



medications within the first 24–48 h after its presentation, with little or no change in final outcome [12,13].

### Epidemiology

Hypertensive crises can account for 25% or more of all medical emergencies presenting in the ED [3], and up to 3% of the total visits to the ED, therefore making it one of the most commonly encountered afflictions in emergency settings. It is estimated that approximately 1% of chronically hypertensive patients will experience a hypertensive crisis in their lifetime [14]. Risk factors for hypertensive crises include old age, African–American heritage, male gender, tobacco abuse, obesity and diabetes mellitus [15,16]. The morbidity and mortality of hypertensive crises are dependent on the degree of target organ damage, adequate BP control and adherence to treatment. In the untreated patients, the mortality rate at 1 year can be as high as 79% [17], and among all patients that present with hypertensive crises, there is a 5-year survival rate of 74% [18].

### Pathophysiology

As with chronic hypertension, the pathophysiology of a hypertensive crisis is considered to be multifactorial. The factors that lead to a hypertensive crisis have not been entirely elucidated, but include mechanical stress, injury, endothelial damage, oxidative stress and renin–angiotensin system activation [19].

It is well known that endothelial damage will cause the rapid release of humoral agents, most noticeably vasoconstrictors that will increase systemic vascular resistance, although the initiating factor is still not well understood [20,21]. The resulting increase in BP will, in turn, increase the mechanical stress and endothelial injury. The subsequent damage to the vascular endothelium will result in the activation of platelets and the coagulation cascade, with the subsequent formation on thrombi resulting in ischemia, as well as the activation and release of proinflammatory cytokines such as IL-6, vasoactive mediators and the renin–angiotensin system. The result of these collective mechanisms can be further hypoperfusion, ischemia and end-organ damage [19,22].

### Clinical presentation

Patients with a hypertensive emergency usually present to the ED with a complaint that is directly related to the presence of end-organ damage; some of the most common clinical presentations include a patient with chest

pain, dyspnea and changes in mental status [3]. It is important to keep in mind that there is no specific BP that is associated with end-organ damage, and the elevation of BP is not the only factor contributing to organ damage. Moreover, the rate of increase should be taken into account [2].

Patients presenting with or as a hypertensive emergency need an immediate reduction in BP to reduce the risk of end-organ damage; a general goal is to reduce mean arterial pressure (MAP) by 15–20% within the first 2 h of treatment. However, in hypertensive urgencies there is no need to achieve a BP control as urgently, and the target BP can be achieved over a period of 24–48 h [19]. In fact, rapid reduction can result in a marked decrease in tissue perfusion, which can result in ischemia or infarction [23–26].

Most individuals presenting to the hospital with chronic hypertension and an elevated BP exhibit a rightward shift of the pressure/flow autoregulation curve with no acute end-organ damage [27]. Vascular injury leads to platelet and fibrin deposition, breakdown of normal autoregulation and, with ischemia, the release of vasoactive substances [27]. Altered autoregulation also occurs in patients with acute severe hypertension, and since end-organ damage is already present, rapid and excessive correction of the BP can further reduce perfusion and propagate further injury [1].

### Operative & postoperative hypertension

A hypertensive crisis may present during any surgical setting, especially during cardiac surgery, major vascular surgery (i.e., carotid endarterectomy and aortic surgery), neurosurgery, head and neck surgery, renal transplantation and major trauma (e.g., burns or head injury). Postoperative hypertension (BP  $\geq$  190 mmHg and/or a diastolic BP of 100 mmHg on two consecutive readings following surgery) [28,29] could result in creating significant adverse sequelae in both cardiac and noncardiac patients. Depending upon the population examined, the incidence of postoperative hypertensive crises varies from 4 to 35% of patients shortly after a surgical procedure [30–32]. Greater attention should be given to precise perioperative BP control, as excursions outside a targeted BP range have been shown to be correlated with an increased risk of 30-day mortality [33]. Individual consideration must be given to this clinical syndrome due to the unique factors in the postoperative period and the

transient nature itself of postoperative hypertension. Patients with perioperative hypertension, as with other forms of severe hypertension, usually have a history of hypertension.

