Clevidipine in acute heart failure: Results of the A Study of Blood *Pressure* Control *in* Acute Heart Failure—A Pilot Study (PRONTO)

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Background Rapid blood pressure (BP) control improves dyspnea in hypertensive acute heart failure (AHF). Although effective antihypertensives, calcium-channel blockers are poorly studied in AHF. Clevidipine is a rapidly acting, arterial selective intravenous calcium-channel blocker. Our purpose was to determine the efficacy and safety of clevidipine vs standard-of-care intravenous antihypertensive therapy (SOC) in hypertensive AHF.

Methods This is a randomized, open-label, active control study of clevidipine vs SOC in emergency department patients with AHF having systolic BP ≥160 mm Hg and dyspnea ≥50 on a 100-mm visual analog scale (VAS). Coprimary end points were median time to, and percent attaining, a systolic BP within a prespecified target BP range (TBPR) at 30 minutes. Dyspnea reduction was the main secondary end point.

Results Of 104 patients (mean [SD] age 61 [14.9] years, 52% female, 80% African American), 51 received clevidipine and 53 received SOC. Baseline mean (SD) systolic BP and VAS dyspnea were 186.5 (23.4) mm Hg and 64.8 (19.6) mm. More clevidipine patients (71%) reached TBPR than did those receiving SOC (37%; $P = .002$), and clevidipine was faster to TBPR ($P = .0006$). At 45 minutes, clevidipine patients had greater mean (SD) VAS dyspnea improvement than did SOC patients (–37 [20.9] vs –28 mm [21.7], $P = .02$), a difference that remained significant up to 3 hours. Serious adverse events (24% vs 19%) and 30-day mortality (3 vs 2) were similar between clevedipine and SOC, respectively, and there were no deaths during study drug administration.

Conclusions In hypertensive AHF, clevidipine safely and rapidly reduces BP and improves dyspnea more effectively than SOC. (Am Heart J 2014;167:529-36.)

Acute heart failure (AHF) presents with a wide spectrum of clinical and hemodynamic manifestations.[1-3] Systolic blood pressure (BP) is an easily monitored hemodynamic parameter discriminating among AHF phenotypes. Using BP, AHF can be classified into normal (120-160 mm Hg), elevated (>160 mm Hg), or low (<120 mm Hg) subgroups,[2,4] each with unique therapeutic recommendations.[5,6] Registry data suggest that nearly half of patients with AHF present with SBP >140 mm Hg.[7]

In AHF with hypertension, symptom onset may be abrupt, presenting as profound dyspnea and acute pulmonary edema. This phenotype may be particularly responsive to BP reduction[1,5,7-9] with marked clinical improvement when vasodilators are administered. This benefit may occur in lieu of large diuretic doses,[4,5,10,11] particularly if pulmonary congestion is from fluid redistribution and left ventricular diastolic dysfunction, rather than increased total volume.[12] Thus, in such patients, the clinical target is immediate BP control, primarily with

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vasodilators. Unfortunately, safety and efficacy data are lacking, and few comparative trials have been conducted. Nitrates, hydralazine, and nicardipine are used most often, but each has limitations. The afterload effects of nitroglycerin are dose dependent and strongly influenced by arterial resistance, causing variable and labile responses.[13] Hydralazine stimulates reflex tachycardia, potentially increasing myocardial oxygen demand and worsening myocardial ischemia.[14] Nicardipine may be challenging to titrate, and evidence for calcium-channel blockers (CCBs) in AHF management is lacking.[15-17]

Clevidipine is a rapidly acting intravenous (IV) antihypertensive. Metabolized in blood, it has a 1-minute half-life that allows rapid titration. Clevidipine lowers BP by selective arteriolar vasodilation and, without venous capacitance effects, increases cardiac output as peripheral vascular resistance declines.[18] Because it has no negative inotropic or chronotropic effects, it may be beneficial in hypertensive AHF.

Our purpose was to determine the efficacy and safety of early treatment with clevidipine or standard-of-care IV antihypertensive therapy (SOC), in emergency department (ED) patients presenting with hypertensive AHF.

