Modification of BP effects from non-CV drugs

William B. White, MD

Professor of Medicine

Chief, Division of Hypertension & Clinical Pharmacology

Calhoun Cardiology Center

University of Connecticut School of Medicine

Farmington, Connecticut

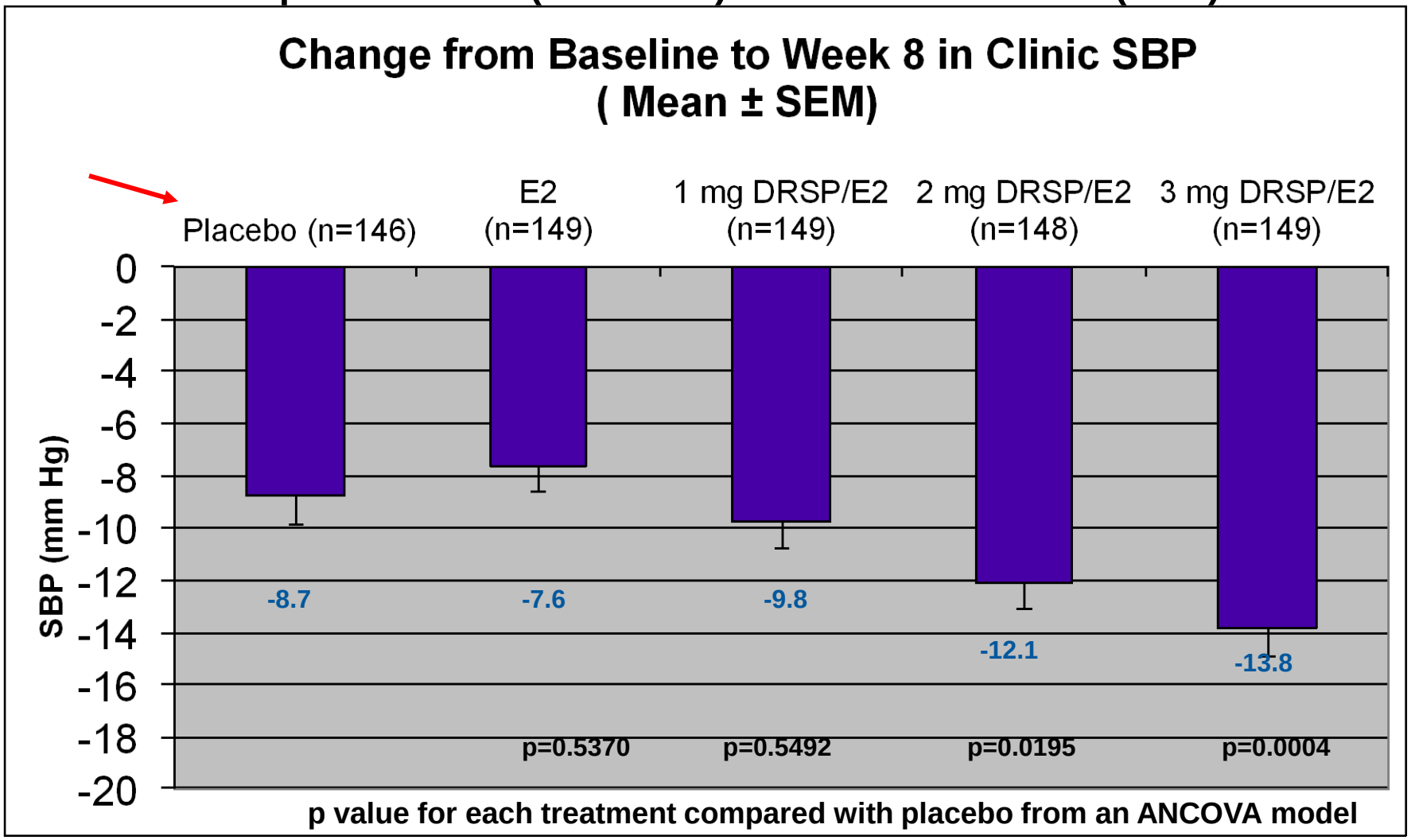
Factors that might influence BP when assessing non-cardiac drugs

- Method of measurement of BP
- Population studied (e.g., normal subjects *vs* target population *vs* higher risk groups)
- Dose and duration of exposure
- Background therapies that might mitigate BP risk

