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# More than Guideline-Research Progress on Compliance of ARNI

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***Abstract:*** *Aims: As a new treatment for heart failure, ARNI have a significant clinical effect. However, the prognosis of patients with heart failure after discharge is not acceptable, which is related to the compliance of ARNI. In this paper, the concept, status quo and influencing factors of ARNI were reviewed, and methods for improving patients' drug compliance were proposed. Methods and results: Through systematic retrieval of literature database MEDLINE, a total of 5 literatures on compliance of ARNI were selected for analysis, and the results showed that compliance of ARNI was between 15% and 35%. The effects of age, gender, ARNI-related economic expenditures, Patient perception of ARNI and concomitant diseases on compliance with ARNI were reviewed Conclusion: The results show that the compliance of patients with heart failure to ARNI is disappointing, and affected by many factors, resulting in a poor prognosis of patients. In the future, physicians should pay more attention to the compliance of ARNI and improve the quality of medical treatment.*

***Keywords:*** *ARNI, drug compliance, heart failure*

## 1. Introduction

The understanding of cardiovascular diseases is constantly improving and developing, among which heart failure (HF) is one of the important cardiovascular diseases [1]. Studies have shown that ARNI has a significant therapeutic effect in the treatment of HF [2]. Sacubitril/Valsartan, the representative drug of ARNI, was first discovered in 2006. It has excellent physical and chemical properties. It is a single tablet compound preparation formed by mixing two components without chemical reaction. Because of its unique two-channel mechanism of action, it can interact with both RAAS system and natriuretic peptide system, making it a innovative and effective drug. However, patients admitted to hospital with HF are at a high risk of readmission and death after discharge [3], especially in patients with acute heart failure (AHF) due to adverse outcomes resulting from poor adherence to ARNI.

Medication compliance refers to the patient's behavior of following the doctor's instructions and taking medication. Drug compliance is an important indicator for the treatment of patients with HF. Gianluigi Savarese [4] et al conducted a 12-month follow-up on the compliance of ACEI, ARB, β blocker and ARNI, and found that the target dose realization rates of these drugs were 15%, 10%, 12% and 30%, respectively. Discontinuation rates were 55%, 33%, 24% and 27%, respectively. ARNI and other drugs has not reached considerable expectations, low compliance will have a negative impact on the prognosis of patients with HF, and the admission rate or all-cause mortality will increase. Therefore, it is necessary to make more perfect and systematic intervention and guidance for compliance with ARNI.

## 2. Effect of ARNI compliance on prognosis of patients with HF

Studies have shown that among HF patients who were discharged from hospital after receiving ARNI during hospitalization, patients with high compliance had a lower rate of hospitalization and all-cause mortality. From October 2015 to September 2018, Nicelli Anthony P [5] and others analyzed and investigated the relationship between compliance and survival rate of 2017 patients who met the treatment conditions of ARNI after discharge from hospital in different time periods, and found that the survival rate of patients with high compliance was much higher than that of patients with low compliance, and the proportion of adverse reactions such as renal function deterioration, hyperkalemia, symptomatic hypotension or vascular edema did not increase. At the same time, Carnicelli Anthony P [6] and others studied the patients from October 2015 to September 2018 based on the proportion of days covered (PDC), and evaluated the drug compliance by drug filling method, and found that PDC≥80% patient with good compliance. All-cause readmission rate of HFrEF patients with PDC≥80% and all-cause mortality

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were significantly lower than those with PDC < 80%. The all-cause readmission rate after one year was 53.50% vs 59.66%, and that of all-cause mortality was 21.38% vs 29.96%, which was lower than the one-year all-cause mortality calculated by Stephen J Greene [7] et al.

There are many different opinions on the influence of ARNI compliance on the prognosis of patients with HF, but generally speaking, the therapeutic effect of these drugs on patients with HF is obvious, which effectively reduces the readmission rate and mortality rate of patients with HF, and the side effects of drugs are not higher than those of other drugs of the same type. However, although ARNI is recommended as Class I drug in many drug guidelines, due to multiple factors such as drug cost, clinical inertia of doctors and so on, most patients with HF who meet the requirements of using this drug fail to use it.

## 3. Compliance status of ARNI

As a new therapeutic drug for patients with HF, the research on drug compliance of ARNI is very important. In many experiments of post-discharge follow-up of patients taking ARNI, the withdrawal rate of ARNI is high, the proportion of patients reaching the target dose is small, and the drug compliance in multiple studies is between 15% and 35% (Table 1) [4,6,8,9,10]. Unsatisfactory drug compliance will lead to poor prognosis of patients and a significant increase in the probability of risk. Analysis and improvement of compliance with such drugs will greatly improve the medical level, which deserves more attention from physicians.

*Table 1: Withdrawal of ARNI in the experiment*

| Research name | Age | Case Load | Area | Follow-Up Time | Arni Drug Compliance |
|---|---|---|---|---|---|
| GDMT[4] | 2016-2019 | 29546 | Sweden, UK and US | 12 months | 30% |
| Get with Guidelines[6] | 2015-2018 | 897 | US | 12 months | 32.9% |
| CHAMP-HF REGISTRY [8] | 2015-2017 | 2885 | US | 12 months | 15% |
| EQ-5D-5L [9] | 2013-2017 | 1188 | Danish | 12 months | 31.3% |
| GDMT [10] | 2012-2019 | 95 | Italian | 4months | 26% |

## 4. Factors affecting compliance of ARNI

### *4.1. Age factor*

Studies show that many drug compliances is related to age, which is an important indicator of drug compliance. Veenis Jesse F [11] et al identified 8,351 patients with HF with a reduced ejection fraction and a mean age of 72.3 ± 11.8 years who were enrolled in 34 Dutch outpatient clinics between 2013 and 2016 as younger than 60 years (13.9%). 60-74 years old (36.0%), and 75 years and older (50.2%), the older HF patients were found to have lower drug compliance and significantly lower prescribing target doses. However, other studies have shown no direct relationship between younger patients and older patients with poor medication compliance in patients with chronic heart failure (CHF) [12].

