Clevidipine in Acute Heart Failure: Results of the PRONTO Study

W. Frank Peacock MD, Abhinav Chandra MD, Douglas Char MD, Sean Collins MD, MSc, Guillaume Der Sahakian MD, Li Ding MA, MS, Lala Dunbar MD, Gregory Fermann MD, Gregg C. Fonarow MD, FACC, Norman Garrison MD, Tristan Hu MA, MS, Patrick Jourdain MD, Said Laribi MD, Phillip Levy MD, MPH, Martin Möckel MD, FESC, FAHA, Christian Mueller MD, Patrick Ray MD, Adam Singer MD, Hector Ventura MD, Mason Weiss MD, FACC, Alex Mebazaa MD

PII: S0002-8703(14)00018-0
DOI: doi: 10.1016/j.ahj.2013.12.023
Reference: YMHJ 4538

To appear in: *American Heart Journal*

Received date: 30 September 2013
Accepted date: 28 December 2013

Please cite this article as: Peacock W. Frank, Chandra Abhinav, Char Douglas, Collins Sean, Der Sahakian Guillaume, Ding Li, Dunbar Lala, Fermann Gregory, Fonarow Gregg C., Garrison Norman, Hu Tristan, Jourdain Patrick, Laribi Said, Levy Phillip, Möckel Martin, Mueller Christian, Ray Patrick, Singer Adam, Ventura Hector, Weiss Mason, Mebazaa Alex, Clevidipine in Acute Heart Failure: Results of the PRONTO Study, *American Heart Journal* (2014), doi: 10.1016/j.ahj.2013.12.023

Clevidipine in Acute Heart Failure: Results of the PRONTO Study

Short title: Clevidipine in AHF: PRONTO Results

W. Frank Peacock, MD[1]
Abhinav Chandra, MD
Douglas Char, MD
Sean Collins, MD, MSc
Guillaume Der Sahakian, MD
Li Ding, MA, MS
Lala Dunbar, MD
Gregory Fermann, MD
Gregg C. Fonarow, MD, FACC
Norman Garrison, MD
Tristan Hu, MA, MS
Patrick Jourdain, MD
Said Laribi, MD
Phillip Levy, MD, MPH
Martin Möckel, MD, FESC, FAHA
Christian Mueller, MD
Patrick Ray, MD
Adam Singer, MD
Hector Ventura, MD

Mason Weiss, MD, FACC

Alex Mebazaa, MD

[1] Corresponding Author

Associate Chairman, Research Director, Emergency Medicine

Baylor College of Medicine, 1504 Taub Loop, Houston, Texas, 77030

Background: Rapid blood pressure (BP) control improves dyspnea in hypertensive Acute Heart Failure (AHF). Although effective antihypertensives, calcium channel blockers (CCB) are poorly studied in AHF. Clevidipine is a rapidly acting, arterial selective intravenous (IV) CCB. Our purpose was to determine the efficacy and safety of clevidipine versus standard of care IV anti-hypertensive therapy (SOC), in hypertensive AHF.

Methods: Randomized, open label, active control study of clevidipine vs. SOC in emergency department AHF patients with systolic BP ≥160mm Hg and dyspnea ≥50 on a 100mm visual analog scale (VAS). Co-primary endpoints were median time to, and percent attaining, a systolic BP within a pre-specified target BP range (TBPR) at 30 minutes. Dyspnea reduction was the main secondary endpoint.

Results: Of 104 patients (mean [SD] age 61 [14.9] years, 52% female, 80% African American), 51 received clevidipine and 53 SOC. Baseline mean [SD] systolic BP and VAS dyspnea were 186.5 [23.4] mmHg, and 64.8 [19.6] mm. More clevidipine patients (71%) reached TBPR than SOC (37%), p=0.002 and clevidipine was faster to TBPR, p=0.0006. At 45 minutes, clevidipine patients had greater mean [SD] VAS dyspnea improvement than SOC, -37 [20.9] vs -28mm [21.7], p=0.02), a difference which 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.

