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REPORTS OF ORIGINAL INVESTIGATIONS

Clevidipine compared with nitroglycerin for blood pressure control in coronary artery bypass grafting: a randomized double-blind study

Comparaison de la clévidipine à la nitroglycérine pour le contrôle de la tension artérielle lors d'un pontage aortocoronarien: une étude randomisée à double insu

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Abstract

Purpose *We tested the hypothesis that clevidipine, a rapidly acting dihydropyridine calcium channel blocker, is not inferior to nitroglycerin (NTG) in controlling blood pressure before cardiopulmonary bypass (CPB) during coronary artery bypass grafting (CABG).*

Methods *In this double-blind study from October 4, 2003 to April 26, 2004, 100 patients undergoing CABG with CPB were randomized at four centres to receive intravenous infusions of clevidipine (0.2-8 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or NTG (0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to a clinician-determined maximum dose rate) from induction of anesthesia through 12 hr postoperatively. The study drug was titrated in the pre-CPB period with the aim of maintaining mean arterial pressure (MAP) within ± 5 mmHg of a clinician-predetermined target. The primary endpoint was the area under the curve (AUC) for the total time each patient's MAP was outside the target range from drug initiation to the start of CPB, normalized per hour ($AUC_{MAP\text{-}D}$). The predefined non-inferiority criterion for the primary endpoint was a 95% confidence interval (CI) upper limit no greater than 1.50 for the geometric means ratio between clevidipine and NTG.*

Results *Total mean [standard deviation (SD)] dose pre-bypass was 4.5 (4.7) mg for clevidipine and 6.9 (5.4) mg for NTG ($P < 0.05$). The geometric mean $AUC_{MAP\text{-}D}$ for clevidipine was 283 $mmHg \cdot min \cdot hr^{-1}$ ($n = 45$) and for NTG was 292 $mmHg \cdot min \cdot hr^{-1}$ ($n = 48$); the geometric means ratio was 0.97 (95% CI 0.74 to 1.27). The geometric mean $AUC_{MAP\text{-}D}$ during aortic cannulation was 357.7 $mmHg \cdot min \cdot hr^{-1}$ for clevidipine compared with 190.5 $mmHg \cdot min \cdot hr^{-1}$ for NTG. Mean (SD) heart rate with clevidipine was 76.0 (13.8) $beats \cdot min^{-1}$ compared*

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Author contributions *Alan F. Merry, Hugh R. Playford,* and *Robert N. Sladen* contributed to the design of the study. *Alan F. Merry* oversaw the conduct of the study, and *Hugh R. Playford* contributed to the conduct of the study. *Alan F. Merry* contributed to all stages of manuscript preparation and revision. *Hugh R. Playford, Yamei Wang, Robert N. Sladen,* and *Guy R. Warman* contributed to manuscript preparation. *Hugh R. Playford, Yamei Wang, Robert N. Sladen, Edwin G. Avery,* and *Guy R. Warman* contributed to manuscript revision, and *Nancy A. Nussmeier* contributed to critical revisions of the article for important intellectual content. *Alan F. Merry* has had access to the data and is the guarantor of the study. *Edwin G. Avery, Nancy A. Nussmeier,* and *Robert N. Sladen* contributed to the acquisition of the data. *Yamei Wang* conducted all data analyses, and *Alan F. Merry* and *Hugh R. Playford* contributed to the data analysis. *Alan F. Merry, Edwin G. Avery, Hugh R. Playford,* and *Yamei Wang* contributed to the interpretation of the data. *Guy R. Warman* was responsible for patient recruitment, data collection, audits, and running the study at the Auckland study site. *Yamei Wang* created the tables.

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with 81.5 (14.4) beats·min^{-1} for NTG. There were no clinically important differences between groups in adverse events.

Conclusion *During CABG, clevidipine was not inferior to NTG for blood pressure control pre-bypass.*

Résumé

Objectif *Nous avons testé l'hypothèse selon laquelle la clévidipine, un bloqueur des canaux calciques dihydropyridiniques à action rapide, n'était pas inférieure à la nitroglycérine (NTG) pour contrôler la tension artérielle avant la circulation extracorporelle (CEC) pendant une chirurgie de pontage aortocoronarien (PAC).*

