Safety and Efficacy of Outpatient Nesiritide in Patients With Advanced Heart Failure

Results of the Second Follow-Up Serial Infusions of Nesiritide (FUSION II) Trial

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Background—Patients with American College of Cardiology/American Heart Association stage C/D heart failure experience substantial morbidity and mortality, but available interventions beyond standard medical and device therapies are limited. Nesiritide relieves dyspnea and reduces pulmonary congestion, but its risk profile is uncertain. Pilot data suggested a potential benefit of nesiritide given as serial outpatient infusions.

Methods and Results—The Second Follow-Up Serial Infusions of Nesiritide (FUSION II) trial was a randomized, double-blind, placebo-controlled trial of outpatient serial nesiritide infusions for patients with American College of Cardiology/American Heart Association stage C/D heart failure. Patients with 2 recent heart failure hospitalizations, ejection fraction <40%, and New York Heart Association class IV symptoms, or New York Heart Association class III symptoms with creatinine clearance <60 mL/min, were randomized to nesiritide (2-μg/kg bolus plus 0.01-μg/kg-per-minute infusion for 4 to 6 hours) or matching placebo, once or twice weekly for 12 weeks. All patients were treated to optimal goals with evidence-based medical/device therapy facilitated by careful disease management during the study. The primary end point was time to all-cause death or cardiovascular or renal hospitalization at 12 weeks. A total of 911 patients were randomized and treated. The primary end point occurred in 36.8% and 36.7% of the placebo and nesiritide groups, respectively (hazard ratio, 1.03; 95% confidence interval, 0.82 to 1.3; log-rank test \( P=0.79 \)). There were no statistically significant differences between groups in any of the secondary end points, including the number of cardiovascular or renal hospitalizations, the number of days alive and out of the hospital, change in Kansas City Cardiomyopathy Questionnaire score, or cardiovascular death. Adverse events were similar between groups; nesiritide was associated with more hypotension but less predefined worsening renal function.

Conclusions—Serial outpatient nesiritide infusions do not provide a demonstrable clinical benefit over intensive outpatient management of patients with advanced American College of Cardiology/American Heart Association stage C/D heart failure. (Circ Heart Fail. 2008;1:9-16.)

Key Words: heart failure ■ kidney ■ natriuretic peptides

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patients with persistently symptomatic heart failure despite the use of guideline-driven, evidence-based pharmacological and device therapy are classified as having American College of Cardiology/American Heart Association (ACC/AHA) stage C or stage D heart failure. These patients have a clinical profile of advanced heart failure and are at high risk for hospitalization and death. Other than heart transplantation and left ventricular support devices, no therapeutic interventions beyond standard therapies have been shown to reduce symptoms or improve outcomes in this population.

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Administration of intermittent infusions of inotropes has been common, but this practice has fallen out of favor because of the lack of evidence for benefit, significant
potential for harm, and guideline recommendations that such therapy should be avoided.\footnote{Palliative care is often the default strategy for these patients. Natriuretic peptides have a protein profile that may be beneficial in advanced or ACC/AHA stage C/D heart failure. Nesiritide is a recombinant form of human B-type natriuretic peptide that exhibits vasodilatory, natriuretic, and lusitropic activity. It has also been associated with neurohormonal antagonism and reverse remodeling.\footnote{Nesiritide is currently indicated for patients with acute decompensated heart failure (ADHF) to reduce pulmonary wedge pressure and improve short-term dyspnea.\footnote{However, its use in ADHF remains in question because of certain safety concerns.\footnote{The benefits and risks of nesiritide for stage C/D heart failure are not known.}}}

