Efficacy and Dosage Pattern of Sacubitril/Valsartan in Chinese Heart Failure with Reduced Ejection Fraction Patients

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Abstract

This study aims to investigate the dosage pattern, efficacy, and safety of sacubitril/valsartan (Sac/Val) in Chinese heart failure with reduced ejection fraction (HFrEF) patients regarding real-world settings. Patients from 27 centers with a confirmed diagnosis of HFrEF and initiated Sac/Val treatment were enrolled. The primary objective was to evaluate the dosage pattern and change of heart failure status. In a final cohort of 983 patients, outpatient Sac/Val treatment demonstrated a similar beneficial effect in NT-proBNP and cardiac function. After initiating the treatment, overall and sub-population showed similar safety and efficacy. Patients who received a higher dose of Sac/Val (> 200 mg/d) demonstrated better improvement in LV function and reduction of NT-proBNP regardless of adjustment. Among Chinese HFrEF patients, Sac/Val showed a comparable reduction in NT-proBNP and improvement in cardiac function. Data further support guideline recommendations of Sac/Val in Chinese population. Optimal up-titration might provide further benefits. Further long-term and prognostic studies are needed.

Keywords Angiotensin receptor-neprilysin inhibitor (ARNI) · Heart failure · Sacubitril/valsartan · Chart review · Real-world data
Introduction

With the population aging and rapid urbanization in China, there are over 300 million people with cardiovascular disease (CVD) [1, 2]. As the end-stage syndrome of various CVD, the growing morbidity of heart failure (HF) increases health burden. In the past decade, numbers of novel pharmacological treatments have been shown to benefit HF patients [3].

Sacubitril/valsartan (Sac/Val), an angiotensin receptor neprilysin inhibitor (ARNI), significantly reduced cardiovascular mortality and HF hospitalizations as compared to angiotensin-converting enzyme inhibitors (ACEI) for patients with heart failure with reduced ejection fraction (HFrEF; LVEF < 40%) [4], was approved in July 2017 in China. Although PARADIGM-HF has a relatively low representation of Asian population, ARNI has been recommended for most HFrEF patients in Chinese and other global HF guidelines [5–7]. The growing evidence regarding the safety and efficacy of ARNI in improving HF outcomes [9–12] demonstrated reduction in NT-proBNP concentration and improvement in echocardiographic markers of cardiac function. [13] Previous studies also demonstrated an early treatment strategy for initiating time, up-titrating, and optimizing dose of ARNI in both hospitalized and outpatient settings could improve clinical outcomes in HFrEF [14–17]. With years of utilization, various data based on the guideline-directed medical therapy (GDMT) showed ARNI initiations were associated with early improvements in patient-reported health status [17, 18]. Furthermore, subgroup analyses regarding different comorbidities also showed additional evidence regarding its safety and effectiveness (e.g., PARADIGM-HF LFT, HRQL) [19–21].

However, the evidence of the titration patterns, prescribed dose, and patient characteristics in real-world clinical practice in the Chinese population were still missing, which limits the translation of conclusions to broad patient populations and the clinical implementation. While the sub-optimal use of ARNI in clinical practice remains high [8], such information is critical to inform physicians on translating the trial results into clinical practice for optimal usage of Sac/Val, especially in routine initiation and dose up-titration.

To better understand the treatment patterns of ARNI and improve clinical management for patients with HFrEF in real-world Chinese setting, this multi-center, retrospective, non-interventional, chart review study—Reality-HF—aims to provide clear dosage pattern, change of heart failure status, and safety report in HFrEF patients who were treated with Sac/Val.

Methods

Study Setting and Population

The study population was composed of HFrEF patients who started to receive Sac/Val from September 2017 to August 2018, at 27 tertiary hospitals in China (Appendix Table 1—list of participating hospitals). Patients were anonymized using a 9-digit number consisting of a 4-digit center number and a 5-digit patient number. The chart review, for HFrEF patients who were prescribed Sac/Val in the identification period (19 September 2017 to 30 August 2018), was extracted from the time of first Sac/Val prescription (index date), 6 months before (pre-index period), and after (post-index period) the index date for the baseline and clinical characteristics of patients (Appendix Fig. 1—study flowchart).

