Eur J Clin Pharmacol (2016) 72:1489–1496
DOI 10.1007/s00228-016-2117-y

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

# Trends in metformin utilisation and dose appropriateness in Australia

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Received: 10 May 2016 / Accepted: 15 August 2016 / Published online: 27 August 2016


**Abstract**
*Purpose* The study aimed to (1) determine the trends in the utilisation of metformin in Australia, (2) determine the appropriateness of metformin dosing in an Australian teaching hospital and (3) gather the opinions of prescribers on the relationship between metformin dose and renal function.
*Methods* National prescription data between 1990 and 2012 were accessed. A retrospective audit (2008–2012) of metformin doses and patient renal function (20 % random sample of all in-patients prescribed metformin) was conducted at St Vincent's Hospital (SVH), Sydney. Prescribers of metformin were interviewed (semi-structured; consultants at SVH) or surveyed (Australian endocrinologists) to gather their understanding of metformin dosing in relation to renal function.
*Results* Metformin utilisation increased fivefold nationally between 1995 and 2012. Metformin tended to be under-dosed in SVH patients with normal renal function (83.5 %) and over-dosed in patients with impaired renal function (estimated glomerular filtration rate (eGFR) <30 mL/min, 50 %). Consultants indicated that metformin doses needed to be reduced in renal impairment. Most endocrinologists (61 %) were comfortable prescribing metformin down to eGFRs around 30 mL/min.
*Conclusion* The use of metformin increased greatly over the period of the study. Metformin is prescribed frequently for patients with eGFR values below the minimal level approved in the product label (60 mL/min). While prescribers expressed their understanding of the need to reduce metformin doses in patients with renal impairment, we found that metformin doses were higher than appropriate in patients with impaired renal function. Metformin may be used safely when renal function is poor provided dosage is appropriately reduced.

**Keywords** Metformin · Renal function · Dosing appropriateness

**Electronic supplementary material** The online version of this article (doi:10.1007/s00228-016-2117-y) contains supplementary material, which is available to authorized users.

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## Introduction

Metformin is the first-line pharmacotherapy for type 2 diabetes mellitus (T2DM) [1]. In the United Kingdom Prospective Diabetes Study (UKPDS) 10-year follow-up, patients taking metformin had reduced cardiovascular mortality beyond that expected for the degree of glycaemic control [2]. In the recent guidelines released by the American Diabetes Association (ADA) [3], it is stated that metformin should be commenced in all newly diagnosed patients, up-titrated to the maximal effective dose and should be continued regardless of any additional therapy requirements.

Metformin is generally considered to be a safe drug, but its use is limited in patients with compromised renal function because of warnings about the risk of lactic acidosis, a potentially life-threatening condition. The product label lists the following contraindication for the use of metformin: 'Renal failure or renal dysfunction (creatinine clearance <60 mL/min)'. A lower cutoff of 30 mL/min is advocated in the *Australian Medicines Handbook* (AMH), the Australian Prescriber and a recent systematic review [4–6]. The UK's NICE and US FDA's guidelines suggest that metformin should be prescribed with caution in patients with estimated glomerular filtration rate (eGFR) of 30–45 mL/min and ceased in patients with eGFR <30 mL/min [7, 8]. Additionally, in New Zealand, dosing is recommended down to creatinine clearances of 15 mL/min [9]. These recommendations that differ from the product information confuse prescribers and patients and have led to many patients with a creatinine clearance <60 mL/min being denied the benefits of this drug. A recent study using the current AMH guidelines classified approximately 20 % of both general community and aged care residents as having potentially inappropriate dosages (too high) of metformin on the basis of renal function [10].

We have studied metformin pharmacokinetics over a wide range of creatinine clearances [11, 12]. From these studies, we suggested that metformin could be administered to patients with creatinine clearances from 15 to 120 mL/min, prescribing lower doses for those with decreased renal function [12].