Méthode *Dans cette étude à double insu menée entre le 4 octobre 2003 et le 26 avril 2004, 100 patients subissant un PAC sous CEC ont été randomisés dans quatre centres à recevoir des perfusions intraveineuses de clévidipine (0,2-8 μg·kg^{-1}·min^{-1}) ou de NTG (0,4 μg·kg^{-1}·min^{-1} à un débit de dose maximal déterminé par le clinicien) de l'induction de l'anesthésie jusqu'à 12 h après l'opération. Le médicament à l'étude était titré au cours de la période avant CEC avec pour objectif de maintenir la tension artérielle moyenne (TAM) dans de 5 mmHg de la cible déterminée par le clinicien. Le critère d'évaluation principal était la surface sous la courbe (SSC) du temps total pendant lequel la TAM de chaque patient se situait hors de la zone cible entre la mise en place du médicament et le début de la CEC, normalisée par heure (SSC_{TAM-D}). Le critère prédéfini de non-infériorité pour le critère d'évaluation principal était une limite supérieure d'un intervalle de confiance (IC) de 95 % pas plus haute que 1,50 pour le ratio moyen géométrique entre la clévidipine et la NTG.*

Résultats *La dose moyenne (ÉT) avant pontage était de 4,5 (4,7) mg pour la clévidipine et 6,9 (5,4) mg pour la NTG ($P < 0,05$). La SSC_{TAM-D} moyenne géométrique de la clévidipine était de 283 mmHg·min·h^{-1} ($n = 45$) et de 292 mmHg·min·h^{-1} ($n = 48$) pour la NTG; le ratio moyen géométrique était de 0,97 (IC 95 % 0,74 à 1,27). La SSC_{TAM-D} moyenne géométrique pendant la canulation aortique était de 357,7 mmHg·min·h^{-1} pour la clévidipine par rapport à 190,5 mmHg·min·h^{-1} pour la NTG. La fréquence cardiaque moyenne (ÉT) avec la clévidipine était de 76,0 (13,8) battements·min^{-1} par rapport à 81,5 (14,4) battements·min^{-1} pour la NTG. Il n'y a pas eu de différence importante d'un point de vue clinique entre les groupes au niveau des complications.*

Conclusion *Pendant le PAC, la clévidipine n'était pas inférieure à la NTG en matière de contrôle de la tension artérielle avant le pontage.*

Blood pressure control is an essential component of cardiac anesthesia.[1,2] It includes proactive controlled hypotension (e.g., for aortic cannulation) as well as prompt treatment of hypertension.[3,4] As many as 50% of patients undergoing cardiac surgery may need intravenous antihypertensive treatment perioperatively to prevent neurologic, cardiovascular, and/or surgical complications.[5,6] This warrants a rapidly acting drug that is safe and effective, and nitroglycerin (NTG) and sodium nitroprusside (SNP) are commonly used for this purpose.[1,7] Nitroglycerin is a water-soluble predominantly venodilating drug that reduces blood pressure through its effects on venous capacitance.[4,6] It is not consistently effective in reducing blood pressure[4] and may cause hypotension or reflex tachycardia.[4,6] Sodium nitroprusside is an arterial and venous vasodilator associated with hypotension, rebound hypertension upon discontinuation, and the potential for cyanide toxicity.[4-6]

Clevidipine is a vascular-selective and arterial-specific dihydropyridine L-type calcium channel antagonist that rapidly reduces blood pressure by acting directly to dilate arteriolar resistance vessels.[7] Cardiac output is maintained, and clinically relevant reflex tachycardia has not been observed in anesthetized patients after cardiac surgery.[7-11] The elimination half-life of clevidipine is approximately one minute, allowing for very precise titration to effect.[7,12,13] As an arterial dilator, clevidipine might provide more rapid and predictable control of blood pressure than NTG without the limitations of SNP. In

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preclinical studies, clevidipine was shown to preserve blood flow to the kidneys,[14] which might mitigate the perioperative renal dysfunction associated with cardiac surgery.[15,16] The safety of clevidipine in managing perioperative blood pressure during cardiac surgery has been studied in three parallel open-label trials in which clevidipine was judged to be as safe as sodium nitroprusside, nitroglycerin, and nicardipine respectively (the ECLIPSE study).[10] In this study, the efficacy of clevidipine *vs* comparator drug was assessed in a secondary analysis using area under the curve (AUC) of blood pressure excursions beyond predetermined upper and lower limits, normalized per hour. Clevidipine was found to be superior for the treatment of acute hypertension from the initiation of study drug infusion through either the removal of the arterial line or 24 hr after study drug initiation, whichever occurred first.

In 2002, before the ECLIPSE study, we decided to undertake a double-blind randomized study to test the hypothesis that clevidipine is not inferior to NTG for control of mean arterial pressure (MAP) during coronary artery bypass grafting (CABG). Data collection was completed in 2004, but various factors delayed the finalization of the study report and subsequent preparation of this manuscript. On the basis of the above discussion, it is our view that this double-blind study is still clinically and scientifically relevant and addresses a question that has not yet been answered.