Introduction

Acute heart failure (AHF) presents with a wide spectrum of clinical and hemodynamic manifestations.[1,2,3] 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 AHF patients 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 [1,5,7,8,9] 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 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.[21,22,23]

Clevidipine is a rapidly acting intravenous (IV) anti-hypertensive. 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.[16] 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 care IV antihypertensive therapy (SOC), in ED patients presenting with hypertensive AHF.

Methods

PRONTO (A Study of Blood Pressure Control in Acute Heart Failure-A Pilot Study) was an international 13-center prospective randomized open label, active control, safety and efficacy trial of AHF patients requiring parenteral anti-hypertensive therapy. PRONTO enrolled men and non-pregnant women, >18 years of age, 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 anti-hypertensive agent within the previous 2 hours (except short-acting non-IV nitrates), had chest pain or ischemic ECG 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 mmHg. The co-primary endpoints were median time to, and percent of patients attaining, SBP within the TBPR, by 30 minutes. Dyspnea reduction was the main secondary endpoint. Exploratory endpoints included the relative percentage admitted, number of procedures (diagnostic and therapeutic) performed, hospital and 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/hr, or until the TBPR was reached. SOC therapy was per institutional standard. During the initial 30 minutes of treatment, clevidipine was administered as mono-therapy except for medical necessity or patient safety. If the desired SBP was not reached within 30 minutes, or not maintained thereafter, alternative anti-hypertensives were allowed per physician discretion, with or without continuation of

study drug. If a clevidipine patient failed to achieve the pre-specified TBPR, additional non-CCB anti-hypertensives were allowed.

Dyspnea was assessed by a 100 mm VAS,[16] where 0 was "no dyspnea" and 100 represented "worst possible dyspnea".[17] The Vasodilation in the Management of Acute CHF (VMAC) scale, a relative 7 point Likert score, and the Provocative Dyspnea Assessment (PDA)[20] 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 was 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/hr (estimated by the Cockcroft-Gault formula) and a BNP ≥ 400 (or NTpro-BNP ≥ 900 pg/mL) corrected for obesity by doubling the BNP if the BMI exceeded 35 kg/m2; or 2) chest X-ray evidence of pulmonary congestion. The minimum creatinine clearance requirement was intended to avoid the confounding effects of GFR on BNP/NT-proBNP.

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

Statistical Analysis

Two populations were analyzed: the "safety population" and the pre-defined "confirmed AHF" population. Dichotomous and continuous data comparisons, respectively, used the Chi-squared test and the t-test, or ANCOVA. VAS by time was analyzed by longitudinal ANCOVA, 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. Statistical inferences of treatment comparisons using p-values were only applied to co-primary endpoints, with those shown for non-primary endpoints 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 1). Of these, 19 (7 clevidipine, 12 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 anti-hypertensive 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 1). 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 2). Anti-hypertensive administration (Table 2) 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 hrs [1.8] for clevidipine and SOC, respectively. Clevidipine patients achieved TBPR more often than SOC (31/44, 71%, vs. 15/41, 37%; p=0.002) and reached this endpoint sooner (p=0.0006), (Figure 1). Clevidipine patients required fewer additional IV therapies for BP management than SOC (16 vs. 51%, p=0.0005). 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 vs. 78 mg, p=0.006).

Compared to 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 blood pressure reduction (Figure 2B). Clevidipine and SOC had similar rates of being within, but not below, TBPR (46 vs. 51%, respectively, p=0.059). In the first 30 minutes, no patient had a SBP <102 mmHg. Overall, 16 patients exceeded their lower TBPR limit; 15 clevidipine and 1 SOC (p<0.001) by a mean [SD] of 8.7 [4.7] and 13 mmHg, respectively. Despite this, no patient developed signs or symptoms of hypo-perfusion on study drug. For the remainder of the study, a SBP <90 mmHg occurred in 3 (6%) clevidipine patients, lasting a median (IQR) of 3.3 minutes (1.3, 6.6), 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 (bpm) changes from baseline to 30 minutes were similar in both cohorts, 3 [10.6] vs. 1 [8.4] bpm for clevidipine and SOC, respectively.

