Implications of Drug-related Increases in Blood Pressure

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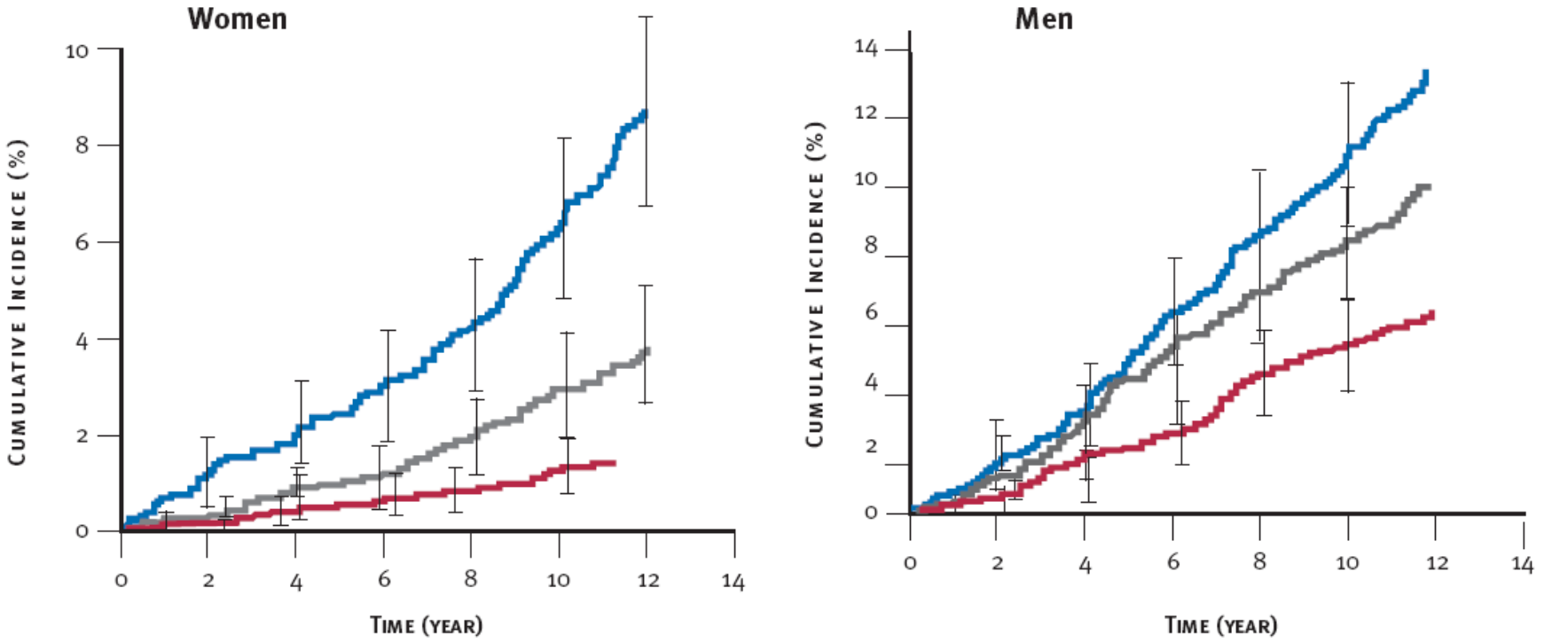
Implications of Drug-related BP Increase

- The causes for concern
  - JNC 7, Framingham
  - Multiple NDA applications demonstrating worrisome CV outcomes in the setting of drug-induced elevations in BP and/or HR
- Precedent – Sibutramine (Meridia) Experience
- Drug A – Elevated BP, small increase CV events in small studies
- What's a Regulator to do?

