Clevidipine in Acute Hypertension: The Evidence of its Therapeutic Value

Joseph Varon
Dorrington Medical Associates, Dorrington St., Houston, TX 77030-3209, USA. The University of Texas Health Science Center at Houston, Houston, TX; The University of Texas Medical Branch at Galveston, Houston, TX. Corresponding author email: joseph.varon@uth.tmc.edu

Abstract: While the chronic form of hypertension is most common; the acute form presents the greater danger, with more frequent and severe complications and poorer short-term prognosis compared to chronic hypertension. Antihypertensive drugs are used to treat acute hypertension according to the condition of the patient, target organ injured, and the resources available to monitor the patient. However, the limited number of medications intended for the aggressive management of acute hypertensive has highlighted the need for newer drugs that offer a rapid decrease of blood pressure (BP) without increasing the possible complications. After ten years of research and trials, clevidipine was approved by the FDA in 2008, and has been widely used to reduce BP when oral therapy is inappropriate. Compared to the few agents previously used for this purpose clevidipine takes the lead due to its shorter duration of action and its lower incidence of adverse events and toxicity rates.

Keywords: clevidipine, calcium channel blockers, hypertensive crisis, hypertensive emergency, hypertensive urgency
Introduction

Chronic hypertension is among the most common medical conditions affecting approximately 72 million people in the United States alone. While the chronic form of hypertension is most common; the acute form presents the greatest danger, with more frequent and severe complications and poorer short-term prognosis as compared to chronic hypertension. Acute elevations in blood pressure (BP) may result in severe clinical conditions such as hypertensive encephalopathy, acute aortic dissection, acute myocardial infarction, acute renal failure, intracranial hemorrhage, acute heart failure, and eclampsia, amongst others. It has been estimated that at least 1% of all hypertensive patients will present to an emergency department (ED) with a hypertensive emergency at some point of their lives.

Most efforts to control the disease chronically are unsuccessful, failing in greater than half of the affected patients. Despite the availability of multiple drugs used for the treatment of hypertension, only 44% of all adults with hypertension achieved systolic BP of less than 140 mm Hg and diastolic BP of less than 90 mm Hg. The main reason for this failure is medical non-compliance. However finding an adequate anti-hypertensive drug that will individually fit each patient according to their particular characteristics (ie, race, age, etiology, associated morbidity, and concomitant therapies) and the nature of their condition (ie, chronic hypertension, acute hypertension, hypertensive emergency, and urgency) has proven difficult to achieve leading to an increasing percentage of hypertensive emergencies.

Antihypertensive drugs are used in the treatment of acute hypertension according to the condition of the patient, target organ injured, and the resources available to monitor the patient. However, the limited number of medications intended for the aggressive management of acute hypertensive has highlighted the need for newer drugs that offer a rapid decrease of BP without increasing the possible complications. Calcium channel blockers (CCB) are, as a group, unique agents in the treatment of acute hypertension. Of them, clevidipine, an intravenous titratable CCB is particularly interesting due to its pharmacokinetic and pharmacodynamic properties. Since its approval by the FDA, the use of clevidipine in settings where acute elevation of BP develop, has been increasing. This manuscript reviews the role of clevidipine in management of acute hypertension and the evidence of its therapeutic value.

Methods

A search of PubMed was conducted using the words clevidipine AND clinical trial [Publication Type], which returned 12 results (Table 1). References provided in these articles found were also searched by citation index to locate other clinical trials that investigated the use of clevidipine in the treatment of hypertension. Cross-referencing of other sources was also performed by the author.

Results

Seven studies are related to the pharmacokinetics and pharmacodynamics of the compound, and five are clinical safety and efficacy trials. In addition, one trial subset analysis was identified through cross-referencing.

Discussion

Pharmacokinetics and pharmacodynamics studies

When examining the role of clevidipine in management of acute hypertension and the evidence of its therapeutic value, it is important to consider the pharmacokinetics and pharmacodynamics of the compound and the safety information contained in the clinical trials as evidence of their therapeutic value.

