

# Metformin: a golden oldie

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**M**etformin has been used in the treatment of type 2 diabetes for 60 years.<sup>1</sup> Past fashions in prescribing have seen metformin come in to and go out of favour. Metformin use has however increased over the last 30 years, as several key publications over that time period have emphasised its efficacy, safety, tolerability and low cost, when compared to alternative therapies.<sup>1</sup> In patients with type 2 diabetes, metformin is now the recommended first-line therapy after exercise and dietary changes.<sup>1</sup>

In this edition of the *New Zealand Medical Journal*, Murray et al discuss trends in New Zealand's recent dispensing patterns of anti-diabetic agents (AAs) in the management of type 2 diabetes, including use of metformin.<sup>2</sup> They show that use of metformin as the first dispensed medication for the treatment of type 2 diabetes increased between 2007 and 2016, when metformin prescribed as initial monotherapy reached 85% of prescriptions.<sup>2</sup> An additional 11% of patients were co-prescribed metformin alongside insulin or a sulphonylurea.<sup>2</sup> This co-prescribing is likely to have been in patients presenting with glucose levels that were sufficiently high, that they were unlikely to respond to metformin alone.<sup>2,3</sup> Murray et al's finding of predominant use of metformin monotherapy as initial choice of AA is a good news story; the available evidence favours metformin as the first line AA given its beneficial effect on cardiovascular (CV) disease risk and weight, and its good safety profile.<sup>1</sup>

The only country to report rates of initial AA therapy using metformin, that are close to that of New Zealand, is the UK. In their primary care setting, use of metformin as first-line therapy reached 91% in 2013.<sup>4</sup> There are of course international differences in pharmaceutical availability and reimbursement schedules, as well as differences in study methodologies, that are likely to explain some of the observed international differences in prescribing patterns. Also, neither the current New Zealand study nor the UK study mentioned above,<sup>4</sup> was

designed to explore the reason(s) why a small minority of patients were not initiated onto metformin, so we do not know if we have reached 'peak metformin' in New Zealand and the UK.

Should New Zealand prescribers aim to use metformin as first-line therapy in virtually all type 2 DM requiring additional treatment over and above lifestyle change? Probably not. It can be surmised that at least some of the patients prescribed alternative AAs would have had a clear contraindication to metformin use, such as renal impairment (eGFR <15ml/min according to recent changes to the New Zealand data-sheet for metformin prescribing),<sup>5,6</sup> and severe hepatic impairment.<sup>5</sup>

Other countries recognise the advantages of metformin and are concerned about their own low rates of metformin initiation. In some countries, prescribers' caution about using metformin partly reflects their attitudes towards 'historical' safety concerns, especially the risk of lactic acidosis in certain patient sub-populations. Reassuringly, the best available current evidence, while admittedly observational in nature, supports use of metformin in patients with stable heart failure and also chronic liver disease.<sup>7</sup> The role of patient-related factors in decision making around choice of initial diabetes therapy in New Zealand is also unknown. Patients rank gastrointestinal (GI) upset as an undesirable side effect of diabetes medications.<sup>8</sup> In clinical practice, patients with pre-existing GI upset may make an active decision to commence an agent with a side effect profile that is a better 'fit' with their underlying comorbidities, even with the knowledge that metformin-related GI upset is usually transient and can be managed using an appropriate dosing schedule.<sup>3,5</sup>

Murray et al cite the bpac<sup>NZ</sup> (Best Practice Advocacy Centre, New Zealand) 2015 diabetes guidelines.<sup>3</sup> Guidelines do not remain 'in-date' and relevant forever and there are some emerging areas of clinical uncertainty associated with metformin

initiation that would benefit from further discussion. For example, prolonged metformin use is associated with vitamin B12 deficiency.<sup>9</sup> Should a baseline B12 measurement therefore be done at the time of metformin initiation, for comparison with later B12 test results? Also, should metformin or indeed any AA initiation be considered routinely in the very elderly, aged 80 years or more? Actuarial information would suggest that this subgroup of patients is unlikely to live long enough to develop a heavy burden of chronic diabetes complications, even if glycaemic control is allowed to sit above traditional target levels. In these patients the loss of quality-adjusted life years due to medication effects may outweigh any gains achieved through improved glycaemic control.<sup>10</sup> At the other end of the age spectrum, current New Zealand registration of metformin restricts use in children,<sup>5</sup> whereas some overseas guidelines include dosing schedules specific to children.<sup>1</sup>

Will a new AA usurp the role of metformin as first-line therapy? The most likely contender in 2017 would be the SGLT2 inhibitors. Several members of this class of AAs appear to confer additional benefits over and above glucose lowering, by offering cardio-protection. SGLT2 inhibitors are cheaper than their injectable competitors, the GLP-1 agonists, but are nevertheless considerably more expensive than metformin. Several SGLT-2 inhibitors are registered for use in New Zealand but none are on the PHARMAC schedule. A definitive evidence-based answer to the clinical question about metformin versus SGLT2 inhibitor use as initial therapy would require a very large randomised controlled trial which included a pharmacoeconomic analysis. Because metformin seems to have its own independent CV risk lowering effects,<sup>1</sup> such a trial should include a CV outcomes analysis. It is however unlikely that a pharmaceutical company would

want to fund this type of CV outcomes trial, as they risk demonstrating that their own product shows equivalence, or possibly inferiority, rather than superiority to metformin. Also, such a trial would need to be very large, which means it would also be very expensive. Funding mechanisms that are independent of the pharmaceutical industry would therefore be difficult to identify.

Metformin stands out as one of a handful of medications that have been around for a long time, but whose star continues to shine brightly in evidence-based guidelines, with a growing number of patients being initiated on to this medication. In this high-use setting, a sufficient number of prescribers will initiate metformin in patients with 'historical contraindications' to its use, thereby helping to increase the amount of available data about metformin use, including its safety profile. Analysis of large observational datasets can then help to define metformin's risk-benefit profile in patient subgroups that have traditionally been excluded from using metformin.

In conclusion, metformin is an affordable medication with a well-documented efficacy and tolerability profile. If prescribed according to guidelines, it is safe. Murray et al show that it is being initiated as the main front-line therapy for type 2 diabetes within New Zealand. Their big picture view of adherence to prescribing guidelines looks positive. The next challenge may be to determine the extent to which metformin prescribing follows safety recommendations, such as those provided by Medsafe. It would also be of interest to study prescriber adherence to current New Zealand guidelines and recommendations, not only at the time of metformin initiation but also with regard to longer-term surveillance of individual patients on metformin, who may over time develop new (emerging) contraindications to metformin use.

**Competing interests:**

Nil.

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