Implications of Using Different Definitions on Outcomes in Worsening Heart Failure

Jacob P. Kelly, MD; Lauren B. Cooper, MD; Dianne Gallup, MS; Kevin J. Anstrom, PhD; Horng H. Chen, MD; Margaret M. Redfield, MD; Christopher M. O’Connor, MD; Robert J. Mentz, MD; Adrian F. Hernanadez, MD, MHS; G. Michael Felker, MD, MHS

Background—In-hospital worsening heart failure (WHF) is an important event that has inconsistent definitions used across trials. We used data from 2 acute heart failure (HF) trials from the National Institutes of Health HF Network, DOSE (Diuretic Optimization Strategies Evaluation) and ROSE (Renal Optimization Strategies), to understand event rates associated with different WHF definitions.

Methods and Results—We pooled data from 668 patients in DOSE and ROSE and assessed the relationship between WHF and the composite end point of rehospitalization, emergency room visits for HF, and mortality through 60 days. We also assessed for a differential relationship between the timing of WHF development and outcomes. The overall incidence of WHF was 14.6% (24.1% in DOSE, 6.3% in ROSE, and 5.0% in DOSE using the ROSE definition). WHF was associated with an increase in the composite end point (hazard ratio [HR], 1.64; 95% confidence interval [CI], 1.11–2.42; P=0.01). However, the association between WHF and outcomes was significantly stronger in ROSE than in DOSE (HR, 2.67; 95% CI, 1.45–4.91; P<0.01 and HR, 1.28; 95% CI, 0.79–2.08; P=0.31, respectively). Development of WHF between baseline to 24 hours compared with 24 to 48 hours or 48 to 72 hours demonstrated a trend toward improved outcomes (HR, 0.49; 95% CI, 0.21–1.17; P=0.11 and HR, 0.45; 95% CI, 0.20–1.04; P=0.06, respectively).

Conclusions—A WHF definition that excluded the intensification of diuretics resulted in a lower event rate but a stronger association with outcomes. These data support the need for continued efforts to standardize WHF definitions in clinical trials.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00577135 (DOSE) and NCT01132846 (ROSE).

Key Words: diuretics ■ heart failure ■ hospitalization ■ outcome assessment (health care)

A
cute heart failure (AHF) is associated with significant morbidity and mortality.1 A subset of patients hospitalized with AHF experience worsening heart failure (WHF) during hospitalization, which is associated with increased risk of worse clinical outcomes.2 WHF is generally considered to require both persistent or worsening signs or symptoms and some escalation of therapy directed at those symptoms. WHF has been an end point in previous and ongoing AHF trials.3,4 Outcomes data from registries and secondary analyses from clinical trials suggest that patients who experience WHF are at increased risk for subsequent events.2,5–7

See Clinical Perspective

There have been several small studies and an analysis of the acute decompensated heart failure national registry that have defined the prevalence and assessed the association between WHF and clinical outcomes.2,6–10 The definitions used in these previous analyses have varied in 2 ways: (1) by whether worsening is a subjective assessment (eg, treating physician making a categorical assessment of WHF on loosely defined scoring system) by the clinician or an objective measure (eg, at least 1 sign, symptom, or radiological evidence of new, persistent, or worsening acute HF requiring the addition of a new intravenous therapy or mechanical support during a patient’s index hospitalization targeted specifically at HF symptoms) and (2) by the variables that constitute escalation of therapy ranging from additional open-label loop or thiazide diuretic to intravenous inotrope/vasodilator therapy or mechanical circulatory support.3,8,9,11–13

Butler et al14 have recently suggested that the clinical implications of inpatient WHF are clear, but there is a need to better understand the underlying pathophysiology of WHF, and the implications of the lack of a consensus definition of WHF that currently exists. We used data from 2 acute HF
trials conducted by the National Heart, Lung, and Blood Institute–sponsored Heart Failure Network to understand how different WHF definitions impact clinical event rates and outcomes.6,12 The influence of the time of development of WHF clinical events was also evaluated.

