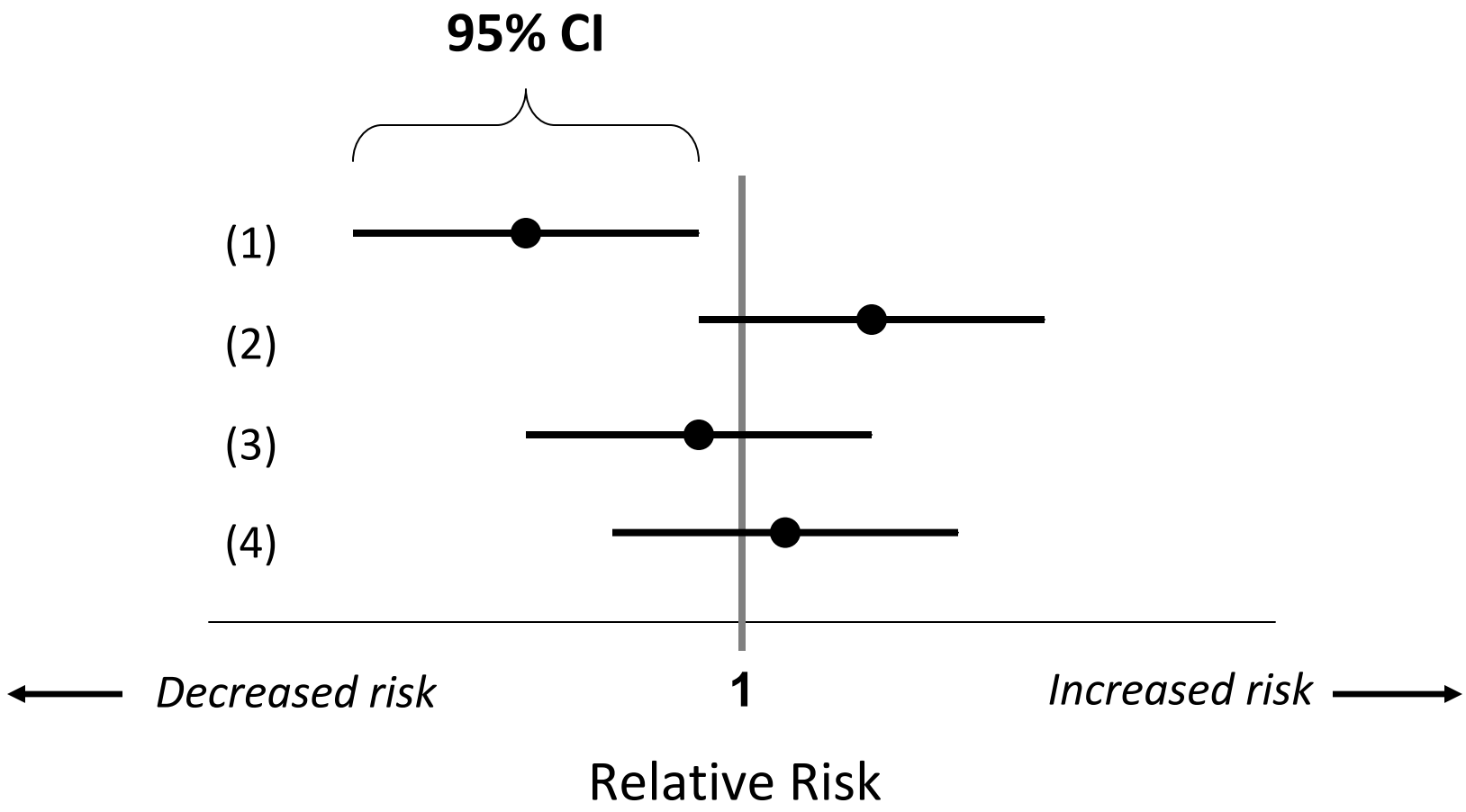
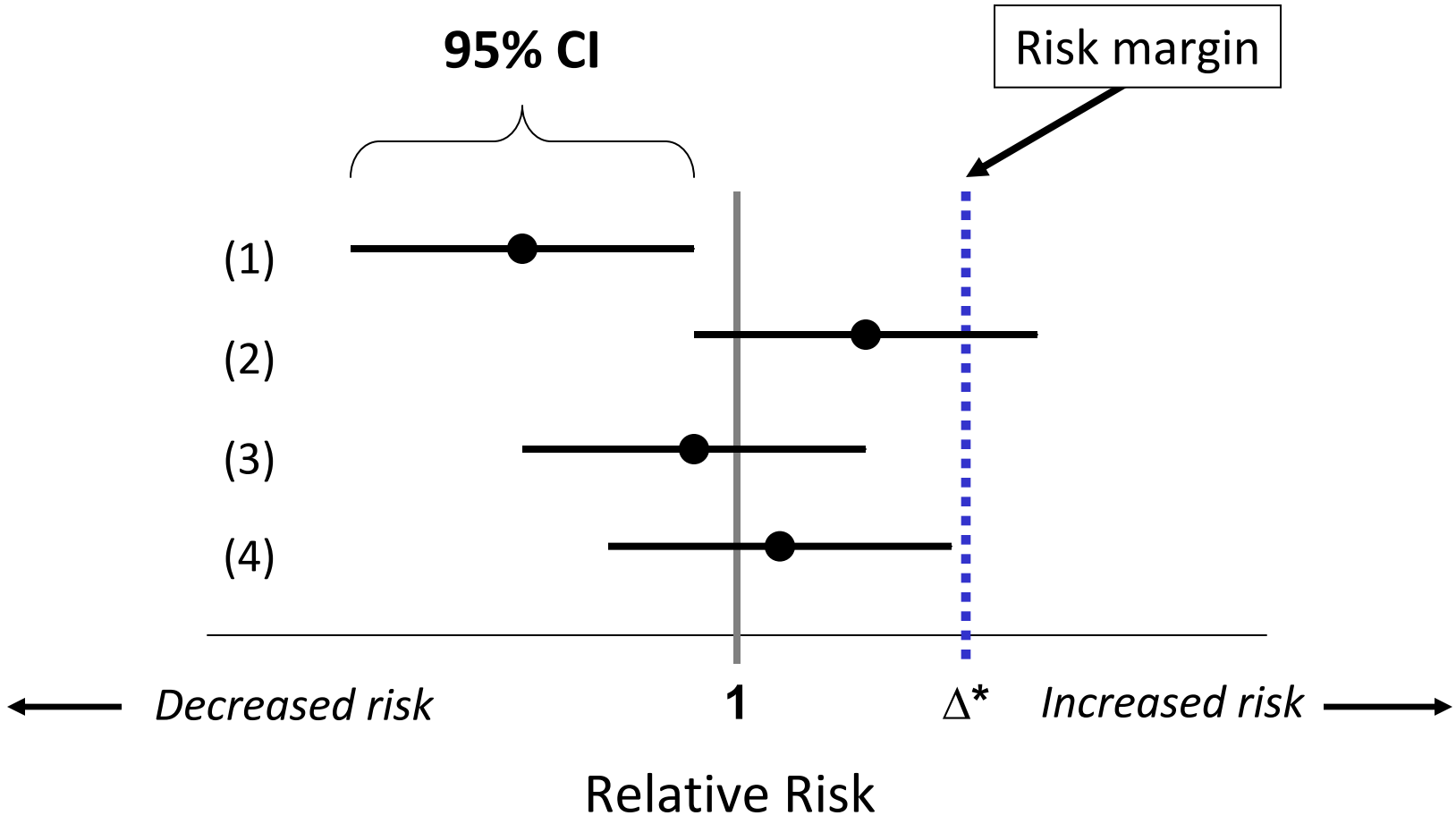


Illustration of Non-Excessive Risk



Notes on Trial Hypotheses

- Risk Improvement can be thought of as a special case of non-excessive risk where the risk margin equals unity (i.e. $\Delta^* = 1$)
- Paradigm of non-excessive risk is similar in constructs as non-inferiority for efficacy but with some key differences

	Efficacy	**Safety**
Control	Active	Placebo/Background
Margin Selection	• Presumed effect size of active control •Preservation of some amount of effect size	• Feasibility • Clinical judgment • Others

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Number of Events Calculation

- Recall: Event-driven trials are information based and designed to observe a certain number of events (*D*)
- Formula

$$D = 4\left[\frac{Z_{\beta} + Z_{1-\alpha/2}}{\ln(\rho/\Delta^*)}\right]^2$$

  - Z_{β} = Quantile corresponding to power (= 1.28 for 90% power)
  - $Z_{1-\alpha/2}$ = Quantile corresponding to Type I error (= 1.96 for two-sided α=0.05)
  - ρ = estimate of the true relative risk
  - Δ^* = risk margin (Δ^* = 1 corresponds to superiority comparison)

Power and Type I Error

- Power considerations
  - ***Increasing*** power requires ***more*** events ($\uparrow Z_\beta = \uparrow D$)
  - For safety, consider highest feasible power; may only have one randomized trial to infer effect sizes
- Type I error rate
  - Require strict control of Type I error at two-sided $\alpha = 0.05$ level
  - ***Decreasing*** Type I error requires ***more*** events ($\downarrow \alpha = \uparrow D$)
    - This implies that trials with multiple comparisons (e.g. interim analyses) would require larger sample sizes

Risk Margin

- Selection of the risk margin is based upon
  - Study feasibility (e.g. If *D* is too large, study may be impractical)
  - Clinical judgment (e.g. What is the most CV risk one would be willing to accept?)
  - Others?
- To rule out a lower risk margin requires more events
  - As Δ^* ***decreases*** *D* ***increases***
- Should the risk margin be based on risk difference (RD) or a relative risk (RR)?

True Relative Risk

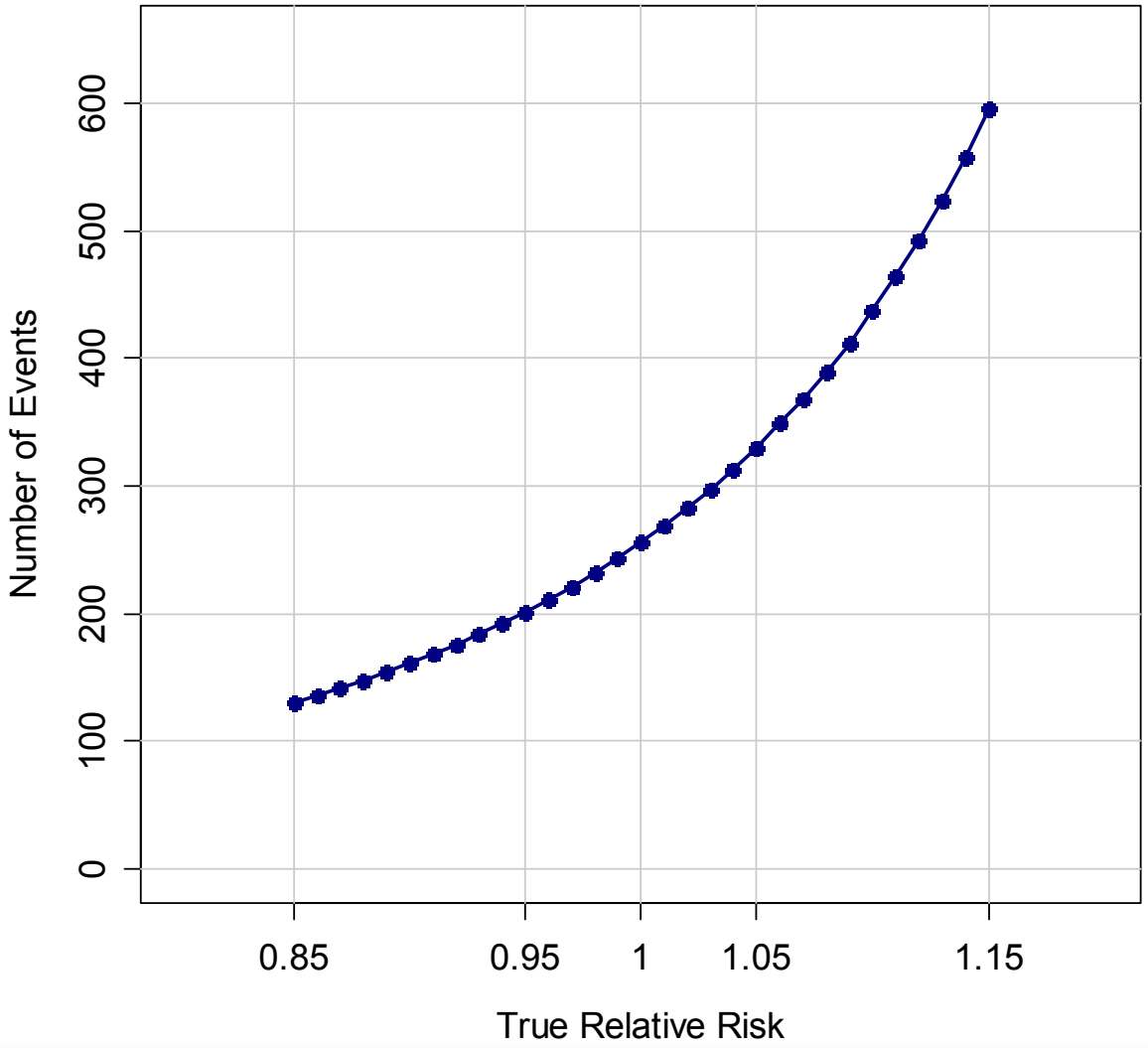
- Relative risk is the population parameter which is **unknown** and the trial is designed to infer this value
- Power calculations require an assumption on what is believed to be the true value of the population parameter (e.g. ρ)
- How to select a "best guess" for the population parameter
  - Efficacy Paradigm:
    - Conduct small trials to obtain a reliable estimate of the population parameter and use this information in sample size calculations
  - CV Safety Paradigm:
    - Parameter of interest (e.g. relative risk) can correspond to a rare event for which little data exist to make a "best guess" in sample size calculations
    - Sample size calculations must make somewhat of a *blind guess* of the value of ρ
- Sample size implication: As ρ converges to Δ^*, D **increases**