Differences in BP Measurement Methods can be Substantial

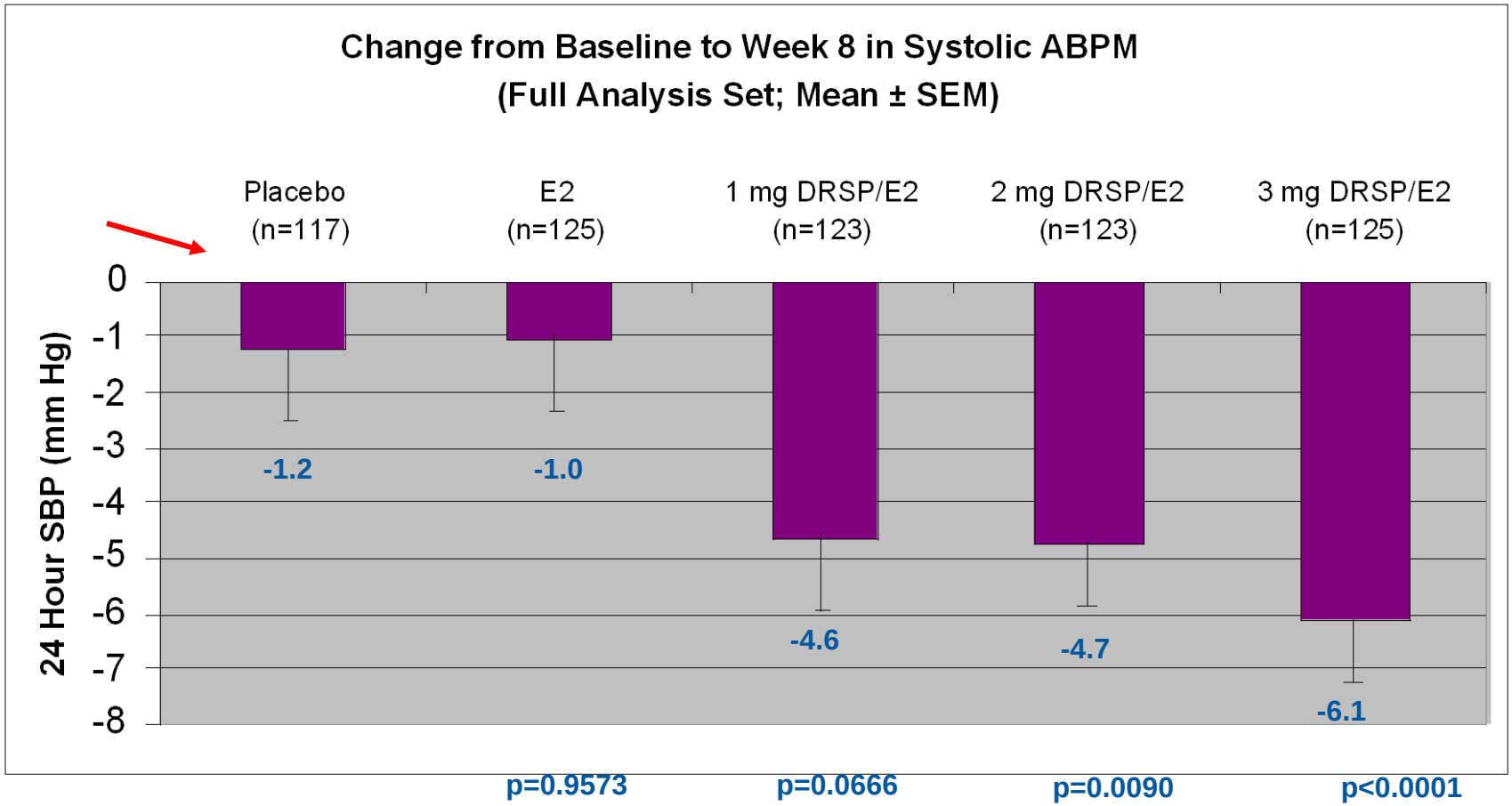
Clinic versus Out-of-Office Measurement in a Placebo Controlled Trial

When Clinic Systolic BP is the Endpoint Drospirenone (DRSP) and Estradiol (E2)



White WB, Hanes V, Pitt B, Chauhan V. *Hypertension* 2006; 48: 246-53

When 24-hour Ambulatory Systolic BP is the Endpoint Drospirenone (DRSP) and Estradiol (E2)



p value for each treatment compared with placebo from an ANCOVA model

White WB, Hanes V, Pitt B, Chauhan V. *Hypertension* 2006' 48: 246-253.

