Advancing personalized medicine in type 2 diabetes through better prediction of drug efficacy

Tye, Sok Cin

DOI:
10.33612/diss.609897284

CHAPTER 8

Summary and future perspectives

SUMMARY

The current management of patients with diabetes is driven by established clinical practice guidelines that are based on evidence derived from clinical trials and population-based studies. Improved glycemic control is considered important as it has been shown for example to retard the development of albuminuria and micro- and macrovascular complications in patients with type 2 diabetes.[1-4] In addition, adequate control of other risk factors, including hypertension, hypercholesterolemia and obesity, is considered important as well to prevent long-term kidney and cardiovascular outcomes.[5-7] The guidelines, however, do not sufficiently take into account the individual variability or heterogeneity in response to the drugs that are used to target these risk factors. This is problematic since a substantial proportion of patients do not show an adequate response to drugs used to manage kidney and cardiovascular complications.[8,9] These patients remain at high risk and are unnecessarily exposed to drugs with potential side effects. It is therefore, important to develop tools or algorithms which could predict the risk of an individual patient or the response to an intervention.

The aim of this thesis was to further develop and refine risk algorithms to determine the long-term risk of kidney and cardiovascular outcomes and the long-term clinical kidney and cardiovascular benefits of drugs used in patients with type 2 diabetes. To this end, we further validated an existing score, the multiple Parameter Response Efficacy (PRE) score, that translates the short-term drug response in multiple kidney and cardiovascular risk markers into a predicted long-term drug effect in type 2 diabetes care. This score could be used and implemented to predict the long-term effect of drugs on clinical outcomes at a population level. If further validated, the score may also be used to predict the drug effect for individual patients, which could lead to a more personalized treatment approach and improved outcomes at an individual level.

Following a general overview of various opportunities and challenges to implement precision medicine, particularly in patients with diabetic kidney disease in the introduction, we have reviewed the common drugs used in patients with type 2 diabetes, such as glucose-, blood pressure (BP)-, and lipid-lowering therapies in **chapter 2**. We have highlighted the importance of a poly-pharmacological treatment approach to reduce kidney and cardiovascular risks in patients with type 2 diabetes. We also provided a detailed description of the clinical or phenotypic features which influence the treatment effects of these drugs and elaborated on the known pharmacogenetics or genetic variations which may alter drug response. From this, it becomes clear that both pharmacogenetics and protein markers can inform personalized medicine approaches for the treatment of diabetes.

Since most patients with type 2 diabetes have several concomitant risk factors, comprehensive risk management requires monitoring and management of multiple risk factors to prevent long-term complications.[7] In **chapter 3**, a post-hoc analysis of the CANVAS and CANVAS-R trials was presented showing the importance of addressing multiple risk markers in patients with type 2 diabetes. This study demonstrated that improvement in multiple risk markers (e.g., HbA1c, systolic BP, urinary-albumin-creatinine ratio (UACR), uric acid, body weight, and hemoglobin) upon initiation of an SGLT2 inhibitor initiation was associated with a greater relative risk reduction for the cardiovascular and kidney outcomes as compared to improvements in single cardiovascular risk marker. These findings are consistent with several observational studies (e.g., the Swedish cohort, and the primary care database from the UK) and clinical trials such as the Steno-2 (Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria) and the NID-2 (Nephropathy in Diabetes Type 2) study, which demonstrated that an intensified multifactorial intervention profoundly reduces the risk of major cardiovascular or kidney events in patients with type 2 diabetes.[10-13] Changes in albuminuria and uric acid showed the strongest associations with all studied outcomes in this study. This suggests the importance of monitoring UACR and uric acid changes in clinical practice as markers of cardiovascular and kidney events, on top of HbA1c, BP, or lipid parameters. Collectively, these data support the need to target multiple risk factors or integrate changes in multiple cardiovascular risk markers into a risk score to predict the risk and the risk change of an individual for both kidney and cardiovascular complications. Such an approach could guide treatment to patients at the highest risk or to those who are most likely to benefit.[14]

