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# Why wait? Early combination therapy in diabetic kidney disease: lessons from CONFIDENCE

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The prevalence of chronic kidney disease (CKD) caused by diabetes mellitus has risen markedly over the past decades, in line with the global increase in type 2 diabetes (T2D). Beyond hyperglycemia, conditions such as obesity, hypertension, atherosclerosis, dyslipidemia, and insulin resistance also contribute to kidney damage, making diabetic kidney disease (DKD) a heterogeneous disorder involving a complex interplay between metabolic dysregulation, hemodynamic changes, and progression of inflammation and fibrosis. Although albuminuria remains a cornerstone for CKD detection, risk stratification, and therapeutic decision-making, a substantial proportion of patients with diabetes and CKD exhibit a non-albuminuric phenotype, highlighting the clinical heterogeneity of DKD beyond traditional albuminuria-based classifications[1].

After decades during which nephroprotection was purely based on renin-Angiotensin system inhibitors (RASi), the emergence of SGLT2 inhibitors (SGLT2i), finerenone (a non-steroidal mineralocorticoid receptor antagonist), and more recently Glucagon-like Peptide-1 (GLP-1) receptor agonists has changed the therapeutic approach to DKD[2]. However, until recently, these drugs were gradually introduced. The COmbinatioN effect of FInerenone anD EmpagliflziN in participants with CKD and T2D (CONFIDENCE) marks a conceptual shift by proposing an approach based on the early combination of complementary treatments[3].

The CREDENCE, DAPA-CKD, and EMPA-KIDNEY trials have clearly demonstrated that SGLT2i slow the decline in estimated glomerular filtration rate (eGFR), reduce major renal events, and lower the risk of heart failure in DKD (and non-diabetic albuminuric) CKD[4-6]. Beyond randomized clinical trials, accumulating real-world evidence has confirmed the nephroprotective effectiveness of SGLT2i across broader and less selected populations, supporting the generalizability of these findings to routine clinical practice[7].

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The very recent KDIGO draft update of the Diabetes and CKD Guideline thus recommends (level 1A) such treatment in DKD[8].

FIDELIO-DKD and FIGARO-DKD[9,10] evaluated the efficacy of finerenone therapy across two overlapping populations, with primary kidney outcomes in FIDELIO-DKD and cardiovascular outcomes in FIGARO-DKD. The prespecified pooled analysis, FIDELITY, demonstrated that finerenone significantly reduced the risk of both renal and cardiovascular outcomes, thereby establishing its role as a key component of contemporary nephroprotective therapy[11]. Similarly, the draft update of the KDIGO Diabetes and CKD Guideline recommends finerenone in subjects meeting the inclusion criteria of FIDELITY (level 1A). Furthermore, finerenone demonstrated a consistent safety and efficacy profile in patients already treated with SGLT2i, supporting concomitant use in clinical practice[12]. Although the studies were not powered to draw definitive conclusions regarding combination therapy, exploratory post-hoc analyses consistently showed lower rates of renal and cardiovascular events among patients receiving triple therapy (RASi, SGLT2i, and finerenone), whether SGLT2i were administered at baseline ($n$ = 877) or initiated during follow-up ($n$ = 1113). Evidence from clinical trials evaluating the renal and cardiovascular effects of SGLT2i and finerenone highlights the prognostic significance of early reductions in albuminuria as a surrogate marker of improved kidney outcomes[13].

These findings support the hypothesis that earlier combination therapy may provide greater nephroprotection than delayed sequential treatment intensification. However, this hypothesis remains to be confirmed by trials evaluating long-term renal and cardiovascular outcomes. CONFIDENCE randomized 800 participants with T2D and CKD [eGFR 30-90 mL/min/1.73 m$^2$; Urine Albumin-Creatinine Ratio (UACR) 100- < 5,000 mg/g], all on RASi, to finerenone, empagliflozin, or their simultaneous combination. Notably, 35% of participants had an eGFR ≥ 60 mL/min/1.73 m$^2$, underscoring the importance of albuminuria screening for CKD detection.

The primary endpoint was the relative change in UACR at 180 days. Median baseline UACR was 579 mg/g. In the FIDELITY program, conducted in a population with a comparable baseline UACR (514 mg/g), early reductions in albuminuria mediated 84% of renal and 37% of cardiovascular treatment benefits[14].

At 6 months, combination therapy reduced albuminuria by 52%, corresponding to an additional 29% reduction *vs.* finerenone and 32% *vs.* empagliflozin alone. The effect emerged within 2 weeks and approached 50% by month 3. In prespecified subgroup analyses, the reduction in UACR with combination therapy was descriptively more pronounced among participants aged ≥ 65 years and those with baseline blood pressure ≥ 130/80 mmHg.

Despite concerns regarding hyperkalemia, hypotension, and the initial eGFR dip, combination therapy improved blood pressure control. Although mean serum potassium changes were similar and below 0.3 mmol/L across groups, concomitant SGLT2 inhibition appeared to attenuate the risk of clinically significant hyperkalemia compared with finerenone monotherapy, although no formal statistical testing was performed. This hypothesis had already emerged in exploratory analyses of FIDELITY, based on plausible pathophysiological mechanisms: increased natriuresis, improved distal sodium delivery, facilitation of potassium excretion. Although CONFIDENCE was not designed to demonstrate a benefit regarding hyperkalemia, the results are reassuring and support the idea that early combination therapy may be better tolerated than initially feared. Interestingly, the Fine-REAL study (a global, prospective, observational study in DKD) recently demonstrated that finerenone was well tolerated, consistent with the safety profile observed in clinical trials. Importantly, most patients in FINE-REAL had baseline serum potassium levels ≤ 5.0 mmol/L (90.4%), providing reassuring real-world evidence supporting the safe implementation of

finerenone in routine clinical practice. Hyperkalemia was reported in 8.1% of participants but led to the discontinuation of treatment in only 1% of cases[15].