The Follow-Up Serial Infusions of Nesiritide (FUSION I) trial was a pilot study designed to evaluate the potential clinical utility of outpatient, intermittent nesiritide infusions in ACC/AHA stage C/D heart failure patients.\footnote{FUSION I yielded neutral results and demonstrated no difference in adverse events for nesiritide compared with usual care. However, a prespecified subgroup analysis of high-risk patients suggested a lower rate of all-cause death and hospitalization and more days alive and out of the hospital for patients randomized to nesiritide than for those randomized to usual care.\footnote{A separate post hoc analysis in patients with estimated creatinine clearance <60 mL/min at baseline also identified lower rates of all-cause hospitalization and all-cause mortality or hospitalization and more days alive and out of the hospital for patients randomized to nesiritide than for those given usual care.\footnote{These hypothesis-generating data supported the development of the present study, the Second Follow-Up Serial Infusions of Nesiritide (FUSION II) trial, to further evaluate the efficacy and safety of serial nesiritide outpatient infusions in advanced or stage C/D heart failure patients.\footnote{}}}}

Methods

FUSION II (Second Follow-Up Serial Infusions of Nesiritide [Natrecor] for the management of patients with heart failure) (ClinicalTrials.gov identifier NCT00091520) was a phase IIIB, prospective, randomized, parallel, multicenter, double-blind trial of nesiritide or placebo infused twice weekly.\footnote{Ground heart failure therapy was administered at the investigator's discretion. However, outpatient administration of positive inotropic agents, intravenous vasodilators, or nesiritide was not allowed. The requirement for inotropic or other vasoactive support was treated as a hospitalization and represented a clinical end point.}

Patient Population

Patients were included in FUSION II if they had had \( \geq 2 \) heart failure hospitalizations or the equivalent within 12 months, with the most recent within the prior 60 days. A hospitalization equivalent was defined as an unscheduled outpatient treatment for ADHF with an intravenous vasoactive drug or 3 unscheduled intravenous diuretic treatments for ADHF within 60 days. Other eligibility criteria included left ventricular ejection fraction \(< 40\%\) within 24 weeks;\footnote{Safety was examined through evaluation of adverse events and serious adverse events, change in serum creatinine, and change in estimated glomerular filtration rate (eGFR) as calculated by the Modification of Diet in Renal Disease equation.\footnote{Serum creatinine was assessed at each outpatient visit. Renal safety was evaluated according to 3 prespecified categories for changes in serum creatinine from baseline: serum creatinine increase of \( >0.5 \text{ mg/dL} \), serum creatinine increase \( \geq 50\% \), and serum creatinine increase \( \geq 2 \text{ mg/dL} \). A clinical renal composite end point was also used to evaluate renal safety. The composite was defined as a renal death or hospitalization or a renal-related serious or nonserious adverse event in combination with the aforementioned 3 categories of serum creatinine increases.}} investigator documentation of consistent New York Heart Association (NYHA) class III or IV symptoms during the previous 60 days\footnote{The statistical analysis plan was developed by the FUSION II steering committee, and statistical analyses were performed by biostatisticians employed by Scios Inc. The estimated sample size for FUSION II was based on event rates observed in the high-risk FUSION I subset.\footnote{A total of 900 patients (600 nesiritide and 300 placebo) were expected to provide 60% and 84% power to detect a 15% (conservative estimate) and 20% (optimistic estimate) relative reduction in 12-week all-cause mortality or cardiovascular and renal hospitalization, respectively, assuming a 50% placebo event rate}} (estimated creatinine clearance \(< 60 \text{ mL/min} \) calculated by the Cockcroft-Gault equation; 24-hour urine collection was also required for NYHA class III patients); and optimal treatment with oral medications and device therapy unless a documented contraindication or intolerance was present. Patients were excluded from participation for any of the following reasons: systolic blood pressure \(< 90 \text{ mm Hg} \), dependence on (or inability to discontinue) intermittent or continuous intravenous vasoactive medications, \( > 2 \) outpatient infusions of vasoactive therapy within 30 days without a hospitalization, biventricular pacemaker within 45 days or a single- or dual-chamber pacemaker, implantable cardioverter-defibrillator within 15 days, cardiogenic shock or volume depletion, and chronic dialysis.

