The use of oral antidiabetic agents in primary care

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BACKGROUND
Guidelines and regulatory documents reflect the potential for chronic kidney disease to impact the efficacy and safety profiles of antidiabetic regimens. We describe the influence of impaired kidney function and its perception by practitioners on the pattern of antidiabetic use in Australian primary care.

METHODS
Antidiabetic agent prescribing was documented for 3893 patients with type 2 diabetes from the National Evaluation of the Frequency of Renal impairment cO-existing with Noninsulin dependent diabetes mellitus (NEFRON) study. Patients with and without impaired kidney function, identified by their practitioner or defined by an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2, were systematically compared.

RESULTS
Most patients received metformin (63%) with sulphonylureas (45%), insulin (13%) and thiazolidinediones (7%) also widely used. Contrary to prescribing guidelines, use of metformin remained frequent (53%) and the proportional usage of sulphonylureas with active metabolites was unchanged in the 23.1% of patients with an eGFR below 60 mL/min/1.73 m^2. Even where prescribers identified impaired kidney function in their patients, prescribing of antidiabetic agents was not significantly modified.

DISCUSSION
Chronic kidney disease is a common companion to type 2 diabetes in Australia. The move to automated eGFR reporting provides an important opportunity for practitioners to identify impaired kidney function and to improve their management of patients with type 2 diabetes.

Chronic kidney disease (CKD) is a common companion to type 2 diabetes in Australian general practice.[1] The presence and severity of kidney disease adversely affects wellbeing, significantly contributes to disease morbidity, and increases the risk of premature death in those with diabetes.[2–5] Chronic kidney disease may also alter the safety profile of antidiabetic agents. In this article we describe the use of antidiabetic agents in patients with impaired kidney function included in the National Evaluation of the Frequency of Renal impairment cO-existing with Noninsulin dependent diabetes mellitus (NEFRON) study.[1]

Methods

Subjects

The NEFRON study was an incident driven survey of patients with type 2 diabetes in Australian primary care. Investigator selection and representation is detailed elsewhere.[1] Expressions of interest (EOIs) were invited from all (18 810) registered general practitioners across Australia in February 2005. A number of EOIs from each stratum, proportional to the census population, were randomly selected to provide a total of 500 investigators. Investigators were requested to provide data on 10–15 consecutively presenting adults with established type 2 diabetes, irrespective of the reason for the visit.

The study was approved by The Royal Australian College of General Practitioners National Research and Evaluation Ethics Committee, and written informed consent was obtained from all participating patients.

Data collection and stratification

Data were collected between April and September 2005. A de-identified case report form captured demographic data, clinical history (including medication usage), results from physical examinations and data from the most recent laboratory tests (including estimated glomerular filtration rate [eGFR]).[1] Impaired kidney function was designated in patients with an eGFR below 60 mL/min/1.73 m^2, determined using the four variable modification of diet in renal disease (MDRD), formula which has been shown to be a reliable tool for identifying Australian patients with type

2 diabetes and impaired kidney function.[6] No attempt was made to standardise results from different laboratories in order to reflect the raw results on which practitioners base assessment and management.

Practitioner assessment of kidney function

General practitioners were asked whether they considered their patient's kidney function to be impaired, and whether the patient's kidney function influenced their choice of medications or dosages. To reflect available resources at the time of the study, no instruction was provided on how kidney function should be estimated or defined. The use of antidiabetic agents was then examined in patients with impaired kidney function, identified by GPs themselves or estimated using the MDRD formula. A detailed report of the ability of GPs to estimate kidney function and identify impairment has been published elsewhere.[7]

Results

Patient characteristics

Data and informed consent were obtained for 3893 adults with type 2 diabetes. Their clinical characteristics have been previously published.[1] Briefly, half were male (52%), with a mean age of 66 years and a median duration of diagnosed diabetes of 6 years. Almost one out of every 4 patients attending their GP had an eGFR below 60 mL/min/1.73 m^2 (23.1%, 95% CI: 21.8–24.5%).[1] Impaired kidney function was most common in patients aged 65 years or over (35%) compared with those aged less than 65 years (9%).[1]

Prescribing of oral antidiabetic agents

Overall, 63.4% of patients with type 2 diabetes attending their GP were treated with metformin, 44.6% with a sulphonylurea and 6.7% with a thiazolidinedione. The overlap between these oral antidiabetic agents is shown in *Figure 1*. Two-thirds of all sulphonylureas (68.2%) were prescribed as dual therapy with metformin. Other oral agents (acarbose and/or repaglinide) were used in less than 1% of patients.

