

The ECLIPSE Trials: Comparative Studies of Clevidipine to Nitroglycerin, Sodium Nitroprusside, and Nicardipine for Acute Hypertension Treatment in Cardiac Surgery Patients

Solomon Aronson, MD, FACC,
FCCP, FAHA, FASE*

Cornelius M. Dyke, MD†

Kevin A. Stierer, MD‡

Jerrold H. Levy, MDS§

Albert T. Cheung, MD||

Philip D. Lumb, MB, BS, FCCM¶

Dean J. Kereiakes, MD#

Mark F. Newman, MD*

BACKGROUND: Acute hypertension during cardiac surgery can be difficult to manage and may adversely affect patient outcomes. Clevidipine is a novel, rapidly acting dihydropyridine L-type calcium channel blocker with an ultrashort half-life that decreases arterial blood pressure (BP). The Evaluation of Clevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events trial (ECLIPSE) was performed to compare the safety and efficacy of clevidipine (CLV) with nitroglycerin (NTG), sodium nitroprusside (SNP), and nicardipine (NIC) in the treatment of perioperative acute hypertension in patients undergoing cardiac surgery.

METHODS: We analyzed data from three prospective, randomized, open-label, parallel comparison studies of CLV to NTG or SNP perioperatively, or NIC postoperatively in patients undergoing cardiac surgery at 61 medical centers. Of the 1964 patients enrolled, 1512 met postrandomization inclusion criteria of requiring acute treatment of hypertension based on clinical criteria. The patients were randomized 1:1 for each of the three parallel comparator treatment groups. The primary outcome was the incidence of death, myocardial infarction, stroke or renal dysfunction at 30 days. Adequacy and precision of BP control was evaluated and is reported as a secondary outcome.

RESULTS: There was no difference in the incidence of myocardial infarction, stroke or renal dysfunction for CLV-treated patients compared with the other treatment groups. There was no difference in mortality rates between the CLV, NTG or NIC groups. Mortality was significantly higher, though, for SNP-treated patients compared with CLV-treated patients ($P = 0.04$). CLV was more effective compared with NTG ($P = 0.0006$) or SNP ($P = 0.003$) in maintaining BP within the prespecified BP range. CLV was equivalent to NIC in keeping patients within a prespecified BP range; however, when BP range was narrowed, CLV was associated with fewer BP excursions beyond these BP limits compared with NIC.

CONCLUSIONS: CLV is a safe and effective treatment for acute hypertension in patients undergoing cardiac surgery.

(Anesth Analg 2008;107:1110-21)

Acute perioperative hypertension and arterial blood pressure (BP) lability affect up to 80% of patients undergoing cardiac surgery^{1,2} and up to 25% of patients undergoing major noncardiac surgery.³ Perioperative BP variation increases the risk for myocardial ischemia, stroke, neurocognitive dysfunction, and bleeding.^{2,4-8}

Since nearly 30% of the United States population is hypertensive, it is not unusual for patients to present for surgery with preexisting hypertension.⁹ The presence of preexisting hypertension increases the likelihood of acute perioperative hypertension and can be a significant risk factor for perioperative BP lability.^{10,11}

The etiology and treatment responsiveness of acute perioperative hypertension differs from chronic hypertension. Acute perioperative hypertension may be transient and is characterized by excessive catecholamine release, peripheral vasoconstriction,¹² and reduced baroreceptor sensitivity.¹³ Acute hypertension has been reported to worsen reperfusion injury,¹⁴ humoral and cellular inflammatory response,^{15,16} and

From the *Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina; †Gaston Memorial Hospital, Gastonia, North Carolina; ‡The Heart Institute at St. Joseph Medical Center, Towson, Maryland; §Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia; ||Department of Anesthesiology and Critical Care, University of Pennsylvania, Philadelphia, Pennsylvania; ¶Department of Anesthesiology, Keck School of Medicine, University of Southern California, Los Angeles, California; and #The Christ Hospital Heart and Vascular Center/The Lindner Research Center, Cincinnati, Ohio.

Accepted for publication May 30, 2008.

Supported by The Medicines Company, Parsippany, NJ.

Jerrold H. Levy is editor of Hemostasis and Transfusion Medicine for the Journal. This manuscript was handled by Charles W. Hogue Jr, and Jerrold H. Levy was not involved in any way with the editorial process or decision.

Address correspondence and reprint requests to Solomon Aronson, MD, FACC, FCCP, FAHA, FASE, Department of Anesthesiology, Duke University Medical Center, Duke South, Room 102 Baker House, Durham, NC 27710. Address e-mail to arons002@mc.duke.edu.

Copyright © 2008 International Anesthesia Research Society
DOI: 10.1213/ane.0b013e31818240db

platelet activation¹⁷ which may compromise microvascular blood flow. In addition, perioperative hypertension increases myocardial oxygen consumption and left ventricular end-diastolic pressure, and contributes to subendocardial hypoperfusion and myocardial ischemia.^{1,6,18} Despite its frequency and potential morbidity, there are no established guidelines for treating acute hypertension in the perioperative patient population and there is significant practice variability.¹⁹

The ideal drug for the management of hypertension in cardiac surgical patients would be a short-acting parenteral drug that is easily and rapidly titratable. Commonly used drugs include sodium nitroprusside, nitroglycerin, β blockers, and calcium channel blockers, as well as volatile anesthetics and sedatives. All of these drugs have limitations related to their potency, tolerance, toxicity, side effects, applicability, onset and offset of action, and ease of use. Clevidipine is a rapid-acting, dihydropyridine L-type calcium channel antagonist with an ultrashort half-life of approximately one min²⁰⁻²³ that decreases arterial pressure by direct arterial vasodilation. It has selective action on arteriolar resistance vessels with no effect on venous capacitance vessels. Reflex tachycardia and tachyphylaxis have not been reported.

The primary objective of this study was to compare the safety of clevidipine to three commonly used perioperative antihypertensive drugs (nitroglycerin, sodium nitroprusside, and nicardipine) in a cardiac surgical population. The secondary end-point of BP control was evaluated by measuring the magnitude and duration of BP excursions above or below a predefined systolic blood pressure (SBP) range.

METHODS

Study Design

The ECLIPSE (Evaluation of Clevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events) trial was conducted in compliance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The study was approved by the IRB at each participating institution. The three studies making up the ECLIPSE trial were performed under IND 65,114 and were registered at clinicaltrials.gov under the identifiers NCT00093886, NCT00093912, and NCT00093925. Written informed consent was obtained from all patients before enrollment. The ECLIPSE trial was randomized, open-label, prospective, and was conducted at 61 medical centers in the United States between April 2004 and October 2006.

Patients 18-yr-of-age or older and scheduled to undergo cardiac surgery (including on- or off-pump coronary artery bypass grafting [CABG], minimally invasive CABG and/or valve replacement or repair surgery) at each participating institution were evaluated for study eligibility. Patients were excluded from

study for the following reasons: women of childbearing potential, cerebrovascular accident ≤ 3 mo before randomization, intolerance to calcium channel blockers, hypersensitivity to sodium nitroprusside, nitroglycerin, or nicardipine, allergy to the lipid vehicle of clevidipine, permanent ventricular pacing, any condition or disease deemed by the investigator to place the patient at risk for participating, or participation in another investigation within 30 days of study start.

The ECLIPSE study consisted of three parallel trials where patients were randomly assigned on a 1:1 basis to receive clevidipine or a comparator drug (sodium nitroprusside, nitroglycerin, or nicardipine). After enrollment and treatment randomization, the need for antihypertensive treatment was determined by the study physician in accordance with department clinical practice and relevant institutional guidelines (e.g., postoperative intensive care unit guidelines).

Drug Administration

Study drug was administered IV, either peripherally or centrally, with an infusion pump. Treatment was titrated to achieve a BP level deemed appropriate by the study physician and continued until discharge from the intensive care unit. Use of nonstudy drug medications to treat hypertension during study drug administration was discouraged. If the desired BP effect was not attained or maintained with either clevidipine or a comparator drug, or if there was a safety concern, an alternative IV antihypertensive could be used per institutional practice to decrease BP. All antihypertensive medications were recorded.

