Clinical Research Protocol

Effectiveness and Safety of Finerenone in Chinese Non-diabetic CKD Patients

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I. Research Background and Significance

Chronic Kidney Disease (CKD) represents a significant global health issue that imposes a considerable burden on public health systems worldwide [1]. CKD is characterized by a gradual and irreversible decline in kidney function over time [2]. The disease progresses through five stages, eventually leading to End-Stage Renal Disease (ESRD) or kidney failure, where patients typically require dialysis or a kidney transplant to survive [3]. Due to the increasing prevalence of aging populations and potential risk factors such as diabetes and hypertension, the incidence of CKD is rising globally [4]. CKD ranks among the top ten causes of death worldwide [5]. The economic costs associated with CKD are substantial for both individuals and society as a whole [6], particularly for the treatment expenses of ESRD which might be prohibitively expensive in the form of dialysis or kidney transplantation [7]. Many healthcare systems in low- and middle-income countries struggle to cope with these costs [8]. As CKD progresses, affected individuals may experience a variety of complications, including cardiovascular disease, anemia, bone disease, and a decline in quality of life [9], often leading to additional healthcare needs and expenses [10]. This disease can profoundly affect patient's lives, impacting their work and daily activities [11]. Such realities may contribute to increased societal costs, including productivity losses and the need for caregiver support [12]. There are disparities in the incidence and treatment of CKD among different socioeconomic groups and regions, with vulnerable populations often experiencing higher rates of the disease and lacking access to adequate care and treatment options [13]. Efforts to prevent and treat CKD encounter various barriers, such as a lack of symptoms in the early stages leading to late diagnosis, and the complexities of managing the risk factors of the condition [14]. The global burden of CKD is immense, impacting health systems, economies, and the quality of life of patients [1]. There is a need for raised awareness, early intervention, and equitable treatment opportunities to address the challenges posed by this disease.

Non-diabetic Chronic Kidney Disease (CKD) poses a significant clinical challenge, with existing treatment methods having limitations [15]. Available approaches are primarily focused on managing the underlying causes of CKD, such as hypertension and proteinuria, to slow disease progression and prevent complications [16]. Common interventions include lifestyle changes, blood pressure control with Angiotensin-Converting Enzyme inhibitors (ACE inhibitors) or Angiotensin Receptor Blockers (ARBs), and the use of Sodium-Glucose Co-Transporter-2 inhibitors (SGLT2 inhibitors) in certain circumstances [17]. However, for CKD without diabetes mellitus (DM), there remains a vital need for novel treatment options for various reasons [1]. New therapies like finerenone show the potential for such advances. Finerenone is a non-steroidal mineralocorticoid receptor antagonist that has been shown to have benefits in studies on patients with CKD and type 2 diabetes, slowing CKD progression and providing cardiovascular protection [18]. Researchers and clinicians are hopeful that this treatment can also be successfully applied to non-diabetic CKD populations, hence there is interest in further research into its efficacy and safety in this particular group [19].

While current non-diabetic CKD treatment strategies include managing hypertension and proteinuria, there is a clear need for new treatment options [20]. Innovative therapies like finerenone that target specific mechanisms of CKD pathology have the potential to improve outcomes and meet the unmet needs of patients with CKD [21]. Further research and clinical trials

are necessary to explore and validate the efficacy and safety of these new therapeutic approaches [22].

Finerenone holds promise for diabetic CKD; however, the lack of evidence for its use in non-diabetic CKD underlines the importance of further clinical research in this area [23]. Such studies would be incredibly valuable for expanding treatment options and improving outcomes for a broader CKD patient population [24].

Nevertheless, the effectiveness and tolerability of finerenone in patients with non-diabetic chronic kidney disease (CKD) have not yet been clearly established [25]. The design of this study aims to determine whether the renal protective benefits of finerenone also apply to non-diabetic CKD patients, including those with an estimated glomerular filtration rate (eGFR) below 15 ml/min/1.73m2 [26]. To our knowledge, our investigation is pioneering in assessing the therapeutic potential and safety profile of finerenone for this specific patient group [27].

II. Research Objective

To assess the progression of kidney disease in non-diabetic CKD patients following the use of finerenone, and to analyze the safety profile of finerenone.

III. Research Content

Investigate the changes in renal function in non-diabetic CKD patients after the administration of finerenone.
Analyze the relationship between the use of finerenone and cardiovascular events.
Evaluate the safety of finerenone treatment.

IV. Research Methodology

(A) Study Design

This project is a single-center, retrospective cohort study.

(B) Study Population

The study population comprises patients who were hospitalized for treatment or followed up on an outpatient basis in the Department of Nephrology, the First Hospital affiliated with Harbin Medical University, starting from December 15, 2023. The baseline for the study is defined as the occasion when a patient with CKD (either as a primary or secondary diagnosis) was first admitted to the nephrology department for hospital treatment or an outpatient visit.
Inclusion criteria:
(1) Patients who were hospitalized or followed up on an outpatient basis in the Department of Nephrology, the First Hospital affiliated with Harbin Medical University, starting from December 15, 2023;
(2) Patients with non-diabetic kidney disease;
(3) Patients with electronic medical records available.

Exclusion criteria:
(1) Type 2 diabetes mellitus;

(2) Patients who refuse to participate.

(C)Study Variables

In accordance with the research objectives, the project will collect the following variables:

Baseline patient characteristics: including age, gender, stage of kidney disease, comorbidities, medication history, etc.

Use of finerenone: including dosage, duration of therapy, etc.

Kidney-related indicators and cardiovascular events: including eGFR, serum creatinine levels, records of kidney disease events (such as renal function decline, initiation of dialysis, or kidney transplantation), and records of cardiovascular events.

