

Treatment of Acute Postoperative Hypertension in Cardiac Surgery Patients: An Efficacy Study of Clevidipine Assessing Its Postoperative Antihypertensive Effect in Cardiac Surgery-2 (ESCAPE-2), a Randomized, Double-Blind, Placebo-Controlled Trial

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BACKGROUND: Acute postoperative hypertension is a well-known complication of cardiac surgery and is associated with postoperative morbidity. Clevidipine, an ultrashort-acting, third-generation dihydropyridine calcium channel blocker, exerts vascular-selective, arterial-specific vasodilation to decrease arterial blood pressure without negatively impacting cardiac function. In this double-blind, placebo-controlled trial, we examined the efficacy and safety of clevidipine in treating postoperative hypertension in cardiac surgery patients.

METHODS: Two hundred six patients undergoing cardiac surgery were randomized preoperatively. Of these, 110 met postrandomization inclusion criteria for the study [systolic blood pressure (SBP) ≥ 140 mm Hg within 4 h of admission to a postoperative setting, and clinically assessed as needing SBP reduction by $\geq 15\%$ from baseline]. Patients received an infusion of either clevidipine ($0.4\text{--}8.0 \mu\text{g kg}^{-1} \text{min}^{-1}$) or 20% lipid emulsion (placebo) for 30 min to a maximum of 1 h unless treatment failure occurred sooner. The primary end point was the incidence of treatment failure, defined as the inability to decrease SBP by $\geq 15\%$ from baseline, or the discontinuation of study treatment for any reason within the 30-min period after study drug initiation.

RESULTS: Clevidipine-treated patients had a significantly lower incidence of treatment failure than placebo patients [8.2% (5 of 61) vs 79.6% (39 of 49), $P < 0.0001$]. Treatment success was achieved in 91.8% of clevidipine-treated patients. Median time to target SBP with clevidipine was 5.3 min (95% confidence interval, 4–7 min). No clinically significant increase in heart rate from baseline was observed. Adverse event rates were similar for both treatment groups.

CONCLUSIONS: Clevidipine is effective and safe in the rapid treatment of acute postoperative hypertension after cardiac surgery.

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Acute postoperative hypertension is an important clinical challenge after cardiac surgery^{1–3} that has been associated with myocardial injury, cerebral ischemia,

hemorrhagic stroke, and surgical bleeding.^{1–7} Perioperative hypertension in cardiac surgery patients is characterized by peripheral vasoconstriction and reduced baroreceptor sensitivity.⁸ Despite its importance, there are no established guidelines for the treatment of postoperative hypertension in this population. For patients needing intensive arterial blood pressure control in the postcardiac surgery setting, the ideal treatment would be a short-acting parenteral drug with fast onset and offset that can be rapidly and predictably titrated to the target arterial blood pressure range, without unwanted drug side effects.^{1,2} The antihypertensive drugs most commonly used for this purpose are nitroglycerin or sodium nitroprusside, with a smaller percentage of patients receiving either β -adrenergic receptor blockers or calcium channel blockers.^{1,3}

Clevidipine is a third-generation dihydropyridine calcium channel blocker that exhibits rapid onset and

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offset because of its metabolism by blood esterases.^{9–12} The half-life of clevidipine after IV administration is approximately 1 min.^{9–11,13,14} Clevidipine acts specifically on vascular smooth muscle as an arterial-specific vasodilating drug that reduces arterial blood pressure without inducing myocardial depression.^{12–14} Given this pharmacologic profile, clevidipine could be a promising drug for the treatment of postoperative hypertension. Prior, smaller, and dose-response studies have suggested that clevidipine may be effective in treating postoperative hypertension in cardiac surgery patients.^{12–15} The purpose of this randomized, double-blind study was to assess the efficacy of clevidipine compared with placebo in treating postoperative hypertension after cardiac surgery. The safety and tolerability of clevidipine were further assessed.

METHODS

The study was a prospective, double-blind, randomized, placebo-controlled trial performed at 15 medical centers between December 2003 and October 2004 to evaluate the efficacy of IV clevidipine in managing postoperative hypertension after cardiac surgery (Appendix lists study sites). Approval of the study was obtained from the Institutional Review Committee at each participating institution and written informed consent was obtained from each patient. The study was performed under IND 65,114 and was registered at clinicaltrials.gov under the identifier NCT00093262.