This present report is an analysis of trends in the utilisation of metformin in Australia and the appropriateness of metformin doses in patients with T2DM admitted to an Australian teaching hospital (St Vincent's Hospital, Sydney). Our recommended appropriate doses have been compared with the actual doses of metformin prescribed during the hospital stay of patients with T2DM. An exploration of opinions of hospital consultants and Australian endocrinologists regarding the use of metformin was undertaken. These data provide a basis for the development and implementation of improved guidelines for clinicians on the safe and effective use of metformin.

## Methods and materials

### Utilisation of metformin in Australia

Data on metformin utilisation (including combination formulations) were provided by the Drug Utilisation Sub Committee (DUSC) of the Department of Health and Ageing (1992–2012) and the Medicare database (1990–2012). DUSC data includes both subsidised[1] and unsubsidised use of metformin, while Medicare data for this study included subsidised use only (accessed via website using item codes outlined in Supplementary Table 1).[2]

Defined daily dose (DDD) is the assumed average maintenance dose per day and is an established method of estimating drug utilisation and is usually expressed as DDDs/1000 population/day [15]. The DDD of metformin is 2000 mg [12]. The total yearly consumption of metformin in Australia derived from the DUSC data sets was used to determine utilisation in the following way:

Utilisation = [Total metformin consumption(mg)/DDD(mg)] × 1000/(Total population × 365).

For the years 1990–2004 and 2006, respectively, metformin utilisation was calculated and published by the Australian Institute of Health and Welfare (AIHW) [13, 14]. DUSC data had not been published for the period 2007–2012 but was made available to the researchers enabling them to the calculate utilisation. Utilisation was also determined from the Medicare data. Population size data were obtained from the Australian Bureau of Statistics (ABS) website.

### T2DM and metformin dosing at St Vincent's Hospital

#### *Metformin utilisation and dosage*

SVH is 300-bed tertiary referral and teaching hospital of the Medical School of the University of New South Wales catering for adult patients. Records of all in-patients prescribed metformin during the period 2008–2012 were extracted retrospectively from MedChart®, the electronic medication management system used at SVH. A random sample (20 %) of these patients was selected for each of these years. Prescribing records for the first admission of a patient each year only were examined. From each sampled admission, the following data were retrieved:

- Metformin orders including formulation, dose schedule and records of administrations[3]
- eGFR (extracted from pathology records, SydPath, SVH)

The average daily dose for the patients in the 20 % sample was estimated. In cases where the dose changed during admission, the daily dose at discharge was used

[1] Subsidised: government pays difference between patient co-payments and cost of drug. For metformin, this applies to concessionary patients namely those aged over 65 years and those with sickness benefits and from a low socio-economic background. Unsubsidised: government pays nothing, applies to non-concessionary patients

[2] Under copayment data began to be incorporated in Medicare data late in 2012 but was not included in the Medicare data accessed for this study.

[3] Administrations for which the corresponding orders spanned the annual cutoff (December 31) into the successive year were counted in the year in which the order was made.

for the calculation. The occasional missed, 'not taken' or delayed doses were not taken into account.

Hospital-wide implementation of MedChart® was completed in 2010, and the 20 % samples in 2008–2009 were extracted from an incomplete database. The wards in which MedChart® was implemented in 2008 and 2009 are shown in Supplementary Table 2.

Hospital prevalence of T2DM was determined per thousand total admissions 2008–2012. These were identified from hospital electronic medical records. For patients with multiple admissions, each admission was treated as a unique event and contributed to the total admissions. The percentage of T2DM patients taking metformin was estimated by extrapolating from the 20 % sample and the hospital prevalence data.

