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Mini-Review

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OXFORD

Combination treatment for the management of chronic kidney disease and type 2 diabetes: a review and practical guidance

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Introduction and Rationale

Clinical Background

- CKD and T2D frequently coexist and amplify clinical risk
- Traditional therapy relied mainly on RAS inhibition and Risk-factor control(Blood pressure, glucose, and lipid control)
- This review focuses on Modern CardioRenal therapy with demonstrated cardiovascular and kidney benefits in CKD and T2D .
- *Context* (RASi), (SGLT2i), (nsMRA), and (GLP-1RA) are key components of guideline-directed medical treatments (GDMT) for chronic kidney disease (CKD) with type 2 diabetes (T2D).
- However, the combined use of these medications remains uncommon in clinical practice, Three-drug and four-drug GDMT are particularly underused.
- Many eligible patients receive only one or two agents.Target doses are also frequently not achieved.
- in part, due to the absence of specific guidance on implementing combination treatment.

Evolution of CKD Therapy

- Modern treatment includes several disease-modifying drug classes.
- SGLT2 inhibitors provide important kidney protection.
- GLP-1 receptor agonists provide metabolic and cardiovascular benefits.
- Non-steroidal MRAs reduce kidney and cardiovascular risk.
- RAS inhibitors remain a foundational component of therapy.
- Together, these therapies target multiple pathways of disease
- The major challenge is combining these therapies effectively.

Clinical Benefits of Modern Therapy

- Large outcome trials have demonstrated important treatment benefits.
- These therapies reduce CKD progression.
- They also reduce hospitalization for heart failure.
- Cardiovascular mortality is reduced with several agents.
- Some therapies also reduce all-cause mortality.
- Most pivotal trials evaluated these agents on background RAS inhibition.
- Prospective trials of all four agents together are still lacking.

Why Combination Therapy?

- these medications have unique mechanisms of action and potential synergies that may mitigate their adverse effects; thereby providing a strong empirical basis for their combined use.
- Combination therapy may provide greater overall risk reduction.
- The main question is how to implement combination therapy safely.

Main Objectives of the Review

- The review has three major objectives:
- (1) summarize the evidence supporting combination GDMT in CKD with T2D,
- (2) propose a practical algorithm to guide the accelerated implementation of quadruple treatment
- (3) discuss strategies to improve the uptake of combination treatment .
- The overall goal is better cardiorenal risk reduction.

Methods and Rationale for Combination Therapy

- The authors searched PubMed from inception to the present.
- Only English-language studies were considered.
- The search included several major drug classes.
- These included RASi, SGLT2i, nsMRA, and GLP-1RA.Diabetes-related studies were also included.
- Priority was given to guidelines and randomized controlled trials.
- different pathways provide a biological basis for combination therapy

SGLT2i and GLP-1RA Evidence

- in a meta-analysis of 12 RCTs of SGLT2i vs placebo on cardiovascular and kidney outcomes in patients with diabetes (n = 73 238), the benefits of SGLT2i were consistent regardless of baseline GLP-1RA use (n = 3065).
- Likewise, a meta-analysis of 3 RCTs (n = 17 072) of GLP-1RA vs placebo showed no dilution of benefit on cardiorenal outcomes with background use of SGLT2i (n = 1743)
- This suggests that GLP-1RA therapy does not dilute SGLT2i benefit.
- The findings support complementary treatment effects.

Finerenone With SGLT2i and GLP-1RA

- FIDELITY analyses evaluated finerenone across background therapies.
- Finerenone benefit was not diminished by SGLT2i use.
- Its benefit was also not diminished by GLP-1RA use.
- although only a small proportion of participants were using SGLT2i or GLP-1RA in these.
- Although these subgroup analyses are considered hypothesis generating, the consistency of treatment effects suggests the mechanism of benefit is unique for each medication class and likely additive .

The CONFIDENCE Trial

- Supporting this hypothesis are findings from the CONFIDENCE trial, directly evaluated combination therapy, Patients had CKD and type 2 diabetes.Participants received empagliflozin, finerenone, or both.

- The primary focus included changes in UACR.

- Combination therapy produced greater albuminuria reduction.

