

BMJ Open Treatment pathways in people with type 2 diabetes mellitus: a nationwide cohort study of new users of metformin monotherapy in New Zealand

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To cite: Guo J, Parkin L, Zeng J, *et al.* Treatment pathways in people with type 2 diabetes mellitus: a nationwide cohort study of new users of metformin monotherapy in New Zealand. *BMJ Open* 2021;**11**:e051884. doi:10.1136/bmjopen-2021-051884

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online. (<http://dx.doi.org/10.1136/bmjopen-2021-051884>).

JG and LP are joint first authors.

Received 31 March 2021
Accepted 15 July 2021



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ABSTRACT

Objectives The aims of this study were to describe the following: (1) the time to change of therapy in patients with type 2 diabetes who had initiated metformin monotherapy as first-line treatment and (2) the sequence in which subsequent therapeutic regimens were introduced.

Design Cohort study.

Setting National study based on linked data from the New Zealand Ministry of Health's National Collections of health and pharmaceutical dispensing data.

Participants People with type 2 diabetes mellitus who initiated metformin monotherapy between 1 January 2006 and 30 September 2014 (n=93 874).

Primary outcome measures Cumulative incidence curves were plotted to show the time taken to move from one regimen to another, while sunburst plots were used to illustrate the sequence in which regimens were introduced.

Results About 10% and 35% of cohort members had moved to a second regimen 1 year and 5 years, respectively, after initiating metformin monotherapy; the majority received a regimen recommended by New Zealand treatment guidelines (mostly metformin and a sulphonylurea). Of those who started a recommended second regimen, 37% and 67% had moved to a third regimen after 1 and 5 years, respectively; the corresponding proportions for those who started an 'other' (not listed as recommended) second regimen were 53% and 75%. Most of those who received a third regimen after a recommended second regimen were dispensed an 'other' third regimen. Of those who moved to a third regimen from an 'other' second regimen, similar proportions received recommended and 'other' third regimens.

Conclusions Real-world type 2 diabetes treatment patterns in New Zealand are complex and not always consistent with guidelines.

INTRODUCTION

Type 2 diabetes mellitus is a major public health issue in New Zealand. Data from the 2018/2019 New Zealand Health Survey (NZHS) suggest that about 6.4% of the overall New Zealand population aged ≥25 years has type 2 diabetes, with even higher proportions

Strengths and limitations of this study

- This nationwide study in New Zealand explored real-world treatment pathways among people with type 2 diabetes who had initiated pharmacological treatment with metformin monotherapy.
- The study was based on a national pharmaceutical claims database that covers the entire population of New Zealand.
- It was not possible to examine the use of antidiabetic drugs which were approved for use but not publicly funded during the study period; however, the proportionate use of these drugs would have been very small.
- Lack of access to detailed clinical data meant it was not possible to explore the appropriateness of changes in treatment, or detect situations in which treatment should have been escalated but was not, or to identify changes in therapy that occurred because of intolerance to metformin.

for Māori (the indigenous people of New Zealand), Pacific and Asian populations.¹ Moreover, the prevalence is increasing over time—according to data from the Virtual Diabetes Register (VDR), the number of people with diabetes (most of whom will have type 2 diabetes) rose progressively between 2010 and 2018.² The true prevalence of type 2 diabetes is likely to be even higher than suggested by the NZHS and VDR estimates as they are based on diagnosed diabetes only.

Good glycaemic control is fundamental to preventing diabetes-related complications and type 2 diabetes management guidelines published by the New Zealand Guidelines Group in June 2011 recommended that treatment is tailored to maintain glycated haemoglobin (HbA_{1c}) <50–55 mmol/mol, or some other target agreed with the patient.³ The guidelines advocated a 3-step approach to pharmacological treatment. First, metformin monotherapy should be initiated

as the first-line treatment and if this is not tolerated or is contraindicated, sulphonylurea monotherapy should be prescribed instead. Alternatively, acarbose could be used, if tolerated. Second, if a patient's HbA_{1c} remains above the agreed target after 3 months, despite optimal dosage and adherence to metformin, a sulphonylurea should be added. If metformin and a sulphonylurea are not tolerated or are contraindicated, or an alternative to insulin is required, then pioglitazone monotherapy could be prescribed, or a dipeptidyl peptidase-4 (DPP-IV) inhibitor. Third, if glycaemic control remains poor after 3 months, despite optimal dosage and adherence to second-line therapy, insulin should be added; isophane insulin is the first choice, but in certain circumstances basal insulin analogues or pre-mixed insulin preparations might be more appropriate. Alternatively, a DPP-IV inhibitor or a glucagon-like peptide-1 (GLP-1) agonist could be used.