*Appropriateness of dose of metformin*

An 'appropriate' daily dose of metformin hydrochloride (mg) was estimated as follows:

$$\text{Appropriate daily dose} = \text{estimated glomerular filtration rate (eGFR)} \times 33 \pm 250\,\text{mg}.$$

This formula was derived from simulations estimating maximum daily doses of metformin appropriate for the creatinine clearance [4] (Table 1). The minimum tablet content of metformin hydrochloride is 500 mg and, therefore, we considered actual doses within 250 mg (i.e. half a tablet) of the ideal to be clinically reasonable. Doses of metformin above or below this range were categorised as 'high' or 'low', respectively. In accordance with the product label, the maximum daily dose was set at 3000 mg/day for the immediate-release formulation and 2000 mg/day for the extended-release formulation. eGFR was assumed to have been constant in a patient until a more recent result was available. eGFR was not available for 10 patients, and these patients were excluded from this analysis. Note that this analysis was conducted retrospectively.

## Opinions of prescribers

*Interviews with SVH consultants*

'High use' departments in 2008–2012 were identified from the MedChart reports. Consultants in these departments were invited ($n$ = 45) to participate in a short semi-structured interview about metformin-prescribing practices (Supplementary Table 3). Eleven consultants were recruited (Supplementary Table 4). Interviews were conducted by a medical student with basic training in qualitative research methods. Interviews were on average 11 min in duration (range 2–30 min). The interviews were audio-recorded and transcribed verbatim. Transcribed interviews were entered into NVivo version 10 (QSR International, Melbourne, Vic, Australia) for organisation. De-identified interview transcripts were reviewed independently by two researchers (JM, SK), and recurrent themes were extracted (JM, SK). An inductive approach to analysis was adopted. The researchers met periodically throughout data collection to discuss emerging themes and determine when theme saturation had occurred (i.e. no new themes were apparent). Any discrepancies in coding were settled by consensus.

**Table 1** Recommended maximal doses of metformin at different levels of renal function derived from simulations from a validated metformin population pharmacokinetic model to ensure that peak plasma concentrations of metformin in 95 % T2DM patients remain below the suggested maximum of 5 mg/L [4]

| Creatinine clearance (eGFR) mL/min | Maximum daily dose of metformin (mg)[a] |
|---|---|
| 15 | 500 |
| 30 | 1000 |
| 60 | 2000 |
| 120 | 3000 |

[a] For the extended-release formulation the maximum daily dose was set to 2000 mg/day

*Survey of Australian endocrinologists*

Australian endocrinologists and advanced trainees were invited (via email and newsletter from the Endocrine Society of Australia and the Australian Diabetes Association) to undertake a short online survey (17 questions via Survey Monkey) on their approach to the use of metformin in T2DM (Supplementary 5). Participants were presented with case scenarios (Supplementary 5) that asked whether they would prescribe metformin in patients with varying degrees of renal impairment. The primary outcome was the percentage of respondents that would prescribe metformin at various degrees of renal function and at which dose. Responses were anonymous. For these data, descriptive statistics included mean and standard deviations. In order to calculate mean maximal dose, doses >2000 mg were estimated to be 2500 mg.

## Results

### Utilisation of metformin prevalence in Australia

Both the Medicare and DUSC datasets indicate a rapid increase in the utilisation of metformin (Fig. 1). The use of metformin in the non-concessionary population was approximately three times less than that of the concessionary population consistent with the fact that T2DM is more prevalent in older patients. The utilisation of metformin in 2012 was 20.1 DDDs per 1000 population per day, representing an approximate fivefold increase since 1995 (Fig. 1).

### Use of metformin and prevalence of T2DM at St Vincent's Hospital

In the 5-year period, 652 hospitalised patients (20 % sample) received metformin for a total of 9362 days. In these patients, the mean dose was 1280 mg daily. No patient developed metformin-associated lactic acidosis (MALA). The number of patients with a diagnosis of T2DM admitted to SVH is shown in Table 2. Similar to the utilisation of metformin, the presentation of T2DM remained approximately constant at about 57 per thousand admissions (Table 2). We estimated that about 45 % of T2DM patients admitted were prescribed metformin (Table 2).