At day 180, the reduction in the urine albumin-creatinine ratio (UACR) with combination treatment was 29% greater than with finerenone alone (least-squares mean ratio of the difference in the change from baseline, 0.71; 95% confidence interval [CI], 0.61-0.82) .

The combination was also 32% more effective than empagliflozin alone.

- These findings support additive kidney effects.

Projected Benefits of Quadruple GDMT

- Quantifying the projected clinical outcome benefits with the 4 components of GDMT (RASi, SGLT2i, nsMRA, and GLP-1RA), an actuarial analysis of the key cardiovascular and kidney trials demonstrated a significant reduction in the risk of major adverse cardiovascular events (hazard ratio [HR] 0.65; 95% CI, 0.55-0.76), CKD progression (HR 0.42; 95% CI, 0.31-0.56), and hospitalization for HF (HR 0.45; 95% CI, 0.34-0.58) with combined quadruple treatment vs RASi monotherapy.
- Taken together, the evidence supports combination treatment; however, longer adequately powered studies are needed to clarify the incremental and relative benefits of combination treatment on clinical outcomes

ENHANCED TOLERABILITY

Hyperkalemia in CKD and Finerenone

- Hyperkalemia is a major example of this concept. Hyperkalemia is commonly defined as potassium ≥5–5.5 mmol/L.
- It is an important treatment-limiting complication.
- The risk is particularly high with RAAS inhibition,RAASi-associated hyperkalemia occurs in 5–10% of patients with CKD.
- Finernone-related hyperkalemia is influenced by kidney function
- The risk increases as eGFR decreases, Risk rises approximately 1.5-fold below an eGFR of 45,It rises approximately twofold below an eGFR of 25.
- Hyperkalemia may therefore limit nsMRA therapy.
- Careful potassium monitoring is essential

Consequences of RAASi Discontinuation

- Hyperkalemia may lead clinicians to reduce or stop RAASi.
- Treatment cessation occurs frequently within the first year.
- 20–45% of patients may discontinue therapy.
- Discontinuation is associated with worse clinical outcomes.
- Mortality and cardiovascular events may increase.
- CKD progression may also accelerate in advanced disease.

SGLT2i and Potassium Homeostasis

- SGLT2 inhibitors may reduce hyperkalemia risk,increase distal sodium delivery, may also increase plasma aldosterone levels.These effects promote renal potassium excretion.
- A meta-analysis included 49,875 participants.Serious hyperkalemia risk was reduced by approximately 16%.
- FIDELIO-DKD provided supportive evidence,Serious hyperkalemia-related events were lower with combination therapy,The rate was 8.1% with SGLT2i plus Finerenone,The rate was 18.7% with finerenone alone.

SGLT2i and RAASi Persistence

- findings collectively suggest that SGLT2i initiation may facilitate continuation of RAASi despite hyperkalemia. Supporting this notion are results from a combined analysis of the CREDENCE and DAPA-CKD trials in which the use of SGLT2i reduced the risk of RASi discontinuation by 15% compared to placebo (HR 0.85; 95% CI, 0.74-0.99) in patients with CKD, over a median duration of 2.2 years .
- Similarly, a recent population-based retrospective cohort study involving approximately 20 000 people with diabetes, CKD, or HF, who were prescribed an SGLT2i and matched to non-users, demonstrated a significantly lower rate of RAASi discontinuation (36% vs 45%)
- These findings support sustained RASi use.

GLP-1RA and Potassium Excretion

- Likewise, GLP-1RA increase the urinary excretion of potassium, likely through inhibition of the sodium-hydrogen exchanger isoform 3 (NHE3) in the proximal tubule, proximal natriuresis, and distal potassium wasting
- The effect is not widely recognized clinically,However, observational evidence supports a possible benefit.
- which have demonstrated a 39% lower risk of any hyperkalemia and a 48% lower risk of moderate to severe hyperkalemia with the use of GLP-1RA as compared to dipeptidyl peptidase-4 (DPP4) inhibitors among adults with T2D .