End Points

The primary end point was time to all-cause death or the first hospitalization for cardiovascular or renal causes from randomization through week 12. Secondary end points included the number of cardiovascular and renal hospital admissions; days alive and out of the hospital; and time to cardiovascular death, all evaluated through week 12. All deaths and hospitalizations were adjudicated by a blinded clinical events committee that used predefined criteria to classify events. Quality of life was also a secondary end point, as assessed by change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score from baseline to week 13. The KCCQ was used because it is a more broadly applicable measure of quality of life than other instruments, and modest variations in the KCCQ score have been deemed to be clinically meaningful.\footnote{The statistical analysis plan was developed by the FUSION II steering committee, and statistical analyses were performed by biostatisticians employed by Scios Inc. The estimated sample size for FUSION II was based on event rates observed in the high-risk FUSION I subset.\footnote{A total of 900 patients (600 nesiritide and 300 placebo) were expected to provide 60% and 84% power to detect a 15% (conservative estimate) and 20% (optimistic estimate) relative reduction in 12-week all-cause mortality or cardiovascular and renal hospitalization, respectively, assuming a 50% placebo event rate}}

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between the combined nesiritide and placebo groups at a 2-sided 0.05. The data analysis was performed on the basis of a modified intent-to-treat principle: All randomized patients who received any study drug were included in the analysis. Demographic and baseline characteristics were summarized by treatment group. Frequencies were reported for categorical variables, and descriptive statistics were reported for continuous variables. The primary analysis was based on adjudicated events. Kaplan-Meier survival curves were generated for the primary end point. The log-rank statistic stratified by dosing frequency was used to test between-group differences at the level of 2-sided 0.05. The magnitude of the treatment effect was estimated with a hazard ratio (HR) from a Cox proportional hazards regression model, stratified by dose frequency.

Kaplan-Meier curves were also generated for time-to-event secondary end points, and the stratified log-rank statistic was used to test between-group differences at the level of α=0.05. The numbers of cardiovascular and renal hospitalizations and days alive and out of the hospital were reported as mean ± SD. Two-way ANOVA models were used to test for treatment effects, adjusted for dose frequency, for the following secondary efficacy end points: number of cardiovascular and renal hospitalizations and days alive and out of the hospital; change in average KCCQ score; and changes from baseline in serum creatinine and Modification of Diet in Renal Disease–determined GFR.

The authors had full access to the data and take responsibility for the integrity of the data. All authors have read and approved the manuscript as written.

Results
A total of 920 patients were randomized. Of these, 9 patients did not receive study drug because of withdrawal from the study or nonadherence to study procedures (Figure 1). Thus, 911 patients constituted the study population. The median duration of therapy was 11.1 weeks in both the nesiritide and placebo once-weekly groups and 11.4 weeks in both the nesiritide and placebo twice-weekly groups. Baseline characteristics were similar between the combined groups (Table 1), and no differences were observed in baseline characteristics between dose frequency groups. Patients had poor systolic function, and more than half of the patients were classified as NYHA class IV. Comorbid conditions were common. Patients randomized to nesiritide had slightly, but statistically significant, lower systolic blood pressure at baseline than patients randomized to placebo (Table 1).

Efficacy
All-cause mortality or cardiovascular and renal hospitalizations through week 12 occurred in 36.8% of the placebo combined group and 36.7% of the nesiritide combined group (HR, 1.03; 95% confidence interval [CI], 0.82 to 1.3; log-rank test 0.79) (Figure 2). The individual components of the composite end point did not differ between treatment groups (Table 2). No significant differences were detected when the analysis was performed at 24 weeks; the Kaplan-Meier estimates for the primary end point were 48.2% and 52.2% for placebo- and nesiritide-treated patients, respectively, by 24 weeks (P=0.38). These findings were consistent among all prespecified subgroups. There were no statistically signif-
significant differences between treatment groups in any of the secondary end points (Table 2).

