Use of Nitroglycerin by Bolus Prevents ICU Admission in Patients with Acute Hypertensive Heart Failure

Suprat Saely Wilson PharmD, BCPS, Gregory M. Kwiatkowski PharmD, BCPS, Scott R. Millis PhD, ABPP, CStat, PStat®, John D. Purakal MD, Arushi P. Mahajan, Phillip D. Levy MD, MPH

PII: S0735-6757(16)30734-3
DOI: doi: 10.1016/j.ajem.2016.10.038
Reference: YAJEM 56211

To appear in: *American Journal of Emergency Medicine*

Received date: 17 September 2016
Revised date: 11 October 2016
Accepted date: 13 October 2016

Please cite this article as: Wilson Suprat Saely, Kwiatkowski Gregory M., Millis Scott R., Purakal John D., Mahajan Arushi P., Levy Phillip D., Use of Nitroglycerin by Bolus Prevents ICU Admission in Patients with Acute Hypertensive Heart Failure, *American Journal of Emergency Medicine* (2016), doi: 10.1016/j.ajem.2016.10.038

Title of Manuscript:
Use of Nitroglycerin by Bolus Prevents ICU Admission in Patients with Acute Hypertensive Heart Failure

Authors List:
Suprat Saely Wilson, PharmD, BCPS [a], Gregory M. Kwiatkowski, PharmD, BCPS [a,1], Scott R. Millis, PhD, ABPP, CStat, PStat® [b], John D. Purakal, MD [b, 2], Arushi P. Mahajan [b, 3], Phillip D. Levy, MD, MPH [b]

[a] Department of Pharmacy Services, Detroit Receiving Hospital/Detroit Medical Center. 4201 St. Antoine Blvd. 1B-UHC, Detroit, MI 48201 USA
[b] Department of Emergency Medicine and Cardiovascular Research Institute, Wayne State University School of Medicine. 4201 St. Antoine Blvd. 6G Detroit, MI 48201 USA

Present Address
[1] Spectrum Health Butterworth Hospital. MC001 100 Michigan St. NE Grand Rapids, MI 49503
[2] 1720 S. Michigan Ave Unit 2718 Chicago, IL 60616
[3] 600 E. Madison Street Ann Arbor, Michigan 48109-1372

Corresponding Author:
Phillip D. Levy, MD, MPH
Professor of Emergency Medicine
Department of Emergency Medicine, Wayne State University School of Medicine
Cardiovascular Research Institute, Wayne State University School of Medicine
4201 St. Antoine Blvd. 6G
Detroit, MI 48201 USA
Phone: +1-313-933-8558
Fax: +1-313-993-8126
Email: plevy@med.wayne.edu

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Keywords:
Nitroglycerin
Bolus nitroglycerin
Resource utilization
Acute heart failure

Prior Presentations:
Results of this research has been presented at the 2012 ACEP Scientific Assembly Research Forum in Denver, CO; October 9, 2012.

Running Title: IV Bolus Nitroglycerin for Acute Heart Failure

ABSTRACT:

Objectives: The purpose of this study was to compare healthcare resource utilization among patients who were given intravenous (IV) nitroglycerin for acute heart failure (AHF) in the emergency department (ED) by intermittent bolus, continuous infusion, or a combination of both.

Methods: We retrospectively identified 395 patients that received nitroglycerin therapy in the ED for the treatment of AHF over a 5-year period. Patients that received intermittent bolus (n=124) were compared to continuous infusion therapy(n=182) and combination therapy of bolus and infusion(n=89). The primary outcomes were the frequency of intensive care unit (ICU) admission and hospital length of stay (LOS).

Results: On unadjusted analysis, rates of ICU admission were significantly lower in the bolus versus infusion and combination groups (48.4% vs. 68.7% vs. 83%, respectively; p<0.0001) and median LOS (IQR) was shorter (3.7 (2.5 to 6.2 days)) compared to infusion (4.7 (2.9 to 7.1 days)) and combination (5.0 (2.9, 6.7 days)) groups; p = 0.02. On adjusted regression models, the strong association between bolus nitroglycerin and reduced ICU admission rate remained, and hospital LOS was 1.9 days shorter compared to infusion therapy alone. Use of intubation (bolus 8.9% vs. infusion 8.8% vs. combination 16.9%; p = 0.096) and BiPAP (bolus 26.6% vs. 20.3% infusion vs. combination 29.2%; p=0.21) were similar as was the incidence of hypotension, myocardial injury, and worsening renal function.