Methods

Study design

We conducted a randomized double-blind double-dummy trial to evaluate the primary hypothesis that clevidipine is not inferior to NTG in clinically managing blood pressure during CABG. The study was conducted at the following four study sites: Green Lane Hospital and Mercy Ascot Integrated Hospitals, Auckland, New Zealand; Texas Heart Institute, Texas; Massachusetts General Hospital, Boston; and Columbia University, New York, USA. The study protocol was approved by the institutional review board or ethics committee responsible for each site (Primary approval was obtained from Auckland Ethics Committee AKY/02/00/160, July 30, 2002. In addition, approval was obtained from Western Institutional Review Board, New York; Partners Human Research Committee, Boston; and St Luke's Episcopal Hospital Institutional Review Board, Houston), and written informed consent was obtained for all patients.

We defined the following study periods: 1) pre-treatment (within seven days prior to surgery); 2) drug administration (from induction of anesthesia until 12 hr from entry into the intensive care unit [ICU]); 3) pre-bypass (from start of study drug administration to start of cardiopulmonary bypass [CPB]); 4) aortic cannulation (from start of blood pressure reduction for aortic cannulation to end of aortic cannulation); 5) perioperative (from induction of anesthesia through the earlier of discharge or day 7), with the day of surgery defined as day 0.

Patient population

Patients were enrolled if they were at least 18 yr old and scheduled for elective CABG with CPB for at least one arterial graft with or without replacement or repair of a single valve. Exclusion criteria included patients scheduled for replacement or repair of both the aortic and mitral valves; cerebrovascular accident within the previous three months; pre-existing left bundle branch block or permanent ventricular pacing; any condition requiring an infusion of NTG that could not be discontinued at least one hour prior to the start of the study drug; prior use of an intra-aortic balloon pump (IABP); renal dialysis; hypertriglyceridemia (fasting triglycerides of $\geq$ 525 mg·dL^{-1} or 6.0 mmol·L^{-1}); intolerance or allergy to calcium channel blockers or any component of the drug vehicle; childbearing potential; any other disease or condition involving undue risk to the patient as a study subject; or enrolment in any other study of an investigational drug or device.

Treatment

All investigators and participating clinical staff were blinded to treatment group. A contract trial statistician used SPSS® software, version 11.1 (SPSS Inc., Chicago, IL, USA) to prepare a site-stratified randomization sequence with a block size of four and a 1:1 ratio across the two treatment groups. On the basis of the list, the statistician prepared sequentially numbered sealed opaque envelopes containing a card with the treatment group assignment, either "clevidipine (active) + NTG (placebo)" or "NTG (active) + clevidipine (placebo)". These were sent to a study drug coordinator within the pharmacy at each site. On the morning of each study day, the drug coordinator, who was independent of the investigators, opened the next sequentially numbered envelope and prepared the appropriate pair of drug and placebo, each into six 50 mL syringes labelled as "study drug a" and "study drug b", and delivered them to the operating room. If unblinding was clinically indicated, a sealed envelope containing a randomization code slip with study drug was also supplied for the investigator to open. Since clevidipine is a white lipid emulsion and NTG is a clear colourless solution, a placebo for each treatment was

required in a double-dummy design to maintain blinding. An intravenous solution of 0.9% sodium chloride was used as the NTG placebo, and an intravenous emulsion of 20% Intralipid® was used as the clevidipine placebo. Each patient received two intravenous infusions administered simultaneously with two syringe pumps (Graseby 3500® anesthetic pump, SIMS Graseby Ltd, Watford, UK). In New Zealand, the pumps were controlled by the anesthesiologist from a single computer using purpose-designed software (Safer Sleep LLC, TN, USA). In the USA, the pumps were controlled by an assistant on the instruction of the anesthesiologist. The rate of administration was set on the basis of infusion rates adjusted as required to control blood pressure through 12 hr after entry into the ICU. For clevidipine, the initial dose was 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to a maximum dose of 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$, with dose rates in excess of 4.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ limited to a total of 120 min. For NTG, the concentration was set to produce double the dose of clevidipine for any given rate. Thus, for example, the initial dose of NTG was 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This was intended to provide sufficient similarity to maintain blinding rather than to produce precisely equivalent effects for any given dose. The anesthesiologists were provided with a guide expressed in terms of the NTG dose rate, with limits. The infusion was to be continued at least at this basal dose for the duration of the study, unless it was in the patient's best interest to do otherwise.