### *4.2. Gender Factors*

Gurgoze Muhammed T [13] et al found that gender and medication adherence (drug possession rate > 0.8) were correlated with the primary focus of all-cause mortality or HF admission during a median follow-up of 3.3 years, 35.1% of men and 31.8% of women achieved PE, and women showed higher medication compliance than men, but the results were not significant. At the same time, the influence of gender differences on drug compliance may not only come from themselves. Baumhakel Magnus [14] et al found that female doctors tend to have a higher target patient dose by recording and analyzing the differences in the drug dose and compliance caused by gender differences between patients and attending doctors. The reason is that female doctors give the same dose to patients of different genders, while male doctors tend to give lower doses and fewer drugs to patients of different genders. Therefore, doctors should also pay attention to the imbalance of treatment caused by gender differences in the process of treating patients.

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### *4.3. Cost Factors*

Drug costs have different effects on drug compliance of patients with different income levels. Tromp J [15] et al found that patients in low-income countries had higher mortality rate than those in high-income countries after being discharged from hospital for one year in a study on the post-discharge prognosis of HF patients with different income levels in the world. Hung Chung-Lieh [16] et al divided 633,098 HF inpatients in the National Health Insurance Research Database from 1996 to 2013 into low, middle- and high-income groups using GDMT prescription rate as the study standard to study their in-hospital mortality. After the discharge readmission rate and mortality rate, it was found that the in-hospital mortality rate of the low-income group was 5.07%, while the in-hospital mortality rate of the middle-income group and the high-income group was 2.47% and 2.51%, respectively, an increase of about two times. Meanwhile, the post-discharge risk of the low-income group also increased two times compared with the high-income group. This reflects that different patients will receive different medication and post-discharge care because of economic conditions.

### *4.4. Psychological factors of patients*

Whether patients have a healthy psychology of actively facing drug treatment is also an important factor affecting drug compliance. Rasmussen AA[9] et al studied whether there was a correlation between anxiety and depression symptoms (HADS-D) of patients with HF in Denmark from April 15, 2013 to April 15, 2014 after three years of follow-up, and found that the higher HADS-D score was associated with noncompliance with ACEI/ARB/ARNI (adjusted OR 1.07, 95% CI:1.03-1.11), suggesting that psychological factors such as depression in the patient might decrease drug compliance.

### *4.5. Drug dose factor*

Dose of drugs will produce different intolerance and non-compliance for different types of patients. Michele Sennil [17] et al found that HFrEF patients with different systolic blood pressure (SBP) had different withdrawal rates for the target dose of ARNI, and patients with HF with lower SBP often had higher dose reduction rate and withdrawal rate. At the same time, they found that gradual titration therapy could improve drug tolerance and compliance of patients with HF.

### *4.6. Complicated disease factors*

Patients with HF may suffer from complicated diabetes mellitus (DM) diseases, which will also affect the compliance of patients with ARNI. Muthiah Vaduganathan[8] et al followed up the compliance of ARNI in 2,085 patients with DM and 2,885 patients without DM among 4,970 patients by CHAMP-HF method for one year, and found that the drug utilization rate of DM patients was 23%, and 1% reached the target dose, while that of non-DM patients was 21%, and 0.5% reached the target dose.

## 5. How to improve compliance of ARNI in patients with HF

For the task of improving compliance of patients with HF after discharge, institutional improvements can be made. Hospitals can establish a system for doctors to regularly follow up patients, and at the same time provide patients with certain preferential policies or free consultation or examination services. At the same time, for patients who have adverse reactions during the treatment, they will be given more care after discharge, such as telephone return visit and other measures. At the same time, hospitals can apply to some foundations for special funds to help patients with HF, which can be used to give patients discounts on the price of treatment drugs, which will effectively improve the drug compliance of patients.

Medication physicians can also take effective measures to improve patient compliance. Doctor before giving the patient to tell drugs for treatment of patients with comprehensive and detailed function and may lead to adverse reactions, need timely attention to the patient's mental state, when found that patients have resistance to drugs must be timely communication with the patient, find out the reason, relieve patients for drug resistance, for patients with serious adverse reactions can be used to reduce the drug dosage, prolong the course of treatment, increase the treatment cycle and other methods, at the same time serious can also be delivered to the psychological doctor for further psychological treatment of patients. Doctors should continue to monitor the medication compliance of every discharged patient, gain the trust of patients through conversation and follow-up, so that patients can better comply with the doctor's advice, improve the medication compliance of patients, and thus improve the treatment rate of patients.

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As patients with HF and other cardiovascular diseases, they should be aware that this is a chronic disease that requires long-term medication to improve their condition. Patients have complex factors such as different cognitive levels, economic conditions and social environment, which means that patients' adherence to medication cannot be consistent. What patients need to do is to fully trust the doctor's advice, timely communicate with the doctor if they have concerns, do not change the dosage or stop medicine without authorization, and be responsible for their own health status. Patients can understand and learn about their diseases through books and the Internet, and realize the importance of drug treatment. Meanwhile, they can adjust themselves by changing their eating habits, changing bad work and rest, and appropriately increasing exercise, which is of great help to improve their drug compliance.

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