Trial Size Scenario

- To explore in detail how various factors affect *D*, we set the following conditions:
  - Risk margin is set to 1.5 ($\Delta^{*}=1.5$)
    - Objective is to rule out a 50% increase in CV risk with active relative to control
  - The true relative risk is assumed to be 1.0 ($\rho = 1.0$)
    - It is assumed that CV risk is equal for both groups
  - Power is set at 90% ($Z_{\beta} = 1.28$)
  - Type I error is set at $\alpha = 0.05$ ($Z_{1-\alpha/2} = 1.96$)

$$D = 256$$

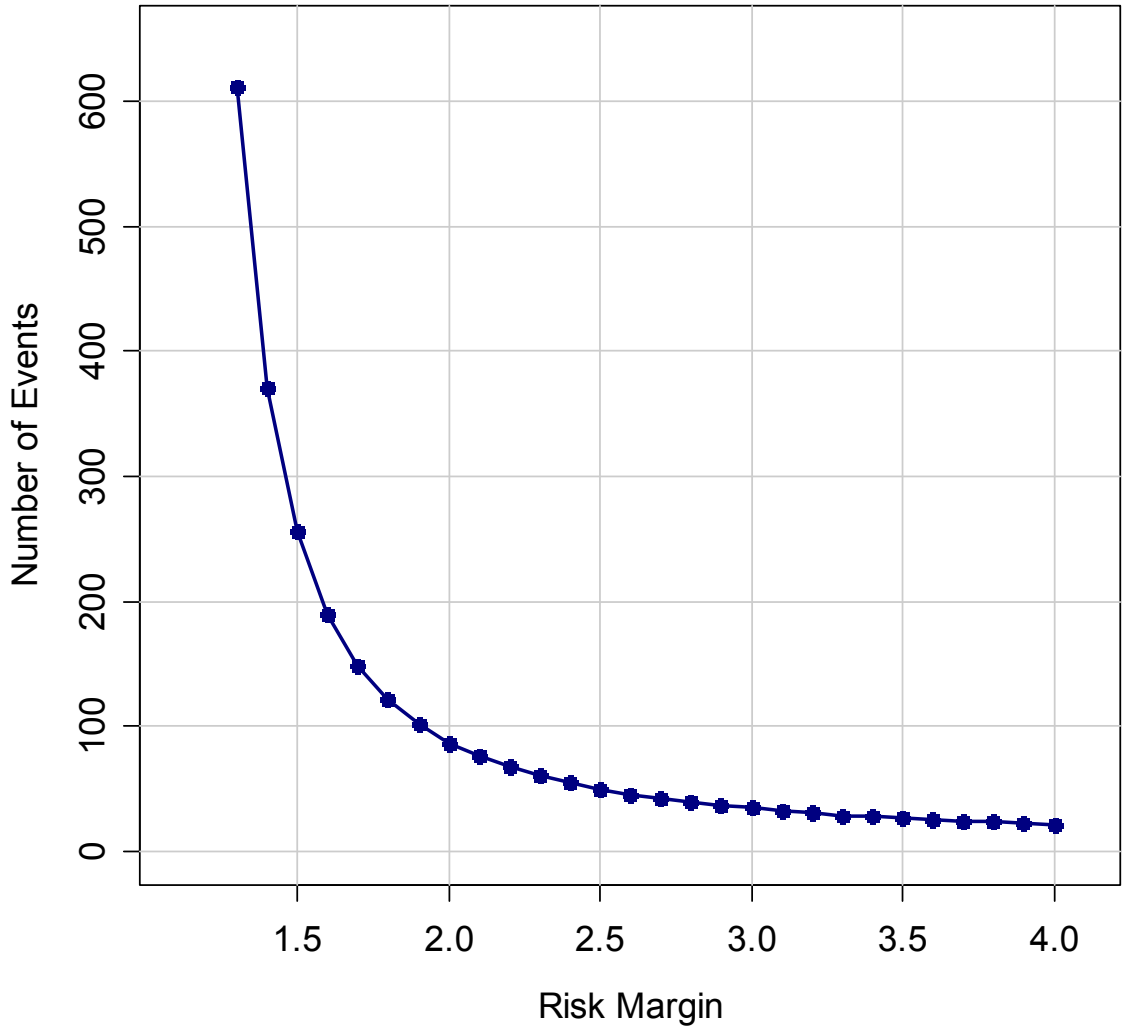
True Relative Risk (ρ) Impact



ρ	D
0.85	131
0.95	202
1.00	256
1.05	331
1.15	596

Assume: $\Delta^*=1.5$, $Z_\beta = 1.28$, $Z_{1-\alpha/2} = 1.96$

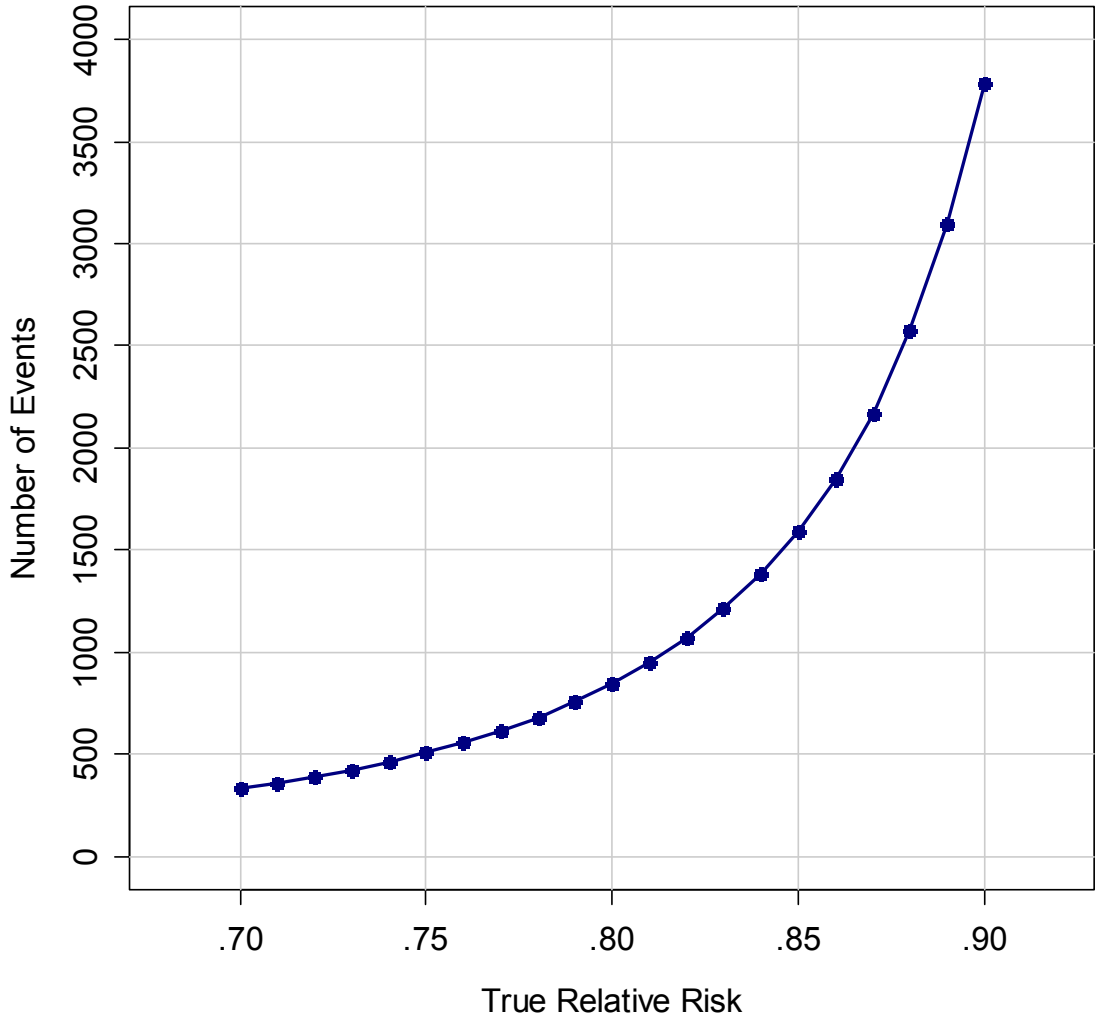
Risk Margin (Δ*) Impact



Δ*	*D*
1.3	611
1.5	256
1.8	122
2.0	88
3.0	35
4.0	22

Assume: $\rho=1.0$, $Z_{\beta} = 1.28$, $Z_{1-\alpha/2} = 1.96$

Risk Improvement ($\Delta^*=1.0$) Objective



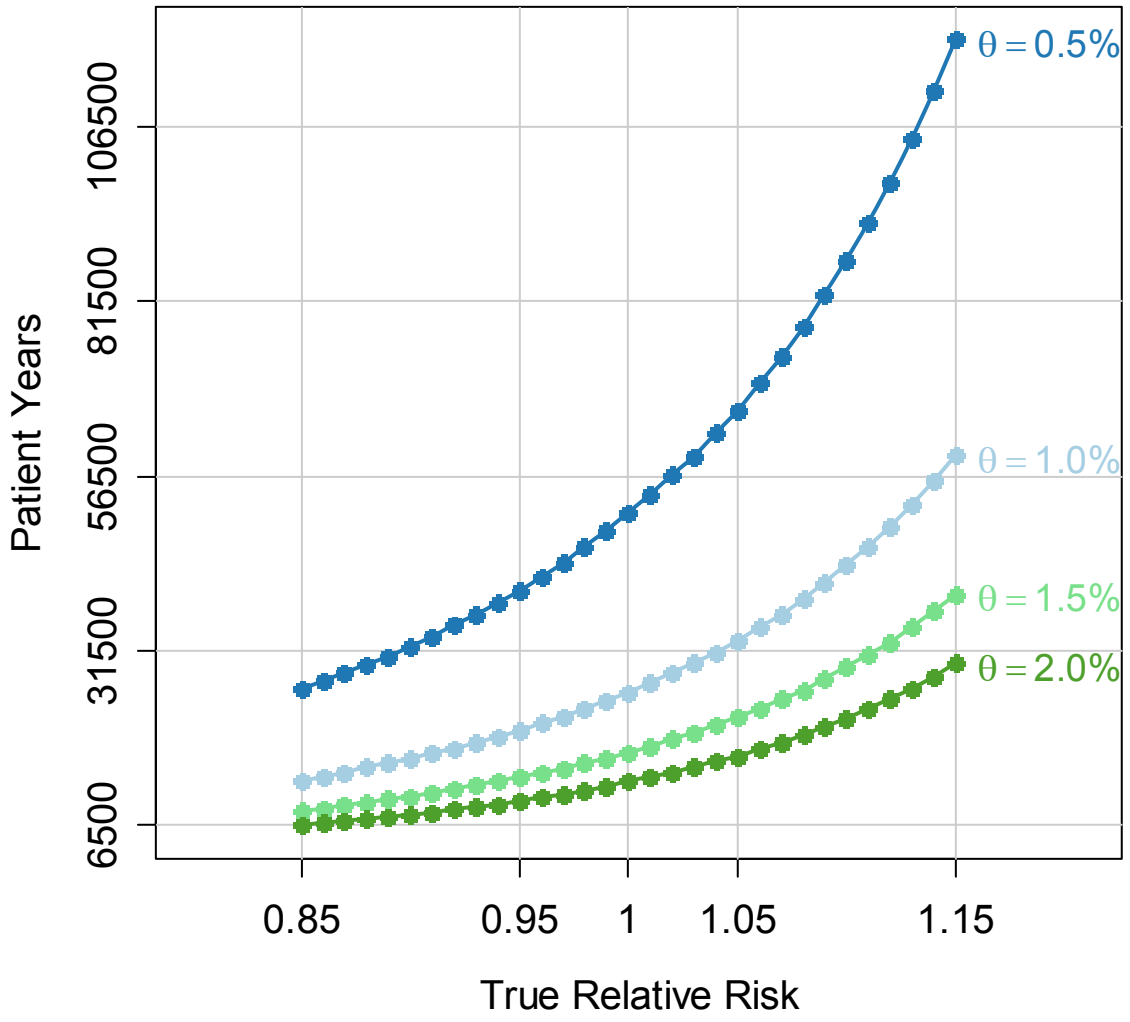
ρ	D
0.70	331
0.75	508
0.80	844
0.85	1592
0.90	3786

Assume: $\Delta^*=1.0$, $Z_\beta = 1.28$, $Z_{1-\alpha/2} = 1.96$

Trial Size – Patient Years

- Rather than expressing trial size by the number of events, trial size can be expressed in terms of patient years (PY)
  - E.g. 1000 patients followed for 2 years = 2,000 PY
- To translate *D* into PY, a patient population is enrolled with an assumed annual event rate (θ)
  - Patient Years = Events/Annual Rate = (D / θ)
- Calculations that follow assume
  - θ = .5%, 1.0%, 1.5%, 2.0%