Study Population and Study Duration

NSAIDs as a Model

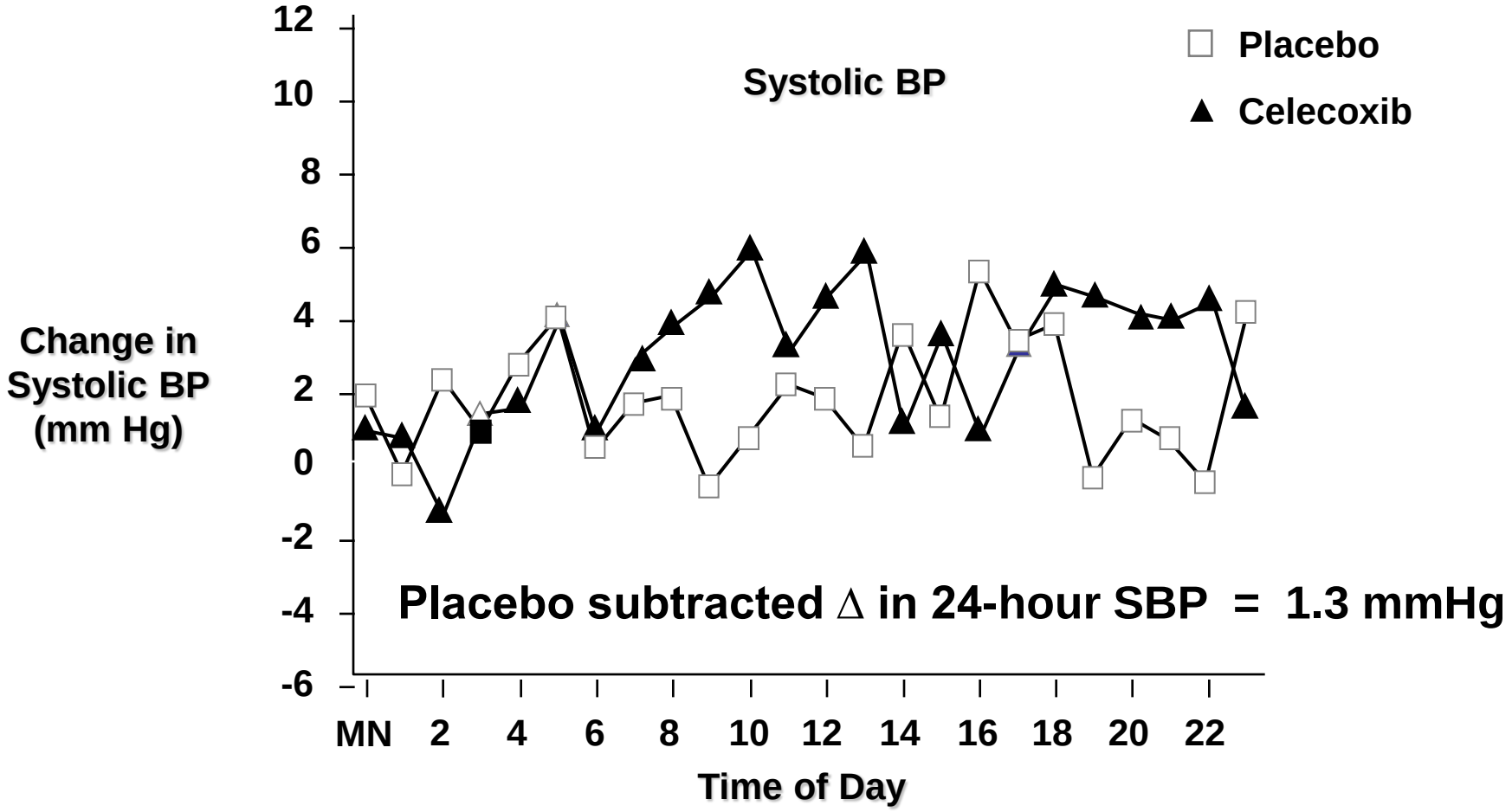
Blood Pressure Changes in Normal Volunteers Following 8 days of NSAIDs

Drug and Dose	Systolic blood pressure (mmHg)		P-value
	Day 1	Day 8	
Diclofenac 75 mg bid	123 ± 5	133 ± 6	0.08
Celecoxib 200 mg bid	124 ± 8	131 ± 5	0.23
Rofecoxib 25 mg OD	**126 ± 8**	**125 ± 8**	**0.94**
8 subjects per treatment group; mean age 54 years old			

Hinz B et al. More pronounced inhibition of cyclooxygenase 2, increase in blood pressure, and reduction in heart rate by treatment with diclofenac compared with celecoxib and rofecoxib. *Arthritis Rheum* 2006; 54: 282-291.

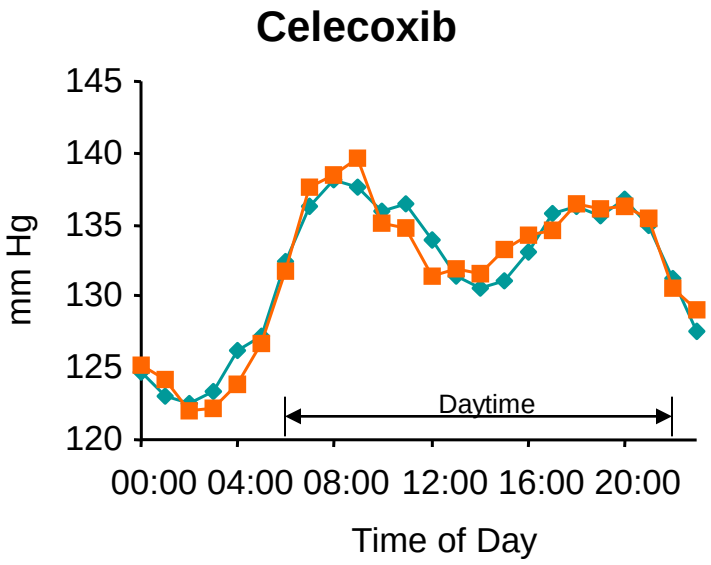
Celecoxib 200 mg BID on Ambulatory Systolic BP in ACE Inhibitor-Treated Hypertensives, non-OA

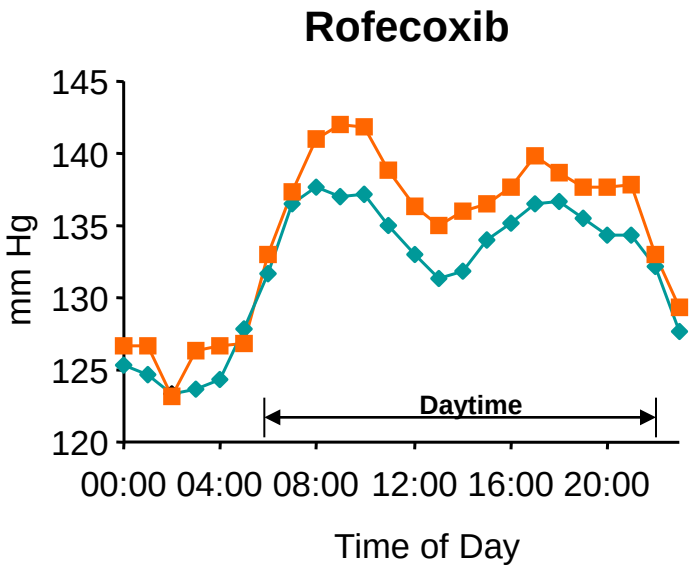
89 men and women/treatment group
mean age = 53 years

