PREDICTING CHRONIC KIDNEY DISEASE IN TYPE 2 DIABETES USING PATIENT-LEVEL SIMULATION: OUTCOMES, MARKERS, RISK FACTORS, AND SEQUELAE IDENTIFIED IN A SYSTEMATIC REVIEW

J Pöhlmann[1], K Bergenheim[2], JJ García Sanchez[3], N Rao[3], RF Pollock[1]

Covalence Research Ltd., London, UK[1], AstraZeneca R&D, Mölndal, Sweden[2], AstraZeneca, Cambridge, UK[3]

COVALENCE RESEARCH

POSB313

Background

- Classification of chronic kidney disease (CKD) is centred on albuminuria and glomerular filtration rate (GFR). Both markers drive CKD progression but have received different attention in general-purpose CKD modelling (focused on GFR) and diabetes-related CKD modelling (focused on albuminuria).[1]
- Research into estimated GFR (eGFR) has shown that changes in eGFR are not linear and need not always be declines.[2] Both the speed of eGFR decline and eGFR variability have been identified as independent predictors of clinical outcomes in patients with type 2 diabetes mellitus (T2DM).[2,3] Notably, non-linear eGFR trajectories have also been observed with sodium glucose co-transporter 2 (SGLT2) inhibitors, a relatively novel class of antidiabetic drugs with renoprotective effects, for which a transient but marked decrease in eGFR is observed before a plateau or a slower decline.[4]
- These intricacies of eGFR and of novel treatments lend themselves to modelling in a patient-level simulation (PLS) framework. PLS models base outcome predictions on risk equations, which, for models investigating CKD progression in T2DM, were reviewed in the present study to identify key risk factor-outcome combinations used in the literature.

Methods

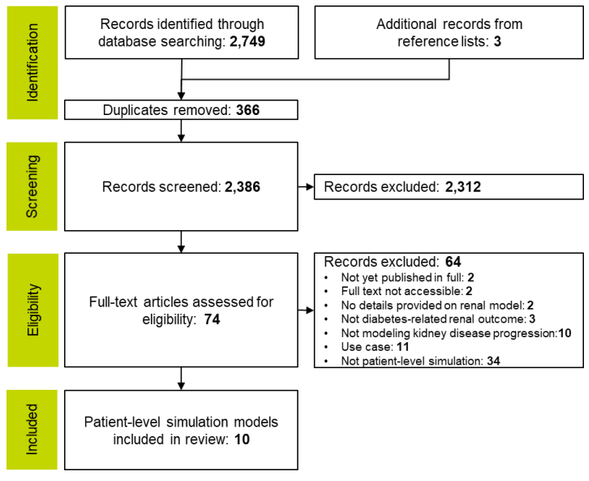
- A systematic literature review (SLR) was implemented in three literature databases (Cochrane Library; Embase, PubMed, including MEDLINE) on March 6, 2021, using search strategies consisting of free-text terms and controlled vocabulary, derived from a previous SLR.[1] No date restrictions were applied, except for conference abstracts in Embase (2019 onwards). Results were complemented by hand searches of reference lists of included studies.
- Records were screened by a single researcher against the inclusion criteria presented in Table 1.
- Data on risk factors and outcomes, including both kidney-related outcome predicted from risk factors and additional outcomes such as sequelae like cardiovascular disease (CVD) predicted from risk factors and kidney-related outcomes, were extracted by a single researcher.
- Risk factors were grouped into clinical, demographic, and treatment-related factors, and frequencies were summarized using *R*.

Table 1 Study inclusion criteria.

Report on a risk equation-based PLS model of CKD progression in T2DM
Not a use case of an otherwise already identified model (e.g., a country-specific use case)
Sufficient detail on risk equations

Results

Figure 1 Flow diagram for study selection.