**Safety**

No differences were observed in the proportion of patients experiencing any adverse event (86.9% placebo versus 88.4% nesiritide; \( P=0.52 \)), serious adverse events (56.5% placebo versus 60.2% nesiritide; \( P=0.32 \), or adverse events requiring permanent study drug discontinuation (25.5% placebo versus 26.9% nesiritide; \( P=0.69 \). Drug-related adverse events were higher for the nesiritide combined groups (27.5% versus 41.8%; \( P<0.001 \), a finding that was driven by hypotension.

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo Combined Groups (n=306)</th>
<th>Nesiritide Combined Groups (n=605)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic and clinical characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>65±12.8</td>
<td>64.9±12.9</td>
</tr>
<tr>
<td>Male</td>
<td>221 (72.2)</td>
<td>426 (70.4)</td>
</tr>
<tr>
<td>Black</td>
<td>72 (23.5)</td>
<td>123 (20.3)</td>
</tr>
<tr>
<td>White</td>
<td>184 (60.1)</td>
<td>392 (64.8)</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>194 (63.4)</td>
<td>387 (64)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>24.6±8.2</td>
<td>25±7.9</td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>141 (46.1)</td>
<td>285 (47.1)</td>
</tr>
<tr>
<td>IV</td>
<td>165 (53.9)</td>
<td>320 (52.9)</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>28.9±7.1</td>
<td>28.3±6.8</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>235 (76.8)</td>
<td>468 (77.4)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>168 (54.9)</td>
<td>329 (54.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>73 (23.9)</td>
<td>127 (21)</td>
</tr>
<tr>
<td>No insulin</td>
<td>83 (27.1)</td>
<td>185 (30.6)</td>
</tr>
<tr>
<td>Moderate/severe renal disease</td>
<td>124 (40.5)</td>
<td>232 (38.3)</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>127 (41.5)</td>
<td>266 (44)</td>
</tr>
<tr>
<td><strong>Laboratory data and vital signs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine*</td>
<td>1.62±0.63</td>
<td>1.65±0.72</td>
</tr>
<tr>
<td>In micromoles per liter</td>
<td>143.2±55.7</td>
<td>145.9±63.6</td>
</tr>
<tr>
<td>GFR†, mL/(min·1.73 m²)</td>
<td>52.5±23.2</td>
<td>52.3±24.4</td>
</tr>
<tr>
<td>Blood urea nitrogen‡</td>
<td>36±20</td>
<td>38±24</td>
</tr>
<tr>
<td>In milligrams per deciliter</td>
<td>12.9±7.1</td>
<td>13.6±8.6</td>
</tr>
<tr>
<td>Sodium§, mmol/L</td>
<td>138±4</td>
<td>138±4</td>
</tr>
<tr>
<td>Systolic blood pressure¶, mm Hg</td>
<td>118±20</td>
<td>115±20</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>75±13</td>
<td>76±14</td>
</tr>
<tr>
<td><strong>Baseline evidence-based therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral loop diuretics</td>
<td>217 (70.9)</td>
<td>469 (77.5)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>119 (38.9)</td>
<td>287 (47.4)</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>41 (13.4)</td>
<td>90 (14.9)</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>159 (52)</td>
<td>296 (48.9)</td>
</tr>
<tr>
<td>( \beta )-Selective ( \beta )-blocker</td>
<td>43 (14.1)</td>
<td>92 (15.2)</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>114 (37.3)</td>
<td>224 (37)</td>
</tr>
<tr>
<td>Nitrites</td>
<td>61 (19.9)</td>
<td>99 (16.4)</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>123 (40.2)</td>
<td>231 (38.2)</td>
</tr>
<tr>
<td>Biventricular pacemaker</td>
<td>80 (26.1)</td>
<td>139 (23)</td>
</tr>
</tbody>
</table>

Values are given as number (percentage) or mean±SD.

*To convert to SI units (μmol/L), multiply by 88.4.

†Calculated with the Modification of Diet in Renal Disease equation: 186.3×(serum creatinine, mg/dL\(^{-1.154}\))×(age, years\(^{-0.203}\))×(0.742 if female)×(1.212 if black).\(^{11,12}\)

‡To convert to SI units (mmol/L), multiply by 0.357.