Clevidipine was initiated at an infusion rate of $0.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and was titrated as tolerated in doubling increments every 90 s up to $3.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Infusion rates above $3.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ were guided by the patient's response and permitted in serial increments of $1.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Infusion rates between 4.4 and $8.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ were administered for no longer than 2 h. Titration to higher infusion rates, up to the maximum infusion rate of $8.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, was required before switching to or adding alternative antihypertensive drugs, assuming that each dose was well tolerated by the patient and there were no safety concerns. Due to protocol-specified lipid load restrictions, no more than 500 mL of clevidipine infusion (formulated in 20% lipid emulsion) was administered in the first 24-h period, and the maximum amount of lipid permitted as part of drug administration was 2.5 g/kg/24 h.

There were no protocol-specified limitations for administering sodium nitroprusside, nitroglycerin or nicardipine and investigators were given freedom to use these drugs as they normally would in clinical practice for treatment of perioperative hypertension. The dose and duration of therapy were recorded. Clevidipine was compared to sodium nitroprusside and nitroglycerin in the preoperative, intraoperative,

and postoperative periods. The comparison of clevidipine with nicardipine was restricted to the postoperative period, since nicardipine is not generally used before or during surgery due to its long half-life and potential for higher serum levels in elderly patients or patients with decreased hepatic metabolism.²⁴

Study End-Points

The primary end-point of the ECLIPSE trials was safety as assessed by the incidence of death, stroke, myocardial infarction (MI), and renal dysfunction from the initiation of study drug infusion through postoperative day 30. Death was defined as all-cause mortality. Stroke (hemorrhagic or ischemic) was diagnosed by a neurologist based on physical examination and/or brain imaging results. The diagnosis of MI was based on the presence of new 12-lead electrocardiogram changes consistent with myocardial injury and/or cardiac iso-enzyme increases. Renal dysfunction was defined as a postoperative serum creatinine level of ≥ 2.0 mg/dL ($177 \mu\text{mol/L}$) and an increase in serum creatinine of ≥ 0.7 mg/dL ($62 \mu\text{mol/L}$) from preoperative baseline, and/or the need for hemodialysis, venovenous filtration, arterial venous filtration, or peritoneal dialysis after surgery. An independent Clinical Events Committee, blinded to treatment, made the final determination as to whether each safety event qualified as a primary end-point based on preestablished criteria uniformly applied to each determination. In addition, CK-MB and serum creatinine laboratory definitions were used as database triggers to identify MI and renal safety end-point events for consideration by the Clinical Events Committee.

The efficacy of clevidipine versus comparator drug for the treatment of acute hypertension was assessed using area under the curve (AUC) analysis of BP excursions beyond predetermined upper and lower limits, normalized per hour ($\text{AUC}_{\text{SBP-D}}$). $\text{AUC}_{\text{SBP-D}}$ was analyzed as the summation of the integrated SBP-time curve excursions, capturing the product of magnitude (mm Hg) and duration (min) of BP outside the predefined SBP ranges. These ranges, chosen to reflect standard clinical practice and prespecified for analysis purposes, were 65–135 mm Hg intraoperatively (from chest incision through chest closure) and 75–145 mm Hg pre- and postoperatively.

$\text{AUC}_{\text{SBP-D}}$ was calculated from the BP recorded from the initiation of study drug infusion through either the removal of the arterial line or 24 h after study drug initiation, whichever occurred first. Preoperatively, BP was recorded every 15 min; intraoperatively, every 5 min; and postoperatively every 15 min for 4 h, then once every hour through 24 h (comparison with nitroglycerin or sodium nitroprusside). For the comparison with nicardipine, BP was recorded every 15 min for the first 6 h, then once every hour through 24 h. Hemodynamic data were measured by arterial line and entered into an electronic database.

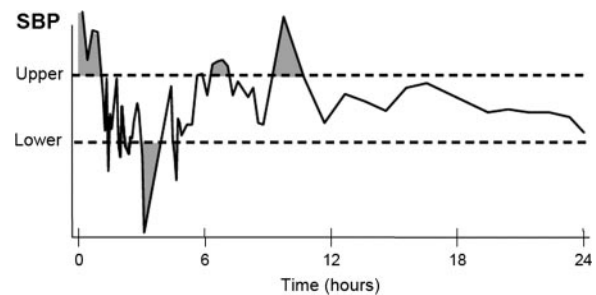


Figure 1. Schematic illustration of the AUC calculation for an individual patient from the ECLIPSE trial. $\text{AUC}_{\text{SBP-D}}$ captures the magnitude and duration of arterial blood pressure (BP) excursions outside the predefined systolic BP (SBP) ranges (65–135 mm Hg intraoperatively, 75–145 mm Hg pre- and postoperatively).

The total area of the SBP-time curve outside (either above or below) the predefined SBP ranges was calculated (Fig. 1) and normalized per hour ($\text{AUC}_{\text{SBP-D}}$). $\text{AUC}_{\text{SBP-D}}$ was expressed in units of mm Hg \times min/h. In addition, vital signs, clinical laboratory data, fluid administration, the incidence of reflex tachycardia, and serious adverse events (SAEs) including the incidence of atrial fibrillation during study drug administration were also captured. SAEs were recorded up to 30 days postoperatively.

Statistical Analysis

All statistical analyses were performed using the SAS[®] system (version 8.2, SAS Institute, Cary, NC) and presented using descriptive statistics. The randomized patient population was defined as all patients who qualified for the study based on prerenalization inclusion and exclusion criteria and were randomized to a treatment group. The modified intent-to-treat population was defined as all patients who were randomized into the trial and met postrandomization criteria for perioperative hypertension. The safety population was all randomized patients who received study drug. This report presents safety results based on analysis of the safety population, and efficacy results based on analysis of the modified intent-to-treat population. Data were pooled to provide an overall event rate for clevidipine and comparator arms. Prespecified analysis of each randomized comparison was also performed. *P* values for the primary end-point analysis were generated using the χ^2 test.

$\text{AUC}_{\text{SBP-D}}$ was summarized descriptively by treatment group as total area of the SBP-time curve above or below the predefined SBP ranges (65–135 mm Hg intraoperatively, 75–145 mm Hg pre- and postoperatively). Due to asymmetric distribution of AUC, descriptive statistics are presented using range (minimum and maximum), inter-quartile range (first quartile [Q1] and third quartile [Q3]), median (second quartile), mean, and sd. *P* values for AUC analysis were generated using the Wilcoxon rank sum test, a

Table 1. Patient Disposition from the ECLIPSE Program

	CLV	NTG	CLV	SNP	CLV	NIC
Patients randomized	312	316	363	376	296	301
Patients who met postrandomization criteria (mITT population)	270	278	297	284	188	195
Patients who did not receive study medication ^a	2	0	1	1	1	1
Patients who received study medication (safety population)	268	278	296	283	188	193
Total safety population		546		579		381

CLV = clevidipine; NTG = nitroglycerin; SNP = sodium nitroprusside; NIC = nicardipine; mITT = modified intent-to-treat.

^a Two patients in the CLV:NIC treatment group did not receive study medication and were excluded from the safety population. In addition, one patient in the same treatment group was randomized to NIC but received CLV instead. This patient was excluded from the NIC safety population and included in the CLV safety population.

nonparametric test applicable to asymmetric distributions. The significance level was designated at the two-sided α level of 5%.

To increase our ability to discriminate among treatment groups in the assessment of BP control, we conducted a *post hoc* analysis in which AUC was calculated as the SBP range was narrowed by incrementally increasing the lower SBP limit by 10 mm Hg, 20 mm Hg, and 30 mm Hg. Additionally, multiple logistic regression analysis was performed to further explore the relationship between the incidence of death and treatment group while controlling for other potential risk factors.