Safety data: including all adverse events recorded.

(D) Data Collection and Data Management

Determine data sources:

The data will primarily be sourced from the hospital's electronic health record HIS system, which may include clinical records, medication administration records, laboratory test results, and radiological reports.

Acquisition of patient information:

Based on the study's inclusion and exclusion criteria, construct a query to compile a list of patients from the hospital database who meet the criteria for CKD.

Creation of data collection forms:

Create a standardized data collection form listing all the information that needs to be gathered. Ensure the form includes all the key variable items involved in the study.

Data extraction:

Use the search and export functions of the EHR system to export the required data points for each patient involved in the study. This includes the patient's basic information, medication usage, laboratory test results, etc. For information that cannot be collected automatically, such as physicians' notes or qualitative descriptions in radiological reports, manually extract or enter these into the data tables.

Data entry and coding:

Enter the extracted data into the data collection forms. To protect patient privacy, encode patient information wherever possible to anonymize patient identity within the dataset. For qualitative data, such as diagnoses or symptom descriptions, develop a standardized coding system that converts them into quantitative data suitable for statistical analysis.

Quality control:

Perform data cleaning on the preliminary collected data, checking for missing data, outliers, and inconsistencies. Conduct data verification to ensure the accuracy and completeness of all data. If possible, have two research assistants perform data extraction and entry independently and reconcile any discrepancies.

Data storage and security:

Ensure that all electronic data is stored on secure, password-protected servers or cloud services. Regularly back up data to mitigate the risk of data loss.

Ethical compliance:

Ensure that all data collection and processing adhere to the ethical guidelines of the hospital and research institution, local medical regulations, and data privacy laws. If direct communication

with patients is necessary to collect data, obtain informed consent from the patient.

V. Statistical Analysis

In a single-center retrospective study, the data analysis process is complex and multi-step, aimed at extracting meaningful conclusions and insights. Below is a detailed description of the data analysis:

Data cleaning:

Prior to formal analysis, data cleaning is conducted to remove incomplete, incorrect, or inconsistent records.

Missing data are appropriately addressed, for example through imputation or deletion of missing entries.

Duplicate records are checked and resolved to ensure the uniqueness of analysis.

Descriptive statistical analysis:

Descriptive statistical analysis is performed on basic patient characteristics, including age, gender, stage of CKD, etc.

Medication usage of finerenone is quantified (dose, duration of treatment, etc.).

Primary and secondary outcome measures are descriptively analyzed (e.g., changes in renal function, incidence of cardiovascular events).

Exploratory Data Analysis (EDA):

Data within the set is visualized using bar charts, box plots, scatter plots, and other visualization tools to explore potential patterns or trends.

Variables potentially affecting study outcomes are extracted for exploration of relationships between variables.

Hypothesis testing:

If the study aims to compare renal function before and after treatment with finerenone, hypothesis testing might be conducted using parametric or nonparametric methods such as paired sample t-tests or Wilcoxon signed-rank tests.

In the presence of multiple groups (e.g., patients with different stages of CKD), methods such as ANOVA or Kruskal-Wallis may be used to compare differences between groups.

Regression analysis:

Linear regression analysis is conducted to assess the degree of association between continuous variables.

Binary logistic regression analysis is utilized for non-continuous outcome variables, such as the occurrence of cardiovascular events.

Multivariate regression analysis may be applied, if appropriate, to adjust for potential confounding factors.

Survival analysis:

If the study includes analysis of follow-up data, such as tracking the progression of CKD, Kaplan-Meier survival curves can be used for description, and Log-rank tests to assess differences between treatment and control groups.

Cox proportional hazards model could be employed to determine the relationship between

treatment and outcomes while adjusting for confounders.
Use of statistical software:

Complex statistical analyses are performed using statistical software packages such as SPSS, Stata, R, or Python.
Data integrity is maintained throughout the analysis, and all analysis steps are documented for later review.
Interpretation of results:

Attention is given to the levels of statistical significance, and methods like Bonferroni correction are applied to address issues of multiple comparisons.
Statistical findings are translated into clinically meaningful narratives that can be understood and used by physicians or researchers.
Discussion and comparison:
Results are compared with existing literature and other studies to discuss possible reasons for any discrepancies.
Limitations of the study findings are highlighted, and areas needing further research are proposed.
Report writing:
Based on the results of the analysis, a research report or scientific paper is composed, including the methods, data analysis process, results, conclusions, and recommendations.
Through these steps, researchers can effectively draw conclusions from large data sets and provide evidence for clinical decision-making or further research. Throughout all these stages, adherence to statistical principles, data privacy regulations, and ethical guidelines is crucial.

VI. Ethics

Ethical Committee Review

The research protocol, informed consent forms, and any materials directly related to the patients must be submitted to the ethics committee for written approval before the research can formally commence. The ethics committee must be notified in writing upon cessation and/or completion of the study. Researchers are required to promptly report any changes occurring in the research work to the ethics committee (such as revisions to the research protocol and/or informed consent forms) and must not implement these changes prior to obtaining the committee's approval, unless the changes are made to eliminate apparent and direct risks to the enrolled patients.

Informed Consent

Each participating entity should apply to their respective ethical committee for either verbal informed consent (waiving the signing of informed consent forms) or a waiver of informed consent according to the actual data retention situation, that is whether follow-up data need to be obtained through contact with patients.

VII. Anticipated Goals

To publish at least one research paper;
To train at least two graduate students and specialist physicians;

VIII. Research Foundation and Working Conditions

Currently, data for 43 cases have been organized, and preliminary statistical results show significant differences.

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