Metformin prescribing patterns in patients with impaired kidney function

Over half (53%) of all patients with an eGFR below 60 mL/min/1.73 m^2 were prescribed metformin (*Figure 2*). This prescribing frequency was only slightly less than observed in patients with normal kidney function (66%, $p<0.01$). This difference was largely explained by reduced metformin use in individuals with an eGFR below 30 mL/min/1.73 m^2, a level usually accepted as representing severe or pre-end stage kidney disease. Nonetheless, even in this subgroup, 28% of patients used metformin.

In patients identified by their GP as having 'impaired kidney function', 57% received metformin (vs. 67% in patients perceived to have normal kidney function, $p<0.01$). However, the recognition of impaired kidney function had no significant impact on metformin prescribing at any given level of eGFR. For example, in patients with an eGFR 30–60 mL/min/1.73 m^2, 54% of patients received metformin where the GP perceived impaired kidney function, and 55% where the GP did not. Metformin use was the same whether or not prescribing was said to be influenced by kidney function (64% vs. 63%, p=NS).

The choice of sulphonylurea

In the NEFRON cohort, gliclazide was the most widely used sulphonylurea, prescribed in 72% of sulphonylurea treated patients. Most of these individuals received the once per day modified release preparation (59%), which was the most used sulphonylurea preparation overall. Seventeen percent of sulphonylurea treated patients received glimepiride, 8% received glibenclamide, and 3% received glipizide.

In patients with an eGFR below 60 mL/min/1.73 m^2, 46% received a sulphonylurea. This prescribing practice was not significantly different from that observed in individuals with normal kidney function (45%) (*Figure 2*). Similarly, the decision to use sulphonylurea was made independent of kidney function. The frequency of prescribing sulphonylureas with active metabolites (glimepiride, glibenclamide) was identical in patients with impaired and normal kidney function (*Figure 3*), and similar whether or not the GP perceived impaired kidney function (11%).

The use of insulin in patients with type 2 diabetes

Insulin was prescribed for 13.3% of NEFRON patients (n=517). Twice daily regimens predominated (69%) over nocturnal alone (14%) or more frequent dosing (16%). Patients with impaired kidney function were more likely to receive insulin (17%) than those with normal kidney function (12%, $p<0.01$). However, this association was eliminated after adjusting for the increased duration of diabetes in patients with CKD. Insulin regimens were not modified by the presence of actual or perceived impairment of kidney function.

Discussion

Chronic kidney disease is common in patients with type 2 diabetes in Australian general practice.[1] These patients are at increased risk of adverse outcomes, including adverse drug reactions (ADRs),[8] cardiovascular events,[5] and premature mortality.[2–4] Impaired kidney function should impact on the type and the intensity of antidiabetic therapy, but contrary to national prescribing recommendations and guidelines[9,10] it is not currently a major determinant of antidiabetic agent usage in Australian primary care.

There have been widely publicised cautions against metformin use in patients with impaired kidney function.[9–11] Current product information documents include a 'boxed warning' (the highest level of regulatory precaution) for metformin use in patients with an eGFR below 60 mL/min/1.73 m^2. However, NEFRON data suggest that prescribing is not greatly influenced by this contraindication; at least every second patient identified as having impaired kidney function or as having an eGFR below 60 mL/min/1.73 m^2, was prescribed metformin. These statistics are consistent with data from European tertiary care settings in which 46–73% of patients on metformin had one or more contraindications or cautions to its use.[11,12]

Although explicitly contraindicated in patients with impaired kidney function, metformin remains a potent antidiabetic agent and there is no clear evidence that prescribing metformin for these patients is harmful. Spontaneous reporting in Australia and the United States suggest an incidence of metformin associated lactic acidosis (MALA) of 1–2 per 20 000 patient years, of which about one-third are fatal.[13,14] A recent