The pharmacokinetics and pharmacodynamics of clevidipine in healthy volunteers after intravenous infusion were studied by Ericsson, et al. Eight healthy volunteers received clevidipine together with a tracer dose of clevidipine for 1 hour as an intravenous infusion. Venous blood samples and effect recordings were taken during infusion and up to 32 hours post infusion, and the excretion of radioactivity in urine and faeces was followed for 7 days. This study established the clearance and volume distribution rates, the short half-life and rapid clearance characteristics of the drug. The authors concluded that Clevidipine is a rapidly metabolized, high clearance drug with an extremely short initial half-life and the half-life for elimination. Hence, the duration of action of clevidipine is extremely short.

The study “In vitro hydrolysis rate and protein binding of clevidipine, a new ultrashort-acting
Clinical trials of Clevidipine.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Title</th>
<th>Journal. Year; Volume (Issue): Pages</th>
</tr>
</thead>
</table>

Calcium antagonist metabolised by esterases, in different animal species and man was also performed by Ericsson, et al to further elucidate the pharmacokinetics and pharmacodynamics of clevidipine by investigating the protein binding and the *in vitro* hydrolysis rate of clevidipine and its enantiomers in the rat, dog and man in different biological matrices including blood and plasma from volunteers with deficient pseudocholinesterase activity. Differences in half-life times in subjects with normal
pseudocholinesterase activity versus the prolonged half-life in pseudocholinesterase deficient volunteers though hydrolysis rates in blood and red blood cells (RBC) were much higher than in plasma suggested that esterases located in the RBC were most important in the blood metabolism of clevidipine. The findings of this study further elucidated the mechanism of metabolism of clevidipine.

Ericsson, and colleagues then studied the clinical and pharmacokinetic results with a new ultrashort-acting calcium antagonist, clevidipine, following gradually increasing intravenous doses to healthy volunteers. This study was essentially a dose ranging study to investigate the safety and tolerability of clevidipine in healthy volunteers during intravenous infusion at gradually increasing dose rates and to obtain preliminary information on the pharmacokinetics and pharmacodynamic effects of the drug. Twenty-five subjects were enrolled in the study resulting in a total of 46 study entries encompassing 20 minute infusions of clevidipine at various target dose rates and ranges. Concentrations of clevidipine, and its primary metabolite, were followed in whole blood, and the pharmacokinetics were evaluated. In this study, the most common adverse events were flush and headache, which were attributed to mechanism of action of clevidipine. The initial and terminal half-life rates of clevidipine were further documented and changes in mean arterial pressure (MAP) over heart rate (HR) with corresponding blood concentrations of clevidipine were also documented. The authors concluded that clevidipine, a high clearance drug with extremely short half-lives, was well tolerated and safe in healthy volunteers at dose rates up to 48 nmol min⁻¹ kg⁻¹. The pharmacokinetics were linear over a wide range of doses. The simple E_max model used in this study was adequate to describe the relationship between the pharmacodynamic response (MAP/HR) and the blood concentrations of clevidipine.

Schiwieler and colleagues investigated the circulatory effects and pharmacology of clevidipine, a novel ultra short acting and vascular selective calcium antagonist, in hypertensive humans. In this study, twenty patients were randomized to intravenously receive either clevidipine or placebo at prespecified target doses. The pharmacokinetics of clevidipine was investigated during steady state and the post-infusion period in patients with mild to moderate hypertension. Moreover, the dose-effect and blood concentration-effect relations and the tolerability of the drug were studied. Each patient received in random order three infusion rates of clevidipine or placebo during 3 separate study days. A dose-dependent reduction in BP and a modest increase in HR were noted. There was a linear relation noted between blood concentration and dose rate in the range studied. Clevidipine was safe and well tolerated with one patient excluded because of an adverse event. Due to its relative safety and short half-life, the authors concluded clevidipine would become a valuable contribution to the drugs used in conditions in which precise and rapid control of BP was needed.

