Nephropathy

Oral hypoglycaemic agents in renal impairment: Is the situation any clearer?

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The papers in this month's digest are loosely connected by exploring current prescribing practice in people with diabetes and chronic kidney disease (CKD). Clemens and colleagues describe the changing use of oral hypoglycaemic agents (OHAs) in an elderly (>65 years) population with CKD in Canada between 2004 and 2013. They found that metformin was used in 27.6% of people with an estimated glomerular filtration rate (GFR) <30 mL/min/1.73 m^2. The message that shorter-acting sulfonylureas (SUs) should not be used in this population seems to have been received, but 9.5% of the cohort were still prescribed glibenclamide in 2013, including 11.4% of those on dialysis. Although gliclazide is relatively short-acting and mostly metabolised in the liver, current guidance in the British National Formulary recommends avoidance in people with severe renal impairment. Safer alternatives such as gliptins are also being prescribed, but it should be remembered that these too can cause hypoglycaemia when taken with SUs, and their dose should be reduced as GFR falls.

Hippisley-Cox et al analysed the GP research database over an 8-year period up to 2015 and matched recorded serious clinical outcomes in 275 000 individuals aged 25–84 years who received OHAs. They found an increased incidence of severe kidney failure with gliptin or glitazone use, and a reduced incidence with metformin. On the other hand, triple therapy was associated with less blindness compared to metformin monotherapy. These findings are, on the face of it, contradictory in terms of the relationship of metformin to microvascular complications in the kidney and eye. However, the results are almost certainly confounded by indication; metformin is contraindicated in people with renal impairment, so prescribing rates should have been lower in this population. People with visual impairment may struggle with multiple therapies, and treatments with a low risk of hypoglycaemia, such as metformin, are likely to be preferred for safety reasons. It would also be incorrect to presume that all visual and renal impairment in this population is diabetes-related. The most common cause of visual loss in the elderly is age-related macular degeneration, and loss of GFR is most often a result of nephrosclerosis. As in the Clemens study, significant numbers of people with advanced CKD were prescribed metformin and SUs. Higher rates of hypoglycaemia were also observed with multiple OHA regimens that included SUs.

Wong et al report the long-term follow-up of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) study, suggesting that people in the intensive glycaemic control arm (based upon modified-release gliclazide) had reduced rates of end-stage renal disease (requiring dialysis or transplantation) or renal death 5.4 years after the study ended. However, there were few events, the indications for dialysis were not standardised and the effect size was greater for people with relatively preserved renal function and lower blood pressure, which requires explanation.

Finally, Muller et al evaluated OHA prescriptions in 301 people with type 2 diabetes referred to nephrology services in four centres in France, and found that 53.5% were using agents or dosages outside recommendations. It made no difference whether the referring doctor was a GP, diabetologist or nephrologist.

What can we conclude from all this? Firstly, we are poor at following prescribing guidance and should do better. The advice on metformin use has been revised in the US and is now in line with that in Europe: caution should be exercised and the dose reduced in people with GFR <45 mL/min/1.73 m^2, and metformin should be avoided in those with GFR <30 mL/min/1.73 m^2 (US Food and Drug Administration, 2016). Secondly, hypoglycaemia is a risk for all those with CKD who are taking SUs; this risk increases as GFR declines and is significant for all SUs and insulin, and for those on multiple therapies. Finally, we need to be wary of associative studies (which can never prove causation) and long-term follow-up of clinical trial cohorts (which can never fully substantiate efficacy). I am not sure that these papers make a murky area any clearer, but they should at least prompt more careful prescribing in this vulnerable population with CKD and diabetes. ■

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Diabetes Obes Metab

Prescribing trends in older people with diabetes and CKD

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 To assess quality of care, the authors of this population-based study examined trends in antihyperglycaemic medication prescribing between 2003 and 2014 in Ontario, Canada, for older adults with diabetes and chronic kidney disease (CKD).

2 The records of 144 252 people aged ≥66 years with CKD (estimated glomerular filtration rate <60 mL/min/1.73 m^2 or receiving chronic dialysis) were studied. The proportion of participants prescribed each available antihyperglycaemic agent was examined in each quarter. Prescription trends by stage of CKD were also analysed.

3 Over the study period, metformin was the predominant therapy. Use of glibenclamide and thiazolidinediones decreased, while gliclazide and dipeptidyl peptidase-4 (DPP-4) inhibitor prescriptions increased. Up to 48.6% of people with stage 3a–5 CKD received glibenclamide and up to 27.6% with stage 4–5 CKD received metformin.

4 Guidelines suggest that several available antihyperglycaemic medications should be used with caution or avoided in this population.

5 The trends towards a decline in the use of glibenclamide and thiazolidinediones, and the increase in prescriptions for gliclazide and DPP-4 inhibitors are welcomed. However, agents that are contraindicated in this population are still being prescribed.