Conclusions: In ED patients with AHF, IV nitroglycerin by intermittent bolus was associated with a lower ICU admission rate and a shorter hospital LOS compared to continuous infusion.

Keywords:
Nitroglycerin
Bolus nitroglycerin
Resource utilization
Acute heart failure

Abbreviations:
AHF = acute heart failure
LOS = length of stay
ICU = intensive care unit
ED = emergency department
IV = intravenous
eMAR = electronic medical record
BiPAP = bi-level positive airway pressure
HF = heart failure
SBP = systolic blood pressure
DBP = diastolic blood pressure

INTRODUCTION

Vasodilators are considered one of the mainstay therapies of acute heart failure (AHF) management. For hypertensive AHF patients, existing guidelines recommend the use of vasodilators to provide preload and afterload reduction [1-4]. Although, vasodilators improve hemodynamics and symptoms in such patients, they provide no apparent benefit on mortality or hospital readmissions [5-7]. For hypertensive AHF, nitroglycerin is the vasodilating agent of choice and when given intravenously (IV), is typically administered as a continuous infusion (dose range 5-400 mcg/min). However, continuous infusions of nitroglycerin have been associated with increased healthcare costs and hospital length of stay (LOS) leading to questions about their utility in management of AHF [6].

When administered in higher doses by intermittent bolus, nitrates result in greater arterial dilation and more substantial reduction in cardiac afterload leading to favorable changes in central pressure dynamics [8,9]. Existing trial data on the use of bolus, high dose nitrates suggest that such hemodynamic effects may be accompanied by lower rates of endotracheal intubation, myocardial infarction, and intensive care unit (ICU) admission [10-12] but the real-world impact of this approach on resource utilization has not been evaluated.

Based on prior work by our research group supporting the use of bolus nitroglycerin therapy [12], its use has become routine in clinical practice as part of the management of dyspneic, ED patients with hypertensive AHF at our institution. Accordingly, we designed the present study to examine the impact of intermittent bolus nitroglycerin therapy on resource utilization, specifically ICU

admission rate and hospital LOS. We hypothesized that administration of nitroglycerin by intermittent bolus would be associated with a lower rate of ICU admission and shorter hospital LOS when compared to continuous infusion.

METHODS

Study Design

This was a retrospective observational cohort study of intravenous nitroglycerin use in ED patients with AHF. This study protocol was approved by Wayne State University institutional review board prior to initiation with waiver of need for informed consent.

Study Setting and Population

All included patients were treated in the ED of Detroit Receiving Hospital, a university-affiliated, urban teaching hospital and is part of the Detroit Medical Center and serves a predominantly African American population in the metropolitan area of Detroit, Michigan for AHF between January 1, 2007 and July 31, 2011. During the study period, Detroit Receiving Hospital had an annual ED census of approximately 100,000 visits, and an average of 1,400 yearly AHF admissions.

Study Protocol

Patients older than 18 years of age who were treated in the ED for AHF as documented in the treatment note and received IV nitroglycerin were included.

Potentially eligible patients were identified by a query of electronic pharmacy orders, enabling comprehensive capture of every patient that received IV nitroglycerin during the study period, regardless of the manner of administration. Once identified, ED treatment notes were reviewed and complete records for those patients with a final primary ED diagnosis of AHF who had specific documentation of AHF as the reason for treatment with nitroglycerin were abstracted. Patients were included only if IV nitroglycerin was started in the ED as documented in the electronic medication administration record (eMAR). Patients were excluded if they were pregnant, had IV nitroglycerin orders but not documented as given on the eMAR or received nitroglycerin for other indications such as acute coronary syndrome, blood pressure management or hypertensive emergency not related to AHF. While there is no clinical protocol for treatment of AHF with IV nitroglycerin at our facility, it is typically reserved for patients with elevated blood pressure (> 160 mm Hg) who have marked dyspnea. When administered by bolus, 10 mg of nitroglycerin is prepared in a 10 mL syringe and given by IV push in increments up to 2 mg every 3-5 min. Nitroglycerin infusions are prepared and administered in a usual clinical manner, with starting dose and titration parameters set by the treating physician. Hospital policy mandates ICU admission for any patient on a titratable vasoactive infusion (nitroglycerin included) at the time of disposition; patients who received IV boluses or who were on infusions in the ED that were discontinued could be admitted to non-ICU settings.

Electronic medical records were reviewed and study variables including demographic information, comorbidities, baseline medications, hemodynamic data, and laboratory values were abstracted. Ejection fraction was recorded if documented in the treatment note or available via echocardiography report within the 12 months preceding the index visit. Nitroglycerin use variables were abstracted from the eMAR and nursing care flow sheets. Information collected included the dose and number of nitroglycerin boluses given as well as starting rate and maximum rate for continuous infusions. Hemodynamic variables such as blood pressure measurements and heart rate along with respiratory rate, and pulse oximetry during the first 180 minutes of presentation were also collected.