Study Population

Patients 18 yr of age or older who were scheduled to undergo cardiac surgery [including on- or off-pump coronary artery bypass graft (CABG) surgery, minimally invasive CABG surgery, and/or valve replacement or repair surgery] were eligible for study entry based on prerandomization inclusion criteria. Patients were excluded from the study for the following: cerebrovascular accident within the past 3 mo; preexisting left bundle branch block or permanent ventricular pacemaker; known intolerance or allergy to calcium channel blockers such as clevidipine or any of its components (such as soybean oil or egg lecithin); or any other disease or condition considered to place a patient at undue risk as a participant in the trial. Women of childbearing potential were required to have a negative urine or serum pregnancy test before participation in the trial. Patients were excluded if they had participated in another therapeutic drug or device trial within 30 days before surgery.

Postoperatively, patients were eligible to receive blinded study drug infusion only after meeting the postrandomization inclusion criteria of hypertension, defined as systolic blood pressure (SBP) ≥ 140 mm Hg within 4 h of arrival in a postoperative setting and clinically assessed by the study site investigator as requiring treatment to decrease SBP by at least 15% from baseline. In addition, only patients expected to

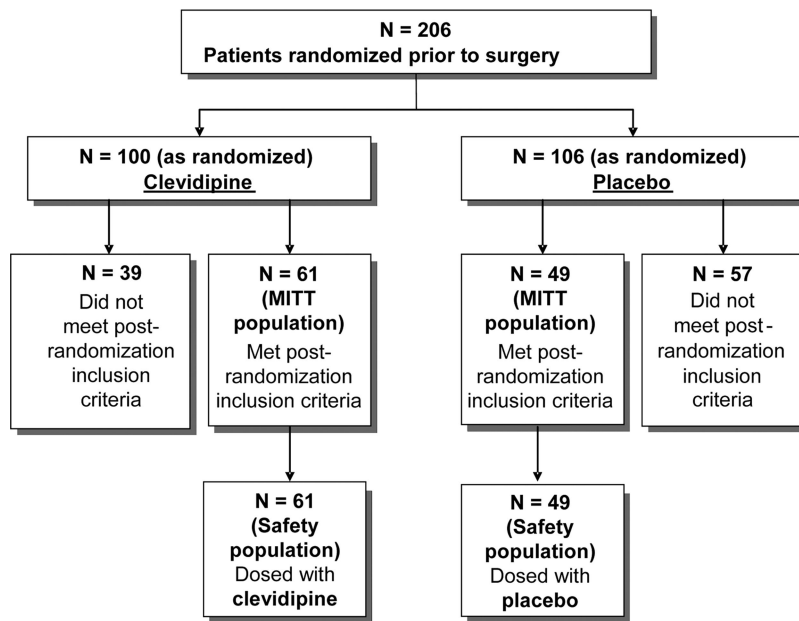
survive more than 24 h after surgery, and those free of any evident or anticipated surgical complications or conditions that would preclude participation in the trial, were eligible to receive study drug.

Study Design

A computer-generated randomization scheme (constructed using SAS software, version 8, SAS Institute Inc, Cary, NC) was used. Randomization was stratified by site in blocks of four in the order that the patients qualified. An interactive voice response system was used on the day of surgery to randomize patients to treatment groups and to assign study medication. Patients meeting postrandomization criteria were treated with clevidipine, supplied in 100-mL single-use glass bottles at a concentration of 0.5 mg/mL in a 20% lipid emulsion, or with placebo, a 20% lipid emulsion identical to the lipid vehicle used for clevidipine and supplied in 100-mL single-use glass bottles. Study infusion was administered for at least 30 min, unless treatment failure occurred, and for a maximum of 1 h. SBP and heart rate were monitored upon the patient's arrival in a postoperative setting, and measured once per minute during the study drug treatment period and for at least 30 min after study drug termination. If necessary, SBP and heart rate assessments continued beyond the minimum 30-min period, until they had stabilized. Clevidipine or placebo was administered via peripheral vein or central venous infusion, using either a syringe or volumetric pump. Treatment with either clevidipine ($0.4 \mu\text{g kg}^{-1} \text{min}^{-1}$) or placebo (at an equivalent infusion rate) was initiated and titrated as tolerated by incrementally doubling the dose approximately every 90 s up to an infusion rate of $3.2 \mu\text{g kg}^{-1} \text{min}^{-1}$. If SBP was not controlled at this rate, serial increments of $1.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ were permitted depending on patient response, not to exceed a maximum infusion rate of $8.0 \mu\text{g kg}^{-1} \text{min}^{-1}$. Upward and downward titration and temporary interruption and restarting of study infusion could be used as needed to achieve target SBP. An attempt to titrate the infusion rate to the maximum of $8.0 \mu\text{g kg}^{-1} \text{min}^{-1}$ was required before treatment failure. Treatment failure was defined as the inability to decrease SBP by $\geq 15\%$ from baseline at any time during the 30-min period from study drug initiation, or premature and permanent discontinuation of the infusion for any reason within the 30-min study period. After treatment failure, an alternative IV antihypertensive drug could be administered per institutional practice.