RESULTS

Patients in the ECLIPSE trial were similar with respect to demographics and medical history across all treatment groups (579 received clevidipine or sodium nitroprusside; 546 clevidipine or nitroglycerin, and 381 clevidipine or nicardipine) (Tables 1 and 2). Pre-existing chronic hypertension was common in all groups and nearly all patients were receiving antihypertensive medications before surgery. Patient characteristics, demographics, and cardiac surgical procedure groups are detailed in Tables 2 and 3. In all treatment groups, CABG was the most commonly performed procedure. Off-pump techniques were used in approximately 10%–20% of patients and the number of valve-related procedures was similar among all groups.

The timing of drug administration among treatment groups is presented in Table 4. In the perioperative clevidipine: nitroglycerin and clevidipine: sodium nitroprusside studies, study drug was primarily initiated during the preoperative or intraoperative period. The majority of patients who initiated antihypertensive treatment pre- or intraoperatively also received therapy in the postoperative setting. Patients in the clevidipine: nicardipine study received the drug postoperatively per protocol as the half-life, volume of distribution, and slow offset of nicardipine was determined to make it less suitable for use in the pre- and intraoperative setting. The median overall infusion duration, total infusion volume, and average infusion rates were greater in the nitroglycerin group compared to patients receiving clevidipine. Overall infusion duration, infusion rates and infusion volumes

were comparable between patients receiving clevidipine and sodium nitroprusside. The duration of infusion was similar between clevidipine and nicardipine with the total fluid volume infused and average infusion rate greater for nicardipine compared to clevidipine. The use of adjunctive, alternative antihypertensive drugs was similar among treatment groups. The use of these drugs for the control of hypertension tended to be higher in the sodium nitroprusside-treated group compared with the clevidipine group; with β blockers most commonly administered. There was also an increased tendency for the use of sodium nitroprusside as a second-line antihypertensive drug in patients treated with nitroglycerin compared to those treated with clevidipine (11% vs 2%, respectively).

The primary outcome, 30-day incidence of death, MI, stroke, or renal dysfunction, for all treatment groups is detailed in Table 5. There was no difference between the pooled clevidipine populations compared with the pooled comparator group for any of the 30-day safety outcome measures. There were no differences in death or adverse outcomes at the time of hospital discharge or Day 7 among groups. Within treatment groups, there were no differences in 30-day outcomes when clevidipine was compared with nitroglycerin and nicardipine. Results for clevidipine compared to sodium nitroprusside were similar as well except for the incidence of 30-day mortality, which was significantly higher in patients who had received sodium nitroprusside compared to clevidipine (4.7% vs 1.7%, $P = 0.0445$). However, multiple logistic regression analysis for treatment effect (clevidipine vs sodium nitroprusside) as an independent variable in a model that included other risk variables such as surgery duration, AUC_{SBP-D} , age, and medical history, showed no statistically significant association between sodium nitroprusside use and 30-day mortality (odds ratio, 1.968, 95% confidence interval, 0.619–6.257, $P = 0.25$). Among 13 patients requiring treatment for hypertension who died in the sodium nitroprusside group, three had hypotension reported as an adverse event.

Comparisons of the pooled data from the entire clevidipine population with the pooled data of the entire comparator group demonstrated that clevidipine was significantly more effective at keeping BP within the prespecified BP range (Table 6, Fig. 2).

Table 2. Demographics, Baseline Characteristics and Medical History (Safety Population)

Parameter	CLV (n = 268)	NTG (n = 278)	CLV (n = 296)	SNP (n = 283)	CLV (n = 188)	NIC (n = 193)
Age (yr)	64.4 ± 10.9	63.9 ± 11.1	64.2 ± 10.9	65.3 ± 11.0	66.1 ± 10.1	66.1 ± 10.2
Sex						
Female	54 (20.1)	71 (25.5)	92 (31.1)	67 (23.7)	62 (33.0)	55 (28.5)
Male	214 (79.9)	207 (74.5)	204 (68.9)	216 (76.3)	126 (67.0)	138 (71.5)
Weight (kg)	88.2 ± 18.7	87.5 ± 19.9	89.2 ± 19.8	86.7 ± 20.1	84.4 ± 19.4	87.9 ± 19.9
Height (cm)	173.4 ± 9.2	171.8 ± 10.2	172.2 ± 9.9	172.2 ± 9.7	171.4 ± 10.7	172.5 ± 10.1
Baseline blood pressure (mm Hg)						
Systolic ^a	142.9 ± 22.7	139.1 ± 28.3	142.1 ± 21.6	141.8 ± 26.1	144.2 ± 19.2	144.0 ± 20.1
Diastolic ^b	71.9 ± 13.3	71.3 ± 14.7	70.7 ± 13.7	70.7 ± 17.2	69.2 ± 12.8	68.4 ± 13.0
Medical history						
Hypertension	224 (83.6)	240 (86.3)	253 (85.5)	228 (80.6)	181 (96.3)*	169 (87.6)
Recent myocardial infarction (<6 mo)	46 (17.2)	51 (18.3)	46 (15.5)	45 (15.9)	39 (20.7)	42 (21.8)
Prior PCI	66 (24.6)	66 (23.7)	60 (20.3)	68 (24.0)	30 (16.0)	38 (19.7)
Prior CABG	10 (3.7)	24 (8.6)	10 (3.4)	11 (3.9)	4 (2.1)	8 (4.1)
Congestive heart failure	35 (13.1)	44 (15.8)	65 (22.0)	52 (18.4)	44 (23.4)	38 (19.7)
Dyslipidemia	209 (78.0)	193 (69.4)	196 (66.2)	191 (67.5)	134 (71.3)	137 (71.0)
Family history of CAD	153 (57.1)	152 (54.7)	169 (57.1)	149 (52.7)	112 (59.6)	120 (62.2)
Cigarette smoker	40 (14.9)	52 (18.7)	66 (22.3)	69 (24.4)	45 (23.9)	38 (19.7)
Diabetes						
Insulin-dependent	23 (8.6)	30 (10.8)	36 (12.2)	29 (10.2)	20 (10.6)	21 (10.9)
Noninsulin dependent	76 (28.4)	62 (22.3)	63 (21.3)	73 (25.8)	48 (25.5)	55 (28.5)
Transient ischemic attack	14 (5.2)	22 (7.9)	14 (4.7)	16 (5.7)	15 (8.0)	11 (5.7)
Stroke	23 (8.6)	20 (7.2)	21 (7.1)	18 (6.4)	16 (8.5)	12 (6.2)
Angina pectoris	164 (61.2)	160 (57.6)	167 (56.4)	170 (60.1)	108 (57.4)	117 (60.6)
Peripheral vascular disease	36 (13.4)	37 (13.3)	46 (15.5)	46 (16.3)	33 (17.6)	28 (14.5)
Prior atrial fibrillation	27 (10.1)	29 (10.4)	39 (13.2)	36 (12.7)	20 (10.6)	18 (9.3)
Prior atrial flutter	6 (2.2)	3 (1.1)	9 (3.0)	7 (2.5)	1 (0.5)	3 (1.6)
Chronic obstructive pulmonary disease	38 (14.2)	29 (10.4)	38 (12.8)	52 (18.4)	26 (13.8)	33 (17.1)
Number of patients who took at least one antihypertensive medication within 2 wk of surgery	221 (82.5)	230 (82.7)	248 (83.8)	234 (82.7)	159 (84.6)	161 (83.4)
Beta blocker	172 (64.2)	192 (69.1)	192 (64.9)	189 (66.8)	132 (70.2)	135 (69.9)
ACE inhibitor	121 (45.1)	114 (41.0)	134 (45.3)	119 (42.0)	71 (37.8)	79 (40.9)
Calcium channel blocker	52 (19.4)	60 (21.6)	68 (23.0)	60 (21.2)	45 (23.9)	28 (14.5)

Data presented as mean ± SD or n (%).