The New Zealand Guidelines Group was disestablished in 2012, however subsequent guidelines and consensus statements from the New Zealand Best Practice Advocacy Centre,⁴ the UK National Institute for Health and Care Excellence,⁵ the Scottish Intercollegiate Guidelines Network,⁶ the European Association for the Study of Diabetes⁷ and the American Diabetes Association⁷ have all recommended a stepwise intensification from metformin monotherapy to dual therapy with oral hypoglycaemic agents, followed by triple therapy with oral agents or the addition of insulin.

The treatment pathways in patients with type 2 diabetes have not been fully explored in New Zealand. One study examined the use of antidiabetic agents in people who commenced drug treatment for type 2 diabetes during a 9-year period (financial years 2007/2008–2015/2016).⁸ The majority of patients initiated metformin monotherapy (increased from 80% to 85% over the study period), while small proportions initiated metformin with insulin (increased from 2% to 5%), metformin with a sulphonylurea (decreased from 10% to 6%), sulphonylurea monotherapy (decreased from 8% to 2%) and other therapy (stable at 1%). The researchers undertook some limited follow-up of patients who commenced drug treatment in 2007/2008, but concluded there was a need for further research, including an exploration of the time to escalation of therapy.

We undertook a national study to describe the treatment pathways in an existing cohort of patients who initiated metformin monotherapy for type 2 diabetes in New Zealand between 2006 and 2014. The specific aims of the study were as follows:

1. To describe the time to change in therapy from:
 - i. Metformin monotherapy to a second therapeutic regimen (overall, recommended, 'other').
 - ii. Recommended second therapeutic regimen to a third therapeutic regimen (overall, recommended, 'other').

- iii. 'Other' second therapeutic regimen to a third therapeutic regimen (overall, recommended, 'other').
2. To repeat the above analyses for the periods before, and after, the publication of type 2 diabetes management guidelines by the New Zealand Guidelines Group in 2011.
3. To describe the sequence in which unique therapeutic regimens were subsequently introduced in patients who initiated metformin monotherapy.

METHODS

Data sources and identification of the study cohort

New Zealand has a universal healthcare system in which hospital care and subsidised prescription medicines are provided to all citizens and permanent residents (about 5 million people).⁹ Summary data regarding pharmaceutical dispensings, hospital discharges, deaths and demographic characteristics are held centrally in the Ministry of Health's National Collections.¹⁰

This study is based on an existing national cohort of people who initiated metformin monotherapy for type 2 diabetes between 1 January 2006 and 30 September 2014. The methods used to derive the original cohort have been described in detail elsewhere¹¹ but, in brief, the Ministry of Health identified all people listed on the VDR² between 1 January 2005 and 31 December 2014, including those who died and those who were not registered with a Primary Health Organisation during any given year. For each of these individuals, the Ministry provided us with the following data from the National Collections, using an encrypted unique patient identifier (the National Health Index (NHI)) as the linkage key: demographic information (from the NHI Collection), details of all publicly funded dispensings of prescription medicines between 1 January 2005 and 31 December 2015 (from the Pharmaceutical Collection), details of any publicly funded hospital discharges between 1 January 1988 and 31 December 2015 (from the National Minimum Dataset), and for those who died between cohort entry (first metformin monotherapy dispensing) and 31 December 2015, the date and causes of death (from the Mortality Collection). We then used these data to identify the cohort for this study, as outlined in online supplemental figure 1.