Methods

Data Source

We performed a pooled analysis from nonoverlapping patients from 2 acute HF trials conducted by the HF Network: ROSE-AHF (Renal Optimization Strategies in Acute Heart Failure) and DOSE-AHF (Diuretic Optimization Strategies Evaluation in Acute Heart Failure) totaling 668 patients. Around 646 patients were available for analysis given the inability to evaluate 4 patients enrolled in both DOSE and ROSE and 18 patients without ascertainment of WHF from randomization to 72 hours (Figure 1). ROSE-AHF was a multicenter, double-blind, placebo-controlled clinical trial that enrolled 360 hospitalized patients with acute HF and renal dysfunction, randomized within 24 hours of admission. Participants were randomized in an open, 1:1 allocation ratio to dopamine or nesiritide.13 Within each group, participants were randomized in a double-blind, 2:1 ratio to active treatment or placebo leading to participants on dopamine (n=122), nesiritide (n=119), and placebo (n=119) with independent comparisons with the pooled placebo group.12,13 The ROSE coprimary end points included 72-hour cumulative urine volume (decongestion end point) and the change in serum cystatin C from enrollment to 72 hours (renal function end point). DOSE was a prospective, double-blind, randomized trial that enrolled 308 patients with acute HF.11 Participants were similarly randomized as in ROSE to receive furosemide administered intravenously by means of either a bolus every 12 hours or continuous infusion and at either a low dose (numerically equivalent to the patient’s previous oral dose given intravenously) or a high dose (2.5x the previous oral dose given intravenously). The protocol allowed specified dose adjustments after 48 hours. Patients were eligible for enrollment in DOSE if they presented to the hospital within the previous 24 hours with acute HF. Acute HF was diagnosed on the basis of the presence of at least 1 symptom (dyspnea, orthopnea, or edema) and 1 sign (rales, peripheral edema, ascites, or pulmonary vascular congestion on chest radiography) of HF. Additional eligibility criteria for DOSE were a history of chronic HF with signs, symptoms, or IV treatment for HF before 72 hours were eliminated from the analyses and the anchor for statistical significance. All statistical computations were generated using SAS version 9.2 (SAS Institute Inc., Cary, NC) or higher.

Definitions

In both trials, WHF was defined as persistent or worsening HF requiring rescue therapy including intravenous vasoactive agents, ultrafiltration, or mechanical support >72 hours after randomization. In addition, in DOSE, the WHF definition also included additional open-label loop or thiazide diuretic. Specifically, WHF had to be treated with open-label loop or thiazide diuretics greater than what the patient was taking at their randomized treatment assignment. Because the ROSE case report form did not record the additional DOSE qualifying definition for WHF, a sensitivity analysis was unable to be performed using each WHF definition in each trial. However, we were able to assess the event rate in DOSE using the stricter ROSE definition. WHF status was documented post-randomization, at 0 to 24 hours, 24 to 48 hours, and 48 to 72 hours post randomization based on protocol defined daily assessments. HF rehospitalization, all-cause mortality, and emergency room (ER) visits for HF were documented by study coordinators and clinicians on a standardized case report form. HF rehospitalization and assessment of adverse events, including death, were evaluated within 60 days after randomization. All clinical end points were investigator reported. Rehospitalization was defined as a hospital stay ≥24 hours. ER visits were defined as a visit to an emergency department related to HF with signs, symptoms, or IV treatment for HF.

Outcomes of Interest

The primary outcome for the current analysis was the composite end point of HF rehospitalization, ER visits for HF, and mortality through 60 days.