Dyspnea

Anti-hypertensive administration (Table 2) is presented as doses within the first half hour, and thereafter. Marked dyspnea improvement paralleled rapid BP lowering in both groups (Figures 2A & 2C) for the first 30 minutes after study drug. At 45 minutes, clevidipine patients had greater mean [SD] VAS dyspnea improvement than SOC, -37 [20.9] vs -28mm [7.1], p=0.02, an effect that persisted for 3 hours. At 1 and 2 hours, VAS dyspnea scores were 33 [24.93] vs. 22 [18.79], (p=0.0203), and 32 [25.5] vs. 18 [16.0], (p=0.0152) for SOC and clevidipine, respectively. Over time, VAS dyspnea scores decreased more with clevidipine than SOC (treatment x time effect, p=0.037). VMAC and PDA scores had non-significant trends toward greater improvement with clevidipine than SOC. To evaluate potential class effects, VAS and SBP lowering vs. time for nitroglycerin and nicardipine subsets were assessed (Figures 2B & 2D). Neither nitroglycerin nor nicardipine improved VAS as quickly as clevidipine.

Adverse events

Endotracheal intubation was required in 1 SOC patient. Five patients expired within 30 days of treatment (3 clevidipine, 2 SOC, p=0.615), and none during study

drug administration. None of these events were considered study drug related by the investigator or DSMB. Clevidipine and SOC patients had a similar incidence of serious adverse events (24vs. 19%) and drug related treatment-emergent adverse events (TEAEs), 10 vs. 13% (Table 3). Mild to moderate headache, predominately with SOC, was the most common TEAE. No clinically significant differences in any labs occurred between groups.

While clevidipine and SOC had similar rates of diagnostic procedures, 14 (28%) and 12 (23%), clevidipine had fewer therapeutic procedures, 0 vs. 9 (17%), (p=0.003), 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=0.0005). Clevidipine also had non-significant trends to fewer hospital admissions, 90% vs. 98%, fewer ICU admissions, 23 vs. 27% , shorter median hospital stays, 4.0 vs. 5.0 days , fewer 30-day all cause ED/hospital readmissions, 15 vs. 17%, and longer out-of-hospital periods before re-hospitalization, 11.0 vs. 5.0 days.

Discussion

In hypertensive AHF patients randomized within 1 hour of ED presentation, clevidipine safely and rapidly reduced SBP and improved dyspnea more effectively than SOC. Further, 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

utilization. These benefits were seen with similar safety profiles as SOC, and no clinically relevant drug-related hypotension occurred. However, while 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, [21,22,23] all provide proscriptions against their chronic oral use. The PRONTO results suggest that guideline specific treatments may be indicated not only for hypotensive patients (i.e., 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 AHF patients.

Beyond this, PRONTO is one of the first randomized AHF trials to enroll patients within 3 hours of hospital arrival. While early intervention benefits are supported by several large registry analyses [19,20] 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 AHF patients. 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. While

such results have potential implications for the more than 500,000 AHF patients 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. [24,25,26] However, a clinically relevant improvement in dyspnea has been an unreachable endpoint for many AHF studies. Because dyspnea is the root cause for hospitalization in the majority 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 blood pressure 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 contra-distinction to volume overload, as the underlying pathologic precipitant for their

symptoms. The mechanism(s) of fluid re-distribution to the alveolar spaces are not well understood, but may involve inflammatory-mediated extravasation. Both inflammatory and neuro-hormonal activation has previously been observed in patients with AHF.[28, 29] While 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, the majority 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. BP generally improves with observation in the emergency department that may reflect a reduction in anxiety and relief of symptoms. However, the incremental dyspnea benefit seen with clevidipine versus SOC in this population of hypertensive AHF patients 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 endpoints 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".[17] Further, 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.[16] Additionally, 18% of patients were excluded from the confirmed AHF cohort post-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 FDA NDA 22-156) reveal similar blood pressure lowering effects on both elderly and Caucasian 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. Further, 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. While 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, e.g. PRONTO used nitroglycerin dosing higher than that in the non-pulmonary artery catheter blinded arm of VMAC.[17]

In conclusion, in this randomized, controlled trial, early treatment of hypertensive AHF patients with 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 AHF patients. Further studies are needed to more fully assess the effects of clevidipine on the outcomes of patients with hypertensive AHF.