Methods

PRONTO was an international 13-center prospective randomized open-label, active control, safety and efficacy trial of patients with AHF requiring parenteral antihypertensive therapy. PRONTO enrolled men and nonpregnant women older than 18 years presenting to an ED with elevated systolic BP (SBP; ≥160 mm Hg). PRONTO was approved by each participating institution's local ethics committee, all patients provided written informed consent, and the trial was registered at Clinicaltrials.gov (NCT00803634). The PRONTO trial was supported by The Medicine's Company (Parsippany, NJ).

Before enrollment, patients were required to have a sitting dyspnea score ≥50 on a 0- to 100-mm (least to most) visual analog scale (VAS) and a physician's clinical diagnosis of AHF with pulmonary congestion by chest auscultation. Patients were excluded if they required endotracheal intubation, had contraindications to clevidipine (Cleviprex; The Medicine's Company), received any antihypertensive agent within the previous 2 hours (except short-acting non-IV nitrates), or had chest pain or ischemic electrocardiogram changes, suspected aortic dissection, myocardial infarction within 14 days, pregnancy, known liver or renal failure, or pancreatitis. Eligible patients were randomized 1:1 to receive either clevidipine or SOC.

At randomization, the treating physician recorded a target BP range (TBPR) to reach a minimum 15% BP reduction from baseline with a range of 20 to 40 mm Hg. The coprimary end points were median time to, and percent of patients attaining, SBP within the TBPR, by 30 minutes. Dyspnea reduction was the main secondary end point. Exploratory end points included the relative percentage admitted, number of procedures (diagnostic and therapeutic) performed, hospital and intensive care unit (ICU) length of stay, and 30-day readmissions.

Clevidipine dosing was at the discretion of the attending physician. The recommended titration was initiation at 2.0 mg/h for 3 minutes, then doubling every 3 minutes to a maximum of 32.0 mg/h, or until the TBPR was reached. Standard-of-care intravenous antihypertensive therapy was per institutional standard. During the initial 30 minutes of treatment, clevidipine was administered as monotherapy, except for medical necessity or patient safety. If the desired SBP was not reached within 30 minutes, or not maintained thereafter, alternative antihypertensives were allowed per physician discretion, with or without continuation of study drug. If a clevidipine patient failed to achieve the prespecified TBPR, additional non-CCB antihypertensives were allowed.

Dyspnea was assessed by a 100-mm VAS,[19] where 0 was "no dyspnea" and 100 represented "worst possible dyspnea." The Vasodilation in the Management of Acute CHF (VMAC)[20] scale, a relative 7-point Likert score, and the Provocative Dyspnea Assessment (PDA),[21,22] performed both seated and supine, were recorded. Dyspnea was evaluated immediately prior to study drug and at 15, 30, 45, 60, 120, 360, and 720 minutes afterward. The initial clinical diagnosis of AHF was confirmed after study drug administration by chest x-ray and/or natriuretic peptide assessment. Historical ejection fraction data were recorded when available. The "confirmed AHF" population, used for all efficacy analyses, consisted of all patients receiving any amount of study drug with either (1) a creatinine clearance >30 mL/h (estimated by the Cockcroft-Gault formula) and a brain natriuretic peptide (BNP) ≥400 (or N-terminal pro-BNP ≥900 pg/mL) corrected for obesity by doubling the BNP if the body mass index exceeded 35 kg/m^2 or (2) chest x-ray evidence of pulmonary congestion. The minimum creatinine clearance requirement was intended to avoid the confounding effects of glomerular filtration rate on BNP/N-terminal pro-BNP.

The safety of a prolonged clevidipine infusion (maximum: 96 hours per protocol) compared with SOC IV was assessed by laboratory parameters, adverse events through 7 days or discharge (whichever occurred first), and serious adverse events through 30 days after randomization. An independent Data and Safety Monitoring Board monitored patient safety throughout the study.