Identifying therapeutic regimens used by members of the study cohort

For each member of the study cohort, we summarised exposure to oral hypoglycaemic agents and insulin during follow-up employing a similar approach to one we have used previously.¹² This involved several steps. First, we combined the dispensing data relating to each of the relevant drugs (online supplemental table) into continuous episodes of use; a continuous episode was defined as a series of dispensings in which the elapsed time between the end date of one dispensed supply and the start date

of the next was ≤ 30 days (online supplemental efigure 2A). We calculated the end date of a dispensed supply by adding the recorded number of days supplied to the date of dispensing; if the days' supply was not recorded in the data the Ministry provided, we set the end date to the earlier of the date of the next dispensing minus 1 day or the date of dispensing plus 90 days (as this is the maximum supply that can be legally provided on one prescription). Second, we summarised the continuous episodes of use of individual drugs into continuous episodes of use of drug classes (online supplemental efigure 2B). Third, we aggregated the data into continuous episodes of use of mutually exclusive therapeutic regimens (online supplemental efigure 3). Follow-up was censored at the earlier of the date of death or 31 December 2015 (end of the study period).

The second and third therapeutic regimens used by individuals, if any, were classified as 'recommended' in accordance with the type 2 diabetes management guidelines published by the New Zealand Guidelines Group in 2011.³ Therefore, recommended second-line therapy was defined as the use of metformin plus a sulphonylurea, or the use of pioglitazone monotherapy, following the use of metformin monotherapy. Any other second therapeutic regimen was classified as 'other'. Recommended third-line therapy was defined as the use, following a second therapeutic regimen (whether recommended or not), of insulin (isophane insulin, basal insulin analogues, or pre-mixed insulin preparations) with or without oral hypoglycaemic agents or short-acting insulin. Any other third therapeutic regimen was classified as 'other'.

Statistical methods

Cumulative incidence curves were plotted to summarise the time taken to move from (1) metformin monotherapy to a second therapeutic regimen (overall, recommended, 'other'), (2) a recommended second therapeutic regimen to a third therapeutic regimen (overall, recommended, 'other') and (3) an 'other' second therapeutic regimen to a third therapeutic regimen (overall, recommended, 'other'). Death was treated as a competing event for all analyses. To estimate the cumulative incidence of change to a recommended regimen, change to an 'other' regimen was considered an additional competing event (and vice versa). All individuals who entered the cohort between 1 January 2006 and 30 September 2014 were included in these analyses. Separate cumulative incidence curves were produced for people who entered the cohort before 1 January 2011 and after 31 December 2011 (pre-guideline and post-guideline groups, respectively).

Sunburst plots were created to illustrate the order in which unique therapeutic regimens were used by cohort members in the first year, first 2 years and first 3 years after cohort entry (among those with ≥ 1 year, >2 years and ≥ 3 years of follow-up, respectively) using methods described by others¹³ and previously employed by our group.¹² Plots were generated for people who entered the cohort at any time between 1 January 2006 and 30 September

2014 and had the required amount of follow-up, as well as those who entered pre-guidelines and post-guidelines. To ensure a clear delineation between prescribing practices before and after the guidelines were published in June 2011, we restricted the pre-guideline analyses to individuals who had completed the requisite years of follow-up (1, 2 or 3 years) before 1 January 2011 and restricted the post-guideline analyses to those who completed the requisite years of follow-up between 1 January 2012 and 31 December 2015.

All dataset manipulations were performed using SAS V.9.4.¹⁴ Sunburst plots and cumulative incidence curves were plotted in R V.3.5.1.¹⁵

Patient and public involvement

The study was based on anonymised routinely collected data and patients were not involved.

RESULTS

A total of 93 874 individuals initiated metformin monotherapy for type 2 diabetes between 1 January 2006 and 30 September 2014 (online supplemental efigure 1). The characteristics of these individuals at cohort entry are shown in table 1.

Figures 1–3 show the proportions of cohort members who moved, over time, from metformin monotherapy to a second therapeutic regimen, from a recommended second therapeutic regimen to a third therapeutic regimen, and from an 'other' second therapeutic regimen to a third therapeutic regimen. About 10% and 35% of cohort members had moved to a second regimen 1 year and 5 years, respectively, after initiating metformin monotherapy; the majority received a recommended regimen (figure 1). Of those who had moved to a recommended second regimen, about 37% and 67% had started a third regimen 1 year and 5 years after treatment intensification (figure 2); the corresponding figures for those who had moved to an 'other' second regimen were 53% and 75% (figure 3). Most of those who received a third regimen after a recommended second regimen were dispensed an 'other' regimen, whereas the proportionate use of recommended and 'other' third regimens was similar among those who moved from an 'other' second regimen. The analogous cumulative incidence curves for individuals who entered the cohort before and after 2011 are shown in online supplemental efigures 4–9. In general, the findings for those who entered the cohort in the pre-guideline and post-guideline years were similar, except for individuals who moved from an 'other' second regimen to a third regimen; in the pre-guideline years higher proportions used an 'other' third regimen, but post-guidelines higher proportions used a recommended third regimen.