### Initial management

There are numerous drugs that are commonly utilized for the management of acute hypertension, but among currently available drugs, none have the ideal combination of vascular selectivity, rapid onset and fast termination of action, with a low incidence of side effects. Nitroprusside and nitroglycerin are both short-acting intravenous vasodilators; nitroprusside has long been the most commonly used drug for hypertensive crises due to its rapid onset of effects and well-demonstrated efficacy, but its use has been decreasing due to severe disadvantages such as low arteriolar selectiveness, toxicity and severe side effects such as tachyphylaxis, reflex tachycardia and rebound hypertension [34]. Nitroglycerin has never been considered a first-line treatment for the management of acute hypertension due to lower efficacy than nitroprusside and other medications, and its known role in causing hypotension and reflex tachycardia [1,17,19].

Another group of medications currently available for acute BP control is the calcium channel blockers, particularly those of the dihydropyridine class. These agents have a demonstrated efficacy and vascular selectivity; however, many of the currently available medications such as nicardipine have a long half-life and prolonged effect that typically last from 4 to 6 h, which is not advantageous [17].

### Role of clevidipine

Clevidipine is the latest generation calcium channel blocker of the dihydropyrimidine family, with characteristics of arterial selectivity, extremely rapid onset of action and high clearance [9,35–37].

### Pharmacokinetics

Clevidipine is structurally similar to other dihydropyridines, but has an extra ester link that allows its rapid hydrolyzation to its inactive carboxylic acid metabolite in the blood (<10% total elimination) and extravascular tissues. Clevidipine is excreted principally through urine and fecal pathways (FIGURE 1) [36]. This results in a high clearance value (median blood clearance is 0.125 l/min<sup>-1</sup>/kg<sup>-1</sup> [37]), coupled with the small volume of distribution of 0.51–0.58 l/kg<sup>-1</sup>, resulting in an ultra-short half-life of approximately

1 min (TABLE 1) [10,37]. This short half-life allows a more rapid titration to the desired effect, as the drug rapidly achieves steady blood concentrations after the infusion is initiated [38,39], and has a negligible effect on BP after the infusion has ended [8]. Clevidipine does not inhibit or induce any cytochrome P450 (CYP) enzyme, and exhibits no clinically relevant drug interactions [101]. Therefore, clevidipine is well tolerated when used concomitantly with  $\beta$ -blockers and other antihypertensive agents.

### Pharmacodynamics

Clevidipine has a rapid onset of effect in 2–3 min [37] and exerts its effect by inhibition of transmembrane influx of calcium ions through the voltage-dependent L-type calcium channels [40]. Like other drugs of the dihydropyridine family, such as nicardipine and nifedipine, a key characteristic of clevidipine is its arterial dilation selectivity. This allows for the rapid reduction of BP by reducing vascular resistance, but without venous dilation, thereby not affecting preload; thus, having minimal effect on cardiac function, it will not affect stroke volume, cardiac output or heart rate [41], making it safe to use in patients with renal or hepatic dysfunction without dose adjustment. Clevidipine is formulated and administered in a lipid emulsion, but has shown no negative net effects on serum triglyceride levels.

Blood pressure reduction with clevidipine is rapidly reversed after discontinuation or reduction of the infusion. In most patients, full recovery of blood pressure is achieved in 5–15 min after the infusion is stopped [101]. In a recent study that compared clevidipine with sodium nitroprusside, there was a significantly greater ( $p < 0.001$ ) increase in heart rate in patients treated with nitroprusside, resulting in a greater demand for oxygen and a greater risk for myocardial ischemia [34]. Clevidipine is not associated with coronary steal or ischemia.

Table 1. Pharmacology of clevidipine.

Characteristic	Value
Class	Dihydropyridine
<b>Pharmacokinetics</b>	
Metabolism	Ester hydrolysis in blood
Metabolite	Inactive carboxylic metabolite H152/81
Plasma protein binding	>99.5%
Volume of distribution	0.51–0.58 l/kg <sup>-1</sup>
Half-life	Phase 1 = 1.6 Phase 2 = 15.5
Blood clearance	0.105 l/min <sup>-1</sup> /kg <sup>-1</sup>