Statistical analysis

Two populations were analyzed: the "safety population" and the predefined confirmed AHF population. Dichotomous and continuous data comparisons, respectively, used the χ^2 test and the *t* test, or analysis of covariance. Visual analog scale by time was analyzed by longitudinal analysis of covariance, including fixed effect of treatment, time, and an interaction term between treatment and time, as well as a covariate of baseline VAS. Time-to-event data were assessed using the log-rank test and Kaplan-Meier method. Statistical inferences of treatment comparisons using *P* values were only applied to coprimary end points, with those shown for nonprimary end points solely to demonstrate the relative data strength.

Results

Patients

Overall, 104 patients (51 clevidipine, 53 SOC) were treated, constituting the "safety" cohort. The mean (SD) age was 61 (14.9) years; more than half were female and African American (Table I). Of these, 19 (7 clevidipine, 12

Table I. Population characteristics and SBP targets

	AHF population (N = 85)		Safety population (N = 104)	
Characteristics	**CLV (n = 44)**	**SOC (n = 41)**	**CLV (n = 51)**	**SOC (n = 53)**
Demographics				
Age (y)*	62 (15.3)	60 (13.9)	62 (14.9)	60 (14.9)
Female (%)	21 (47.7)	22 (53.7)	25 (49.0)	29 (54.7)
African American (%)	32 (72.7)	34 (82.9)	39 (76.5)	44 (83.0)
BMI (kg/m^2)*	34.6 (9.6)	34.8 (12.0)	34.5 (9.2)	33.5 (11.3)
Medical history				
Hypertension (%)	42 (95.5)	40 (97.6)	48 (94.1)	50 (94.3)
Coronary artery disease (%)	18 (40.9)	16 (39.0)	18 (35.3)	19 (35.8)
Diabetes (%)	23 (52.3)	21 (51.2)	27 (52.9)	26 (49.1)
COPD (%)	10 (22.7)	9 (22.0)	12 (23.5)	10 (18.9)
HF hospitalization in last year (%)	20/29 (69.0)	19/31 (61.3)	23/34 (67.6)	23/37 (62.2)
Ejection fraction (%)*†	45.4 (14.9)	44.3 (14.0)	45.0 (15.1)	45.1 (14.0)
Baseline HR, VAS, laboratory and x-ray results				
Baseline HR (beats/min), IQR (Q1, Q3)	84.5 (70, 90)	82.0 (66, 97)	86.0 (70, 94)	85.0 (68, 101)
Baseline dyspnea VAS (mm)*	65.0 (18.8)	67.7 (20.6)	64.8 (18.0)	64.8 (21.2)
BUN (mg/dL)*	19.6 (13.5)	19.8 (13.4)	21.3 (15.4)	26.4 (40.3)
Creatinine (mg/dL)*	1.4 (1.0)	1.4 (1.1)	1.6 (1.4)	2.1 (4.3)
Sodium (mmol/L)*	139.5 (6.4)	141.5 (4.7)	139.8 (6.1)	141.8 (4.6)
cTnT > 0.1 ng/mL (%)	6/36 (16.7)	8/30 (26.7)	8/43 (18.6)	12/41 (29.3)
BNP (pg/mL)*	894.5 (755.4)	924.5 (952.3)	948.2 (954.3)	1022.9 (1122.9)
Confirmed AHF, n (%)				
Chest x-ray	15 (34)	10 (24)	15 (29)	12 (23)
Laboratory	14 (32)	9 (22)	14 (28)	11 (21)
Both	15 (34)	22 (54)	15 (29)	22 (42)
Total	44 (100)	41 (100)	44 (86)	45 (85)
Baseline SBP*	189.5 (26.4)	187.5 (20.5)	188.2 (25.0)	184.8 (21.9)
SBP targets (mm Hg)				
High SBP target*	156.7 (14.5)	155.6 (13.9)	155.6 (14.1)	153.8 (15.4)
% Difference between initial SBP and high target*	−16.5 (8.7)	−16.5 (7.4)	−16.6 (8.4)	−16.2 (8.4)
Low SBP target*	130.0 (13.1)	129.0 (14.5)	129.1 (12.9)	127.8 (14.6)
% Difference between initial SBP and low target*	−30.6 (8.8)	−30.9 (7.0)	−30.7 (8.4)	−30.4 (7.7)

Abbreviations: *CLV*, Clevidipine; BMI, body mass index; *COPD*, chronic obstructive pulmonary disease; *HF*, heart failure; *HR*, heart rate; *IQR*, interquartile range; *BUN*, blood urea nitrogen; *cTnT*, cardiac troponin T; *miTT*, modified intention to treat.
* Reported as mean (SD).
† Safety: n = 26 for CLV, n = 26 for SOC. mITT: n = 23 for CLV, n = 22 for SOC.