GUIDELINES AND PRACTICAL GUIDANCE

Current Guideline Recommendations

- Current guidelines support combination therapy in CKD and T2D,The ADA and KDIGO provide complementary recommendations.
- The ADA guidelines recommend the initiation of SGLT2i with/without GLP-1RA as the first-line therapy on top of maximally tolerated RASi and highlight nsMRA as an additional risk-based option.
- Furthermore, the guidelines recommend the simultaneous initiation of SGLT2i and nsMRA in adults with a UACR ≥100 mg/g due to evidence of safety and beneficial effects on albuminuria.
- KDIGO recommends maximally tolerated RASi therapy,SGLT2i are also considered first-line therapy,GLP-1RA can be added for additional cardiorenal protection, nsMRA therapy is another potential second-line strategy.
- The overall goal is reduction of residual cardiorenal risk.

Unanswered Clinical Questions

- Current guidelines do not fully define treatment sequencing.
- The optimal order of drug initiation remains uncertain.
- The ideal interval between medications is also unclear.
- Management of adverse effects requires practical guidance,This includes hyperkalemia and eGFR decline.
- Hypotension and hypoglycemia are additional concerns.

PROPOSED TREATMENT ALGORITHM

Table 1 Universal criteria to establish treatment eligibility for quadruple "cardiorenal" GDMT

Eligible for combination treatment			Exclude from treatment
Type 2 diabetes			Hyperkalemia (serum potassium ≥5 mmol/L)
AND			BP < 100/60 mmHg or known orthostatic hypotension
High risk for kidney disease progression			
eGFR ≥ 25 mL/min/1.73 m^2 and UACR > 30 mg/g			AKI requiring dialysis within last 3 months
			Immunosuppression
AND			
			Uncontrolled diabetic retinopathy
High cardiovascular risk			
			Established HFrEF on MRA
History of myocardial infarction, stroke or peripheral artery disease	OR	*Multiple cardiovascular risk factors Age ≥ 55 + one of hyperlipidemia, hypertension, or atrial fibrillation*	Recurrent history of DKA
			Type 1 diabetes
			Frailty

Abbreviations: AKI, acute kidney injury; BP, blood pressure; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical treatments; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; UACR, urine albumin-creatinine ratio.

