Type 2 diabetes beyond glycaemic control

Summary

Type 2 diabetes is a chronic disorder characterized by high blood glucose levels. It is a rapidly growing global health concern with increasing prevalence, large expenses, and high social, psychological, and societal burden. People with type 2 diabetes are highly heterogeneous in terms of metabolic profile, underlying causes, disease course, disease burden, and number of comorbidities and complications. This heterogeneity makes type 2 diabetes very difficult to treat and calls for a subclassification of people with type 2 diabetes in order to tailor treatment to each individual patient.

The treatment goal in type 2 diabetes is to lower blood glucose levels. In clinical practice, long term blood glucose levels are measured with glycated haemoglobin type A1c (HbA1c) levels in the blood. Evaluating this metric is a very clinical approach to treating a human being and does not necessarily reflect how a person is as a whole. A more patient-centred approach to treatment is to evaluate a patient's perspective on his or her health by measuring quality of life (QoL).

High blood glucose levels in type 2 diabetes cause damage to tissues across the body. Therefore, this disease is associated with various complications. Microvascular complications include retinopathy, nephropathy, and neuropathy. Macrovascular complications include cardiovascular disease, stroke, and peripheral arterial disease (PAD). One of the most highly feared complications is diabetic foot ulcer (DFU) and subsequent lower limb amputation (LLA). Since diabetes affects systems across the body, the drugs used in treatment of this disease are often highly pleiotropic. Drugs are registered with the aim of lowering blood glucose levels, but often have other effects too. These effects can be either beneficial or adverse, and are often researched in studies after the drugs' market access. In order to study these effects, pharmacoepidemiology is a valuable field of work, since it uses real-world data from large databases to evaluate side drug effects in daily practice?. Appropriate study design is of utter importance when using real-world data in order to minimize bias and confounding arising from the uncontrolled setting in which data is gathered.

The objective of this dissertation was to study the population with type 2 diabetes and the potential unintended effects of glucose-lowering treatment. In **Chapter 2**, we aimed to map the heterogeneous population of people living with type 2 diabetes in terms of characteristics, and both classical (HbA1c) and newer (QoL) outcomes. In **Chapter 3**, we aimed to investigate the risk of LLA and DFU with several newer glucose-lowering drug classes.

In **Chapter 2.1**, we were able to replicate the previously identified subgroups of type 2 diabetes (moderate age-related diabetes (MARD), moderate obesity-related diabetes (MOD), severe insulin deficient diabetes (SIDD), severe insulin resistant diabetes (SIRD)) in The Maastricht Study by adopting a nearest centroid approach. We observed that people in the SIDD subgroup were less likely to reach glycaemic control. Moreover, we observed that not only the "severe" subgroups (SIDD and SIRD) scored low in terms of QoL, but also the MOD subgroup

which is labelled as "moderate". As the subgroups and their names are derived from clinical parameters, we concluded that disease severity of the subgroups is not paralleled by QoL. This calls for reconsideration of the subgroup names before implementation in clinical practice, as non-neutral nomenclature could affect disease perception of patients, healthcare providers and the society.

Chapter 2.2 revolved around prediction of treatment outcomes in The Maastricht Study, in terms of HbA1c and QoL using various machine learning algorithms. Prediction was aimed at identifying those who are likely not going to reach treatment goals within a year. Predicting inadequate glycaemic control yielded good performance statistics. However, predicting deterioration of QoL did not seem feasible. Further tuning of the models is required to improve prediction of these outcomes. Additionally, the use of subgroups discussed in **Chapter 2.1**, or the use of a diabetes-specific QoL scale might help in improving prediction of deterioration of QoL. Ultimately, these models could help target the people who need most attention and care of health care professionals.

In **Chapter 2.3**, we used data from the Clinical Practice Research Datalink (CPRD) GOLD in order to investigate the incidence of DFUs. We observed a decline in first registered DFUs over time, which could be indicative of improved care. However, investigating DFUs with observational data remains challenging, as DFUs often go unnoticed and are likely to be underrecorded.