Medical charts of patients with the following characteristics were for data abstraction: (1) 18 years of age or older; (2) confirmed diagnosis of HFrEF by investigator; (3) patients prescribed Sac/Val during the identification period; (4) patient has at least 1 follow-up visit after index date. Patients who participated in other clinical study and confirmed pregnancy were excluded. To be noted, for the diagnosis of HFrEF, patients were first identified by the International Classification of Diseases-10: 150 (heart failure), and then checked by the results of echocardiogram for reduced left ventricular ejection fraction (LVEF).

To describe the study population, characteristics of demographics, comorbidities (anemia, hypertension (HTN), diabetes mellitus (DM), chronic kidney disease (CKD), chronic obstructive pulmonary disease), heart failure history, and physical examination were collected. Information on Sac/Val dosage, changes of heart failure status, and the parameters of comorbidities were also collected through the available charts. The 50 mg of Sac/Val contains 24 mg of sacubitril and 26 mg of valsartan. The total dosages in daily use were documented and further analyzed (mg/d).

This study protocol was approved by the independent Ethics Committee of the First Affiliated Hospital of Nanjing Medical University and China National Center for Biotechnology Development (GH0402).

Primary and Secondary Objectives

The primary objective was to evaluate the dosage changes (e.g., increased dosage—up-titrated) in HFrEF patients receiving Sac/Val and their heart failure status based on functional and biomarker tests. Dosage at the index date to month 6 post-indexing date and its titration change were documented. Simultaneously, the New York Heart Association (NYHA) classification and NT-proBNP levels from
baseline to months 1, 2, 3, 4, 5, and 6 post-indexing date in HFrEF patients receiving Sac/Val were documented.

Secondary objectives were to describe the treatment patterns and clinical status of HFrEF patients receiving Sac/Val over time. Exploratory secondary objectives also included the subgroup analysis of the Sac/Val dosage pattern in HFrEF patients by their comorbidities (HTN, DM, CKD) and corresponding parameters—systolic blood pressure (SBP) and diastolic blood pressure (DBP), serum creatinine, serum potassium, and echocardiographic parameters.

**Data Management**

After the trained site investigators reviewed charts from hospital databases based on the inclusion/exclusion criteria, medical records of the eligible patients were extracted and anonymized. Admission information, drug administration record, diagnostic and treatment procedure records, laboratory results, physician notes, discharge summary, etc. collected using a web-based electronic case report form (eCRF) were encrypted and uploaded to a secured server ensuring confidentiality and privacy of individuals. Data from all participating hospitals were then combined for further analysis.

**Statistical methods**

Independent statistical specialists at ClinChoice Inc. adopted PASS®11 and SAS®9.4 software (or higher version) package to the following statistical analysis. All tests were 2-sided, and \( P < 0.05 \) were considered statistically significant.

Missing values were not replaced. If prescription of Sac/Val or other drug classes were discontinued permanently, then the endpoints would be considered missing. Counts of missing values for both continuous and categorical variable were calculated. Descriptive data analyses were carried out to describe patient profiles, dosage pattern of Sac/Val, treatment patterns, and clinical parameters.

Continuous variables are presented as the means (standard deviations, SDs) with normal distribution or medians with interquartile ranges (IQRs) with non-normal distribution. Comparison was performed using the unpaired Student’s \( t \)-test or the Mann–Whitney \( U \)-test based on their distribution. Categorical variables are presented as numbers (%) and were compared using the Pearson \( \chi^2 \) test.

The assessment of differences in changes in NT-proBNP levels was based on analysis of covariance (ANCOVA) model. The response variable is the change from baseline in NT-proBNP level at each follow-up time point; age, sex, body mass index (BMI), SBP, creatinine, previous ACEI/angiotensin II receptor blockers (ARB) treatment, follow-up time points, and interaction between follow-up time points, and different target dose groups as fixed effects; and logarithm of baseline NT-proBNP as covariate.

### Results

#### Baseline

The detailed baseline characteristics are shown in Table 1. In total, 983 patients were eligible for this study. The mean age was 57.3 years, and 80.5% patients were male. There were 46.2% of patients who had a history of HTN; 27.2% patients had history of DM; 12.4% patients had CKD; 38.8% of patients had a history of coronary heart disease (CHD);
and 17.5% of patients had a history of myocardial infarction. ACEI/ARB were prescribed in 59.2% of patients prior to the Sac/Val treatment. Beta-blockers were prescribed in 66.6% of patients, and mineralocorticoid receptor antagonists (MRA) were prescribed in 63.9% of patients. The N-terminal pro B-type natriuretic peptide (NT-proBNP) level at baseline was 2480.61 pg/mL.