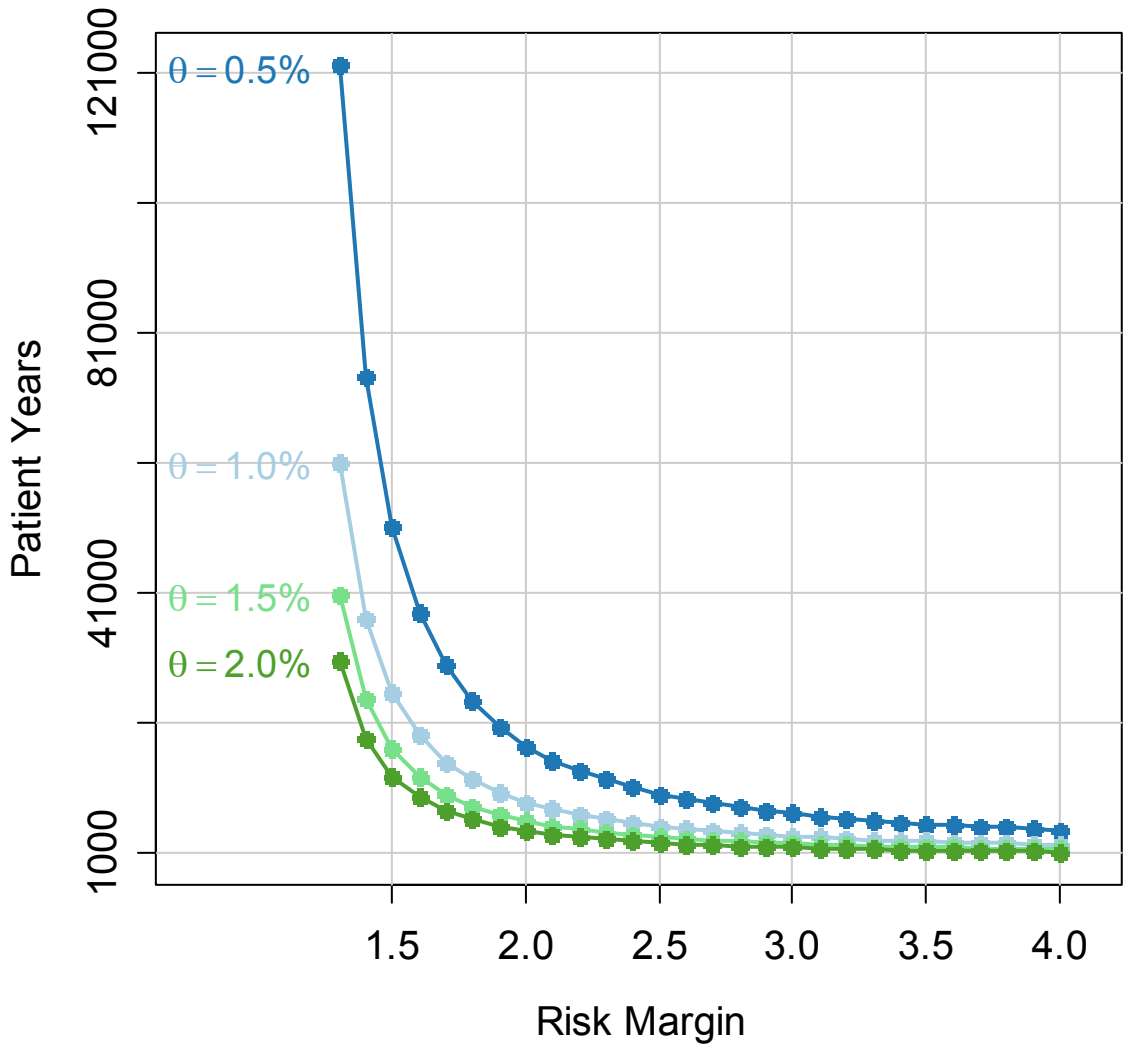
True Relative Risk (ρ) Impact



θ	PY (ρ=1)
5/1000	51,200
10/1000	25,600
15/1000	17,067
20/1000	12,800

Assume: $\Delta^*=1.5$, $Z_{\beta} = 1.28$, $Z_{1-\alpha/2} = 1.96$

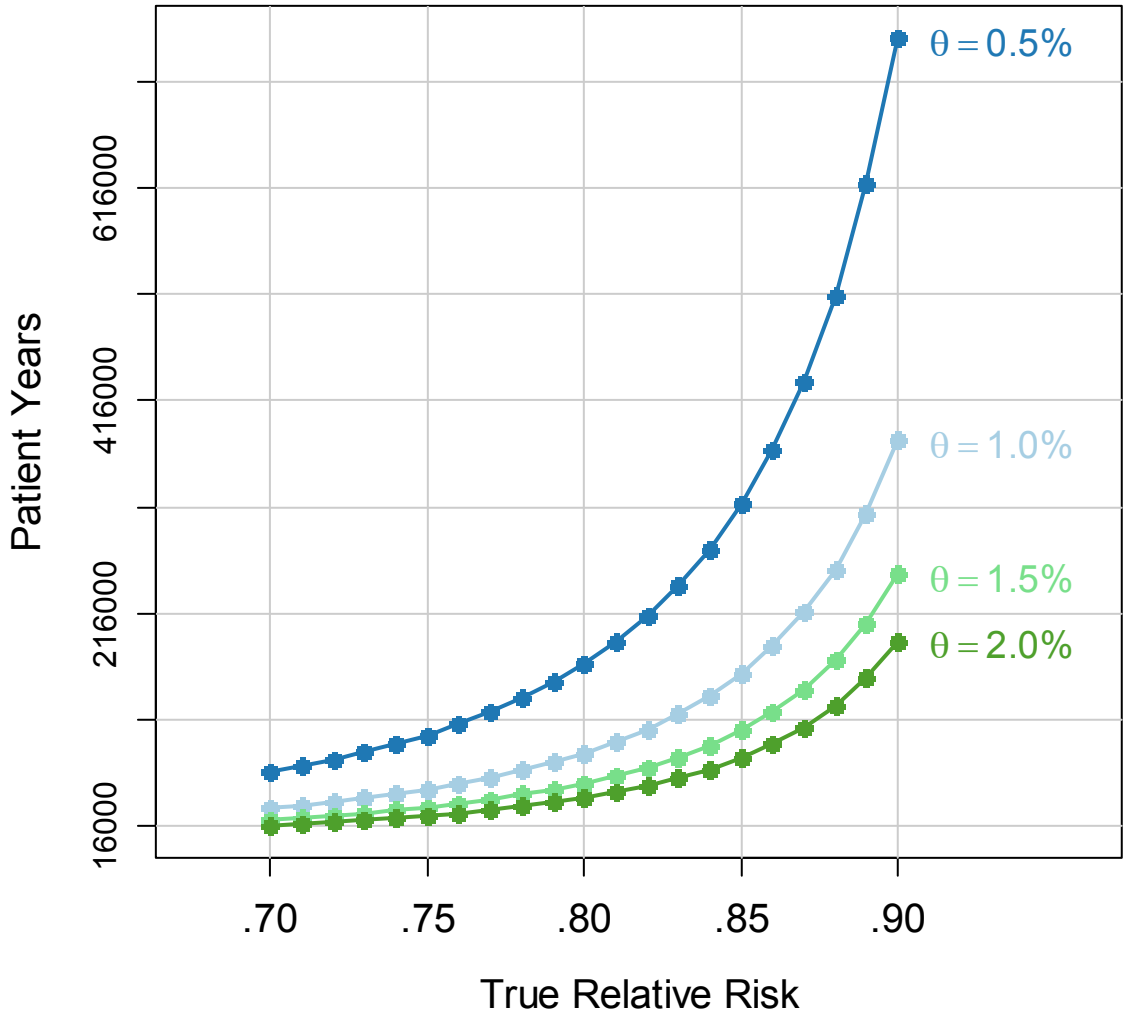
Risk Margin (Δ*) Impact



θ	PY (Δ*=1.4)
5/1000	74,200
10/1000	37,100
15/1000	24,733
20/1000	18,550

Assume: $\rho=1.0$, $Z_{\beta} = 1.28$, $Z_{1-\alpha/2} = 1.96$

Risk Improvement ($\Delta^*=1.0$) Objective



θ	*PY (ρ=0.85)*
5/1000	318,400
10/1000	159,200
15/1000	106,133
20/1000	79,600

Assume: $\Delta^*=1.0$, $Z_{\beta} = 1.28$, $Z_{1-\alpha/2} = 1.96$

Trial Size Summary

- Objective of the trial (risk improvement vs. non-excessive risk) has major implications on size of ***D***
  - As the risk margin increases from 1.0, fewer events (*D)* are needed for a given ρ
- The true relative risk (ρ) is **unknown** with *limited data* available to derive a **reliable estimate**
  - The assumed value can have significant impacts on *D*
- Observation of the *D* events occurs by following patients for a certain number of years; the higher the annual event rate, fewer patient years are needed to observe the *D* events

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Primary Analysis

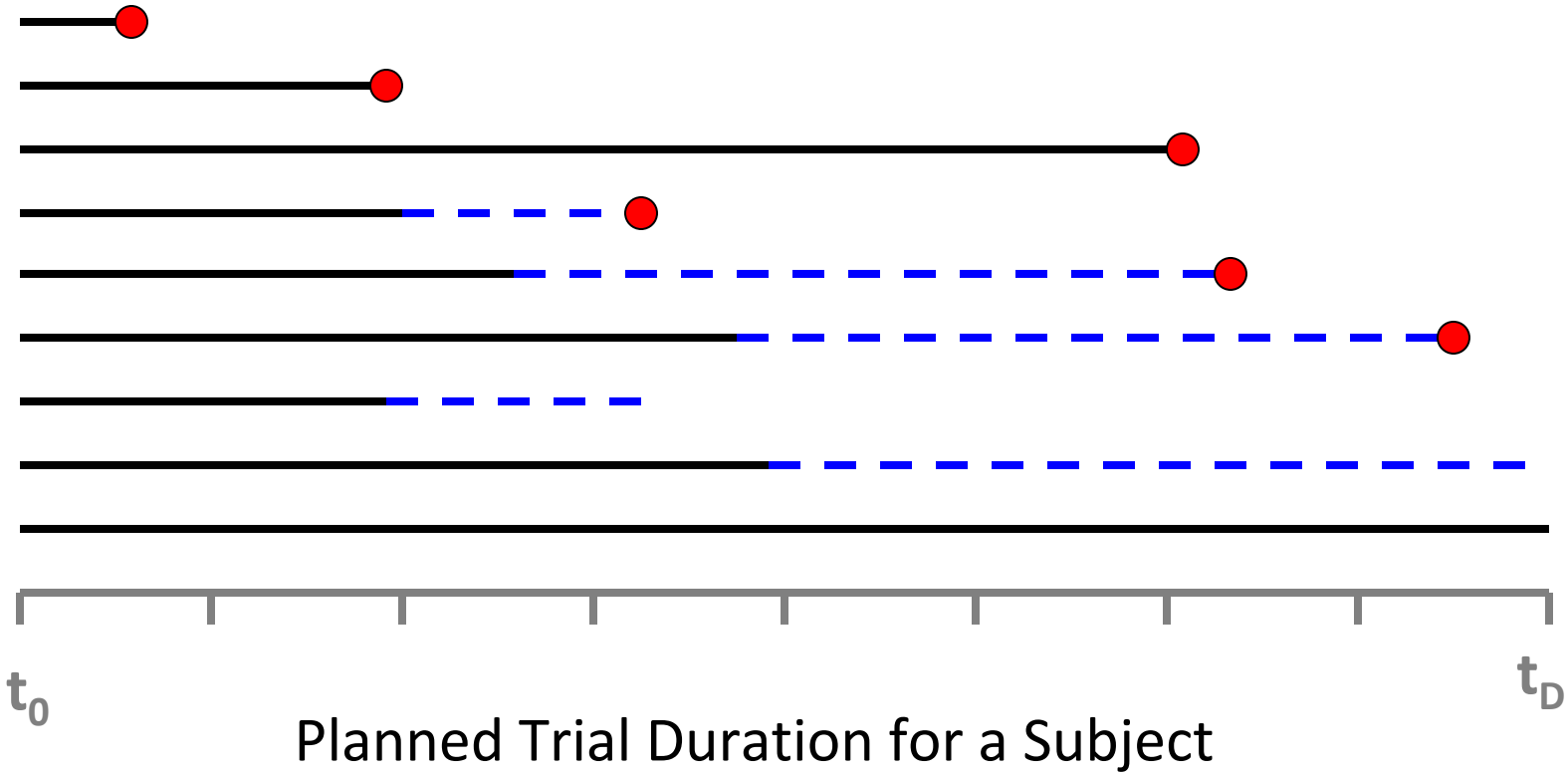
- The primary endpoint is the time to the first confirmed (and adjudicated) MACE (or MACE+)
- Model: Cox Proportional Hazards Model with treatment as a factor
  - May also include any other pre-specified baseline factors
- For non-excessive risk comparisons, appropriately α-adjusted CI's of the hazard ratio are used to compare to the risk margin
- Question remains on what analysis population should be considered primary

Analysis Populations

- **Dropout rates in efficacy**: In typical 1 year weight loss trials, the percent of subjects that discontinue treatment is high
  - For one year trials completion rate varies by trial and product
    - Recent applications: completers range from 55% to 75%
    - Subjects randomized to placebo tend to have higher discontinuation rates than active treatment
- **Dropout rates in safety**: CV outcome trial designs may result in **higher** treatment discontinuation rates for several reasons
  - Proposed rules for treatment discontinuation (e.g. lack of efficacy, sustained increases in vital signs)
  - Longer trial durations
- Subjects would be encouraged to remain in trial for CV assessments
    - Two epochs for which subjects can be assessed (on-treatment epoch and off-treatment epoch)

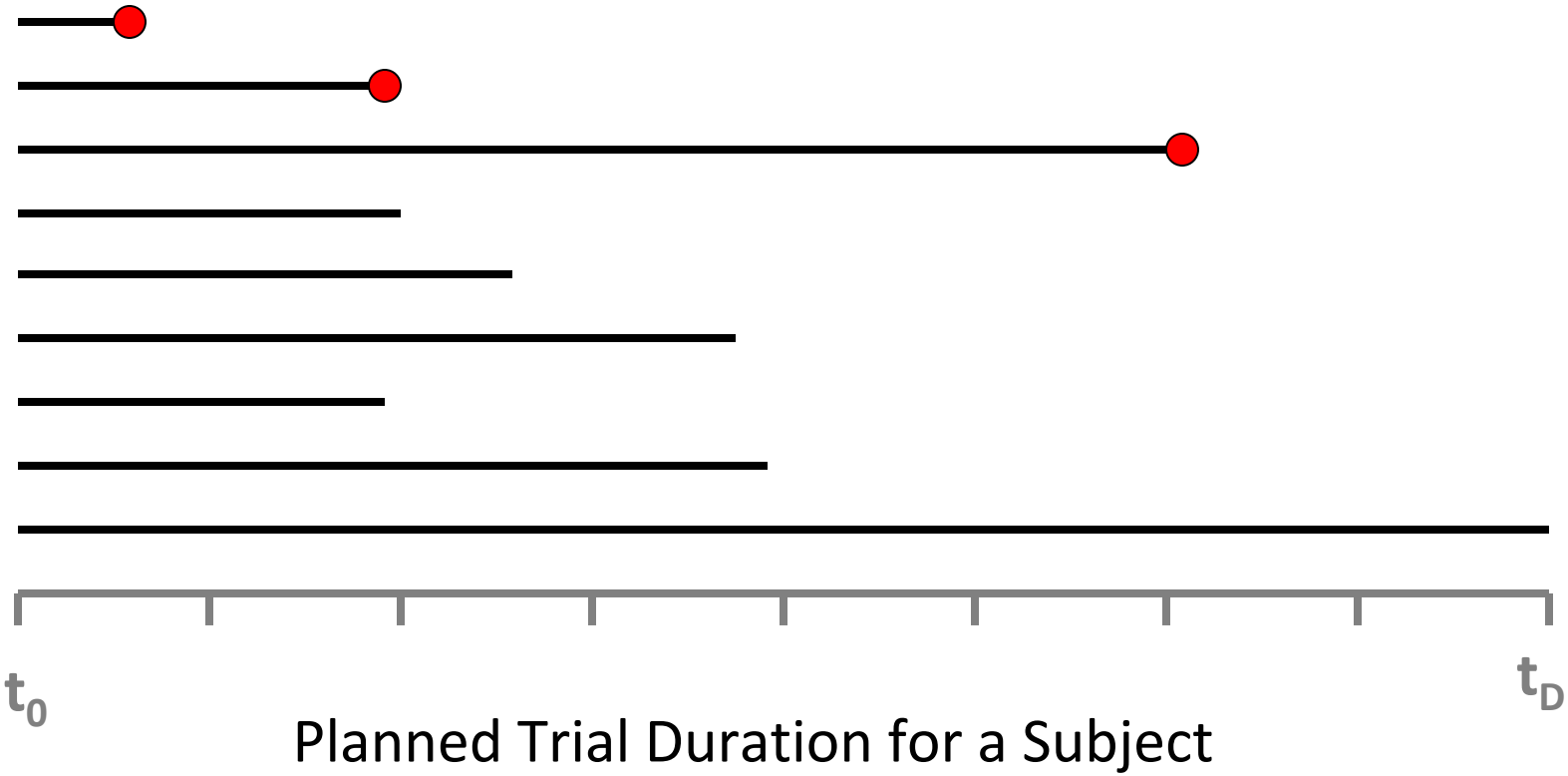
Analysis Populations

Total-Time Analysis Population = On-Treatment + Off Treatment



Analysis Populations

On-Treatment Analysis Population = On-Treatment Epoch Only



Analysis Populations

- In a Total-Time analysis population
  - Censoring occurs when a subject is *no longer followed*
    - Events are counted that occur both on and off treatment
- In an On-Treatment analysis population
  - Censoring occurs when a subject *discontinues treatment*
    - Events occurring off-treatment are not counted
- Both analysis populations preserve randomization
- Analysis populations may address different clinical questions
- Thus, there remains the question of which is the more appropriate analysis population

Two-Stage Approach for Safety

- In a two-stage approach: the criteria for determining trial success is a sliding bar
  - In such an approach, one must define two risk margins
    - Δ_1^* = risk margin for stage 1
    - Δ_2^* = risk margin for stage 2
    - Where $\Delta_2^* < \Delta_1^*$
  - Trials are powered to rule out the risk margin for stage 2 (Δ_2^*)
  - The risk margin for stage 1 (Δ_1^*) is assessed using a fraction of the total number of events
- Such an approach can be used where pre-approval is based on Δ_1^* with a post-marketing requirement that post-approval be based on Δ_2^*
  - This two-stage approach is used in assessing CV risk in treatments for Type II diabetes ($\Delta_1^* = 1.8$ and $\Delta_2^* = 1.3$)

Conditional Power

- In a two-stage approach, there is a possibility that a treatment is approved when in fact the risk is greater than the post-approval risk margin
  - An example: Pre-approval risk margin = 2.2 and Post-approval risk margin = 1.5
    - Study was powered *assuming* the true relative risk was **1**
    - However, if the **true relative risk = 1.51** then there is approximately a 34% probability of meeting the 2.2 risk margin despite the fact that the 1.51 > 1.5.
- This suggests that pre-approval results need to be evaluated in terms of the likelihood the trial can meet the post-approval risk margin for a two-stage approach

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Concluding Remarks

- Dedicated cardiovascular safety outcome trials do pose unique challenges in design and analysis
  - Clinical considerations are pertinent to powering the trial and how analysis will be performed
- The following is a summary of some of the key issues which will have merit on how the trials are powered and analyzed
  1. Selection of the trial objective (risk improvement or non-excessive risk?)
  2. For non-excessive risk comparisons; one needs to define how to measure excess risk (**absolute risk** or **relative risk**?)
     - Decisions on absolute risk should consider the annual event rate
  3. What analysis population should be considered primary (total-time versus on-treatment)?