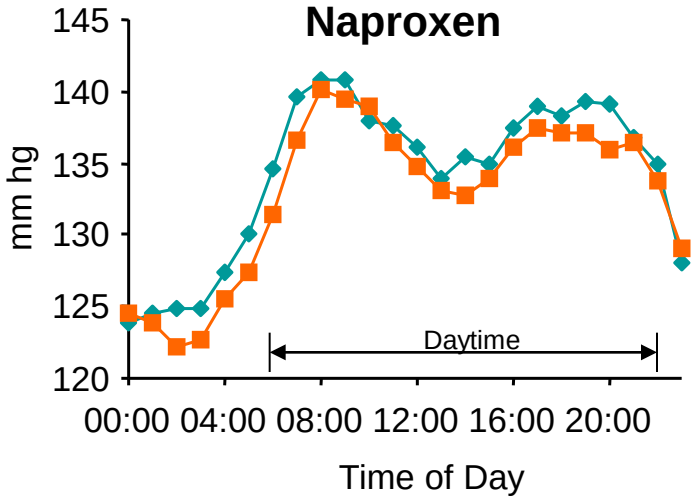


White WB et al. *Hypertension.* 2002;39:929-934.

CRESCENT Trial - 24-hr Systolic BP at Baseline and Week 6 in OA patients with Hypertension and Type 2 Diabetes







Baseline
Week 6

~135/group
Mean age, 62-64 yrs

00:00 = Midnight
ABPM initiated at 09:00 ± 2 hr
Morning dose administered within 5 min of initiating ABPM

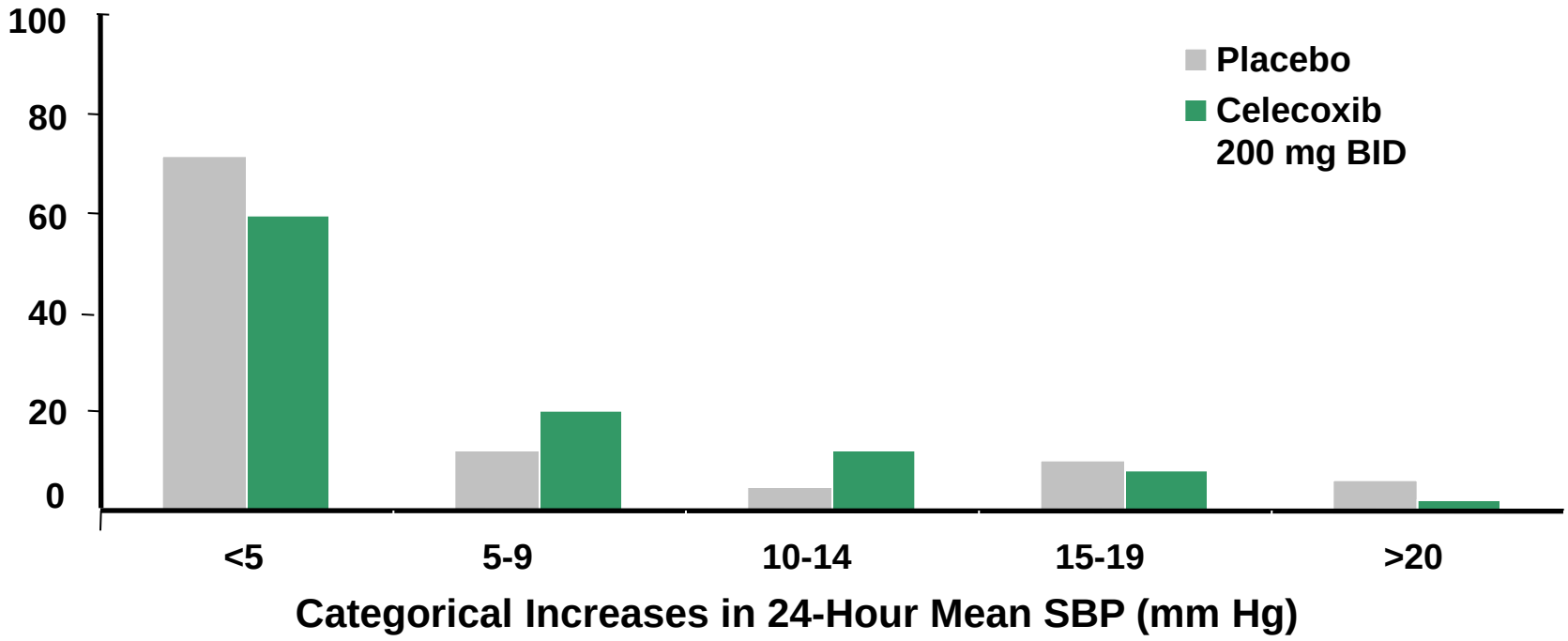
Sowers J and White WB et al. *Arch Intern Med* 2005; 165: 161-168.