In the study pharmacokinetics and arteriovenous differences in clevidipine concentration following a short- and a long-term intravenous infusion in healthy volunteers, Ericsson, et al investigated the pharmacokinetics of clevidipine after 20 minute and 24 hour intravenous infusions, and the relationship between the arterial and venous concentrations and the hemodynamic responses to clevidipine in healthy volunteers. Four volunteers received clevidipine for 20 minutes, and 8 subjects were administered clevidipine intravenously for 24 hours at 2 different dose rates. Arterial and venous blood samples were drawn for pharmacokinetic evaluation, and BP and HR were recorded. The mean arterial blood clearance of clevidipine and the mean volume of distribution at steady state were determined, and the results were consistent with those of previous studies. Interestingly, the duration of the infusion had negligible effect on the pharmacokinetic parameters, and the context-sensitive half-time for clevidipine, simulated from the mean pharmacokinetic parameters derived after 24 hour infusion at the highest dose, was <1 minute. The arterial blood levels reached steady state within 2 minutes of the start of infusion and were about 2 × as high as those in the venous blood at steady state. The peak response preceded the peak venous concentration and was slightly delayed from the peak arterial blood concentration. This led the authors to conclude that clevidipine was a high clearance drug with a small volume of distribution, resulting in extremely short half-lives in healthy subjects. The initial rapid increase in the arterial blood concentrations and the short equilibrium time between the blood and the
biophase suggested that clevidipine could be rapidly titrated to the desired effect.

As part of building and understanding the pharmacokinetic profile of clevidipine, a study was conducted to determine the role of different enantiomers (ie, (−)R- and (+)S-clevidipine) of the compound.13 Twenty patients received 3 out of 5 randomized treatments with clevidipine. The pharmacokinetics of the separate enantiomers were evaluated by analysis of blood concentrations vs. time curves. The derived pharmacokinetic parameters were used to simulate the time for 50 and 90% post-infusion decline following various infusion times of rac-clevidipine. The results showed there were only minor differences between the estimated pharmacokinetic parameters of the separate enantiomers. The mean blood clearance values of (−)R- and (+)S-clevidipine were comparable, and the corresponding volumes of distribution at steady state were also similar. The context-sensitive half-time was approximately 2 min regardless of stereochmical configuration, and a 90% decline in concentration was achieved approximately 10 minutes for both stereochmical configurations following clinically relevant infusion times with clevidipine. The authors of the study (Enantioselective pharmacokinetics of the enantiomers of clevidipine following intravenous infusion of the racemate in essential hypertensive patients) concluded that both enantiomers were high-clearance compounds with similar blood clearance values. The volume of distribution for the enantiomers was only slightly different, likely due to differences in the protein binding. Moreover, the use of a single enantiomer as an alternative to the racemic clevidipine would not offer any clinical advantages.

A dose ranging study was conducted to investigate the pharmacodynamics and pharmacokinetics of clevidipine in the treatment of hypertension in postoperative cardiac surgical patients by Bailey and colleagues.14 Postoperative cardiac surgical patients were randomized to receive placebo or 1 of 6 doses of clevidipine. Hemodynamic parameters were recorded and blood samples were drawn for determination of clevidipine plasma concentrations during infusion and after discontinuation of clevidipine. The results of this study demonstrated significant decreases in MAP and systemic vascular resistance at doses ≥1.37 μg/kg⁻¹/min⁻¹. There were no changes in heart rate, central venous pressure (CVP), pulmonary artery occlusion pressure, or cardiac index with increasing doses of clevidipine. The clevidipine C₅₀ value for a ≥10% decrease in MAP was 9.7 μg/l and for a ≥20% decrease in MAP was 26.3 μg/l. The early phase of drug disposition had a half-life of 0.6 minutes. The context-sensitive half-time was <2 minutes for up to 12 hours of administration. It was concluded that clevidipine effectively decreased systemic vascular resistance and MAP without changing HR, cardiac index, or cardiac filling pressures.