Acknowledgements

PRONTO was sponsored by The Medicines Company

The authors recognize J.A. Campagna, M-Yi Hu, L. Ding, D. Montgomery, D. Johnson, for their contributions to this study.

Table 1. Population Characteristics and Systolic Blood Pressure Targets

Characteristics	AHF Population (n=85)		Safety Population (n=104)	
	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*	34.6 (9.6)	34.8 (12.0)	34.5 (9.2)	33.5 (11.3)
Past 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, Lab and X-ray Results				
Baseline HR (bpm) 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 Laboratory Both Total	 15 (34) 14 (32) 15 (34) 44 (100)	 10 (24) 9 (22) 22 (54) 41 (100)	 15 (29) 14 (28) 15 (29) 44 (86)	 12 (23) 11 (21) 22 (42) 45 (85)

Baseline SBP*	189.5 (26.4)	187.5 (20.5)	188.2 (25.0)	184.8 (21.9)
Systolic Blood Pressure Targets (mmHg)				
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)

*reported as Mean (SD); $ safety: n=26 for CLV, n=26 for SOC; mITT: n=23for CLV, n=22 for SOC

Table 2. IV Antihypertensive Study Drug Dosing (safety population)

Time Frame	Drug Name (n), dosing unit	Mean of Individual Pt Median Infusion Rates (SD)	Infusion Rates, Min/Max	Total Dose Administered, Mean (SD), (mg)
Initiation of study drug to 30 minutes	Clevidipine (51), mg/hr	6.4 (3.4)	1.0/16.0	4.6 (3.1)
	Standard-of-Care Medications			
	Nitroglycerin (30), mcg/min	40.8 (40.9)	3.3/200	1.3 (1.4)
	Nicardipine (16), mg/hr	6.2 (2.6)	1.0/10.0	3.2 (1.4)
	ISDN (4), mg/hr	180.5 (254.1)	1.0/540	4.75 (4.9)
	Hydralazine (1), mg	n/a	n/a	20 (single bolus)
	Diltiazem (1), mg	n/a	n/a	5 (single bolus)
	Nitroprusside (1), mcg/min	13.3	13.3/13.3	0.4
From 30 minutes until infusion stopped	Clevidipine (51), mg/hr	7.6 (5.4)	1.0/24.0	26.4 (36.9)
	Standard-of-Care Medications			
	Nitroglycerin (30), mcg/min	65 (60)	3.3/233	55.3 (97.5)
	Nicardipine (16), mg/hr	8.2 (4.0)	1.0/15.0	15.4 (13.0)
	ISDN (4), mg/hr	61 (103.3)	1.0/ 180	12.01 (4.8)
	Hydralazine (1), mg	n/a	n/a	n/a
	Diltiazem (1), mg	10	10/10	38.7
	Nitroprusside (1), mcg/min	13.3	13.3/13.3	3.0

	Drug Name (n)	Median Duration (hrs) 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	

1 n/a = not applicable

2

Table 3. Study Drug Related Treatment-Emergent Adverse Events (safety population)

Category	**CLV (n=51)**	**SOC (n=53)**	**Total (n=104)**
Number (%) of patients with at least one 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)

Figure 1. Time to Achieve TBPR within 30 Minutes (AHF population)