Outlier values vary around mean increases

NSAIDs as a Model

Effects of Celecoxib in Hypertensives on ACE Inhibitor Therapy – Outlier Assessment

Patients With Categorical Increases in 24-Hour SBP at Week 4

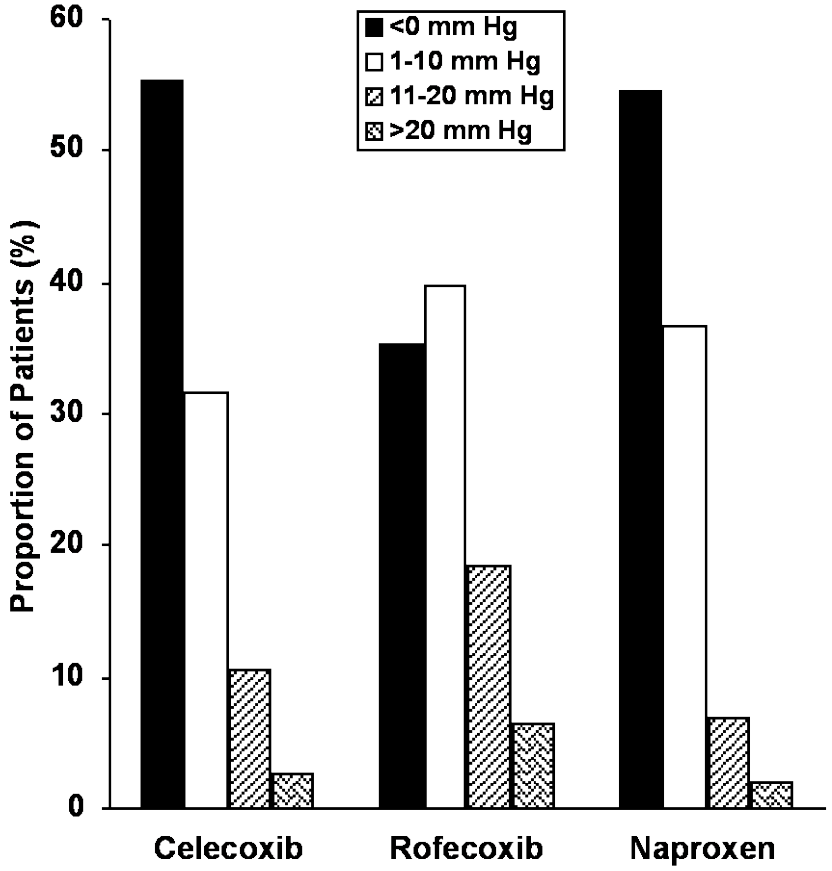


There were no significant differences in the proportions at any of the given thresholds.

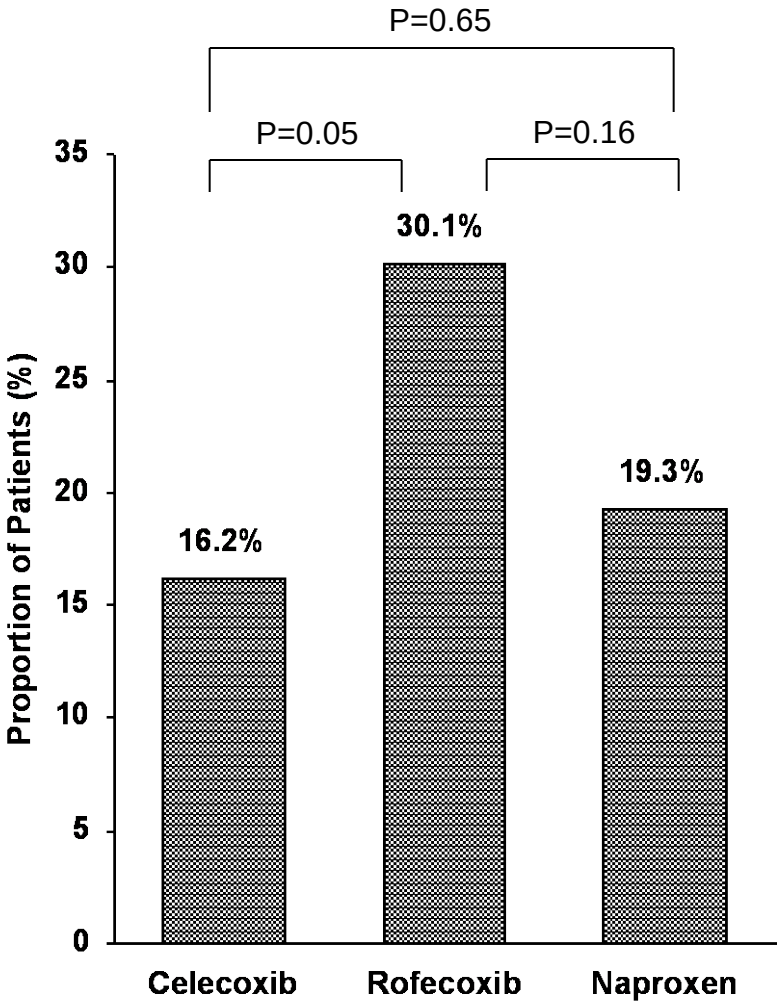
White WB et al. *Hypertension*. 2002;39:929-934.