Data on disposition from the ED (admission to ICU or non-ICU setting), LOS (ED, ICU, total hospital), and need for airway management in the ED (bi-level positive airway pressure [BiPAP] or endotracheal intubation) were recorded. Length of stays was abstracted from the hospital's bed tracking status application. Heart failure specific hospital readmission rates through 30 days were also tracked using the electronic medical record (which captures visits to any of four hospitals that comprise the Detroit Medical Center system in the metropolitan area of Detroit, MI), using date of discharge as time 0. The investigators were not blinded to the purpose of the study. Charts were reviewed by a resident physician, a pharmacist, and a medical student. All data abstracted by the medical student was then reviewed by the pharmacist investigator. All discrepancies between the medical student and the pharmacist abstractions were adjudicated by consensus of all three reviewers. Abstractors were trained

by the principal investigator using a single data dictionary that contained definitions for each variable and coded response to be entered on the standardized abstraction form to ensure uniform data collection and accuracy. Abstractors were trained by the principal investigator using a single data dictionary that contained definitions for each variable and coded response to be entered on the standardized abstraction form to ensure uniform data collection and accuracy. Missing data were coded as not available and any uncertainty regarding data variables or coding were reconciled by the principal investigator.

Outcome Measures

All patients in the study were analyzed for characterization of the treatment course in the ED. The primary outcome variables of interest were the need of ICU admission, defined as admitted to the ICU from the ED, and hospital LOS. Patients who were evaluated by the ICU team but not admitted to the ICU were classified as not requiring ICU admission. The main secondary outcomes were the ED and ICU LOS, and the incidence of adverse events including: hypotensive episodes, defined as SBP < 90 mmHg at any time during the first 180 minutes post nitroglycerin administration; incidence of acute myocardial injury, defined as an increase in cardiac troponin of at least 0.25 ng/ml within the first 24 of presentation; and interval development or worsening of renal dysfunction, determined by an increase in serum creatinine by 0.5 or more during the first 24 and 48 hours of presentation. Other outcomes included the rates of mechanical ventilation and BiPAP use in the ED.

Data Analysis

Included patients were categorized into three groups: 1) bolus nitroglycerin group (Bolus), which included patients who received one or more intermittent bolus doses ≥ 0.5 mg of IV nitroglycerin; 2) continuous infusion of nitroglycerin group (Infusion), which included those who received a continuous infusion of IV nitroglycerin without any administration of intermittent nitroglycerin bolus doses; and 3) combination of intermittent bolus and continuous infusion of IV nitroglycerin group (Combination), which included those that received both bolus followed by continuous dosing of IV nitroglycerin. Baseline characteristics were analyzed using descriptive statistics and reported as proportions, mean (standard deviations [SD]) or median (interquartile range [IQR]) when appropriate. Categorical variables were analyzed chi-square test. Analyses of continuous variables were compared using an unpaired *t*-test, Wilxocon test, Kruskal-Wallis test or one-way ANOVA as appropriate. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant. Stata 14.1 was used for all analyses.

As this study was observational (i.e., patients were not randomly assigned to treatment), standard methods to compare the three groups could not be used because of potential bias in treatment assignment. To approximate the causal effect of differing treatments on ICU admission and hospital LOS, we used a treatment-effects estimator. Stata offers six different treatment-effects estimators to address nonrandom treatment assignment. Under correct model specification,

all the estimators generally produce similar results. Regression adjustment uses contrasts of averages of treatment-specific predicted outcomes to estimate treatment effects and was chosen here as it is a natural base-case estimator when one knows some of the determinants of the outcome. Unlike propensity score matching and nearest-neighbor matching, regression adjustment can also handle more than two groups making it appropriate for a three group comparison. The following covariates were used in our regression adjustment as they may influence both the decision to use different treatments and both primary outcome measures: age, gender, race, initial troponin, initial brain natriuretic peptide (BNP), initial systolic blood pressure (SBP), initial heart rate, initial respiratory rate, initial oxygen saturation, past medical history of chronic heart failure (HF), past medical history of hypertension, use of BiPAP and use of mechanical ventilation. As ICU admission was a binary outcome, logistic regression was used as the functional form. Length of stay was treated as a count variable with use of a Poisson functional form.