Several risk algorithms have been developed previously to predict the kidney risk or prognosis in patients with type 2 diabetes.[15] Most algorithms, such as the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) or the KFRE (Kidney Failure Risk Equation) risk equations, use clinical characteristics to predict disease outcomes.[16,17] However, risk scores which integrate early changes in biomarkers upon initiation of a drug are uncommon. The PRE score is an algorithm that integrates multiple drug-induced short-term biomarker changes to predict the long-term prognosis of an individual and the effect of a drug on clinical outcomes.[18-23] In **chapter 4**, we compared the existing ADVANCE risk score and the KFRE risk equation with the PRE score in terms of kidney risk prediction as well as in predicting the kidney protective effect of an angiotensin receptor blocker (losartan) in patients with type 2 diabetes and nephropathy using the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) trial dataset. In terms of kidney risk prediction, all three risk algorithms demonstrated good performance. However, the PRE score outperformed the ADVANCE risk equation and the KFRE score to predict the long-term efficacy of a drug to reduce the risk of kidney outcomes

This supports the use of the PRE score to predict long-term drug efficacy.

The PRE score integrates early drug effects on multiple cardiovascular risk markers and thereby overcomes a fundamental issue we face in predicting treatment effects during the drug development process and in clinical trials. During drug development, the drug evaluation is usually targeted toward a single risk marker. For example, HbA1c improvement has been traditionally the surrogate marker for assessing the effect of blood glucose-lowering drugs. However, many drugs exert effects on multiple risk markers beyond the targeted (so-called on-target) risk marker. These effects on the off-target risk factor may influence the ultimate clinical outcome as well and should, therefore, not be ignored. The integration of multiple short-term drugs induced biomarker changes may therefore result in a better prediction of the ultimate long-term effect of a drug on clinically meaningful outcomes.[24] In **chapter 5**, we have applied the PRE score in the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial dataset to ascertain the role of multiple short-term drug-induced biomarker changes for predicting treatment effects. The EMPA-REG OUTCOME trial is the first cardiovascular outcome trial of the SGLT2 inhibitors consisting of 7020 participants with type 2 diabetes at high risk of cardiovascular events. We observed that empagliflozin reduces several risk markers such as HbA1c, systolic BP, blood pressure, UACR, body weight, and uric acid. Short-term drug-induced changes on the kidney or cardiovascular risk markers were then modelled to predict the long-term efficacy of the drug. In the overall population, the PRE score underestimated the treatment effect of empagliflozin on both cardiovascular and kidney outcomes. A likely explanation for the underestimation is the lack of inclusion of biomarkers that could better reflect the cardiovascular or kidney mechanisms of SGLT2 inhibitors, such as markers reflecting autophagy, mitophagy, inflammation and fibrosis. In addition, the EMPA-REG OUTCOME trial was not designed to assess the effect of empagliflozin on kidney outcomes. Very few participants had chronic kidney disease (CKD) at baseline, and kidney function was relatively stable in many participants. It could well be that in participants with established kidney disease, the PRE score more adequately predicts the kidney protective effect of empagliflozin. This notion is supported by a subgroup analysis we conducted among participants with elevated albuminuria levels greater than 30 mg/g. In this subgroup, the PRE score better predicted the treatment effect of empagliflozin on the kidney outcome, and the predicted relative risk reduction was similar compared to the observed relative risk reduction. This suggests that the kidney protective mechanism of empagliflozin may potentially be dependent on baseline albuminuria. The EMPA-KIDNEY (The Study of Heart and Kidney Protection with Empagliflozin) trial is recently finished but the results are not yet available. The trial was designed to assess the kidney protective effects of empagliflozin in a broad cohort of patients with CKD with and without type 2 diabetes.[25] By selecting a subgroup of

patients from the EMPA-REG OUTCOME trial who fulfilled the inclusion criteria of the EMPA-KIDNEY trial, we found that the predicted risk reduction for the composite kidney and cardiovascular death outcome was mostly dependent on changes in UACR in these patients.

To broadly implement the PRE score, the score should predict the effect of multiple drugs with different mechanisms of action. We, therefore, assessed in **chapter 6** the efficacy of the PRE score for glucagon-like peptide-1 receptor agonists (GLP-1 RA). To this end, we applied the PRE score on data from the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial to predict the effect of a GLP-1 RA, liraglutide, on kidney and cardiovascular outcomes in patients with type 2 diabetes and high cardiovascular risk. We found that the PRE score was able to predict the kidney outcome similar to the observed risk reduction by integrating the favorable effects of liraglutide on HbA1c, systolic BP, UACR, body weight, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and potassium. In addition, we estimated the effect of a GLP-1 RA for the composite kidney and cardiovascular death outcome in a subgroup of patients fulfilling the ongoing FLOW (A Research Study to See How Semaglutide Works Compared to Placebo in People with Type 2 Diabetes and Chronic Kidney Disease) trial inclusion criteria. The FLOW trial assessed the efficacy of once-weekly semaglutide in delaying the progression of end-stage kidney disease, or death due to kidney or cardiovascular causes in patients with type 2 diabetes. We again found that UACR reduction was expected to be the key driver for reducing the risk of the composite kidney and cardiovascular death outcome in this population.