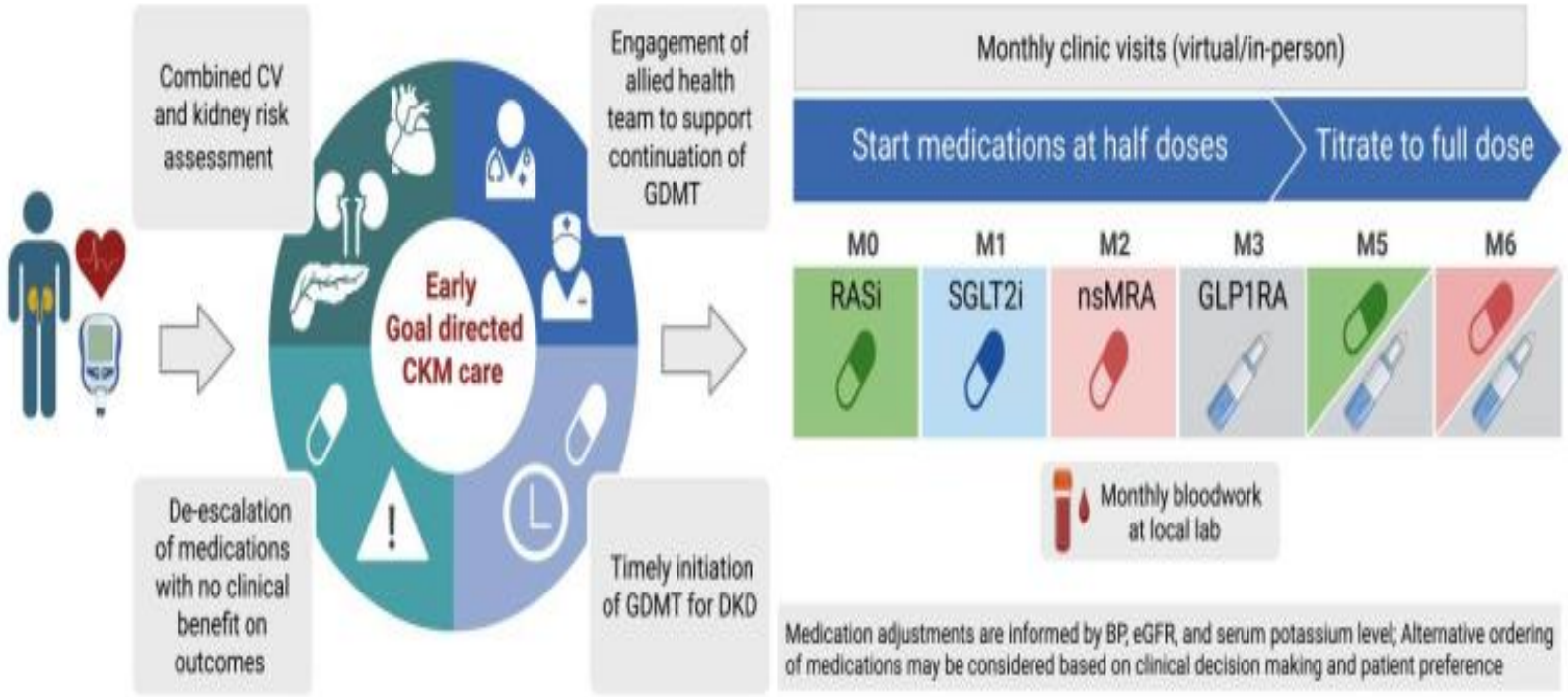


Figure 1: Goal-directed CKM care for people with CKD and T2D.

Limitations of Personalized Medicine Alone

- Personalized medicine may not solve treatment underuse.
- Individual drug classes are already underprescribed.
- This problem is particularly prominent among older adults.
- High-risk patients may paradoxically receive fewer therapies.
- Risk scores may therefore delay rather than accelerate treatment.

Real-World Underuse of SGLT2i,GLP-1RA and Finerenone

- A Veterans Health Administration analysis included 1,197,880 adults,The study covered 2019–2020, Only 12% of patients with CKD received SGLT2i ,Only 10% received GLP-1RA.
- Uptake was lower in advanced kidney disease. Treatment was also lower despite high cardiovascular risk.
- Dose optimization of finerenone is also inadequate.
- The FINE-REAL study included 1,916 patients. Participants had T2D and CKD.
- Only 18.4% of eligible patients underwent dose escalation.
- This demonstrates a major implementation gap.
- Starting therapy alone is insufficient without appropriate titration.

Pretreatment Clinical Optimization

- Clinical optimization should occur before drug initiation.
- Baseline cardiovascular-kidney-metabolic risk should be assessed.
- Blood pressure should be optimized.
- Serum potassium should also be optimized.
- Non-beneficial medications should be considered for deprescribing.
- Shared decision-making should occur before treatment escalation.