SOC) did not meet the predefined confirmed AHF criteria: 15 (7 clevidipine, 8 SOC) lacked evidence of pulmonary congestion, and 4 (0 clevidipine, 4 SOC) had protocol deviations (prior antihypertensive agents or insufficient symptoms). This resulted in a confirmed AHF population of 85 (44 clevidipine, 41 SOC). The demographics, medical histories, and baseline characteristics were similar for the safety and confirmed AHF cohorts, and there were no differences between groups based on treatment allocation (Table I). Overall, the mean baseline VAS dyspnea score was 65 mm.

Therapy

Choice of SOC IV antihypertensives was per physician preference and institutional SOC. Most (87%) SOC patients received nitroglycerin IV (57%) or nicardipine IV (30%) titrated to achieve SBP in TBPR (Table II). Antihypertensive administration (Table II) is presented as doses within the first half hour and thereafter. Mean (SD) door-to-study drug time was 3.2 (1.9) and 2.7 (1.8) hours for clevidipine and SOC, respectively. Clevidipine patients achieved TBPR more often than SOC (31/44 [71%] vs 15/41 [37%], $P = .002$) and reached this end point sooner ($P = .0006$) (Figure 1). Clevidipine patients required fewer additional IV therapies for BP management than did SOC patients (16% vs 51%, $P = .0005$). The majority in both groups received diuretics (75% clevidipine, 83% SOC). Of those given furosemide (75% clevidipine, 76% SOC), the clevidipine cohort received lower doses (58 mg vs 78 mg, $P = .006$).

Compared with SOC, clevidipine is more effective at BP reduction (Figure 2A). However, if nitroglycerin is excluded from the SOC, clevidipine and nicardipine appear equally effective at BP reduction (Figure 2B). Clevidipine and SOC had similar rates of being within, but not below, TBPR (46% vs 51%, respectively; $P = .059$). In the first 30 minutes, no patient had a SBP <102 mm Hg. Overall, 16 patients exceeded their lower TBPR limit, 15 clevidipine and 1 SOC ($P < .001$), by a mean (SD) of 8.7

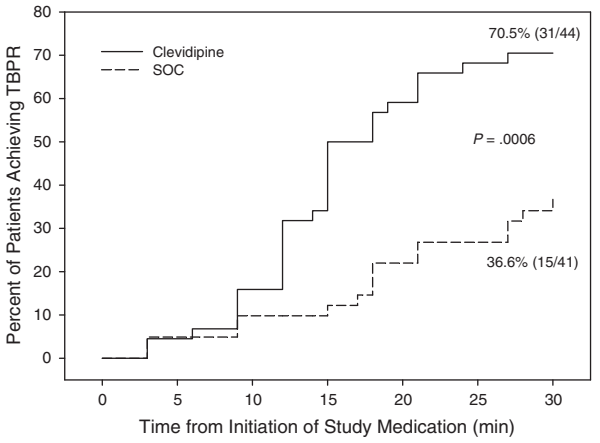
Table II. IV antihypertensive study drug dosing (safety population)