The studies presented in the previous chapters focused on drug effect prediction at the population level. In **chapter 7**, we used a multivariable approach to estimate the effect of canagliflozin on the composite kidney and heart failure risk for *individual* patients with type 2 diabetes. We performed a post-hoc analysis of the CANVAS (Canagliflozin Cardiovascular Assessment Study) trial to estimate each individual's 5-year risk for developing kidney or heart failure events. We calculated the absolute treatment effect of canagliflozin for individual patients included in the trial. Subsequently, we showed that a multivariable risk-based approach based on clinical or combined clinical and novel biomarkers outperformed the treatment strategy using single surrogate markers, such as HbA1c or UACR, to guide the initiation of SGLT2 inhibitors in patients with type 2 diabetes. We also showed that there was a wide variation in predicted risk for the composite kidney or the composite heart failure outcomes and in the treatment effect (i.e., the absolute risk reductions) in the CANVAS population. We demonstrated that a multivariable risk-based treatment approach is likely to prevent more kidney or heart failure events in patients with type 2 diabetes and may lower the number of patients needed to treat than a HbA1c or UACR-guided treatment strategy.

FUTURE PERSPECTIVES

A number of studies have demonstrated that multiple clinical and genetic markers can predict the response to drugs used in the management of type 2 diabetes.[26-28] However, the translation of these research findings into clinical practice is limited. This can, in part, be explained by the fact that the prediction of an individual's drug response is complex and influenced by disease factors, patient characteristics, as well as environmental, social, and cultural factors.[29] This broad array of determinants makes it difficult to precisely predict how an individual patient responds to therapy. Despite these difficulties, understanding why patients respond so differently to drugs remains an important area of research. It can be expected that more validated biomarkers will become available to tailor therapy, which should ultimately reduce the risk of disease complications and improve the prognosis of patients with type 2 diabetes.

Routine monitoring of multiple risk factors in patients with type 2 diabetes

We demonstrated that improvements in more than one cardiovascular risk marker are associated with a reduced risk of cardiovascular and kidney outcomes and that, particularly, an early reduction in albuminuria showed a strong association with kidney failure. This has been observed in other studies in the past.[30,31] However, the implementation of routine monitoring of albuminuria or multiple biomarkers simultaneously is not yet optimal. For example, a recent study in the United States demonstrated that the rates of UACR testing in patients with type 2 diabetes highly vary across institutions and remain suboptimal in primary care settings.[32] The American Diabetes Association recommends at least annual UACR screening for all patients with type 2 diabetes and two times UACR screening per year for type 2 diabetes patients with eGFR 30 to 60 ml/min/1.73m^2 and UACR greater than 300 mg/g.[33] Increased awareness on the importance for albuminuria screening in primary care practice is necessary for early detection and treatment of cardiovascular or CKD risk factors, in addition to the current monitoring of traditional cardiovascular risk makers (e.g. blood pressure, HbA1c, lipids). Furthermore, the integration of kidney biomarkers in cardiovascular risk scores could be beneficial given that kidney risk markers can in part, predict cardiovascular risk. To achieve this, studies should show that screening for albuminuria is effective in identifying patients at high risk of either cardiovascular disease or kidney events and that such an approach is cost-effective. The Check@Home consortium in the Netherlands will initiate a population-wide home-based screening study (ClinicalTrials.gov Identifier: NCT04295889) for albuminuria. It is hoped that this study will highlight the cost-effectiveness of population screening for albuminuria and increase awareness among healthcare providers and patients.

Further development of the PRE score

The PRE score integrates early changes in multiple risk markers to predict the efficacy of an intervention on long-term kidney outcome. The PRE score is validated for patients with type 2 diabetes and has shown to accurately predict the renal and cardiovascular effect of ARBs, the renal effects of an endothelin receptor antagonists, and GLP-1 RA.[18,23,34,35] The unique feature of the PRE score is that it can be applied to any drug or population with short-term biomarker changes after treatment initiation available.