### Clinical trials

#### ■ ESCAPE-1

Recent trials include the Efficacy Study of Clevidipine Assessing Its Preoperative Antihypertensive Effect in Cardiac Surgery (ESCAPE-1), a trial in which 105 patients scheduled for cardiac surgery that either had or recently had hypertension were randomized into two groups in which one received a 0.4–0.8 µg/kg/min infusion of clevidipine, while the other group received an infusion of 20% lipid emulsion. The clevidipine group had a significantly lower rate of treatment failure (failure to reduce SBP by more than 15% from the baseline BP or the termination of infusion) than the placebo group (7.5 vs 82.7%;  $p < 0.0001$ ). Clevidipine patients reached the targeted BP at a median time of 6 min, while the median time for placebo patients could not be determined due to the small number of patients who actually reached the target BP [35]. In this and other studies, clevidipine reduced BP to target in more than 90% of patients with perioperative hypertension [35,42]. The authors concluded that clevidipine was effective in rapidly decreasing blood pressure preoperatively to targeted blood pressure levels, and was well-tolerated in patients scheduled for cardiac surgery.

#### ■ ESCAPE-2

The Efficacy Study of Clevidipine Assessing Its Postoperative Antihypertensive Effect in Cardiac Surgery-2 (ESCAPE-2) is a double-blind, placebo-controlled trial that examined and compared the efficacy and safety of clevidipine in the setting of hypertension in post-cardiac surgery patients. The trial consisted of 110 patients that met criteria for post-operative hypertension who were randomized to receive either 0.4–0.8 µg/kg/min or a 20% lipid emulsion for 30 min to a maximum of 1 h. The clevidipine group had a significantly better success rate (91.8%;  $p < 0.0001$ ), defined as the absence of treatment

failure, than the placebo group, which had a success rate of just 20.4%. The clevidipine-treated group also showed a considerably greater reduction in MAP than the placebo group 2 min after the respective infusion was started ( $p = 0.0004$ ): -5.9%, which equates to -5.7 mmHg, in the clevidipine group, versus -0.1%, which corresponds to a decrease in 0.1 mmHg, in the placebo group. The increased efficacy of clevidipine is more evident when comparing the greatest mean change: in the clevidipine group there was a reduction of 28.1 mmHg, compared with a reduction of -8.9 mmHg in the placebo group ( $p < 0.0001$ ) [43]. In ESCAPE-2, it was demonstrated that clevidipine was effective and safe in the rapid treatment of acute postoperative hypertension after cardiac surgery.

#### ■ VELOCITY

The Prolonged Infusion of Clevidipine Results in Safe and Predictable Blood Pressure Control in Patients with Acute Severe Hypertension (VELOCITY) trial consisted of an open-label, single-arm, multicenter study of 126 patients who presented to the ED or intensive care unit with acute hypertension. The goal of the study was to determine the percentage of patients whose SBP dropped below a preset intended target with an initial dose of 2 mg/h within 3 min (safety end point, i.e., overshoot), as well as the percentage that reach an individualized target range within 30 min (efficacy end point). In this trial, clevidipine showed a rapid and effective reduction in BP, with a decrease of 6% (i.e., 12 mmHg) within the 3-min mark, and a reduction of 15% within 9.5 min. The trial also demonstrated the efficacy of clevidipine in a relatively long-term infusion, with a 27% (i.e., 55 mmHg) reduction in BP at 18 h after the initiation of the infusion [44]. The 18 h was pre-specified by study design. Likewise, VELOCITY demonstrated that clevidipine is safe and effective in subsets of patients with severe hypertension and heart failure or renal dysfunction. This data is consistent with data obtained from the ESCAPE trials, which showed a first reduction of 15% from the baseline at a median time of 6 min in the ESCAPE-1 trial, and 5.3 min in ESCAPE-2. The authors concluded that clevidipine, dosed in a non-weight-based manner, was safe and effective in a cohort of patients with severe hypertension at a starting dose of 2 mg/h, followed by simple titration during 18 h or more of continuous infusion. Patients were effectively managed via simple blood pressure cuff monitoring throughout.

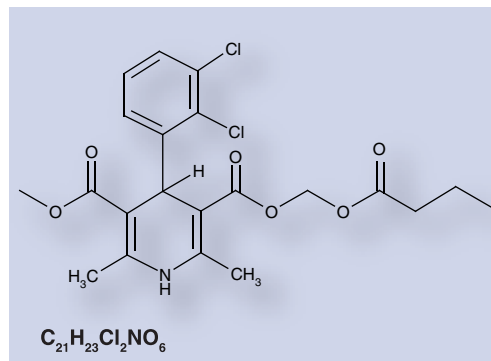


Figure 1. Clevidipine.

