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Economic Implications of *Nesiritide* Versus *Dobutamine* in the Treatment of Patients With Acutely Decompensated Congestive Heart Failure

Gregory de Lissovoy, PhD, David M. Stier, MD, Gabrielle Ciesla, MSc, Mark Munger, PharmD, and Andrew J. Burger, MD

Pooled data from trials comparing nesiritide with dobutamine for treatment of acute decompensated congestive heart failure were combined with national hospital cost data in an economic model. Results indicate that the acquisition cost of nesiritide is fully offset by decreased hospital costs. **©2003 by Excerpta Medica, Inc.**

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Although nesiritide improves patient outcomes relative to dobutamine,[1] the drug is more expensive, and its impact on overall cost of care and cost effectiveness is uncertain. Using data from 2 recent clinical trials (Comparative and Prospective Randomized Evaluation of Cardiac Ectopy With Dobutamine or Nesiritide Therapy [PRECEDENT] trials), we modeled clinical and economic outcomes of nesiritide versus dobutamine for patients emergently hospitalized with symptomatic decompensated heart failure (HF)

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Designed primarily to gather safety and clinical experience, the Comparative study enrolled 305 patients at 46 clinical sites during early 1997.[2] Patients were randomly assigned to either standard care (n = 101) or 1 of 2 doses of nesiritide: 0.015 μg/kg/min (n = 102) or 0.030 μg/kg/min (n = 102) with investigators blinded as to nesiritide dosage. Choice of standard care agent and dosage was left to the discretion of the investigators and therefore unblinded; dobutamine was selected in 57% of cases (n = 58).

The PRECEDENT study compared the effects of nesiritide with those of dobutamine on ventricular arrhythmias and heart rate while accumulating safety and clinical experience.[3] In late 1998, 255 subjects were enrolled at 46 clinical sites and randomly assigned to 1 of 3 regimens on an open-label basis: nesiritide 0.015 μg/kg/min (n = 85), nesiritide 0.030 μg/kg/min (n = 84), or dobutamine (n = 86). All patients underwent Holter monitoring during the 24 hours before initiation of the study drug and throughout the first 24 hours of treatment.

Cost of medical care is ideally determined by collecting billing data or by tabulating resource utilization during treatment and valuing each resource according to a standard unit price. Because neither of the clinical trials documented charges or resource utilization, we used the Monte Carlo simulation to estimate treatment cost and survival in hypothetical cohorts of 1,000 patients treated with nesiritide or dobutamine. The model was programmed in Microsoft Excel (Microsoft, Redmond, Washington). Clinical parameters were derived using pooled data from the Comparative and PRECEDENT studies for patients treated with dobutamine and those who received nesiritide 0.015 μg/kg/min. Patients receiving nesiritide 0.030 μg/kg/min were excluded because this dose was not used in subsequent nesiritide trials.

From an exhaustive list of side effects and adverse events among patients enrolled in the trials, we identified events during the initial hospital admission that were both clinically significant and likely to generate consumption of additional medical resources. For example, we included symptomatic hypotension but excluded asymptomatic hypotension because the latter would not be expected to result in additional treatments or medical procedures. These event rates were used as model parameters to predict clinical course

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TABLE 1 Pooled Incidence of Clinically Important Events in the Comparative and PRECEDENT Studies

Study Event	Percent of Patients Experiencing Events		
	Nesiritide* (n = 188)	Dobutamine (n = 144)	p Value
Cardiac arrest	2.7	3.6	0.746
Any ventricular tachycardia	17.6	19.1	0.774
Sustained ventricular tachycardia	1.6	3.5	0.297
Nonsustained ventricular tachycardia	18.0	16.0	0.769
Ventricular bigeminy	1.6	5.0	0.106
Angina pectoris	9.1	6.4	0.550
Hypotension (symptomatic)	17.1	5.7	0.000
Readmission for HF	4.0	9.4	0.030
Death within 6 mos	16.0	25.0	0.030

*Includes only data for patients who received nesiritide 0.015 μg/kg/min.