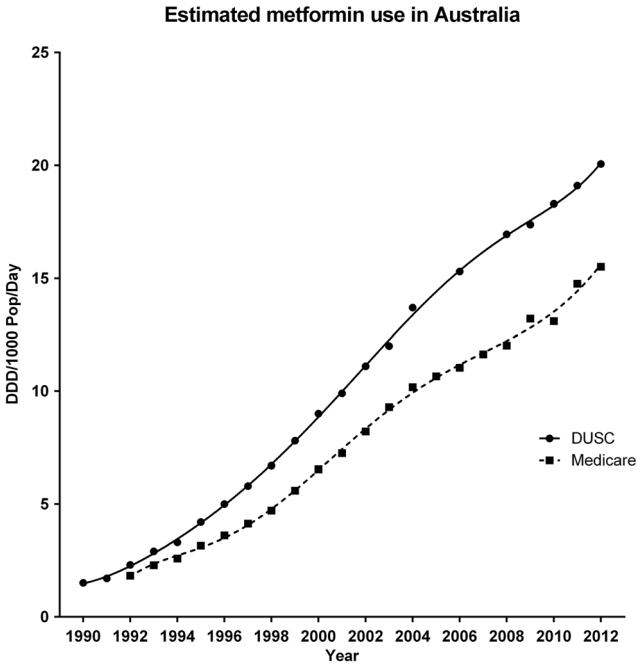


**Fig. 1** Estimated utilisation of metformin Australia from DUSC (subsidised and non-subsidised) and Medicare (subsidised) data. The data shows the numbers of patients receiving metformin if the daily dose was 2000 mg metformin. *DDD* = defined daily dose per 1000 population/day. Source: DUSC and Medicare Databases

### Appropriateness of metformin daily dose

The number of initial doses categorised as low, appropriate and high varied with the renal function ($\chi^2$, $P < 0.0001$). The major mismatch occurred for patients with poor renal function, although numbers are small (Table 3). Half of patients with low renal function (eGFR <30 mL/min/1.73 $m^2$) were found to be prescribed doses that were greater than recommended while most patients with better renal function (eGFR >30 mL/min/1.73 $m^2$) were under-dosed. Overall, 76 % of patients in our sample were administered a low daily dosage, 18 % received an appropriate dosage and 6 % a high daily dosage of metformin (Table 3).

### Opinions of St Vincent's Hospital consultant prescribers of metformin

*Interviews with prescribers exploring their attitudes to metformin use and dosing*

All participants viewed metformin as an effective treatment for T2DM. While the majority of consultants reported prescribing metformin regularly, not many initiated the drug. One consultant (interviewee 10) said:

> 'I would rarely start metformin for patients on my own but I would often prescribe it for my patients as continuing care'.

Doctors explained that if they initiated metformin, their initial dose was typically between 500 and 1000 mg a day. Otherwise, doctors said they simply prescribed the dose which patients had been taking prior to admission. Doctors explained that they were comfortable prescribing metformin at eGFRs as low as 20–30 mL/min/1.73 $m^2$, and this was reflected in the substantial numbers in this eGFR range actually prescribed metformin. Doctors said that the maximum dose they were willing to prescribe for this group was from 500 to 1000 mg. Official product label was often reported to be the resource of choice for prescribers.

Renal failure and the related risk of lactic acidosis and gastrointestinal intolerance were frequently reported reasons for reducing the dose or stopping metformin. Several consultants mistakenly identified hypoglycaemia as a risk associated with use of metformin, and some viewed this as a reason to stop the drug. However, most doctors preferred to continue with metformin if possible.

One consultant [8] said:

> 'I love metformin so much that I will do everything I can to convince someone to retrial it'.

