APPENDIX A

Evidence Table

Studies evaluating the intermittent use of nesiritide for chronic heart failure

Authors/Year	Study Design	Demographics	Intervention, Outcome Measures, Instruments	Results	Methodological Comments (Limitations)
Yancy, Saltzberg, Berkowitz, Bertolet, Vijayaraghavan, Oren, Burnham, Walker, Horton, Silver; 2004 FUSION I Trial	A multicenter, open-label, pilot study that randomly assigned subjects to usual treatment only compared to usual treatment plus weekly infusions of nesiritide in a 1:1:1 ratio. Intention to treat analysis was followed.	Eligible patients were 18 years and older, had a NYHA class III or IV, and had 2 or more hospital admissions for ADHF within the preceding 12 months. Study involved 210 subjects (sample size was determined empirically). Study involved the use of a prospective RAS (Risk Assessment Score) based on known prognostic factors.	Subjects were assigned to 1 of 3 treatment groups: (1) usual care, (2) usual care plus 0.005 µg/kg/min of nesiritide given for 4-6 hours preceded by a bolus of 1.0µg/kg bolus, (3) usual treatment plus 0.01 µg/kg/min of nesiritide given for 4-6 hours preceded by a 2.0 µg/kg bolus. Safety and tolerability were the primary endpoints, assessed by adverse events, serious adverse events, discontinuation in the study, lab assessment and vital signs. The Minnesota Living with	At baseline the only significant difference between treatment groups was the increased prevalence of atrial fibrillation in the usual treatment group. A total of 1,645 nesiritide infusions were administered. All treatment groups had a similar frequency of adverse events, and experienced improved quality of life. Although there was no statistically significant differences in outcomes for the 3 treatment groups, prospectively defined high risk sub-	Small sample size, (sample size arbitrarily chosen- no effect size stated, Insufficiently powered to detect statistical difference. Open label study is prone to investigator bias. Study had short duration. Definition of "usual care" was left to the discretion of the investigator. High-risk sub-group was defined prospectively.

		69 subjects received usual care, 72 subjects received usual care plus 0.005 μg/kg/min of nesiritide, and 69 0.01 μg/kg/min.	Heart Failure Questionnaire was also used. All-cause deaths and hospitalizations, Deaths, All cause hospitalizations, Days alive and out of hospital, and RAS scores were measured.	groups demonstrated significant decreases in cardiovascular events. There were no statistically significant differences in deaths or hospitalizations. Subjects receiving nesiritide showed trends for more days alive and out of the hospital compared to subjects receiving usual care.	
Sheikh-Taha; 2005	A single center, nonrandomized, open label prospective study.	All subjects were 18 years and older, had NYHA class III or IV. Subjects receiving maximum oral therapy with diuretics, ACE inhibitors, ARBS, hydralazine, nitrates, β-blockers and spironolactone. Also patients intolerant of or refractory to intermittent	At each visit, subjects received a bolus of 2μg/kg of nesiritide, followed by 0.01 μg/kg/min of nesiritide, given over a four to six hour period. Patients also received a 4-6 hour infusion of iv dobutamine 4-6 μg/kg/min. or milrinone followed by a maintenance	At the beginning of the study, 9 subjects were in the NYHA class III, and 2 were in class IV. After 3 months of treatment, 7 patients remained in class III, and 4 patients moved to class II; no subject remained in class IV. Of the 11 subjects, 6 had improvement in NYHA class, 5 remained	Open label research design prone to investigator bias Did not follow intention to treat protocol. Small sample size. Lack of randomization. Short follow-up period.

		IV inotropic therapy with dobutamine or milrinone. 14 patients were initially recruited for the study, but 11 remained the study (7 males, 4 females); the mean SD age was 69 +/-8 years.	infusion of 0.1750-.375 µg/kg/min. Nesiritide doses were were adjusted downward in patients with renal insufficiency. Subjects were followed for three months.	in the same class, and 0 regressed (p=1.0). The number of hospital admissions due to exacerbation of HF did decrease (11 vs 5; p=0.0253), and the number of visits to the HF clinic declined from 5.6 per month to 4 per month (p=0.0749). The intermittent administration of nesiritide along with other drugs was well tolerated by most subjects.	No controls. No effect size stated. Confounding effects of variables not adjusted for.
Josephson, Barnett; 2004	Case study	36 subjects, all with decompensated heart failure refractory to standard therapy. 475 infusions of nesiritide were administered.	Subjects received 2mcg/kg bolus, followed by 0.01 µg/kg/min of nesiritide, given over a 4 to 6 hour period.	12 weeks post infusion, 71% of patients were alive and had no hospitalization compared to 52% in the FUSION I trial. Mean hospital days for nesiritide pts 1 yr prior to nesiritide was 9 days. After	No comparison group. Small sample size. QOL measures not identified. Only 12-wk mortality reported. Though study

				treatment with nesiritide, the mean number of hospital days was 6.5 days. Mortality rate at 12 wks was 5.7 for high risk pts receiving nesiritide, compared to the FUSION I trial.	divided group into high risk and low risk groups, it only reported numbers for high-risk subjects, but not for low-risk subjects.