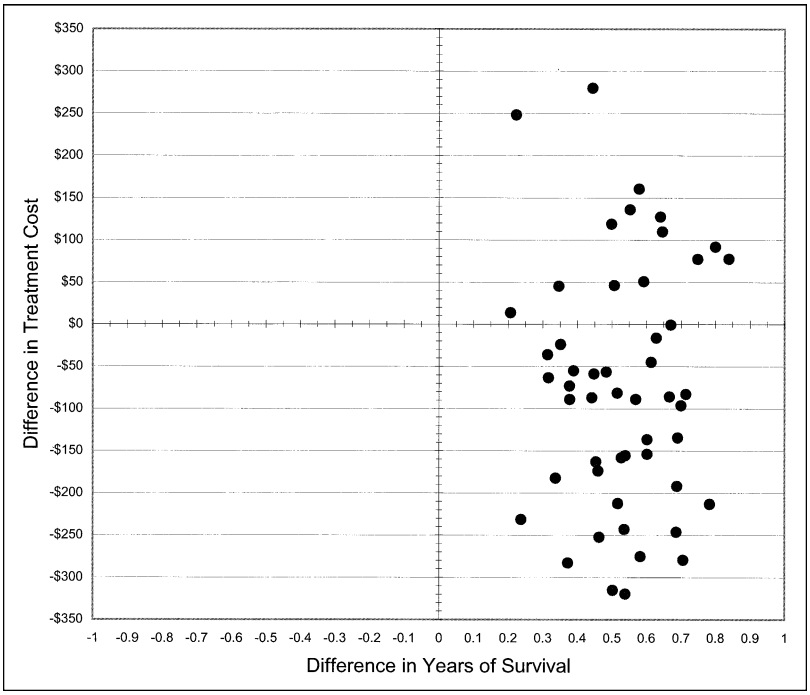

FIGURE 1. Results of 51 consecutive simulations: difference in survival and cost of nesiritide relative to dobutamine.

during initial hospital admission, likelihood of readmission, and survival status at 6 months (Table 1).

For each hypothetical patient, the model first assigns gender and age as random functions. In the actual pooled trial data, age and gender distributions were slightly different across study groups. Male subjects constituted 68% of the nesiritide and 63% of the dobutamine cohorts. Mean age for the nesiritide group was 63 ± 14 years versus 62 ± 14 years for the dobutamine group. To avoid a potential source of cost variation unrelated to study drug, the modeled gender and age distributions were equalized (63% male, mean age 62 ± 14 years).

Next, the model sets flags for the possible occurrence of each of the significant clinical events during the initial admission according to the frequencies as listed in Table 1. For example, each simulated patient treated with nesiritide had a 17.1% chance of experiencing symptomatic hypotension during the initial admission. Similarly, the model then predicts whether the patient was readmitted within 21 days for treatment of HF. Finally, survival status at 6 months from date of randomization is determined.

We estimated the cost of the initial hospital admission by statistically matching the characteristics of admissions simulated by the model with records from a national hospital discharge database, the 1999 Health Care Utilization and Cost Project (HCUP) National Inpatient Survey.[4] HCUP summarizes inpatient hospital stays according to patient demographics, admission and discharge status, diagnosis and procedure codes, length of stay, and billed charge. From the HCUP hospital records, we selected those with a primary diagnosis of HF using a published algorithm for identifying this condition in an administrative database.[5] We excluded cases in which (1) admission was not categorized as "urgent" or "emergent"; (2) secondary diagnoses included trial exclusionary criteria, such as pulmonary hypertension; and (3) values were missing for length of stay, total charge, age, or gender.