Hypertension is *the* major risk factor for premature CVD



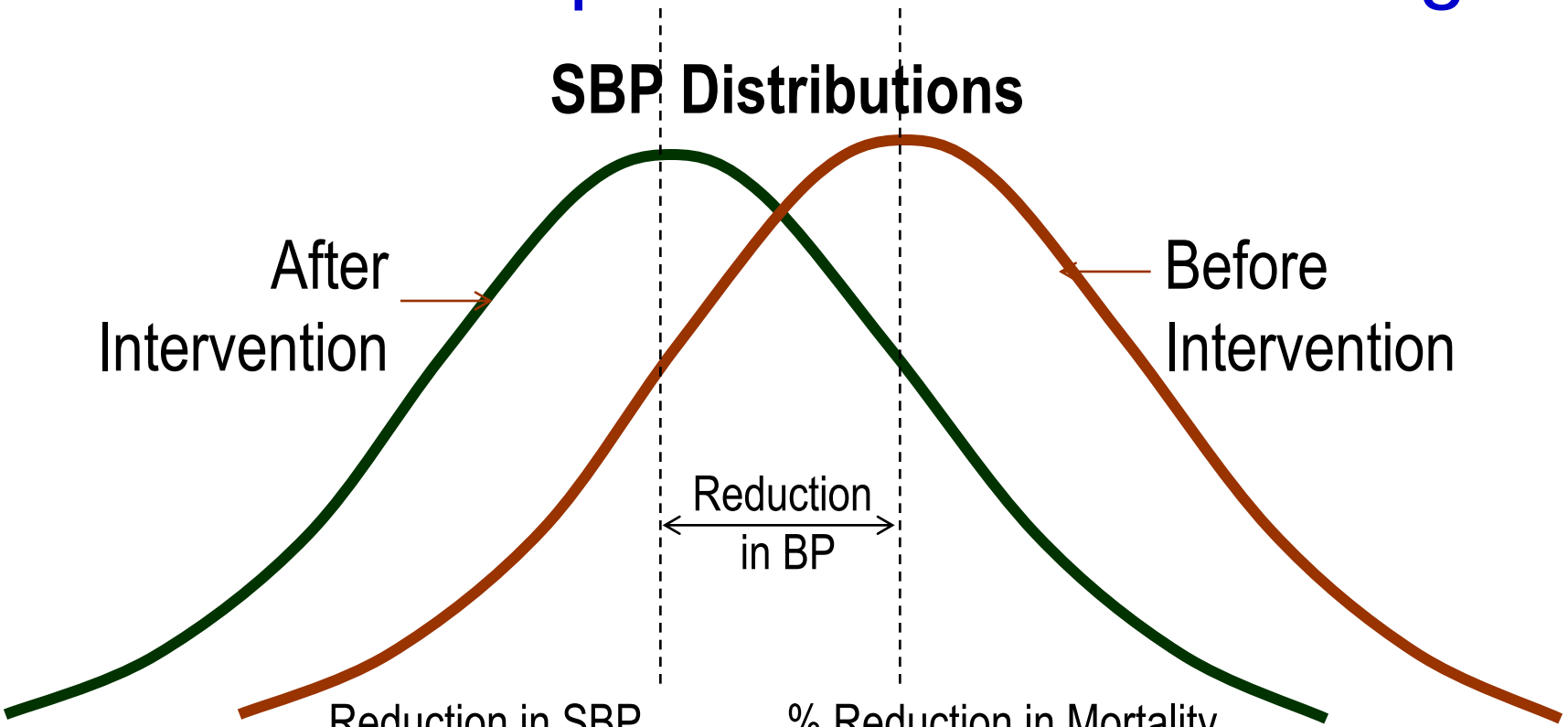
Number at Risk							
Optimal	1,875	1,867	1,851	1,839	1,821	1,734	887
Normal	1,126	1,115	1,097	1,084	1,061	974	649
High normal	891	874	859	840	812	722	520

Number at Risk							
Optimal	1,005	995	973	962	934	892	454
Normal	1,059	1,039	1,012	982	952	892	520
High normal	903	879	857	819	795	726	441

High Normal Normal Optimal

JNC VII

JNC 7 Population-Based Findings



Reduction in SBP mmHg	% Reduction in Mortality Stroke	CHD	Total
2	–6	–4	–3
3	–8	–5	–4
5	–14	–9	–7

Sibutramine

Sibutramine (Meridia)

- SNRI
- Approved in 1997 for weight management
- Sibutramine can increase BP, HR, or both
- Taken off market in 2010
  - Excessive CV risks
  - Based data from the Sibutramine Cardiovascular Outcomes, or SCOUT Trial

Sibutramine Cardiovascular Outcomes Trial (SCOUT)

- 10,744 men and women aged ≥55 with
  - history of CV disease
  - and/or type 2 diabetes mellitus with at least one other CV risk factor
- 6-week single-blind lead-in, then db randomized to sibutramine or placebo
- Primary – time to first nonfatal MI, nonfatal CVA, resuscitation after cardiac arrest, or CV death