Prior to induction of anesthesia for each patient, the surgeon and anesthesiologist conferred and agreed on the target MAP for the pre-bypass period (for the primary outcome variable) and also for the aortic cannulation period. The aim was for MAP to be maintained within 5 mmHg of these targets. The study drug was titrated at the discretion of the attending anesthesiologist to manage MAP. This was supplemented as necessary by standard clinical maneuvers, such as alterations in the depth of anesthesia, administration of fluids, and the administration of other vasoactive drugs, and these steps were recorded. If the result was clinically unsatisfactory, then, at the discretion of the anesthesiologist, the study drug was discontinued for a 15-min interval, and the patient was managed as per normal clinical practice before resuming the infusion. If a patient required the study drug to be discontinued a second time for the same medical reason, the study drug was not restarted. Unblinding of the study was permitted if it was deemed necessary for the safe management of the patient.

For consistency in the administration of anesthesia, the following agents were to be used (in doses at the clinical discretion of the anesthesiologist): fentanyl, midazolam, etomidate, and a muscle relaxant of the anesthesiologist's choice. Anesthesia was to be maintained with isoflurane in oxygen and/or propofol.

Data collection

Physiologic data, including ST segment changes, were collected from standard anesthesia monitors using a computerized monitoring system (Safer Sleep LLC, TN, USA).[17] Arterial and central venous pressures were measured via intra-arterial and central venous catheters from time of insertion until study drug discontinuation 12 hr after entry to the ICU. Blood and urine samples were taken for analysis during the pre-treatment period, at entry to the ICU, 12 and 24 hr post-ICU entry, and every 24 hr until the end of the defined perioperative period. Twelve-lead electrocardiograms (ECGs) were obtained during the pre-treatment period, 24 hr post-ICU entry, and at the end of the defined perioperative period.

Study endpoints

The primary endpoint of the study was blood pressure control. This was defined as the total area of the MAP time curve outside (i.e., both above and below) the clinician predefined target range from study drug initiation until initiation of CPB (the pre-bypass period), normalized per hour ($AUC_{MAP\text{-}D}$ in units of mmHg × $min \cdot hr^{-1}$). $AUC_{MAP\text{-}D}$ for the aortic cannulation period was also analyzed. During the pre-CPB period, the number of study drug adjustments required to control MAP was recorded, and the mean heart rate was also documented.

An adverse event was defined as any unintended unfavourable clinical sign or symptom, any new illness or disease or deterioration of existing illness or disease, or any clinically relevant deterioration in laboratory variables (e.g., hematological, biochemical, hormonal) or other clinical tests (e.g., ECG, *x-ray*), whether or not they were considered related to the treatment. Treatment-emergent adverse events were defined as adverse events that occurred after initiation of the study drug and were either not present at baseline or increased in severity compared with baseline. Each reported adverse event was rated serious or non-serious, graded mild, moderate, or severe, and evaluated with respect to its relationship with the study drug. Renal glomerular function was assessed by measuring serum creatinine preoperatively, 12 and 24 hr postoperatively, and daily from day 1 until discharge. Renal tubular function was assessed by urinary N-acetyl-glucosaminidase (NAG) levels, normalized for urinary creatinine. Sodium and potassium excretion, and urinary osmolality, as well as total fluid input and output for the duration of study drug administration were also measured.

Statistical analysis

The trial was designed to examine the hypothesis that the efficacy of clevidipine for managing blood pressure is non-

inferior to the efficacy of NTG during the pre-CPB period. Since the frequency distribution of AUC_{MAP-D} established from an earlier study[18] was log normal, the study power was calculated on the basis of log(e) transformed data. Blood pressure control was compared by determining the geometric mean (defined as the *n*th root of the product of *n* data values) of AUC_{MAP-D} for each treatment group and obtaining the geometric means ratio and the corresponding 95% confidence interval (CI). For the primary efficacy endpoint, we defined inferiority as the geometric mean AUC_{MAP-D} for clevidipine being more than 50% inferior (i.e., $> 50\%$ higher) than the geometric mean AUC_{MAP-D} for NTG. This definition was chosen on the basis that a 50% difference would be clinically relevant and large enough to allow some latitude for the challenges of managing an unfamiliar medication in a blinded fashion. Thus, to meet pre-specified non-inferiority criteria, the upper limit of the CI for the geometric means ratio for clevidipine and NTG could be no greater than 1.50. We estimated that 50 patients per treatment group would be needed to provide at least 80% power to show non-inferiority with $\alpha \leq 0.025$ (one-sided) assuming a coefficient of variation of 0.8 in both groups (a coefficient of variation of 0.9 was found in previous work,[18] but we assumed slightly greater precision because automated blood pressure recording was used in our study).

Descriptive statistics were used to summarize data. Laboratory test results were normalized according to normal ranges obtained from each individual study site, except for urinary sodium, potassium and creatinine (which were obtained from non-cumulative urine samples), and NAG (which is considered investigational, not a standard diagnostic test). Analyses were performed using SAS® statistical software, version 8.02 (SAS Inc, Cary, NC, USA).