**Primary Objective**

**Dosage Patterns and Utilization of Sac/Val**

There were 35.7% and 51% of patients who initiated Sac/Val in ≤50 mg/d and 100 mg/d, respectively (Fig. 1A). Compared with the initial dose, 56.7% of patients had a dose change during the follow-up period. During the 6-month follow-up, there were 291 (35.7%) patients up-titrated steadily. The proportion of patients who up-titrated showed an upward trend (Fig. 1B), and patients who received ≥200 mg dose up-titrated from the initial dose of ≤50 and 100 mg gradually increased (Fig. 1C).

**Change in Plasma NT-proBNP Level and NYHA Functional Classification**

During the 6 months of treatment, a favorable effect was observed on the plasma NT-proBNP level from baseline after initiating Sac/Val. Although the changes did not show significance in every time-point, NT-proBNP were significantly decreased especially in the early stage of treatment (1 week, 2 weeks, and 1 month vs baseline, all \( P < 0.0001 \), Fig. 2).

In a model further adjusted with age, sex, BMI, SBP, and creatinine (Table 2), the difference of log-transferred NT-proBNP level in the follow-up time-points remained statistically significant compared to baseline (1 month vs baseline, OR = 1.304, 95% CI (1.019, 1.670), \( P = 0.0351 \); 3 months vs baseline, OR = 2.343, 95% CI (1.616, 3.398), \( P < 0.0001 \); 6 months vs baseline, OR = 2.587, 95% CI (1.381, 4.848), \( P = 0.0031 \)).

**Secondary Objective**

**Echocardiographic Parameters**

Table 3 demonstrates the results of echocardiographic parameters with each follow-up time-point. Compared with baseline, patients with HFrEF after 6 months of treatment with Sac/Val have showed varying degrees of improvement in the echocardiographic parameters.

Mean LVEF was 29.96 (6.72) % in baseline, and the LVEF at each follow-up time-point after baseline showed varying increase (1 month, 32.82 (9.51), \( P < 0.0001 \); 3 months, 37.13 (11.15), \( P < 0.0001 \)).

Mean Left ventricle diastolic diameter (LVDd) at baseline was 66.54 (10.03) mm, and the LVDd at each follow-up time-point decreased significantly from baseline (1 month, 66.50 (11.88), \( P < 0.0001 \); 3 months, 63.94 (10.58), \( P < 0.0001 \)).

Mean left atrial diameter (LAD) at baseline was 47.75 (8.09) mm, and the LAD at each follow-up time-point of left atrial diameter (LAD) also decreased significantly from baseline (1 month, 45.57 (8.70), \( P < 0.0001 \); 3 months, 44.87 (7.74), \( P < 0.0001 \)).

**Safety Analysis**

During 6 months of treatment with Sac/Val, 21 (2.1%) patients had increased serum creatinine (≥3.5 mg/dl / 309.4 umol/L); 43 (4.4%) patients had increased serum potassium (≥5.5 mmol/L); and 26 (2.6%) patients complained episode of symptomatic hypotensive events.

Most of the increased creatinine events occurred among the CKD patients (15 out of 122, 12.3%, \( P < 0.001 \)). Occurrence of increased potassium were also significantly higher in CKD patients (13 out of 122, 10.7%, \( P = 0.003 \)).

**Fig. 1** Dosage pattern. A Dosage summary of Sac/Val in each follow-up period. B Dose titration pattern of Sac/Val in each follow-up period. C Initiating dose and dosage changes in 1 month, 3 months, and 6 months. Initiation: The dose of Sac/Val for the first prescription. *The percentage calculation was based on the existing data.
Re-hospitalization Rate

There were 743 (75.6%) patients who had at least one hospitalization event 6 months prior to the index date. After initiation of Sac/Val, there were 368 (37.4%) patients who were hospitalized during follow-up. Regardless of the baseline dose and titration mode, the hospitalization rate of patients showed a downward trend (Appendix Fig. 3—hospitalization at each follow-up).