The resultant analysis file contained 133,998 discharge records. Billed charges were converted to cost by applying the Medicare cost-to-charge ratio and adjusted to the 2001 level price based on the hospital producer price index.[6] Professional fees were not included; therefore, the economic analysis reflects a hospital perspective. We used multivariate regression to explain cost of an HCUP admission as a function of age, gender, presence of specific secondary diagnosis codes equivalent to the clinical events listed in Table 1, and a random error term reflecting underlying variability in cost for otherwise identical cases.

For each simulated patient, the model applied demographic characteristics and the set of clinical event flags to the regression coefficients to predict cost of initial admission. Added to that cost was a price for either nesiritide or dobutamine. According to the pooled clinical trial data, infusion duration was 44.4 hours for nesiritide (equal to 2 vials of drug) and 62.0 hours for dobutamine (3 vials of drug). Cost per vial was set at the wholesale acquisition cost of $380 for nesiritide and the median average wholesale price of

TABLE 2 Detailed Model Results: Components of Treatment Cost and Survival

Component of Treatment Episode	Nesiritide (n = 1,000)	Dobutamine (n = 1,000)	Difference*
Cost at initial admission: (study drug cost not included)	$10,969 ± 72	$11,091 ± 80	$−122 ± 91
Cost at initial admission: (including study drug cost)	$11,729 ± 72	$11,127 ± 80	$602 ± 91
Cost of HF readmission	$345 ± 57	$1,029 ± 99	$−685 ± 114
Cost of treatment episode (initial admission plus HF readmission)	$12,074 ± 93	$12,156 ± 129	$−83 ± 145
Remaining years of life	4.84 ± 0.10	4.30 ± 0.15	0.54 ± 0.15

*Difference = nesiritide − dobutamine.
Data are presented as means ± SE.

$12 for dobutamine, according to the *Red Book*.[7] Average per-patient cost of study drug was $760 for nesiritide and $36 for dobutamine.

Neither of the clinical trials recorded detailed information about clinical events during a readmission after the initial index admission. Based on HCUP data, the cost for a simulated patient's subsequent hospital admission, if that occurred, was estimated as the mean cost of an urgent HF admission for a person with similar demographics.

Finally, the model predicts each simulated patient's survival status (alive or dead) at the 6-month end of follow-up as derived from the pooled trial data.[8] To gain some sense of the implications of differential survival, the model applied a surviving patient's age and gender to lifetable data that projects remaining years of life according to historical mortality in the United States population.[9] Because patients with severe congestive HF are at increased risk of death, the model assumes that actual survival is only 26% of normal life expectancy, with a median survival of approximately 5 years after diagnosis.[10]

Because model parameters are probabilistic, results vary slightly with every iteration. This is an inherent feature of the Monte Carlo simulation, which is designed to reveal the full spectrum of outcomes that would likely be observed in actual practice.[11] Figure 1 depicts 51 consecutive simulations as points on a graph depicting the cost-effectiveness plane. The x-axis defines the difference (nesiritide versus dobutamine) in projected years of survival; a positive value indicates that the duration was longer for patients treated with nesiritide relative to dobutamine. In this set of 51 simulations, the mean (median) difference in survival was +0.53 (0.54) years with mean difference in survival ranging from +0.21 to +0.84 years. Difference in cost is given on the y-axis. Here, positive values indicate that nesiritide was relatively more costly than dobutamine and vice versa. Mean (median) difference in cost was −$73 (−$83) with a range from −$310 to +$280. Detailed results for the iteration with median difference in cost, as shown in Figure 1, are given in Table 2.

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Results of this simulation suggest that for this group of patients with acutely decompensated HF, the relatively high acquisition cost for nesiritide is fully offset by a less resource-intensive initial hospital admission and a lower rate of readmission within 21 days. Compared with dobutamine, nesiritide appears to offer a survival advantage that translates into additional years of life. However, the magnitude of added longevity is speculative because of the fragile health status of many patients with HF. Based on a finding of cost-neutrality coupled with increased survival, nesiritide appears cost effective relative to dobutamine as treatment for patients with acutely decompensated HF.

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