Title: Day vs. Night: Does time of presentation matter in Acute Heart Failure? A secondary analysis from the RELAX-AHF Trial

Short title: Acute heart failure and circadian rhythm

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Abstract:

Background: Signs and symptoms of heart failure can occur at any time. Differences between acute heart failure (AHF) patients who present at nighttime vs. daytime and their outcomes have not been well studied. Our objective was to determine if there are differences in baseline characteristics and clinical outcomes between AHF patients presenting during daytime vs. nighttime hours within an international, clinical trial.

Methods: This is a post-hoc analysis of the RELAX AHF trial, which randomized 1,161 AHF patients to serelaxin vs. placebo, both in addition to usual AHF therapy. Pre-specified end points of the primary trial were used: dyspnea, 60-day HF/RF (heart failure/renal failure) re-hospitalization or cardiovascular (CV) death, and 180-day CV death. Both unadjusted and adjusted analyses for outcomes stratified by daytime vs. nighttime presentation were performed.

Results: Of the 1161 RELAX-AHF patients, 775 (66.8%) patients presented during daytime and 386 (33.2%) at nighttime. Baseline characteristics were largely similar, though daytime patients were more likely to be male, have greater baseline body weight, higher NYHA class, history of atrial fibrillation, and more peripheral edema than nighttime patients. No differences in dyspnea relief or 60-day outcomes were observed. However, daytime presentation was associated with greater risk for 180-day CV death after adjustment (HR 2.28, 95% CI 1.34-3.86; c-statistic 0.82 (95%CI 0.78-0.86)).

Conclusion: In this secondary analysis of the RELAX-AHF trial, baseline characteristics suggest daytime presenting patients may be more gradual worsening of chronic heart failure. AHF patients who presented at night had less risk for 180-day CV death, but similar risk for 60-day CV death or re-hospitalization and symptom improvement as patients who presented during the daytime.

Keywords: acute heart failure, circadian rhythm, serelaxin

Introduction

Symptoms and signs of acute heart failure (AHF) occur at any time, driving patients to seek care. Observed differences in characteristics and outcomes between AHF patients presenting during daytime vs. nighttime hours suggest potential different pathophysiological mechanisms or differences in disease severity.[1-3] Other acute cardiovascular processes, leading to myocardial infarction, myocardial ischemia, and sudden cardiac death occur more frequently in the early morning hours:[4] Circadian rhythms may contribute to their respective disease mechanisms.[5]

Attempts to better understand potential circadian interactions from acute heart failure (AHF) clinical trials have been limited by operational constraints: Patients are primarily enrolled during 'working' hours — Monday through Friday, 0800 to 1700. However, more recent trials narrowed the window of randomization, allowing greater scrutiny of potential circadian differences. Differences might spur further investigation into the pathogenic mechanisms; this may also have implications for clinical trial design. Thus, we conducted a post-hoc analysis of the RELAX-AHF trial to study potential differences in characteristics and outcomes for patients who present during daytime hours vs. nighttime hours and weekend/holidays.

Methods

This is a post-hoc analysis from the RELAX-AHF trial, whose design and main results have been previously reported. [6-9] Briefly, RELAX-AHF was an international, multi-center, randomized, double-blind, placebo-controlled trial that enrolled 1161 patients hospitalized for AHF. The upper limit of randomization was 16 hours from first presentation to the hospital. Patients received either serelaxin or matching placebo for 48 hours, both in addition to usual AHF care.

Per pre-specified eligibility criteria, all patients had shortness of breath, elevated natriuretic peptide levels, a chest x-ray with evidence of congestion, mild to moderate renal insufficiency (≥30 - ≤ 75 ml/min/1.73m2), a systolic blood pressure > 125 mmHg, and had received at least 40 mg of intravenous furosemide (or equivalent) therapy. All clinical trial sites were IRB or Ethics Committee approved to participate in RELAX-AHF. The trial was registered on clinicaltrials.gov, NCT00520806. The original RELAX-AHF study was sponsored by Corthera Inc, a Novartis company. Statistical support was provided by Novartis, however, the authors are solely responsible for the design and conduct of this study, as well as the drafting and editing of the paper and its final contents.

Differentiation of Weekend/Holidays and Daytime vs. Nighttime

Across 11 countries, 96 sites contributed at least one patient to the trial. Saturday and Sunday were considered weekend for all countries except Israel, where Friday after noon and Saturday were considered weekend days. National and regional non-working holidays days were also counted as a weekend day. All other days were considered weekdays. Patients were classified based on time of randomization.