Results

Baseline and procedural characteristics and study drug exposure

One hundred and fourteen patients were enrolled in the study from October 4, 2003 to April 26, 2004, with 57 patients randomized to receive clevidipine and 57

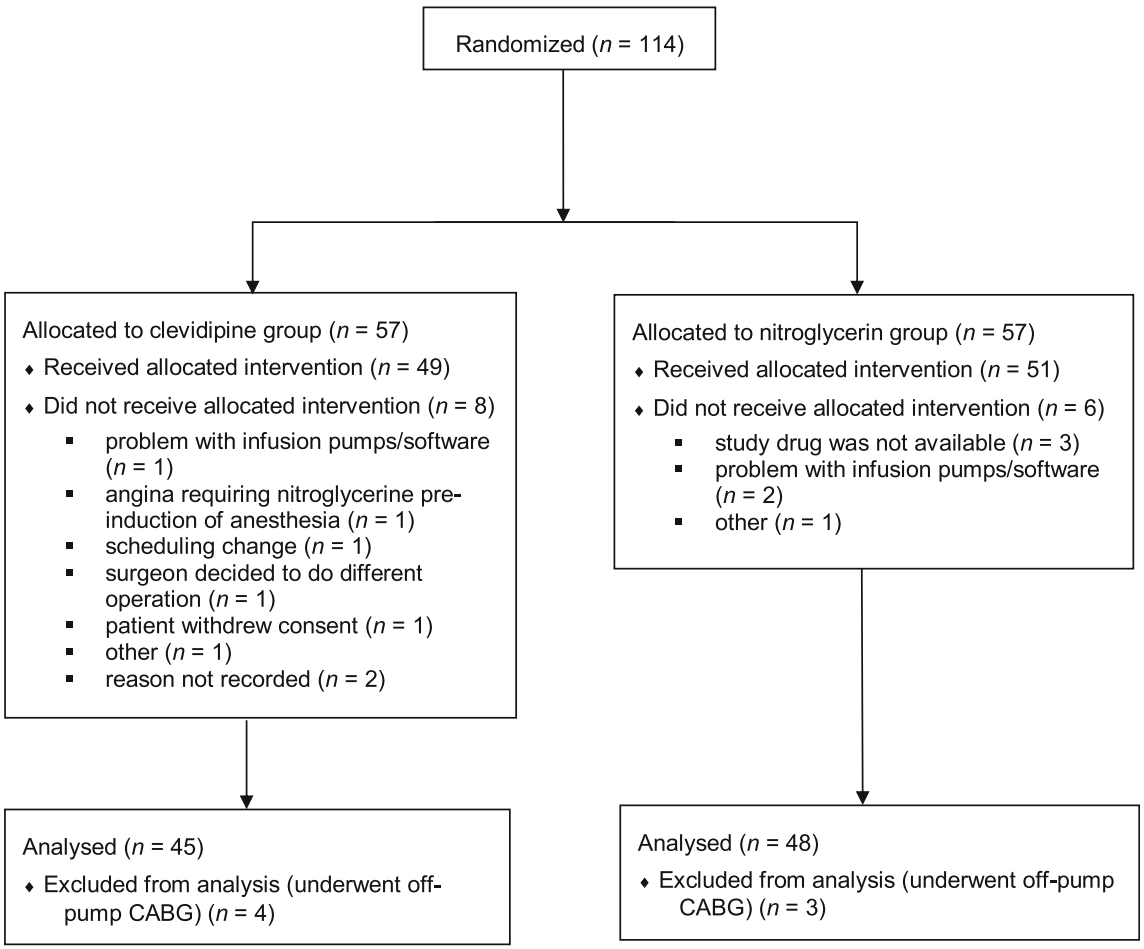

Figure Diagram of participant flow through the study

randomized to receive NTG (Figure). Forty-nine patients received clevidipine and 51 received NTG. All patients received the study drug as randomized and underwent at least one post-baseline assessment. As a result of a transfer to a different surgeon, seven patients (four from the clevidipine group and three from the NTG group) underwent off-pump CABG despite being originally scheduled for CABG with CPB. Since these patients did not meet the study inclusion criteria, they were excluded from analysis of the primary efficacy endpoint.

The two treatment groups were well balanced with respect to demographics, procedural characteristics, and cardiovascular risk factors (Tables 1 and 2). The time from the start of infusion to the start of bypass, aortic cannulation, and duration of bypass were comparable between treatment groups. The mean target MAP defined for the pre-bypass period was also similar between groups.