Time frame	Drug name (n), dosing unit	Mean of individual patient median infusion rates (SD)	Infusion rates, min/max	Total dose administered (mg), mean (SD)
Initiation of study drug to 30 min	Clevidipine (51), mg/h	6.4 (3.4)	1.0/16.0	4.6 (3.1)
	Standard-of-care medications			
	Nitroglycerin (30), μg/min	40.8 (40.9)	3.3/200	1.3 (1.4)
	Nicardipine (16), mg/h	6.2 (2.6)	1.0/10.0	3.2 (1.4)
	ISDN (4), mg/h	180.5 (254.1)	1.0/540	4.75 (4.9)
	Hydralazine (1), mg	NA	NA	20 (single bolus)
	Diltiazem (1), mg	NA	NA	5 (single bolus)
	Nitroprusside (1), μg/min	13.3	13.3/13.3	0.4
From 30 min until infusion stopped	Clevidipine (51), mg/h	7.6 (5.4)	1.0/24.0	26.4 (36.9)
	Standard-of-care medications			
	Nitroglycerin (30), μg/min	65 (60)	3.3/233	55.3 (97.5)
	Nicardipine (16), mg/h	8.2 (4.0)	1.0/15.0	15.4 (13.0)
	ISDN (4), mg/h	61 (103.3)	1.0/180	12.01 (4.8)
	Hydralazine (1), mg	NA	NA	NA
	Diltiazem (1), mg	10	10/10	38.7
	Nitroprusside (1), μg/min	13.3	13.3/13.3	3.0

	Drug name (n)	Median duration (h) of infusion	Min/Max duration of infusion
Duration of IV antihypertensive infusion	Clevidipine (51)	2.15	0.4/14.0
	Standard of care		
	Nitroglycerin (30)	2.6	0.5/20.3
	Nicardipine (16)	1.3	0.7/2.35
	Nitroprusside (1)	4.3	–
	Hydralazine (1)	0.02	–
	Diltiazem (1)	4.4	–
	Isosorbide dinitrate (4)	2.3	0.02/6.0

Abbreviation: *NA*, Not applicable; *SDN*, Isosorbide dinitrite.

Figure 1



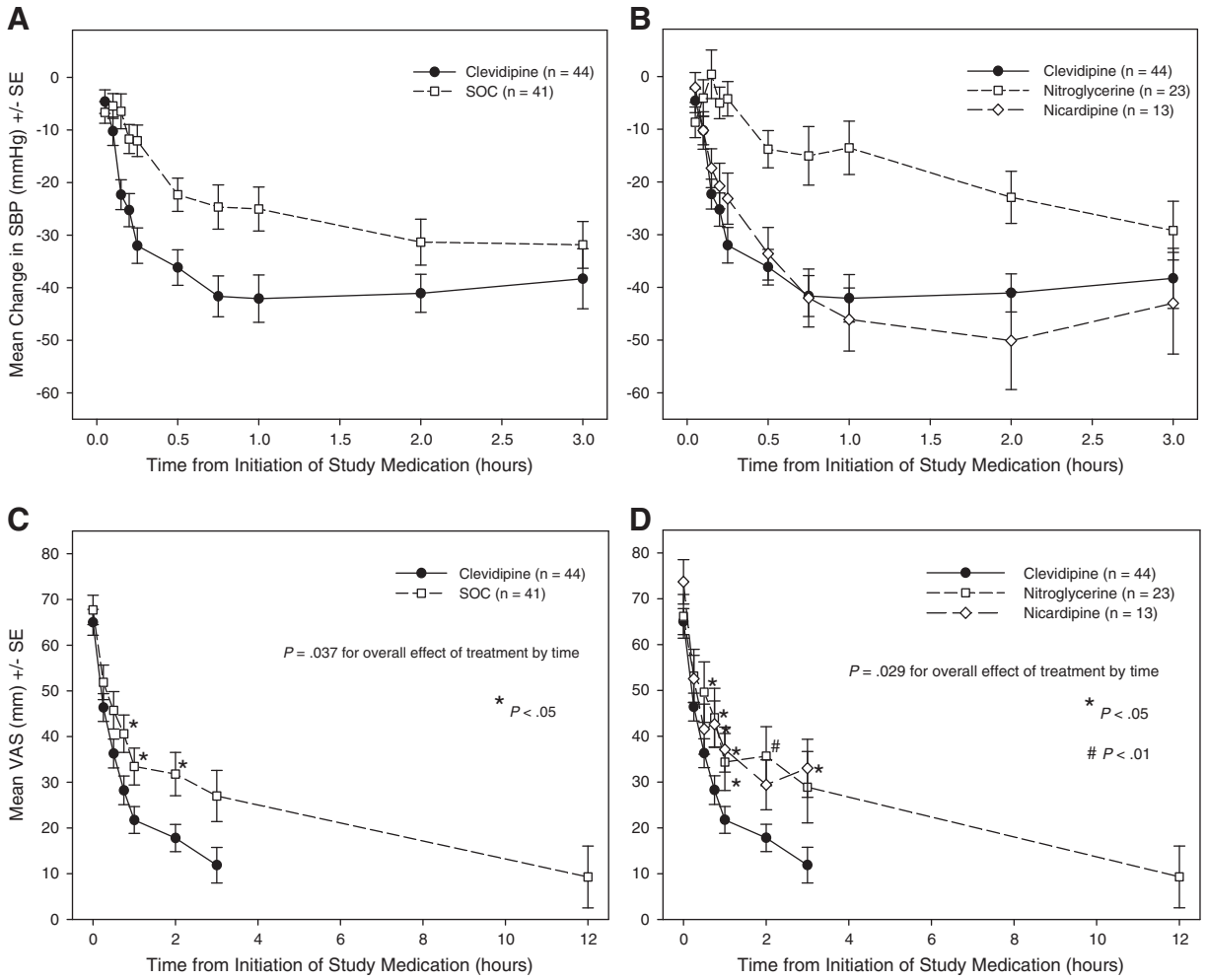
Time to achieve TBPR within 30 minutes (AHF population).

