IMPACT OF NESIRITIDE ON TREATMENT OF ACUTE DECOMPENSATED HEART FAILURE (ADHF): EVIDENCE FROM A U.S. HOSPITAL DATABASE

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ABSTRACT

OBJECTIVE: Compare impact of nesiritide (a recombinant natriuretic peptide approved for intravenous treatment of ADHF) administration within first day versus after first day on in-hospital outcomes using an inpatient claims database of 400+ US hospitals and 600,000+ discharges (PREMIER).

METHODS: From 681,690 discharges during 2003 and 2004 in the PREMIER database, we studied patients with DRG 127 at discharge and ICD 9 codes for primary diagnosis of CHF. First day nesiritide (D1) was defined as nesiritide + diuretic administration within 1st day of hospital admission; post-first-day administration (post-D1) was defined as nesiritide administration after first hospital day with diuretic therapy during first day. Four outcomes variables were analyzed: discharge status, hospital and ICU LOS, and hospitalization cost. Propensity matching and propensity covariate adjustments were performed in all regression analyses to remove bias in between-group comparisons.

RESULTS: In all, 8126 patient discharge episodes were identified as D1 and 793 as post-D1. The D1 group had reduced mortality odds versus post-D1 (0.46, 95% CI: 0.36, 0.59, $P<0.0001$). Hospital and ICU LOS were shorter for D1 versus post-D1 (–4.5 days [95% CI: –4.9, –4.2, $P<0.0001$] and –1.7 days [95% CI: –2, –1.5, $P<0.0001$], respectively). Hospital costs were lower for D1 patients (D1 – Post D1): –$6642 (95% CI: –$7226, –$6058, $P<0.0001$). Adjusted and unadjusted analyses on all four outcomes were consistent and achieved statistical significance.

CONCLUSION: This analysis demonstrated that in two groups of propensity-matched hospitalized patients, those treated with nesiritide within the first day of hospital admission have better outcomes than those treated with nesiritide later. These findings are based on retrospective data sources. A recently announced prospective randomized, controlled global clinical trial enrolling 7,000+ patients (ASCEND-HF) will provide additional information.

BACKGROUND

- An estimated 5 million Americans suffer from heart failure (HF), with 550,000 new cases diagnosed annually.[1]
- As the disease progresses, HF patients often require hospitalization for acutely decompensated heart failure (ADHF).[2]
- In fact, in persons over the age of 65 years, ADHF was the leading hospital discharge diagnosis in 2000.[3]
- In-hospital mortality is estimated between 4-8%, but varies between 2-22% depending on a patient's clinical presentation.[4,5]
- The estimated total costs (both direct and indirect) of HF in the US in 2006 were $29.6 billion, of which over 50% is estimated to be for hospital care.[1]
- The Heart Failure Society of America (HFSA) guidelines recommend that intravenous (IV) vasodilators (nesiritide, nitroglycerin, or nitroprusside) may be considered as adjunctive therapy in patients hospitalized for ADHF to rapidly alleviate symptoms of congestion and/or may be considered in patients with advanced HF who have persistent severe HF despite aggressive treatment with diuretics and standard oral therapies. Furthermore, the HFSA guidelines recommend that when adjunctive therapy for ADHF treatment in the absence of low cardiac output syndrome, vasodilators should be considered instead of IV inotropes.[6]
- Early goal-directed therapy employing the early use of IV vasoactive drugs, such as nesiritide, may improve patient outcomes.[7]

OBJECTIVES

- To assess the impact of early therapy with nesiritide on patient outcomes using a secondary data source.
- To compare patient outcomes between "early users" and "late users" by a propensity-matched regression analysis that can potentially reduce sample selection bias in the absence of randomization to treatment.