Figure 4 shows the proportions and sequence of use of unique therapeutic regimens in the first year, first 2 years and first 3 years following initiation of metformin monotherapy, counting only the first exposure to any

Table 1 Characteristics of cohort members at entry

Characteristic	Number (%) (n=93874)
Sex	
Female	45 056 (48.0)
Male	48 818 (52.0)
Age group (years)	
<25	1349 (1.4)
25–34	4510 (4.8)
35–44	12 004 (12.8)
45–54	22 800 (24.3)
55–64	24 889 (26.5)
65–74	18 262 (19.5)
≥75	10 060 (10.7)
Ethnicity (prioritised)*	
Māori	14 884 (15.9)
Pacific	12 337 (13.1)
European	49 191 (52.4)
Asian (non-Indian)	6 727 (7.2)
Indian	6 098 (6.5)
Middle Eastern/Latin American/African	1 150 (1.2)
Other	188 (0.2)
Unknown	3 299 (3.5)
Socioeconomic deprivation (NZDep2013 decile)†	
1 (least deprived)	5 619 (6.0)
2	6 263 (6.7)
3	6 607 (7.0)
4	7 321 (7.8)
5	8 016 (8.5)
6	8 318 (8.9)
7	10 469 (11.2)
8	11 049 (11.8)
9	13 820 (14.7)
10 (most deprived)	16 199 (17.3)
Unknown	193 (0.2)

*Self-identified ethnicity categorised according to the Ministry of Health Ethnicity Data Protocols.²⁶

†New Zealand Deprivation Index, an area-based measure of social deprivation.²⁷

given regimen across the full study period. Of the cohort members who moved from metformin monotherapy to a second therapeutic regimen in the first year of follow-up, about 72% used metformin plus a sulphonylurea and a very small proportion used pioglitazone monotherapy (the recommended second-line therapies), while 14% used sulphonylurea monotherapy, 10% used insulin-containing regimens and smaller proportions used various other regimens. Of those who moved to a third regimen in the first year of follow-up, the majority who

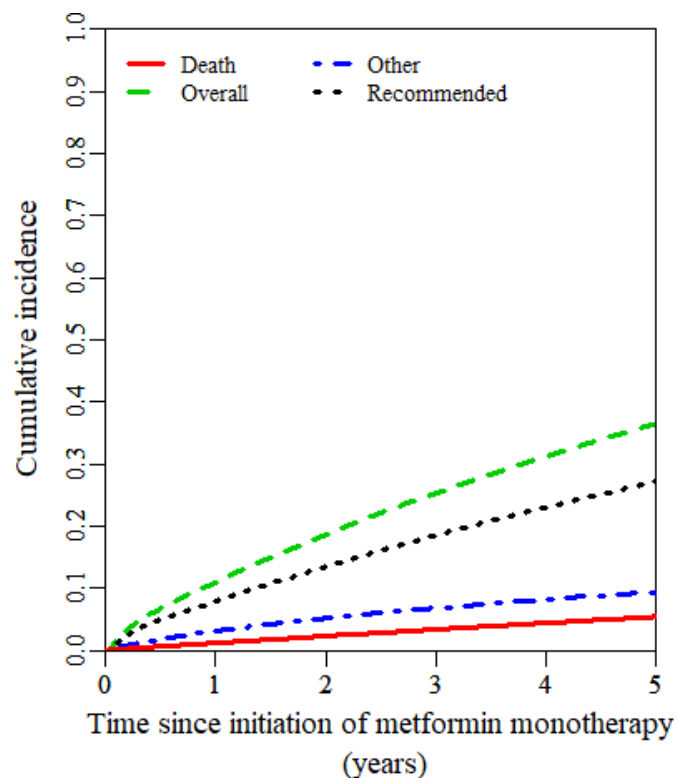


Figure 1 Time taken from initiation of metformin monotherapy to change to a second therapeutic regimen.

had used metformin plus a sulphonylurea as a second regimen moved to sulphonylurea monotherapy, while the majority of those on metformin plus insulin moved to