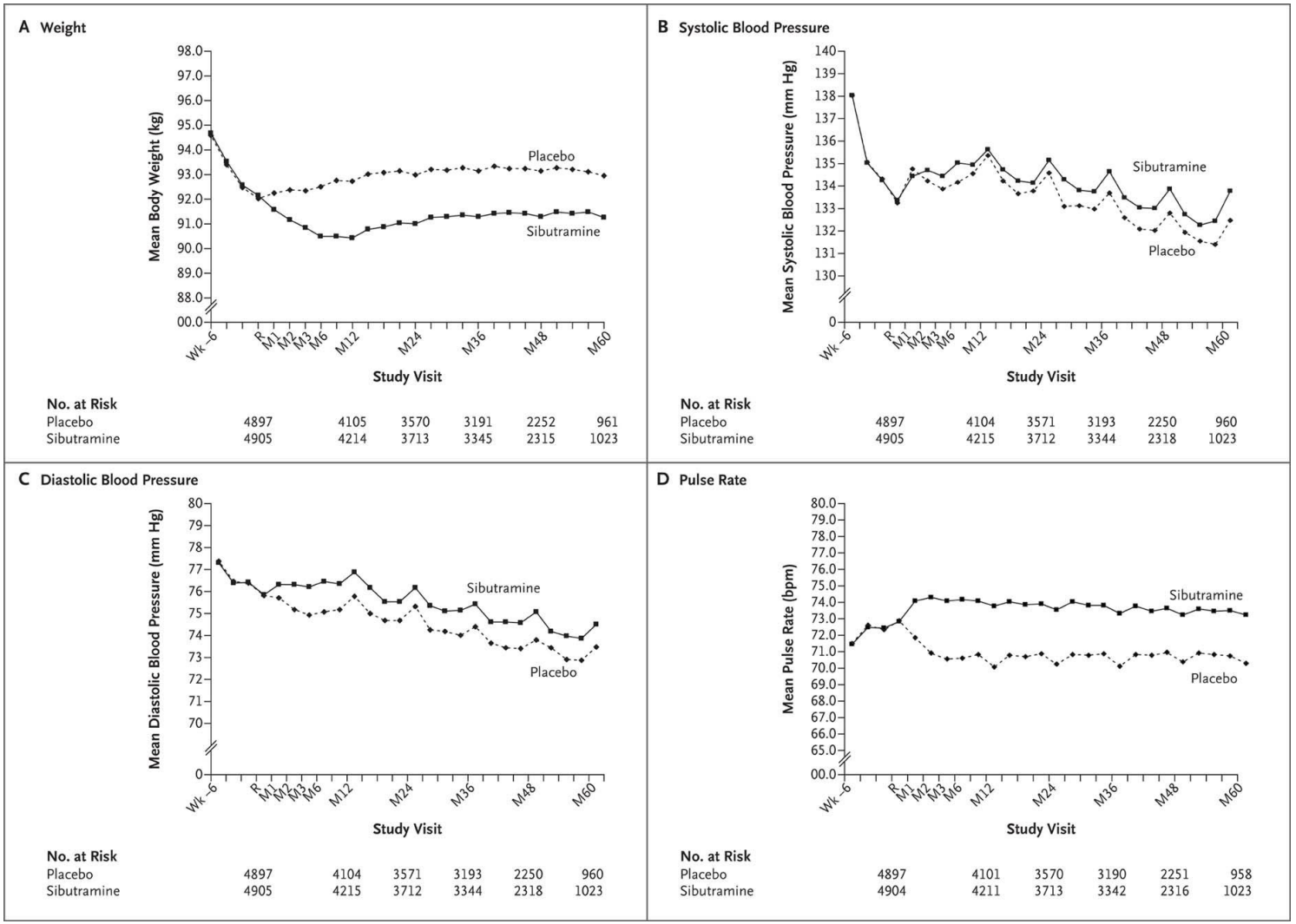
SCOUT

- Mean age 63
- Mean f/u 3.4 years,
- Mean weight loss 2.6 kg in lead-in with further