Daytime and nighttime were determined based on previous studies: daytime (08h00 to 19h59) and nighttime (20h00 to 07h59).[2, 3] Patients were classified based on presentation time, not randomization for day vs. night analyses. Presentation was defined as the first recorded time of entry into the hospital system, most commonly via the ED.

Outcomes

The following pre-specified outcomes were analyzed: 1) Change in patient reported dyspnea assessed by the area under the curve representing the change from baseline

measured using a 100-mm visual analog scale (VAS) from baseline to day 5; the worst possible dyspnea VAS score was assigned following death or worsening heart failure. 2) cardiovascular (CV) death or HF/Renal Failure (RF) rehospitalization through day 60; and 3) CV death through day 180. Reasons for rehospitalizations through day 60 and cause of deaths through day 180 were adjudicated by an independent, blinded committee. The association of these outcomes with daytime vs. nighttime presentation as well as weekday vs. weekend/holiday randomization were explored.

Statistical Analysis

Data were analyzed using two separate categorizations: Presentation during daytime vs. nighttime and randomization on weekend/holidays vs. weekdays.

Continuous variables are summarized as means and standard deviations, geometric means and associated 95% confidence intervals (CIs), or medians and interquartile range as appropriate; frequencies and percent are given for categorical variables. Groups were compared using ANOVA, t-test, Wilcoxon rank sum test or chi-square test as appropriate. Poisson regression was used to calculate and compare the estimated enrollment rates for weekend/holiday and working days.

Both unadjusted and adjusted (using linear regression or Cox models as appropriate) analyses of outcomes between daytime vs. nighttime and weekday vs. weekend/holidays were performed. A multivariable linear regression model was developed in the placebo group for the dyspnea VAS AUC to day 5 using backwards selection, with a criterion for retention of $P<0.10$, from baseline patient clinical characteristics and routine laboratory measures. The mean or mode within treatment group was substituted for missing continuous or categorical predictors, respectively. For those predictors where the

non-linear contribution of the association of a restricted cubic spline transformation with the outcome was significant (P<0.10), the non-linear transformation with the lowest Akaike's Information Criterion was chosen from among a dichotomized, trichotomized, linear spline or quadratic or cubic polynomial transformation. The effects of daytime v. nighttime presentation and weekday v. weekend/holiday randomization on the outcome were then adjusted for those variables associated with the outcome in the placebo group. Multivariable Cox regression models for 60-day HF/RF rehospitalizations or CV death and 180-day CV mortality were developed using similar methodology. Baseline covariates found to be prognostic of each outcome variable were included in the adjusted models, with appropriate transformations for non-linear associations. Covariates found to be prognostic of dyspnea VAS AUC to day 5 were age, US-like, weight, body temperature (linear spline at 36.3), dyspnea on exertion, hypertension, mitral regurgitation, history of atrial fibrillation or flutter, alkaline phosphatase, sodium, $\log_2$ troponin T (linear spline at -4.9), dyspnea VAS score (cubic), and uric acid (cubic). Covariates found to be prognostic of 60-day CV death or HF/RF rehospitalization were white race, NYHA class 30 days before, systolic BP, respiratory rate, number of HF hospitalizations in the past year, orthopnea (ordinal), asthma or bronchitis or COPD, hyperthyroidism, lymphocytes %, BUN, phosphate (cubic), sodium, and total protein (linear spline at 68). Covariates found to be prognostic of CV mortality through day 180 were US-like, systolic BP, orthopnea (ordinal), angina, hyperthyroidism, mitral regurgitation, atrial fibrillation/flutter at screening, lymphocytes %, white blood cell count, BUN, sodium, potassium, calcium, total protein, $\log_2$ troponin T, and $\log_2$ NT-proBNP. "US like" is defined by the following countries: United States, France, Netherlands, Israel, Spain, Germany, Italy, and Poland. Non-US like includes patients from Argentina, Hungary, and Romania.

For consistency, we have used the same multivariable models for each secondary RELAX-AHF manuscript. For each model, adjusted R^2 (for continuous outcome) or C-index (for time-to-event outcome) are reported, given the potential risk of overfitting. Thus, adjusted R^2 values from five-fold cross-validations are presented. C-indexes from five-fold cross-validations are also presented."