DEFINITIONS

- Early use: Use of nesiritide within 1st day of hospital admission
- Late use: Use of nesiritide after 1st day in addition to standard therapy
- Propensity score[8-12]: "The propensity score for an individual is the probability of being treated conditional on (based only on) the individual's covariate values. Intuitively, the propensity score is a measure of the likelihood that a person would have been treated using only their covariate scores"[8] and is estimated by a logistic regression. "Rosenbaum and Rubin[10] showed that the propensity score is a balancing score and can be used in observational studies to reduce bias using specific adjustment mechanisms (e.g. matching, covariate adjustment, or stratification)."[8]
- Matched analysis: Patients matched based on propensity score, similar to a case control study

DATA SOURCE

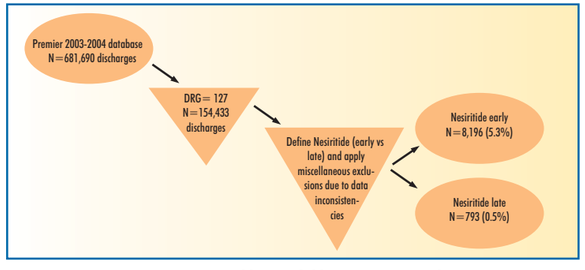
- Premier Perspective Comparative Database (PCD)*
- PCD is the nation's largest hospital drug utilization and financial database derived from detailed hospital discharge data, with limited patient-level data (see Methods below).
- The Perspective Comparative Database includes more than 500 acute care facilities and approximately 80 million patient records.
- The hospitals represent all geographical areas of the US, a broad range of bed sizes, teaching and non-teaching hospitals, and urban and rural facilities.
- Patient-level data go through 95 quality assurance and data validation checks.

*Source: http://www.premierinc.com/quality-safety/tools-services/prs/services/perspectiverx.jsp.
Database was accessed through a research contracting agreement between Premier Inc. and Scios Inc.

METHODS

Selection of Study Sample

- To be eligible for this analysis, patients must have met the following criteria:
  - Received study drugs (nesiritide and standard of care, which primarily includes diuretics, IV nitroglycerin)
  - Had a primary ICD-9 diagnosis of CHF: 402.01, 402.10, 402.11, 402.91, 404.01, 404.03, 404.11, 404.12, 404.13, 404.90, 404.91, 404.93, 428.0, 428.1, 428.9
  - Discharged from hospital with a DRG 127
  - Discharged from January 1, 2003, through December 31, 2004



Main Outcomes Measures

- Length of hospital stay (LOS)
- Days in ICU
- Total cost of hospitalization
- In-hospital mortality

Variables Available in Premier Database

- Hospital level: Teaching status, bed size
- Provider characteristic: Attending physician type
- Patient level
  - Age, gender
  - Primary and secondary diagnoses and procedures (ICD codes)
  - DRG
  - APR-DRG risk score*
  - Admission, discharge type (discharge status)
  - LOS, cost, charge
  - In-hospital mortality
  - Date treatment started, doses administered
- Region, hospital ID, primary payor

*All Patient Refined Diagnosis Related Group (APR-DRG) Benchmarking Software, a severity-of-illness and risk-of-mortality adjustment tool, a proprietary 3M software.