### ■ ECLIPSE

The Evaluation of Clevidipine in the Perioperative Treatment of Hypertension Assessing Safety Events (ECLIPSE) evaluated 1964 cardiac surgical patients who were enrolled in three random groups assigned to compare the clevidipine to three intravenous antihypertensive drugs: nicardipine, nitroglycerin and nitroprusside. Prior to the surgery, the patient's BP was monitored and the drug was administered if needed. The investigators determined the 'BP excursions', which were defined as how long and how much the systolic BP was over or under the predetermined BP ranges that were considered acceptable for each patient [42]. In all three trials, clevidipine was superior in providing BP control, with almost half of the BP excursion in relation to the other three agents (3.8 vs 7.8 mmHg × min/h), as well as the narrowest SBP range both pre- and post-operatively and during surgery, with 105–145 mmHg and 93–135 mmHg, respectively.

Clevidipine had almost half the BP excursions that nitroglycerin and nitroprusside had, with 4.14 vs 8.87 mmHg × min/h and 4.37 vs 10.5 mmHg × min/h, respectively. When compared with nicardipine, there was no important difference in the pre-/post-operative period in BP excursions (1.76 mmHg × min/h vs 1.79 mmHg × min/h) [42]. Moreover, clevidipine reduced BP to target in more than 90% of patients with perioperative hypertension [35,42]. The ECLIPSE trial also demonstrated that clevidipine not only offers better BP control, but also showed a noticeable decrease in mortality when compared with nitroprusside, with a death rate of 1.7% for clevidipine versus 4.7% for nitroprusside at 30 days post-operative. There were no significant differences with regards to stroke, heart attack or kidney damage [42]. In this study, it was demonstrated that clevidipine was a safe and effective treatment for acute hypertension in patients undergoing cardiac surgery, and afforded more precise and titratable BP control compared with sodium nitroprusside or nitroglycerin.

### Adverse effects

Clevidipine has also been shown to be a well-tolerated drug, with almost no reported adverse effects in the various trials. The ESCAPE-1 and -2 trials demonstrated that the most notable adverse effect was the increase in heart rate, which was relatively small and had no clinical significance. The VELOCITY trial reported no serious adverse events and, most importantly, no episodes of rebound hypertension. Other adverse

effects reported were flushing, headache, fever, atrial fibrillation, acute renal failure and nausea (TABLE 2) [35]. In the ECLIPSE trial, there were no differences in death or adverse outcomes at the time of hospital discharge or day 7 among any of the treatment groups. Across all pivotal studies, it has been determined that clevidipine is a safe and effective treatment for patients with severe hypertension, those scheduled for cardiac surgery, those with acute hypertension undergoing cardiac surgery, and in the rapid treatment of acute postoperative hypertension after cardiac surgery [35,42–44].

### Clevidipine dosing

Clevidipine is easy to use and is initiated with a non-weight-based starting dose, followed by simple titration to a target BP. It may be administered as a loading dose of 1–2 mg, followed by repeated incremental doubling of the dose at 90 s intervals until the desired BP is achieved. As the BP approaches goal, it is advised to increase the dose by less than doubling, and lengthen the time between dose adjustments to every 5–10 min. An increase of approximately 1–2 mg/h will generally produce an additional 2–4 mmHg decrease in systolic pressure. The desired therapeutic response for most patients occurs at doses of 4–6 mg/h. Patients with severe hypertension may require doses up to 32 mg/h [101]. Clevidipine is administered by either a central or peripheral line, providing convenience and flexibility. When treatment with clevidipine is no longer required, patients can be easily and successfully transitioned to oral therapy.

### Conclusion

Clevidipine has an extremely fast onset and offset of action and arteriolar selectivity. It is easy to use and is initiated with a non-weight-based starting dose, followed by simple titration to a target BP. Reduction in BP with clevidipine is rapidly reversed after discontinuation or reduction of the infusion. Structurally, it is similar to other agents of the dihydropyridine family, but contains an extra ester link that allows the

Table 2. Frequency of adverse effects.