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Cardiovascular Outcomes Trials
Experience with Rimonabant and Sibutramine

Eric Colman, M.D.
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
March 28, 2012

Outline

- Rimonabant and the **C**omprehensive **R**imonabant **E**valuation **S**tudy of **C**ardiovascular **End**points and **O**utcomes (CRESCENDO)
- Sibutramine and **S**ibutramine **C**ardiovascular **Out**comes (SCOUT)
- Comparison of Subject Demographic Characteristics
- Summary/Conclusion

Rimonabant and CRESCENDO

Rimonabant

- Cannabinoid-1 receptor antagonist
- Developed for the treatment of obesity
  - placebo-subtracted weight loss ~ 5%
  - favorable effects on HDL-C, TG, HbA1c, and BP
  - adverse neuropsychiatric effects
- Approved by European Medicines Agency in 2006
- FDA Advisory Committee recommended against approval in 2007

CRESCENDO

- **C**omprehensive **R**imonabant **E**valuation **S**tudy of **C**ardiovascular **End**points and **O**utcomes
- Randomized, double-blind, placebo-controlled trial ~ 18,500 subjects
- Primary endpoint
  - Major Adverse Cardiovascular Events (MACE): cardiovascular disease (CVD) death, non-fatal MI, non-fatal stroke

CRESCENDO

- December 2005 – July 2008
- Inclusion criteria
  - Age > 55 years
  - Abdominal obesity
  - Overt CVD within 3 years, or
  - At least 2 major CVD risk factors

CRESCENDO

- Major CVD risk factors
  - Type 2 diabetes mellitus
  - At least two features of metabolic syndrome in addition to increased waist circumference
  - Renal artery disease
  - Asymptomatic cerebrovascular or peripheral artery disease
  - Advanced age (men > 65, women > 70)
  - Elevated hsCRP
- Prespecified subgroups
  - Overt CVD
  - At-Risk for CVD

CRESCENDO

- Sample size calculation
  - 90% power
  - 15% reduction in the HR for MACE
  - Two-sided α of 0.05
- 1600 MACE
- 3% annual MACE rate in control group
- ~ 53,000 patient-years of exposure

CRESCENDO
Baseline Demographics

	Placebo (n=9314)	Rimonabant (n=9381)
Age	64 years	64 years
% Female	36%	36%
% White	84%	84%
BMI	33 kg/m^2	33 kg/m^2
Hx MI	36%	36%
Hx stroke	18%	17%
Diabetes	60%	61%
Hypertension	88%	88%
Hypercholesterolemia	82%	82%

CRESCENDO

- November 2008, regulatory authorities in Ireland, France, and Germany requested cessation of clinical research with rimonabant due to concern about serious psychiatric adverse reactions
- CRESCENDO terminated after a mean exposure to study drug of 13.8 months (planned minimum 33 months)

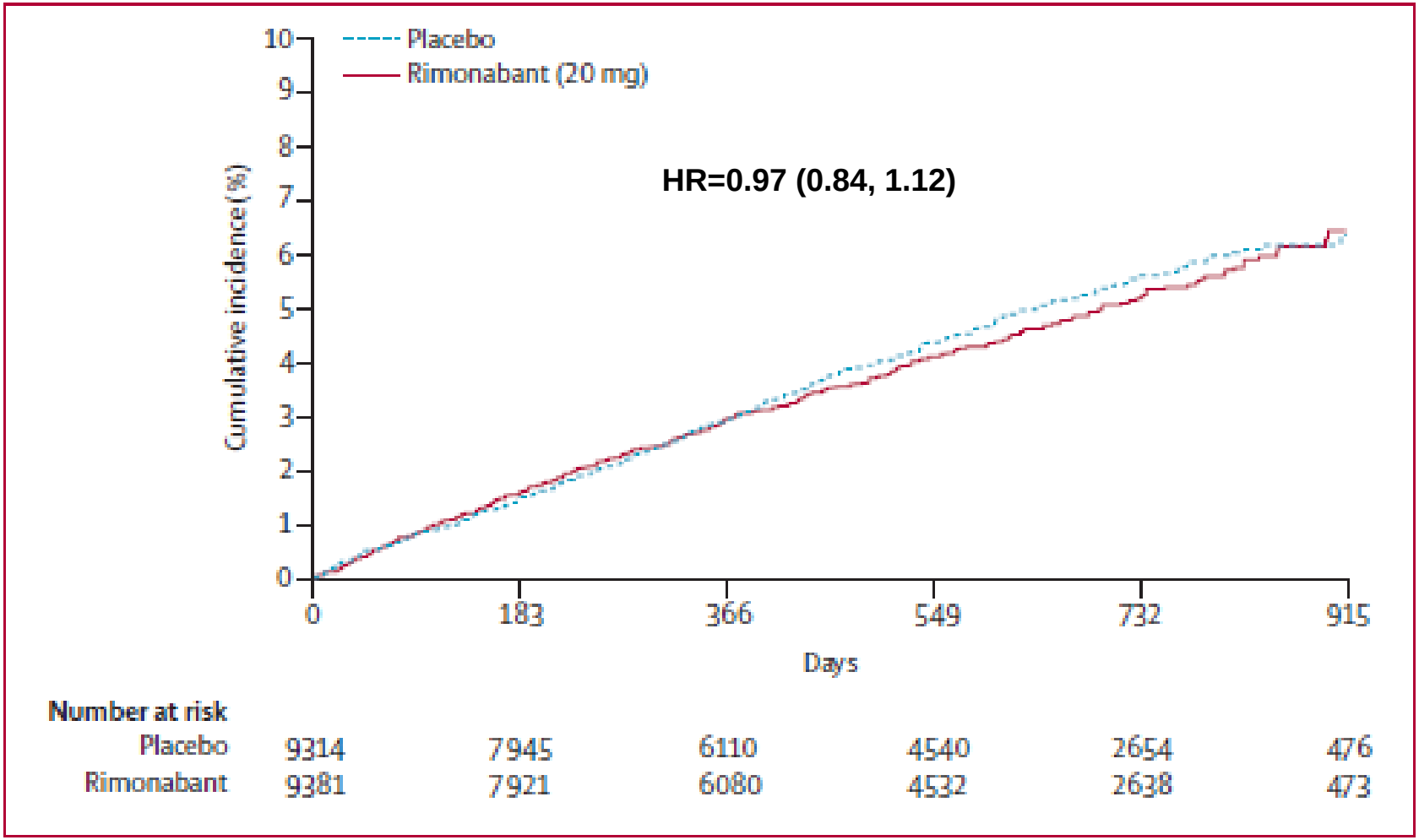
Efficacy Outcome – Intention-to-Treat Population

	Placebo N=9314	Rimonabant N=9381	P-value
MACE	375 (4.0%)	364 (3.9%)	0.68
CV death	123 (1.3%)	122 (1.3%)	0.95
MI	144 (1.5%)	138 (1.5%)	0.72
Stroke	146 (1.6%)	135 (1.4%)	0.50

MACE HR = 0.97 (95% CI 0.84, 1.12)

CRESCENDO

MACE - Overall Population



Kaplan-Meier curves for time to first occurrence of MACE

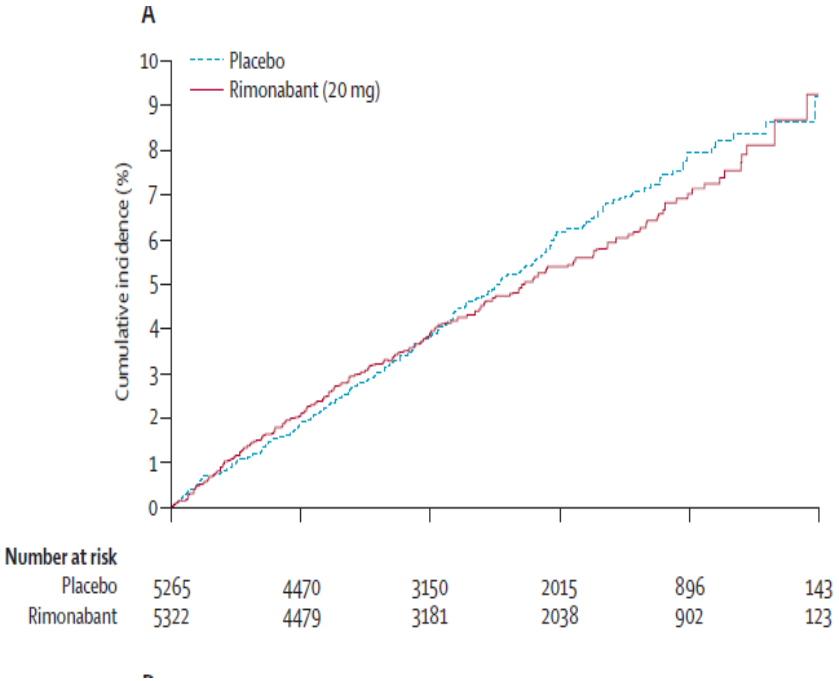
Topol E. Lancet 2010

CRESCENDO

MACE - Subgroup Analyses

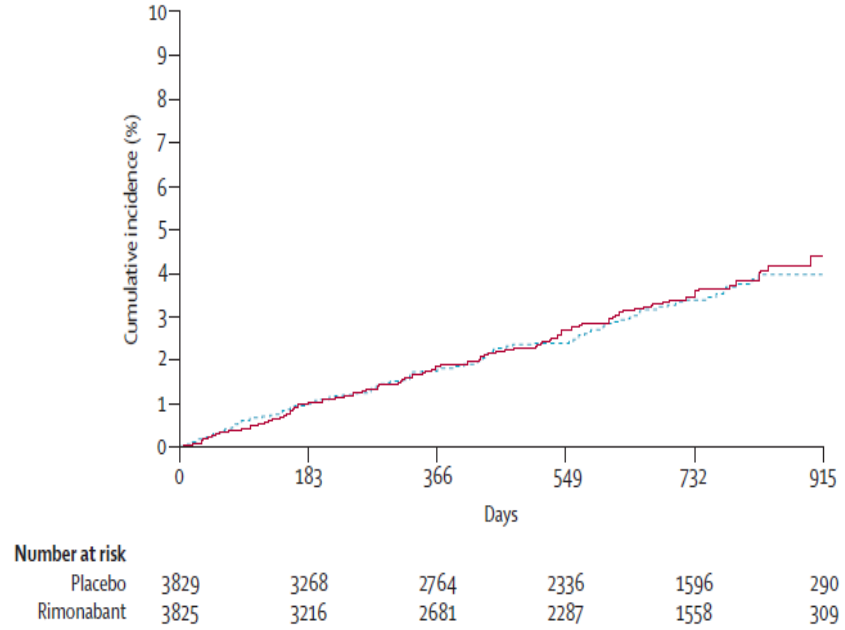
Overt CVD

HR=0.95 (0.80, 1.13)



At-Risk for CVD

HR=1.03 (0.79, 1.35)



Kaplan-Meier curves for time to first occurrence of MACE

Topol E. Lancet 2010

Sibutramine and SCOUT

Sibutramine

- Norepinephrine and serotonin reuptake inhibitor
- Developed for the treatment of obesity
  - Placebo-subtracted weight loss ~ 4%
  - Favorable effects on HDL-C and TG
  - Inconsistent effects on measures of glycemia
  - Placebo-subtracted increases in BP of 1-3 mmHg and heart rate of 3-5 bpm
- Approved by FDA in 1997

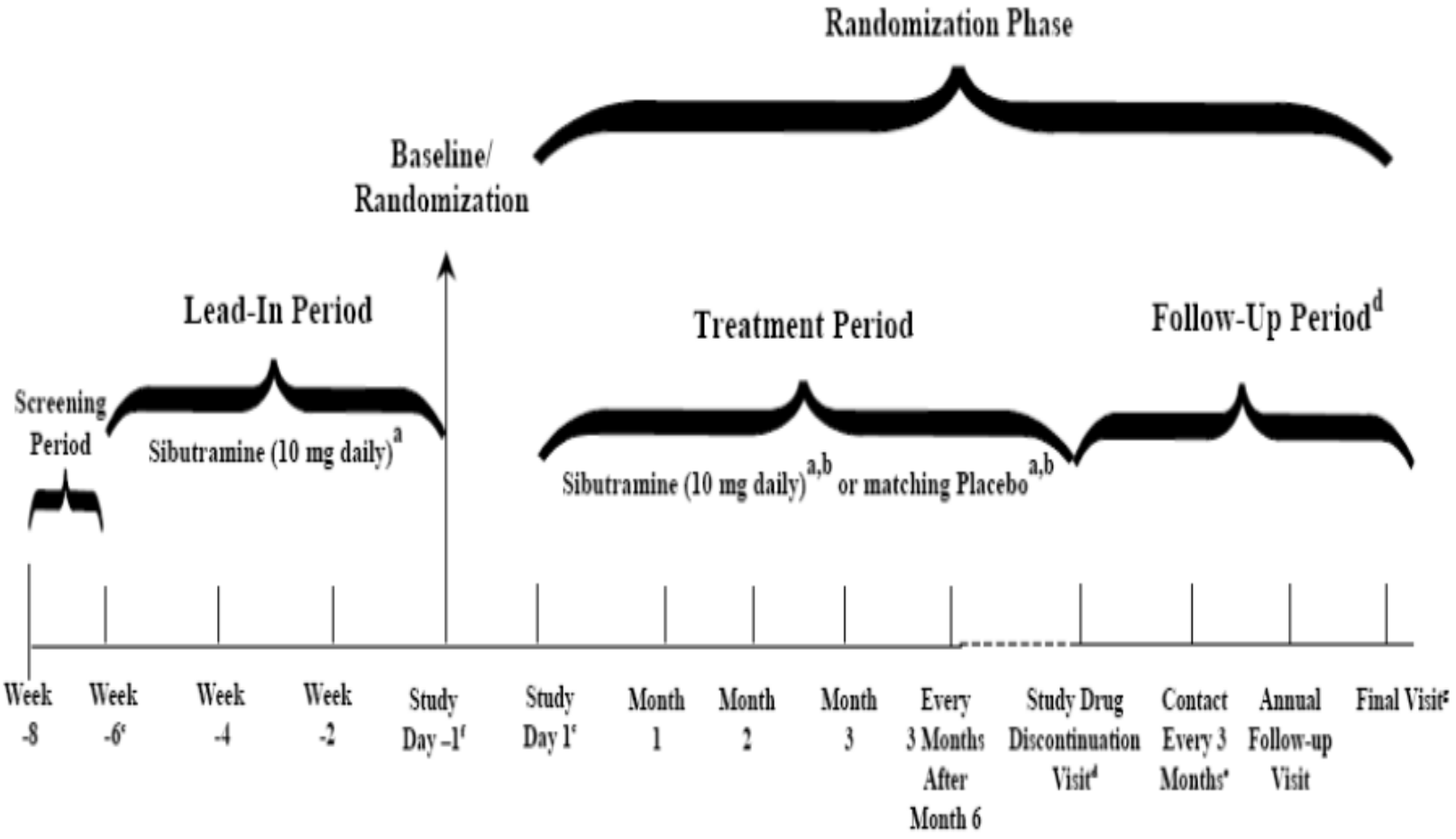
SCOUT

- **S**ibutramine **C**ardiovascular **Out**comes trial
- Randomized, double-blind, placebo-controlled trial ~ 10,000 subjects
- Primary endpoint
  - MACE: CV death, non-fatal MI, non-fatal stroke, resuscitated cardiac arrest
- January 2003 – March 2009