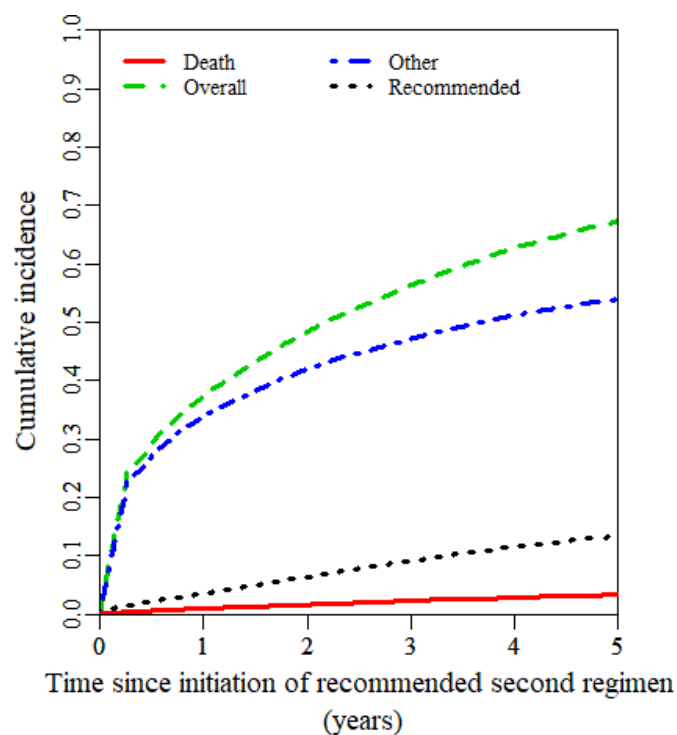


Figure 2 Time taken from initiation of a recommended second therapeutic regimen to change to a third therapeutic regimen.

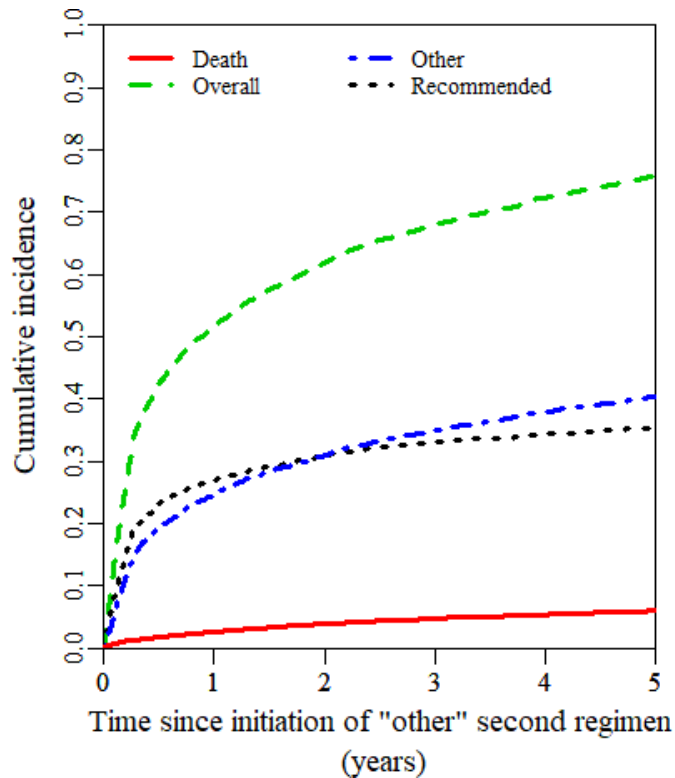


Figure 3 Time taken from initiation of an ‘other’ second therapeutic regimen to change to a third therapeutic regimen.

insulin alone, and the majority on sulphonylurea monotherapy moved to metformin plus a sulphonylurea. The proportions of cohort members who moved to second and third regimens increased with longer follow-up times, but the general patterns of regimen use remained the same. The corresponding sunburst plots for the pre-guideline and post-guideline periods are shown in online supplemental efigures 10 and 11.