  1.7 kg loss in DB for active therapy

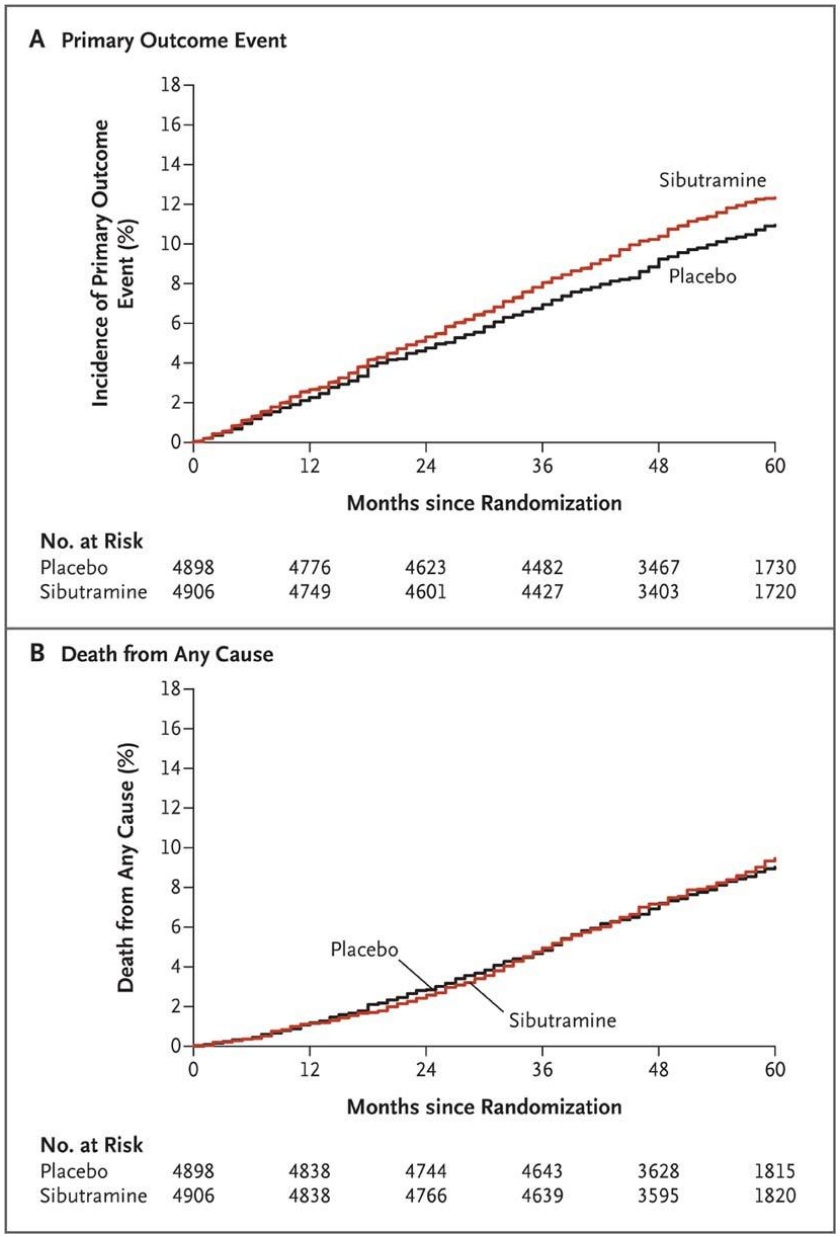
BP Trends in SCOUT

Consistently and significantly higher mean BP in SBT arm



James WPT et al. N Engl J Med 2010;363:905-917

- Primary outcome:
  - 11.4% for SBT
  - 10.0% for Pl
  - (HR 1.16; 95% CI, 1.03 to 1.31; P = 0.02)
- Possible explanations:
  - Increased BP
  - Increased HR
- Author Conclusion:
  - SBT should not be used in patients with CV disease