**Table 2** Prevalence of T2DM admissions and metformin use at SVH

| Year | T2DM[a] | Total diabetes | Total admissions | T2DM/total diabetes (%) | T2DM (per thousand admissions) | Number of patients taking metformin[b] | Percentage (%) of T2DM taking metformin |
|---|---|---|---|---|---|---|---|
| 2008[c] | 1820 | 1950 | 38,774 | 93.3 | 47 | N/A | – |
| 2009[c] | 1887 | 2034 | 38,010 | 92.8 | 50 | N/A | – |
| 2010 | 1699 | 1821 | 38,378 | 93.3 | 44 | N/A | – |
| 2011 | 1551 | 1652 | 38,968 | 93.9 | 40 | 930 | 56.3 |
| 2012 | 1700 | 1818 | 39,164 | 93.5 | 43 | 1030 | 56.7 |

[a] These data reflect the diagnoses as entered by the medical records department 'coders' who have examined the medical records of all patient admissions. Each admission is treated as unique; this includes multiple admissions for an individual patient

[b] The number of patients taking metformin was extrapolated from the original 20 % sample

[c] Also note the electronic prescribing system was not fully implemented in the hospital until 2011

Consultants were more inclined to consider adding other anti-hyperglycaemic drugs such as insulin, sulfonylureas or newer oral anti-hyperglycaemic drugs to metformin rather than stopping the metformin.

Doctors explained that the most frequent blood chemistry results monitored were renal function followed by measures of blood glucose control. Blood chemistry results that indicate lactic acidosis such as bicarbonate and/or lactate levels were mentioned less frequently.

*Online National Survey of endocrinologists and endocrinology trainees*

Of 119 respondents who agreed to undertake the survey, 115 completed it (response rate 97 %). Seventy-four percent ($n$ = 85) of the respondents were consultant endocrinologists, while the remaining were advanced trainees in endocrinology ($n$ = 30). The majority ($n$ = 83) worked predominantly in the public sector.

Almost all respondents (97 %) reported that they would use metformin in patients with an eGFR of 50 mL/min/1.73 $m^2$, with a maximum dose range of 500 to 2000 mg (mean 1450 ± 43 mg) of extended-release metformin. Sixty-one percent of respondents indicated that they would use metformin in patients with eGFR of 35 mL/min/1.73 $m^2$ (mean dose 913 ± 41 mg). In patients with eGFR below 20 mL/min/1.73 $m^2$, only 7 % reported that they would use metformin (dose 500 to 1000 mg, mean 688 ± 91 mg).

## Discussion

This study revealed an approximately fivefold rise in metformin use in Australia between 1995 and 2012 in comparison to a twofold rise in the prevalence of T2DM in the same time period [13–15]. Contrary to the product label, the drug was prescribed in patients with renal impairment but doses were greater than recommended in the severely renally impaired. In patients with creatinine clearances greater than 30 mL/min, there was an opportunity to increase dosage.

This study covers a long-time period during which there have been a number of changes to policy, guidelines, awareness of T2DM and its complications and the availability of newer anti-diabetic agents. The UKPDS study published in 1998 established metformin as the drug of first choice for newly diagnosed type 2 diabetic patients by demonstrating its superiority over the sulphonylureas and insulin with respect to cardiovascular mortality [2]. Over the time period studied, several new drug classes have been introduced for treating T2DM including thiazolidinediones, dipeptidyl dipeptidase-

**Table 3** Appropriateness of daily dosage of metformin at various levels of eGFR

| eGFR (mL/min/1.73 $m^2$) | Low dose | Appropriate dose | High dose | Total number of patients |
|---|---|---|---|---|
| <30 | 6 (30 %) | 4 (20 %) | 10 (50 %) | 20 |
| 30–59 | 128 (67 %) | 46 (24 %) | 18 (9 %) | 192 |
| 60–89 | 222 (82 %) | 38 (14 %) | 12 (4 %) | 272 |
| ≥90 | 142 (85 %) | 26 (15 %) | 0 (0 %) | 168 |
| Total | 498 (76 %) | 114 (18 %) | 40 (6 %) | 652 |

The data are derived from the 20 % of patients per annum (first admission per annum only) prescribed metformin as retrieved from MedChart