Based on our 2007 paper that showed an absolute reduction in the ICU admission rate of approximately 40% with bolus IV nitroglycerin (12), a minimum of 71 patients per group were needed to have 90% power to detect an equivalent or greater effect size, with a 0.05 two-sided significance level.

RESULTS

A total of 1,227 patients were identified from our pharmacy electronic medication orders. Of these, 395 patients (124 Bolus; 182 Infusion; and 89

Combination) met the eligibility criteria based on review of ED treatment records and were included in the study (Figure). The most common reasons for exclusion were non-AHF indication for nitroglycerin and IV nitroglycerin ordered but not documented as given on the eMAR. Demographics and baseline clinical characteristics of study patients are summarized for all three study groups in Table 1. There were no significant differences among all three groups with respect to age, gender, or race with a majority of the study patients being African American. Initial SBP and diastolic blood pressure (DBP) were significantly higher in the Combination group. There were a total of 4 patients that had initial systolic blood pressure ≤ 100 mm/Hg that received nitroglycerin therapy (2 in bolus group, 1 in infusion group and 1 in combination group). Patients that received continuous therapy of nitroglycerin alone had significantly lower baseline respiratory rate than the other two groups. Bolus patients were more likely to have a history of chronic HF, chronic obstructive pulmonary disease (COPD), and atrial fibrillation, and were more likely to be on guideline directed medical therapy for chronic HF (Table 2).

In the Bolus group, the median (IQR) total dose of nitroglycerin was 2 (1, 2) mg; 79% of patients received one dose, 14.6% received two doses, 4% received three doses, and three patients received at least four doses of bolus nitroglycerin. One patient received 10 repeat doses of bolus nitroglycerin for a total of 20 mg. The median (IQR) starting rate of nitroglycerin infusion in the Infusion group was 20 (10, 30) mcg/min with a maximum rate of 35 (20, 50) mcg/min. In the Combination group, the median (IQR) dose of the boluses was 2

(2,4) mg, with 40.5% receiving one dose, 28.1% two doses, 9% receiving three doses, and 12.4% received four or more nitroglycerin boluses. The median (IQR) starting rate of nitroglycerin infusion was 20 (10, 40) mcg/min and the maximum rate was 60 (30,100) mcg/min in these patients. The median (IQR) duration of nitroglycerin infusion therapy was 16 (5.2, 41.5) hours in the Infusion group and 16.5 (5, 38.9) hours in the Combination group. Similar proportions of patients received at least one dose of IV furosemide (70.2% Bolus vs. 75.8% Infusion vs. 73% Combination; p=0.54) with a median (IQR) initial furosemide dose of 60 (40, 80) mg in the Bolus vs. 60 (40, 80) mg in the Infusion group vs. 60 (40, 80) mg in Combination (p=0.76). Hemodynamic and respiratory effects over the first 180 minutes post nitroglycerin administration are shown in an online appendix.

Primary and secondary outcomes are presented in Table 3. In the unadjusted analysis, patients who received nitroglycerin bolus therapy alone were significantly less likely to require ICU admission (48.4% vs. 68.7% Infusion vs. 83% Combination; p<0.0001) and median (IQR) total hospital LOS was significantly shorter: Bolus = 3.7(2.5, 6.2) days; Infusion = 4.7 (2.9, 7.1) days; and Combination = 5.0 (2.9, 6.7) days; p=0.02. There were no differences in the duration of ED or ICU LOS among the study groups. The rates of mechanical ventilation were statistically similar but there was a trend toward higher rates in the Combination group (16.9% vs. 8.9% Bolus vs. 8.8% Infusion, p=0.096). The use of BiPAP were also similar across all groups (p=0.21). In-hospital mortality rate was similar as well (2 (1.7%) Bolus group vs. 7 (4%) Infusion group vs. 3

(3.5) Combination group; p=0.52) but hospital readmission within 30 days was significantly higher among in the Infusion group (65% vs. 33% Bolus vs. 28.5% Combination group; p=0.001).

Table 4 describes the incidence of adverse events. Overall, there were no differences in the rates of hypotension, myocardial injury, or worsening renal function between the three groups. None of the patients that had initial SBP ≤100 mmHg experienced hypotension.