Results

All 1161 patients enrolled in the RELAX-AHF trial comprised the cohort for analysis.[7] Of those, 775 (66.8%) patients presented during the daytime and 386 (33.2%) at nighttime. Figure 1 shows the numbers of patients who presented at each hour.

Baseline characteristics, stratified by daytime vs. nighttime presentation, are summarized in Table 1. Overall, daytime and nighttime patients were similar, with the following exceptions: nighttime patients were more likely to be women, had a lower body weight, were more likely to have been enrolled in Eastern Europe, and be in NYHA Class II in the month prior to presentation, and had a lower prevalence of peripheral edema compared to daytime patients. Nighttime presentation was also associated with a slightly higher high sensitivity troponin level, but less atrial fibrillation at time of screening, less history of CRT implants, and less beta blocker use. Time from presentation to randomization was longer in nighttime patients. (Supplemental Figure 1)

Working Days vs. Weekend/Holidays Randomization

A much smaller number of patients were enrolled on the weekend/holidays (n=106) compared to weekdays (n=1055). (Supplemental Figure 1b) Enrollment during weekdays was over 4 fold greater than weekend/holidays (enrollment rate ratio = 4.2 (95%CI 3.44-

5.13). Baseline characteristics are presented in Supplemental Table 1 and were largely similar between groups. Of note, patients enrolled during the week were younger by almost 4 years, with significantly lower proportion of women enrolled. Weekend enrollment was greatest in Eastern Europe. Weekday patients were more likely to have an EF < 40%, more NYHA Class III (but less Class II and IV), and more devices implantations. They were also more likely to have edema at baseline. 100% of weekend patients presented with rales vs. 94% of weekday patients. The time from presentation to randomization was similar for both groups.

Timing of Presentation or Randomization and Relationship to Outcomes

Daytime vs. Nighttime

There were no differences in dyspnea improvement (VAS AUC through 5 days) or 60-day HF or RF re-hospitalization by day or nighttime presentation. However, daytime patients were at an increased risk of 180-day CV death, which approached statistical significance without covariate adjustment (HR 1.62, (95% CI 0.99-2.64), p = 0.0546; c-statistic 0.55 (0.50-0.59)), but was statistically significant after multivariable adjustment (HR 2.28, (95% CI 1.34-3.86); c-statistic 0.82 (95%CI 0.78-0.86) p=0.0023). Survival curves are shown in Figure 2.

Weekday vs. Weekend/Holidays

Although limited by smaller numbers, no significant differences were seen in any of the three unadjusted analyses, though greater differences in dyspnea were seen in weekend/holiday patients compared to day vs. night. (Table 2b) After multivariable adjustment, weekday patients had significantly less improvement in dyspnea (mean

difference -458.6 mm-hour, 95% CI -922.6-5.5, p=0.0528) compared to weekend/holiday patients. In terms of mortality and re-hospitalization, weekday patients experienced significantly less CV death or HF/RF re-hospitalization through day 60 (HR 0.55, 95% CI 0.34-0.91,p=0.0194) c-index 0.74 (0.70-0.78)), however, no differences in 180-day CV death were seen.

Treatment Effect by Daytime vs. Nighttime Presentation or Weekend/Holidays vs Weekday Randomization

A similar analysis stratifying by treatment was also performed. No statistically significant interactions between treatment (serelaxin vs. placebo) and either daytime versus nighttime presentation or workday versus weekend/holiday enrollment were observed for any of the three outcomes examined (data not shown).

Discussion

In this post-hoc analysis from RELAX-AHF, approximately two thirds of enrolled patients presented during daytime hours and 90% were randomized on a weekday. Overall, we found: 1) Nighttime patients were at significantly less risk for 180-day CV death; 2) Weekend/holidays patients had greater dyspnea improvement through 5 days; however, 3) Weekend/holidays patients were at greater risk for 60-day CV death or HF/RF re-hospitalization; they were not at greater risk for 180-day CV death. No treatment interactions were observed. Unsurprisingly, most trial patients were enrolled during weekday business hours. A longer time from presentation to randomization occurred for nighttime patients though there was no difference between weekday and weekend/holidays patients.

Within the limitations of a clinical trial population, timing of presentation may identify a different phenotype of AHF.[10, 11] While baseline characteristics were similar overall, nighttime patients were more likely to be female, lighter in weight, have NYHA class II symptoms vs. Class III, less atrial fibrillation, and less peripheral edema, though with slightly higher high-sensitivity troponin T levels. This suggests nighttime patients may be more rapid onset vs. a gradually worsening chronic HF phenotype. Our analysis suggests nighttime patients are a lower risk group, despite the median NT-proBNP of 5228 ng/L.