The use of non-study drug medications and procedures specifically for the treatment of hypertension were prohibited for patients participating in the trial during the first 30 min of study infusion, unless treatment failure occurred. Drugs with antihypertensive properties were permitted during study drug administration only when used for a condition other than hypertension. The use of concomitant sedatives,

Figure 1. Schemata of patient randomization and inclusion in the treatment and placebo groups. The modified intent-to-treat (MITT) population consisted of patients who met prespecified postrandomization inclusion criteria and were thus qualified to receive blinded study drug infusion as treatment for postoperative hypertension. All MITT patients received study drug with actual treatment identical to randomization; thus, the safety and MITT populations were identical in this study.



anesthetics/analgesics, vasodilators, and β -blockers was recorded.

Study Outcome

The primary end point was the incidence of treatment failure, defined as the inability to decrease SBP by $\geq 15\%$ from baseline or the premature and permanent discontinuation of study treatment for any reason within the 30-min period after study drug initiation. Three categories of treatment failure were prospectively defined: lack of efficacy, insufficient efficacy, and safety reason. Lack of efficacy was defined as no change or an increase in SBP from pretreatment baseline, or failure to achieve more than a nominal reduction in SBP within an acceptable timeframe as determined by the site investigator. Insufficient efficacy was defined as the inability to achieve a reduction in SBP by $\geq 15\%$ from baseline before the end of the 30-min treatment period. Treatment failure due to a safety reason was defined as the occurrence of an adverse event (AE) occurring or worsening in severity after the initiation of study drug infusion, which resulted in permanent discontinuation of study drug.

Secondary end points included: time to the first reduction of SBP by $\geq 15\%$ from baseline; change in mean arterial blood pressure (MAP) from baseline [calculated as $\text{MAP} = (\text{SBP} + 2 \times \text{diastolic blood pressure})/3$]; and change in heart rate. The incidence of AEs was assessed from the time of study drug initiation until hospital discharge or 7 days postoperatively, whichever came first. Laboratory variables (hematology and serum chemistry) and vital signs (respiratory rate and temperature in addition to MAP and heart rate) were assessed.

Statistical Analysis

Sample size was determined based on the assumption that clevidipine would be more effective than

placebo for decreasing SBP. Assuming a treatment failure rate of $< 60\%$ for patients treated with clevidipine compared with 88% for patients receiving placebo, it was calculated that 50 patients per treatment group would provide at least 85% power to demonstrate a difference between groups at a two-sided significance level of 0.05.

Efficacy analyses were performed on the modified intent-to-treat (MITT) population, defined as all randomized patients who met the prespecified postrandomization inclusion criteria immediately before the initiation of blinded study drug infusion. Safety analyses were performed on the safety population, defined as all randomized patients who were administered study drug. Categorical parameters, including the primary efficacy end point, were analyzed using the χ^2 test. Continuous parameters were analyzed using an analysis of covariance model for absolute change from baseline with treatment as a factor and baseline as a covariate, and an analysis of variance model for percentage change from baseline with treatment as a factor. Time to reduction of SBP by $\geq 15\%$ was analyzed as a time-to-event parameter, using the log-rank test and Kaplan-Meier survival analysis.

RESULTS

A total of 206 patients were enrolled preoperatively and randomized either to the clevidipine group ($n = 100$) or the placebo group ($n = 106$) (Fig. 1). Of those randomized, 61 clevidipine patients and 49 placebo patients met the postrandomization inclusion criteria (MITT population), and received clevidipine or placebo. All MITT patients received study infusions, and thus, the safety population and the MITT population were the same.

Baseline demographics and cardiac risk factors were generally comparable between the two treatment

Table 1. Baseline Patient Characteristics (MITT Population)

Variable	Clevidipine (N = 61)	Placebo (N = 49)	P
Age (yr), mean (SD)	63.8 (12.6)	62.3 (11.8)	0.5410
Age ≥65 yr	33 (54.1)	17 (34.7)	0.0422
Male patients	47 (77.0)	38 (77.6)	0.9502
Weight (kg), mean (SD)	82.7 (16.8)	84.2 (17.3)	0.6548
Height (cm), mean (SD)	171.1 (7.7)	171.1 (10.6)	0.9669
Baseline postoperative SBP (mm Hg), mean (SD)	147.4 (8.4)	150.5 (11.8)	0.1097
Prior myocardial infarction	15 (24.6)	15 (30.6)	0.4809
Prior PCI	11 (18.0)	9 (18.4)	0.9639
Prior CABG	1 (1.6)	2 (4.1)	0.4344
Family history of CAD	29 (47.5)	27 (55.1)	0.4305
Hypertension	51 (83.6)	41 (83.7)	0.9925
Congestive heart failure	12 (19.7)	5 (10.2)	0.1721
Dyslipidemia	35 (57.4)	26 (53.1)	0.6508
Diabetes	21 (34.4)	17 (34.7)	0.9766
Cigarette smoker	9 (14.8)	15 (30.6)	0.2493
Transient ischemic attack	0 (0.0)	3 (6.1)	0.0501
Stroke	4 (6.6)	4 (8.2)	0.7472
Angina pectoris	26 (42.6)	31 (63.3)	0.0313
Peripheral vascular disease	8 (13.1)	6 (12.2)	0.8918