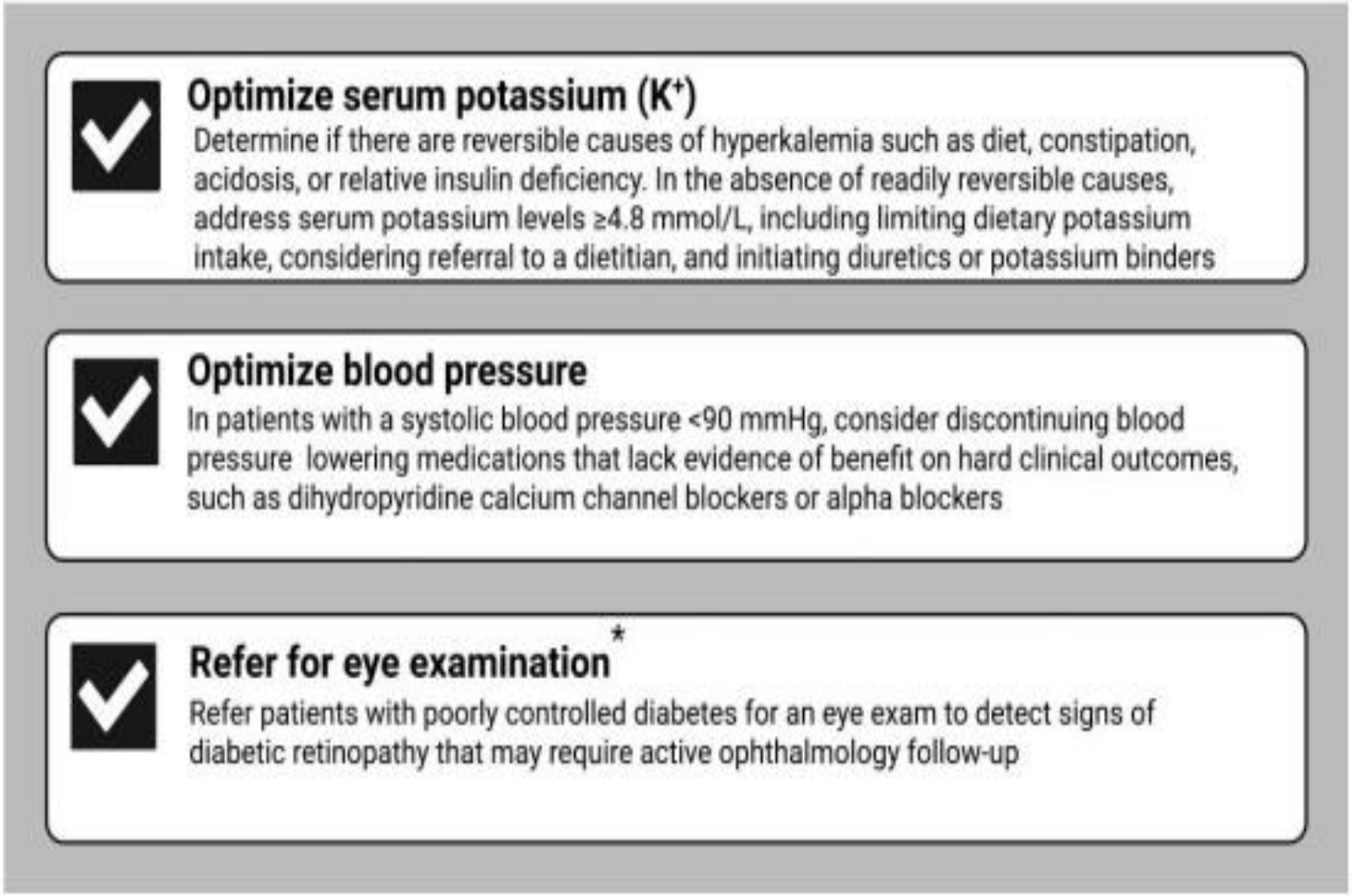


Figure 2 Clinical optimization prior to the initiation of combination cardiorenal GDMT. *

Eye examinations are particularly relevant before initiating GLP-1RA treatment due to the suggested increased risk of worsening diabetic retinopathy with this class, though this risk is thought to be primarily related to the rapid reduction of hyperglycemia in individuals with poor glycemic control and pre-existing retinopathy (52).

Six-Month Treatment Strategy

- The proposed strategy aims for four-drug GDMT within six months.
- The first four months focus on sequential initiation.
- One major medication class is introduced each month.
- The final two months focus on dose optimization.
- Safety assessments occur monthly.
- The schedule can be modified according to patient factors.

Month 1: RAS Inhibition

- RASi is recommended as the initial therapy in treatment-naive patients.
- It should initially be started at approximately half the target dose, due to their foundational role in delaying CKD progression and improving related comorbidities, including hypertension , as well as their low cost.
- Most modern outcome trials were conducted on background RASi.
- Not all patients can tolerate RASi therapy, RASi intolerance should not prevent further treatment.
- SGLT2i ,GLP-1RA trials included patients unable to receive RASi.
- Subsequent disease-modifying therapy can therefore continue.

Month 2: SGLT2 Inhibitor

- SGLT2i should be introduced at the target dose.
- Dedicated kidney outcome trials support full-dose initiation.
- The class provides broad cardiorenal protection, Administration is generally simple,Tolerability is favorable in appropriate patients, Cost barriers are also decreasing as generic options emerge.

SGLT2i Eligibility

- SGLT2i can be initiated with HbA1c below 10%.
- An eGFR of at least 20 mL/min/1.73 m^2 is recommended.
- The therapy can often be continued below this eGFR.
- Continuation may extend until renal replacement therapy begins.
- The glucose-lowering effect declines with lower eGFR.
- Kidney and cardiovascular benefits remain clinically important.

Month 3: Choosing Finerenone or GLP-1RA

- The third medication depends on clinical characteristics.
- Important factors include cardiovascular disease,Weight and glycemic control should also be considered.
- Blood pressure and patient preference are relevant.
- Finerenone may be prioritized in selected high-risk patients.
- GLP-1RA may be favored for metabolic and ASCVD benefits.