In a related study by Zhang JG et al, it was determined that immediately after the intravenous infusion of clevidipine, the compound is hydrolyzed primarily by blood esterases into inactive metabolites (esterases in extravascular tissue also have moderate participation), including hemiacetal ester and butyric acid, which do not have a relevant effect on any CYP450 enzyme.21 The kidney is responsible for the elimination of at least 60% of the drug and the remainder in the feces.22 During this first minute, the drug goes through the first phase of its elimination, and as much as 85%–90% is eliminated at this point. The remainder of the drug is metabolized and has a terminal half-life of approximately 15 minutes.22,23 Moreover, approximately 99.5% of the clevidipine in human plasma is bound to proteins, and this binding capacity is non-concentration dependent.12,22,24 This unique metabolism pattern is not prone to be affected by hepatic dysfunction, and its rapid elimination contributes to a rapid recovery of BP.23

Clinical Safety and Efficacy Trials
In 2003 in a double blind, randomized trial entitled Comparison of clevidipine with sodium nitroprusside in the control of blood pressure after coronary artery surgery, Powroznyk and colleagues compared sodium nitroprusside (SNP) and clevidipine in the management of postoperative hypertension and monitored hemodynamic changes in patients undergoing coronary artery bypass graft surgery (CABG)15 as postoperative hypertension occurs in 30%–50% of all patients undergoing the procedure.25 The study included 30/39 patients who met the inclusion criteria divided in 2 groups. One group received active clevidipine and SNP placebo, and the other received active SNP and clevidipine placebo. The variables...
evaluated were efficacy of the drug in controlling arterial pressure, the number of dose-rate adjustments necessary to achieve that goal, and the hemodynamic impact of the drug. The study results showed no relevant differences between the efficacy of clevidipine and that of SNP. There was no a significant difference between the number of dose-rate adjustments required for each drug; however, statistically significant data was obtained from the monitoring of vitals. Concerning HR, the SNP group showed a significantly greater increase compared with clevidipine ($P < 0.0001$), however it is a well known effect of SNP to induce compensatory tachycardia. Changes in the CVP were more accentuated with SNP as well, highlighting the marked selectivity of clevidipine for arterioles. The study concluded that the overall efficacy was similar for both drugs.$^{15}$

**ESCAPE-1 Trial**

The ESCAPE-1 trial (Clevidipine effectively and rapidly controls blood pressure preoperatively in cardiac surgery patients: the results of the randomized, placebo-controlled efficacy study of clevidipine assessing its preoperative antihypertensive effect in cardiac surgery-1) was performed on 150 hypertensive patients scheduled for cardiac surgery that received either clevidipine or placebo (ie, lipid emulsions) infusion for 30 minutes.$^{16}$ Patients were assessed with a baseline echocardiogram, laboratory screening, vital sign recordings, and careful monitoring of baseline systolic BP (SBP) and diastolic BP (DBP). A comparison between the treatment failure of both-clevidipine and placebo was performed to evaluate efficacy. Treatment failure included the inability to lower SBP by $>15\%$ from baseline. Further assessments were included time to target BP, change in mean arterial pressure (MAP), change in heart rate (HR), and long- and short-term AEs. This clinical trial was the first to demonstrate the efficacy of clevidipine in significantly lowering the rate of treatment failure compared with placebo (clevidipine 7.5\% versus placebo 82.7\%, $P < 0.0001$).

