Maastricht University

Tailored therapy in type 2 diabetes

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Summary

Diabetes has become an epidemic problem due to increases in life expectancy and obesity. More than 9% of the adult population has a diagnosis for diabetes, of which approximately 90% has type 2 diabetes. There are several treatment options including metformin, sulphonylureas (SUs), thiazolidinediones (TZDs), glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter-2 (SGLT-2) inhibitors and insulin. As there are many treatments options available, each with different advantages and disadvantages, the importance and opportunity for tailored therapy is evident. However, based on the current literature and guidelines there are some questions that remain unanswered, particularly the unintended effects of glucose-lowering agents in a real-life setting. Therefore, the overall objective of this thesis was to study the unintended effects and utilisation of glucose-lowering agents in patients with type 2 diabetes in population-based cohorts (**Chapter 1**).

In **Chapter 2.1** we determined whether treatment with SUs only in patients with renal impairment was associated with a higher risk of hypoglycaemia compared to metformin-only users in a population-based cohort study using routinely collected data from general practices in England (Clinical Practice Research Datalink [CPRD] database). This study found that the risk of hypoglycaemia was significantly higher in current users of SUs compared to current metformin users (adjusted Hazard Ratio [aHR] 2.50; 95% Confidence Interval [CI] 2.23-2.82]), and this risk was even higher in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (aHR 4.96; 95% CI 3.76-6.55). The risk of hypoglycaemia was also significantly higher in patients with a high dose and with glibenclamide use. Of interest, gliclazide, the recommend SU of first choice in many countries, showed a similar risk of hypoglycaemia compared to other SUs.

As hypoglycaemia is associated with an increased risk of cardiovascular events, it was of great clinical interest to investigate the association between the use of SUs and the risk of cardiovascular events. **Chapter 2.2** described the results of a study in which we investigated the association between the use of individual SUs and the risk of a first ever acute myocardial infarction (AMI) and all-cause mortality, in a population-based cohort study using primary care data from the CPRD database. No differences in risk of a first ever AMI (aHR 1.02; 95% CI 0.70-1.50) or all-cause mortality (aHR 0.97; 95% CI 0.80-1.17) were observed comparing gliclazide use with non-gliclazide SU use. Similar results were found for each individual SU. These results provide additional evidence to the on-going debate regarding the safety profile of SUs, and in particular the comparative profiles among the different SUs. As **Chapter 2.1 and 2.2** suggest

that gliclazide is not safer than other SUs, current guidelines recommending gliclazide as first choice SU should be carefully evaluated for revision.

Continuing with the evaluation of unintended effects from glucose-lowering agents, **Chapter 2.3** of this thesis assessed the association between the risk of non-alcoholic fatty liver disease (NAFLD) and the use of TZDs and GLP-1 receptor agonists compared with the use of SUs and insulins, respectively. Additionally, we calculated the incidence of hepatocellular carcinoma (HCC) in users of TZDs and GLP-1 receptor agonists. We conducted a population-based cohort study using primary care data from the CPRD database (2007-2018). The risk of NAFLD was 68% lower in patients prescribed a TZD than in those prescribed a SU. In contrast, no difference in risk of NAFLD was observed comparing GLP-1 receptor agonist use with insulin use. Several sensitivity analyses were performed, and results remained similar. Therefore, results of **Chapter 2.3** endorse the use of TZDs for selected patients at risk of NAFLD, provided that contraindications and side effects are considered. Studies investigating the effect of GLP-1 receptor agonists on NAFLD are inconclusive and large and well-executed RCTs are likely required to assess the effect of GLP-1 receptor agonists on NAFLD resolution. As the number of HCC events was too low, only descriptively crude incidence rates were reported and no conclusions could be drawn related to this outcome.

In **Chapter 2.4** the results of another pharmacoepidemiologic study that investigated the use of incretin agents (DPP-4 inhibitors and GLP-1 receptor agonists), and the risk of pancreatic cancer are presented. Results of this retrospective population-based cohort study in CPRD (2007-2012) showed that current users of a non-insulin glucose-lowering agent had a 4.3-fold increased risk and incretin users had a 7.5-fold increased risk of pancreatic cancer when compared to non-diabetic patients. However, when compared to users of other non-insulin glucose-lowering agents, there was no higher risk of pancreatic cancer in users of incretins. Moreover, there was no relationship with the duration of use in incretin user. This all taken together suggested that there was considerable confounding by disease severity and no causal relationship between incretin use and pancreatic cancer. It was not the use of incretin agents, but diabetes itself that was associated with a higher risk of pancreatic cancer.

Finally, in **Chapter 2.5** the safety of SGLT-2 inhibitors was investigated. This chapter investigated the association between SGLT-2 inhibitor use and the risk of major osteoporotic fractures and explored if changes in body mass index (BMI) influences this association. The study was another cohort study using data from the UK CPRD (2013-2018). No increased risk of fractures in current users of SGLT-2 inhibitor compared to current users of SUs (aHR 1.19; 95% CI 0.80-1.79) was identified. This finding remained

consistent after stratification by BMI change. However, when results were stratified by cumulative dose, the highest cumulative dose category was associated with an increased fracture risk (aHR 2.10, 95% CI 1.11-3.99). Thus, other mechanisms than weight loss might be of influence and further research is warranted to clarify this.

Results from Chapter 2.1 through Chapter 2.5 underline that tailored therapy is essential for optimal treatment of a patient with type 2 diabetes. Over the last decade, treatment guidelines worldwide were adjusted to make this possible, including the NICE (National Institute for Health and Care Excellence) guideline in the UK, which was updated in 2015. As it is of great interest to investigate whether the implementation of the updated guideline resulted in more individualised prescribing, the objective of **Chapter 3** was to identify patient-specific factors associated with early metformin treatment modification among type 2 diabetes patients before and after implementation of the updated 2015 NICE guideline. This population-based cohort study using data from CPRD (2009-2016) showed that after implementation of the updated guideline, patients were less likely to receive SUs (62.3% vs 41.3%) or TZDs (4.7% vs 2.2%) and more likely to receive DPP-4 inhibitors (15.8% vs 27.1%) or SGLT-2 inhibitors (0.8% vs 9.9%). Overall, initiation of a second-line therapy was associated with similar determinants before and after implementation of the updated guideline. However, some determinants influenced general practitioners' prescribing differently after implementation of the updated guideline compared to before, including a high BMI and heart failure. This indicates that a first step towards tailored prescribing was made after introduction of the new NICE guideline. However, not all determinants that are important to consider when prescribing second-line glucose-lowering agents, such as older age and a history of hypoglycaemia, influenced general practitioner's prescribing in our study.

In **Chapter 4** the main results of these studies were discussed, including the main methodological limitations of the individual studies, (i.e., bias and confounding). Implications for general practice, future research and policy, as hitherto shortly addressed, were extensively discussed in **Chapters 4 and 5**.