Adverse effect	Frequency (%)
Flushing	40
Fever	18.9
Atrial fibrillation	13.2
Acute renal failure	9.4
Nausea	5.7

**Executive summary****Introduction**

- Acute elevations in blood pressure (BP) can result in hypertensive encephalopathy, acute aortic aneurysm, myocardial infarction, renal failure and heart failure.

**General aspects of acute hypertension**

- Hypertensive urgency is an acute elevation in BP with no end-organ damage.
- A hypertensive crisis is an acute elevation in BP associated with end-organ damage.

**Epidemiology**

- Hypertensive crises account for more than 25% of all medical emergencies presenting to the emergency department.
- Approximately 1% of chronic hypertensive patients will experience a hypertensive crisis.

**Pathophysiology**

- Factors that lead to hypertensive crises include: mechanical stress, endothelial damage, oxidative stress and renin-angiotensin system activation.

**The role of clevidipine: pharmacokinetics**

- Similar to other dihydropyridines, but with an extra ester link that allows rapid hydrolyzation in the blood.
- High clearance rate and small volume of distribution result in a half life of 1–3 min.
- Allows the rapid titration to desired effect and rapid offset of action.

**The role of clevidipine: pharmacodynamics**

- The main characteristics of clevidipine include: arterial dilation selectivity, which allows for the rapid reduction of BP without affecting preload and cardiac function.

**ESCAPE-1**

- Clevidipine showed a significantly lower rate of treatment failure than placebo (7.5 vs 82.7%).
- Clevidipine patients reached the target BP in a median time of 6 min.

**ESCAPE-2**

- Patients in the clevidipine group showed a mean arterial pressure reduction of 5.9% within 2 min of infusion, with a maximum reduction of 28.1 mmHg.

**VELOCITY**

- Clevidipine patients had a reduction in mean arterial pressure of 6% within 3 min, 15% at 9.5 min and 27% at 18 h after start of infusion.

**ECLIPSE**

- Clevidipine was superior in providing BP control, with almost half the BP excursions when compared with nitroprusside, nicardipine and nitroglycerin.
- When compared with nitroprusside, clevidipine provided a significant reduction of mortality: 1.7 vs 4.7%.

rapid hydrolyzation in blood and extravascular tissues. As clevidipine is a pure afterload reducer, it does not affect central venous pressure. Studies show clevidipine is well-tolerated and effective in patients with severe hypertension and heart failure or renal dysfunction. In addition, clevidipine can be simply and safely monitored with a blood pressure cuff, reducing the need for more invasive monitoring. These characteristics, coupled with its small volume of distribution, result in the rapid and easy titration to the desired effect, making clevidipine clearly superior to other agents commonly used in the management of acute hypertension.

Clevidipine is a promising new agent that has been shown to be highly effective in rapidly lowering BP. It has also been proven to be well-tolerated with only minor side effects. It combines the rapid onset of action of commonly used nitroprusside with the vascular selectivity and safety of nicardipine.

**Future perspective**

With an estimated worldwide prevalence of up to 1 billion people, chronic hypertension is by far one of the most common diseases. Acute hypertension will affect approximately 1% of these patients. The therapies previously available for the management of hypertensive crises are less than ideal. Some medications, such as nitroprusside, although quite effective in controlling BP, are plagued by severe adverse effects, while others such as nifedipine are hindered by a long onset and termination of action.

Trials such as ESCAPE-1, ESCAPE-2, VELOCITY and ECLIPSE have demonstrated that clevidipine is not only an extremely effective drug in controlling BP, but is also safe and well tolerated. There is no doubt that clevidipine, with its rapid onset and termination of action, efficacy and safety, is a promising agent that will greatly impact the prognosis, morbidity and mortality of patients with acute severe hypertension.

### Financial & competing interests disclosure

Dr Varon has received honoraria for lectures from PDL Pharmaceuticals and The Medicines Company, and has served as a consultant for The Medicines Company. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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#### ■ Website

- 101 The Medicines Company, I: Cleviprex™ (clevidipine butyrate) prescribing information (online) (updated 2008 August; cited 25 August 2008)  
[www.cleviprex.com/media/ClevidipinePI.pdf](http://www.cleviprex.com/media/ClevidipinePI.pdf)