Statistical Analysis and Clinical End Points

Demographics, physical and laboratory findings, medical history, and therapies were summarized as frequencies and percentages for categorical variables and by medians and 25th and 75th percentiles for continuous variables. Baseline characteristics were compared using Wilcoxon rank-sum test for continuous variables and Pearson χ² tests for categorical variables. We assessed the relationship between the development of WHF within 72 hours of randomization and timing of development of WHF (early versus late) and the composite end point of HF rehospitalization, ER visits for HF, and mortality through 60 days. Cox proportional hazards models using landmark analysis were used to evaluate time to first event in the composite end point from 72 hours to 60 days. Cox proportional hazards models using landmark analysis were used to evaluate time to first event in the composite end point from 72 hours to 60 days. Subjects experiencing the composite end point before 72 hours were eliminated from the analyses and the anchor for time to event was 72 hours. Cox proportional hazards models using landmark analysis were used to evaluate time to first event in the composite end point from 72 hours to 60 days. Subjects experiencing the composite end point before 72 hours were eliminated from the analyses and the anchor for time to event was 72 hours. Analyses in which both trials were combined, the models were adjusted for trial; otherwise, all models were unadjusted for any potential confounders. Statistical significance was assessed using 2-sided P values, with values <0.05 considered statistically significant. All statistical computations were generated using SAS version 9.2 (SAS Institute Inc., Cary, NC) or higher.

Results

W HF occurred in 14.6% of patients in the pooled cohort—24.1% in DOSE and 6.3% in ROSE (Table 1).
Using the ROSE definition in the DOSE trial cohort decreased the WHF event rate to 5.0% in the DOSE cohort of patients (Table 2). Patients who developed WHF within 72 hours post randomization were generally similar to those that did not with regard to age, race, sex, comorbidities, and hospitalization for HF in the previous year. Patients who developed WHF had higher baseline daily diuretic use than patients who did not develop WHF ($P=0.003$). Vital signs, physical examination findings, and laboratory values were similar for patients with and without WHF, with the exception of median systolic blood pressure, which was lower in patients with WHF ($P=0.03$). A larger percentage of patients who did not develop WHF had a history of peripheral edema when compared with subjects with WHF ($P<0.01$).

Table 2. WHF Rates According to Trial Definition

<table>
<thead>
<tr>
<th>Therapy</th>
<th>DOSE Trial</th>
<th>ROSE Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOSE WHF definition</td>
<td>72/299 (24.1%)</td>
<td>N/A</td>
</tr>
<tr>
<td>ROSE WHF definition</td>
<td>15/299 (5.0%)</td>
<td>22/347 (6.3%)</td>
</tr>
</tbody>
</table>

N/A indicates not applicable; and WHF, worsening heart failure.
In ROSE, WHF events were driven by treatment with IV vasoactive agents (90.9%) and ultrafiltration in 1 patient (4.5%; Table 3). WHF events in DOSE were largely driven by additional loop diuretic, thiazide, or metolazone (90.3%) compared with intravenous vasoactive agents (12.5%).

An overall test was performed before subgroups were analyzed utilizing a 3 df test because there were 4 groups (no WHF, 0- to 24-hour WHF, 24- to 48-hour WHF, and 48- to 72-hour WHF). We report the following: for DOSE (3 df) 

\[ P = 0.27, \text{ for ROSE (3 df) } P = 0.0026, \text{ and all patients (3 df) } P = 0.0089. \]

The unadjusted hazard ratios (HRs) of the composite end point of 60-day death, HF rehospitalization, and ER visits for HF for those who developed WHF through 72 hours versus those who did not are presented in Table 4. Patients who develop WHF within 72 hours of admission had a significantly higher risk of death, HF rehospitalization, or HF ER visit through 60 days (combined data set HR, 1.64; 95% confidence interval [CI], 1.11–2.42; \( P = 0.01 \)). When the components of the combined data set are evaluated using the individual trial definitions, the association between WHF and worse clinical outcomes remain significant in ROSE (unadjusted HR, 2.67; 95% CI, 1.45–4.91; \( P = 0.002 \)) but not in DOSE (unadjusted HR, 1.28; 95% CI, 0.79–2.08; \( P = 0.31 \)). The unadjusted HRs of the composite end point for DOSE patients whose WHF was only treated with additional diuretics and DOSE patients who met the ROSE definition versus those DOSE patients who did not develop WHF are presented in Table 5. The hazard for the composite end point did not differ between those DOSE patients whose WHF was only treated with additional diuretics versus those DOSE patients who did not develop WHF (HR, 0.97, 95% CI, 0.55–1.7; \( P = 0.90 \)), whereas the hazard of the composite end point was 3.4× larger in those DOSE patients who met the ROSE definition versus DOSE patients with no WHF (HR, 3.4; 95% CI, 1.6–7.14; \( P = 0.001 \)).