In the logistic regression model, probability of being admitted to the ICU was 48% in the Bolus group, compared to 67% for the Infusion group and 79% for the Combination group. The difference between Bolus and Infusion groups was statistically significant (p = 0.006), but no difference was found between the Combination and Infusion groups (p = 0.052). In the Poisson regression model, patients in the Bolus group had an average hospital LOS of 4.4 days compared to 6.3 days for the Infusion group and 7.3 days for the Combination group. Again, there was a statistically significant difference in hospital LOS between Bolus and Infusion groups (p = 0.01) but not between Combination and Infusion groups (p = 0.27). Because COPD prevalence was different between groups, we re-ran the models including adjustment for COPD. While our logistic regression model for ICU admission failed to converge due to the low overall prevalence (19%) of COPD in our study cohort, the Poisson model evaluating LOS was stable, with no impact of COPD on outcome. We then analyzed our data excluding patients with a history of COPD and the unadjusted rate of ICU admission remained lower in the Bolus group (43.7% vs. 68.2% Infusion vs.

83.1% Combination; p <0.0001). To enable convergence, we compared the Bolus group with a pooled group including both Infusion and Combination patients, and found a statistically significant absolute reduction in the ICU admission rate among Bolus patients of 25% (p=0.001). Using the same approach, we did not find a significant difference in hospital LOS between Bolus (5.1 days) and Infusion/Combination therapy (6.5 days); p=0.054.

DISCUSSION

Based on this retrospective analysis, intermittent bolus nitroglycerin is a viable alternative to continuous infusion in patients with AHF, providing similar clinical effectiveness with a 20-30% reduction in the need for ICU admission and a decrease in hospital LOS of 2-3 days. Because this was a retrospective study with unbalanced cohorts, we used the adjusted models to accounted for confounders that were clinically relevant variables such as age, gender, race, biomarkers of myocardial stress and injury, baseline blood pressure, oxygenation status, and use of accessory ventilatory support, as well as underlying history of chronic HF and found that the association between bolus nitroglycerin and improved resource utilization was maintained. While we did not adjudicate the determination of AHF, relying instead on what was reported by the treating clinician in the medical record, there was stability in our findings related to both ICU admission rate and LOS with exclusion of (and accounting for) COPD patients, making it less likely that group differences were due to misdiagnosis of undifferentiated dyspnea.

We acknowledge that at least some of this difference reflects the requirement for ICU admission in patients on titratable vasoactive infusions at our hospital. However, in institutions such as ours where a nitroglycerin or other vasoactive infusion mandates admission to the ICU, such admission could be avoided by use of bolus administration rather than a continuous infusion of nitroglycerin. As nitroglycerin confers no direct benefit on mortality or other hard end-points when used to treat AHF, our findings challenge the use of continuous nitroglycerin infusions, suggesting that they can be safely and effectively supplanted using a bolus approach.

These data support our earlier work that showed a reduction in ICU admission with intermittent bolus nitroglycerin; however, unlike that study, we did not find any clear benefit on the rates of mechanical ventilation or BiPAP with the use of intermittent bolus therapy [12]. While this difference may be attributable to the lower total dose of bolus nitroglycerin used by clinicians in this analysis (median 2 mg vs median 6 mg), present results reflect real-world practice and a dosing regimen that was based solely on clinical need as determined by the treating physician.

Though not tracked in prior study, use of combination therapy with intermittent bolus followed by continuous infusion was also associated with a lower rate of AHF specific readmission within 30 days compared to the use of bolus nitroglycerin or infusion therapy alone. Whether this signals a true treatment effect or a consequence of treatment-propensity related bias is not clear. Patients that received combination therapy were less likely to have a

history of chronic HF and, as such, might inherently be at lower risk for post-discharge adverse events. That said, they were also more hypertensive and tachypneic at presentation than the other two cohorts, potentially indicating a more severe acute disease with a greater degree of respiratory distress, thus requiring a more aggressive therapy with combination of bolus and continuous infusion. Despite this, there was no significant difference in the rates of intubation or BiPAP compared to other groups, suggesting that intermittent bolus nitroglycerin may provide clinical benefit above and beyond an infusion alone approach in patients with more severe clinical manifestations without additional adverse events.

In addition to effectiveness signals, we found no statistical difference in adverse event rates, including the incidence of hypotension or myocardial injury with the use of intermittent bolus nitroglycerin, either alone or in combination with a continuous infusion. In fact, 2 patients in the bolus group had initial blood pressures of 84/55 and 96/69 received 1 and 2 mg of bolus nitroglycerin with no adverse events. This was potentially a concern with the use of high doses of nitroglycerin given that previous evidence indicated a decrease in myocardial blood flow in patients with coronary heart disease given sublingual nitroglycerin [13] Combined with prior literature [10,12], our results suggest that bolus nitroglycerin can be safely used alone or in combination with standard continuous infusion of IV nitroglycerin in patients with AHF.