6 The authors call for strategies to improve drug prescribing in this vulnerable group.

Clemens KK, Liu K, Shariff S et al (2016) Secular trends in antihyperglycaemic medication prescriptions in older adults with diabetes and chronic kidney disease: 2004–2013. *Diabetes Obes Metab* **18**: 607–14

BMJ

Diabetes treatments and risks of complications

Readability	✓✓✓
Applicability to practice	✓✓
WOW! Factor	✓✓

1 The aim of this study was to quantify the risks of five key clinical outcomes, including severe kidney failure, associated with prescribed diabetes drugs.

2 Primary care data from 469 688 adults aged 25–84 years with a diagnosis of T2D were assessed in a population-based open cohort study.

3 Cox proportional hazards models were used to assess the associations between six classes of hypoglycaemic drugs and risk of each outcome, adjusting for potential confounding outcomes.

4 Findings indicated that although the numbers of participants prescribed gliptin or glitazone monotherapy were relatively low, the risk of severe kidney failure was significantly increased compared with metformin monotherapy, despite adjustments for serum creatinine and other risk factors at baseline (adjusted hazard ratio, 2.55; 95% confidence interval, 1.13–5.74).

5 The risk associated with dual therapy with gliptins or glitazones in combination with sulfonylureas were similar to the risk with sulfonylureas alone.

6 These findings appear to be consistent with other reports of the safety of glitazones and the renally excreted gliptins.

7 The authors conclude that, while these results are subject to residual confounding, they could have implications for the prescribing of hypoglycaemic drugs.

Hippisley-Cox J, Coupland C (2016) Diabetes treatments and risk of amputation, blindness, severe kidney failure, hyperglycaemia, and hypoglycaemia: open cohort study in primary care. *BMJ* **352**: i1450

Diabetes Care

Long-term benefits of intensive glucose control on ESRD

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! Factor	✓✓

1 To assess the long-term effects of intensive glucose control on risk of end-stage renal disease (ESRD) and other outcomes, a post-trial follow-up study of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial participants was conducted.

2 Survivors, who had previously been randomised to intensive or standard glucose control, were invited to take part in the follow-up. Rates of ESRD (defined as the need for dialysis or kidney transplantation or death due to kidney disease) were recorded overall and according to baseline chronic kidney disease (CKD) stage.

3 Participants (n=8494) were followed for a median 5.4 additional years. The mean difference in HbA_{1c} between the groups observed at the end of the original trial was lost by the first post-trial visit.

4 The reduction in risk of ESRD with intensive control during the in-trial period (7 vs 20 events; hazard ratio [HR], 0.35; 95% confidence interval [CI], 0.15–0.83; P=0.020) persisted after a total of 9.9 years of follow-up (29 vs 53 events; HR, 0.54; 95% CI, 0.34–0.85; P<0.01).

5 The effects were greater in earlier-stage CKD and at lower baseline systolic blood pressure levels. The impact of intensive glucose control on mortality or major cardiovascular events was not adversely affected by CKD at baseline.

6 These findings provide strong evidence of the renal benefits of intensive glucose lowering.

Wong MG, Perkovic V, Chalmers et al (2016) Long-term benefits of intensive glucose control for preventing end-stage kidney disease. *Diabetes Care* **39**: 694–700

J Diabetes Complications

T2D and CKD: Prescribing of oral antidiabetes drugs

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓

1 The aim of this observational study was to examine to what extent oral antidiabetes drugs (OADs) are adequately prescribed to people with T2D and chronic kidney disease (CKD).

2 The practice patterns of 13 nephrologists at four nephrology consultation centres in France were studied over a 3-month period. Drug dosages for 301 consecutive adults attending with T2D and CKD were detailed.

3 The CKD Epidemiology Collaboration (CKD-EPI) equation was used as the reference method for calculating estimated glomerular filtration rate (eGFR).

4 It was found that 53.5% of individuals were outside the prescribing recommendations, mostly for metformin and for sitagliptin (30% and 17.9% of the cohort, respectively).

5 Among those consulting a nephrologist for the first time (n=90), 61.1% were outside recommendations (P=0.1). For those seeing a diabetologist (n=103), the figure was 63.1% (P=0.09).

6 The proportion of prescriptions outside guidelines was strongly affected by the method used for evaluating eGFR and by whether the treatment was prescribed by a specialist or GP.

7 The authors conclude that to improve health quality and safety, there is an urgent need for standardised guidelines on estimation of GFR for drug dosing and OAD usage across countries and specialties.

Muller C, Dimitrov Y, Imhoff et al (2016) Oral antidiabetics use among diabetic type 2 patients with chronic kidney disease. Do nephrologists take account of recommendations? *J Diabetes Complications* **30**: 675–80

"There is an urgent need for standardised guidelines on estimation of glomerular filtration rate for drug dosing and oral antidiabetes drug usage across countries and specialties."

Reference from commentary

US Food and Drug Administration (2016) *FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function*. FDA, Silver Spring, MD, USA. Available at: http://bit.ly/1SKKYdP (accessed 17.08.16)