The safety of clevidipine was evaluated by HR changes and the rate and type of AEs observed. Clevidipine was shown to be well tolerated with an AE profile similar to that of placebo and consistent with outcomes expected in cardiac surgery.$^{26,27}$ A modest increase in heart rate was observed during clevidipine administration, as has been reported with other IV dihydropyridines$^{28,29}$ and in studies of clevidipine in essential hypertension and postcardiac surgery.$^{14,15}$ Clevidipine and placebo were both produced no considerable changes in HR after infusion discontinuation and the HR increase initially observed was not substantial. Both treatment groups presented similar rates of AEs, including pyrexia, atrial fibrillation, acute renal failure, and nausea in descending order. All were more frequently noted in clevidipine treated patients; however the difference was not statistically significant. Despite some limitations, the study demonstrated clevidipine was successful in decreasing SBP by $\geq15\%$ from baseline in 92.5\% of the cases in a mean time of 6 minutes after infusion.$^{16}$

A limitation Escape-1 was that it could not be designed to evaluate clevidipine during surgery for ethical reasons (ie, not treating hypertension), and therefore involved a somewhat artificial preoperative treatment strategy. Moreover, another potential study limitation was the influence of premedication on arterial blood pressure. Because Escape-1 was designed as an acute assessment of antihypertensive treatment over 30 minutes, and included comparison of active treatment to placebo, it was unlikely that any effects of premedication on study results would have gone unnoticed.

**ESCAPE-2 Trial**

This ESCAPE-2 trial (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.) evaluated the efficacy of clevidipine in treating postoperative hypertension.$^{17}$ In this trial, 110 out of 206 patients met the inclusion criteria and received infusions of clevidipine and placebo. The design of the study and the variables observed in this trial were the same as those in ESCAPE-1. The study outcome revealed that clevidipine was significantly more successful than placebo in achieving treatment goals (91.8\% success rate with clevidipine versus 20.4\% with placebo, $P < 0.0001$). Decrease in SBP was achieved in 5.3 minutes (median time) with clevidipine. A significantly larger decrease in the MAP was observed in the clevidipine group at 2, 5, 10, and 15 minutes after the infusion (mean change in
Clevidipine evidence of its value

MAP −5.7 mmHg versus −0.1 mmHg in the placebo group, \( P = 0.0004 \). The efficacy of clevidipine was most evident when comparing the greatest mean change. The greatest mean change was 28.1 mmHg with clevidipine, compared to 8.9 mmHg for placebo \( (P < 0.0001) \). In this study, 94.7% of the patients treated with clevidipine reached the target SBP, and only 1 patient required the maximum titration. Adverse event rates were similar for both treatment groups with no clinically significant increases in HR or acute adverse hemodynamic events. No reflex tachycardia was observed in the clevidipine group and the median highest HR recorded was 93 beats per minute (bpm). Common AEs observed more frequently in the clevidipine group, included nausea, atrial fibrillation, and insomnia. Clevidipine was discontinued in 1 patient because of atrial fibrillation, reported as a nonserious AE that resolved without sequelae on the same day after discontinuing study drug infusion. Both studies (ESCAPE-1 and -2) demonstrated clevidipine was a safe and efficacious when used in the perioperative setting, predominantly due to its rapid onset and offset of action and easy titration. The ECLIPSE trial, consistent with the ESCAPE 1 and 2 and VELOCITY trial, demonstrated that clevidipine is a safe and effective drug for the treatment of acute hypertension, but also demonstrated that clevidipine offers a more precise and titratable blood pressure control when compared to nitroprusside and nitroglycerin. The incidences of SAEs were similar among all groups. The incidence of the most commonly reported AEs, including atrial fibrillation and sinus tachycardia, were similar for clevidipine and the comparator drugs. Atrial fibrillation was reported as an AE at an incidence of 33.6% vs. 32.0% (clevidipine vs. nitroglycerin); 36.1% vs. 32.2% (clevidipine vs. sodium nitroprusside); and 35.6% vs. 35.2% (clevidipine vs. nicardipine), all \( P = NS \). Clinical laboratory data including change in triglyceride levels were similar between clevidipine and the comparator drugs. In this trial, clevidipine administration did not cause an increase in triglyceride levels. Limitations of the study include the open-label design. Moreover, clevidipine was dosed in a standard fashion at all study sites, while comparator drugs were administered according to institutional practice.