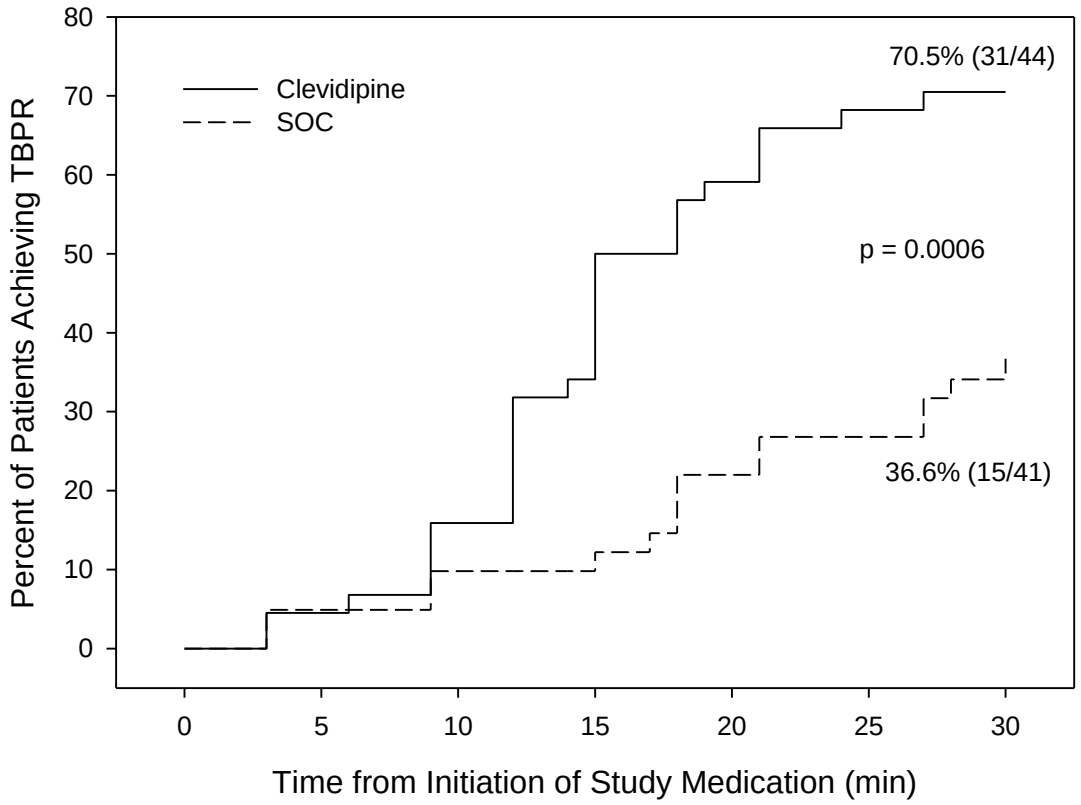
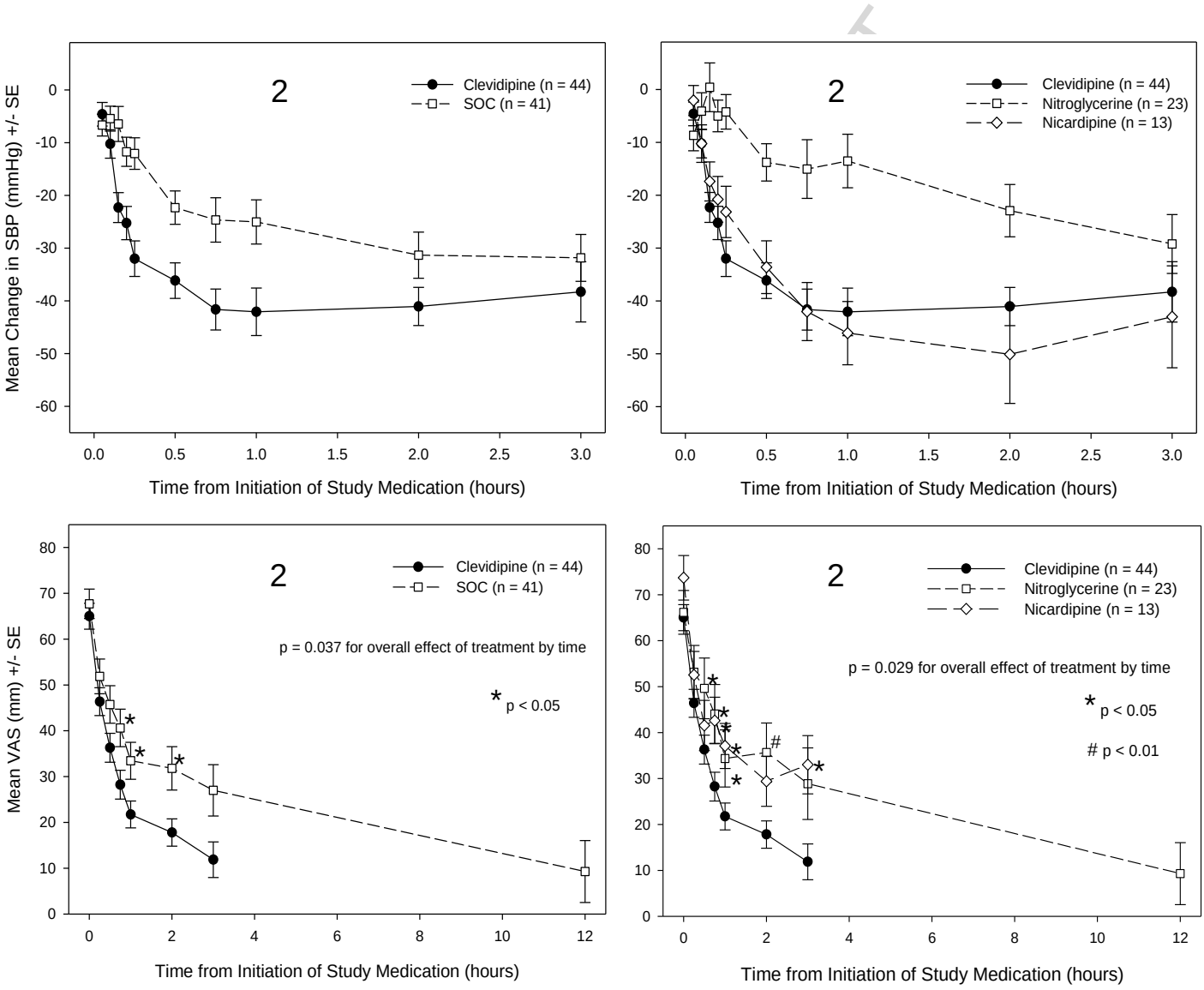