Patients who developed WHF from baseline to 24 hours compared with those who did not develop WHF had no difference in outcomes in the pooled or individual cohorts (pooled cohort [HR], 0.99; 95% CI, 0.50–1.97; \( P = 0.99 \); DOSE [HR], 0.80; 95% CI, 0.34–1.85; \( P = 0.60 \); and ROSE [HR], 1.50; 95% CI, 0.47–4.76; \( P = 0.49 \); Figure 2). Patients who developed WHF from 24 to 48 and 48 to 72 hours in the pooled cohorts tended to have worse outcomes compared with patients who did not develop WHF (HR, 2.02; 95% CI, 1.10–3.70; \( P = 0.02 \); and HR, 2.20; 95% CI, 1.25–3.87; \( P = 0.006 \), respectively). However, patients who developed WHF from 48 to 72 hours tended to have worse outcomes than patients who did not develop WHF in ROSE (HR, 4.32; 95% CI, 1.88–9.95; \( P = 0.001 \)) but not in DOSE (HR, 1.53; 95% CI, 0.73–3.20; \( P = 0.26 \)).

The HRs and 95% CI of death, HF rehospitalization or ER visit for HF based on timing of the development of WHF is presented in Figure 3. There was a trend toward worse outcome in patients who had later development of WHF (24–48 and 48–72 hours) compared with earlier development of WHF (0–24 hours).

### Discussion

Using 2 clinical trials evaluating different treatment strategies in acute decompensated HF, we found that the use of different definitions of WHF yielded distinct outcome rates with differential associations with clinical outcomes. Specifically, the use of intensification of diuretics in the definition of WHF led to modestly higher clinical event rates. However, a much stronger association with clinical outcomes was observed when additional diuretic use was not included. Furthermore, when using the more stringent definition from ROSE in patients from DOSE, there was a 3.4-fold worse hazard of experiencing 60-day death, HF rehospitalization, or HF ER visit when compared with DOSE patients with no WHF. There was a trend toward worse outcomes in patients who developed WHF later compared with earlier in the pooled cohorts. Thus, continued efforts to standardize WHF definitions in clinical

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**Table 3. Qualifying Therapies Among Subjects Who Developed WHF**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>DOSE (n=72), n (%)</th>
<th>ROSE (n=22), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV vasoactive agent</td>
<td>9 (12.5)</td>
<td>20 (90.9)</td>
</tr>
<tr>
<td>Mechanical or circulatory support</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>0 (0)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Loop diuretic, thiazide, or metolazone</td>
<td>65 (90.3)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*WHF was reported on the case report form with qualifying therapies listed below. The specific qualifying therapy was listed below with the option to select (or not) one or more qualifying therapies.

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**Table 4. Unadjusted Association of Worsening Heart Failure Through 72 Hours With 60-Day Death, Heart Failure Rehospitalization, and Heart Failure Emergency Room Visits (Worsening Heart Failure vs No Worsening Heart Failure)**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>n Events, n (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients†</td>
<td>638 166 (26.0)</td>
<td>1.64 (1.11–2.42)</td>
<td>0.01</td>
</tr>
<tr>
<td>DOSE</td>
<td>291 81 (27.8)</td>
<td>1.28 (0.79–2.08)</td>
<td>0.31</td>
</tr>
<tr>
<td>ROSE</td>
<td>347 85 (24.5%)</td>
<td>2.67 (1.45–4.91)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

* Patients who died, had a Heart Failure rehospitalization, or Heart Failure emergency room visit within the first 72 hours were excluded from the analysis.