The VELOCITY Trial

VELOCITY (Clevidipine, an intravenous dihydropyridine calcium channel blocker, is safe and effective for the treatment of patients with acute severe hypertension) was a phase III, open-label,
single-arm, multicenter study, designed to evaluate the use of clevidipine in patients presenting severe hypertension.19 The trial included 126 patients presenting to the ED or the intensive care unit with persistent severe hypertension, defined as SBP $> 180 \text{ mmHg}$ and/or DBP $> 115 \text{ mmHg}$, assessed 2 consecutive times with an interval of $\geq 15$ minutes in between each. The goal of VELOCITY was to ascertain the percentage of patients whose SBP decreased below a preset intended target after an initial dose of 2 mg/hr within a period of 3 minutes (safety endpoint, ie, overshoot rate), as well as the percentage of patients that reached an individualized target range within 30 minutes (efficacy endpoint). Patients that matched the inclusion criteria underwent a physical examination—including urinalysis, funduscropy, 12-lead ECG, and chest radiography to determine the presence of acute or chronic target organ damage including at least one of the following: abnormal funduscropy with hypertensive changes, congestive heart failure, left ventricular hypertrophy, proteinuria or hematuria, neurologic signs, positive troponin or creatine kinase MB, or symptomatic coronary syndrome with ischemic ECG changes. Patients were also screened by past medical history, baseline laboratory, and medication history. Clevidipine was administered and titrated according to the prescribing information7 and response of the patient and after 18 hours, oral therapy could be administered if needed. During the infusion, BP and HR were constantly monitored; blood samples were obtained in a regular pattern, and AEs were recorded. The results revealed 90.5% of the patients enrolled were treated with clevidipine only, meaning that other antihypertensives were unnecessary to achieve the goal BP levels. The desired BP range was accomplished within the first 30 minutes after the infusion in 88.9% of the patient population in a median time of 10.9 minutes, and 91.3% of the patients underwent successful transition to oral therapy.

Safety, results were also positive. In the Velocity safety population, 39.7% of patients experienced at least 1 AE after clevidipine initiation, and 8.7% of patients experienced at least 1 serious AE. Headache was the most frequently reported AE, with an overall incidence of 6.3% (8/126), followed by nausea (4.8%; 6/126), chest discomfort (3.2%; 4/126), and vomiting (3.2%; 4/126). The median pulse was 82 bpm at 3 minutes, and within the immediate 30 minute period, the mean increase observed was 10 bpm over the baseline.

The frequency of AEs, severity, and possible relationship to clevidipine were similar in the long-term cohort. Adverse effects included headache, nausea, chest discomfort, and vomiting in descending order. Patients in the safety population most often had AEs categorized by the investigator as mild (13.5%) or moderate (17.5%) in severity, as opposed to severe (8.7%). Safety patients most often had AEs assessed by the investigator as unrelated to clevidipine (30.2%) vs. related (9.5%). Two of 126 patients complained of pruritus at the infusion site.

During this study, clevidipine was neither associated with any clinically significant changes in laboratory test results (eg, triglyceride levels), nor showed increased risk of renal injury. Overall, the findings of the VELOCITY trial were consistent to those encountered in other large trials, and clevidipine was once again demonstrated to be a safe and manageable drug for treating severe hypertension.19

The VELOCITY trial further established that clevidipine is both safe and effective in patients with underlying severe HTN, heart failure or renal dysfunction. This data is compatible with data obtained from both ESCAPE trials. The authors concluded that clevidipine is a safe and effective drug in the rapid management of severe hypertension at a non-weight-based dose of 2 mg/hr followed by simple infusion titration to desired BP during 18 hours of more.