P values based on the *t* test (continuous variables) or χ^2 test (categorical data). Table data expressed as number (percentage) unless otherwise noted.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; MITT = modified intent-to-treat population consisting of all patients who met prespecified postrandomization inclusion criteria and were thus qualified to receive blinded study drug infusion as treatment for postoperative hypertension; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; SD = standard deviation.

Table 2. Procedural Characteristics (MITT Population)

Parameter	Clevidipine (N = 61)	Placebo (N = 49)
Primary CABG only	33 (54.1)	35 (71.4)
Primary valve repair or replacement surgery only	17 (27.9)	6 (12.2)
Primary combination CABG and valve repair or replacement surgery	8 (13.1)	6 (12.2)
Repeat CABG only	0 (0.0)	1 (2.0)
Repeat valve repair or replacement surgery only	2 (3.3)	1 (2.0)
Repeat combination CABG and valve repair or replacement surgery	1 (1.6)	0 (0.0)

P = 0.2162 for overall comparison of procedures and treatment groups (Cochran-Mantel Haenszel test). Table data expressed as number (percentage) unless otherwise noted.

CABG = coronary artery bypass grafting; MITT = modified intent-to-treat population, consisting of all patients who met prespecified postrandomization inclusion criteria and were thus qualified to receive blinded study drug infusion as treatment for postoperative hypertension.

groups (Table 1). Although mean age was similar in the two groups, there was a higher percentage of patients ≥65 yr old in the clevidipine group ($P = 0.04$). On the other hand, there were more patients with a history of angina in the placebo group ($P = 0.03$; Table 1). Both treatment groups demonstrated baseline characteristics consistent with a typical cardiac surgery patient population.¹⁶

There was a numerically higher percentage of primary CABG procedures in the placebo group and a higher percentage of primary valve repair or replacement surgery in the clevidipine group (Table 2). However, overall, the type of index surgical procedure was similar between the clevidipine and placebo groups ($P = 0.2162$).

Prior and concomitant medications are summarized in Table 3. Analgesic and sedative administration was comparable between the two treatment groups. Postoperatively and before study drug administration, 55.7% of clevidipine patients received IV nitroglycerin, versus 36.7% of placebo patients ($P = 0.047$). During study drug administration this was reversed, 36.1% vs 44.9% (clevidipine versus placebo patients; $P = 0.347$). In addition, 32.7% of placebo patients received sodium nitroprusside during the 30-min treatment period, compared with only 1.6% in the clevidipine group.

Efficacy

Treatment success (absence of treatment failure, as previously defined) was achieved in significantly more clevidipine-treated patients than placebo-treated patients (91.8% vs 20.4%, $P < 0.0001$) (Table 4). Five clevidipine patients were reported as having treatment failure for any cause. Three patients had the study infusion terminated for safety reasons (described below). For the remaining two patients, a decrease in SBP by ≥15% from baseline was not achieved over the 30-min treatment period.

The median time to target SBP with clevidipine was 5.3 min (95% confidence interval, 4–7 min). In the placebo group, too few patients achieved the target SBP decrease to enable calculation of this value. Clevidipine-treated patients showed a significantly greater decrease in MAP than placebo-treated patients at 2 min after study drug initiation [mean change -5.7 mm Hg (-5.9%) vs -0.1 mm Hg (-0.1%), $P = 0.0004$], and this significant difference was sustained at 5, 10, and 15 min after study drug initiation. During the 30-min treatment period, the greatest mean change

Table 3. Prior/Concomitant Postoperative Medications (MITT Population)