SCOUT

- Inclusion criteria
  - Age > 55 years
  - BMI 27 – 45 kg/m^2
  - BMI 25 to 26.9 kg/m^2 with abdominal obesity
  - Hx CVD or type 2 diabetes with an additional CV risk factor or both
- Prespecified subgroups
  - CV + DM
  - CV
  - Diabetes

SCOUT - Design



SCOUT

- Sample size calculation
  - 80% power
  - 11.5% reduction in the HR for MACE
  - Two-sided α 0.05
- 2160 MACE
- Assume 7% annual MACE rate in control group
- ~ 31,000 patient-years of exposure

SCOUT

- Lower than expected primary event rate during first 15 months
- Recruitment restricted to subjects with CV + diabetes
- Study follow-up extended from 5 years to 6 years

SCOUT
Baseline Demographics

	Placebo (n=4898)	Sibutramine (n=4906)
Age	63 years	63 years
% Female	42%	43%
% White	96%	97%
BMI	34 kg/m^2	34 kg/m^2

Approximately 40% of subjects in each treatment group discontinued study drug prematurely

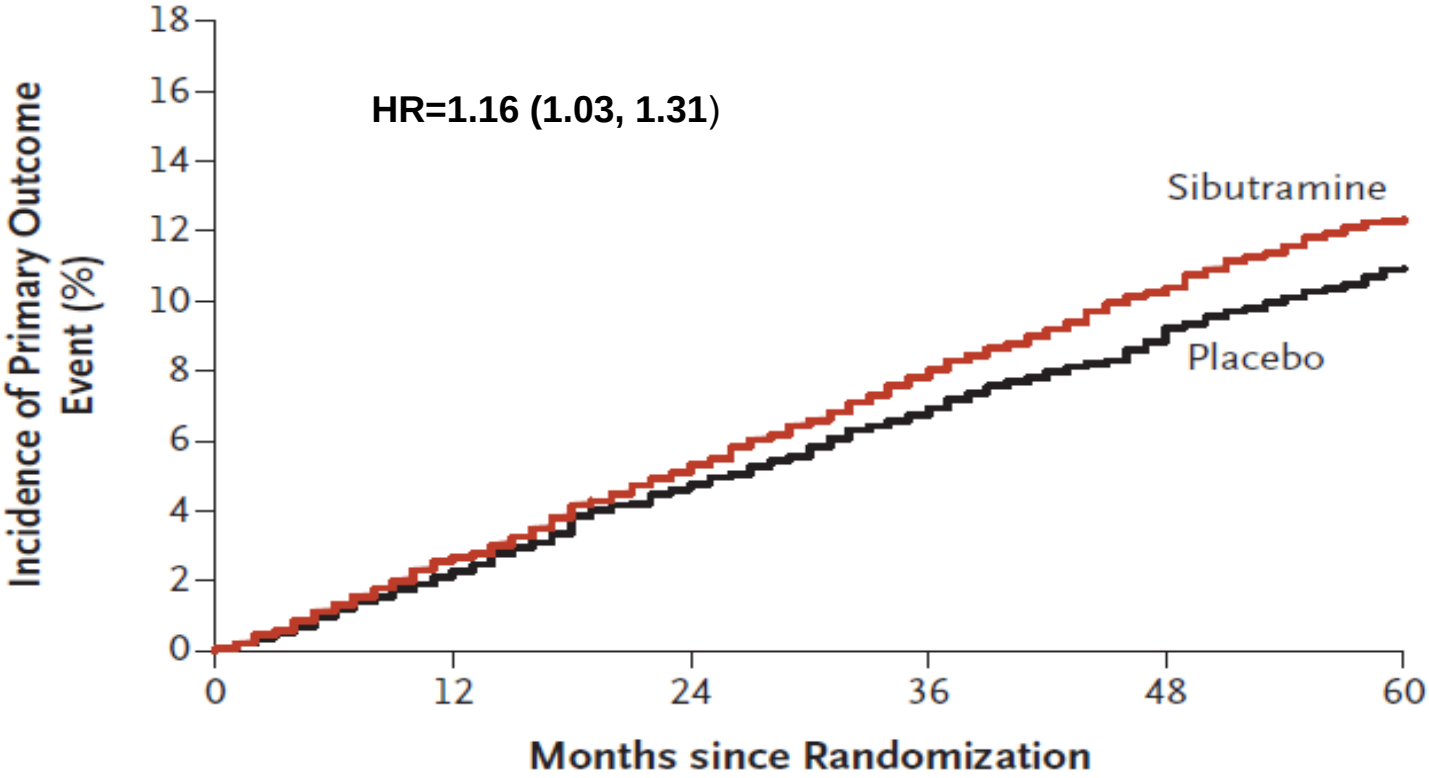
SCOUT
Primary Efficacy Outcome

- SCOUT stopped after 6 years and 1051 primary events
- Mean exposure to study drug ~ 3.5 years

Efficacy Outcome – Intention-to-Treat Population				
	Placebo N=4898	Sibutramine N=4906	HR (95% CI)	P-value
MACE	490 (10%)	561(11.4%)	1.16 (1.03, 1.31)	0.02
CV death	229 (4.7%)	223 (4.5%)	0.99 (0.82, 1.19)	0.90
MI	159 (3.2%)	200 (4.1%)	1.28 (1.04, 1.57)	0.02
Stroke	95 (1.9%)	127 (2.6%)	1.36 (1.04, 1.77)	0.03
RCA	7 (0.1%)	11 (0.2%)	1.58 (0.61, 4.08)	0.34

RCA=resuscitated cardiac arrest

SCOUT
MACE - Overall Population



No. at Risk						
Placebo	4898	4776	4623	4482	3467	1730
Sibutramine	4906	4749	4601	4427	3403	1720

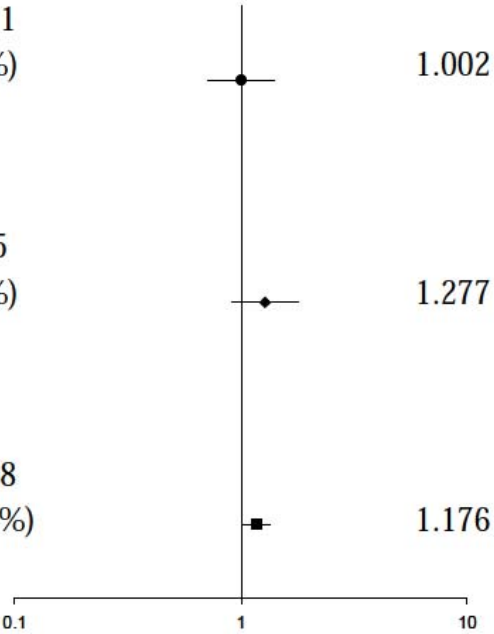
Kaplan-Meier curves for time to first occurrence of MACE

James, NEJM, 2010

SCOUT

MACE - Subgroup Analyses

Group	Number (%) with endpoint		Favors SBT	Favors PBO	HR	95% CI	*P* value	Interaction *P* value
	Sibutramine	Placebo						
DM Only	N = 1151 69 (6.0%)	N = 1141 70 (6.1%)			1.002	0.718, 1.398	0.992	0.560
CV Only	N = 722 73 (10.1%)	N = 745 61 (8.2%)			1.277	0.907, 1.798	0.161	
CV + DM	N = 3016 418 (13.9%)	N = 2998 359 (12.0%)			1.176	1.021, 1.354	0.024	



SBT = sibutramine; PBO = placebo

SCOUT
Analysis Populations

- MACE
  - Intention-to-treat: HR=1.16 (95% CI, 1.03, 1.31)
  - On-drug: HR=1.21 (95% CI, 1.05, 1.43)
- MACE plus revascularization procedures
  - Incidence in placebo group, 17.5%
  - Incidence in sibutramine group, 18.9%
  - HR=1.10 (95% CI, 0.99, 1.20)

Subject Demographics
Compare and Contrast

Rimonabant
Subject Demographics

	Rimonabant CRESCENDO	**Rimonabant** Diabetes	**Rimonabant** Non-Diabetes
		Phase 3 Clinical Trials	
Age (years)	64	56	45
% Caucasian	84	89	84
% Female	51	51	82
BMI kg/m^2	34	34	38

Sibutramine Subject Demographics

	Sibutramine SCOUT	**Sibutramine** Diabetes	**Sibutramine** Non-Diabetes
		Phase 3 Clinical Trials	
Age (years)	63	54	43
% Caucasian	96	83	99
% Female	43	51	81
BMI kg/m^2	34	31	33

Summary/Conclusion

- CRESCENDO and SCOUT - randomized, placebo-controlled clinical trials – designed to examine the effect of drug-induced weight loss on risk for MACE
- Powered to detect 15% and 11.5% reductions, respectively, in the hazard ratio for MACE
- Sample size: 18,500 and 10,000, respectively
- Enrolled subjects with and without CVD

Summary/Conclusion

- Compared with the "typical" phase 3 clinical trials of sibutramine and rimonabant, populations enrolled in CRESCENDO and SCOUT were older, composed of more males and type 2 diabetics, and included many more subjects with a history of CVD
- Annual incidence rate of MACE in control groups from CRESCENDO and SCOUT ~ 3.0% to 4.0%
- Annual incidence rate of MACE in "typical" phase 3 clinical trials of recently reviewed obesity drugs < 0.5%

Acknowledgment

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Mary Parks

Curt Rosebraugh

Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes:

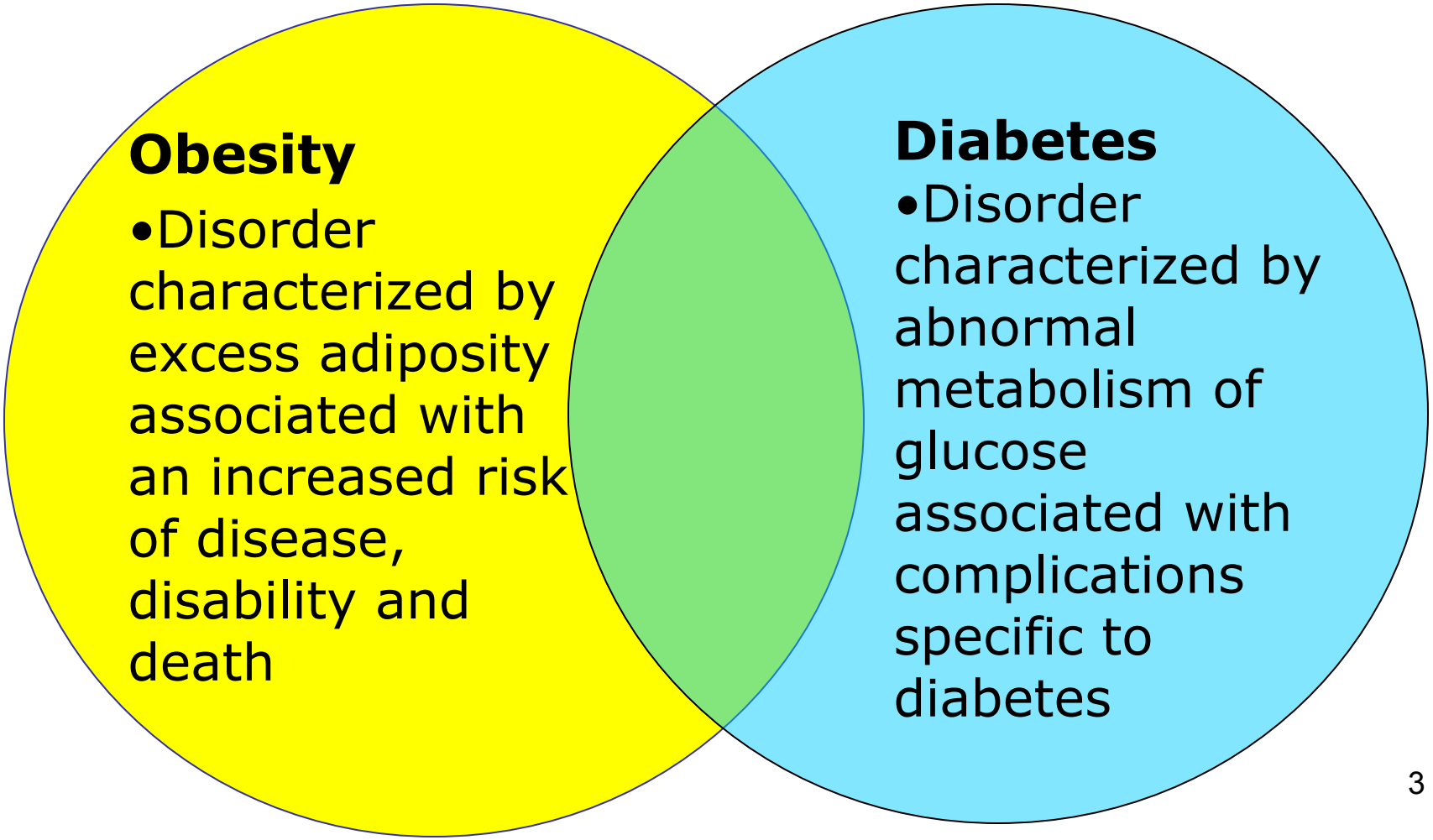
Rationale and Key Features of The Guidance For Industry

Jean-Marc Guettier, M.D.
Acting Team Leader: Diabetes
HHS, FDA, CDER, OND, ODE II, DMEP