§1 mEq/L is equal to 1 mmol/L.

\( P=0.043. \)
Hypotension was reported in 32.4% of the nesiritide combined groups and 18% of the placebo combined groups ($P = 0.001$). A higher rate of both symptomatic (11.7% versus 6.2%; $P = 0.009$) and asymptomatic (24.8% versus 13.4%; $P < 0.001$) hypotension was reported among nesiritide patients. An analysis performed by baseline systolic blood pressure demonstrated no evidence of increased death or a composite of increased death or cardiovascular or renal hospitalization for nesiritide compared with placebo among patients with baseline systolic blood pressure $\leq 100$ mm Hg, 101 to 120 mm Hg, or $>120$ mm Hg. Notably, there was no difference in serious adverse events or adverse events that caused permanent study drug discontinuation between groups.

Fewer patients randomized to nesiritide experienced serum creatinine increases $>0.5$ mg/dL, compared with those randomized to placebo ($P = 0.046$). There was no evidence of protocol-specified renal harm associated with nesiritide compared with placebo when the composite renal end point was evaluated (Figure 3). Serum creatinine increased slightly, but significantly, in the placebo group compared with the nesiritide group at outpatient weeks 2, 3, 5, and 12 ($P < 0.05$). A similar pattern was also observed in the subgroup of patients with baseline eGFR $<60$ mL/min. Patients randomized to nesiritide did not exhibit increases in serum creatinine greater than those seen in the placebo group at any time point. Correspondingly, eGFR significantly increased from baseline in patients randomized to nesiritide compared with placebo at weeks 2, 3, 5, and 6. eGFR appeared to be higher at 12 weeks for patients randomized to nesiritide compared with those randomized to placebo, but this was not statistically significant ($P = 0.082$).

Optimization of evidence-based medicine occurred in the overall cohort during the course of the study. The following

### Table 2. Primary and Secondary End Points

<table>
<thead>
<tr>
<th></th>
<th>Placebo Combined (n = 306)</th>
<th>Nesiritide Combined (n = 605)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality or cardiovascular/renal hospitalization*</td>
<td>111 (36.8)</td>
<td>218 (36.7)</td>
<td>1.03 (0.82, 1.3)</td>
<td>0.79</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>29 (9.6)</td>
<td>56 (9.5)</td>
<td>1.01 (0.64, 1.58)</td>
<td>0.98</td>
</tr>
<tr>
<td>Cardiovascular/renal hospitalization</td>
<td>101 (33.9)</td>
<td>191 (32.9)</td>
<td>0.99 (0.78, 1.26)</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cardiovascular or renal hospitalizations†</td>
<td>0.8±1.9</td>
<td>1.0±4</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>No. of cardiovascular hospitalizations only†</td>
<td>0.6±1.65</td>
<td>0.9±3.97</td>
<td>0.286</td>
<td></td>
</tr>
<tr>
<td>No. of renal hospitalizations only†</td>
<td>0±0</td>
<td>0±0.23</td>
<td>0.116</td>
<td></td>
</tr>
<tr>
<td>No. of days alive and out of the hospital†</td>
<td>74.8±17.5</td>
<td>72.5±20.5</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Change in KCCQ overall summary score‡</td>
<td>14.2±21.1</td>
<td>13±24.1</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death‡</td>
<td>27 (9.2)</td>
<td>47 (8.1)</td>
<td>0.91 (0.57, 1.46)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Values are given as number (percentage) or mean±SD.
*Kaplan-Meier percentages.
†Assessed through the end of week 12.
‡From baseline to week 13.
improvements were observed from baseline: angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 59% at baseline to 82% at follow-up; β-blockers, 65% at baseline to 87% at follow-up; aldosterone antagonists, 37% at baseline to 55% at follow-up; and diuretics, 75% at baseline to 94% at follow-up (Figure 4). Outpatient infusions of positive inotropic drugs were infrequent during the study, occurring in 2% of patients in both groups. The overall use of positive inotropic drugs at any time during the study (including during hospitalization) was 21% in the nesiritide group and 19% in the placebo group. The mean number of outpatient intravenous diuretic courses administered was 2.1 in the nesiritide group and 2.5 in the placebo group.