4 inhibitors (DPP-4 inhibitors) and glucagon-like-peptide-1 agonists (GLP-1 agonists). More recently (after the period of this study), the sodium-glucose co-transporter 2 inhibitors (SLGT-2 inhibitors) were introduced. Despite these new entries to the market, a recent meta-analysis of clinical outcomes and adverse effects of glucose-lowering agents (including the newer ones) confirmed that metformin should be the drug of first choice for initiating therapy in T2DM [16]. Metformin has been contraindicated in renal impairment for many years. Normally, when a drug is entirely cleared by the kidneys, as is the case with metformin, the advice is to reduce the dose in renal impairment; however, this has not been the case for metformin. The contraindication in renal impairment has arisen from the fear of MALA. While the product label still maintains the contraindication of prescribing metformin in patients with creatinine clearance <60 mL/min, many countries have published clinical guidance that supports its use in patients with more severe renal impairment but many prescribers, especially in primary care, remain uncertain and confused [6–9].

### National use

While a large increase in the utilisation of metformin was found in Australia, this is not an isolated result. One study found an increase of metformin utilisation in the range of 2–5-fold in ten European countries over a similar time period as the present study [17]. Similarly, several other single country/region studies have found some increase in metformin utilisation including the USA, Ireland, the Netherlands and Portugal [18–20]. On the other hand, studies from Canada and Taiwan document metformin utilisation to be stable [21, 22]. The reasons for these contrasts in uptake are not established but are worthy of more exploration.

Our finding of the disproportionate increase in the use of metformin expressed as DDD/1000 population/day compared to the prevalence of T2DM in Australia may be explained by several factors. Clinical studies have established the safety of metformin in T2DM patients with renal impairment increasing prescriber confidence in using the drug in renal impairment that is common in T2DM. There is increasing use of the drug for off-label indications, for example, for treating prediabetes, obesity and polycystic ovary syndrome. Increased concern about adverse reactions to the major alternative drug classes, especially sulfonylureas and thiazolidinediones, has also likely led to increased use of metformin. Other factors that may explain this discrepancy are changes in dosages (i.e. increasing doses) as well as changes in persistence/adherence over time (i.e. higher persistence/adherence over time).

Approximately 45 % of the hospitalised patients (2011–2012) with a diagnosis of T2DM in our study were prescribed the drug on admission. However, the hospital use of metformin may underestimate the community use of metformin as it was ceased in some patients on admission to hospital and, therefore, not included in our database of patients prescribed metformin. This might represent concern about continuing the drug in patients with other risk factors for lactic acidosis such as decompensated cardiac failure. Unlike the national data, the hospital prevalence of T2DM per admission has remained relatively steady over the study period. Perhaps admissions are less likely over time with better community care of T2DM patients.

### Appropriateness of metformin dosage at SVH

A feature of the analysis of the dosage of metformin in SVH patients was that it was often low in patients with eGFR values over 30 mL/min. This raises the question of whether the response to metformin could be increased by using a greater dosage in this population. On the other hand, a major finding of the present study was that 25 % of metformin-treated patients had eGFR values below 60 mL/min. This degree of renal impairment is listed as a contraindication and given a 'black box' warning in the product label. It is important to note that MALA did not develop in any patient. Our current findings support our own and other researchers' previous suggestion [4, 23–25] that the lower limit of 60 mL/min in the product label should be reduced (to 30 mL/min, with some suggesting dosing down to 15 mL/min) in line with recommendations in the *Australian Medicines Handbook*, the Australian Prescriber and other recent publications [4–6]. The advisability of prescribing reduced dosages for patients with renal impairment is made clear in this recent guidance. Also the signs of impending MALA have been presented, and it is recommended that T2DM patients taking metformin be aware of these warning signs and circumstances where there is increased risk of MALA. These include nausea, vomiting, dehydration and acutely deteriorating renal function [26].