Figure 2. A and B: Mean Change in SBP during the First 3 Hours of Study Drug Administration. C and D: Mean VAS for First 12 hours of Study Drug Administration. (AHF population)



References

[1] Cotter G, Moshkovitz Y, Milovanov O, et al ; Acute heart failure: a novel approach to its pathogenesis and treatment. Eur J Heart Fail 2002; 4:227-34.

[2] Gheorghiade M, Zannad F, Sopko G, et al; International Working Group on Acute Heart Failure Syndromes. Acute heart failure syndromes: current state and framework for future research. Circulation 2005; 112:3958-68.

[3] Mebazaa A, Gheorghiade M, Piña IL, et al. Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. Critical Care Med 2008; 36(1 Suppl):S129-S139.

[4] Filippatos G and Zannad F. An Introduction to acute heart failure syndromes: definition and classification. Heart Fail Rev 2007; 12:87-90.

[5] Kirk JD, Filippatos G, Gheorghiade M, et al, for the Society of Chest Pain Centers Acute Heart Failure Committee. Acute heart failure treatment. Crit Pathways in Cardiol 2008; 7:103-10.

[6] Ander DS, Maisel A, Hollander JE, et al; Society of Chest Pain Centers Recommendations for the evaluation and management of the observation stay acute heart failure patient: a report from the Society of Chest Pain Centers Acute Heart Failure Committee. Crit Pathway in Cardiol 2008; 7:83-121.

[7] Adams KF Jr, Fonarow GC, Emerman CL, et al, for the ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the

first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005; 149:209-16.

[8] Weintraub NL, Collins SP, Pang PS, et al; Acute heart failure syndromes. emergency department presentation, treatment, and disposition: current approaches and future aims: a scientific statement from the American Heart Association.
American Heart Association Council on Clinical Cardiology and Council on Cardiopulmonary,Critical Care, Perioperative and Resuscitation. Circulation. 2010 Nov 9;122(19):1975-96.

