

Optimizing Finerenone Therapy: A Comprehensive Review Using the “Finerenone Pentad”

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ABSTRACT

Chronic kidney disease (CKD) is a pressing global health concern, often intertwined with comorbid conditions such as type 2 diabetes mellitus (T2DM) and cardiovascular complications. Managing CKD in T2DM patients requires a multifaceted approach, and emerging therapeutic options are increasingly essential. Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, has shown considerable promise in addressing the intricate cardiorenal needs of these patients. To maximize the effectiveness of this therapy, we propose the approach of “Finerenone Pentad” which can be utilized as a checklist while starting and subsequently monitoring the finerenone therapy. This structured approach offers guidance on patient selection, monitoring and outcome evaluation, ensuring a holistic approach to the care of individuals with T2DM and CKD.

Keywords: Chronic kidney disease, type 2 diabetes, selective nonsteroidal mineralocorticoid receptor antagonist

Chronic kidney disease (CKD), often exacerbated by the presence of type 2 diabetes mellitus (T2DM), represents a challenging medical condition, both for patients and health care providers.¹ In the search for therapeutic solutions, finerenone has emerged as a promising option.²⁻⁴ This selective nonsteroidal mineralocorticoid receptor antagonist (MRA) addresses the cardiovascular and renal complications frequently encountered in T2DM patients with CKD.² The concept of “Finerenone Pentad” framework provides a comprehensive strategy for optimizing patient selection, monitoring and outcome assessment, with the ultimate aim of enhancing patient care (Table 1 and Fig. 1).

THE PATIENT SELECTION PENTAD

In the first component of the “Finerenone Pentad”, the focus is on selecting the most suitable patients for finerenone therapy. To qualify for this treatment, individuals should present a combination of specific inclusion and exclusion criteria.

- **Inclusion criteria:** These encompass five crucial points, including a diagnosis of T2DM with CKD, potassium levels ≤ 5 mmol/L, estimated glomerular filtration rate (eGFR) ≥ 25 mL/min/1.73 m², a urine albumin-to-creatinine ratio (UACR) of ≥ 30 mg/g and men and women above ≥ 18 years.²⁻⁴ These criteria ensure that the therapy is directed toward patients who stand to benefit the most from finerenone’s cardiorenal protective effects.
- **Exclusion criteria:** Five specific factors necessitate the exclusion of certain patients. These encompass those already receiving spironolactone or eplerenone, concomitant use with strong CYP3A4 inhibitors, pregnant or lactating patients, those with severe hepatic impairment (Child-Pugh C), and those diagnosed with adrenal insufficiency.²⁻⁵ These exclusions help prevent potential complications and ensure patient safety.
- **Universal nondiscriminatory criteria:** Apart from the defined inclusion and exclusion criteria, there is no requirement for additional considerations when prescribing finerenone. The medication can be administered irrespective of the patient’s glucophenotype (including glycated hemoglobin [HbA1c] levels and T2D duration),⁶ barophenotype,⁷ concomitant therapy for diabetes (sodium-glucose cotransporter-2 inhibitor [SGLT2i]/insulin/glucagon-like peptide-1 receptor agonist [GLP-1RA]),^{6,8,9} atherosclerotic cardiovascular

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Table 1. The Pentad of Finerenone

Selection Pentad		
5 points for inclusion <ul style="list-style-type: none"> • T2DM with CKD • Potassium ≤ 5 mmol/L • eGFR ≥ 25 mL/min/1.73 m² • UACR ≥ 30 mg/g • Men and women ≥ 18 years 	5 points for exclusion <ul style="list-style-type: none"> • With spironolactone/epirenone • Strong CYP3A4 inhibitors • Pregnancy/Lactation • Severe hepatic impairment (Child-Pugh C) • Adrenal insufficiency 	5 points regardless <ul style="list-style-type: none"> • Glucophenotype • LVH and HF status • Concomitant therapy for diabetes: SGLT2i/insulin therapy/GLP-1RA • ASCVD status • Barophenotype
Monitoring Pentad <ul style="list-style-type: none"> • Serum potassium • UACR • eGFR • Blood pressure • Serum creatinine 	Outcome Pentad <ul style="list-style-type: none"> • Reduced risk of ESKD by 1/5 • Reduced risk of HHF by $>1/5$ • Reduced UACR by 32% • Reduced cardiovascular mortality risk by 12% • Low clinical impact of hyperkalemia with incidence rate of permanent discontinuation at 1.7% 	