In the studies described in this thesis, the PRE score in general was more adequate in predicting the kidney than cardiovascular outcomes of GLP-1 RA and SGLT2 inhibitors. However, the PRE score also underestimated the kidney outcomes of SGLT2 inhibitors in patients with normoalbuminuria in the EMPA-REG OUTCOME trial. It is possible that some of the kidney protective effects of SGLT2 inhibitors were not captured by the current markers included in the PRE score. For example, the inclusion of tumor necrosis factor receptor (TNFR)-1, TNFR-2 and kidney injury molecule-1, which have been shown to predict early diabetic kidney disease, might improve the PRE score in this population.[36,37] The PRE score also did not sufficiently capture the cardiovascular effects of GLP-1 RA and SGLT2 inhibitors. Additional biomarkers, such as those reflecting oxidative stress, inflammation or fibrosis, might be included in the future to improve the prediction of cardiovascular outcomes in patients with type 2 diabetes.[38] For example, the combined use of high-sensitivity Troponin T, soluble ST2, and insulin-like growth factor binding protein 7 were found to better discriminate individuals who will benefit from cardioprotective effects of SGLT2 inhibitors.[39] The PRE score can be potentially applicable to test the efficacy of other classes of drugs, such as newer GLP-1RA/GIP (glucagon-like peptide-1 receptor agonist/ glucose-dependent insulinotropic polypeptide) or PCSK-9 (Proprotein convertase subtilisin/kexin type 9) inhibitors, although it is recommended that validation studies will be needed before the PRE score is applied to these new drug classes. The PRE score also assumes that the short-term effect on biomarkers is sustained during prolonged follow-up. However, it is possible that patients do not adhere to their medication during prolonged follow-up or that concomitant medications are prescribed that cancel or enhance the drug effect on long-term clinical outcomes. It would be interesting in future studies to explore these aspects in more detail.

Individual patients show variable treatment responses in multiple risk markers. For example, although drugs for the treatment of diabetes are developed to improve the target surrogate HbA1c outcome, a patient may experience additional effects on other risk markers. Since each of the response biomarkers changes can be independently associated with cardiovascular and/or kidney outcomes, it is important to monitor multiple biomarker changes within an individual and integrate these responses

into a predicted drug efficacy score. The final study in this thesis illustrated that a multivariable risk-based approach could guide the initiation of SGLT2 inhibitor therapy and might lead to lower numbers to treat to prevent a kidney or heart failure outcome in comparison to the HbA1c or UACR-guided treatment initiation. Using the PRE score to guide individualized prediction of drug effects is promising, but this has to be validated in future studies.

Other considerations with respect to personalized medicine in patients with diabetes

Several studies have focused on the use of genetic, phenotypic, and biomarker clusters to stratify patients based on their prognosis and to guide treatment selection.[40-42] A handful of genetic loci and polymorphisms of drug metabolizing enzymes or transporters influencing pharmacokinetics or pharmacodynamics have been identified for diagnosis, prognosis, and treatment response variation. At the same time, several attempts to better stratify type 2 diabetes patients were made. For example, the genetic clusters proposed by Udler et al,[41] the data-driven clusters by Ahlqvist et al,[40] and the palette model described by McCarthy have demonstrated that diabetes is a heterogeneous disease and that patients vary in their underlying pathophysiology.[43] A better understanding of the underlying pathophysiology of diabetes and its complications may help in the future to guide clinically available and new therapies. In this respect, clinical decision support tools that integrate cluster or biomarker data may help the clinician in daily practice. Such decision tools or data platforms could integrate individual molecular information or use the multivariable risk-based approach to guide treatment selection in patients with type 2 diabetes. In other disease areas such as in oncology, a decision support system known as the phenotypic medicine platform has been used to identify the right immunomodulating drugs at a right dose for patients to achieve the best possible therapeutic outcomes. This could be used as an example to reposition this platform for the treatment of type 2 diabetes.

To conclude, monitoring multiple risk factors, including risk markers traditionally not included in cardiovascular or kidney risk scores such as UACR and uric acid, to guide personalized treatment among patients with type 2 diabetes and CKD is essential. Furthermore, the use of a multiple risk-markers based response efficacy score, such as the PRE score, could support the prediction of long-term drug effects for a new drug at a population level in future clinical trials. Particularly for predicting cardiovascular outcomes, however, further studies including additional biomarkers are required. Finally, the potential benefits of the PRE score to predict treatment response at an individual level will require further validation studies to achieve the goal of personalized medicine and to move from a one-size-fits-all to a one-fit-for-every-one approach.