This finding of lower baseline risk of nighttime supports previous registry work from the Japanese ATTEND registry (4) where better outcomes were reported for nighttime presenting patients. However, in ATTEND, once adjusted for presenting SBP, the differences were no longer significant. In a different study by Minami et.al., significant SBP differences between daytime and nighttime patients were observed, suggesting distinct phenotypes of AHF may present during the day vs. night. We did not find any differences in baseline SBP in our analysis. An older study exploring the chronobiology of acute pulmonary edema,[1] found the majority of acute pulmonary edema cases occurred at night. While the explanatory mechanism remains unclear, the authors suggested the potential impact of lying flat with subsequent increased venous return as a potential precipitant in at-risk individuals. Thus, patients presenting at nighttime seem more likely to have a clinical presentation of acute pulmonary edema whereas those presenting during daytime are more likely to have fluid overload and peripheral edema as the main cause of decompensation. Although these patients may appear more acutely ill at time of presentation vs. slowly worsening chronic HF, paradoxically, these patients who present

with higher SBP may have lower longer term risk. This may also explain their worse prognosis as daytime patients may be a more gradual worsening chronic HF phenotype.[12]

Patients enrolled during nighttime had a longer time from presentation to randomization. This is probably related to reduced research staffing during night times. This relative lag time at night compared to daytime may be important if earlier initiation of therapies is found to be beneficial. It must be, however, noted that no interaction between time from presentation to treatment and outcomes was found in two recent trials.[13, 14]

Of note, no differences in timing of presentation to randomization occurred on weekend/holidays, when study staff might also be less available. Discordant signals of greater dyspnea improvement in weekday patients, but more CV death or HF/RF re-hospitalization suggest a weak or absent relationship between symptom improvement and 60-day outcomes. Despite less risk for 60-day outcomes, no improvement in 180-day CV death was observed for weekend/holidays patients. In OPTIMIZE HF, approximately 22% of patients were hospitalized on a weekend. No differences in 60-90 day mortality or rehospitalizations were observed.[15]

Overall, this study suggests future AHF trials should enroll AHF patients irrespective of day or night to maximize generalizability.

Limitations:

As a post-hoc analysis, unmeasured confounders may be present due to the lack of randomization between groups, despite their similar baseline characteristics and adjusted analysis. As this is a clinical trial population with strict eligibility criteria, these findings should not be applied to the general AHF population. External validation of our findings in a more general AHF population is needed. It is worth highlighting that certain high risk

features were excluded from this clinical trial population, such as significant anemia, significant arrhythmias, severe infections, ACS, patients with significant underlying valve disease, transplant patients, vented patients, or those requiring inotropic therapy – all known markers of risk. At the same time, only patients with mild to moderate renal insufficiency were included and only those with elevated natriuretic peptide levels, along with significant symptoms at rest or with minimal exertion. A particular criterion was the elevated SBP > 125 required for RELAX AHF; specifically for our study, the mean SBP was 142mmHg (SD 17). When compared to other published registries such as ADHERE, OPTIMIZE HF, and EurObservationl, our average SBP is remarkably similar (ADHERE mean SBP 144mmHg (SD 32.6),[16] OPTIMIZE HF 142.6mmHg (33.2),[17] and EurObservational 133mmHg (29).[18] Overall, less heterogeneity of a clinical trial population as well as similarity in baseline characteristics supports our hypothesis generating findings vs. attribution to other co-morbid conditions or precipitants.

Conclusion

In this post-hoc analysis from RELAX-AHF 2, nighttime patients presented with unique clinical characteristics compared to daytime patients; most notably less peripheral edema. They were also associated with lower risk for 180-day CV death than daytime presenting patients. Although further work is needed to confirm these findings, especially from a mechanistic standpoint, trial enrollment strategies to capture these patients are needed to ensure generalizability of study findings.

Disclosures:

Peter Pang is or has been in the last one year a Consultant for: Janssen, Medtronic, Novartis, Trevena, scPharmaceuticals, Cardioxyl, Roche Diagnostics, Relypsa, Honoraria: Palatin Technologies Research Support: Roche, Novartis, PCORI, Indianapolis EMS, IU CTSI

Cotter and Davison: are employees of Momentum Research

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