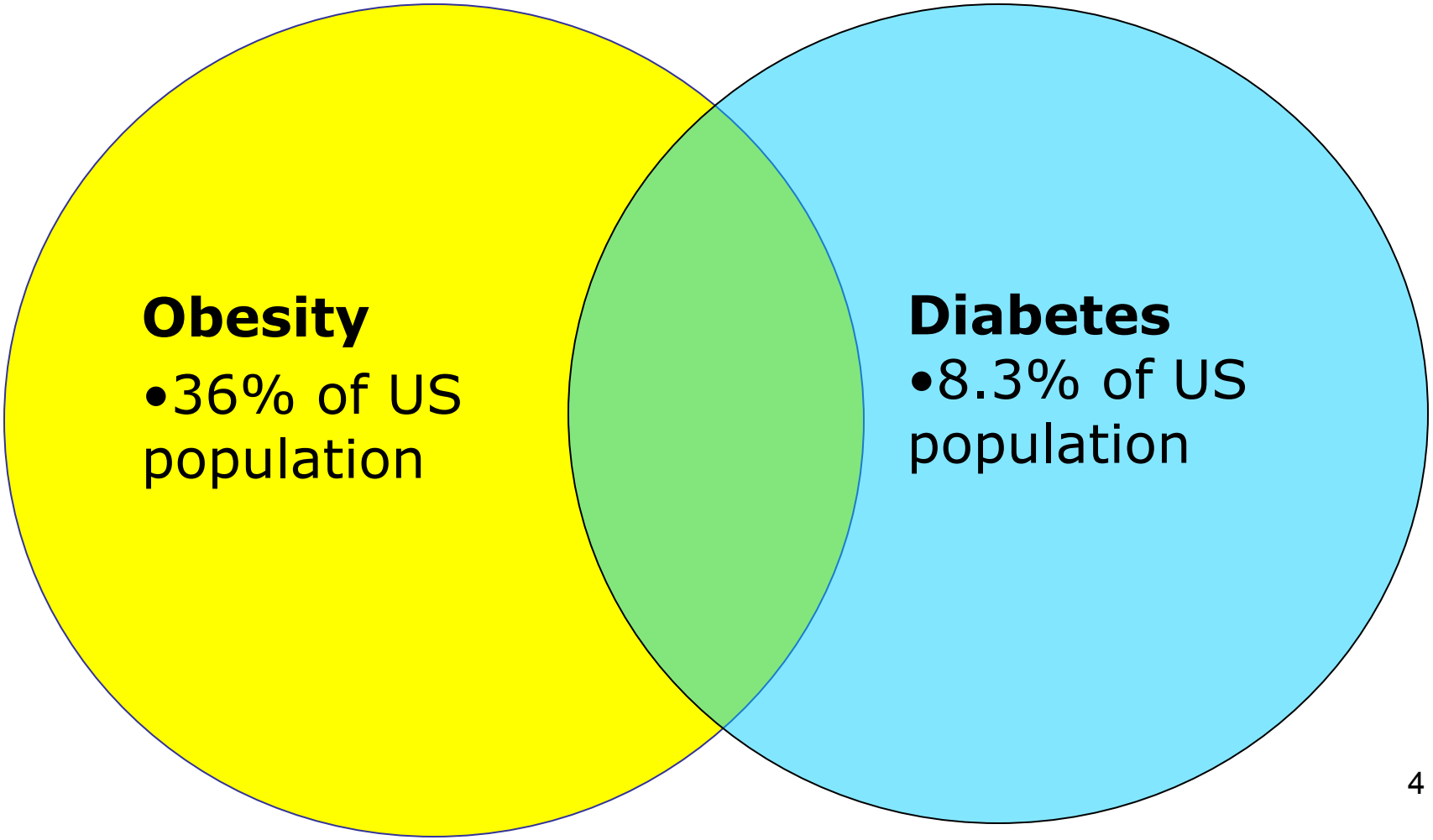
Outline

1. Background
2. Diabetes programs before CV guidance
3. July 2008 Advisory Committee Meeting
4. Guidance recommendations
5. Guidance implementation
6. Diabetes programs after CV guidance