CRESCENT Trial – Outlier Analysis in OA Patients with HTN and Diabetes

Distribution of changes in ABPM systolic blood pressure at Week 6



Proportion of normotensive patients who became hypertensive* at Week 6



*Hypertensive: Ambulatory Systolic Blood Pressure ≥ 135 mm Hg

Sowers J and White WB et al. *Arch Intern Med* 2005; 165: 161-8

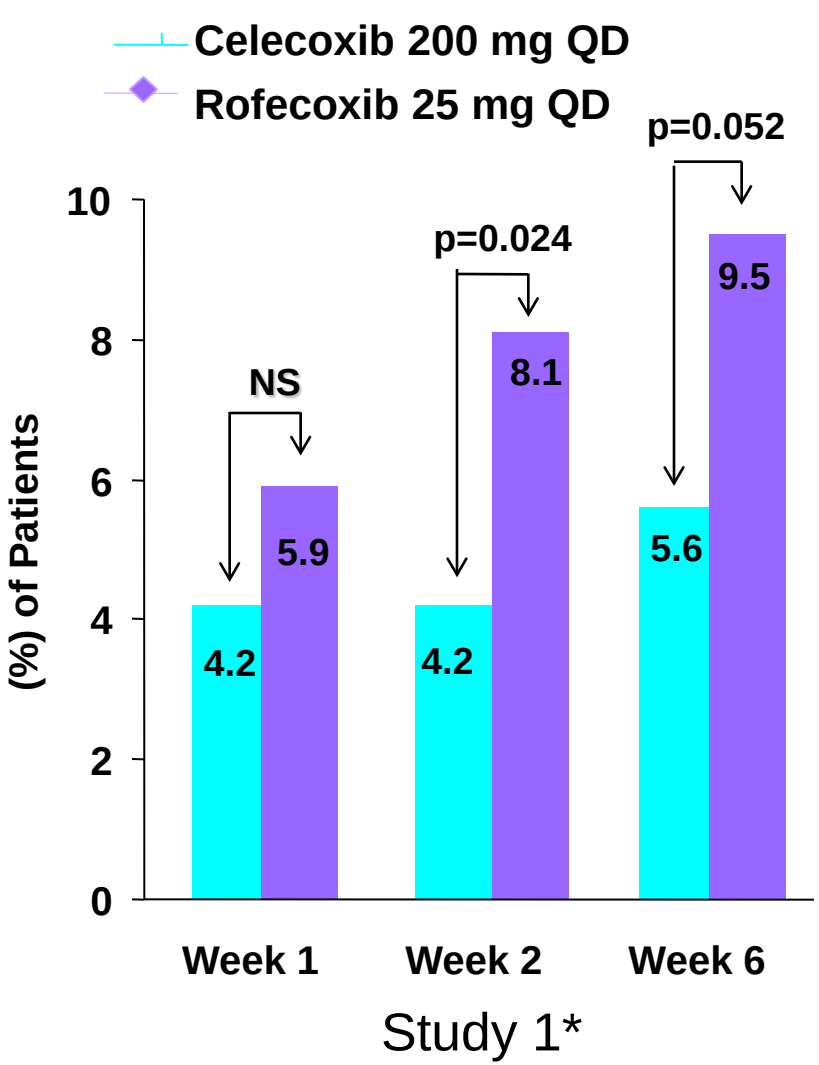
Outlier Analysis for Clinic Systolic BP after 13 weeks In Osteoarthritis Patients

		Naproxcinod (NO donator naproxen)		Naproxen
	Placebo	750 mg *bid*	375 mg *bid*	500 mg *bid*
N at week 13	**607**	**662**	**405**	**522**
Mean age, yrs	**61.7**	**61.6**	**60.5**	**61.7**
≥ 5 mmHg	**26.7**	**28.4***	**26.9***	**34.3****
≥ 10 mmHg	**15.8**	**15.3***	**18.0**	**20.7†**
≥ 20 mmHg	**3.6**	**2.4**	**4.2**	**5.9**