In **Chapter 3.1**, we studied the association of incretin-based therapy with DFU and DFU-related outcomes in CPRD Aurum with linked hospital data. Since incretins are active throughout the body and there is some evidence for their role in wound healing and neuroprotection, we hypothesized that these drugs could aid in preventing DFUs and/or related events. Indeed, we observed a lower risk of DFU, DFU-related hospitalization, and mortality with both dipeptidyl peptidase 4 inhibitors (DPP4-Is) versus sulfonylureas (SUs) and glucagon-like peptide-1 receptor agonists (GLP1-RAs) versus insulin. Moreover, we observed a lower risk of LLA with GLP1-RA use versus insulin use. Since the median follow-up time of this study was approximately 1 year, studies with longer follow-up duration are required to confirm these findings. Nevertheless, this study showed that incretin-based therapy might be promising strategy in people at risk of DFU.

We investigated the risk of LLA with another drug class, sodium-glucose co-transporter-2 inhibitors (SGLT2-Is) in CPRD GOLD in **Chapter 3.2**. Additionally, we aimed to investigate the suggested potential mechanism of LLA with SGLT2-I use: hypovolaemia. A trial reporting an almost twofold increased risk of LLA with the SGLT2-I canagliflozin raised a lot of concern among patients and clinicians. However, we observed no increased risk of LLA with SGLT2-Is versus SUs, with or without signs of hypovolaemia, or concomitant antidiuretic or antihypertensive use. Although this finding was in line with several meta-analyses, some other studies contradicted our conclusion. This could be due to comparing SGLT2-Is to GLP1RAs.

In **Chapter 3.3** we decided to investigate the origin of these contrasting findings when comparing SGLT2-Is to GLP1-RAs further in the Danish National Health Service database. We did this by investigating the risk of LLA with SGLT2-Is and GLP1-RAs separately, but using the same comparator group, SUs. These three drugs are used in the same line of treatment in Denmark. We observed a lower risk of LLA with GLP1-RAs versus SUs, and no changed risk of LLA with SGLT2-Is versus SUs. We mimicked what previous studies have done in a post-hoc analysis, by comparing SGLT2-Is directly to GLP1-RAs. In this analysis, we did observe a higher risk of LLA with SGLT2-Is, indicating that this is indeed what has been happening in previous studies. In patients with PAD, the risk of LLA was higher irrespective of the drug they used. This finding indicates that GLP1-RAs might not reduce the risk of LLAs through a PAD-related pathway. The results of this study could help in taking away some of the concerns around SGLT2-Is and the risk of LLA, and simultaneously put forward GLP1-RAs as a potential treatment strategy in people at increased risk of LLA.

Another concern with SGLT2-I use is the risk of fractures. There are various theories as to why SGLT2-Is could increase the risk of fractures, with one of them being the effect of weight loss associated with SGLT2-I use. A lower BMI is associated with an increased fracture risk. SGLT2-I use is in turn associated with a reduction in BMI. Therefore, in **Chapter 3.4**, we investigated the association between SGLT2-I use, changes in BMI, and the risk of major osteoporotic fractures in CPRD GOLD. Our results indicated there was no increased risk of fracture with SGLT2-I use, irrespective of change in BMI.

Chapter 4 combines all studies into a comprehensive discussion of the interpretation of the conclusions, methodological considerations, the impact of potential bias and confounding, and how the studies of this dissertation relate to other published work in the field. Additionally, perspectives for additional research are provided in **Chapter 4** and **Chapter 5**. Finally, the societal and scientific impact of the research reported in this dissertation are discussed in **Chapter 5**.

In conclusion, the heterogeneity of the population with type 2 diabetes calls for an additional subclassification to tailor therapy to each individual. It is important to take both clinical perspectives and patient perspectives into consideration when treating a patient, as metabolic derangement is not necessarily reflected in a patient's QoL. However, it remains challenging to predict disease course from both these perspectives. Another important aspect of the treatment of type 2 diabetes is the potential adverse effects of glucose-lowering drugs, in particular relating to DFU and LLA. We found no indications for harmful effects of SGLT2-Is, but we did observe protective effect of incretin-based therapy on DFU and LLA. The results of the studies in this dissertation add to the growing body of evidence highlighting the need for tailored therapy in type 2 diabetes, as well as the pleiotropic, protective effects of incretin-based therapy beyond glycaemic control.