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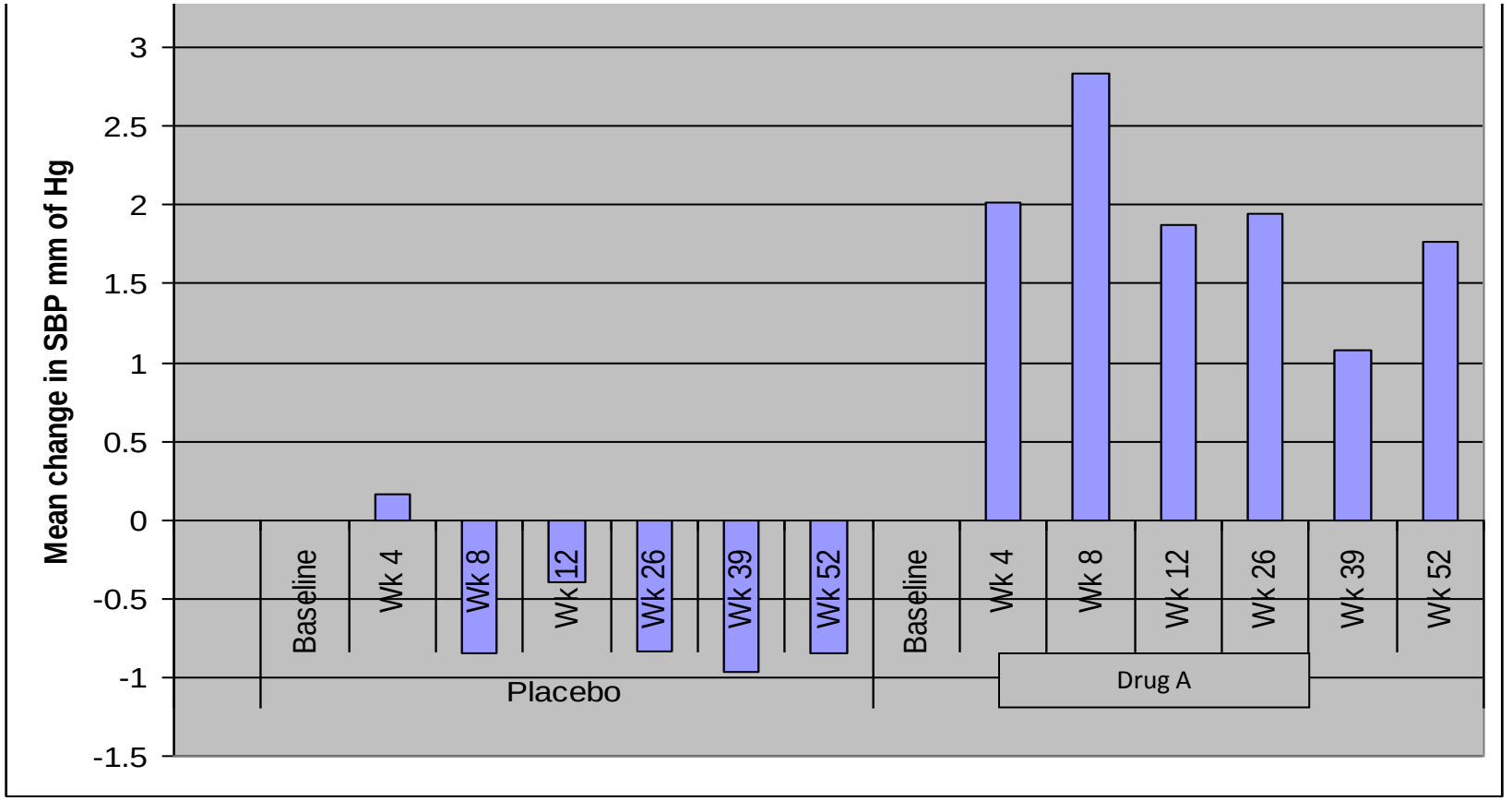
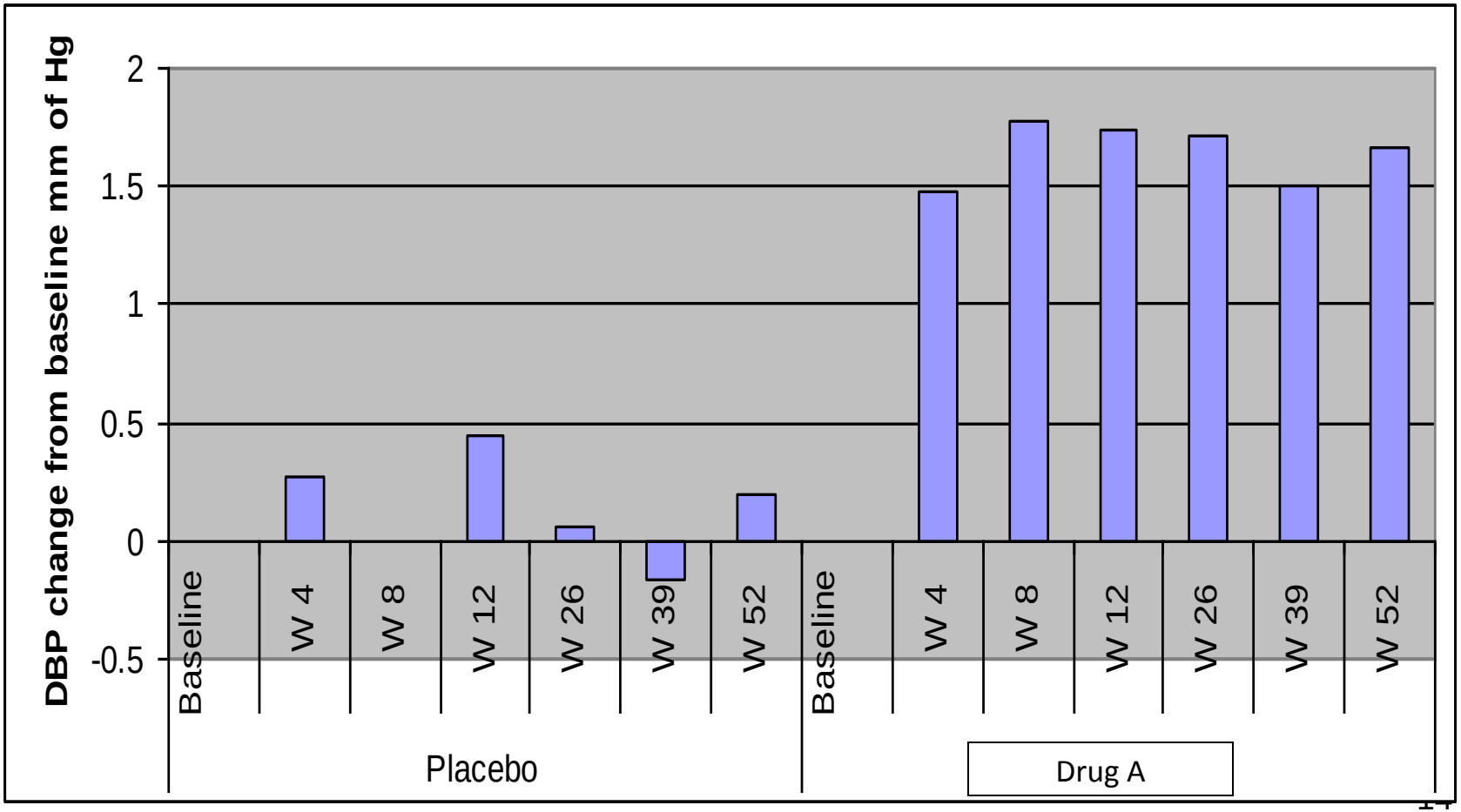
A Recent Example: Drug A