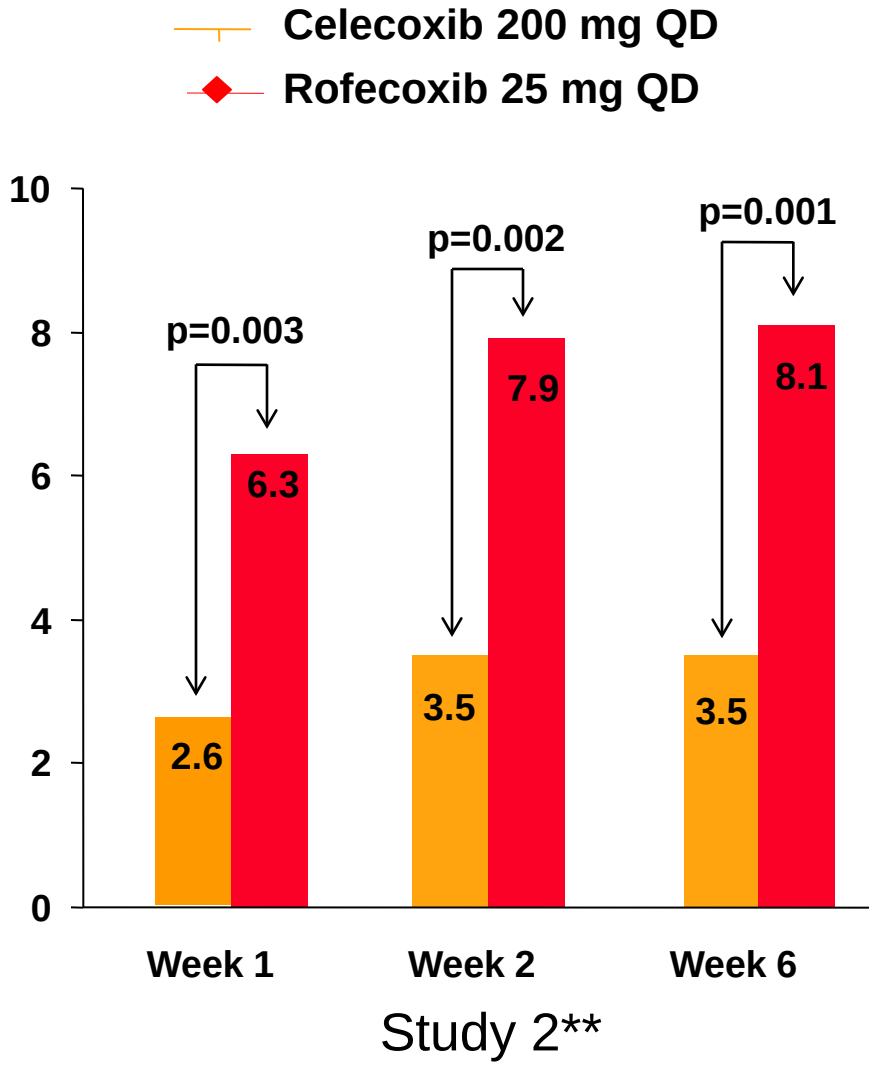
***p* < 0.02 compared to naproxen 500 mg.
***p* < 0.05 compared to placebo.
†*p* = 0.055 compared to placebo.

White WB et al. *Am J Cardiol* 2011; 107: 1338-45.

Clinic Systolic BP Elevations over Time (> 20 and > 140 mmHg) in Older Patients with OA



Study 1*

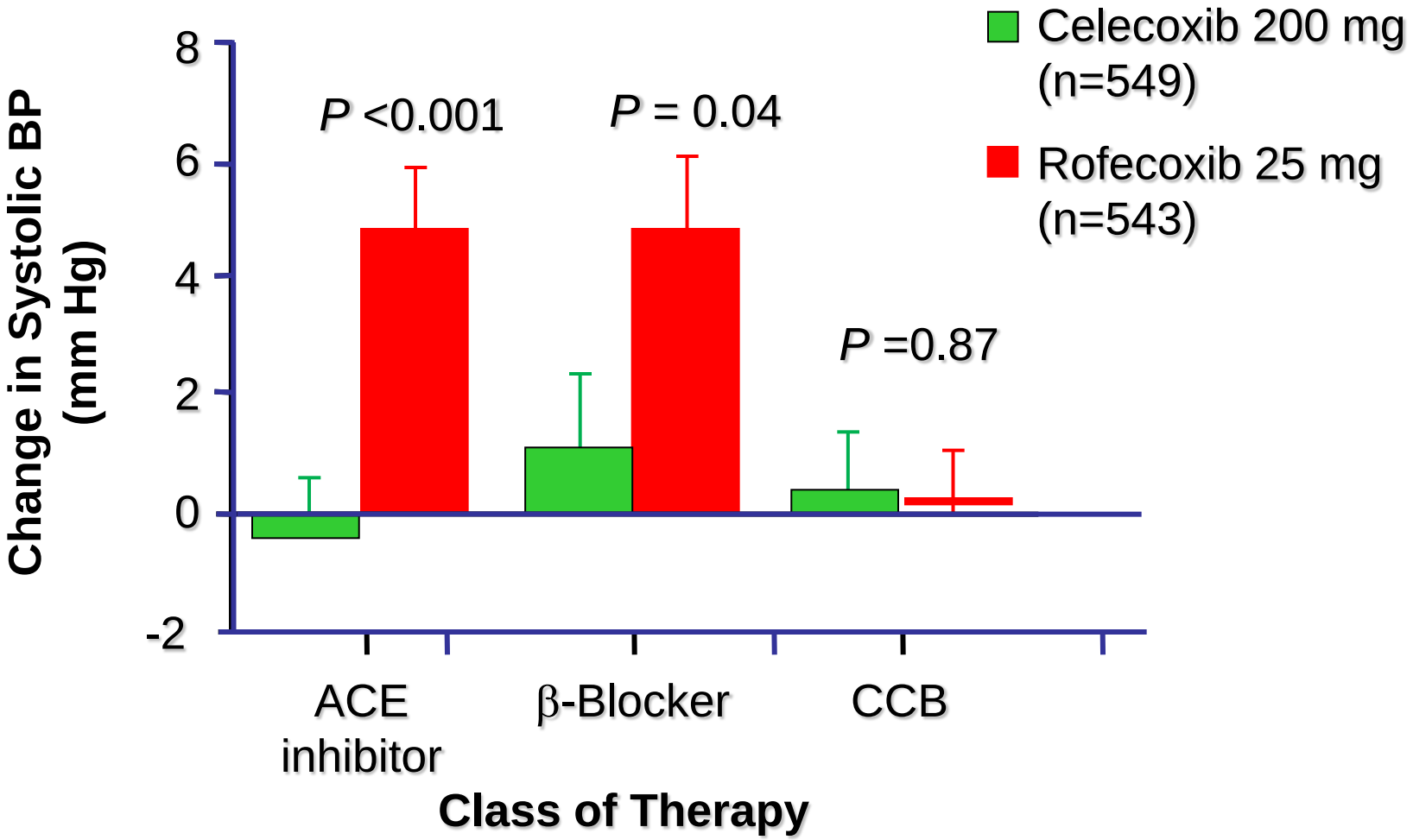


Study 2**

1. *Whelton A, et al. Am J Ther 2001;8:85-95 (400 subjects/group, mean age 68 yrs)
2. ** Whelton A, White WB. Am J Cardiol. 2002;90:959-963. (550 subjects/group, mean age 73