WHEN TO PRIORITIZE FINERENONE

- Finerenone may be preferred in patients with heart failure.
- This includes HF with LVEF ≥40%.
- High residual albuminuria is another important indication.
- Starting dose depends on eGFR.
- An eGFR of 25–59 requires 10 mg/day.
- An eGFR ≥60 allows a starting dose of 20 mg/day.

WHEN TO PRIORITIZE GLP-1RA

- GLP-1RA provide strong metabolic benefits.
- They also reduce ASCVD risk.
- They are useful when glycemic targets remain unmet.
- They may be particularly valuable in obesity.
- Treatment should begin at a low dose.
- A quarter starting dose may reduce GI adverse effects.

Months 5–6: Dose Optimization

- RASi should be titrated toward the maximum tolerated dose.
- Finerenone should also be titrated appropriately.
- GLP-1RA should be gradually increased toward evidence-based doses.
- Titration follows successful initiation of each drug class.
- Monthly safety assessments should guide dose changes.
- The goal is effective therapy with acceptable tolerability.

Why Sequential Combination Therapy?

- Starting several agents simultaneously may increase adverse effects.
- Starting fewer drugs at maximal doses has similar concerns.
- Sequential introduction allows closer safety monitoring.
- Lower initial doses can improve tolerability.
- Different mechanisms may also produce therapeutic synergy.
- The strategy aims to maximize benefit while limiting toxicity.

MANAGEMENT OF ADVERSE EFFECTS

Major Safety Concerns

- Safety concerns can delay combination treatment.
- Four major problems require active monitoring,These include hyperkalemia and eGFR decline, Hypotension is another important issue,Hypoglycemia is relevant with insulin or secretagogues.
- Pretreatment optimization can reduce these risks.

Hyperkalemia Monitoring and Management

- Potassium should be checked after starting RASi or finerenone.
- The recommended interval is 2–4 weeks.
- Reversible causes should first be investigated: Diet, constipation, acidosis, and insulin deficiency are relevant causes.
- Diuretics can increase urinary potassium excretion when appropriate.(Loop diuretics, Thiazides may be added in selected patients
- Potassium binders may also permit continuation of disease-modifying therapy.(sodium polystyrene sulfonate,
- Patiromer and sodium zirconium cyclosilicate are newer options)
- Dietary assessment should be considered, Dietician referral may be useful.

eGFR Dip After Treatment

- A transient eGFR decline is expected with some therapies,
- This can occur after RASi initiation, It may also follow SGLT2i or nsMRA initiation.
- The decline is usually hemodynamic rather than structural, It may persist for one to three months. A 10–15% decline is commonly reported.

Acceptable eGFR Decline

- Some trials reported eGFR declines up to 30%.
- The average decline was approximately 4–5 mL/min/1.73 m^2.
- The initial decline may predict long-term kidney preservation.
- Combination therapy can produce a larger early dip.
- CONFIDENCE demonstrated a reversible early decline.
- Therefore, an early eGFR dip does not automatically indicate toxicity.

Management of ≥30% eGFR Decline

- An eGFR decline of ≥30% requires reassessment.
- The measurement should be repeated within 2–4 weeks.
- Hemodynamically active therapy should not be increased immediately.
- Non-drug causes of acute kidney dysfunction should be investigated.
- Temporary treatment interruption or dose reduction may sometimes be necessary, depend on the clinical context.
- Diuretics should also be reassessed.
- Renal ultrasound may be required to exclude structural causes.

Hypotension Management

- Blood pressure may fall after cardiorenal GDMT initiation.
- RASi, SGLT2i, and nsMRA should not start with SBP <90 mmHg.
- Symptomatic orthostatic hypotension is also a concern.
- Monitoring is especially important in older or frail patients.
- Non-disease-modifying BP drugs should be adjusted first.
- RASi discontinuation should generally be a later strategy.

Hypoglycemia Management

- Hypoglycemia risk depends strongly on concomitant therapy.
- Insulin and secretagogues are the major contributors.
- SGLT2i glucose-lowering efficacy decreases with reduced eGFR.
- GLP-1RA maintain glucose-lowering effects across kidney function.
- GLP-1RA should not be escalated with frequent severe hypoglycemia.
- Concomitant glucose-lowering therapy must be adjusted appropriately.