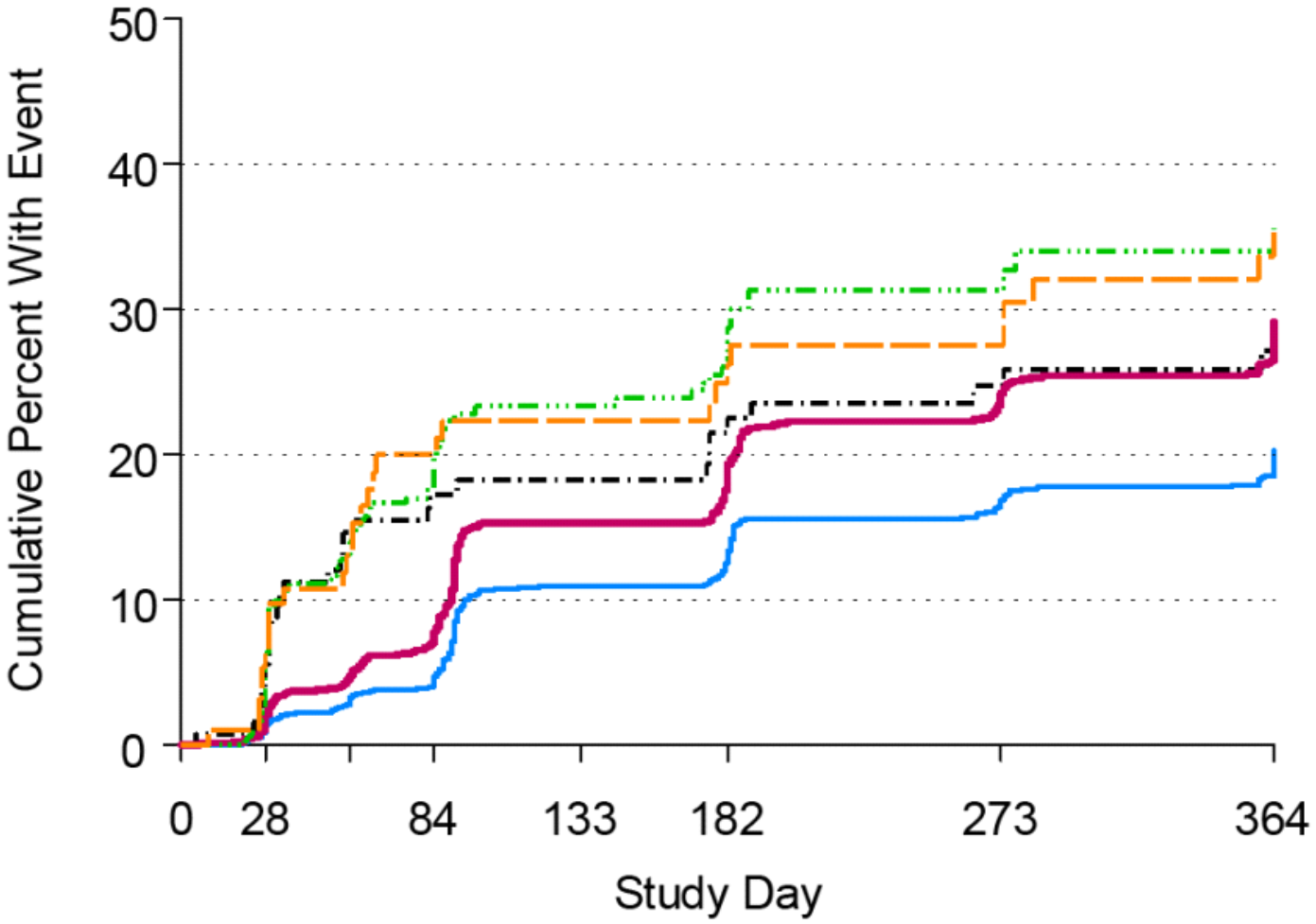
Drug A Phase 3 data: Adjusted Change from Baseline in Mean Systolic BP over Time