Medication	Before study drug administration		During study drug administration	
	Clevidipine (N = 61) n (%)	Placebo (N = 49) n (%)	Clevidipine (N = 61) n (%)	Placebo (N = 49) n (%)
Analgesia and sedation after surgery				
All patients receiving at least one analgesic or sedative	25 (41.0)	17 (34.7)	27 (44.3)	20 (40.8)
Morphine	4 (6.6)	5 (10.2)	10 (16.4)	10 (20.4)
Fentanyl	5 (8.2)	2 (4.1)	6 (9.8)	2 (4.1)
Meperidine	2 (3.3)	0 (0.0)	2 (3.3)	1 (2.0)
Propofol	16 (26.2)	11 (22.4)	17 (27.9)	10 (20.4)
Midazolam	2 (3.3)	0 (0.0)	1 (1.6)	2 (4.1)
Dexmedetomidine	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Other ^a	2 (3.3)	4 (8.2)	2 (3.3)	3 (6.1)
β -Blockers/vasodilators after surgery ^b				
All patients receiving at least one β -blocker or vasodilator	37 (60.7)	20 (40.8)	25 (41.0)	36 (73.5)
Esmolol	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.1)
Metoprolol	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Nicardipine	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Nitroglycerin	34 (55.7)	18 (36.7)	22 (36.1)	22 (44.9)
Sodium nitroprusside	4 (6.6)	2 (4.1)	1 (1.6)	16 (32.7)
Other ^c	10 (16.4)	4 (8.2)	9 (14.8)	4 (8.2)

^a Including acetic acid derivatives and related substances, adrenergic and dopaminergic drugs, amides, amino acids, aminoalkyl ethers, desflurane, Class IB or III antiarrhythmics, anticholinesterases, and barbiturates.

^b For β -blockers/vasodilators, drugs listed are those administered prior to study drug administration and during the first 30 min of study drug administration only.

^c Including adrenergic and dopaminergic drugs.

MITT = modified intent-to-treat population, consisting of all patients who met prespecified postrandomization inclusion criteria and were thus qualified to receive blinded study drug infusion as treatment for postoperative hypertension.

Table 4. Summary of Study End Points (MITT Population)

Parameter	Clevidipine (N = 61)	Placebo (N = 49)	P
Treatment failure, all cause ^a	5 (8.2)	39 (79.6)	<0.0001
Lack of efficacy	0 (0.0)	37 (75.5)	<0.0001
Insufficient efficacy	2 (3.3)	2 (4.1)	1.0000
Safety reason	3 (4.9)	0 (0.0)	0.2521
Treatment success	56 (91.8)	10 (20.4)	<0.0001
Time to target SBP ^b (min), median (95% CI)	5.3 (4–7)	NE ^c	<0.0001

P values based on χ^2 test (treatment failure and treatment success); Fisher's exact test without adjustment of multiple comparisons (lack of efficacy, insufficient efficacy, and safety reason); or log-rank test (time to target SBP). Table data expressed as number (percentage) unless otherwise noted.

^a Defined as the premature and permanent discontinuation of study drug infusion because of lack of efficacy (increase, no change, or nominal change in SBP); for safety reasons; or because of insufficient efficacy (inability to decrease SBP by at least 15% from baseline) within the 30-min treatment period.

^b Defined as time to first reduction of SBP by at least 15% from baseline.

^c Not estimable due to too few patients achieving the prespecified SBP target.

CI = confidence interval; MITT = modified intent-to-treat population, consisting of all patients who met prespecified postrandomization inclusion criteria and were thus qualified to receive blinded study drug infusion as treatment for postoperative hypertension; NE = not estimable; SBP = systolic blood pressure.

from baseline MAP was -28.1 mm Hg (-28.9%) in the clevidipine group compared with -8.9 mm Hg (-8.7%) in the placebo group ($P < 0.0001$). Almost all (54 of 57, 94.7%) clevidipine patients reached the target SBP at an infusion rate of ≤ 3.2 $\mu\text{g kg}^{-1} \text{min}^{-1}$ (Table 5). Overall, only one clevidipine patient was titrated to the maximum rate, 8.0 $\mu\text{g kg}^{-1} \text{min}^{-1}$.

Among placebo patients with treatment failure ($n = 39$), the following drugs were administered as alternative IV therapy for hypertension: nitroglycerin (19 patients), sodium nitroprusside (15 patients), fentanyl (one patient), metoprolol (one patient), and esmolol (one patient); two patients did not receive an alternative IV

drug. The five clevidipine patients with treatment failure received as alternative IV therapy: nitroglycerin (two patients) and sodium nitroprusside (one patient); two patients did not receive an alternative IV drug.

Safety

No evidence of reflex tachycardia was observed in the clevidipine group during the 30-min infusion period (Fig. 2). At baseline, median heart rate was 90.0 bpm (range, 45–142) for clevidipine-treated patients compared with 90.0 bpm (range, 67–135) for placebo-treated patients. The median highest heart rate within

Table 5. Study Drug Infusion Rates Needed to Achieve Target SBP (Safety Population)

