

**Blood Pressure Control with
Clevidipine Compared with
Nitroglycerin, Sodium Nitroprusside, or
Nicardipine in the Treatment of
Peri-operative Hypertension:**

**Results of the Three Randomized
ECLIPSE Trials**

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Disclosures

- ▶ Abbott (Research Support)
- ▶ Baxter (Speaker)
- ▶ Medwave (Director)
- ▶ Regado Biosciences (Consultant)
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Background

- ▶ Peri-operative HTN is associated with life-threatening complications¹⁻²
- ▶ As many as 56% of cardiac surgery patients experience acute HTN requiring an IV agent^{1,3-4}
- ▶ Current antihypertensive therapies are not without limitations

¹Cheung, A. *J Card Surg*, 2006, S8

²Aronson, S. *Anesth Analg* 2002; 94:1079-84

³Estafanous, F. *Am J Cardiol*, 1980, p685;

⁴Landymore, R. *Can J Surg*, 1980

Rationale

- ▶ Clevidipine is a rationally designed IV dihydropyridine calcium channel blocker with an ultrashort half-life (~1 min)
- ▶ **Phase I & II** studies (300 pts) demonstrated:
 - Dose: 2–16 mg/hr effective¹
 - Rapid onset: BP control in 5 min²
- ▶ **Phase III** safety program required for FDA registration
 - Evaluation: Death, MI, Stroke, Renal Dysfunction
 - Comparators: Nitroglycerin (NTG), Sodium nitroprusside (SNP), Nicardipine (NIC)

¹Bailey J. *Anesthesiology* 2002;96:1086-94

²Levy J. *Anesth Analg* 2006 (in press)

Objectives

Primary

- ▶ Investigate the safety of Clevidipine in peri-operative HTN

Secondary

- ▶ Evaluate adverse events
- ▶ Examine blood pressure control

Inclusion Criteria

Pre-randomization

- ▶ ≥ 18 years of age
- ▶ Written informed consent
- ▶ Planned CABG, OPCAB, MIDCAB surgery and/or valve repair/replacement surgery

Post-randomization

- ▶ Require treatment for peri-operative HTN

Exclusion Criteria

- ▶ Women of child bearing potential
- ▶ CVA \leq 3 months of randomization
- ▶ Intolerance to calcium channel blockers
- ▶ Hypersensitivity to NTG, SNP or NIC
- ▶ Allergy to the lipid vehicle
- ▶ Permanent ventricular pacing
- ▶ Any disease/condition that would put the patient at risk
- ▶ Participation in another trial within 30 days

Treatment

▶ Clevidipine

- Initiated 2 mg/hr
- Titrated doubling increments Q 90s to 16 mg/hr
- 40 mg/hr maximum

▶ Comparators (NTG, SNP, NIC) admin per institutional practice

▶ Treatment duration up to discharge from the ICU

▶ Concomitant anti-hypertensives discouraged

Endpoints

Primary* (*Cumulative rate of clinical outcomes at 30 days*):

- ▶ Death
- ▶ MI: *symptomatic presentation, enzyme release, &/or new ECG changes*
- ▶ Stroke: *Hemorrhagic or ischemic*
- ▶ Renal Dysfunction: *Cr >2.0 with min absolute ↑ of 0.7*

Secondary

- ▶ SAEs through day 7
- ▶ BP control during the first 24 h

* Blinded CEC adjudication of all primary measures

Statistical Methods

▶ Assumptions

- Sample size (1500 pts) recommended by FDA for safety profile assessment

▶ Descriptive analytical methods

- Pre-specified safety analysis population (*pts according to actual treatment received*)
- Data pooled to provide an overall event rate for Clevidipine & comparator arms
- Pre-specified analysis of each randomized comparison

Patient Disposition

	Clevidipine	Comparators
Randomized patients	971	993
Met post-randomization criteria	755	757
Safety population	752	754
Completed study	715	719
Did not complete study	37	35
Withdrew consent	0	1
Physician decision	1	0
Lost to follow up	15	6
Adverse experience	0	0
Patient death	20	28
Other	1	0