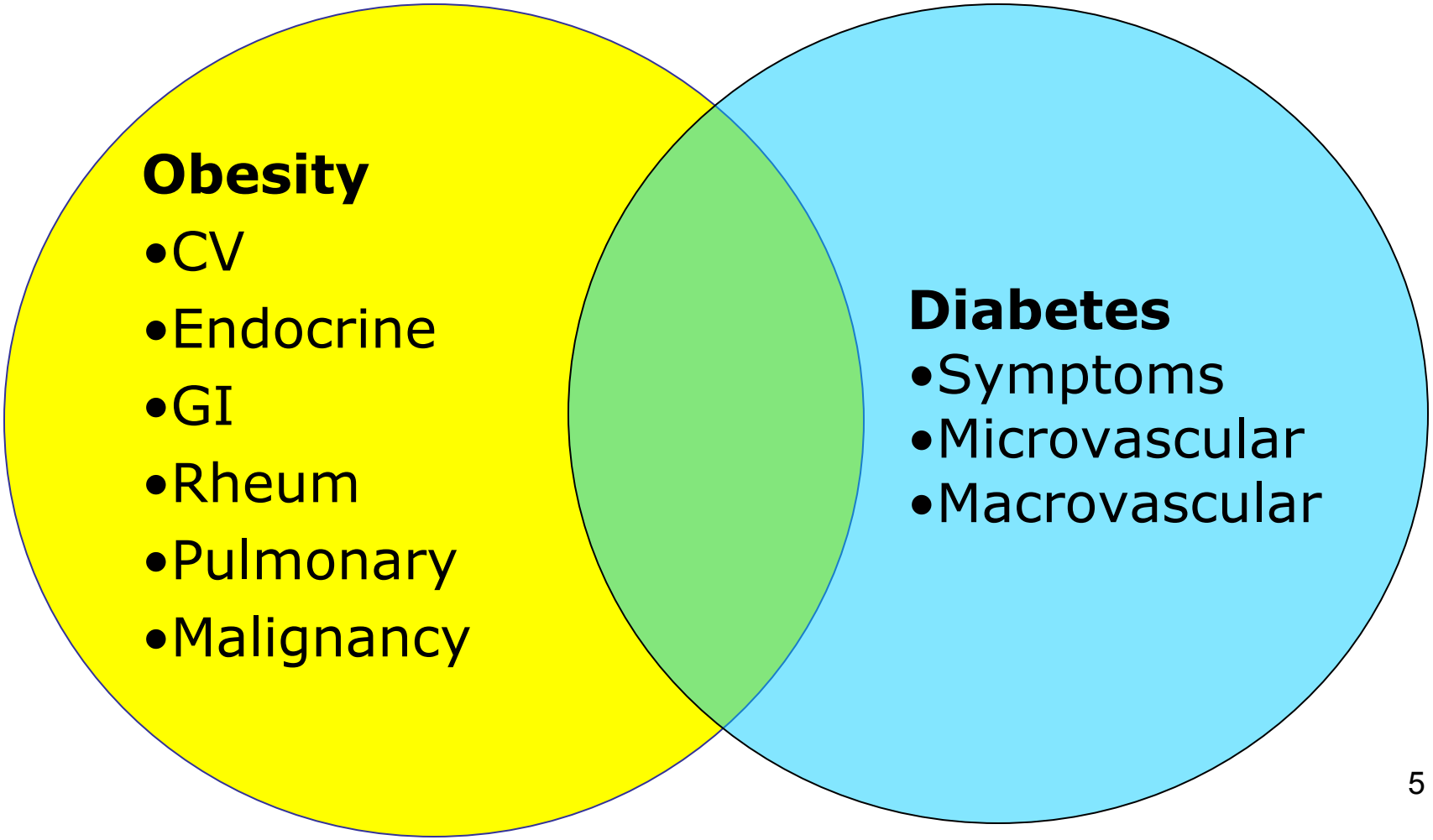
Obesity and Diabetes
Characteristics



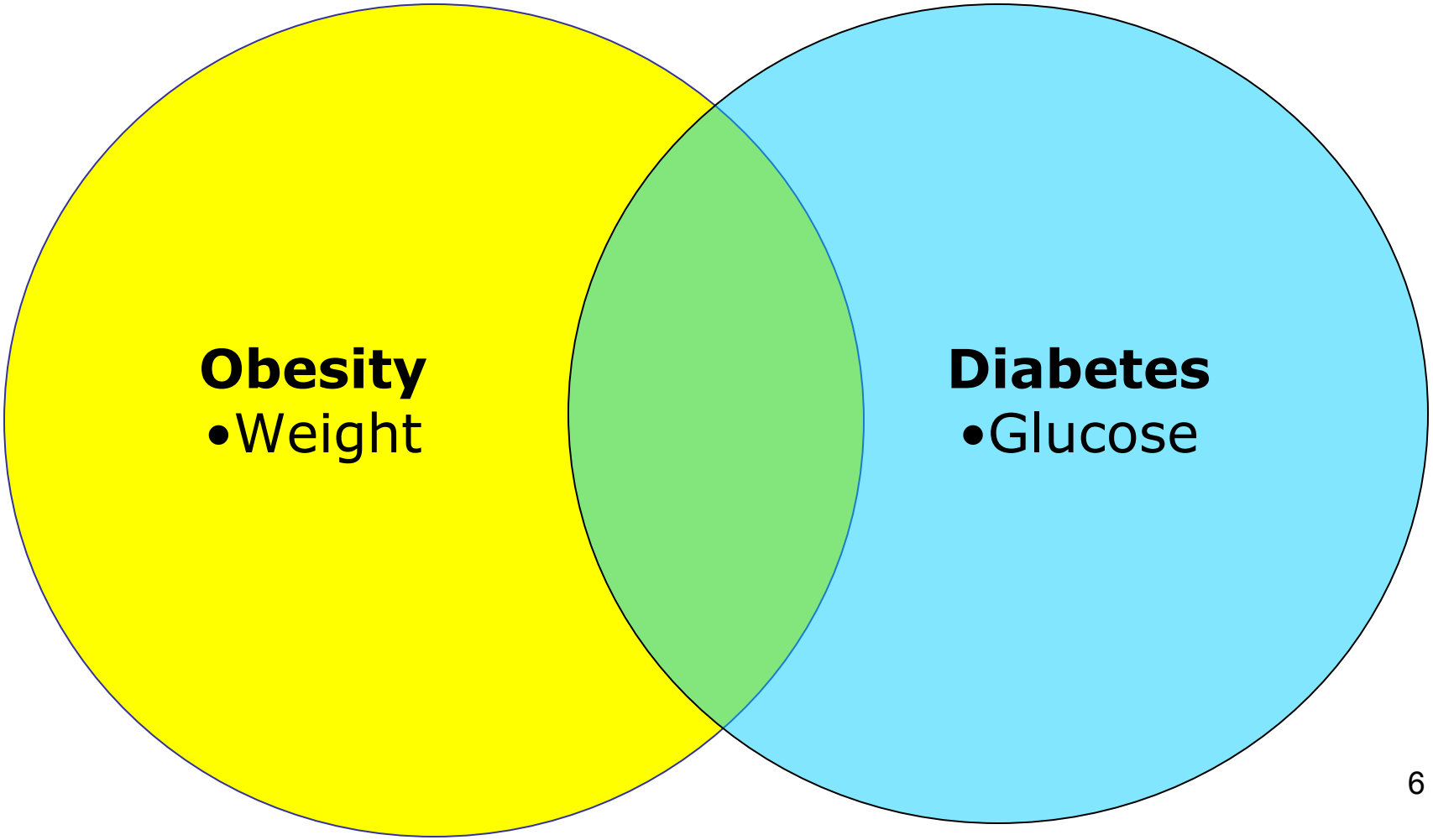
Obesity and Diabetes
Prevalence



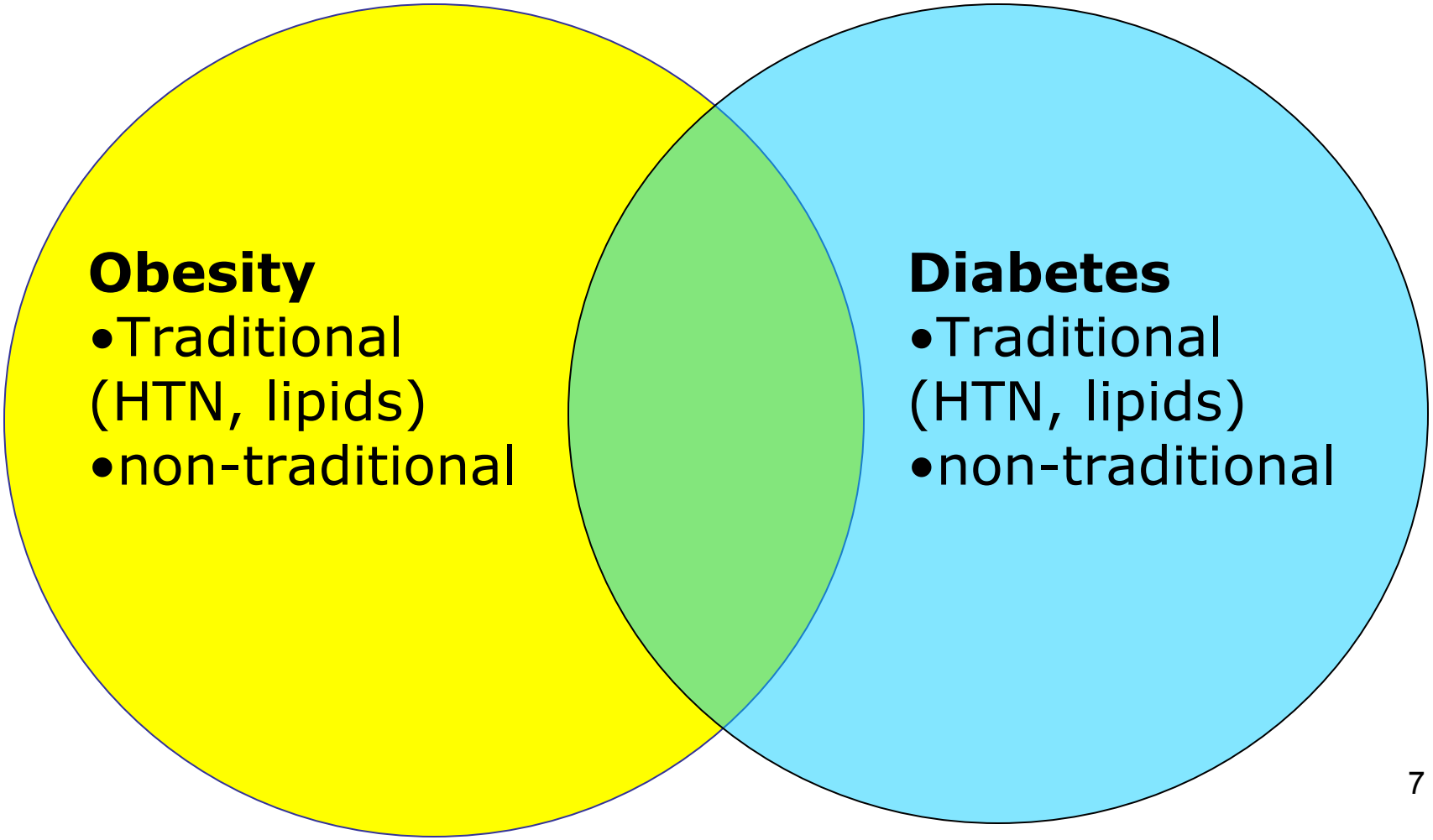
Obesity and Diabetes
Morbidity



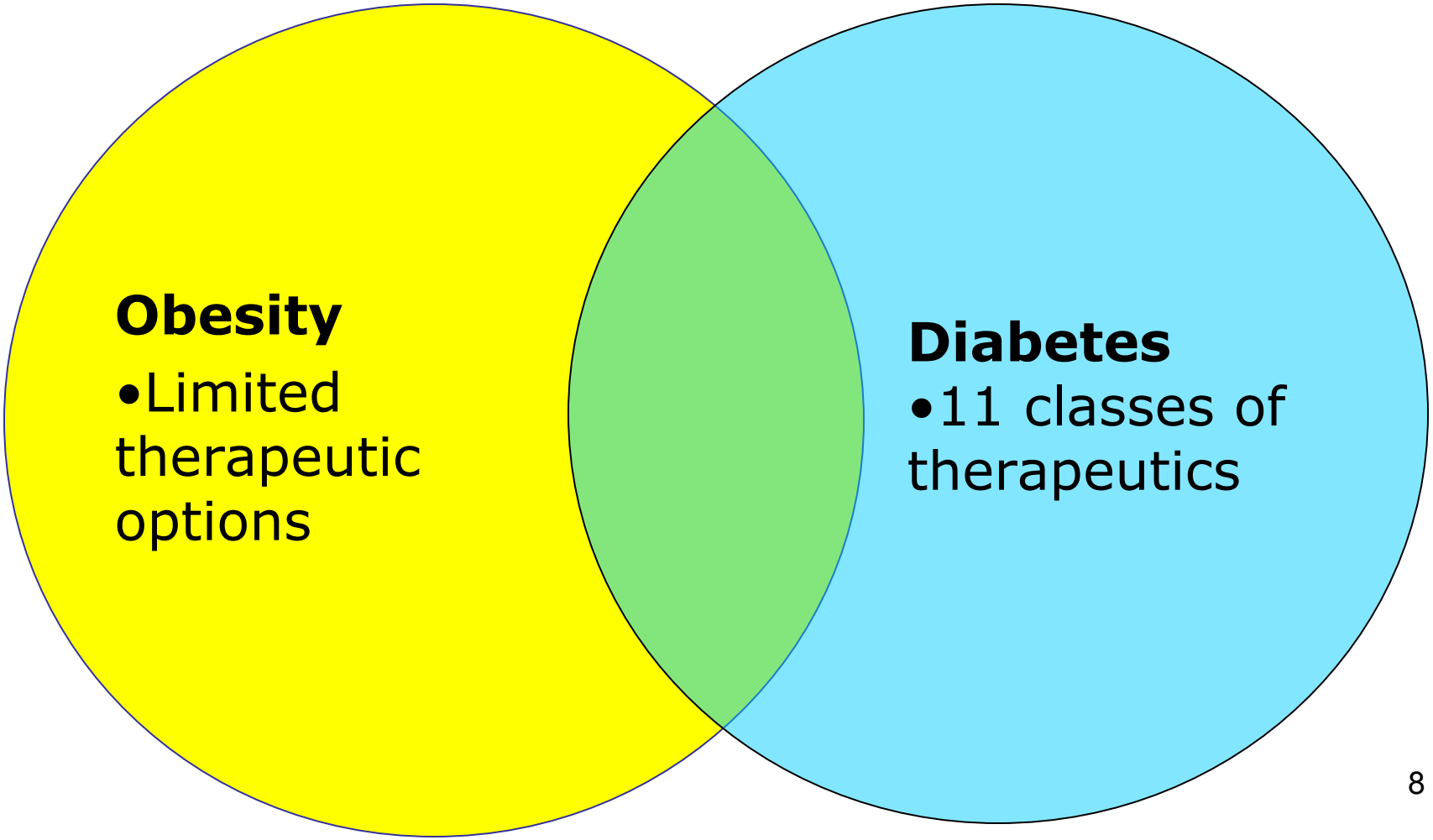
Obesity and Diabetes
Pathobiologic Target



Obesity and Diabetes
CV Risk Factors



Obesity and Diabetes
Therapy



Diabetes Facts

- U.S. Prevalence (2011)
  - 25.8 million individuals (8.3% of the population)
  - 10.9 million are ≥ 65 years old
- Morbidity
  - Leading cause of kidney failure, non-traumatic lower-limb amputations, and new cases of blindness in US adults
  - Leading cause of heart disease and stroke
  - Risk of heart disease and stroke is 2-4 times normal
- Mortality
  - Risk of death from heart disease is 2-4 times normal
  - In adults ≥ 65 years old; CVD often listed as the cause of death in diabetes-related death certificates
    - Heart disease noted in 68%
    - Stroke noted on 16%

CDC: National diabetes fact sheet

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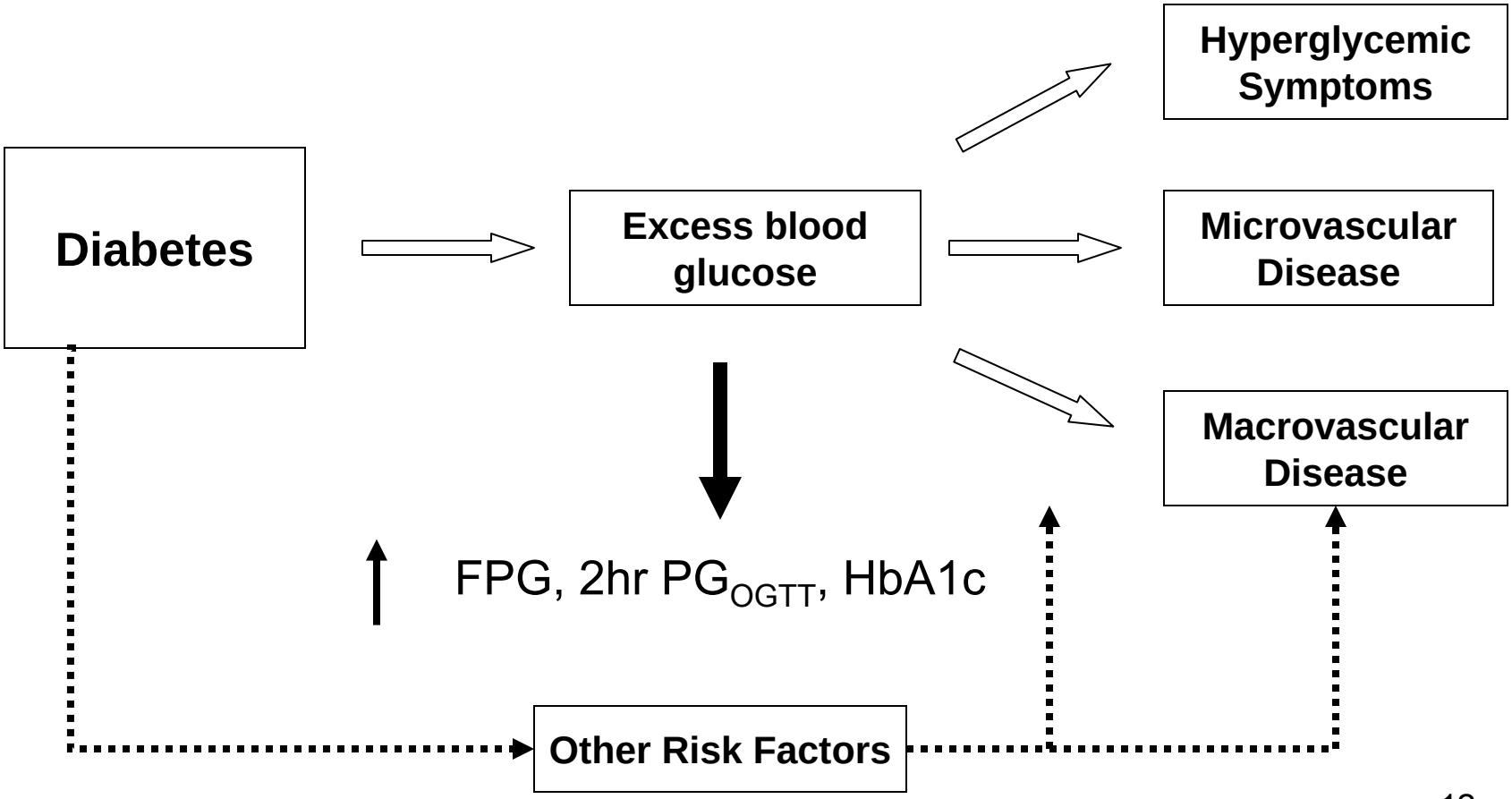
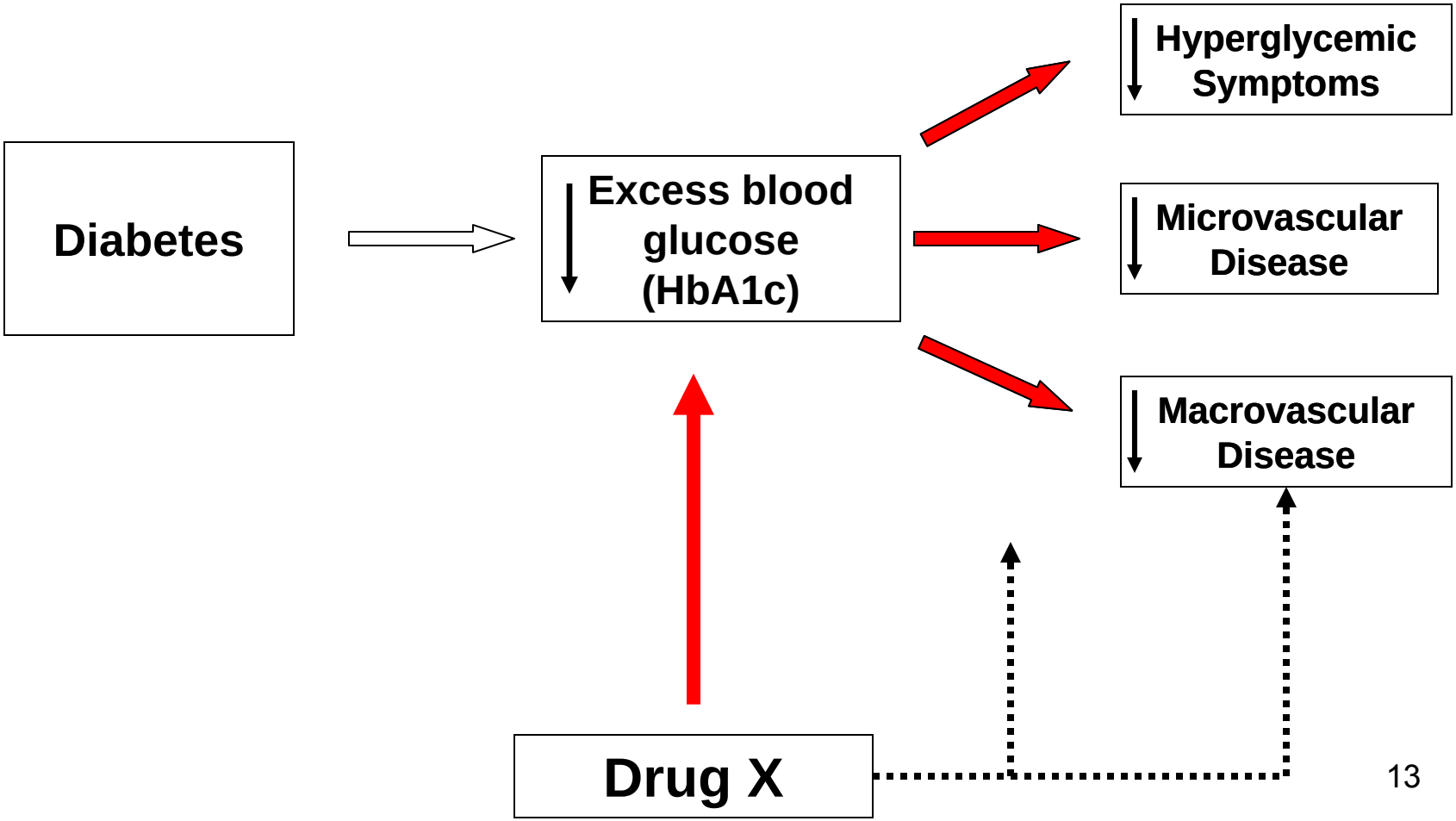
CDC: National diabetes fact sheet

Diabetes: Disease Model



Diabetes: Therapeutic Model



Benefit of Targeting Glucose

- Acute
  - Improves symptoms and signs of hyperglycemia
- Chronic
  - Reduces onset and progression of microvascular complications
    - Diabetes Control and Complications Trial: Type-1 DM
    - Kumamoto and United Kingdom Prospective Diabetes Studies: Type-2 DM
  - Not consistently associated with a reduction in macrovascular disease risk

DCCT *NEJM* 1993;329:977-86.
UKPDS33 *Lancet* 1998;352:837-53.
UKPDS34 *Lancet* 1998;352:854-65.

Glucose Control and CV Risk

- Strategies to Improve Glucose Control:
  - Decreased CV risk and decreased mortality
    - DCCT and EDIC studies
    - UKPDS 10-year follow-up study
  - Early termination due to increased overall mortality
    - ACCORD
  - No effect on CV risk or mortality
    - ADVANCE
    - VADT
- Specific Therapeutics
  - Suggestion of CV risk
    - Tolbutamide; UGDP study
    - Recent examples

EDIC: *NEJM* 2005 353, 2643–2653
UKPDS *NEJM* 2008 359, 1577–1589
ACCORD: *NEJM* 2008 358, 2545–2559
ADVANCE; *NEJM* 2008 358, 2560–2572
VADT: *NEJM* 2009 360, 129–139

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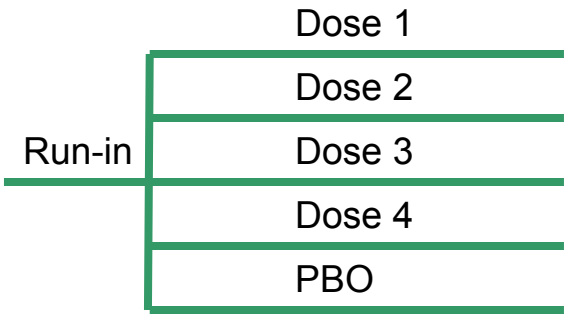
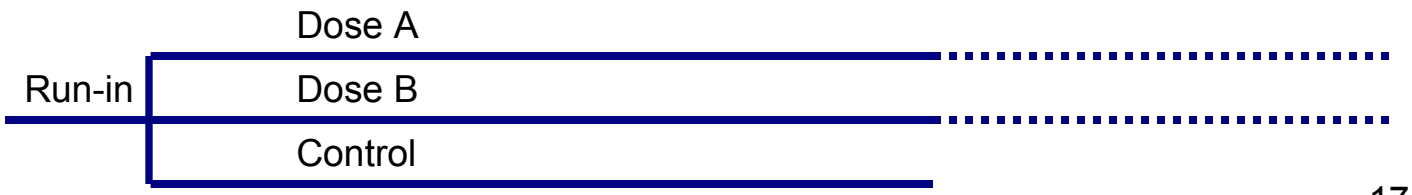
T2DM Program Before CV-Guidance

- Clinical benefit demonstrated in terms of glucose control

–Phase 2 studies: 12-week RD, DB, PBO controlled dose finding studies



–Phase 3 studies: 6-month RD, DB, controlled confirmatory studies



T2DM Program Before CV-Guidance

- Recommended investigational product exposure
  - 2500 total subjects exposed in phase 2/3 with at least
    - 1300 to 1500 subjects for 12 months
    - 300 to 500 subjects for 18 months
- Safety data
  - 6-month confirmatory controlled studies
  - 6-18 months controlled or uncontrolled extensions
- Safety analyses
  - Descriptive; Not powered to exclude excess risk
- Suggested off target safety risk
  - Evaluated by prospective trials adequately powered to exclude excess risk pre or post marketing