The starting infusion rate and overall duration of infusion were similar in the clevidipine-treated and NTG-treated patients (Table 3). The total volumes of drugs infused were also fairly similar and were consistent with the pre-specified dosing scheme (Table 3).

Table 1 Anthropometric, baseline, and procedural characteristics

	Clevidipine $n = 49$	Nitroglycerin $n = 51$
Age, years; mean (SD)	65.8 (11.3)	63.2 (12.3)
Sex		
Male, *n* (%)	40 (81.6)	43 (84.3)
Female, *n* (%)	9 (18.4)	8 (15.7)
Weight, kg; mean (SD)	79.7 (15.9)	82.1 (18.5)
Height, cm; mean (SD)	170.4 (9.0)	170.5 (12.4)
ASA Physical Status* *n* (%)		
I	0 (0.0)	0 (0.0)
II	0 (0.0)	1 (2.0)
III	29 (59.2)	33 (64.7)
IV	19 (38.8)	16 (31.4)
V	1 (2.0)	0 (0.0)
Body Mass Index, $kg \cdot m^{-2}$; mean (SD)	27.4 (5.1)	28.2 (5.2)
Index Procedure, *n* (%)		
CABG	43 (87.8)	45 (88.2)
CABG plus valve surgery	6 (12.2)	6 (11.8)
Target MAP, pre-CPB, mmHg; mean (SD)	76.1 (7.0)	76.4 (7.9)
Target MAP, aortic cannulation, mmHg; mean (SD); CLV $n = 49$, NTG $n = 49$	64.6 (11.9)	63.6 (10.4)
Duration of bypass, (min); median [interquartile range]; CLV $n = 47$, NTG $n = 51$	96.0 [75, 122]	95.0 [78, 114]
Duration of aortic cannulation, (min); median [interquartile range]; CLV $n = 35$, NTG $n = 38$**	6 [5, 10]	6 [5, 11]
IABP used, *n* (%)	2 (4.1)	0 (0.0)
Number of grafts, *n* (%)		
1	2 (4.1)	4 (7.8)
2	5 (10.2)	10 (19.6)
3	31 (63.3)	22 (43.1)
4	8 (16.3)	13 (25.5)
5	3 (6.1)	2 (3.9)

ASA = American Society of Anesthesiologists; CABG = coronary artery bypass grafting; CLV = clevidipine; CPB = cardiopulmonary bypass; IABP = intra-aortic balloon pump; MAP = mean arterial pressure; SD = standard deviation; NTG = nitroglycerin

*ASA physical status unknown for 1 NTG-treated patient

**Seven patients went to off pump; in 20 CPB patients, bypass time was not recorded

Blood pressure control

Clevidipine met the predefined non-inferiority study criterion. The geometric means ratio for the primary study endpoint $AUC_{MAP\text{-}D}$ was 0.97 (95% CI: 0.74 to 1.27). The geometric mean $AUC_{MAP\text{-}D}$ during aortic cannulation was 357.7 $mmHg \cdot min^{-1} \cdot hr^{-1}$ for clevidipine compared with 190.5 $mmHg \cdot min^{-1} \cdot hr^{-1}$ for NTG. No clinically important differences in the number of study drug adjustments or administered boluses were observed (Table 3).

Table 2 Medical history

	Clevidipine $n = 49$ *n* (%)	Nitroglycerin $n = 51$ *n* (%)
Angina	37 (75.5)	32 (62.7)
Hypertension	35 (71.4)	33 (64.7)
Hypercholesterolemia	30 (61.2)	28 (54.9)
Diabetes	13 (26.5)	19 (37.3)
Prior Myocardial Infarction	11 (22.4)	9 (17.6)
Peripheral Vascular Disease	7 (14.3)	4 (7.8)
Smoker (within preceding 6 months)	6 (12.2)	11 (21.6)
Prior PCI	6 (12.2)	7 (13.7)
Aortic or Mitral Valve Replacement with CABG	5 (10.2)	7 (13.7)
Stroke	4 (8.2)	4 (7.8)
Transient Ischemic Attack	3 (6.1)	2 (3.9)
Congestive Heart Failure	2 (4.1)	6 (11.8)
Chronic Obstructive Pulmonary Disease	2 (4.1)	5 (9.8)
Prior CABG	2 (4.1)	2 (3.9)