GLP-1RA and Hypoglycemia: Dose Adjustment

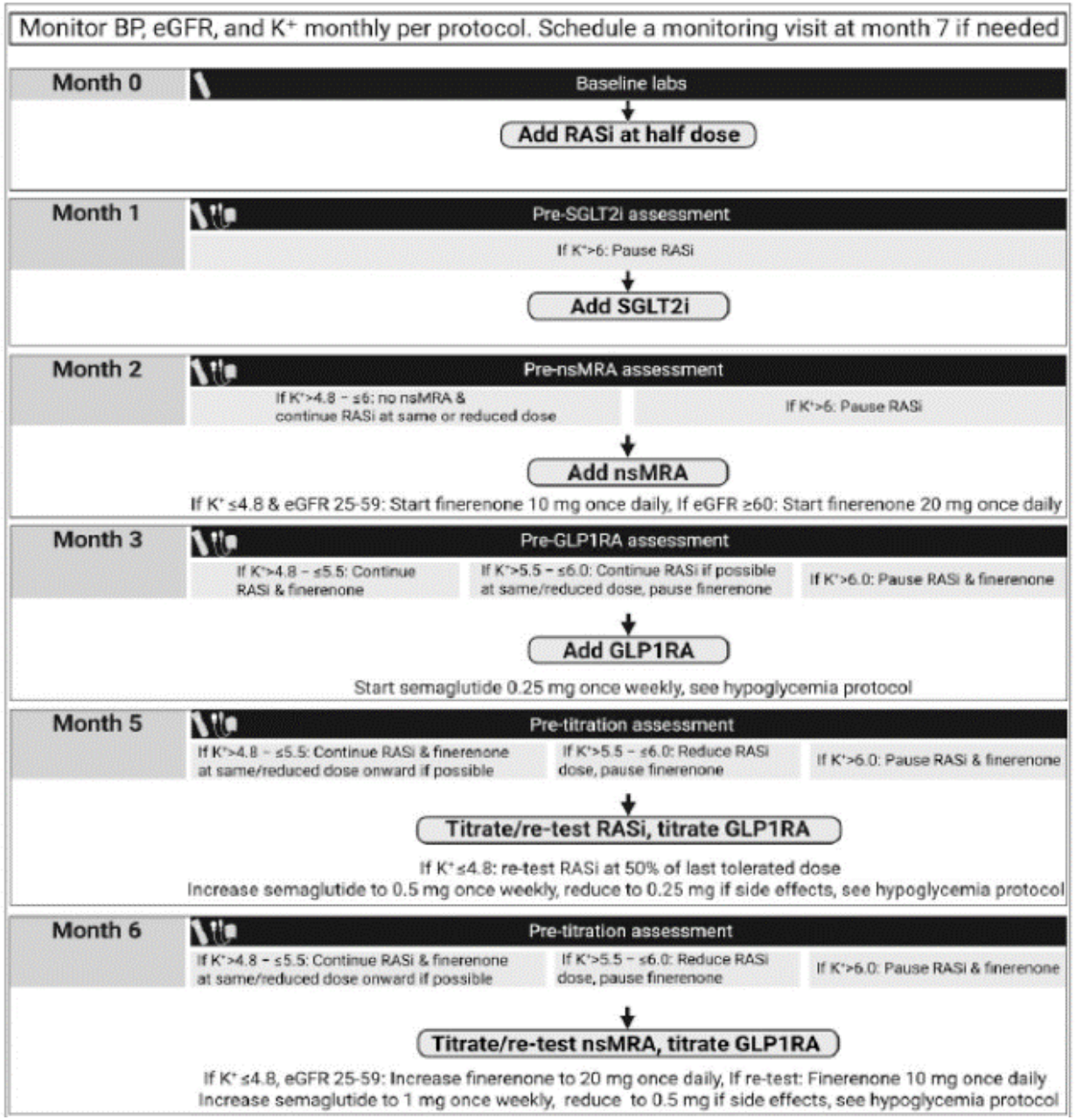
- Two or more weekly level 2 or 3 episodes require caution.
- This is particularly important when glucose falls below 3.0 mmol/L.
- With HbA1c >8%, dose reduction is usually unnecessary.
- With HbA1c ≤8%, secretagogues should be reduced or stopped.
- The secretagogue dose can be reduced by 50%. Insulin dose may be reduced by 10–20%.