(4.7) and 13 mm Hg, respectively. Despite this, no patient developed signs or symptoms of hypoperfusion on study drug. For the remainder of the study, a SBP <90 mm Hg occurred in 3 (6%) clevidipine patients, lasting a median (interquartile range) of 3.3 (1.3, 6.6) minutes and in 1 (2%) SOC patient lasting 13 minutes. Symptomatic hypotension occurred in 1 patient, 3.5 hours after clevidipine termination. There were no differences in BP response related to ejection fraction. Finally, mean (SD) heart rate changes from baseline to 30 minutes were similar in both cohorts, 3 (10.6) beats/min vs 1 [8.4] beats/min for clevidipine and SOC, respectively.

Dyspnea

Antihypertensive administration (Table II) is presented as doses within the first half hour and thereafter. Marked dyspnea improvement paralleled rapid BP lowering in both groups (Figure 2A and C) for the first 30 minutes after study drug. At 45 minutes, clevidipine patients had greater mean (SD) VAS dyspnea improvement than did SOC patients (−37 [20.9] mm vs −28 mm [7.1], $P = .02$), an effect that persisted for 3 hours. At 1 and 2 hours, VAS dyspnea scores were 33 (24.93) vs 22 (18.79; $P = .0203$) and 32 (25.5) vs 18 (16.0; $P = .0152$) for SOC and clevidipine, respectively. Over time, VAS dyspnea scores decreased more with clevidipine than SOC (treatment × time effect, $P = .037$). Both VMAC and PDA scores had nonsignificant trends toward greater improvement with clevidipine than SOC.

Figure 2



A and **B**, Mean change in SBP during the first 3 hours of study drug administration. **C** and **D**, Mean VAS for the first 12 hours of study drug administration (AHF population).

To evaluate potential class effects, VAS and SBP lowering vs time for nitroglycerin and nicardipine subsets were assessed (Figure 2B and D). Neither nitroglycerin nor nicardipine improved VAS as quickly as clevidipine.

Adverse events

Endotracheal intubation was required in 1 SOC patient. Five patients died within 30 days of treatment (3 clevidipine, 2 SOC; $P = .615$) and none during study drug administration. None of these events were considered study drug related by the investigator or Data and Safety Monitoring Board. Clevidipine and SOC patients had a similar incidence of serious adverse events (24% vs 19%) and drug-related treatment-emergent adverse events (TEAEs; 10% vs 13%) (Table III). Mild to moderate headache, predominately with SOC, was the most common TEAE. No clinically significant differences in any laboratory studies occurred between groups.