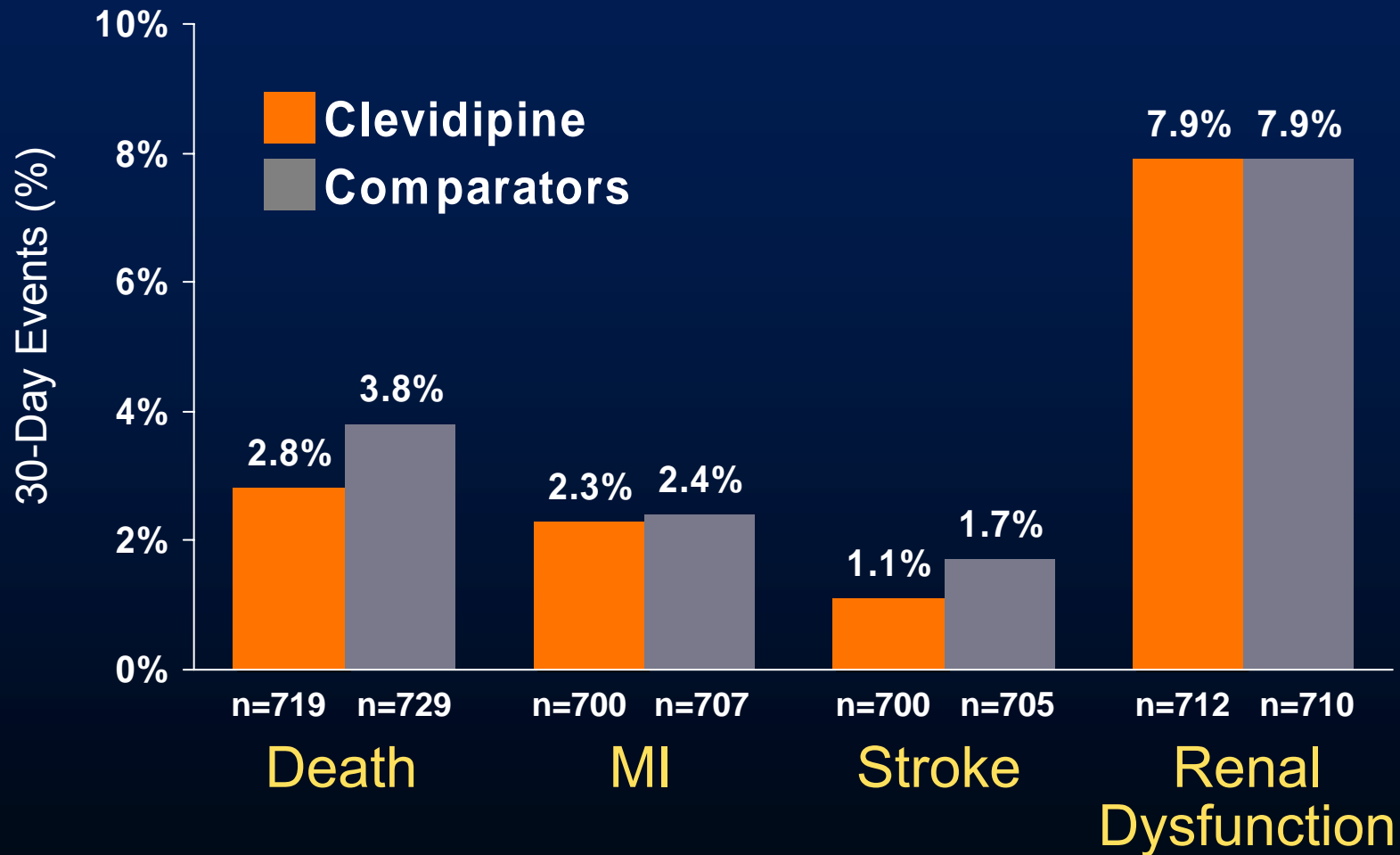
Baseline Characteristics

	Clevidipine n=752	Comparators n=754
Age, median (range)	65 (24-87)	66 (19-89)
Male	72%	74%
Caucasian	82%	83%
Hx HTN	88%	85%
CHF	19%	18%
Insulin dependent diabetes	11%	11%
COPD	14%	15%
Recent MI (< 6 mos)	17%	18%
Prior CABG	3%	6%

Procedural Characteristics

	Clevidipine n=752	Comparators n=754
Surgery duration, median hrs	3.32	3.23
Procedure		
CABG	77%	77%
Valve replacement/repair	14%	12%
CABG & Valve replacement/repair	9%	11%
Other	0.3%	0.1%