LIMITATIONS

This study has several limitations. First, it was based on clinical data derived from a single institution that serves an urban population in the metropolitan area of Detroit. Therefore, our study, which was almost 90% African American, and related findings (especially the in-hospital mortality rate) may not be generalizable to a more heterogeneous HF population. Our institution also serves a predominantly under resourced community and many of our patients are unable to obtain prescriptions or accurately describe their medications, which makes it difficult to accurately capture such data. As a result, patients in our study have lower reported usage of HF guideline directed medical therapy such as angiotensin-converting-enzyme inhibitor, angiotensin II receptor blockers, beta-blockers, and loop-diuretics. However, as we focused on immediate interventions and in-hospital outcomes, home medications are less likely to have had an impact on our targeted end-points. The retrospective nature of our study could pose bias as well, as investigators were not blinded to outcome when extracting data. Misclassification for some data elements and the diagnosis of AHF itself may also have occurred since we relied solely on documentation as available in the electronic medical record. Similarly, the retrospective nature of our study limited our ability to perform complete data abstraction for some measures as information was incomplete or missing. Moreover, as we only had access to medical records from a single hospital system, 30-day readmission data may be an underestimate. Lastly, we only included patients who received nitroglycerin as part of routine AHF management, and thus cannot comment on the general effectiveness of nitroglycerin for AHF.

However, our goal was not to compare nitroglycerin with other AHF therapies, focusing instead on the route of administration when such therapy is clinically indicated.

CONCLUSIONS

When IV nitroglycerin is used to treat AHF, administration by intermittent bolus is associated with fewer ICU admissions and shorter hospital LOS compared to standard infusion therapy. Safety and effectiveness with a bolus approach is similar as well, challenging the need for continuous nitroglycerin infusions in the management of AHF, Such findings warrant study in a future prospective, randomized, multicenter trial .

Acknowledgments: None

REFERENCES

[1] Viau DM, Sala-Mercado JA, Spranger MD, O'Leary DS, Levy PD. The pathophysiology of hypertensive acute heart failure. Heart 2015;101:1861-7.

[2] McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14:803-69.

[3] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239.

[4] Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Laribi S, et al. Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. Eur J Heart Fail 2015;17:544-58.

[5] Ho EC, Parker JD, Austin PC, Tu JV, Wang X, Lee DS. Impact of Nitrate Use on Survival in Acute Heart Failure: A Propensity-Matched Analysis. J Am Heart Assoc 2016;5.

[6] Gradman AH, Vekeman F, Eldar-Lissai A, Trahey A, Ong SH, Duh MS. Is addition of vasodilators to loop diuretics of value in the care of hospitalized acute heart failure patients? Real-world evidence from a retrospective analysis of a large United States hospital database. J Card Fail 2014;20:853-63.

[7] Alexander P, Alkhawam L, Curry J, Levy P, Pang PS, Storrow AB, et al. Lack of evidence for intravenous vasodilators in ED patients with acute heart failure: a systematic review. Am J Emerg Med 2015;33:133-41.

[8] Kelly RP, Gibbs HH, O'Rourke MF, Daley JE, Mang K, Morgan JJ, et al. Nitroglycerin has more favourable effects on left ventricular afterload than

apparent from measurement of pressure in a peripheral artery. Eur Heart J 1990;11:138-44.

[9] Munir S, Guilcher A, Kamalesh T, Clapp B, Redwood S, Marber M, et al. Peripheral augmentation index defines the relationship between central and peripheral pulse pressure. Hypertension 2008;51:112-8.

[10] Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet 1998;351:389-93.

[11] Sharon A, Shpirer I, Kaluski E, Moshkovitz Y, Milovanov O, Polak R, et al. High-dose intravenous isosorbide-dinitrate is safer and better than Bi-PAP ventilation combined with conventional treatment for severe pulmonary edema. J Am Coll Cardiol 2000;36:832-7.

[12] Levy P, Compton S, Welch R, Delgado G, Jennett A, Penugonda N, 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.

[13] Cohn PF, Maddox D, Holman BL, Markis JE, Adams DF, See JR, et al. Effect of sublingually administered nitroglycerin on regional myocardial blood flow in patients with coronary artery disease. Am J Cardiol 1977;39:672-8.