Table 2  Difference in log-transferred NT-proBNP compared to baseline

| Follow-up time | Available N  | <200 mg/d, 95% CI | ≥ 200 mg/d, 95% CI | OR  | P     |
|----------------|--------------|--------------------|---------------------|-----|-------|
| 1 months       | 861          | 0.601 (0.520, 0.694) | 0.460 (0.377, 0.563) | 1.304 (1.019, 1.670) | 0.0351 |
| 3 months       | 430          | 0.733 (0.577, 0.930) | 0.313 (0.235, 0.416) | 2.343 (1.616, 3.398) | <0.0001 |
| 6 months       | 133          | 0.759 (0.531, 1.084) | 0.293 (0.175, 0.492) | 2.587 (1.381, 4.848) | 0.0031 |

Model adjusted for age, sex, body mass index, SBP, creatinine, previous ACEI/ARB treatment, different target dose groups, follow-up time points, and interaction between follow-up time points as fixed effects

95% CI 95% confidence interval; OR odd ratio

Table 3  Echocardiogram measurements

| Parameter       | Baseline | 1 month | 2 months | 3 months | 4 months | 5 months | 6 months |
|-----------------|----------|---------|----------|----------|----------|----------|----------|
| LVEF (%)        | 820      | 381     | 143      | 166      | 127      | 112      | 92       |
| Median          | 29.94    | 31.3    | 36.0     | 36.0     | 36.0     | 33.5     | 37.5     |
| Change from baseline (Median) | 2.8     | 4       | 6        | 5        | 4        | 6        |
| Mean (SD)       | 29.96 (6.72) | 32.82 (9.51) | 35.95 (9.53) | 37.13 (11.15) | 36.31 (12.38) | 35.87 (13.30) | 38.39 (11.44) |
| Change from baseline (Mean) | 4.14 | 6.49 | 7.82 | 6.81 | 7.04 | 8.63 |
| *P value        | <0.0001  | <0.0001 | <0.0001  | <0.0001  | <0.0001  | <0.0001  | <0.0001  |
| LVDd (mm)       | 834      | 381     | 143      | 166      | 127      | 112      | 92       |
| Median          | 66.0     | 66.0    | 65.0     | 61.0     | 64.0     | 65.0     | 64.0     |
| Change from baseline (Median) | −1  | −1 | −2 | −2 | −1 | −2 |
| Mean (SD)       | 66.54 (10.03) | 66.50 (11.88) | 65.70 (10.44) | 63.94 (10.58) | 65.82 (17.95) | 66.26 (13.92) | 63.98 (9.25) |
| Change from baseline (Mean) | −1.55 | −2.20 | −3.29 | −1.70 | −2.64 | −3.69 |
| *P value        | <0.0001  | <0.0001 | <0.0001  | <0.0001  | 0.0044   | <0.0001  |
| LAD (mm)        | 765      | 368     | 137      | 157      | 124      | 110      | 89       |
| Median          | 47.0     | 45.0    | 46.0     | 44.0     | 44.5     | 45.0     | 43.0     |
| Change from baseline (Median) | −2 | −2 | −3 | −2 | −2 | −3 |
| Mean (SD)       | 47.75 (8.09) | 45.57 (8.70) | 46.55 (7.90) | 44.87 (7.74) | 44.49 (7.97) | 46.70 (8.96) | 44.78 (6.51) |
| Change from baseline (Mean) | −1.85 | −2.44 | −3.74 | −3.35 | −2.26 | −3.17 |
| *P value        | <0.0001  | <0.0001 | <0.0001  | <0.0001  | 0.0114   | <0.0001  |

LVEF left ventricle ejection fraction; LVDd left ventricle diastolic diameter; LAD left atrial diameter; SD standard deviations. *Paired T-test
Subgroup Analysis

In the subgroup analyses with different medical histories, comparing the patients with/without previous AECI/ARB treatment or comorbidities (e.g., HTN, DM, CKD, CHD, DCM), there were no significant difference in the 6-month reduction of NT-proBNP and the improvement of LVEF (Appendix Fig. 4—subgroup analysis of comorbidity).