Study drug titrated up to doses ($\mu\text{g kg}^{-1} \text{min}^{-1}$)	$\geq 15\%$ SBP reduction from baseline ^a	
	Clevidipine (N = 61) n (%)	Placebo (N = 49) n (%)
>0–0.4	16 (26.2)	2 (4.1)
>0.4–0.8	21 (34.4)	2 (4.1)
>0.8–1.6	9 (14.8)	4 (8.2)
>1.6–3.2	8 (13.1)	0 (0.0)
>3.2–4.7	3 (4.9)	3 (6.1)
>4.7–6.2	0 (0.0)	1 (2.0)
>6.2–7.7	0 (0.0)	1 (2.0)
Up to 8.0	0 (0.0)	0 (0.0)

^a Fifty-seven of 61 patients in the clevidipine group and 13 of 49 patients in the placebo group (safety population) achieved a $\geq 15\%$ reduction of SBP from baseline. One of the 57 patients in the clevidipine group achieved a $\geq 15\%$ reduction of SBP from baseline at 2 min of study drug infusion but discontinued treatment at 4 min because of safety reasons; thus, the patient is not included in Table 4 in the group of patients achieving treatment success. Three of the 13 placebo patients who achieved a $\geq 15\%$ reduction of SBP from baseline subsequently experienced an increase in SBP during the 30-min treatment period, and discontinued study drug due to lack of efficacy; thus, these patients are not included in Table 4 with those achieving treatment success.

SBP = systolic blood pressure.

the 30-min treatment period was 93.0 bpm (range, 57–152) for clevidipine patients and 91.5 bpm (range, 67–150) for placebo patients. Treatment failure for safety reasons was reported for three of the clevidipine-treated patients. Clevidipine was discontinued in one patient because of atrial fibrillation, reported as a non-serious AE that resolved without sequelae on the same day. It was discontinued in two patients before the end of the 30-min treatment period: in one because of a decrease in SBP from 140 to 100 mm Hg in about 3 min, and in the other, from 140 to 108 mm Hg in about 5 min.

AE rates during the 7 days after surgery in the clevidipine and placebo treatment groups were comparable. A total of 63.9% (39 of 61) of patients in the clevidipine group and 57.1% (28 of 49) of patients in the placebo group had at least one AE reported after study drug initiation. AEs reported $\geq 10\%$ in the clevidipine group included: nausea (clevidipine 21.3% versus placebo 12.2%); atrial fibrillation (21.3% vs 12.2%); and insomnia (11.5% vs 6.1%). AEs reported $\geq 10\%$ in the placebo group included nausea and atrial fibrillation as just described, and edema (clevidipine 8.2% versus placebo 12.2%) and atelectasis (clevidipine 3.3% versus placebo 10.2%). None of these differences reached statistical significance.

There were no deaths during the study period. The incidence of serious AEs was similar in both treatment groups, at 16.4% for clevidipine-treated patients and 12.2% for patients treated with placebo. No single serious AE occurred in more than two patients. Within the clevidipine group, serious AEs reported in two patients (3.3%) included pneumonia (versus 0% in the placebo group), respiratory failure, atrial fibrillation, and postprocedural hemorrhage (all versus 2.0% placebo). Only one serious AE, thrombophlebitis occurring in one patient approximately 2 days after

clevidipine administration (versus 0% placebo-treated patients), was assessed by the site investigator to be possibly related to study drug. The remaining serious AEs were assessed by the site investigators as unrelated. No clinically important differences in the results of laboratory tests or in the assessment of respiratory rate or body temperature were found between treatment groups.

DISCUSSION

In this prospectively randomized, placebo-controlled, double-blind study in patients undergoing cardiac surgery with acute postoperative hypertension, we have demonstrated that clevidipine achieved a 91.8% success rate in decreasing SBP by at least 15% within the 30-min treatment period. Target SBP was achieved within 4 to 7 min after initiation of the clevidipine infusion at a dose $\leq 3.2 \mu\text{g kg}^{-1} \text{min}^{-1}$ in 95% (54/57) of patients, and was accomplished without the occurrence of clinically apparent acute hemodynamic AEs. These findings suggest that clevidipine is effective for the rapid treatment of acute postoperative hypertension in the cardiac surgery patient.

The present study evaluated cardiac surgery patients in the immediate postoperative period as a high-risk population needing careful blood pressure management,^{1–3} characterized by a high prevalence of comorbidities,⁸ and unable to receive oral medication for adequate blood pressure control. Acute postoperative hypertension appears to be mediated predominantly by increased sympathetic activation and is induced by an increased systemic vascular resistance secondary to arterial vasoconstriction.^{1–3,7,8} When the primary cause of sympathetic activation cannot be identified or treated, IV antihypertensive therapy combining rapid onset and offset of effect, selective arterial dilation and lack of toxicity or other unwanted drug effects would be desirable.^{1,2,17}