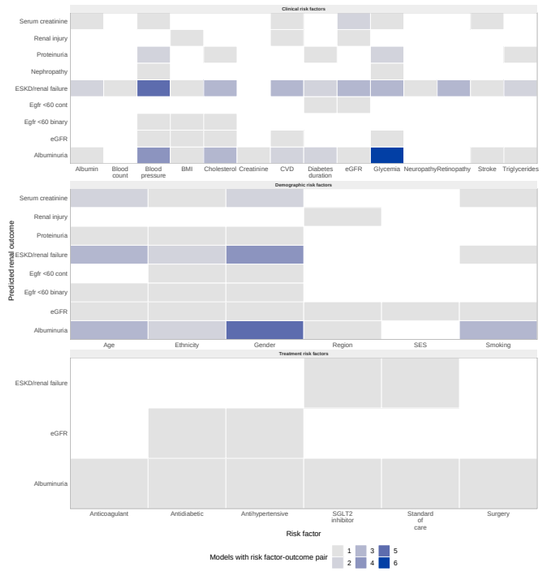


Titles and abstracts of 2,386 records were screened and full texts of seventy-four studies were reviewed, with ten PLS models included in the review (Figure 1).

Between them, the 10 PLS models used 33 equations to predict 21 kidney disease-related outcomes, most frequently ESKD (12 [36%] risk equations), albuminuria (8 [24%]), and eGFR (6 [18%]).

Risk factors most frequently used as predictors of renal outcomes were BP (10% of all risk equations) and glycemia (9%) among clinical and gender (9%) and age (6%) among demographic risk factors. Treatment-related factors were less frequently used.

Figure 2 Risk factors for renal outcomes in PLS models.

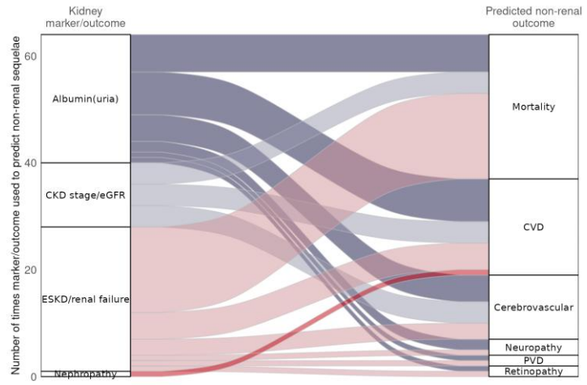


ESKD and eGFR were predicted from a diverse range of risk factors (Figure 2):

Clinical: Blood pressure, cholesterol, glycemia, and eGFR were used most frequently to predict ESKD, while eGFR was predicted from BP, cholesterol, and glycemia. The main risk factor to predict albuminuria was glycemia.
Demographic: Age, ethnicity, and gender were frequently used to predict ESKD, eGFR, and albuminuria.
Treatment: Treatment-related risk factors were most frequently used for predicting albuminuria (Figure 2).

In 16 equations of non-kidney outcomes predicted from kidney disease, markers and outcomes, mortality was found to be most frequently predicted (9 [56%] risk equations), followed by CVD (4 [25%]) (Figure 3). Cerebrovascular disease (2 [13%]) and neuropathy (1 [6%]) were less frequently modelled.

Figure 3 Frequencies of kidney-related markers predicting non-kidney outcomes.



Conclusions

- The kidney-related outcomes most frequently included in PLS models were ESKD and eGFR; the most frequently used risk factors were BP, glycemia, age, and sex (but not, for example, urine albumin-to-creatinine ratio). Mortality was the most frequent outcome predicted from kidney disease.
- Risk factor use was consistent with the literature, but models differed in which factors were included and rarely explained their choice. Modelling CKD in T2DM might benefit from improved justification of endpoint and risk factor selection.
- Some relevant kidney outcomes were not modelled, including time to dialysis, which can be prolonged using treatments such as SGLT2 inhibitors, thereby significantly reducing costs.[555] Reporting such outcomes would provide additional estimates around the impact of novel therapies, but may increase complexity and make results more challenging to communicate, e.g., to health technology assessment agencies

References

1. Sugrue DM, *et al.*, PharmacoEconomics 37, 1451-68, 2019.
2. Ali I, *et al.* BMC Nephrol 22, 82, 2021.
3. Jun M, *et al.*, Diabetes Obes Metab 23, 1420-5, 2021.
4. Mosenzon O, *et al.*, Lancet Diabetes Endocrinol 7, 606-17, 2019.
5. Durkin M & Blais J, Diabetes Ther 12, 499-508, 2021.

Supported by AstraZeneca

Presented at Virtual ISPOR Europe 2021, Topic: Methodological & Statistical Research, 1 December 2021.