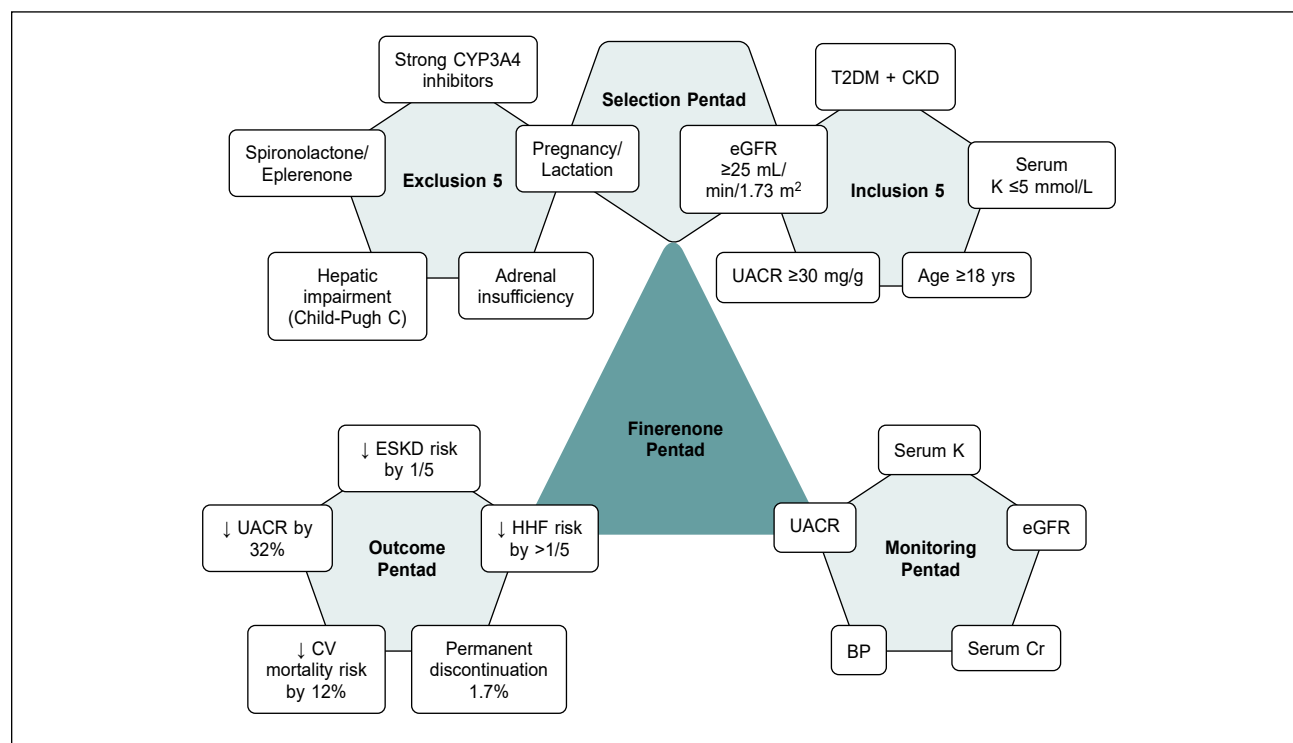


Figure 1. Finerenone Pentad.

disease (ASCVD),¹⁰ left ventricular hypertrophy (LVH) and heart failure (HF) status.^{11,12}

THE MONITORING PENTAD

Upon selecting patients for finerenone therapy, the monitoring phase incorporates consideration of a few specific parameters. The following aspect of the framework delineates five essential factors that health care professionals should observe during the treatment

course to assess and monitor the prognostic outcomes of the patients.

➤ **Serum potassium:** Due to its distinct structure and mode of action (MoA), the rates and intensity of hyperkalemia is significantly lower compared to steroidal MRA (Spironolactone) as noted in Phase II clinical trials and Amber like post hoc subanalysis.^{13,14} However, regular monitoring is imperative to mitigate potential adverse events.

The proposed potassium monitoring protocol suggests an initial assessment after 1 month of drug initiation to allow for optimal stabilization. Subsequent evaluations, following the standard protocol, are recommended every 4 months if the patient remains stable. In the event of potassium levels going beyond 5.5 mmol/L, it is advised to withhold the drug for a minimum of 72 hours and reintroducing it when levels fall below 5 mmol/L.²⁻⁴

- **Blood pressure:** Hypertension is a common concern in CKD patients. Regular blood pressure monitoring is essential to maintain optimal cardiovascular health, as well as to monitor the control of hypertension.¹⁵ Finerenone is noted to cause a mild reduction in blood pressure levels to the tune of 3-4 mmHg in the doses recommended for CKD with T2DM³ as opposed to steroidal MRAs¹³ and is not a primary therapeutic objective, which hinges primarily on its anti-inflammatory and antifibrotic properties.
- **UACR:** It offers valuable insights into kidney function and the progression of kidney disease.¹⁶ Regular assessments enable health care providers to gauge the effectiveness of finerenone therapy in slowing the deterioration of renal function.
- **eGFR:** eGFR is a critical parameter for assessing kidney function.^{16,17} Continuous monitoring helps clinicians make necessary adjustments to therapy and ensures that the treatment aligns with the patient's renal status.
- **Serum creatinine:** Regular assessments of serum creatinine levels provide crucial information about kidney function and the impact of therapy.¹⁸ This parameter aids health care professionals in gauging the patient's renal health over time.