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention

Table 3 Study drug administration

	Clevidipine $n = 49$ median [Q1,Q3]	Nitroglycerin $n = 51$ median [Q1,Q3]
Duration of infusion (hr)	16.2 [14.8, 17.7]	16.3 [15.1, 17.4]
Start infusion rate ($mL \cdot hr^{-1}$)	2.0 [1.8, 2.5]	2.0 [1.8, 2.5]
Start infusion rate ($mg \cdot hr^{-1}$)	1.0 [0.9, 1.3]	2.0 [1.8, 2.5]
Weight-adjusted start infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.21 [0.20, 0.23]	0.41 [0.40, 0.46]
Total infusion amount during first 24 hr (mL)	49.5 [31.0, 74.8]	49.2 [33.6, 76.0]
Total dose during first 24 h (mg)	24.8 [15.5, 37.4]	49.2 [33.6, 76.0]
	$n = 44$	$n = 45$
During the pre-CPB period:		
Number of study drug adjustments	8 [4.5, 18]	6 [2, 16]
Number of bolus doses	0 [0, 3.5]	0 [0, 1]
Mean infusion rate ($mL \cdot hr^{-1}$)	3.7 [2.3, 6.7]	3.5 [2.3, 4.8]
Mean infusion rate ($mg \cdot hr^{-1}$)	1.9 [1.2, 3.4]	3.5 [2.3, 4.8]
Mean infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.37 [0.28, 0.64]	0.73 [0.46, 1.10]
Total dose (mg)	3.3 [1.6, 5.9]	4.7 [2.9, 9.4]
Duration between start of infusion and start of bypass (hr)*	1.4 [1.0, 2.1]	1.6 [1.2, 1.9]

*Clevidipine $n = 42$, nitroglycerin $n = 45$. CPB = cardiopulmonary bypass

Table 4 Additional data by treatment group

	Clevidipine $n = 49$	Nitroglycerin $n = 51$
Heart rate during study drug administration, $beats \cdot min^{-1}$; mean (SD)	76.0 (13.8)	81.5 (14.4)
Total fluid input, mL; mean (SD)	6,226.0 (2,643.0)	6,672.0 (1,931.5)
Total fluid output, mL; mean (SD)	4,406.2 (1,539.7)	4,260.6 (2,018.9)
No. cardiac ischemic episodes requiring therapeutic interventions, *n* (%)		
None	47 (95.9)	47 (92.2)
1 episode	1 (2.0)	3 (5.9)
2 episodes	0 (0)	1 (2.0)
4 episodes	1 (2.0)	0 (0)
Incidence of acute MI, *n* (%)	11 (22.4)	9 (17.6)
Criteria for MI, *n* (%):		
New significant Q-wave on ECG	0 (0.0)	1 (2.0)
Elevated CK-MB or troponin T	11 (22.4)	8 (15.7)
% change in serum creatinine ($mg \cdot dL^{-1}$),[a] mean (SD)	24.6 (48.6)	18.3 (34.5)
% change in creatinine clearance ($mL \cdot min^{-1}$),[b] mean (SD)	−13.3 (20.3)	−11.2 (16.0)
% change in normalized N-acetyl-glucosaminidase ($U \cdot mg^{-1}$),[c] mean (SD)	710.1 (806.4)	861.2 (1,557.7)

CK-MB = creatine kinase; ECG = electrocardiogram; MB fraction; MI = myocardial infarction; NTG = nitroglycerin; SD = standard deviation

[a] from mean baseline to highest mean postoperative value. Clevidipine $n = 47$; NTG $n = 51$

[b] from mean baseline to lowest mean postoperative value. Clevidipine $n = 47$; NTG $n = 51$

[c] from mean baseline to highest mean postoperative value. Clevidipine $n = 45$; NTG $n = 48$

Table 5 Adverse events occurring in ≥ 3% of patients by treatment group

	Clevidipine $n = 49$ n (%)	NTG $n = 51$ n (%)
Patients with at least one TEAE	31 (63.3)	30 (58.8)
Hypotension	13 (26.5)	8 (15.7)
Pyrexia	5 (10.2)	5 (9.8)
Atelectasis	4 (8.2)	3 (5.9)
Anemia	3 (6.1)	5 (9.8)
Hypokalemia	3 (6.1)	1 (2.0)
Hyperglycemia	3 (6.1)	2 (3.9)
Platelet function test abnormal	3 (6.1)	1 (2.0)
Ischemia	2 (4.1)	1 (2.0)
Urine output decreased	2 (4.1)	1 (2.0)
Abnormal liver function test	2 (4.1)	0 (0.0)
Pain	2 (4.1)	4 (7.8)
Pulmonary congestion	2 (4.1)	1 (2.0)
Pneumothorax	2 (4.1)	0 (0.0)
Incision site complication	2 (4.1)	5 (9.8)
Myocardial infarction	2 (4.1)	1 (2.0)
Hypocalcemia	2 (4.1)	1 (2.0)
Hyperkalemia	2 (4.1)	0 (0.0)
Confusional state	2 (4.1)	0 (0.0)
Atrial fibrillation	1 (2.0)	5 (9.8)
Hypertension	1 (2.0)	4 (7.8)
Pericarditis	0 (0.0)	3 (5.9)
Nausea	0 (0.0)	4 (7.8)
Renal failure acute	0 (0.0)	2 (3.9)