CLV = clevidipine; NTG = nitroglycerin; SNP = sodium nitroprusside; NIC = nicardipine; SD = standard deviation; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; CAD = coronary artery disease; ACE = angiotensin-converting enzyme.

^a Based on n = 263 (CLV), n = 272 (NTG); n = 294 (CLV), n = 279 (SNP); n = 188 (CLV), n = 192 (NIC).

^b Based on n = 263 (CLV), n = 271 (NTG); n = 294 (CLV), n = 280 (SNP); n = 187 (CLV), n = 192 (NIC).

* P < 0.05, CLV versus NIC.

In an analysis of the individual treatment cohorts, clevidipine was significantly more effective at keeping BP within the prespecified range compared with nitroglycerin or sodium nitroprusside (Table 6, Fig. 3). The median total AUC_{SBP-D} (representing SBP-time curve excursions outside the prespecified SBP ranges) was significantly lower for patients treated with clevidipine than for patients treated with nitroglycerin (4.14 mm Hg × min/h vs 8.87 mm Hg × min/h; P = 0.0006). In addition, patients treated with nitroglycerin did not meet the target BP range as often compared with clevidipine. The median AUC above the target BP range was significantly lower for clevidipine-treated patients compared to nitroglycerin-treated patients (2.76 mm Hg × min/h vs 7.94 mm Hg × min/h;

P = 0.0002). The AUC below the target range was similar between these groups.

For patients treated with clevidipine, the median total AUC was significantly lower compared with patients treated with sodium nitroprusside (4.4 mm Hg × min/h vs 10.5 mm Hg × min/h; P = 0.0027). In addition, patients treated with sodium nitroprusside had significantly greater SBP-time excursions outside the target BP range, both above and below (overshoot) compared to clevidipine. Above the target BP range, median AUC for clevidipine compared with sodium nitroprusside was 2.97 mm Hg × min/hr and 6.61 mm Hg × min/h, respectively (P = 0.031). Below the target BP range, mean AUC for clevidipine compared with sodium nitroprusside was 2.30 mm

Table 3. Cardiac Surgical Procedures Performed (Safety Population)

	CLV (n = 268) n (%)	NTG (n = 278) n (%)	CLV (n = 296) n (%)	SNP (n = 283) n (%)	CLV (n = 188) n (%)	NIC (n = 193) n (%)
Overall procedure duration (h)	3.42 ± 1.23	3.35 ± 1.00	3.44 ± 1.23	3.62 ± 1.40	3.50 ± 1.05	3.56 ± 1.24
Primary surgery						
CABG only	210 (78.4)	198 (71.2)	211 (71.3)	198 (70.0)	145 (77.1)	151 (78.2)
Valve surgery only	32 (11.9)	31 (11.2)	42 (14.2)	37 (13.1)	17 (9.0)	17 (8.8)
CABG and valve surgery	11 (4.1)	19 (6.8)	29 (9.8)	33 (11.7)	19 (10.1)	16 (8.3)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	1 (0.5)
Repeat surgery						
CABG only	7 (2.6)	24 (8.6)	4 (1.4)	5 (1.8)	2 (1.1)	5 (2.6)
Valve surgery only	4 (1.5)	3 (1.1)	8 (2.7)	3 (1.1)	2 (1.1)	1 (0.5)
CABG and valve surgery	4 (1.5)	3 (1.1)	2 (0.7)	7 (2.5)	1 (0.5)	2 (1.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CABG with CPB	175 (65.3)	196 (70.5)	218 (73.6)	215 (76.0)	145 (77.1)	151 (78.2)
OPCAB	57 (21.3)	49 (17.6)	28 (9.5)	28 (9.9)	22 (11.7)	23 (11.9)
Valve replacement ^a	43 (16.0)	50 (18.0)	66 (22.3)	72 (25.4)	28 (14.9)	31 (16.1)
Mitral	5 (11.6)	15 (30.0)	7 (10.6)	11 (15.3)	2 (7.1)	4 (12.9)
Tricuspid	2 (4.7)	2 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aortic	37 (86.0)	34 (68.0)	59 (89.4)	62 (86.1)	26 (92.9)	27 (87.1)
Pulmonary	2 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Valve repair ^b	9 (3.4)	8 (2.9)	17 (5.7)	11 (3.9)	12 (6.4)	6 (3.1)
Mitral	9 (100.0)	8 (100.0)	17 (100.0)	10 (90.9)	12 (100.0)	6 (100.0)
Tricuspid	0 (0.0)	1 (12.5)	1 (5.9)	1 (9.1)	0 (0.0)	0 (0.0)
Aortic	0 (0.0)	1 (12.5)	0 (0.0)	1 (9.1)	0 (0.0)	1 (16.7)
Pulmonary	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data presented as mean ± sd or n (%).

CLV = clevidipine; NTG = nitroglycerin; SNP = sodium nitroprusside; NIC = nicardipine; sd = standard deviation; CABG = coronary artery bypass grafting; CAD = coronary artery disease; OPCAB = off pump coronary artery bypass; CPB = cardiopulmonary bypass.

^a For categories under valve replacement, percentages are based on n = 43 (CLV), n = 50 (NTG); n = 66 (CLV), n = 72 (SNP); n = 28 (CLV), n = 31 (NIC).

^b For categories under valve repair, percentages are based on n = 9 (CLV), n = 8 (NTG); n = 17 (CLV), n = 11 (SNP); n = 12 (CLV), n = 6 (NIC).

Table 4. Study Drug Administration (Safety Population)

Parameter	CLV (n = 268)	NTG (n = 278)	CLV (n = 296)	SNP (n = 283)	CLV (n = 188)	NIC (n = 193)
Patients initiating study drug during						
Preoperative period, n (%)	92 (34.3)	119 (42.8)	52 (17.6)	34 (12.0)	0 (0)	0 (0)
Intraoperative period, n (%)	145 (54.1)	132 (47.5)	161 (54.4)	158 (55.8)	0 (0)	0 (0)
Postoperative period, n (%)	31 (11.6)	27 (9.7)	83 (28.0)	90 (31.8)	188 (100)	193 (100)
Patients dosed with study drug during						
Preoperative period, n (%)	92 (34.3)	119 (42.8)	52 (17.6)	34 (12.0)	0 (0)	0 (0)
Intraoperative period, n (%)	229 (85.4)	245 (88.1)	209 (70.6)	185 (65.4)	0 (0)	0 (0)
Postoperative period, n (%)	187 (69.8)	226 (81.3)	219 (74.0)	204 (72.1)	188 (100)	193 (100)
Overall infusion duration, including periods when infusion stopped (h) ^a						
Median	6.4	12.0	6.7	5.4	7.1	7.9
Q1, Q3	2, 16	4, 24	2, 17	2, 18	2, 17	3, 18
Total infusion volume (mL) ^b						
Median	21.8	74.8	26.5	25.6	56.4	163.8
Q1, Q3	6.3, 74.2	24.1, 209.1	7.1, 97.1	5.5, 129.4	13.7, 142.9	42.7, 376.2
Average infusion rate (mL/h) ^b						
Median	6.2	11.3	6.4	8.5	7.9	33.6
Q1, Q3	4.4, 10.2	6.1, 22.7	4.5, 10.2	4.1, 17.4	4.5, 12.9	18.9, 48.8

CLV = clevidipine; NTG = nitroglycerin; SNP = sodium nitroprusside; NIC = nicardipine; Q1 = Quartile 1; Q3 = Quartile 3.

^a Overall infusion duration starts from the initiation of first infusion to the end of last infusion.

^b Based on n = 268 (CLV), n = 277 (NTG); n = 296 (CLV), n = 281 (SNP).

Hg × min/h and 8.38 mm Hg × min/h, respectively (P = 0.0006).

There were no differences in the median AUC at predetermined target BP ranges of 75–145 mm Hg

postoperatively for patients treated with nicardipine compared to clevidipine (Table 6, Fig. 3).