Table 1: Demographic and baseline clinical characteristics

	Bolus (n=124)	Infusion (n=182)	Combination (n=89)	p-value
Age (yr)	56 (27, 71)	56 (49, 69)	57 (49, 68)	0.70
Male	61 (49.6)	99 (54.4)	42 (47.2)	0.49
African American	109 (87.9)	161 (88.5)	79 (88.8)	0.41
Ejection fraction on admission (%)	35 (20, 55) (n=98)	30 (20, 50) (n=131)	35 (20, 55) (n=70)	0.23
Baseline brain natriuretic peptide (pg/ml)	1685 (618, 4013) (n=118)	1839 (840, 3785) (n=171)	2100 (784, 2663) (n=86)	0.063
BUN, initial (mg/dL)	19 (14, 28)	21 (15, 32)	21 (13, 42)	0.73
Scr, initial (mg/dL)	1.2 (1.0, 2.0)	1.3 (1.1, 2.1)	1.4 (1.0, 3.1)	0.14
Troponin, initial (ng/ml)	0.11 (0.05, 0.32)	0.06 (0.04, 0.14)	0.09 (0.05, 0.20)	0.0018

Initial vital signs				
SBP (mm Hg)	186 (169, 212)	184 (159, 210)	206 (186, 231)	<0.001*
DBP (mm Hg)	110 (95, 121)	110 (92, 125)	120 (106, 139)	0.003*
Heart rate (bpm)	108 (92, 128) (n=119)	107 (94, 120) (n=179)	117 (98, 128) (n=89)	0.13
Pulse oxygenation (%)	95 (88, 98) (n=122)	97 (92, 99) (n=168)	95 (89, 98) (n=81)	0.17
Respiratory rate (breaths per minute)	24 (20, 32) (n=119)	22 (18, 28) (n=175)	28 (21, 34) (n=85)	<0.001†

Continuous data are presented as median (IQR); categorical data are presented as n (%)

BUN = blood urea nitrogen; Scr = serum creatinine; SBP = systolic blood pressure; DBP=diastolic blood pressure

*No statistical difference between high dose bolus and continuous infusion nitroglycerin groups

†No statistical difference between high dose bolus nitroglycerin and HD + infusion groups

Table 2: Patient Medical and Medication History

	Bolus (n=124)	Infusion (n=182)	Combination (n=89)	p-value
Past medical history				
Atrial Fibrillation	16 (13.0)	5 (2.7)	3 (3.4)	0.001
Coronary Artery Disease	22 (17.7)	30 (16.5)	11 (12.4)	0.55
Chronic Kidney Disease	14 (11.3)	19 (10.4)	6 (6.7)	0.52
Chronic heart failure	89 (71.8)	96 (52.7)	40 (44.9)	<0.001
Chronic obstructive pulmonary disease	37 (29.8)	28 (15.4)	12 (13.5)	0.002
Diabetes mellitus	45 (36.6)	68 (37.4)	23 (25.8)	0.15
End stage renal disease	17 (13.7)	11 (6.0)	17 (19.1)	0.004

Hypertension	101 (81.5)	136 (74.7)	78 (87.6)	0.04
Myocardial Infarction	16 (12.9)	16 (8.8)	9 (10.1)	0.51
Stroke	3 (2.4)	8 (4.4)	4 (4.5)	0.63
Home medications				
ACE Inhibitor/ARB	54 (43.5)	71 (39)	28 (31.5)	0.20
Aspirin	52 (41.9)	54 (29.7)	19 (21.3)	0.005
Beta-Blocker	75 (60.5)	78 (42.9)	40 (44.9)	0.007
Digoxin	10 (8.1)	10 (5.5)	1 (1.1)	0.08
Hydralazine	20 (16.1)	22 (12.1)	13 (14.6)	0.59
Isosorbide Mononitrate/ Dinitrate	28 (22.6)	32 (17.6)	13 (14.6)	0.31
Loop Diuretic	55 (44.4)	60 (33)	21 (23.6)	0.006
Non-loop Diuretic	10 (8.1)	10 (5.5)	6 (6.7)	0.67
MRA	11 (8.9)	11 (6.0)	3 (3.4)	0.26

Data are reported as n (%)