TIMING, IMPLEMENTATION, AND FUTURE DIRECTIONS

TIMING OF TREATMENT INITIATION

- Traditional care often introduces medications gradually over 12–24 months.
- This approach may delay important cardiorenal protection.
- Cardiovascular benefits can appear within approximately 1 month.
- Kidney benefits may become evident within 6–12 months.
- Delayed initiation therefore represents a missed opportunity for risk reduction.
- An accelerated strategy may be more appropriate for patients with high kidney and cardiovascular risk.

Figure 3
Proposed algorithm for early implementation of combination GDMT for CKD and T2D.
*Level 2 hypoglycemia is a glucose level <3.0 mmol/L. Level 3 hypoglycemia is characterized by an altered mental and/or physical status requiring assistance for treatment of hypoglycemia, regardless of glucose level (53).



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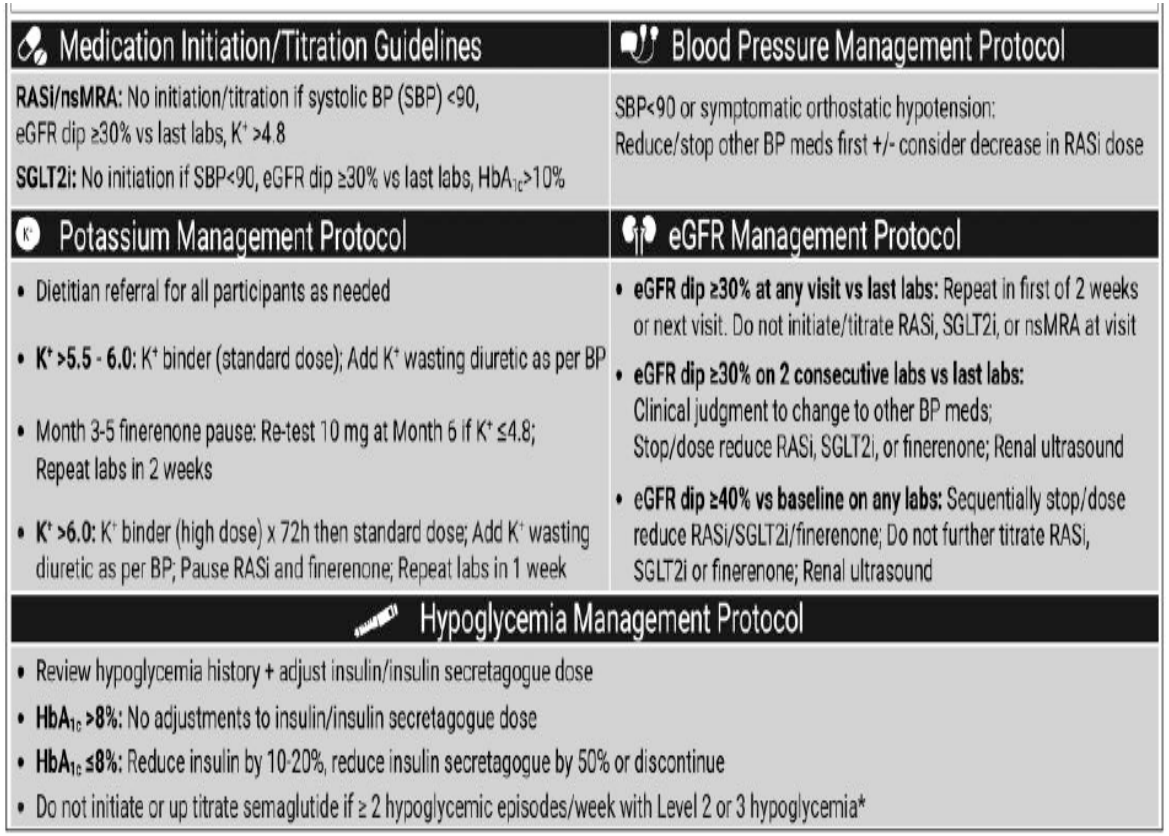

Thank you