When the target BP range was narrowed by raising the lower limit threshold by increments of 10 mm Hg,

Table 5. Summary of Primary End-point-Clinical Events Committee-Adjudicated 30-Day Events (Safety Population)

Event	CLV (N = 268) n/N (%)	NTG (N = 278) n/N (%)	P
Death	7/252 (2.8)	9/266 (3.4)	0.69
Myocardial infarction	8/246 (3.3)	9/260 (3.5)	0.90
Stroke	4/245 (1.6)	6/260 (2.3)	0.59
Renal dysfunction	17/248 (6.9)	21/260 (8.1)	0.60
	CLV (N = 296) n/N (%)	SNP (N = 283) n/N (%)	
Death	5/286 (1.7)	13/274 (4.7)	0.04
Myocardial infarction	4/281 (1.4)	6/264 (2.3)	0.46
Stroke	3/282 (1.1)	4/262 (1.5)	0.63
Renal dysfunction	24/284 (8.5)	24/265 (9.1)	0.80
	CLV (N = 188) n/N (%)	NIC (N = 193) n/N (%)	
Death	8/181 (4.4)	6/189 (3.2)	0.53
Myocardial infarction	4/173 (2.3)	2/183 (1.1)	0.37
Stroke	1/173 (0.6)	2/183 (1.1)	0.60
Renal dysfunction	15/180 (8.3)	11/185 (5.9)	0.38
	All CLV (N = 752) n/N (%)	All comparators (N = 754) n/N (%)	
Death	20/719 (2.8)	28/729 (3.8)	0.26
Myocardial infarction	16/700 (2.3)	17/707 (2.4)	0.88
Stroke	8/700 (1.1)	12/705 (1.7)	0.38
Renal dysfunction	56/712 (7.9)	56/710 (7.9)	0.99

For each end-point, patients are excluded from the denominator if the last follow-up visit was before 30 days postrandomization and no associated end-point was reported.

CLV = clevidipine; NTG = nitroglycerin; SNP = sodium nitroprusside; NIC = nicardipine; CEC = clinical events committee.

Table 6. Summary of AUC_{SBP-D} by Treatment Group (Modified Intent-to-Treat population)

AUC _{SBP-D} , mm Hg × min/h	CLV (N = 269)	NTG (N = 278)
Mean ± SD	16.3 ± 39.02	44.48 ± 109.23
Median	4.14*	8.87
Min, Max	0, 425	0, 927
Q1, Q3	0.61, 14	0.98, 37
	CLV (N = 295)	SNP (N = 284)
Mean ± SD	24.33 ± 62.01	39.51 ± 88.25
Median	4.37†	10.5
Min, Max	0, 706	0, 889
Q1, Q3	0.07, 22	0.59, 42
	CLV (N = 187)	NIC (N = 194)
Mean ± SD	28.02 ± 68.45	35.84 ± 105.28
Median	1.76	1.69
Min, Max	0, 568	0, 1104
Q1, Q3	0, 25	0, 26
	All clevidipine (N = 751)	All comparators (N = 756)
Mean ± SD	22.37 ± 56.89	40.4 ± 100.71
Median	3.79‡	7.79
Min, Max	0, 706	0, 1104
Q1, Q3	0.07, 19	0.14, 35

CLV = clevidipine; NTG = nitroglycerin; SNP = sodium nitroprusside; NIC = nicardipine; AUC_{SBP-D} = area under the SBP-time curve, representing the magnitude and duration of excursions outside of predefined target SBP ranges, normalized per hour.

* P = 0.0006, CLV versus NTG.

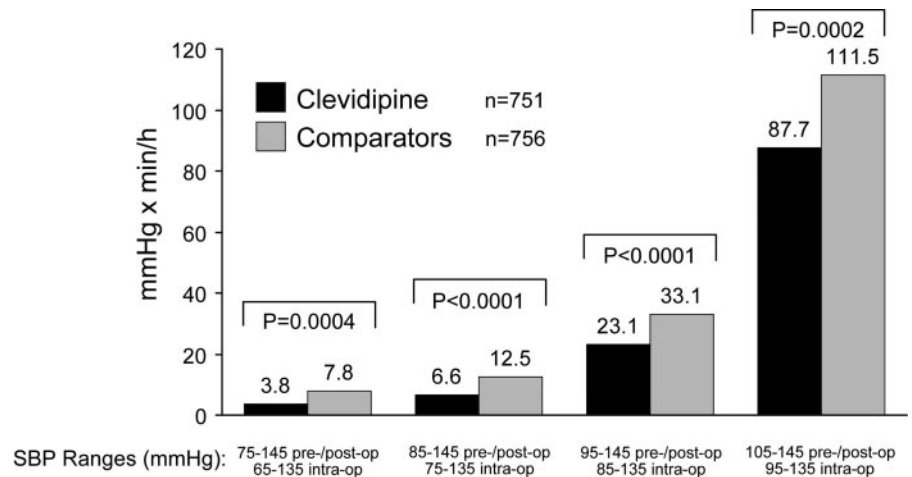
† P = 0.0027, CLV versus SNP.

‡ P = 0.0004, all CLV versus all comparators.

there was a direct and progressive increase in the difference of AUC for the pooled comparisons (Fig. 2) as well as each comparator drug when compared to

clevidipine (Fig. 3). When the threshold for the lower BP range was 30 mm Hg higher (i.e., a narrower SBP range of 40 mm Hg), patients treated with clevidipine

Figure 2. Blood pressure (BP) control as assessed by AUC_{SBP-D} (representing systolic BP (SBP)-time curve excursions outside of defined SBP ranges) for the pooled clevidipine population compared to the pooled comparator population. AUC_{SBP-D} as median values.



had significantly smaller SBP-time excursions outside of this range than patients treated with nicardipine (77.0 mm Hg \times min/h vs 101.6 mm Hg \times min/h, $P = 0.0231$) or sodium nitroprusside (100.2 mm Hg \times min/h vs 127.9 mm Hg \times min/h, $P = 0.0068$) (Fig. 3).

The incidence of the most commonly reported adverse events, including atrial fibrillation and sinus tachycardia, were similar for clevidipine and the comparator drugs. Atrial fibrillation was reported as an adverse event at an incidence of 33.6% vs 32.0% (clevidipine versus nitroglycerin); 36.1% vs 32.2% (clevidipine vs sodium nitroprusside); and 35.6% vs 35.2% (clevidipine vs nicardipine), all $P = NS$. The incidences of SAEs were similar among all groups and are listed in Table 7. Clinical laboratory data including change in triglyceride levels were similar between clevidipine and the comparator drugs. Clevidipine, which is administered in a lipid emulsion, did not cause an increase in triglyceride levels.

DISCUSSION

In the current study, clevidipine was shown to be as safe as its comparator drugs for the treatment of perioperative hypertension based on a similar frequency in the primary outcome of the 30-day incidence of death, MI, stroke, or renal dysfunction. When individual treatment comparisons were considered, there were no differences in the frequency of this primary outcome between patients receiving clevidipine compared with nitroglycerin, sodium nitroprusside, or nicardipine. We did observe a lower mortality rate, though, for patients treated with clevidipine compared with those receiving sodium nitroprusside, although this difference was only notable as a trend in a multiple logistic regression analysis. Our results further show that clevidipine was a more effective antihypertensive drug based on our analysis of the time and extent SBP was above or below the predefined BP ranges (AUC analysis for BP excursions) than nitroglycerin or sodium nitroprusside at any perioperative SBP range and better than nicardipine when the postoperative SBP range was reduced to 40

mm Hg from the predefined 70 mm Hg (Fig. 3). Clevidipine and nicardipine were similar in maintaining BP within the prespecified ranges, but this analysis was limited to the postoperative period based on the protocol design.