† Model has been adjusted for trial participant was enrolled in.

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**Table 5. Unadjusted Association of WHF Through 72 Hours With 60-Day Death, Heart Failure Rehospitalization, and Heart Failure Emergency Room Visits in DOSE Patients (DOSE, Diuretic Only vs ROSE Definition vs No WHF)**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>n Events, n (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOSE (diuretic-only WHF) vs no WHF</td>
<td>291 81 (28.0)</td>
<td>0.97 (0.55–1.70)</td>
<td>0.90</td>
</tr>
<tr>
<td>ROSE def. vs no WHF</td>
<td></td>
<td>3.40 (1.62–7.14)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and WHF, worsening heart failure.

* Patients who died, had a Heart Failure rehospitalization, or Heart Failure emergency room visit within the first 72 hours were excluded from the analysis.

† Model is not adjusted for trial participant as our definition includes adjustment for trial.
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Different Definitions in WHF

trials are needed to optimize the utility of WHF as an end point in future studies.

Development of WHF during a patient’s clinical course has emerged as a key indicator in clinical practice and trials that predicts future clinical events. Clinicians and clinical trialists are using WHF to identify high-risk patients and increase event rates in clinical trials given its association with clinical outcomes. RELAX-AHF2 (The Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF Clinical Trial) is evaluating the efficacy of serelaxin in an ongoing clinical trial enrolling 6800 patients using WHF as a coprimary end point. The phase III, multicenter, randomized, double-blind, placebo-controlled TRUE-AHF trial (Trial of Ularitide’s Efficacy and Safety in Patients with Acute Heart Failure) is evaluating ularitide intravenous infusion in patients with acute decompensated HF with WHF as a coprimary end point in 2100 patients contributing to >9000 total patients in current trials utilizing in-hospital WHF as a component of the primary outcome.\(^1\) WHF is a valuable clinical end point that merits continued and even increased use because it predicts and closely aligns with mortality and hospital readmission.

The prevalence of WHF ranges from 5\% to 42\%.\(^2,3,8,9,11,12,16–19\) Most studies have defined WHF based on signs and symptoms of worsening HF requiring some escalation in therapy.

In the largest AHF trial, the ASCEND-HF study (Acute Study of Clinical Effectiveness of Neseritide in Decompensated Heart Failure), the incidence of WHF was 5\% with an associated mortality of 41.5\% through 180 days with WHF defined as intravenous or mechanical therapy in addition to typical clinical signs and symptoms of worsening HF.\(^7\) A secondary analysis in the acute decompensated heart failure national registry, revealed a WHF prevalence of 11\%, which was also defined as the need for an escalation of therapy (specifically inotropic medications or intravenous vasodilator therapy) resulting in mortality at 30 days and 1 year of 19\% and 50\%, respectively.\(^2\) The largest clinical trial and registry of AHF reveal that despite variations in definitions, the strong association with mortality remains. Use of a universal definition for WHF will improve clarity in communication between clinicians, investigators, and regulatory approval officials while allowing future studies to unravel the mechanistic and clinical nuances behind WHF.

If a specific point in time is associated with worse outcomes, then a targeted intervention can be deployed. However, the pooled analysis of ROSE and DOSE demonstrated a trend toward worse outcomes with later development of WHF suggesting future studies should focus on earlier use of vasoactive or mechanical therapies. These findings are contrary to previous evidence from secondary