Primary Endpoint



Primary Endpoint by Treatment Comparison

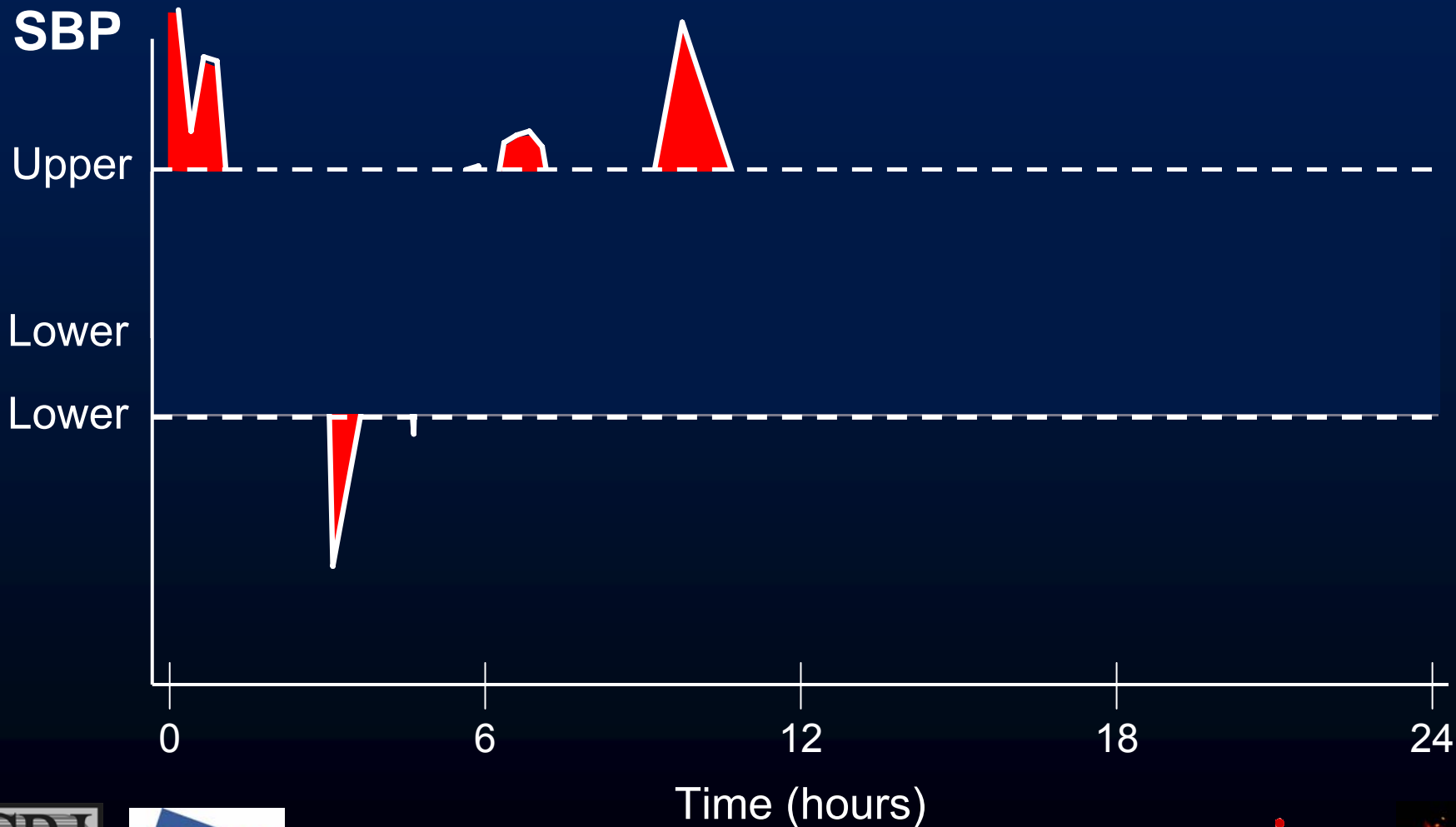
	Clevidipine	NTG	Clevidipine	SNP	Clevidipine	NIC
Death	2.8%	3.4%	1.7%	4.7%*	4.4%	3.2%
MI	3.3%	3.5%	1.4%	2.3%	2.3%	1.1%
Stroke	1.6%	2.3%	1.1%	1.5%	0.6%	1.1%
Renal Dysfunction	6.9%	8.1%	8.5%	9.1%	8.3%	5.9%