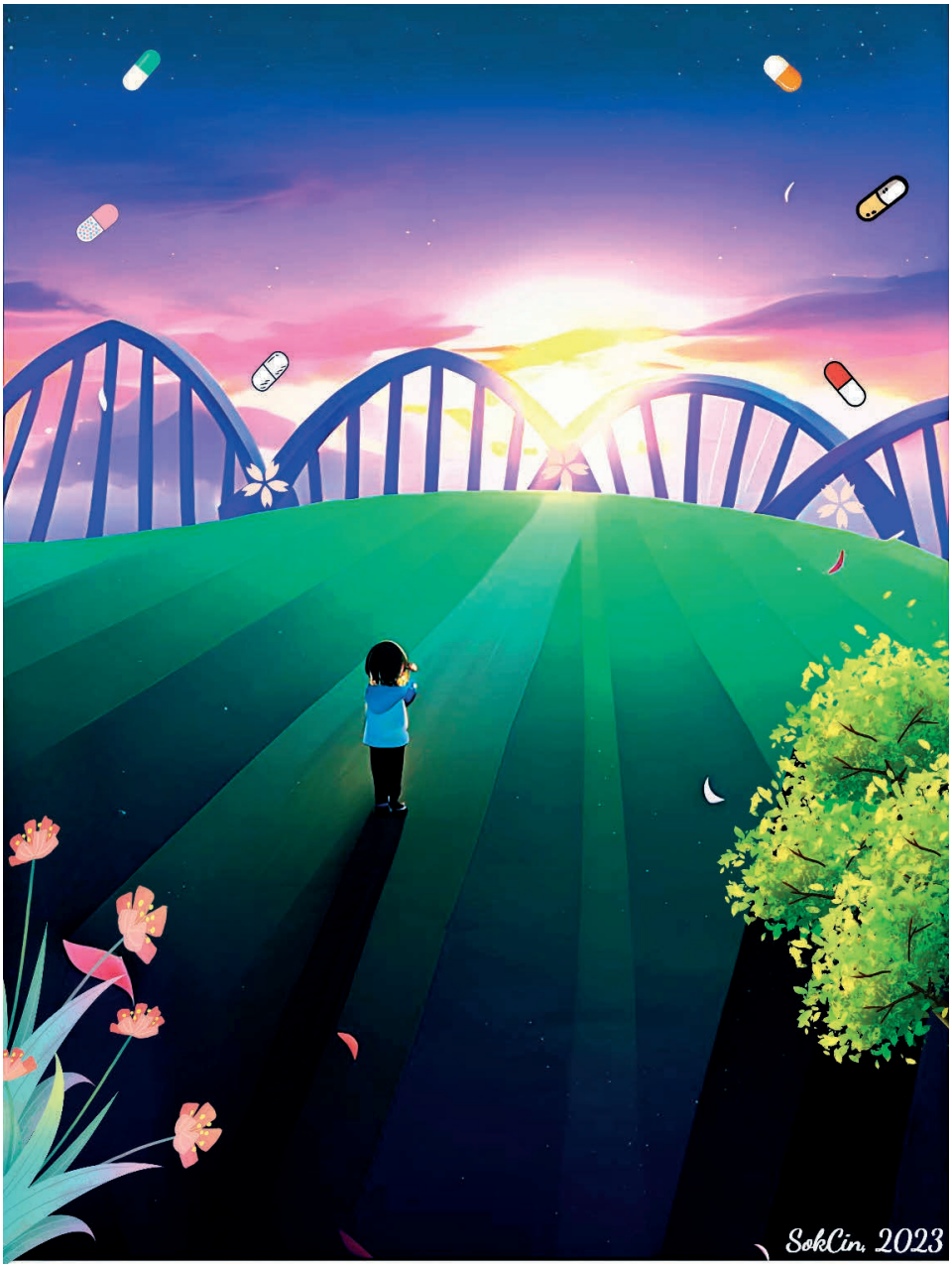
REFERENCES

1. Maiorino MI, Longo M, Scappaticcio L, et al. Improvement of glycemic control and reduction of major cardiovascular events in 18 cardiovascular outcome trials: an updated meta-regression. *Cardiovasc Diabetol* 2021; **20**(1): 210.
2. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359**(15): 1577-89.
3. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009; **52**(11): 2288-98.
4. Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. *Arch Intern Med* 2012; **172**(10): 761-9.
5. American Diabetes Association Professional Practice C. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. *Diabetes Care* 2022; **45**(Suppl 1): S144-S74.
6. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020; **41**(2): 255-323.
7. Joseph JJ, Deedwania P, Acharya T, et al. Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes: A Scientific Statement From the American Heart Association. *Circulation* 2022; **145**(9): e722-e59.
8. Parving HH, de Zeeuw D, Cooper ME, et al. ACE gene polymorphism and losartan treatment in type 2 diabetic patients with nephropathy. *J Am Soc Nephrol* 2008; **19**(4): 771-9.
9. Petrykiv SI, de Zeeuw D, Persson F, et al. Variability in response to albuminuria-lowering drugs: true or random? *Br J Clin Pharmacol* 2017; **83**(6): 1197-204.
10. Hamada S, Gulliford MC. Multiple risk factor control, mortality and cardiovascular events in type 2 diabetes and chronic kidney disease: a population-based cohort study. *Bmj Open* 2018; **8**(5): e019950.
11. Rawshani A, Rawshani A, Franzen S, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2018; **379**(7): 633-44.
12. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; **358**(6): 580-91.
13. Sasso FC, Pafundi PC, Simeon V, et al. Efficacy and durability of multifactorial intervention on mortality and MACEs: a randomized clinical trial in type-2 diabetic kidney disease. *Cardiovasc Diabetol* 2021; **20**(1): 145.
14. Basu S, Sussman JB, Berkowitz SA, Hayward RA, Yudkin JS. Development and validation of Risk Equations for Complications Of type 2 Diabetes (RECODe) using individual participant data from randomised trials. *Lancet Diabetes Endocrinol* 2017; **5**(10): 788-98.
15. Buchan TA, Malik A, Chan C, et al. Predictive models for cardiovascular and kidney outcomes in patients with type 2 diabetes: systematic review and meta-analyses. *Heart*

2021; **107**(24): 1962-73.
16. Jardine MJ, Hata J, Woodward M, et al. Prediction of kidney-related outcomes in patients with type 2 diabetes. *Am J Kidney Dis* 2012; **60**(5): 770-8.
17. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA* 2011; **305**(15): 1553-9.