TEAE = treatment-emergent adverse event; NTG = nitroglycerin

TEAEs were defined as AEs that occurred after initiation of the study drug and were either not present at baseline or increased in severity compared with baseline

Data sorted in descending order in the clevidipine group

Other assessments related to blood pressure control

During study drug administration, the mean (SD) heart rate with clevidipine was 76.0 (13.8) beats·min^{-1} compared with 81.5 (14.4) beats·min^{-1} for NTG. There were no clinically relevant differences between clevidipine and NTG in the number of myocardial ischemic episodes requiring therapeutic interventions, the incidence of acute myocardial infarction (MI), total blood loss, total fluid input, or total fluid output (see Table 4).

Adverse events

The incidence and types of adverse events were similar for the clevidipine and NTG treatment groups (Tables 4 and 5) and typical of a cardiac surgery patient population.[A] One patient death occurred in each group. At least one serious adverse event was reported in 12 patients in the clevidipine treatment group *vs* nine patients in the NTG group. Hypotension was reported as an adverse event in 13 patients who received clevidipine and eight who received NTG. Five patients in each group permanently stopped the medication due to an adverse event. All five clevidipine-treated patients withdrew due to hypotension, and hypotension was a reason for study withdrawal in three NTG-treated patients. The other patients withdrew due to venous injury and ischemia. In one of the patients with hypotension on NTG, there was also post-procedural hemorrhage, atrial fibrillation, and cardiogenic shock, and the patient eventually died. In all other cases, the adverse events resolved. No clinically relevant differences in postoperative serum triglyceride levels (expressed as a change from baseline) were observed, and no patient in either treatment group had hypertriglyceridemia (defined as serum triglyceride levels of > 525 mg·dL^{-1} before laboratory value normalization).

Discussion

In this randomized double-blind double-dummy study of patients undergoing CABG, clevidipine was not inferior to NTG for overall blood pressure control pre-bypass. These results are consistent with those of prior investigations of the pharmacologic properties of clevidipine.[7-13] Previous studies have investigated clevidipine in the context of cardiac surgery, but none have employed the distinctive methodology of the present study.[8-11] The three ECLIPSE trials were open label, and their primary endpoint was safety rather than efficacy; furthermore, unlike our study, the target blood pressures used in the ECLIPSE trials were not tailored to individual patients. In the ESCAPE-2 trial and in the studies of Kieler-Jensen *et al.*,[8] Bailey *et al.*,[9] and Powroznyk *et al.*,[18] postoperative rather than intraoperative hypertension was investigated.

Tachycardia is undesirable during surgery, and in the presence of underlying ischemic heart disease,[3,4,6] there may be potential value in a drug with less risk of reflex tachycardia than NTG. Heart rate was a little lower during clevidipine administration than during NTG administration, but the difference was probably not of clinical relevance. This aspect of clevidipine pharmacology may warrant further investigation. There was no clinically relevant difference between the groups in the incidence of complications.

During aortic cannulation, patients in the clevidipine-treated group had more blood pressure variability outside the target MAP than the NTG-treated group, as shown by

[A] Cardene I.V. Prescribing Information. Fremont, CA: PDL BioPharma Inc.; Revised April 2008.

$AUC_{MAP\text{-}D}$. Rapid and accurate control of blood pressure during critical periods of cardiac surgery is important, so this finding is noteworthy. There was no difference between groups in overall surgical fluid input or output. The lipid content of the clevidipine formulation did not appear to influence triglyceride serum concentration, which remained similar between treatment groups.

The demographic and medical characteristics of our patient population appeared consistent with that of the overall clinical CABG patient population.[19,20] Furthermore, there were no clinically relevant differences between groups in the adverse events reported in this study, and these events were characteristic of outcomes following CABG.[19,20]

An obvious limitation of our study is its small size in relation to the incidence of complications. It is also possible that practitioners who were unfamiliar with clevidipine and blinded to the study drug adjusted both drugs as they would NTG. This could possibly be advantageous for NTG and detrimental to obtaining optimal results with clevidipine. Given the opportunity to gain greater experience with clevidipine, the same anesthesiologists might obtain better results using it open label. On the other hand, for investigational purposes, the double-dummy blinded design of the study is one of its strengths.

In conclusion, we showed that clevidipine was not inferior to NTG for the management of MAP pre-bypass in patients undergoing CABG.

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