T2DM Program Before CV-Guidance

	Drug-A	Drug-B
Total exposed phases 2 and 3 (n)	~3400	~3400
Exposed for ≥ 6 months (n)	~2300	~2700
Exposed for ≥ 12 months (n)	~800	~2000
Total patient years (years)	~2200	~3800
Age > 65 yrs (%)	~20%	~15%
Mean DM duration (years)	~7 years	~4 years
Mean BMI (kg/m2)	~30	~32
History of ASCVD (%)	~10%	~5.5%
Total "MACE" events (n)	26	40
Event rate comparator (event/100 patient-year)	1.2	1.3

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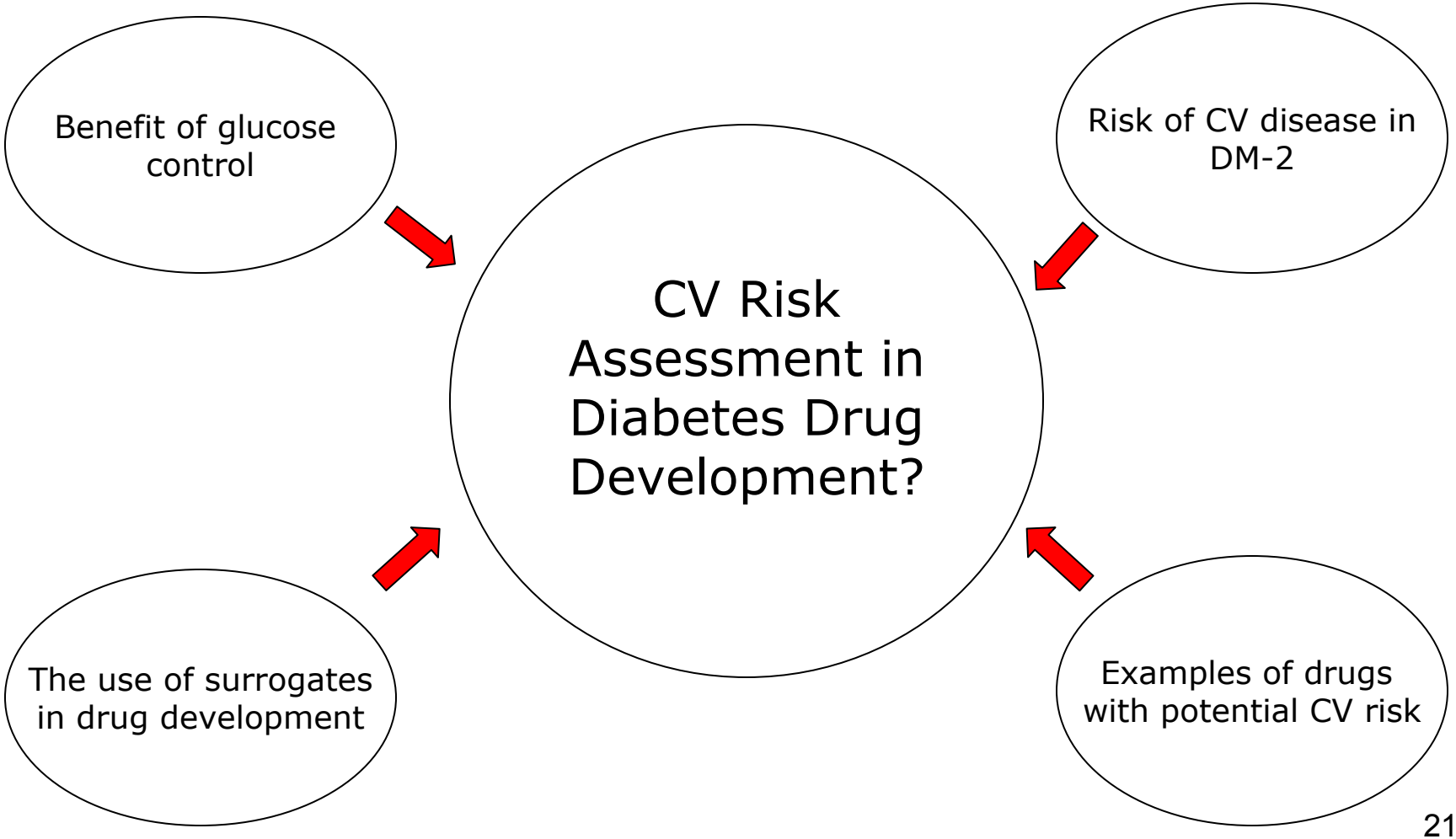
Advisory Committee: July 2008



Advisory Committee Meeting: July 2008

- Endocrinologists, diabetologists, cardiologists, statisticians and drug safety experts convened to discuss
  - Type of assessment needed (i.e., meta-analysis or dedicated study)
  - Timing of assessment (i.e., pre or post-approval)
  - Drugs to assess (i.e., all vs. only those drugs with safety signals)
  - Types of products (i.e., marketed vs. only new anti-diabetic)

Advisory Committee Meeting: July 2008

With regards to the type of assessment the following specific points were discussed

- Primary objective (i.e., to show benefit vs. to exclude risk)
  - Define an unacceptable level of risk
- Primary endpoint (i.e., MACE vs. other)
- Population (i.e., healthy vs. sick)
- Treatment comparator (placebo vs. active)
- Handling of glucose deterioration (i.e., rescue vs. withdrawal)
- Management of other CV risk factors (local care vs. protocol specified)
- Handling of cardiovascular endpoints (blindly and independently vs. other)

Advisory Committee Meeting: July 2008

"It should be assumed that an anti-diabetic therapy with a concerning CV [cardiovascular] safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. ***For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial, or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk?"***

14 **yes** votes 2 **no** votes

If "yes", please discuss when such a study should be conducted?

Most members were in favor of starting the study during the pre-approval period and completing the study during the post-approval period

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2008 Guidance Recommendations

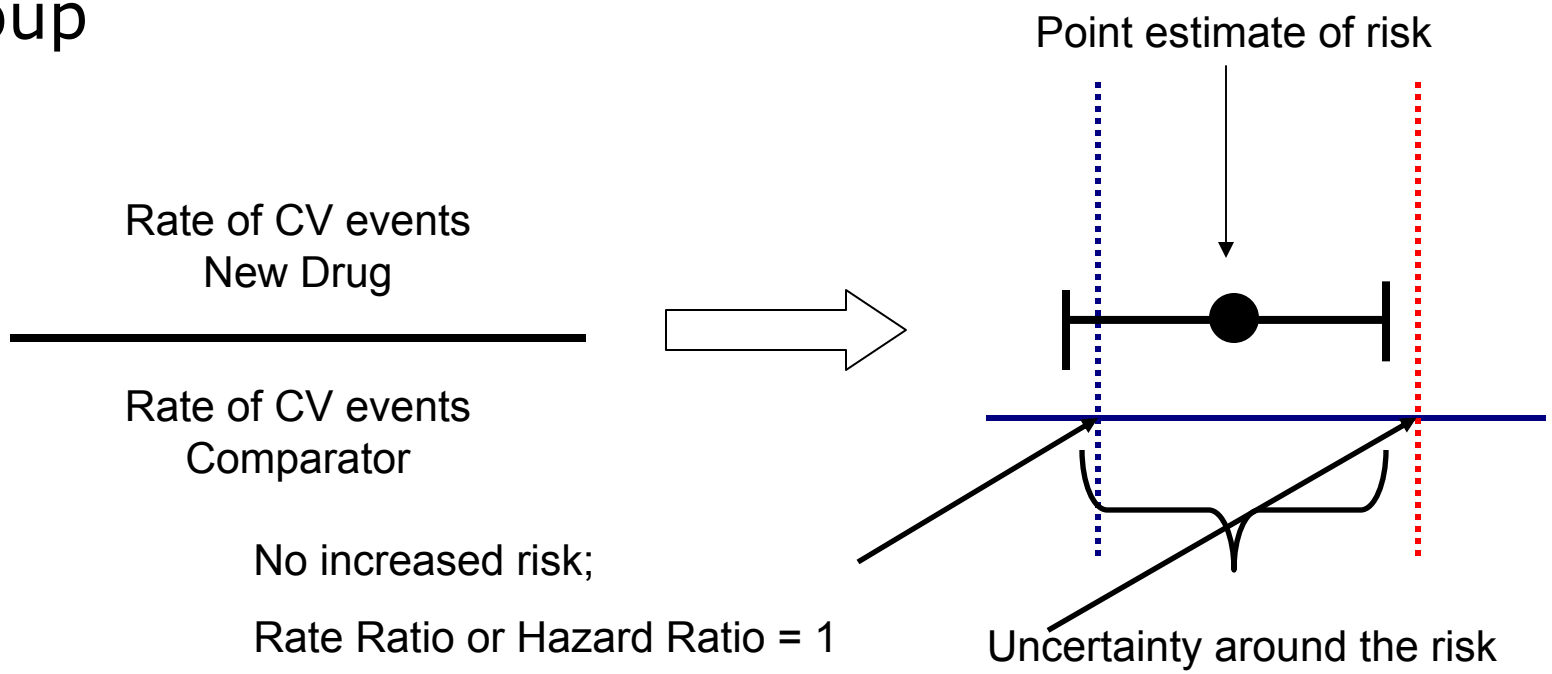
- Final guidance published December 2008
- Reaffirms HbA1c as the primary efficacy endpoint for glucose reduction
- Notes vulnerability of patients with diabetes to cardiovascular disease
- **Asks sponsors to demonstrate that new therapies for type 2 diabetes do not unacceptably increase cardiovascular risk**

2008 Guidance Recommendations

- Establish an independent CV endpoint committee to adjudicate CV death, nonfatal MI and stroke (MACE)
- Design phase 2/3 trials to allow performance of a pre-specified meta-analysis of major cardiovascular events
- Enroll patients at increased risk for cardiovascular disease
- Submit a protocol prospectively describing the statistical methods for the proposed meta-analysis

2008 Guidance Recommendations

- Use of a rate ratio to compare the incidence of major cardiovascular events with the investigational agent to the incidence in the control group



Statistical Considerations

- Two sets of hypotheses
  - **Set 1:** Null hypothesis HR > 1.8 vs. Alternate hypothesis HR ≤ 1.8
  - **Set 2:** Null hypothesis HR > 1.3 vs. Alternate hypothesis HR ≤ 1.3
- Goal is to test each null hypothesis and reject both (i.e., non-inferiority for both margins)
- Testing can occur simultaneously (pre-market data sufficiently strong to reject both) or sequentially
- Probability of falsely rejecting the null (alpha-error) is set at 2.5% for each null hypothesis

Margins and Regulatory Decision

UPPER BOUND OF 95% CI FOR RATE or HAZARD RATIO	CONCLUSION
>1.8	Inadequate to support approval
>1.3 but <1.8*	Postmarketing trial(s) needed to show definitively <1.3
<1.3*	Postmarketing cardiovascular trial(s) generally not necessary

CI=confidence interval
*with a reassuring point estimate

Approach Rationale

- A two tiered approach was selected
  - Allows marketing of a product after some reassurance of CV safety
  - Requires that additional assurance of CV safety be provided after marketing
- This approach aimed to balance the need for adequate CV safety assurance with the need to make new therapies for diabetes available
- The additional uncertainty at approval is tolerated because improved glycemic control provides benefits.

Margin Selection Rationale: 1.8

- Ruling out 1.3 pre-approval would significantly delay new drug availability
  - ~ 615 events* would be required to have 90% power to rule out 1.3.
  - This number of events is at least an order of magnitude larger than that seen in development programs prior to the guidance
- Ruling out 1.8 with 90% power requires fewer (~125) events*
  - This represents a large number of CV events compared to that seen in programs prior to the guidance

*Estimates based on a logrank test; assuming a true relative risk of 1, a 1:1 randomization and a one-tailed alpha-error of 2.5%.

Margin Selection Rationale: 1.3

- Relative risk margins of 1.2, 1.3 and 1.4 were considered
- 1264* events would be needed to rule out a relative risk of 1.2 with 90% power
  - More than twice the number of events compared to 1.3
  - Assuming a 2-4%/year event rate 10-20,000 followed for 3 years
- A relative risk of 1.4 (FDA meta-analysis) observed with rosiglitazone for acute ischemic events was considered to be excessive
- 1.3 has been used in other settings for excluding excessive cardiovascular risk (e.g., COX-2 inhibitors)

*Estimates based on a logrank test; assuming a true relative risk of 1, a 1:1 randomization and a one-tailed alpha-error of 2.5%.

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Analysis of CV Risk

- The guidance provides flexibility with regards to both the type of study(ies) and the statistical considerations that can be used to evaluate CV risk in diabetes programs
  - Prospectively planned meta-analysis of phase 2 and 3 trials
  - A dedicated CV outcomes trial
  - Combination of both
- Thus far, more than 20 plans have been submitted and reviewed. Each of them differs.

Examples of Proposals

- Meta-analysis of phase 2 and 3 data in higher risk patients (to address 1.8 margin)
- Meta-analysis combining data from both phase 2 and 3 studies and from a dedicated cardiovascular safety trial
- Analysis from a single dedicated safety trial in high risk patients
- Superiority trials to demonstrate cardiovascular benefit
- It appears that all sponsors have planned or **will have to conduct a dedicated CV safety trial** to exclude a relative risk increase of 1.3

Common Design Features

- Assessment of CV risk is prospectively implemented
- Selection criteria aim to include individuals at higher risk of CVD
- Duration of exposure is increased through controlled extension
- The capture and definition of CV endpoints are standardized
- MACE +/- hospitalization for unstable angina is primary endpoint
- Events of interest are adjudicated by a blinded independent clinical endpoint committee

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6. **Diabetes programs after CV guidance**

Examples: Excluding 1.8

	Drug-A	Drug-B	Drug-C	Drug-D
Total exposed phases 2 and 3 (n)	~3400	~3400	**~5500**	**~5200**
Exposed for ≥ 6 months (n)	~2300	~2600	**~4700**	**~3600**
Exposed for ≥ 12 months (n)	~800	~1100	**~2500**	**~500**
Total patient years (years)	~2200	~3800	**~5500**	**~2500**
Age > 65 yrs (%)	~20%	~15%	**~20%**	**~25%**
Mean DM duration (years)	~7 years	~4 years	**~6**	**~7**
Mean BMI (kg/m2)	~30	~32	**32**	**31**
History of ASCVD (%)	~10%	~5.5%	**~40%**	**~30%**
Total MACE events (n)	26	40	**~110**	**~110**
Event rate comparator (event/100 patient-year)	1.2	1.3	**~1.6**	**~3.8**

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- Mary Parks, MD, Division Director,
- Eric Colman, MD, Deputy Division Director
- Hylton Joffe, MD, Team Leader Diabetes

Office of Drug Evaluation II

- Curt Rosebraugh, MD, MPH; Director

Division of Biometrics II

•Todd Sahlroot, PhD, Deputy Director

Division of Biometrics VII

•Mat Soukup, PhD; Team Lead