18. Smink PA, Miao Y, Eijkemans MJ, et al. The importance of short-term off-target effects in estimating the long-term renal and cardiovascular protection of angiotensin receptor blockers. *Clin Pharmacol Ther* 2014; **95**(2): 208-15.
19. Smink PA, Hoekman J, Grobbee DE, et al. A prediction of the renal and cardiovascular efficacy of aliskiren in ALTITUDE using short-term changes in multiple risk markers. *Eur J Prev Cardiol* 2014; **21**(4): 434-41.
20. Schievink B, de Zeeuw D, Smink PA, et al. Prediction of the effect of atrasentan on renal and heart failure outcomes based on short-term changes in multiple risk markers. *Eur J Prev Cardiol* 2016; **23**(7): 758-68.
21. Schievink B. Heart failure induced by aleglitazar treatment can be predicted based on short-term response in multiple risk markers: University of Groningen; 2016.
22. Idzerda NMA, Stefansson BV, Pena MJ, Sjostrom DC, Wheeler DC, Heerspink HJL. Prediction of the effect of dapagliflozin on kidney and heart failure outcomes based on short-term changes in multiple risk markers. *Nephrol Dial Transplant* 2020; **35**(9): 1570-6.
23. Idzerda NMA, Clegg LE, Hernandez AF, et al. Prediction and validation of exenatide risk marker effects on progression of renal disease: Insights from EXSCEL. *Diabetes Obes Metab* 2020; **22**(5): 798-806.
24. Heerspink HJ, Grobbee DE, de Zeeuw D. A novel approach for establishing cardiovascular drug efficacy. *Nat Rev Drug Discov* 2014; **13**(12): 942.
25. Group E-KC. Design, recruitment, and baseline characteristics of the EMPA-KIDNEY trial. *Nephrol Dial Transplant* 2022; **37**(7): 1317-29.
26. Dennis JM, Shields BM, Henley WE, Jones AG, Hattersley AT. Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. *Lancet Diabetes Endocrinol* 2019; **7**(6): 442-51.
27. Tofte N, Lindhardt M, Adamova K, et al. Early detection of diabetic kidney disease by urinary proteomics and subsequent intervention with spironolactone to delay progression (PRIORITY): a prospective observational study and embedded randomised placebo-controlled trial. *Lancet Diabetes Endo* 2020; **8**(4): 301-12.
28. Loganadan NK, Huri HZ, Vethakkan SR, Hussein Z. Genetic markers predicting sulphonylurea treatment outcomes in type 2 diabetes patients: current evidence and challenges for clinical implementation. *Pharmacogenomics J* 2016; **16**(3): 209-19.
29. Pearson ER. Type 2 diabetes: a multifaceted disease. *Diabetologia* 2019; **62**(7): 1107-12.
30. Coresh J, Heerspink HJL, Sang Y, et al. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. *Lancet Diabetes Endocrinol* 2019; **7**(2): 115-27.
31. Heerspink HJ, Kropelin TF, Hoekman J,