* p = 0.045

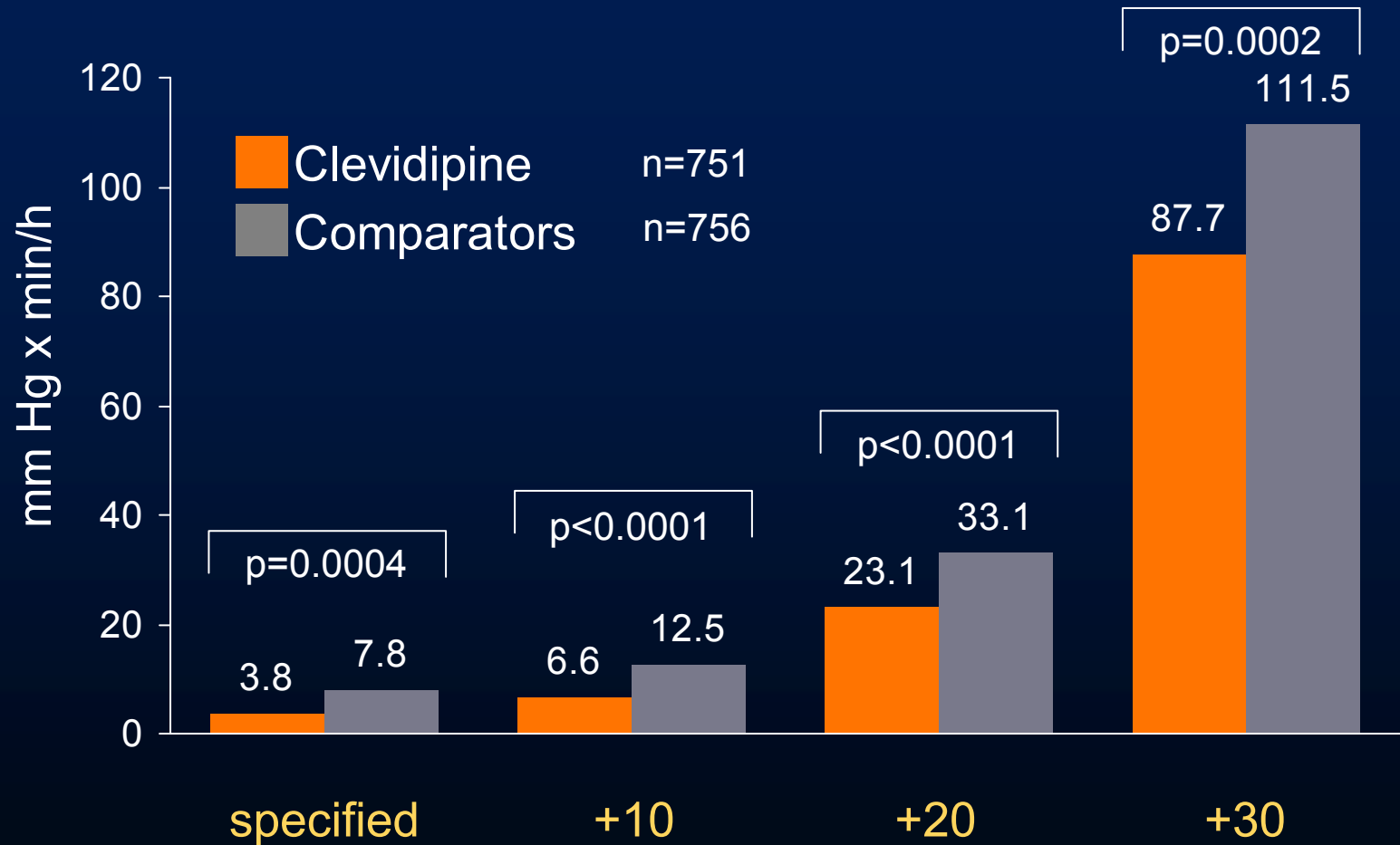
Serious Adverse Events

	Clevidipine n=752	Comparators n=754
Total	17.7%	20.0%
AFIB	2.4%	2.4%
Respiratory failure	1.1%	2.5%
ARF	2.3%	1.7%
Ventricular fibrillation	0.9%	1.5%
Cardiac arrest	0.5%	1.1%
CVA	0.5%	1.1%
Post-procedural hemorrhage	0.5%	1.1%

