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Drug utilisation study on metformin use in renal impairment

Executive summary

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Metformin is a first-line treatment for most patients with type 2 diabetes mellitus, but it is contraindicated in patients with certain acute and chronic conditions – including chronic renal dysfunction – because of the feared risk of lactic acidosis. While different guidelines agree on the recommendation to discontinue use of metformin in patients with a glomerular filtration rate (GFR) below 30 ml/min, guidelines differ on the renal impairment threshold that should trigger cautious use and potential dose reduction, with recommended GFR thresholds varying between 60 and 45 ml/min. This report describes a series of epidemiologic analyses among pharmacologically treated type 2 diabetes patients to examine prevalence of renal impairment in metformin users, use of metformin according to stage of renal impairment, and safety with regard to change in renal function, discontinuation/switching of antidiabetic treatment, and lactic acidosis.

The study used data from routine medical databases to conduct cross-sectional analyses of drug utilisation, and cohort analyses of safety outcomes among patients with medically treated type 2 diabetes from Denmark and the United Kingdom (UK). The combined source population comprised 6.9 million persons. Use of metformin and other antidiabetic drugs was identified by issued (the UK) and filled (Denmark) prescriptions. Renal function was assessed and staged by the estimated glomerular filtration rate (eGFR), computed from serum creatinine measurements, age, and sex. Lactic acidosis was captured by relevant diagnostic codes or by an elevated blood lactate level. Data on covariates, including comorbidity, comedication, and labs were also obtained from the medical databases. These databases included the Danish health and administrative registries, covering the population of the North and Central Denmark Regions, and the Clinical Practice Research Datalink (CPRD), covering ~6% of the UK population.

In the drug utilisation analysis, we described characteristics of new and prevalent metformin users and users of other antidiabetic drugs (non-metformin users) with regard to renal function, demographics, comorbidity, and comedication. Similarly, the characteristics were cross-tabulated according to level of renal impairment. Incidence rate of lactic acidosis was estimated for metformin users and users of other antidiabetic drugs.

This report provides data on use of metformin according to renal function, and estimates the incidence rate of renal impairment and lactic acidosis in a representative sample of 172,052 medically treated diabetes patients in Denmark and the UK.

Distributions of age, most comorbidities, and mean daily dose of metformin were similar in the two countries. As expected, metformin was the most widely used antidiabetic drug with metformin users comprising 73.2% of the study population in Denmark and 92.3% in the UK. We found a considerable number of new metformin users with eGFR values below 45 ml/min/1.73m^2 at study inclusion; 16% of metformin users in Denmark and 26% of metformin users in the UK. Surprisingly, we found similar mean metformin dose in patients with low eGFR level at study inclusion. Most metformin users continued the medication after decline in eGFR, while a considerable proportion discontinued or switched antidiabetic treatment when eGFR dropped below 30 ml/min/1.73m^2. However, almost one-third of patients with low eGFR at study inclusion had improved renal function during the follow-up. The incidence rate of first decline in renal dysfunction in Denmark was 6.81 (95% CI: 6.67-6.95) per 100 person-years in metformin users and 9.91 (95% CI: 9.65-10.19) in users of other antidiabetic drugs. In the UK, the corresponding incidence rates were 7.85 (95% CI: 7.77-7.94) and 14.1 (95% CI: 13.6-14.6), respectively.

The incidence rate of lactic acidosis was 12.85 (95% CI: 8.29-19.92) per 100,000 person-years for metformin users in Denmark and 5.44 (95% CI: 3.68-7.75) per 100,000 person-years for metformin users in the UK. The incidence rate of lactic acidosis users of other antidiabetic drugs was 5.39 (95% CI: 2.02-14.37) per 100,000 person-years in Denmark, while no users of other antidiabetic drugs in the UK were identified with lactic acidosis. The higher incidence rate in Denmark than in the UK may be due to differences in the case ascertainment methods including the use of diagnostic coding for lactic acidosis. Because of the low number of cases with lactic acidosis it was not possible to conduct adjusted analysis, and the unadjusted incidence rate ratio estimated in Denmark was imprecise; incidence rate ratio = 2.23

(95% 0.75-6.62) comparing metformin users with users of other antidiabetic drugs. Metformin users were younger and had fewer risk factors for lactic acidosis so the association is unlikely due to measured confounding. Rather, information bias may explain the association, as the feared risk of lactic acidosis may increase surveillance and diagnostic coding of lactic acidosis in metformin users.