Unintended effects of anti-hyperglycaemic drugs studied in population-based cohorts

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Valorisation Addendum

Knowledge valorisation refers to the “process of creating value from knowledge, by making knowledge suitable and/or available for social (and/or economic) use and by making knowledge suitable for translation into competitive products, services, processes, and new commercial activities” (adapted definition based on the National Valorisation Committee 2011:8). In this addendum the societal relevance of the results presented in this thesis will be discussed as well as the possibilities for valorisation of our results.

Healthcare problem

Osteoporosis is defined as a systematic bone disease characterized by low bone mass and deterioration of the microarchitecture of the bone, leading to bone fragility and propensity to fracture. It has been estimated that about 22 million women and 3.5 million men suffered from osteoporosis in Europe in 20101. The worldwide annual estimated costs of hip fractures, both direct and indirect, were $34.8 billion in 1990 and are expected to increase to $131 billion in 20202.

Type 2 diabetes mellitus (T2DM) is a chronic disease characterised by high blood glucose levels. Estimations showed that about 422 million people suffered from diabetes (all types) in 20143. Patients with T2DM have to take anti-hyperglycaemic drugs to control their blood glucose levels, often for the rest of their lives. This has a huge impact on patient’s lives as well as on healthcare costs.

T2DM has been associated with an increased risk of fracture. Different mechanisms have been proposed which partly explain this increased risk, including an increased risk of falling, reduced bone strength or quality and the use of anti-hyperglycaemic drugs. However, the effect of recently introduced anti-hyperglycaemic drugs, the incretin agents, on fracture risk in the population at large was unclear.

Investigational approach

In this thesis the potential association between newly marketed drugs and fracture risk was investigated using “real-life” data. The class of incretin agents includes two different drug types, dipeptidyl peptidase 4 inhibitors (DPP4-I) and glucagon-like peptide 1 receptor agonists (GLP1-RAs). The association between incretin agents and fracture risk was studied separately for the two types of incretins. In addition, the association was studied using two separate databases, one representative for the UK population and one representative for the Danish population. Thereafter the results were combined to further investigate the potential association between use of incretin agents and risk of fracture. This was followed by a study investigating long-term DPP4-I use (up to 8.5 years) and risk of fracture using the UK database.
Main findings

In contrast to the first results of a meta-analysis of adverse events data\(^4\) we were not able to show an association between use of incretin agents, either DPP4-I or GLP1-RA, and risk of fracture in the population at large. In the different individual studies we did not find a reduced risk of fracture, with use of DPP4-Is or GLP1-RA\(s\). In addition, when the results were combined in a meta-analysis, we were also not able to show a reduced risk of fracture. Moreover, when the duration of follow-up was extended we were still not able to show a reduced risk of fracture with long-term use (up to 8.5 years) of DPP4-Is.

Target population

The results of this thesis are important for general practitioners (GPs) making clinical decisions regarding treatment of T2DM patients, especially those at high fracture risk. Use of thiazolidinediones, another type of anti-hyperglycaemic drugs, has been associated with an increased risk of fracture. In patients at a high fracture risk those drugs are therefore not preferred. In this thesis it was shown that use of incretin agents was not associated with fracture risk. They may therefore be prescribed in patients with T2DM at high fracture risk, without increasing their fracture risk even further.

Based on the results of a first meta-analysis of adverse events data of clinical trials a 40% reduction of fracture risk with use of DPP4-Is was shown\(^5\). This may have led to the preferred prescribing of DPP4-Is as compared to other second-line treatment for T2DM patients. However, only a small number of studies were included and the total number of fractures was only 63. Based on the results from the presented pharmacoepidemiological studies in this thesis it can be concluded that there is no association between use of DPP4-Is or GLP1-RA\(s\) and risk of fracture. There is therefore no reason to preferably prescribe DPP4-Is or GLP1-RA\(s\) to patients with T2DM based on the potential protective effect on fracture risk with these incretin agents.

Recently, updated meta-analyses, including a larger number of trials, have been published and reported no association between use of DPP4-Is and fracture risk\(^5,6\). This shows that a meta-analysis of adverse events data with only a small number of trials included could lead to biased results and should therefore be interpreted with caution.

When interpreting the results of pharmacoepidemiological studies potential sources of bias and confounding need to be considered, as these may have a large influence on the final results. However, when performed well, pharmacoepidemiological studies are relatively cheap option to study drug-outcome associations which can be used to prevent unnecessary expensive clinical trials investigating the same drug-outcome associations. In addition, with pharmacoepidemiological studies it is possible to investigate associations using data from real-life patients, which is expected to better represent clinical practice than the data of patients included in randomised controlled trials.
Innovation and future research

Although we showed that use of DPP4-Is and GLP1-RAs was not associated with fracture risk, more research is still needed. Especially the potential association between use of GLP1-RAs and fracture needs to be further studied. Long-term GLP1-RA use needs to be investigated as well as research investigating whether there is indeed a different association between the different GLP1-RA types (liraglutide and exenatide), and fracture risk.

With the studies in Chapter 3 we showed that drug dispensing data in combination with Maastricht Study data can be used to perform pharmacoepidemiological studies, with new unique parameters, such as bone strength and bone micro-architecture, which are often not available in electronic health care databases. This makes the Maastricht Study a very unique cohort and gives many opportunities for future research and valorisation of the results. For instance, data from the Maastricht study could be used to study the potential effects of anti-hyperglycaemic drugs on bone mechanical parameters.

Another option for future studies with use of data from the Maastricht Study is investigating the association between different bone strength and micro-architecture parameters and the trabecular bone score (TBS). This bone score is a novel texture parameter reflecting pixel gray-level variations in dual X-ray absorptiometry (DXA) images. DXA data will be available in the near future in the Maastricht Study which then could be studied in combination with bone strength and micro-architecture parameters as well as in combination with the use of different anti-hyperglycaemic drugs.
References