In our analysis of dosing at SVH, we found 82 % of patients had potentially inappropriate (both low and high) dosages of metformin (Table 3). This is in contrast to the 20 % found by Huang et al. in community and aged care residents [10]. We used a sliding scale definition of an 'appropriate' dose according to graduated renal function, while Huang et al. used a more restricted definition as advised in the AMH, namely a maximum of 2 g daily for creatinine clearances of 60–90 mL/min and 1 g daily for 30–60 mL/min. With our definition, derived from simulations from our model of metformin pharmacokinetics, we identified a large number of cases with dosages that could potentially be increased. Our rate of inappropriately high doses was only 6 % contrasting with Huang et al. where the majority of their inappropriate dosing rates was high at ~20 %. For patients with glomerular filtration rates of 30–60 mL/min, we accepted

doses of between 1000 and 2000 mg/day while the AMH sets a limit of 1000 mg/day for this range of renal function.

### Interviews with metformin prescribers and survey of endocrinologist

The consultant clinicians interviewed at SVH had a high opinion of metformin as a useful drug. This is reflected in the literature with metformin being the preferred drug for initiating treatment of T2DM. Generally, the clinicians were aware that metformin was contraindicated in patients with renal impairment and also understood that the dose needed to be reduced in these patients. They were comfortable prescribing metformin for patients with renal function down to 30 mL/min, concordant with Australian guidelines [6]. We found that Australian endocrinologists were comfortable with dosing metformin in patients with severe renal impairment (30 mL/min).

Despite the knowledge of hospital clinicians on the safe use of metformin that was similar to endocrinologists nationally, we found discrepancies with actual prescribing practices. There was a trend towards under-dosing in patients with normal renal function and some degree of high dosing in patients with poor renal function.

### Strengths and limitations

The major strength of this study is that we have combined different data sources and analyses to provide a complete picture on metformin prescribing in Australia. There are many studies that look at drug utilisation; however, not many combine this with prescribing practice at the patient level or exploration of the knowledge and attitudes of prescribers. Our results may not apply directly to other countries as Australia's health system and subsidised medicines access scheme differ but the general trends in usage and attitudes to prescribing metformin are likely to be similar across countries. Our audit was conducted retrospectively, and the publication we used to base our appropriate dose metric was not published until 2013 after the period being studied. So clinicians were unaware of the best practice relating to metformin dose selection.

## Conclusion

Pleasingly, the rates of prescribing metformin for T2DM are increasing. Although the approaches to the use of metformin was varied among hospital consultants, endocrinologists and advanced trainees, almost all would use metformin in patients with an eGFR below 60 mL/min/1.73 $m^2$ and many at eGFRs that are considerably lower again despite the contraindication in the product label. We encourage the use of metformin in patients with renal impairment with the caveats that doses are adjusted with respect to renal function and that the symptoms and signs of MALA are understood and monitored by patients and prescribers. An update of the product label is well overdue and is an important step towards achieving safer and more effective use of the drug in T2DM patients with renal impairment.

**Acknowledgments** The authors would like to thank Ms. Agata Szylczak, Medical Records SVH, and Ms. Maxine Robinson, Secretary, Drug Utilisation Sub Committee of Pharmaceutical Benefits Advisory Committee, Pharmaceutical Benefits Scheme. The study was supported by the National Health and Medical Research Council Program under grants APP 568612 and APP 1054146 and Australian Research Council Linkage under grant LP0990670.

**Author's contributions** J Moon was responsible for data collection, data entry, data analysis and preparation of manuscript; SS Kumar for data entry, data analysis and preparation of manuscript; GG Graham for data analysis and preparation of manuscript; MT Baysari for data analysis and preparation of manuscript; KM Williams for data analysis and preparation of manuscript; W Chen for data collection and data analysis; A Viardot and JR Greenfield for clinical guidance and preparation of manuscript; and RO Day for clinical guidance, data analysis and preparation of manuscript.

**Compliance with ethical standards**

**Conflict of interest** The authors declare no conflicts of interest.

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