Limitations of the VELOCITY trial are that the trial was performed as an open-label uncontrolled study. However, it was designed to permit the use of concomitant intravenous antihypertensive therapy at any time if needed; thus, each patient effectively served as his or her own control. The definition for severe hypertension used in this study (systolic blood pressure $> 180 \text{ mmHg}$ and/or diastolic blood pressure $> 115 \text{ mmHg}$) was developed according to clinical experience. No universally accepted definition exists for severe hypertension.31,32 The patient population studied represented a mixture of hypertensive urgencies and emergencies. It is possible, therefore, that the patients without acute end-organ injury would not all have received intravenous antihypertensive therapy in routine clinical practice but would have been treated with oral antihypertensive agents.
VELOCITY Subset Analyses
There has been VELOCITY trial subset analyses performed in patients with renal dysfunction and acute heart failure. In subset of the Velocity trial, a safety and efficacy analysis of clevidipine used in 24 patients with moderate to severe renal dysfunction (>50% on dialysis) found clevidipine rapidly and effectively lowered BP, was not associated with excessive or precipitous drops in BP, and had similar results in patients with or without renal dysfunction. Targeted BP control was rapidly achieved in 8.5 minutes and was maintained for the specified 18 hours duration after which most patients (88%) effectively transitioned to oral therapy within 6 hours of clevidipine termination. In this high risk subpopulation most AE’s were assessed as unrelated to clevidipine treatment. This supports the relative safety of this product. The safety results of this subgroup analysis in patients with renal dysfunction are also consistent with the results of the overall VELOCITY trial.

The safety and efficacy of clevidipine was also assessed in a VELOCITY subset analysis of patients with acute heart failure. In this group of 19 patients presenting with acute heart failure, the median time or treatment with clevidipine to a patient-specific prespecified initial target range (ITR) of SBP to be achieved within 30 minutes was 11.3 minutes. Most patients (94%) reached ITR within 30 minutes. No patient had hypotension below the ITR and heart rate remained stable. At 18 hours, 16/19 patients had received continuous clevidipine infusion and their SBP was reduced by mean of 50 mmHg (25%) from baseline. There were no treatment-related AEs, or AEs that led to clevidipine discontinuation. Likewise, the results of this subgroup analysis in patients with acute heart failure are also consistent with the results of the overall VELOCITY trial.

Conclusions
Clevidipine is characterized by a very fast onset and offset of action, and as a result its use was first intended to control acute hypertensive. It has a unique metabolism, which occurs in the blood and in extravascular tissues by esterases, giving it an initial half-life of <3 minutes and an almost null rate of toxicity because its metabolites are inactive. Its metabolism is also an attribute that ranks clevidipine over other available short acting drugs, because its metabolism does not occur in the liver or in the kidneys, there are no restrictions to using clevidipine in patients with hepatic or renal dysfunction. Furthermore, clevidipine has cardioprotective role when infused in compromised myocardium.

After ten years of research and trials, clevidipine was approved by the FDA in 2008, and has been widely used to reduce BP when oral therapy is inappropriate. Its use in the perioperative settings, mainly in cardiac surgery, has been shown to be beneficial, and compared to the few agents previously used for this purpose (eg, sodium nitroprusside, nitroglycerin), clevidipine takes the lead due to its shorter duration of action and its lower incidence of AEs and toxicity rates.

Acknowledgements
The author would like to thank Richard Pistolese for his editorial assistance in the preparation of this manuscript.

Disclosure
This manuscript has been read and approved by the author. This paper is unique and not under consideration by any other publication and has not been published elsewhere. The peer reviewers of this paper report no conflicts of interest. Dr. Varon has received honoraria for lectures from PDL Pharmaceuticals, Baxter Healthcare and the Medicines Company, and has served as a consultant for EKR Pharmaceuticals, Baxter Healthcare and the Medicines Company. The author confirms that he has permission to reproduce any copyrighted material.

References