Acute perioperative hypertension, first identified as a risk factor for adverse cardiovascular outcome in 1929,²⁵ is predominantly mediated by an increase in sympathetic activity, resulting in arteriolar vasoconstriction and increased systemic vascular resistance.²⁶ Although intraoperative hemodynamic abnormalities have been reported to be associated with death, stroke, renal dysfunction, perioperative MI, and increased mortality, these studies often used a small sample size and lacked statistical power, were retrospective and included discontinuous data, included methods specific to certain patient populations and/or surgical procedures, and were not analyzed to determine specific target BP thresholds.²⁷⁻³⁰ Therefore, they provide limited information on the impact of perioperative hypertension management on patient outcomes. An association between hypertension and postoperative surgical bleeding has also been demonstrated.³¹ In part because of these strong associations, and because of other practical safety concerns related to the hydraulic pressure and aortovascular stress-strain modulation requirements during cardiac surgery with cardiopulmonary bypass (e.g., cannulation and decannulation), and the requirements of the postoperative period for weaning from mechanical ventilation and analgesia, manipulation and control of BP is commonly used during cardiac surgery.

Currently, nitroglycerin and sodium nitroprusside are commonly used during cardiac surgery to control BP; however, both have significant limitations. Nitroglycerin is a relatively weak arteriolar vasodilator with a primary effect on dilating venous capacitance vessels to reduce preload. Sodium nitroprusside also produces significant venodilation and causes reflex tachycardia, as well as inhibition of hypoxic pulmonary vasoconstriction, increase in intracranial pressure, and a redistribution of blood flow away from

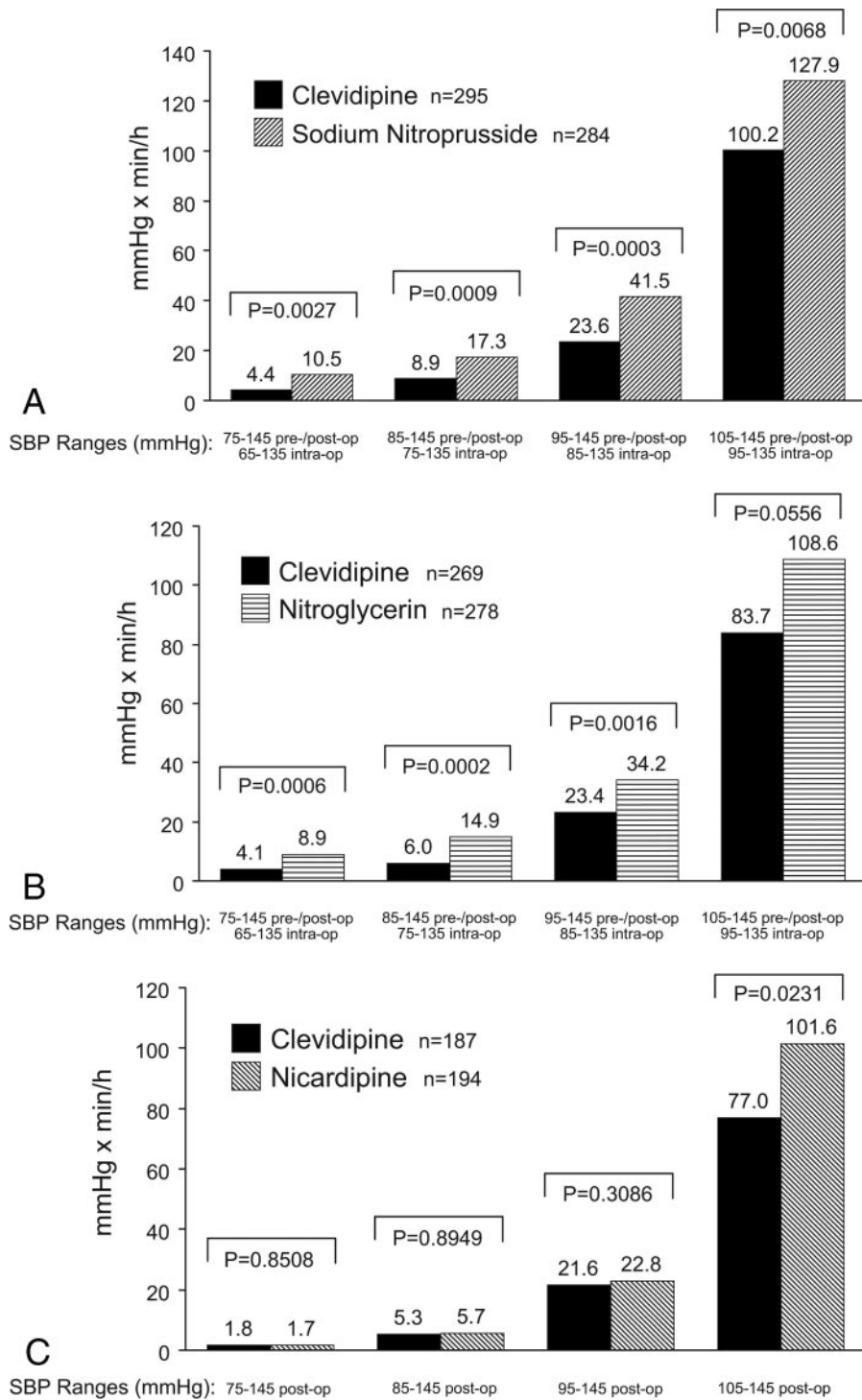


Figure 3. Blood pressure control as assessed by AUC_{SBP-D} excursions outside of defined systolic blood pressure ranges for clevidipine compared to sodium nitroprusside (perioperative), nitroglycerin (perioperative) and nicardipine (postoperative) AUC_{SBP-D} as median values.

vital end-organs^{1,2} including the kidney³² and gastrointestinal tract. The use of sodium nitroprusside also is associated with systemic cyanide toxicity, a risk that may be accelerated during cardiac surgery requiring cardiopulmonary bypass.³³ Sodium nitroprusside may be difficult to titrate and is recognized to cause unwanted (“overshoot”) hypotension and hypertension. In a study comparing sodium nitroprusside with nicardipine, patients treated with sodium nitroprusside needed more time to reach target BP goals and required more dose adjustments. The venodilatory

effects of sodium nitroprusside may produce unpredictable swings in BP in patients with diastolic dysfunction or hypovolemia.³⁴ Nicardipine, a dihydropyridine calcium channel blocker, may be limited for use in the acute preoperative and intraoperative setting because of its long half-life, slower offset of action, and potential for increased serum levels in elderly patients or patients with altered hepatic function.²⁴ Additionally, bolus doses of nicardipine, after IV infusion, appear to be needed to obtain the rapid onset of action seen with other vasodilator drugs like sodium nitroprusside.³⁴

Table 7. Incidence of Events Reported as Serious Adverse Events (Combined Groups)

Serious adverse event	Clevidipine (n = 752)	Comparators (n = 754)
Patients with at least one serious adverse event	17.7%	20.0%
Atrial fibrillation	2.4%	2.4%
Respiratory failure	1.1%	2.5%
Acute renal failure	2.3%	1.7%
Ventricular fibrillation	0.9%	1.5%
Cardiac arrest	0.5%	1.1%
Cerebrovascular accident	0.5%	1.1%
Postprocedural hemorrhage	0.5%	1.1%

SAE by Day 7/discharge.

Clevidipine is a third-generation dihydropyridine calcium channel blocker, specifically designed for treatment of acute hypertension, with a rapid onset and offset of action. The characteristic of fast onset and offset is due to an easily hydrolyzable ester group in the clevidipine molecular structure²² which is rapidly metabolized by esterases in the blood and vascular tissues upon IV administration. The resulting ultra-short half-life of approximately 1 min^{20–22} makes clevidipine an attractive drug for patients who need rapid BP adjustments over time.

Implications for these data may become important as the selection of drugs to more narrowly control acute hypertension in the surgical and critical care setting is further investigated and guidelines are defined. This is also important because preexisting hypertension, especially among the elderly surgical population, is present in more than two-thirds of all patients ≥ 60 yr,⁹ with upwards of 90% prevalence in cardiac surgery,³⁵ and has been identified as an important risk factor for adverse outcome.^{4,35}

Limitations of the study include the open-label design. However, adjudication of study end-points by an independent Clinical Events Committee was used to minimize any potential bias. Additionally, by protocol, clevidipine was dosed in a standard fashion at all study sites, whereas comparator drugs were administered according to institutional practice. This limitation enabled a real-world analysis that was more applicable to actual clinical practice.