**Discussion**

In this trial testing serial outpatient nesiritide administration in ACC/AHA stage C/D heart failure patients, nesiritide was not shown to reduce the risk of death or cardiovascular or renal hospitalizations at 12 weeks compared with optimal medical management. Although FUSION II was conducted in outpatients with stage C/D heart failure and represents a different patient population from those with ADHF, in whom concerns about nesiritide use have been raised,5,6 there was no evidence of worsening renal function when the drug was intermittently infused once or twice weekly over 4 to 6 hours for 12 weeks. Additionally, no signal of an adverse mortality effect was detected; however, this trial was underpowered to conclusively evaluate clinical outcomes. A higher rate of adverse events related to hypotension was reported; however, no differences were observed in serious adverse events or adverse events that required study drug discontinuation, and no evidence of an adverse effect of nesiritide on clinical events among systolic blood pressure subgroups was detected. Thus, these data may serve to diminish the safety concerns associated with nesiritide use, but it is important to note that they do not resolve these concerns. The safety findings of FUSION II, particularly with regard to renal function, are consistent with 2 other recent studies.
Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery (NAPA) and BNP for Cardiorenal Decompensation Syndrome (BNP-CARDS). The BNP-CARDS study showed no difference between nesiritide and placebo in the proportion of patients with a ≥20% rise in serum creatinine or in absolute serum creatinine change. A large mortality trial in patients with ADHF is planned to further address the safety and efficacy of nesiritide in the acute heart failure population.

Notably, the present study illustrates the influence of optimization of guideline-driven evidence-based therapy on outcomes even in patients with advanced heart failure. In the FUSION I subgroup analysis of similar patients, all-cause mortality and hospitalization occurred in 78% of the usual-care group and 52% of the nesiritide group, with 12-week mortality rates of 17% and 5% for the usual-care and nesiritide groups, respectively. In comparison, the placebo event rates in FUSION II were substantially lower by ~50%.

This finding likely results in part from the following improvements in background therapy observed from FUSION I to FUSION II: carvedilol, 8% to 50%; implantable cardioverter-defibrillator, 25% to 39%; and cardiac resynchronization therapy, 9% to 24%. Avoidance of deleterious therapies may also have contributed because 35% of patients in FUSION I were treated with outpatient positive inotropic agents before randomization, compared with 1% to 2% in FUSION II.

In addition, 58% of standard-care patients in FUSION I were treated with outpatient inotropes during the protocol, versus only 2% of placebo patients in FUSION II. These changes in background therapy between FUSION I and FUSION II may explain, in part, the difference between the expected event rate on which sample size estimates were based and the actual event rate observed in FUSION II.

By design, FUSION II included 1 or 2 half-days weekly when patients interacted closely with a heart failure management team. The potential benefits of this contact are immeasurable, but this level of care is beyond what can feasibly be provided in routine care settings. The repeated clinical evaluation provides opportunities for clarification and reinforcement of the medical regimen and lifestyle modifications and for therapeutic intervention. During these visits, >50% of patients received diuretic infusions, which may have averted hospitalizations for fluid overload. The enhanced contact also provided more opportunity for titration of recommended therapies, as evidenced by the increased use of evidence-based pharmacological and device therapies as described. Nevertheless, despite the excellent provision of evidence-based heart failure care during the study, the mortality rate approached 10% at 12 weeks, and almost 40% of patients had experienced a fatal event or required a cardiovascular or renal hospitalization within 3 months. These data demonstrate the continued unmet need to identify effective strategies to improve outcomes for these high-risk patients.