![Forrest plot of the pooled and individual ROSE and DOSE clinic trials demonstrating the hazard ratio of developing worsening heart failure (WHF) compared with no development of WHF with outcomes of 60-day death, heart failure (HF) rehospitalization, and emergency room visit for HF.](http://circ.ahajournals.org/lookup/doi/10.1161/CIRCHEARTFAILURE.117.006694)
analyses from the ASCEND-HF and PROTECT clinical trials (Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function). Although there are complexities when comparing patient characteristics from different trial data sets, data across multiple studies suggest that patients who develop WHF seem similar with regard to certain baseline characteristics including age and number of comorbidities. A post hoc analysis from the PROTECT trial found no difference in early (days 2–3 after randomization) versus late (4–7 days after randomization) development of WHF.20 Similarly, no differential relationship was found between clinical outcomes and early versus late WHF in ASCEND-HF, where early WHF occurred in the first 3 days of index hospitalization and late WHF started at 4 days and continued through index hospital discharge or day 30.7 However, these are post hoc analyses and the use of different definitions for early and late development of WHF precludes direct comparison. Using a similar definition for WHF with the same time points to record important clinical events in trials evaluating WHF will allow clear communication and pooled analyses across trials that are able to tease out important clues into the underlying WHF.

The pooled analysis of ROSE and DOSE demonstrate that using a different definition for WHF may potentially yield different incidences and associated clinical event rates. A secondary analysis of the PROTECT trial that incorporated a low versus high intensity definition of WHF partially supports this finding. The PROTECT analysis revealed incidence rates of 11.7% and 2.9%, respectively, for low- and high-intensity WHF definitions, without an increased association with worse outcomes in the higher intensity definition.20 The pooled analysis of the PROTECT and RELAX-AHF trials used a similar WHF definition to our definition, which supports this finding. The PROTECT analysis revealed incidence in early (days 2–3 after randomization) versus late (4–7 days after randomization) development of WHF.20 Similarly, no differential relationship was found between clinical outcomes and early versus late WHF in ASCEND-HF, where early WHF occurred in the first 3 days of index hospitalization and late WHF started at 4 days and continued through index hospital discharge or day 30.7 However, these are post hoc analyses and the use of different definitions for early and late development of WHF precludes direct comparison. Using a similar definition for WHF with the same time points to record important clinical events in trials evaluating WHF will allow clear communication and pooled analyses across trials that are able to tease out important clues into the underlying WHF.

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The findings of our analysis should be considered in light of several limitations. This was a retrospective analysis pooling results from 2 separate clinical trials. ROSE and DOSE were clinical trials with specific but similar inclusion and exclusion criteria that may differ from other populations. The available data from the case report forms did not allow evaluation of the DOSE WHF definition in the ROSE trial patients. Multiple statistical tests involving the composite end point were evaluated, but no methods were utilized to adjust for multiple comparisons; however, an overall test was performed before further subgroup analyses were analyzed.

Conclusions

The results from this pooled analysis of 2 acute HF clinical trials emphasize the importance of using a standardized definition for WHF. Various definitions lead to different incidence rates of WHF and limit the precision of predicting event rates and outcomes. There was trend toward worse outcomes in patients who developed later versus earlier WHF. A WHF definition that incorporates intensification of diuretics may increase event rates without strengthening the association with worse clinical outcomes. Using a standardized WHF definition in clinical trials may facilitate more effective assessments of future pharmaceutical or device therapies in the war on acute HF.

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References

In the context of clinical trials, worsening heart failure (WHF) is an emerging end point that is increasingly being used as a component of a composite end point. However, the definitions used in previous analyses and clinical trials have varied with regard to the subjectivity of their assessment and how intense an escalation of therapy is required to qualify as a WHF event. Using 2 acute HF trials with different intensity WHF definitions, we found that use of different definitions of WHF yielded distinct event rates and differential associations with clinical outcomes. Intensification of diuretics led to higher clinical event rates, whereas the use of a more stringent definition of WHF that required more than additional diuretic led to a 3.4-fold worse hazard of experiencing 60-day death, HF rehospitalization, or HF Emergency Room visit when compared with patients with no WHF. Our study highlights the importance of standardizing WHF definitions in clinical trials to optimize the utility of WHF as an important clinical end point in future studies.
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