de Zeeuw D, Reducing Albuminuria as Surrogate Endpoint C. Drug-Induced Reduction in Albuminuria Is Associated with Subsequent Renoprotection: A Meta-Analysis. *J Am Soc Nephrol* 2015; **26**(8): 2055-64.

32. Stempniewicz N, Vassalotti JA, Cuddeback JK, et al. Chronic Kidney Disease Testing Among Primary Care Patients With Type 2 Diabetes Across 24 U.S. Health Care Organizations. *Diabetes Care* 2021; **44**(9): 2000-9.
33. American Diabetes A. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2021. *Diabetes Care* 2021; **44**(Suppl 1): S151-S67.
34. Tye SC, de Vries ST, Wanner C, Denig P, Heerspink HJL. Prediction of the Effects of Empagliflozin on Cardiovascular and Kidney Outcomes Based on Short-Term Changes in Multiple Risk Markers. *Front Pharmacol* 2021; **12**: 786706.
35. Tye SC, de Vries ST, Mann JFE, et al. Prediction of the Effects of Liraglutide on Kidney and Cardiovascular Outcomes Based on Short-Term Changes in Multiple Risk Markers. *Front Pharmacol* 2022; **13**: 786767.
36. Coca SG, Nadkarni GN, Huang Y, et al. Plasma Biomarkers and Kidney Function Decline in Early and Established Diabetic Kidney Disease. *J Am Soc Nephrol* 2017; **28**(9): 2786-93.
37. Sen T, Li J, Neuen BL, et al. Effects of the SGLT2 inhibitor canagliflozin on plasma biomarkers TNFR-1, TNFR-2 and KIM-1 in the CANVAS trial. *Diabetologia* 2021.
38. Berezin AE, Berezin AA. Circulating Cardiac Biomarkers in Diabetes Mellitus: A New Dawn for Risk Stratification-A Narrative Review. *Diabetes Ther* 2020; **11**(6): 1271-91.
39. Vaduganathan M, Sattar N, Xu J, et al. Stress Cardiac Biomarkers, Cardiovascular and Renal Outcomes, and Response to Canagliflozin. *J Am Coll Cardiol* 2022; **79**(5): 432-44.
40. Ahlqvist E, Storm P, Karajamaki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endo* 2018; **6**(5): 361-9.
41. Udler MS, Kim J, von Grotthuss M, et al. Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: A soft clustering analysis. *PLoS Med* 2018; **15**(9): e1002654.
42. Nair ATN, Wesolowska-Andersen A, Brorsson C, et al. Heterogeneity in phenotype, disease progression and drug response in type 2 diabetes. *Nature Medicine* 2022; **28**(5): 982-+.
43. McCarthy MI. Painting a new picture of personalised medicine for diabetes. *Diabetologia* 2017; **60**(5): 793-9.



The new horizon in management of diabetes

This figure illustrates a diabetes patient marching towards a new horizon for the treatment of his condition. The sunrise behind the hill represents the contribution and current revolution of omics technology and data science. The pills over the clouds denotes the availability of new treatment options over the last decade. The patient look forward a new horizon where novel biomarkers discoveries and robust algorithms development could identify patients at high risk in early stages, inform prognosis, and guide treatment decisions to ensure that each patient receives the most effective and personalized treatment, minimizing the risk of long-term complications and maximizing the chances of a positive outcome.