Although the increased creatinine events mainly occurred in the subgroup of CKD patients, results showed the median of serum creatinine, potassium, and estimated glomerular filtration rate remained stable during the Sac/Val treatment compared to baseline (All \( P > 0.05 \), Fig. 3).

Also, compared to baseline, patients who received a higher dose of ARNI (\( \geq 200 \) mg/d) showed a significant reduction in NT-proBNP (\( P = 0.0351 \)) and improvement of cardiac function (\( P = 0.0076 \)) in follow-up (Table 4, Fig. 4).

Discussion

To the best of our knowledge, the current study firstly reviewed the efficacy of ARNI in HFrEF patients regarding real-world setting in Mainland China. The effects reflected in reduction of NT-proBNP and improvement in cardiac function. A higher dose of ARNI (\( > 200 \) mg/d) might contribute to a better improvement. These results further support the generalization of the previous RCT results in Chinese population.

Despite the various evidence regarding ARNI treatment in HF, most of these RCTs and registered studies were conducted with certain trial criteria and/or among the predominantly non-Hispanic White populations, which limit the results generalized into other ethnic subgroups [22–24]. Also, the adverse effects such as renal dysfunction and hyperkalemia, hypotension, angioedema, and other systemic impact for racial and ethnic differences were the other main areas of concern. While Asian patients with HF are often younger and have worse outcomes than the global average [25–27], it has also been suggested that the ethnic differences [28–30] in tolerability, efficacy, and safety of cardiovascular drugs may be derived from the physical characteristics, pharmacokinetics, innate genetic polymorphisms, lifestyle, etc. Meanwhile, these ethnic and population differences in salt sensitivity and natriuretic peptide–mediated mechanism [21, 31] might also cause a distinct pharmacological effect in treating heart failure for Chinese population.

Understanding the ethnic differences in heart failure treatment will help us develop more personalized diagnosis and could optimize patient management. In previous analysis focused on Taiwan region [32], the composing proportion of comorbidities and medications in baseline was different from our study; and the study only included BNP as the heart failure biomarker which is known to be affected by nepri-lysin inhibitor [33, 34]. In addition, similar Asian population of Japanese HF patient with renal dysfunction showed ARNI was a promising option to preserve the renal function.
and improve clinical outcomes [35, 36], but the small-scale and short follow-up impeded the generalization. Therefore, our real-world data from Mainland China provided a certain verification of the effectiveness and safety.

Regarding the dosage and titration aspect, the initiating time, up-titrating, and optimizing dose of ARNI contribute to the improvement in HF prognosis [8, 37]. In a Japanese population, Sac/Val therapy initiated at a lower dose was safe and may be effective in Japanese heart failure patients [38]. In the present study, we observed that patients often initiated with sacubitril/valsartan at a relatively lower dose have difficulty in up-titrating the dose due to the concerns of orthostatic hypotension. After initiating treatment with Sac/Val, the current dosage patterns in both overall and sub-population of different comorbidities were safe and well-tolerated, similar to the previous results. Therefore, we are emphasizing the importance of target dose optimization and GDMT where proper medical and social supports are needed in clinical practice.

NT-proBNP as the benchmark heart failure biomarker offers prognostic information, independent of standard clinical predictors, and refines risk stratification. Although reference interval could be affected by various factors, the overall diagnostic performance of NT-proBNP remained in different population [39, 40]. As shown in these studies [4, 8, 11, 41] and more, treatment with ARNI has significant reductions in NT-proBNP especially observed as early as 2 weeks which were sustained throughout the treatment period. Our result demonstrated a reduction of NT-proBNP in the early stage after initiation which consisted with the previous studies, suggesting that Chinese patients could derive similar benefit from Sac/Val in improving NT-proBNP and cardiac function.

Also, patients who received a higher dose in the study showed a better improvement. Compared with the patients who failed to up-titrate during outpatient follow-up, patients who received a higher dose of ARNI (> 200 mg/d) demonstrated a better improvement in LV function and reduction of NT-proBNP. The improvement of NT-proBNP remained significantly higher in > 200 mg/d group in the adjusted model which further supports the significance to improve this sub-optimal treatment pattern in Mainland China.