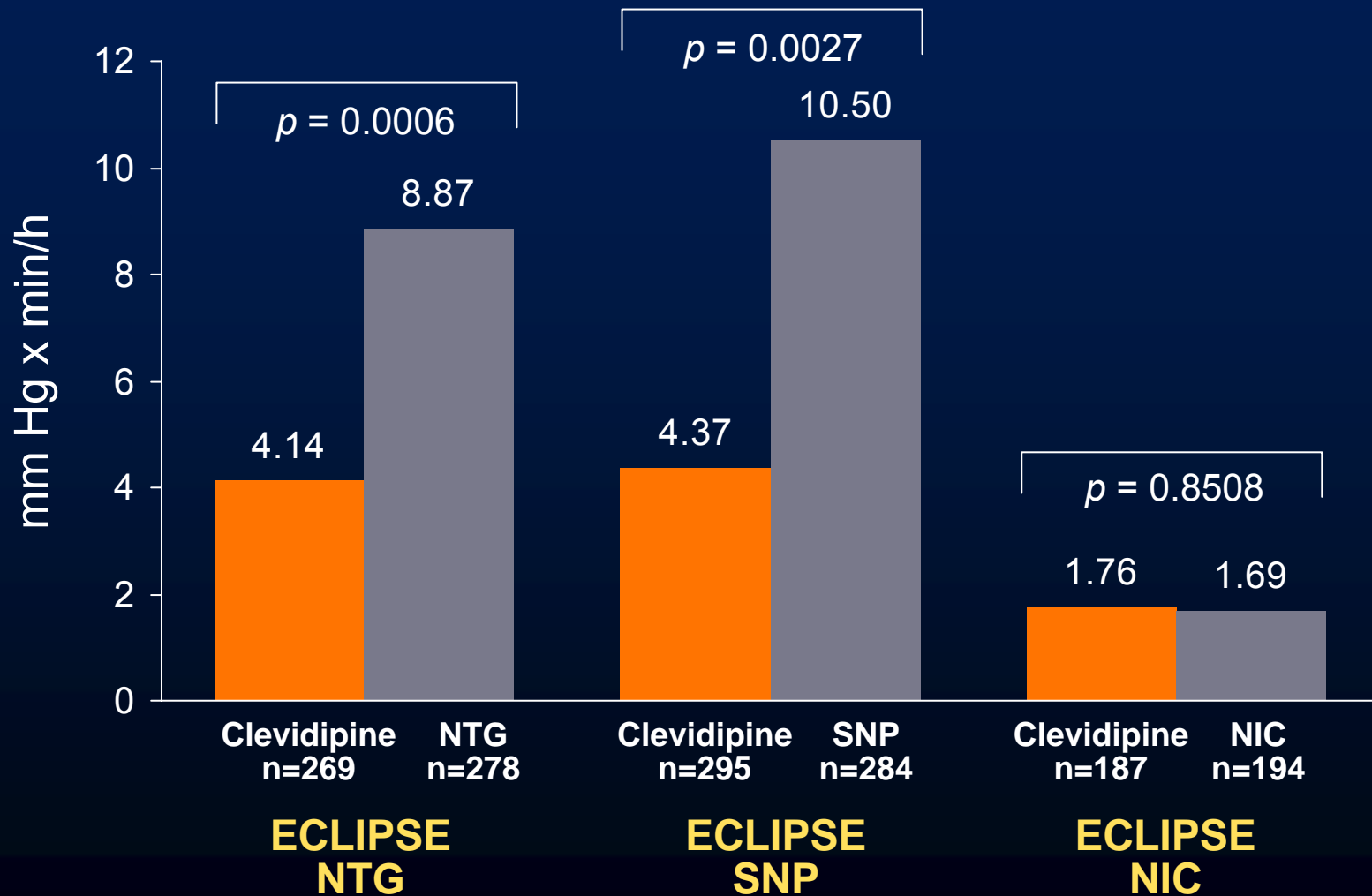
ECLIPSE Secondary Endpoint: Systolic Blood Pressure Control Over 24 Hours