Uncontrolled postoperative hypertension may be associated with a number of postoperative complications including surgical bleeding, myocardial injury, cerebral ischemia, and hemorrhagic stroke.^{1–7} Although the benefit of postoperative blood pressure control for improving patient outcome is unclear, it is generally considered prudent to control postoperative hypertension in cardiac surgical patients, often to a SBP of < 140 mm Hg.^{1,3,17} Unfortunately, there are few formal guidelines or a clear consensus as to the choice of antihypertensive drug, threshold for initiating treatment, or treatment goals. In any treatment algorithm of postoperative hypertension, pain, and anxiety must always be excluded first, and appropriate analgesia and sedation are essential prerequisites to the initiation of antihypertensive therapy.¹ This approach was incorporated into the current study protocol, which permitted the use of postoperative concomitant sedating/analgesic/anesthetic medications before study

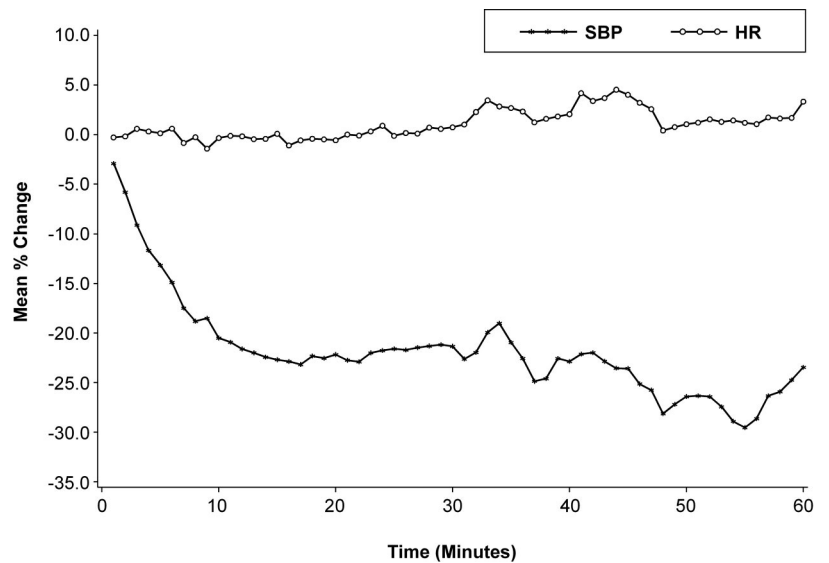


Figure 2. Clevidipine-treated patients. Mean percent change from baseline in systolic blood pressure (SBP; modified intent-to-treat population) and in heart rate (HR; safety population), demonstrating a rapid onset of SBP-decreasing effect and stable HR.

drug administration, and the use of these medications was comparable in both the clevidipine and placebo groups.

Although a larger proportion of clevidipine patients than placebo patients received nitroglycerin before study drug initiation, once the infusion started this proportion reversed. Additionally, almost one third of placebo patients received sodium nitroprusside during study drug infusion. These changes were because of treatment failure in the placebo patients, 19 of whom received nitroglycerin and 15 of whom received sodium nitroprusside as alternative IV anti-hypertensive therapy after treatment failure.

Nitroglycerin and sodium nitroprusside are established and effective medications for blood pressure control, but both produce venodilation.^{1,18} This decrease in preload can induce blood pressure lability, abrupt hypotension and reflex tachycardia, especially in the intravascular volume-depleted patient or those with diastolic dysfunction. Sodium nitroprusside has other undesirable effects, such as coronary steal syndrome and the potential for cyanide toxicity.^{1,2,6,8,18,19} Dihydropyridine calcium channel blockers such as nicardipine and clevidipine decrease blood pressure by selective arterial dilation and have no effect on cardiac preload.^{1,2,12,18} Nicardipine has a relatively slow onset, undergoes hepatic biotransformation and has a prolonged duration of action. In contrast, clevidipine has a rapid onset and offset, undergoes rapid ester hydrolysis in the blood independent of liver function, and has no known toxic metabolites.^{12,18}

Like other dihydropyridine calcium channel blockers, clevidipine has minimal, if any, negative inotropic effect on cardiac function. Theoretically, this could facilitate reflex tachycardia, but in the current study we observed no clinically significant increases in heart rate or acute adverse hemodynamic events. This finding is consistent with studies using more invasive monitoring that have demonstrated no adverse hemodynamic effect from clevidipine.¹³⁻¹⁵ The underlying

mechanism for the absence of reflex tachycardia in anesthetized patients treated with clevidipine is not known, but may be related to attenuation of the baroreceptor response because of sedation and anesthesia,¹² and/or to the masking of reflex increases in sympathetic stimulation by the intensity of the background sympathetic activation already present as a result of surgical and postoperative stress.^{1,8}