The use of adjunctive, alternative antihypertensive drugs was similar between groups. Patients who received nitroglycerin received more second-line sodium nitroprusside administration for the control of hypertension, suggesting that nitroglycerin, in addition to the increased AUC above the target SBP limit, is an ineffective antihypertensive drug in cardiac surgical patients. An important and consistent finding from all three studies with clevidipine was that the BP results after treatment with clevidipine were remarkably similar, indicating that predictable BP control can

be achieved with clevidipine throughout the operative setting.

The primary purpose of this study was to evaluate the safety of clevidipine compared with other commonly used antihypertensive drugs in patients undergoing cardiac surgery. Although the composite safety end-point of 30-day death, MI, stroke, or renal dysfunction was similar among the treatment groups, we did find that patients treated with clevidipine had a lower mortality rate than those treated with sodium nitroprusside. It is possible that these observations were due to confounding factors among the treatment groups not considered in our analysis. Indeed, the number of patients undergoing higher-risk combined CABG and cardiac valve surgery was higher in the sodium nitroprusside group compared with the clevidipine group, although this difference was not statistically significant (primary and repeat combination CABG and valve surgery for clevidipine versus sodium nitroprusside: $P = 0.18$). In addition, the small number of observed events in this analysis may have led to a type I error. Regardless, whether the drug choice for treating perioperative hypertension can modify risk for mortality after cardiac surgery requires further prospective study.

ACKNOWLEDGMENTS

The authors acknowledge the work of the GPRO study group/ECLIPSE investigators in the conduct of this trial. A large number of individuals contributed to the completion of this research, including:

Randleman CD Jr, MD, Byrne N, Cardio-Thoracic Surgeons, PC, Birmingham, AL; Mancao MY Jr, MD, Huckaby D, Discovery Alliance International, Inc., Pensacola, FL; McCoy CP, MD, Marden J, RN, Research Support Personnel LLC, Wichita, KS; Stone ME, MD, Mitchell-Bligen M, RN, Mount Sinai School of Medicine, New York, NY; Warltier DC, MD, PhD, Hudetz J, PhD, Zablocki V.A. Medical Center, Milwaukee, WI; Cheung AT, MD, University of Pennsylvania Medical Center, Philadelphia, PA; Augoustides YG, MD, University of Pennsylvania Medical Center, Philadelphia, PA; DeBoer DA, MD, Brown P, PA, Saint Francis Hospital, Evanston, IL; Casterline JB, MD, Sauers L, RN, BSN, Cardio-Thoracic Surgeons, PC, Birmingham, AL; Moustoukas N, MD, Ruth Anna Wanstrath, BSN, Touro Infirmary, New Orleans, LA; Sharma R, MD, Gunn G, Criterion Research, Inc., St. Petersburg, FL; Eaton M, MD, Bailey L, RN, University of Rochester, Rochester, NY; Daon E, MD, Legler S, Saint Lukes Hospital, Kansas City, MO; Higgs W, MD, Trice A, RN, Discovery Alliance-Mobile Infirmary Medical Center, Mobile, AL; Levy JH., MD, Egan K, Emory Hospital, Atlanta, GA; Sladen RN, MD, Park H, Columbia University College of Physicians and Surgeons, New York, NY; Bonvino S, MD, Koppiseti S, Montefiore Medical Center, New York, NY; Savransky Y, MD, Moltz KS, PA, Montefiore Medical Center, New York, NY; Kereiakes DJ, MD, Garza D, RN, Lindner Clinical Trial Center, Cincinnati, OH; Mora-Mangano C, MD, Plonowska M, MD, Stanford University Medical Center, Stanford, CA; Chen JC, MD, Gervacio A,

Kaiser Permanente Medical Center, Honolulu, HI; Miller DL, MD, Chien G, MD, Marshall P, MS, Portland V.A. Medical Center, Portland, OR; Gheissari A, MD, Parker S, RN, Providence Saint Joseph Medical Center, Burbank, CA; Faluccci O, MD, Ponton T, RN, Virginia Commonwealth University Medical Center, Richmond, VA; Lumb PD, MB BS FCCM, McIntee D, Los Angeles County and University of Southern California Medical Center, Los Angeles, CA; Stella JF, DO, Enger EL, PhD, Heart Care Research Foundation, Blue Island, IL; Reardon MJ, MD, Davydov D, MD, The Methodist Hospital, CTSU, Houston, TX; Tahta S, MD, Hanneman A, RN BSN, The International Heart Institute, Missoula, MT; Singla N, MD, Villalobos L, MHA CRC, Huntington Memorial Hospital, Pasadena, CA; Doty J., MD, Flores J, RN, Salt Intermountain Health Care, Salt Lake City, UT; Rongione AJ, MD, Kelly SL, RN, Rx Trials at Inova Fairfax Hospital, Falls Church, VA; Harlan JL, MD, Burks J, RN BSN, Cardiothoracic Surgeons, PC, Birmingham, AL; Boylan M, MD, Allen K, Whiteside Research, Duluth, MN; Johnston G, MD, Crews L, RN, Saint Joseph Research Center, Tacoma, WA; Van Meter C Jr, MD, Kersker L, RN, Ochsner Clinic Foundation, New Orleans, LA; Kanchuger MS, MD, Ahmed R, New York University Medical Center, New York, NY; Katz D, MD, Degelia A, MemorialCare Medical Centers, Laguna Hills, CA; Richardson J Jr, MD, Phillips K, RN, Cardio-Thoracic Surgeons, PC, Birmingham, AL; Klodell CT, MD, Staples NL, RN, University of Florida Health Science Center, Gainesville, FL; Lichtenthal PR, MD, A.V. Patula, University of Arizona Medical Center, Tucson, AZ; Shenaq SA, MD, M. Bolos, Michael E DeBaKey V.A. Medical Center, Houston, TX; Russell I, MD PhD, Tarnow JL, RCP RR, University of California San Francisco, San Francisco, CA; Minkowitz H., MD, Lindley P, Memorial Hermann Health-care System, Houston, TX; Stierer K, MD, Dudek A, RN, Midatlantic Cardiovascular Associates, Towson, MD; Malias MA, MD, Parker NJ, RN CCRC, Health First Clinical Research Institute, Melbourne, FL; Roth EM, MD, Crone DS, RN BSN, Sterling Research Group, Ltd., Cincinnati, OH; Silverman NA, MD, P. Lowes, Henry Ford Hospital, Detroit, MI; Cammack PL, MD, Wallace-Jones M, LPN, Drug Research and Analysis Corporation, Montgomery, AL; Osborn TC, MD, Bittman M, Tomball Regional Hospital, Houston, TX; Avery E, MD, Donnelly A, RN, Massachusetts General Hospital, Boston, MA; Kwan SK, MD, Wallace-Jones M, LPN, Drug Research and Analysis Corporation, Montgomery, AL; Arthur Grimball, MD, Fosythe M, Cardiothoracic Surgery Center, PLC, Jackson, TN; Gitter R, MD, Khitin H, Thoracic and Cardiovascular Surgeons, PC, Birmingham, AL; Ronson RS, MD, Armstrong K, RN, Lamberth and Ronson, PC, Birmingham, AL; Magovern CJ, MD, Guarino T, RN, Morristown Memorial Hospital, Morristown, NJ; Reynolds RR, MD, Robertson MA, RN, Cardiac and Thoracic Surgical Associates, Ltd., Richmond, VA; Richardson J Jr, MD, Phillips K, RN, Cardio-Thoracic Surgeons, PC, Birmingham, AL; Wolfgang T, MD, Wittenbraker M, ACNP, Cardiac and Thoracic Surgical Associates, Mechanicsville, VA; Hahn C, MD, Bartle K, NP, Cardiac and Thoracic Surgical Associates, Richmond, VA; Bladergroen MR, MD, Wittenbraker M, ACNP, Cardiac and Thoracic Surgical Associates, Richmond,

VA; Dyke C, MD, Deal N, RN, Carolina Cardiovascular and Thoracic Surgery Associates, Gastonia, NC.