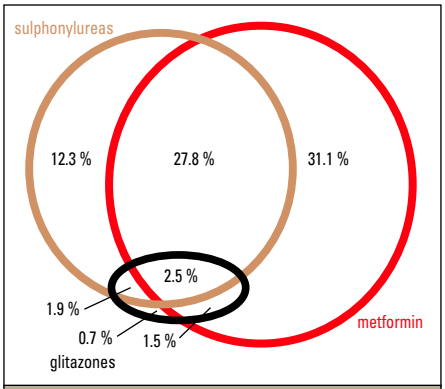

Figure 1. Venn diagram showing the pattern of oral antidiabetic usage in patients with type 2 diabetes in Australian general practice

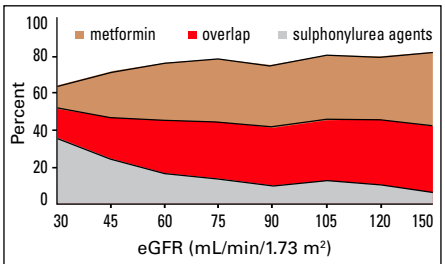

Figure 2. Use of metformin and sulphonylurea agents according to eGFR in patients with type 2 diabetes

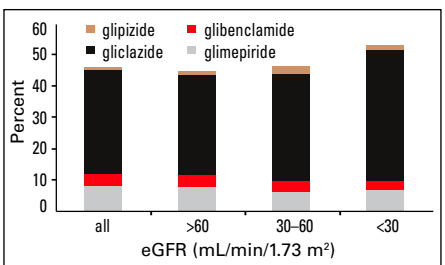

Figure 3. Use of different sulphonylurea agents in patients with type 2 diabetes, stratified by eGFR

Cochrane review analysed 47 846 patient years of treatment from all known prospective comparative and observational studies (n=206) and found no cases of fatal or nonfatal lactic acidosis during metformin treatment.[15] Such findings might support the current prescribing patterns for metformin in Australia, even though current prescribing guidelines do not.[9,10] However, others reviewing this area have made interpretation along a more conservative *primum non nocere* line.[13,14]

In the case of sulphonylureas, the pharmacological rationale for prescribing precautions is more distinct, as active metabolites of some agents (eg. glibenclamide, glimepiride) may accumulate in patients with impaired kidney function and lead to hypoglycaemia. By comparison, sulphonylureas with inactive metabolites (eg. gliclazide, glipizide) appear to be associated with reduced hypoglycaemia risk in these patients.[16–18] Despite these clear pharmacological differences, kidney function had no impact on sulphonylurea prescribing. Although the use of sulphonylureas with inactive metabolites already predominates in Australia, 10% of individuals with an eGFR below 30 mL/min/1.73 m^2 (11% of individuals with normal kidney function) still used a sulphonylurea whose pharmacokinetics are significantly influenced by kidney function. Even when patients were identified by their GP as having moderate to severe impairment of kidney function, 10% continued to be treated with a sulphonylurea with an active renally cleared metabolite.

The NEFRON data have some limitations in assessing national prescribing of antidiabetic agents. As a clinic based, incident driven study, there is an inherent bias toward patients who regularly attend in primary care. Selection bias in relation to participating investigators and enrolled diabetic patients cannot be ruled out, although every effort was made to ensure representative investigator distribution and enrolment of consecutive patients. NEFRON investigators had comparable mean age (50 vs. 52 years) and worked a comparable number of hours per week (43 vs. 41 hours) to reported figures for GPs nationally.[19] The geographic representativeness of the investigators is published elsewhere.[1]

Despite potential residual biases, while prescribing of oral antidiabetic agents in the NEFRON cohort significantly diverges from recommended practice, it is consistent with reports from regional and centre based studies.[20]

Finally, we have no data on the incidence of MALA or hypoglycaemia in our study population and cannot report on other potential strategies for reducing ADR risk (such as dose reduction) which may be partly effective for renally cleared sulphonylureas. However, there is no clear evidence that metformin dose is correlated to plasma lactate concentrations[21] or MALA risk.

Implications for general practice

- The prescribing of antidiabetic agents in Australian general practice is not significantly influenced by the presence of impaired kidney function.
- General practitioners should be encouraged to make use of automated eGFR reporting to not only identify impaired kidney function in their patients, but also to improve their management of patients with type 2 diabetes.

Conflict of interest: Andrew Weekes is an employee of Servier Laboratories (Australia) Pty Ltd, manufacturers of gliclazide. Merlin Thomas is supported by grants from the National Health and Medical Research Council, Diabetes Australia, Kidney Health Australia and the Juvenile Diabetes Research Foundation Australia.

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