Cumulative AUC at Targeted BP Ranges

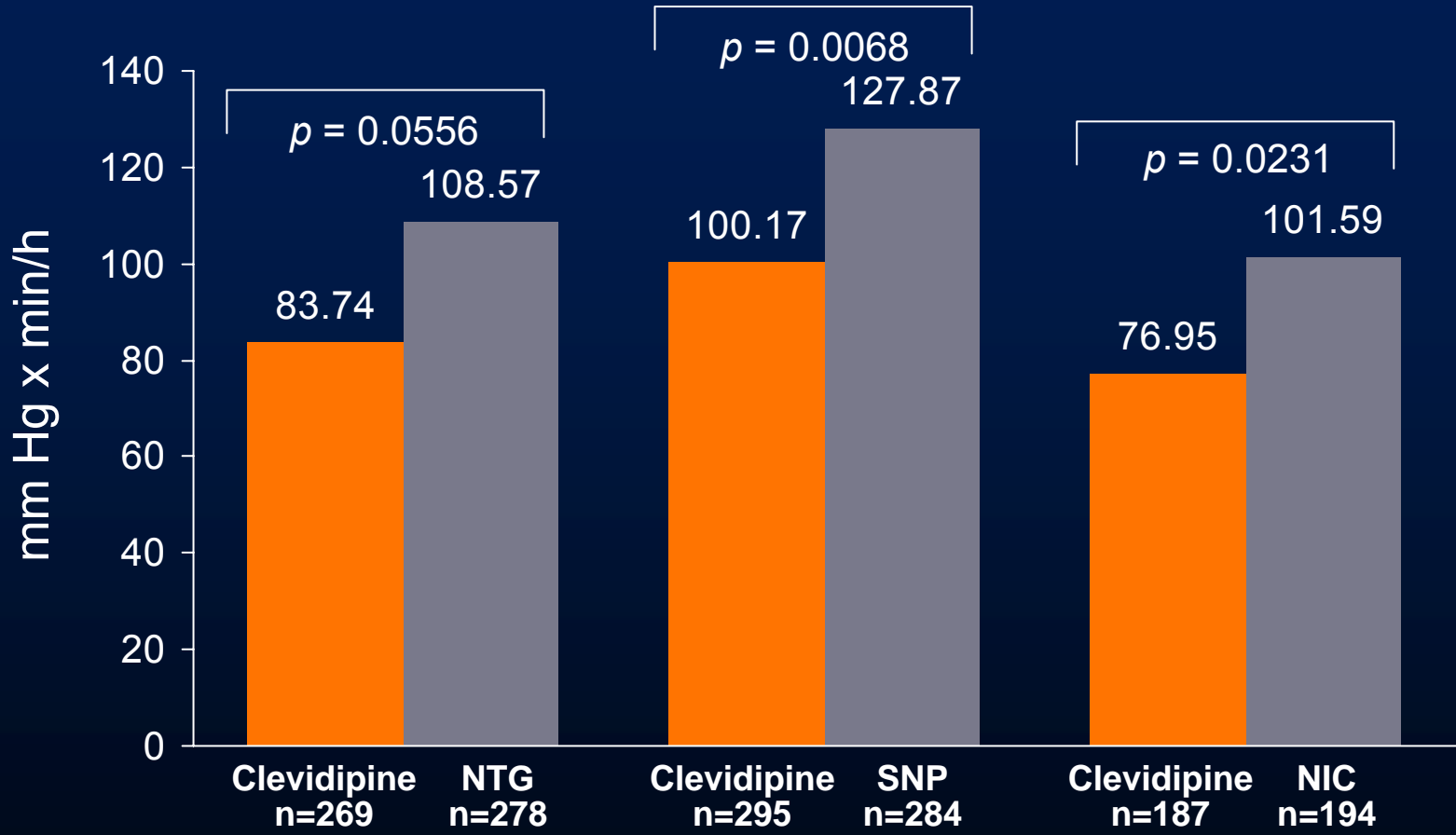


Pre-specified SBP Range: AUC by Treatment Comparison



Range = Pre-/post-op SBP 75-145, Intra-op SBP 65-135

Elevated SBP Range: AUC by Treatment Comparison



**ECLIPSE
NTG**

**ECLIPSE
SNP**

**ECLIPSE
NIC**

Range = Pre-/post-op SBP 105-145, Intra-op SBP 95-135



Conclusions

- ▶ Clevidipine is a safe alternative to therapy with commonly used antihypertensive agents
- ▶ Clevidipine demonstrated superior blood pressure control as assessed by integral analysis of excursions outside specified ranges over time