[9] Nieminen MS, Böhm M, Cowie MR, et al; Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: The Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2005; 26:384-416.

[10] Wuerz RC, Meador SA. Effects of prehospital medications on mortality and length of stay in congestive heart failure. Ann Emerg Med 1992; 21:669-74.

[11] Levy P, Compton S, Welch R, et al. Treatment of severe decompensated heart failure with high-dose intravenous nitroglycerin: a feasibility and outcome analysis. Ann Emerg Med 2007; 50:144-52.

[12] Cotter G, Moshkovitz Y, Kaluski E, et al; The role of cardiac power and systemic vascular resistance in the pathophysiology and diagnosis of patients with acute congestive heart failure. Eur J Heart Fail 2003; 5:443-51.

[13] Haber HL, Simek CL, Bergin JD, et al; Bolus intravenous nitroglycerin predominantly reduces afterload in patients with excessive arterial elastance. J Am Coll Cardiol 1993; 22:251-7.

[14] Rhoney D, Peacock WF. Intravenous therapy for hypertensive emergencies. Part I. AJHP 2008; 66(15):1343-52.

[15] Nordlander M, Sjoquist PO, Ericsson H, et al; Pharmacodynamic, pharmacokinetic and clinical effects of clevidipine, an ultrashort-acting calcium antagonist for rapid blood pressure control. Cardiovasc Drug Rev 2004; 22:227-50.

[16] Mebazaa A, Pang PS, Tavares M, et al; The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. Eur Heart J 2010; 31, 832–41.

[17] Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA 2002; 287(12):1531-40.

[18] Pang PS, Cleland JG, Teerlink JR, et al; for the Acute Heart Failure Syndromes International Working Group. A proposal to standardize dyspnoea measurement in clinical trials of acute heart failure syndromes: the need for a uniform approach. Eur Heart J 2008; 29: 816-24.

[19] Maisel AS, Peacock WF, McMullin N, et al; Timing of immunoreactive B-type Natriuretic Peptide levels and treatment delay in acute decompensated heart failure: an ADHERE (Acute Decompensated Heart Failure National Registry) analysis. J Am Coll Cardiol 2008; 52:534-40.

[20] Peacock, WF, Emerman C, Costanzo MR, et al; Early vasoactive drugs improve heart failure outcomes. Congestive Heart Failure 2009; 15:256-64.

[21] Hunt SA, Abraham WT, Chin MH, et al; 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009; 119:e391– e479

[22] Lindenfeld J, Albert NM, Boehmer JP, et al; HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail 2010; 16:e1-194.

[23] McMurray JJ, Adamopoulos S, Anker SD, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Heart Journal 2012; 33: 1787–1847.

[24] Metra M, Teerlink JR, Felker GM, et al. Dyspnoea and worsening heart failure in patients with acute heart failure: results from the Pre-RELAX-AHF study. Eur J Heart Fail 2010; 12:1130-9.

[25] Metra M, Cleland JG, Weatherley BD, et al; Dyspnoea in patients with acute heart failure: an analysis of its clinical course, determinants, and relationship to 60-day outcomes in the PROTECT pilot study. Eur J Heart Fail 2010; 12:499-507.

[26] Metra M, O'Connor CM, Davison BA, et al; Early dyspnoea relief in acute heart failure: prevalence, association with mortality, and effect of rolofylline in the PROTECT Study. Eur Heart J 2011; 32:1519-34.

[27] Lloyd-Jones D, Adams RJ, Brown TM, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics—

2010 Update A Report From the American Heart Association. Circulation. 2010;121:e46-e215.

[28] Pohar B, Horvat M. Influence of hemodynamic changes on neuroendocrine response in acute heart failure. Int J Cardiol 1997; 60:263–71.

[29] Sato Y, Takaysu Y, Kataoka K, et al. Serial circulating concentrations of C-reactive protein, Interleukin (IL)-4 and IL-6 in-patients with acute left heart decompensation. Clin Cardiol 1999;22:811–3.