ACE inhibitor = angiotensin-converting-enzyme inhibitor

ARB = angiotensin II receptor blockers

MRA = mineralocorticoid receptor antagonist

Table 3: Primary and secondary outcomes

	Bolus (n=124)	Infusion (n=182)	Combination	p-value			
				Overall	Bolus vs. Infusion	Bolus vs. Combination	Infusion vs. Combination
Primary outcomes:							
ICU admission	60 (48.4)	125 (68.7)	74 (83.0)	<0.0001	<0.0001	<0.0001	0.006
Hospital length of stay, days	3.7 (2.5, 6.2)	4.7 (2.9, 7.1)	5.0 (2.9, 6.7)	0.02	0.006	0.039	0.84
Secondary outcomes:							
ICU Length of stay, days	2.5 (1.6, 3.9) (n=56)	2.7 (1.3, 4.9) (n=124)	2.1 (1.2, 4.0) (n=75)	0.60	0.56	0.71	0.33
ED Length of stay, hours	6.4 (2.6, 14.1)	6.3 (4.0, 12.6)	5.9 (3.0, 10.9)	0.43	0.40	0.90	0.21
BiPAP rate	33 (26.6)	37 (20.3)	26 (29.2)	0.21	0.20	0.68	0.10
BiPAP duration, hours	3.9 (2.01, 13.6)	8.2 (3.5, 22.1) (n=37)	6.6 (3.6, 14.3) (n=26)	0.38	0.15	0.37	0.59

	(n=33)						
Mechanical ventilation rate	11 (8.9)	16 (8.8)	15 (16.9)	0.096	0.98	0.079	0.05
Length of mechanical ventilation, days	1.1 (0.6, 1.7)	1.1 (0.9, 2.0)	1.2 (0.9, 1.8)	0.79	0.98	0.65	0.53
Readmission for AHF within 30 days	17 (13.7)	43 (23.6)	4 (4.5)	0.001	0.001	0.736	0.01

Data are reported as n (%) or median (IQR)

ICU = intensive care unit

ED = emergency department

BiPAP = bi-level positive airway pressure

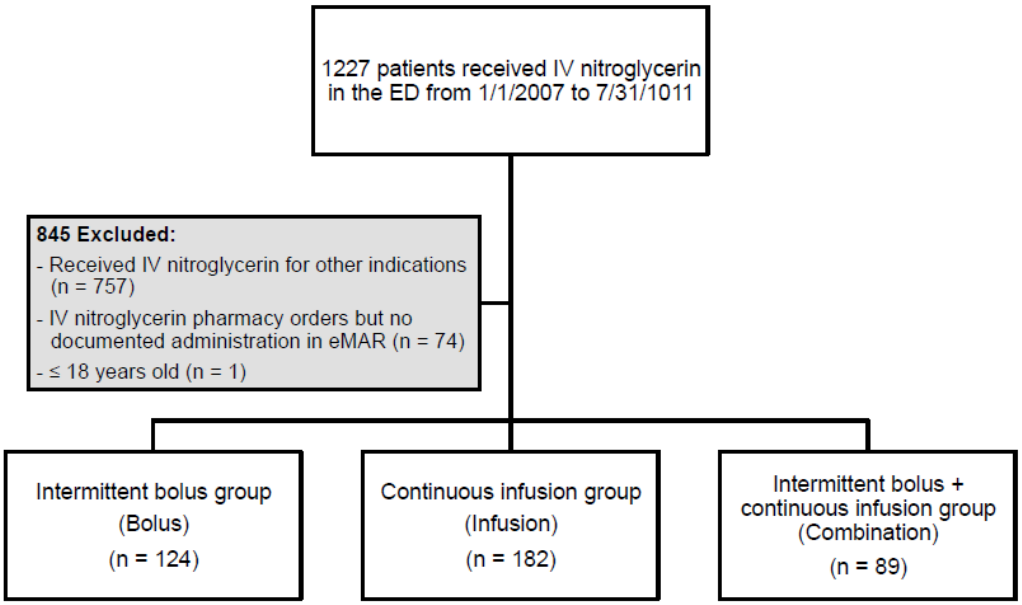
AHF = acute heart failure

Table 4: Adverse events

	Bolus (n=124)	**Infusion (n=182)**	**Combination (n=89)**	P-Value
Incidence of hypotension	2 (1.9) (n=108)	2 (1.3) (n=159)	5 (6) (n=82)	0.068
Incidence of myocardial injury on serial troponin measurement	11 (12.4) (n=89)	29 (17.2) (n=169)	10 (12.8) (n=78)	0.49
24 hour increase in Scr by ≥ 0.5	11 (11.7) (n=94)	14 (9.2) (n=152)	11 (1.3) (n=82)	0.59
48 hour increase in Scr by ≥ 0.5	8 (8.5) (n=94)	20 (12.9) (n=155)	5 (6.7) (n=75)	0.28
RIFLE criteria	(n=54)	(n=117)	(n=46)	0.13
0	46 (85.2)	109 (93.2)	37 (80.5)	
1	6 (11.1)	7 (6.0)	6 (13)	
2	2 (3.7)	1 (0.8)	3 (6.5)	

Data are reported as n (%)

Scr = serum creatinine



ED = emergency department. eMAR = electronic medication administration record

Figure 1: Flow Diagram for Patient Inclusion