In real-world clinical practice, up-titration of ARNI remains challenging due to inherent risks of these untoward adverse effects such as symptomatic hypotension, kidney function impairment, and/or hyperkalemia. Nonetheless, previous studies showed Sac/Val led to a lower incidence of renal deterioration compared with ACEI or ARB alone [42, 43]. Similar beneficial effects in patients with CKD on kidney function and albuminuria [44, 45]. In the safety and subgroup analysis of the current study, the benefits of Sac/Val were not modified by the comorbidity. Similar safety and improvement trend in keeping with prior reports were found in our result, suggesting the previous evidence could be generalized to Chinese HFrEF patients. In selected patients, especially CKD patients, closer follow-ups are needed for monitoring the possible adverse reaction when initiated within outpatient settings.

To our knowledge, this study represents the first analysis providing the initiation of the ARNI treatment patterns in China. Our data suggests that the up-titration of ARNI remains sub-optimal in real-world clinical practice in Mainland China. On the other hand, treatment with ARNI under the current dosage was safe even in patients

| Table 4 Cardiac improvement in different dosage group | | |
|------------------------------------------------------|-------------|-----------|
| Characteristics | < 200 mg/d (N=644) | ≥ 200 mg/d (N = 340) | P |
| Age, Mean (SD)  | 57.8 (14.64)  | 56.2 (15.07)  | 0.150 |
| Male, n (%)     | 508 (79.0%)  | 284 (83.5%)  | 0.086 |
| BMI (kg/m2)     | 24.24 (4.114) | 25.46 (4.347) | 0.0012 |
| Valid N         | 490  | 216  | 0.0076 |
| Mean (SD)       | 29.77 (6.943) | 30.29 (6.171) | 0.0351 |
| Follow-up LVEF (%) | 253  | 171  | 0.0012 |
| Valid N         | 35.38 (11.017) | 39.85 (10.887) | 0.0351 |
| Mean (SD)       | 2650.90 | 2371.00 | 0.0351 |
| Follow-up NT-proBNP (pg/mL) | 273  | 157  | 0.0351 |
| Valid N         | 2015.00  | 982.00  | 0.0351 |
with CKD. Improved recognition in primary health care and titration management of ARNI are needed for advance up-titration and optimal treatment.

**Limitation**

Our study represents the first real-world evidence of the ARNI dosage pattern and clinical efficacy in Chinese HFrEF patients. However, several limitations exist for our analysis, as this is a retrospective, observational study. Incomplete data and lack of internal validity in certain aspect might have led to bias and/or limited the generalization. Secondly, a relatively short follow-up limited the assumption of further outcome of all-cause mortality and treatment effects. Thirdly, safety reporting was only done on comorbidity and an aggregate level; the long-term survival details of each patient were not available. Lastly, the improvement of re-hospitalization might be the effect with standard heart treatment and not be solely driven by Sac/Val. A prospective cohort study with longer follow-up period could further eliminate the bias of these factors.

**Conclusion**

In this retrospective real-world analysis, sacubitril/valsartan demonstrated a similar efficacy and safety in Mainland Chinese HFrEF patients, which is characterized by the NT-proBNP reduction and cardiac function improvement. The current dosage pattern in Mainland China remained sub-optimal, and proper up-titration of ARNI and enhanced medical management might be needed.

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**Author Contribution** XL. L and JM. Z. conceived the idea of this article and project administration. S.S., XY.L, SG.L, and X.Z. completed the work of acquisition of data. IF.C. shared the task of analysis, interpretation of data, and manuscript writing. X.S., Q.L, J.Y., DC.X., M.Z., CL.D, JF.W, F.Y., and Y.Z. participated in visualization and data curation. All authors participated in discussing and revising the manuscript. All authors reviewed the manuscript.

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**Data Availability** Derived data of this study are available from the corresponding author XL. L on reasonable request.

**Declarations**

**Ethics Approval and Consent to Participate** The study was conducted in accordance with the principles of the Declaration of Helsinki and relevant policies in China, and the study protocol was approved by the independent Ethics Committee of the First Affiliated Hospital of Nanjing Medical University and China National Center for Biotechnology Development (GHO402). Informed consent was waived by the independent Ethics Committee of the First Affiliated Hospital of Nanjing Medical University due to retrospective nature of the study.

**Consent for Publication** Not applicable.

**Competing Interests** The authors declare no competing interests.

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