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Can we De-Escalate Pharmaco-Therapies For Certain Patients Living with Type 2 Diabetes and Chronic Kidney Disease?

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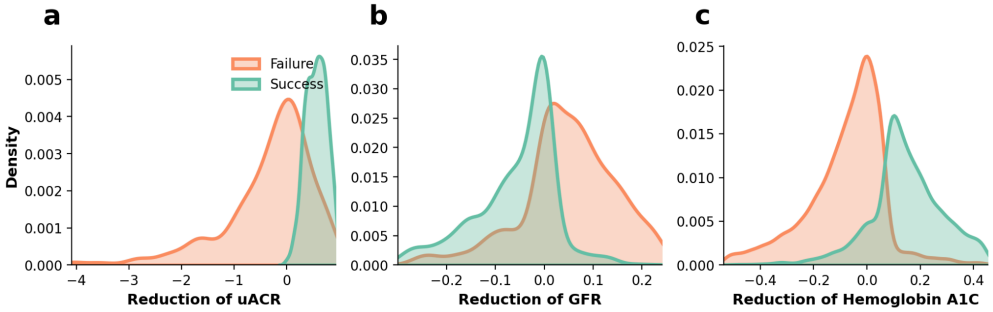
Background and aims. Chronic kidney disease (CKD) develops in 30-40% of people with type 2 diabetes mellitus (T2D) with a progression that is potentially intensifying beyond simple addition. The present study explores therapeutic interventions where superior outcomes have been achieved using alternatives to a simple combination of each pathology's guideline recommendations.
Materials and methods. A neural network was first created to reproduce UK national clinical guidelines for T2D and CKD management with an 89% accuracy. Relying on real-world evidence (RWE) of UK primary care, a transfer learning methodology was then applied on 18644 therapeutic decision timepoints, learning from clinical outcomes how to better achieve dual T2D & CKD optimisation targets here defined as min 7% relative HbA1c reduction for values >48 mmol/mol and either a non-decreasing eGFR for 30<eGFR<90 ml/min/1.73 m^2 or a 30% relative uACR reduction for uACR> 30 mg/g, all within one year.



Shapley values are used on 22486 treatment decision timepoints to define similar digital twin cohorts in an independent test set for whom alternative therapies to the guidelines show both statistically significant better outcomes and counterfactual evidence of the contrary (p-values < 0.01).
Results. Therapies tested for an adult patient population (n=22486, mean±SD age 75±17.1 yr; M 56% vs F 44%; HbA1c 8.4±4%, eGFR 77± 26.3 ml/min/1.73 m^2, uACR 30±61.7 mg/mmol) included 16839 with T2D and independently 10144 with CKD. Two types of machine learning recommended therapeutic deviations from guidelines resulted in average 14% or 17% improvement in probability of dual outcome success for a total of 357 or 208 therapies decreasing the overall pharmacological burden: combining an ACEi/ARB with an SGLT-2i (ΔHbA1c -0.3%, ΔeGFR +0.45 ml/min/1.73 m^2) rather than with metformin-based dual therapy (ΔHbA1c -0.1%, ΔeGFR -1.63 ml/min/1.73 m^2), and de-escalating from an ACEi/ARB combined with a metformin-based triple therapy or insulin regimen (ΔHbA1c -0.4%, ΔeGFR -1.74 ml/min/1.73 m^2) to a dual therapy with two oral antidiabetic drugs (ΔHbA1c -0.4%, ΔeGFR +0.61 ml/min/1.73 m^2). An additional group of deviations from guidelines provide fertile ground for discussions with experienced clinicians.
Conclusion. Observations from RWE outcomes question both a rather siloed interpretation of comorbidity under guidelines and a joint expected outcome of therapies that is not always additive, sometimes even amounting to a de-escalation to improve the outcome. The results represent practical steps towards personalised precision medicine for cardiovascular comorbidity in routine clinical practice and require further testing in prospective studies.