REFERENCES

1. Haas CE, LeBlanc JM. Acute postoperative hypertension: a review of therapeutic options. *Am J Health Syst Pharm* 2004;61:1661-75
2. Cheung AT. Exploring an optimum intra/postoperative management strategy for acute hypertension in the cardiac surgery patient. *J Card Surg* 2006;21 (Suppl 1):S8-S14
3. Dix P, Howell S. Survey of cancellation rate of hypertensive patients undergoing anaesthesia and elective surgery. *Br J Anaesth* 2001;86:789-93
4. Aronson S, Boisvert D, Lapp W. Isolated systolic hypertension is associated with adverse outcomes from coronary artery bypass grafting surgery. *Anesth Analg* 2002;94:1079-84
5. Reich DL, Bennett-Guerrero E, Bodian CA, Hossain S, Winfree W, Krol M. Intraoperative tachycardia and hypertension are independently associated with adverse outcome in noncardiac surgery of long duration. *Anesth Analg* 2002;95:273-7
6. Weiss SJ, Longnecker DE. Perioperative hypertension: an overview. *Coron Artery Dis* 1993;4:401-6
7. Charlson ME, MacKenzie CR, Gold JP, Ales KL, Topkins M, Shires GT. Intraoperative blood pressure. What patterns identify patients at risk for postoperative complications? *Ann Surg* 1990;212:567-80
8. Charlson ME, MacKenzie CR, Gold JP, Ales KL, Topkins M, Fairclough GP Jr, Shires GT. The preoperative and intraoperative hemodynamic predictors of postoperative myocardial infarction or ischemia in patients undergoing noncardiac surgery. *Ann Surg* 1989;210:637-48
9. Ong KL, Cheung BM, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. *Hypertension* 2007;49:69-75
10. Ragot S, Herpin D, Siche JP, Poncelet P, Mallion JM. Relationship between short-term and long-term blood pressure variabilities in essential hypertensives. *J Hum Hypertens* 2001;15:41-8
11. Kaplan NM, Lieberman E, Neal W. Kaplan's clinical hypertension. 8th ed. Philadelphia, PA: Lippincott, Williams & Wilkins, 2002;28-9
12. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206-52
13. Estafanous FG, Tarazi RC. Systemic arterial hypertension associated with cardiac surgery. *Am J Cardiol* 1980;46:685-94
14. Granger DN. Ischemia-reperfusion: mechanisms of microvascular dysfunction and the influence of risk factors for cardiovascular disease. *Microcirculation* 1999;6:167-78
15. Herskowitz A, Mangano DT. Inflammatory cascade: a final common pathway for perioperative injury? *Anesthesiology* 1996;85:957-60
16. Hennein HA, Ebba H, Rodriguez JL, Merrick SH, Keith FM, Bronstein MH, Leung JM, Mangano DT, Greenfield LJ, Rankin JS. Relationship of the pro-inflammatory cytokines to myocardial ischemia and dysfunction after uncomplicated coronary revascularization. *J Thorac Cardiovasc Surg* 1994;108:626-35
17. Kobzar G, Mardla V, Ratsep I, Samel N. Platelet activity before and after coronary artery bypass grafting. *Platelets* 2006;17:289-91
18. Leslie JB. Incidence and aetiology of perioperative hypertension. *Acta Anaesthesiol Scand Suppl* 1993;99:5-9
19. Vuylsteke A, Feneck RO, Jolin-Mellgård Å, Latimer RD, Levy JH, Lynch C III, Nordlander ML, Nyström P, Ricksten SE. Perioperative blood pressure control: a prospective survey of patient management in cardiac surgery. *J Cardiothorac Vasc Anesth* 2000;14:269-73

20. Ericsson H, Fakt C, Höglund L, Jolin-Mellgård Å, Nordlander M, Sunzel M, Regårdh CG. Pharmacokinetics and pharmacodynamics of clevidipine in healthy volunteers after intravenous infusion. *Eur J Clin Pharmacol* 1999;55:61-7
21. Ericsson H, Fakt C, Jolin-Mellgård Å, Nordlander M, Sohtell L, Sunzel M, Regårdh CG. Clinical and pharmacokinetic results with a new ultrashort-acting calcium antagonist, clevidipine, following gradually increasing intravenous doses to healthy volunteers. *Br J Clin Pharmacol* 1999;47:531-8
22. Nordlander M, Sjöquist PO, Ericsson H, Rydén L. Pharmacodynamic, pharmacokinetic and clinical effects of clevidipine, an ultrashort-acting calcium antagonist for rapid blood pressure control. *Cardiovasc Drug Rev* 2004;22:227-50
23. Bailey JM, Lu W, Levy JH, Ramsay JG, Shore-Lesserson L, Prielipp RC, Brister NW, Roach GW, Jolin-Mellgård Å, Nordlander M. Clevidipine in adult cardiac surgical patients: a dose-finding study. *Anesthesiology* 2002;96:1086-94
24. Halpern NA, Alicea M, Krakoff LR, Greenstein R. Postoperative hypertension: a prospective, placebo-controlled, randomized, double-blind trial, with intravenous nicardipine hydrochloride. *Angiology* 1990;41:992-1004
25. Sprague HB. The heart in surgery. An analysis of the results of surgery on cardiac patients during the past ten years at the Massachusetts General Hospital. *Surg Gynecol Obstet* 1929;49:54-8
26. Prys-Roberts C, Greene LT, Meloche R, Foëx P. Studies of anaesthesia in relation to hypertension. II. Haemodynamic consequences of induction and endotracheal intubation. *Br J Anaesth* 1971;43:531-47
27. Schmidt M, Scheunert T, Steinbach G, Schirmer U, Marx T, Freitag N, Reinelt H. Hypertension as a risk factor for cerebral injury during cardiopulmonary bypass. Protein S100B and transcranial Doppler findings. *Anaesthesia* 2001;56:733-8
28. Basali A, Mascha EJ, Kalfas I, Schubert A. Relation between perioperative hypertension and intracranial hemorrhage after craniotomy. *Anesthesiology* 2000;93:148-54
29. Cernaianu AC, Vassilidze TV, Flum DR, Maurer M, Cilley JH Jr, Grosso MA, DelRossi AJ. Predictors of stroke after cardiac surgery. *J Card Surg* 1995;10(4 Pt 1):334-9
30. Stone JG, Foëx P, Sear JW, Johnson LL, Khambatta HJ, Triner L. Risk of myocardial ischaemia during anaesthesia in treated and untreated hypertensive patients. *Br J Anaesth* 1988;61:675-9
31. Viljoen JF, Estafanous FG, Tarazi RC. Acute hypertension immediately after coronary artery surgery. *J Thorac Cardiovasc Surg* 1976;71:548-50
32. Reid GM, Muther RS. Nitroprusside-induced acute azotemia. *Am J Nephrol* 1987;7:313-5
33. Cheung AT, Cruz-Shiavone GE, Pochettino JA, Bavaria JE, Ochroch EA. Cardiopulmonary bypass, hemolysis, and nitroprusside-induced cyanide production. *Anesth Analg* 2007;105:29-33
34. Halpern NA, Goldberg M, Neely C, Sladen RN, Goldberg JS, Floyd J, Gabrielson G, Greenstein RJ. Postoperative hypertension: a multicenter, prospective, randomized comparison between intravenous nicardipine and sodium nitroprusside. *Crit Care Med* 1992;20:1637-43
35. Aronson S, Fontes ML, Miao Y, Mangano DT; Investigators of the Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation. Risk index for perioperative renal dysfunction/failure: critical dependence on pulse pressure hypertension. *Circulation* 2007;115:733-42