Drug A Phase 3 data: Adjusted Change from Baseline in Mean Diastolic BP over Time



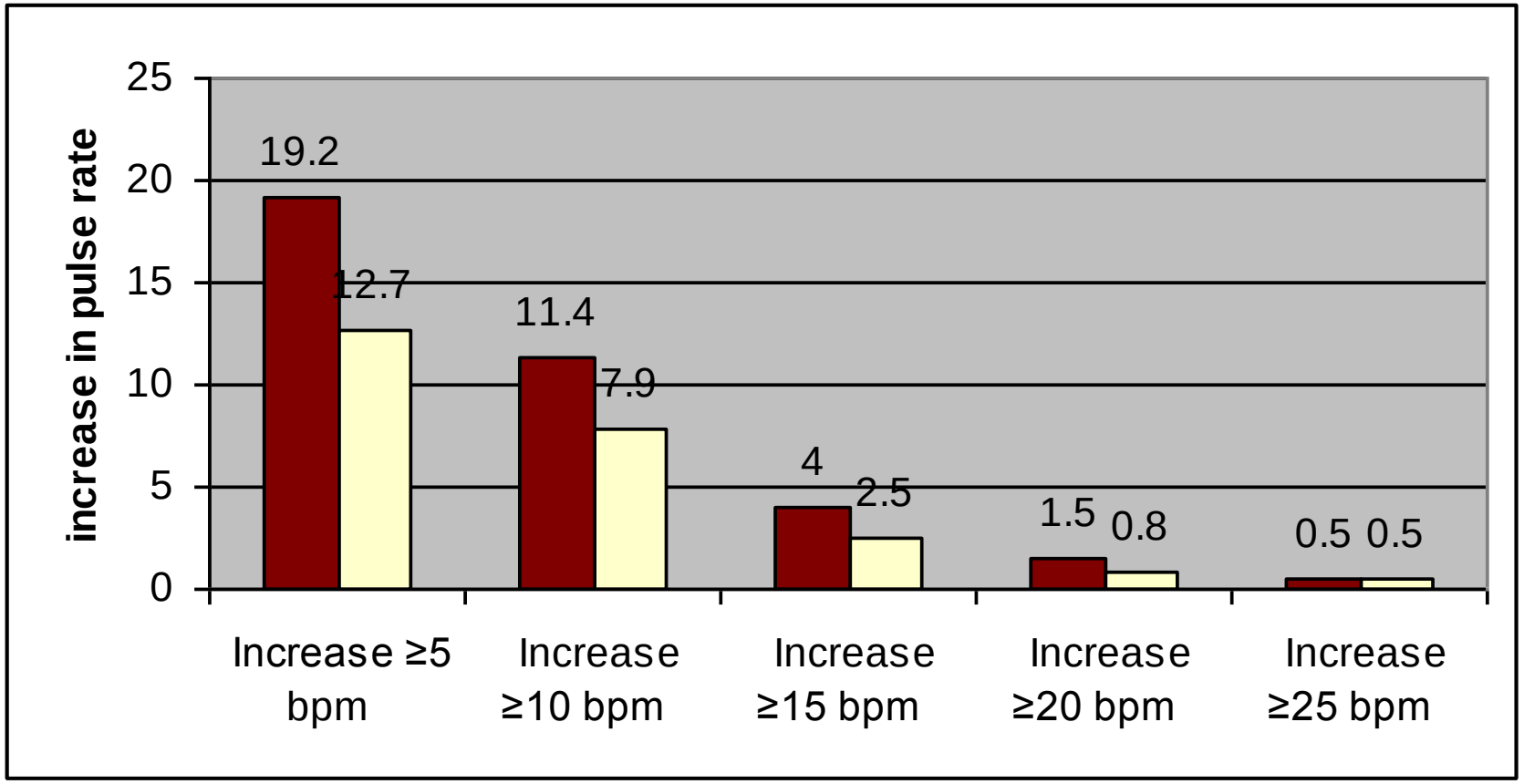
Drug A Phase 3 Data: Kaplan-Meier Analysis
Time to First SBP >140 mm Hg or DBP >90 mm