Combination therapy in CONFIDENCE was associated with a greater initial decline in eGFR, which, together with reduced albuminuria, is consistent with a hemodynamic mechanism that further attenuates glomerular hyperfiltration, a recognized nephroprotective effect shared by several CKD therapies. This concept is particularly important in clinical practice because clinicians sometimes incorrectly interpret this initial decline as drug-induced kidney injury, leading to premature discontinuation of treatment. A better understanding of this dynamic is essential for optimizing the use of combination therapy.

A very recent post hoc analysis of CONFIDENCE[16] demonstrated that the superior efficacy of combination therapy compared with either monotherapy remained consistent across all baseline eGFR and UACR categories. Irrespective of treatment allocation, higher baseline eGFR and UACR were independently associated with greater reductions in albuminuria at day 180; UACR reduction was greater by 7% per 10 mL/min/1.73 $m^2$ higher baseline eGFR, and by 9% per log-unit higher baseline UACR. The safety profile was overall consistent across all subgroups. No significant heterogeneity was observed in adverse events - including hyperkalemia, symptomatic hypotension, or an acute decline in eGFR greater than 30% - according to baseline UACR or eGFR strata. As expected, the risk of hyperkalemia tended to be higher among participants with lower baseline eGFR. Symptomatic hypotension was uncommon, occurring in only two participants across the entire study population, both of whom were in the combination therapy group and had a baseline eGFR < 60 mL/min/1.73 $m^2$.

The authors recognize several limitations of CONFIDENCE, including the 180-day duration of the study, the moderate sample size, and the absence of longitudinal systolic blood pressure data, which may represent an important mediator of the observed treatment effect. These limitations restrict the ability to assess the durability of albuminuria reduction, the long-term safety profile, and whether the observed surrogate benefit translates into improved renal and cardiovascular outcomes across broader populations. Interestingly, approximately 23% of participants were receiving a GLP-1 receptor agonist at baseline. Although the antiproteinuric effect of combined empagliflozin and finerenone remained consistent regardless of background GLP-1 receptor agonist use, no data were available regarding the duration of exposure to these agents before randomization, nor were changes in body mass index systematically assessed during follow-up. Nevertheless, the role of GLP-1 receptor agonists in nephroprotection is rapidly evolving. The FLOW trial, the first dedicated kidney outcome trial with a GLP-1 receptor agonist, demonstrated that semaglutide significantly reduced the risk of major kidney outcomes and cardiovascular death in patients with T2D and CKD[17]. These findings further support the role of GLP-1 receptor agonists as nephroprotective agents beyond their glucose-lowering effects and raise the possibility that they may become an integral component of future multidrug nephroprotective strategies alongside Renin-Angiotensin System (RAS) inhibitors, SGLT2i, and finerenone. Whether simultaneous initiation of these complementary therapies provides additional cardiorenal benefit remains an important question for future clinical trials.

Multiple therapies are now available to slow DKD progression; however, the optimal strategy for implementation, whether simultaneous or sequential initiation, remains debated. Beyond biological efficacy, implementation of early multidrug therapy will also depend on healthcare system factors, including drug access, reimbursement policies, treatment costs, and long-term patient adherence, which may influence the feasibility of this approach in real-world settings.

The historical sequential strategy largely reflected the timeline of drug development rather than a truly integrated pathophysiological approach to DKD management.

The CONFIDENCE findings question the traditional sequential treatment paradigm and support further evaluation of earlier combination therapy. The findings raise the possibility that delaying treatment intensification until disease progression becomes evident may represent a missed opportunity, although confirmation based on long-term clinical outcomes is still required.

Current advances in nephrology strongly echo the progress achieved in heart failure, where the early introduction of multiple therapies targeting complementary pathophysiological pathways has transformed patient outcomes through robust evidence demonstrating reductions in mortality and heart failure hospitalizations. Although the evidence supporting early multidrug therapy in DKD remains less mature than in heart failure, the CONFIDENCE trial provides proof of concept that simultaneously initiating finerenone and an SGLT2 inhibitor is feasible, well tolerated, and achieves greater reductions in albuminuria than either agent alone. Whether the greater reduction in albuminuria observed with this strategy translates into superior long-term renal and cardiovascular outcomes remains to be demonstrated in adequately powered clinical outcome trials with longer follow-up. Nevertheless, these findings provide a strong rationale for further evaluating early multidrug nephroprotective strategies combining RAS inhibitors, SGLT2i, finerenone, and GLP-1 receptor agonists in patients with DKD. Another important area requiring further attention is identifying biomarkers that predict greater or lesser benefit from specific nephroprotective therapies, thereby advancing nephrology toward precision medicine[18].

## DECLARATIONS

### Authors' contributions

Wrote the first draft: Ponlot E

Contributed equally to the conception and critical revision of the manuscript, and approved the final manuscript: Ponlot E, Jadoul M

### Availability of data and materials

Not applicable.

### AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool ChatGPT (version GPT-5.6 Luna, released 2026-08-09) was used solely for language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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### Conflicts of interest

Jadoul M is a speaker and consultant for both AstraZeneca and Boehringer Ingelheim. Ponlot E declares no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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