The SBP threshold and treatment goal (decrease in SBP by $\geq 15\%$ from baseline) chosen for the current study are consistent with other studies and clinical practice.^{19,20} The efficacy of clevidipine is comparable with the treatment response observed with nicardipine and sodium nitroprusside in postoperative cardiac surgery patients.^{19,20} However, the time to achieve the therapeutic goal of target blood pressure (4–7 min) is much shorter than that reported previously with nicardipine (14 min) or sodium nitroprusside (30 min under the administration conditions specified by the previous study for this drug).²⁰ The authors explained the paradoxical delay in blood pressure goal achievement with sodium nitroprusside as due to cautious titration,²⁰ similar to that recommended for avoiding excessive hypotension with sodium nitroprusside.²¹

There was no significant increase in AEs associated with clevidipine treatment versus placebo. Although the incidence of atrial fibrillation was more frequent in the clevidipine group, it is still well within the range reported for cardiac surgery patients.^{22,23} One possible explanation is the larger proportion in the clevidipine group of valvular surgery patients (Table 2) who are at increased risk for postoperative atrial fibrillation.²² The differences observed may reflect a fluctuation of incidences of uncommon AEs because of a small sample size. Three recently completed large-scale trials of clevidipine ($n = 1506$) found a similar incidence of atrial fibrillation in clevidipine-treated and comparator-treated patients.²⁴

The present study (Efficacy Study of Clevidipine Assessing its Postoperative Antihypertensive Effect in Cardiac Surgery-2) demonstrates that clevidipine provides effective control of postoperative hypertension in cardiac surgery patients. Data from this study and from the Efficacy Study of Clevidipine Assessing its Preoperative Antihypertensive Effect in Cardiac Surgery-1 trial,²⁵ which demonstrated similar efficacy findings for clevidipine administered preoperatively to patients scheduled for cardiac surgery, may provide a foundation for further clinical studies. The combination of rapid onset of selective arterial vasodilation and rapid elimination without toxic metabolites suggests that clevidipine could be considered as a first-line IV antihypertensive drug for the treatment of postoperative hypertension after cardiac surgery.

APPENDIX

The following clinical investigators and research coordinators participated in and made significant contributions to the conduct of this study (affiliations listed are those that were current at the time of the study): S. Aronson, MD, P. Porcelli, MacNeal Hospital, Berwyn, IL; E. Daon, MD, M. Borkon, MD, R.S. Stuart, MD, M. Stephan, St. Luke's Hospital – Kansas City, Kansas City, MO; W.R. Higgs, MD, D. Kyriazis, MD, M.E. Damrich, MD, C. Maltese, MD, R. O'Gorman, MD, D.H. Mull, MD, J. Stephens, Discovery Alliance – Mobile Infirmiry Medical Center, Mobile, AL; J. Levy, MD, K. Tanaka, MD, K. Egan, S. Chan, Emory University Hospital, Atlanta, GA; P.D. Lumb, MD, R.V. Patel, MD, J. Szenohradszky, MD, R. Patel, M. Cunningham, MD, D. McIntee, Keck School of Medicine, University of Southern CA, Los Angeles, CA; C.P. McCoy, MD, B. Emanuel, MD, C.A. Johnson, MD, C. Batemann, DO, S. Casey, RN, D.G. Pruit, LPN, J. Marden, RN, Wesley Medical Center, Wichita, KS; C. Mora-Mangano, MD, P. van der Starre, MD, C. Guta, MD, E. Jackson, MD, A. Mignea, MD, Stanford University School of Medicine, Stanford, CA; M.J. Reardon, MD, J.-C.M. Wilkes, MD, J. Hanley, Discovery Alliance – Methodist Hospital/Diagnostic West Pavilion, Houston, TX; L. Shore-Lesserson, MD, M. Stone, MD, D. Bronheim, MD, I. Hollinger, MD, A. Lichtman, MD, W. Kimber-Winfrey, RN, Mount Sinai School of Medicine, New York, NY; N.K. Singla, MD, V.M. Ankevar, MD, L. Villalobos, Huntington Memorial Hospital, Pasadena, CA; R.N. Sladen, MBChB, H. Playford, MBBS, R. Fromento, MPH, J. Lu, H. Park, Columbia University – College of Physicians and Surgeons, New York, NY; M. Stiegel, MD, G. Schwarz, Carolinas Medical Center, Charlotte, NC; J. Stella, DO, V. Kucich, MD, R. Applebaum, MD, R. Gasior, MD, R. Veeragandham, MD, P. Alexander, MD, M. Lubienski, MD, E. Enger, PhD, Heart Care Research Foundation, Blue Island, IL; S. Tahta, MD, S. Hiro, MD, M. Maxwell, MD, H. Garrick-Boehm, International Heart Institute of Montana, Missoula, MT; D.C. Warltier, MD, S.D. Gandhi, MD, Z.

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