Although clevidipine and SOC had similar rates of diagnostic procedures (14 [28%] and 12 [23%]), clevidipine had fewer therapeutic procedures (0 vs 9 [17%], $P = .003$), respectively, defined as arterial line, intubation, defibrillation, pacemaker placement, dialysis, coronary revascularization, and/or surgery. The percent of patients receiving any concomitant IV antihypertensives was 16% with clevidipine vs 51% with SOC ($P = .0005$). Clevidipine also had nonsignificant trends to fewer hospital admissions (90% vs 98%), fewer ICU admissions (23% vs 27%), shorter median hospital stays (4.0 days vs 5.0 days), fewer 30-day all-cause ED/hospital readmissions (15% vs 17%), and

Table III. Study of drug-related TEAEs (safety population)

Category	CLV (n = 51)	SOC (n = 53)	Total (n = 104)
No. (%) of patients with at least 1 related TEAE	5 (9.8%)	7 (13.2%)	12 (11.5%)
Preferred term	**n (%)**	**n (%)**	**n (%)**
Headache	1 (2.0)	7 (13.2)	8 (7.7)
Abdominal discomfort	1 (2.0)	0	1 (1.0)
Abdominal pain	1 (2.0)	0	1 (1.0)
Flushing	1 (2.0)	0	1 (1.0)
Myalgia	1 (2.0)	0	1 (1.0)
Nausea	1 (2.0)	0	1 (1.0)
Ventricular tachycardia	1 (2.0)	0	1 (1.0)
Blurred vision	1 (2.0)	0	1 (1.0)

Abbreviation: *CLV*, Clevidipine.

longer out-of-hospital periods before rehospitalization (11.0 days vs 5.0 days).

Discussion

In hypertensive patients with AHF randomized within 1 hour of ED presentation, clevidipine safely and rapidly reduced SBP and improved dyspnea more effectively than did SOC. Furthermore, the speed to BP control with clevidipine paralleled dyspnea resolution. This benefit was accompanied by the need for fewer additional IV antihypertensives, lower total doses of furosemide, and exhibited consistent trends toward reduced resource use. These benefits were seen with similar safety profiles as SOC, and no clinically relevant drug-related hypotension occurred. However, although there was no symptomatic hypotension in either group on study drug, there was a greater proportion of clevidipine patients who exceeded their lower TBPR limit.

Few trials report on the use of IV CCBs in AHF; no major cardiovascular or HF society guidelines recommend their acute use; and with the exceptions of amlodipine or felodipine,[15-17] all provide proscriptions against their chronic oral use. The PRONTO results suggest that guideline-specific treatments may be indicated not only for hypotensive patients (ie, inotropic support) but also for hypertensive patients. The PRONTO study adds specific efficacy data and supports guideline-specific mention of clevidipine in the management of hypertensive patients with AHF.

Beyond this, PRONTO is one of the first randomized AHF trials to enroll patients within 3 hours of hospital arrival. Although early intervention benefits are supported by several large registry analyses,[21,23] no large prospective randomized trial has demonstrated similar AHF outcomes. That marked and rapid dyspnea improvement occurred in both PRONTO treatment groups suggests that time to treatment may be an important parameter to consider in the management of hypertensive patients with AHF. The >60-mm decrease in dyspnea VAS exceeds that of any prior major AHF trial. By demonstrating a relationship between symptom relief and door-to-treatment time, the results of PRONTO confirm previous retrospective work that time to therapy is important, supporting a greater emphasis on the impact of early therapy during the acute phase of illness. Although such results have potential implications for more than 500,000 patients with AHF who present with severe dyspnea and hypertension each year to US hospitals,[7] prospective validation is needed. As such, door-to-treatment time should be considered in future therapeutic trial designs and tracked as a metric in registries of routine clinical care.