Drug A Phase 3 Data: Subjects (%) with Shifts in Blood Pressure Categories

Blood Pressure Category on Treatment →	Stage 1 Hypertension 140-159/90-99		Stage 2 Hypertension ≥160/100	
Baseline Blood Pressure Category ↓	Placebo	**"A"**	Placebo	**"A"**
	Percent of subjects			
Normal BP: <120/80 mm Hg	3.4	**3.6**	0.1	**0.3**
Pre-hypertension: 120-139/80-89 mm Hg	16.4	**22.0**	1.8	**3.3**

Drug A Phase 3 Data:
Subjects (%) w/ Increase in Pulse Rate at Week 52



Maroon = Drug A
Beige = Placebo

Five Phase 3 Trials : All Cardiovascular and Cerebrovascular SAEs

	Placebo N=1612 SEY=1030	**Drug A N=2498 SEY= 1392**
Cardiac (Identified by SMQs: Ischemic heart disease, cardiomyopathy, cardiac arrhythmias)	4	**17**
Cerebrovascular	2	**7**
Hypertension	0	**5**

Five Phase 3 Trials: FDA Adjudication of Major Adverse Cardiac Events (MACE)

	Placebo SEY=1030	Drug A SEY=1392
MACE •CHD death •New MI (non-procedure-related MI) •New onset of unstable angina requiring hospitalization •Unscheduled revascularization procedures	1	**5**
MACE "hard endpoints" + TIA/CVA •CHD-death •New MI (Non-procedure-related MI) •All cause TIA/CVA	1	**6**

Drug A Post-market Cardiovascular and Cerebrovascular Events

- 31 AERS reports since 2008
  - 23 females, 8 males
  - average age 54 years
- Average time to AE onset was 43 days
- 11 cases with life-threatening AEs and 17 cases with hospitalization
- 3 fatalities related to CV events

Summary

- BP is a principal determinate of cardiovascular adverse outcomes. The data for HR is less clear
- Lowering BP lowers risk for CV outcomes
- Some drugs that cause mild elevations in BP/HR overall are demonstrating numerically elevated CV adverse outcomes in clinical trials and post-market
- BP elevations are often seen concurrently with HR elevations
- FDA is seeing these effects in approval applications from multiple divisions
- SCOUT suggests that drug-induced elevations of BP (and HR) above placebo increase the risk for CV outcomes, though risk models demonstrating this have not been prospectively validated
  - *Implications for benefit-risk assessments of new drugs*

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