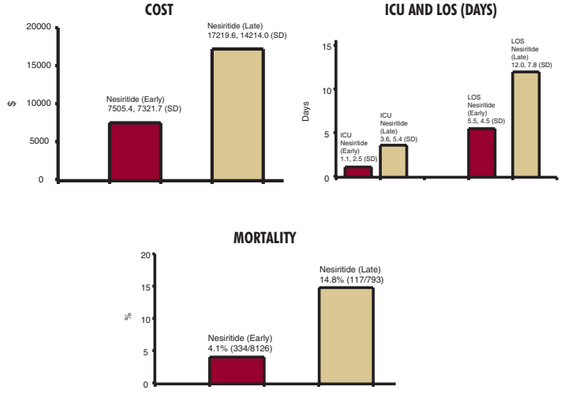
RESULTS

SELECTED BASELINE CHARACTERISTICS

	Nesiritide Early (N=8,126)	Nesiritide Late (N=793)	Discharges with DRG=127 (N=154,433)
Age (yrs) Mean (SD)	71.8 (13.1)	71.0 (13.3)	72.3 (14.1)
Gender Female (%)	45.0	41.2	54.6
Primary Payor Medicare (%)	76.2	74.1	76.1
APR-DRG Risk Score (%)			
1	8.7	1.6	9.6
2	51.8	25.1	54.0
3	33.2	49.3	31.5
4	6.3	24.0	4.9
Type of admission (%)			
Emergency	56.1	50.4	52.9
Urgent	11.7	12.6	11.5
Unknown	23.1	29.3	27.9

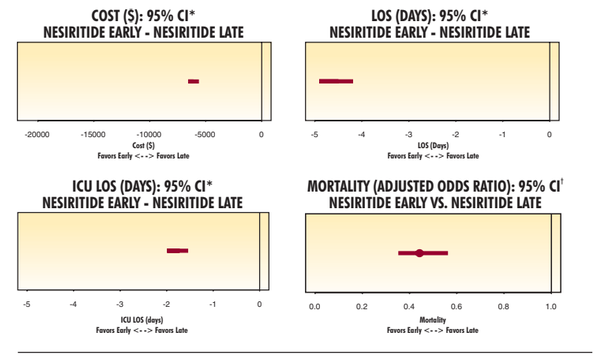
- In the early nesiritide group (nesiritide use within 1st day of hospital admission), 5.1%, 1.2%, and 0.8% of the patients were given dobutamine, milrinone, or nitroglycerin, respectively, after day 1 during their hospital stay.
- In the late nesiritide group (nesiritide use after 1st day in addition to standard care), 73.4%, 18.2%, and 23.7% of patients were given dobutamine, milrinone, or nitroglycerin, respectively, during their hospital stay (day 1 or after) as part of standard care.
- In the overall heart failure cohort (DRG = 127, N = 154,433), 5.5% received dobutamine, 1.1% milrinone, 13.1% nesiritide, and 6.8% nitroglycerin.
- In the overall heart failure cohort, ICU LOS, hospital LOS, and total cost varied within a wide range. These outcomes were as follows (mean [SD], 25th-95th percentile): ICU LOS: 0.6 days [2.2], 0.0-4.0; Hospital LOS: 5.2 days [6.5], 3.0-13.0; Total cost: $6,251 [$9,031], $2,861-$16,318.

UNADJUSTED RESULTS*



*All results are statistically significant, $P<0.0001$.

RISK-ADJUSTED DIFFERENCES BETWEEN EARLY AND LATE NESIRITIDE USE



*Negative scale implies better outcome. †Less than 1 implies better outcome.

LIMITATIONS

- Present analysis uses data from an observational study. Treatment was not assigned by randomization.
- Most appropriate statistical analysis (propensity-matched method) has been performed in this analysis to reduce or eliminate sample selection bias.[8-12]
- Propensity score analysis is not a replacement for randomization.
- Premier data is based on limited information claims
  - Time (in hours) to 1st IV therapy post admission is not available.
  - Hospital discharge is the unit of analysis; readmission rate is not available.
  - Specific clinical characteristics and laboratory data of individual patients are not available.

CONCLUSIONS

- The present analysis showed that improved in-hospital outcomes (mortality, hospital and ICU lengths of stay, and cost) occurred by administration of nesiritide therapy within first day of hospital admission vs. after the first day.
- These findings are based on limited data sources and need further validation from well-designed controlled clinical studies.
- A large double-blind, randomized, multi-national, multi-center outcomes study of nesiritide in the management of patients with acute decompensated heart failure, ASCEND-HF, is recruiting patients, and will provide additional infomration.

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DISCLOSURE
- Authors
  - Robert J. DiDomenico, PharmD: Research support, speakers bureau - Scios Inc.
  - Nishan Sengupta, PhD: Employee - Johnson & Johnson.
  - Chris Barker, PhD: Employee - ALZA Corporation.
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