Regarding symptoms, dyspnea severity drives hospital presentation, serves as the primary determinant of need for hospital admission, and is associated with worse outcomes.[24-26] However, a clinically relevant improvement in dyspnea has been an unreachable end point for many AHF studies. Because dyspnea is the root cause for hospitalization in most of the 1 million[27] annual US HF admissions, strategies for its relief have potentially valuable implications. In AHF presentations, therapeutic treatment time should be considered in future trial design and may represent a potential quality improvement metric.

Clevidipine was associated with more rapid and sustained dyspnea resolution than SOC, suggesting that hemodynamics may be more important than volume removal in hypertensive AHF. Clevidipine's effects on dyspnea appear, therefore, to be partially independent of BP reduction and may indicate a unique mechanism of action that warrants further study.

Our data add to the existing body of literature and further support the hypothesis that these patients have an underlying "vascular redistribution" phenotype, in contradistinction to volume overload, as the underlying pathologic precipitant for their symptoms. The mechanism(s) of fluid redistribution to the alveolar spaces is not well understood, but may involve inflammatory-mediated extravasation. Both inflammatory and neurohormonal activation has previously been observed in patients with AHF.[28,29] Although the 12-hour period required for dyspnea resolution with SOC may be the result of diuretic-induced volume removal, it is clinically unlikely that a significant amount of diuretic-induced volume reduction occurred within the time frame of the dyspnea relief associated with the clevidipine arm of this study. In fact, most of dyspnea relief in the clevidipine cohort had occurred within 1 hour of therapy (Figure 2C). Whether a 3-hour infusion of clevidipine improves dyspnea due to a unique mechanistic consequence vs SOC, or was function of time to treatment, was not studied but remains an area of ongoing investigation. Blood pressure generally improves with observation in the ED that may reflect a reduction in anxiety and relief of symptoms.

However, the incremental dyspnea benefit seen with clevidipine vs SOC in this population of hypertensive patients with AHF suggests that specific therapy can result in more rapid symptom relief.

Limitations

PRONTO is a small study, powered to evaluate reductions in SBP rather than discriminate secondary end points of length of stay, ICU admissions, and revisits. Doses of nitrates were relatively low; however, they were consistent with previous blinded randomized controlled studies of "standard care."[20] Furthermore, we report dyspnea differences measured by VAS, but not Likert or PDA scores. This may result from small sample size or insensitivity of the latter measures, as others have found similar dyspnea score disparity.[19] In addition, 18% of patients were excluded from the confirmed AHF cohort after the enrollment. This may be due to low and diagnostically confounding natriuretic peptide levels in patients with preserved ventricular function and early presentation. The demographic constitution of our study is also in marked contrast to other AHF studies, with a much higher proportion of African American patients. However, African Americans are more prone to the development of hypertensive HF. The PRONTO data reflect the population for whom such an approach may be most applicable, as data from other studies (clevidipine Food and Drug Administration NDA 22-156) reveal similar BP-lowering effects on both elderly and white patients. Further studies of clevidipine's dyspnea benefit in all populations are warranted.

Lastly, PRONTO was an open-label design. Clevidipine, an opaque white lipid emulsion, creates a significant blinding challenge. Furthermore, its rapid clinical onset and offset make its presence readily apparent, even if physically blinded. The open-label design of the trial could have impacted our results. For dyspnea relief, although the VAS score differential was robust, VMAC and PDA assessments of dyspnea were not similarly affected by treatment. Although SOC results could have been from a lack of aggressive titration, several factors contradict this: (1) SOC patients had obvious improvements in dyspnea; (2) adverse events related to delayed or inadequate care occurred rarely (only 1 SOC patient required endotracheal intubation vs other studies with rates of 27%[11]); and (3) SOC medication doses were consistent with approved labeling and prior studies; for example, PRONTO used nitroglycerin dosing higher than that in the nonpulmonary artery catheter blinded arm of VMAC.[20]

In conclusion, in this randomized, controlled trial, early treatment for hypertensive patients with AHF receiving clevidipine was more effective than standard of care in controlling BP and improving dyspnea. Use of clevidipine was also safe, suggesting that it may be appropriate therapy in the management of patients with AHF. Further studies are needed to more fully assess the effects of clevidipine on the outcomes of patients with hypertensive AHF.

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