eGFR and serum creatinine are important parameters for assessment of renal function alongside UACR.¹⁶⁻¹⁸ The use of finerenone demonstrates a potential reduction in the decline of eGFR within 12 months. However, a mild initial eGFR decline of 3-4 mL may occur in the first 1-4 months of finerenone initiation, this typically remains within 30% mirroring the pattern seen with many renal protective drugs. There have been no increased incidences of acute kidney injury noted with finerenone in the Phase III clinical trials.^{2,4}

The transient decline in GFR noted with many reno-protective drugs such as angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers

(ARBs) or SGLT2i is a pharmacological effect leading to a new physiological renal function set point.¹⁹

Patient education plays a really crucial role here so as to prevent undue alarm, as this initial dip aligns with the drug's long-term renal stabilization effect.

THE OUTCOME PENTAD

The final component of the "Finerenone Pentad" outlines specific outcomes that therapy aims to achieve or evaluate during the treatment process. These outcomes are quintessential in assessing the success of finerenone therapy.

- **Reduced risk of ESKD:** A primary objective of finerenone therapy is to slow down the progression of kidney disease and subsequently the risk of end-stage kidney disease (ESKD), which has been seen to be reduced by 20%.^{2,3} ESKD poses significant challenges for patients and is often associated with a reduced quality of life.²⁰ The reduction in ESKD risk represents a major benefit for individuals receiving this treatment.
- **Reduced risk of HHF:** Hospitalization for heart failure (HHF) is a critical concern in patients with T2DM and CKD.²¹ Therapy aims to reduce the risk of HHF by more than 20%,^{2,3} further improving the patient's quality of life and reducing the burden on health care resources.
- **Reduced UACR:** Another key outcome is the reduction in UACR by 32%,³ and this change is seen within 1-4 months of initiation with finerenone and is sustained. This decrease signifies an improvement in kidney function and a slowing of kidney disease progression as well as provides significant cardiovascular risk benefit.
- **Reduced cardiovascular mortality:** In addition to renal benefits, finerenone therapy aims to lower cardiovascular mortality risk by 12%²² and sudden cardiac death by 25%.²² Cardiovascular events are a major cause of morbidity and mortality in this patient population,²³ and this reduction represents a significant improvement in overall patient outcomes.
- **Low clinical impact of hyperkalemia:** Managing hyperkalemia is a common concern with MRAs.² Despite a hyperkalemia incidence rate of 14% compared to placebo in FIDELITY analysis, clinical impact rates were minimal, with a specific incidence rate of permanent discontinuation set at 1.7%.³ With an average increase of 0.2 mmol,

only 4.5% of the patients exceeded a potassium level of 6 mmol/L.²⁴ This ensures the safety and tolerability of the treatment.

RECOMMENDED POSITIONING OF FINERENONE FOR CARDIORENAL PROTECTION

Over the past few years, there has been a notable paradigm shift in the management of patients, from an organ-specific strategy to a more holistic patient-centric approach, with guidelines recommending regular routine screening of individuals with T2D using UACR and eGFR for early diagnosis of CKD and cardiovascular risk, along with a multifactorial approach towards management. In addition to the traditional standard of care including lifestyle modifications, glycemic control, blood pressure regulation and lipid management, which form the cornerstone/foundation of therapy, agents conferring cardiovascular and kidney benefits such as ACEIs/ARBs, SGLT2i and finerenone have firmly established themselves as the “three pillars” of therapy for slowing kidney disease progression and reducing development of heart failure and risk of cardiovascular death in patients with CKD in T2D, with a Level A recommendation for these drugs.²⁵⁻²⁸ Nonsteroidal MRAs like finerenone are now recommended along with other medications for cardiovascular and kidney protection rather than as alternatives when other treatments have not been effective.²⁶

A proposed approach recommends optimizing the dose of ACEI/ARB to a maximally tolerated level initially and subsequently introducing the other two drugs, i.e., Finerenone and SGLT2i with at least a week’s interval in between to allow for equilibration of kidney function before the addition of the next agent.²⁸ Early initiation of combination therapy with this triad is advocated due to their distinct yet complementary MoA facilitating a more comprehensive disease management approach.²⁹

CONCLUSIONS

The “Finerenone Pentad” is a comprehensive, patient-centric framework that empowers health care professionals to provide high-quality care for individuals with T2DM and CKD. By following the selection, monitoring and outcome criteria, clinicians can offer a well-rounded approach to address the complex cardiorenal needs of these patients.

In conclusion, this framework allows for the effective optimization of finerenone therapy. The structured approach empowers health care providers to make data-driven decisions, targeting the reduction of ESKD,

HHF, cardiovascular mortality and other complications while ensuring the safe and effective management of hyperkalemia.

Author Contributions

All authors contributed substantially to the article concept and were accountable for the accuracy of the information contained in the article.

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Data Availability

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Competing Interests

Pravin Manjrekar, Aparajita Praharaj and Amaninder Mann are employees of Bayer.

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