Mitigation of Risk of Increasing Blood Pressure

Risk Mitigation ? Background Antihypertensive Therapy (6 week trial)



Whelton A, White WB. *Am J Cardiol.* 2002;90:959-963.

Conclusions

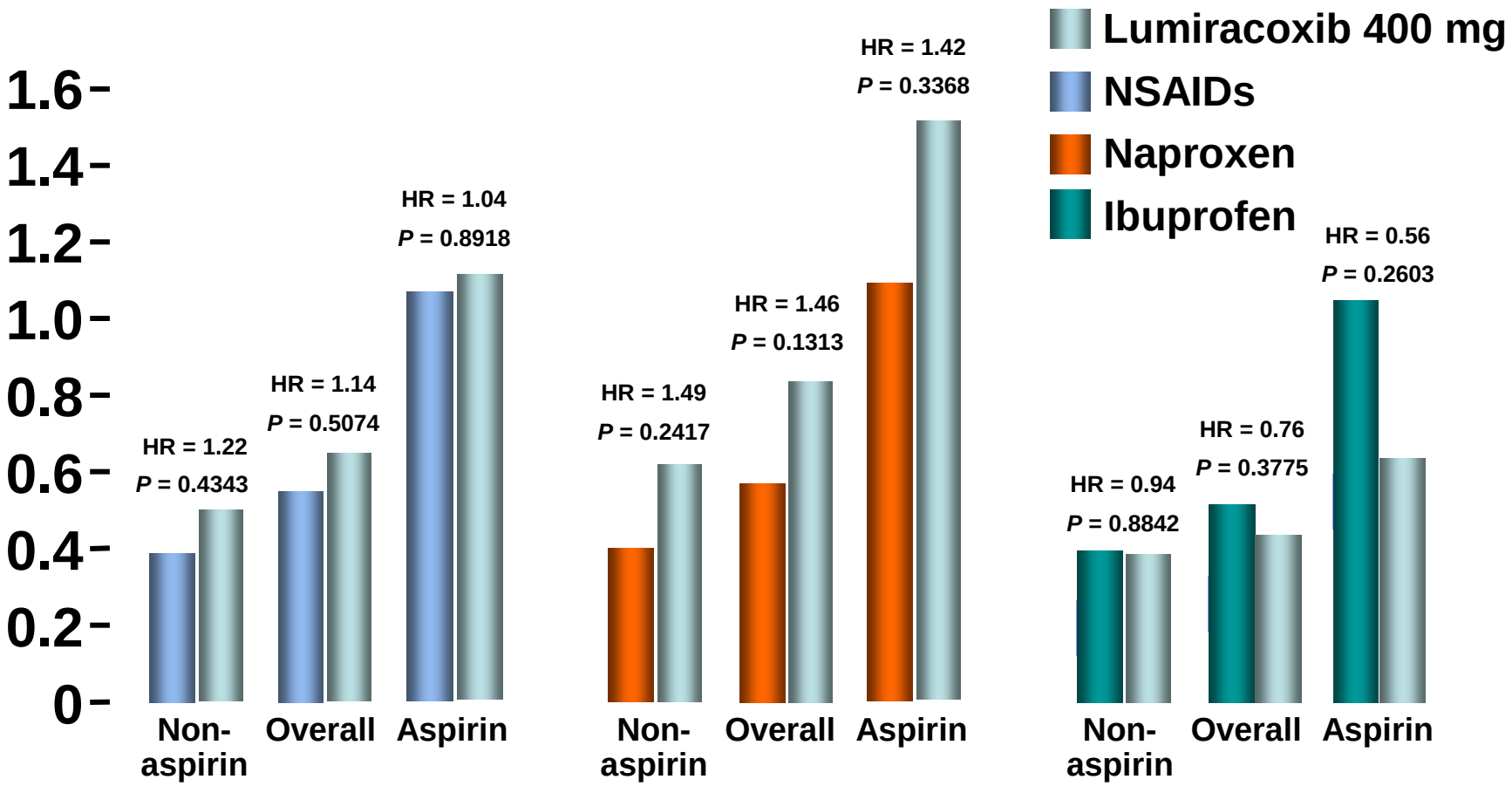
- The method of measurement of BP has important impact for a variety of reasons
- The population studied may yield varying results
- ≥ 6 weeks is likely needed to evaluate full off-target BP effect
- Ascertainment of mitigation of BP effects of non-CV drugs may be helpful in those drugs with important benefits

Additional Slides if Time Permits

Can Small Blood Pressure Increases Predict CV Risk in Non-CV Trials?

Lumiracoxib 400 mg and Specific NSAIDs in TARGET

Cumulative incidence rate of MACE (%)



Farkouh ME, et al. *Lancet*. 2004;364(9435):675-684.