Limitations

Because of the much lower than expected event rates, FUSION II was underpowered to evaluate the effect of nesiritide on the primary end point. The resulting power calculation based on the observed placebo event rates yielded only 37% power to detect a conservative relative risk reduction of 15% between groups. In retrospect, a sample size of 3500 patients would have been needed for 90% power to detect this treatment effect. However, it should be noted that on the basis of the actual results, the wide confidence limits with a nearly indistinguishable event rate between active treatment and placebo exclude a benefit in the primary end point as small as 15%, making it relatively unlikely that an important positive effect was missed.

A defined disease management strategy per se was not mandated by protocol because there are not yet any established guidelines or metrics for disease management. However, the frequent clinic visits resulted in de facto disease management, yielding process-of-care strategies that may have varied between centers. Approximately 25% of sites were not North American. No data suggest geographic differences in outcomes, but disease assessment and management may also have varied between sites as a function of geography and prevailing clinical practice.

Secular changes in the uptake of guideline-driven evidence-based therapies and implementation of disease management processes may have resulted in improved outcomes in the control population that were unanticipated. The potential for this to occur in heart failure trials should be considered in future study designs.

Conclusions

Despite these limitations, FUSION II provides important data that further our understanding of advanced or ACC/AHA stage C/D heart failure. These patients have NYHA class III or IV symptoms, frequent recent hospitalization episodes, poor left ventricular function, and marginal to reduced renal function. Even patients with advanced heart failure are able to benefit from further improvements in evidence-based care. It is important to note that their event rate remains quite high, and poor outcomes still occur despite appropriate disease management. Serial outpatient nesiritide infusions do not provide a demonstrable clinical benefit over intensive outpatient management of patients with advanced ACC/AHA stage C/D heart failure. On the basis of these data, there is no indication for intermittent outpatient nesiritide infusions in patients with stage C/D heart failure. Although the safety data from FUSION II mute the concerns about harm associated with nesiritide use, the question is not fully resolved. The patient population, setting, and duration of infusions in FUSION II differ from those for hospitalized patients with ADHF, and therefore important safety questions in the setting of ADHF still require further study. Finally, it is evident that the best care for patients with ACC/AHA stage C/D heart failure should be truly optimal guideline-driven, evidence-based medical and device therapy with frequent and careful clinical follow-up. Further approaches to address this ill patient population represent new directions for research.

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References


CLINICAL PERSPECTIVE

Patients with advanced heart failure represent a unique clinical challenge. These patients typically have class III or IV symptoms, poor left ventricular systolic function, multiple prior hospitalizations, and marginal if not reduced renal function. They have a high likelihood for repeat hospitalizations and have a worrisome short-term mortality risk. The available treatment options beyond evidence-based medical and device therapy for American College of Cardiology/American Heart Association stage D heart failure are limited and include the following: ventricular replacement strategies, eg, heart transplantation, left ventricular assist devices, and, perhaps in the future, regenerative biological technologies; investigational protocols; and palliative care. Previous data suggested that nesiritide as an intermittent infusion might be helpful. However, in the Second Follow-up Serial Infusions of Nesiritide (FUSION II) trial, a randomized controlled clinical trial, there was no evidence of improved survival or decreased hospitalizations for adjunctive once- or twice-weekly nesiritide infusions over optimal background therapy. Continued attention to optimizing evidence-based therapy and careful follow-up appeared to be beneficial, however. It is somewhat reassuring that no evidence of renal harm or excess mortality was seen in this study, but because this patient population is different from hospitalized patients with heart failure and the drug was dosed differently, some concerns about nesiritide and its safety profile for acute decompensated heart failure should remain. On the basis of this study, nesiritide should not be given as an intermittent outpatient infusion for advanced heart failure. Pending more research, the current goal should be optimization of guideline-driven evidence-based therapy, with the recognition that even patients with advanced disease may still derive a benefit from further improvements in therapy.
Safety and Efficacy of Outpatient Nesiritide in Patients With Advanced Heart Failure: Results of the Second Follow-Up Serial Infusions of Nesiritide (FUSION II) Trial
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