We also undertook sensitivity analyses to investigate whether the high proportion of ‘other’ third therapeutic regimens among those who had received a recommended second regimen was likely to have been an artefact of how the regimens were constructed—for example, cohort members who appeared to have moved from *metformin monotherapy* to *metformin plus sulphonylurea* to *sulphonylurea monotherapy* might have been instructed by their doctors to switch from metformin monotherapy to sulphonylurea monotherapy, rather than to add the sulphonylurea to metformin. We therefore explored the impact on the cumulative incidence curves of excluding second and any subsequent therapeutic regimens with a duration of <15 days, <30 days and <60 days. While this slightly decreased the proportions moving to second and third regimens, the overall patterns in relation to the use of recommended and ‘other’ regimens were very similar to the cumulative incidence curves in the main analyses.

DISCUSSION

In this national cohort study of people who initiated metformin monotherapy for type 2 diabetes during a 9-year period, we found that relatively small proportions of cohort members moved to a second therapeutic regimen in the first few years of follow-up. The majority of these people received a second-line regimen recommended by contemporaneous New Zealand treatment guidelines (almost all metformin plus a sulphonylurea). Although most of those who moved to a third regimen from a recommended second regimen received an ‘other’ regimen, there was evidence of improvement over time, with a higher proportion transitioning to a recommended third regimen.

This study has several strengths. It is the first nationwide study in New Zealand to have undertaken an in-depth

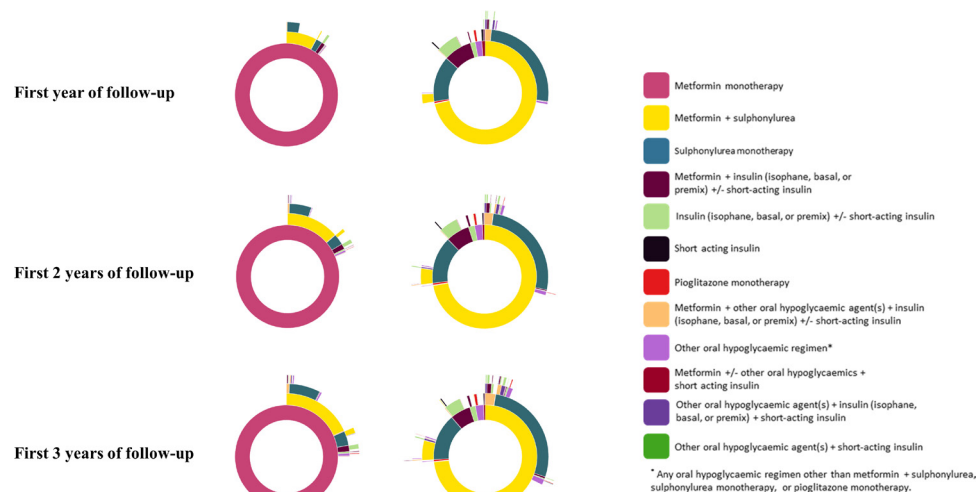


Figure 4 Proportions and sequence of use of unique therapeutic regimens in the first year, first 2 years and first 3 years following initiation of metformin monotherapy. The sunburst plots on the left illustrate the proportions of metformin monotherapy users (inner ring) who moved to a second regimen (second ring), the proportions who moved to a third regimen (third ring) according to the second regimen they had used, and so on, in the first year, first 2 years and first 3 years of follow-up. The plots on the right show, in more detail, the second regimens that were used (inner ring), as well as the subsequent regimens.

exploration of treatment pathways in people with type 2 diabetes over an extended period. The use of the Pharmaceutical Collection as a source of information about diabetes treatments is a further strength—the database contains records of subsidised dispensings of medicines for the entire population of New Zealand and it is likely that these records are virtually complete since pharmacists are not remunerated for such dispensings unless they submit a reimbursement claim. Although the Pharmaceutical Collection does not include medicines dispensed in hospital, it does include medicines prescribed at discharge as patients collect these from community pharmacies.

The study also has some limitations. First, we were unable to examine the use of antidiabetic drugs which were approved for use but not publicly funded during the study period as they were not included in the Pharmaceutical Collection. However, while three DPP-IV inhibitors (saxagliptin, sitagliptin and vildagliptin), a GLP-1 agonist (exenatide), and a sodium-glucose co-transporter 2 (SGLT2) inhibitor (dapagliflozin) were approved but unfunded,¹⁶ we expect that the proportionate use of these drugs would have been very small because of the associated financial burden for patients (personally paying the full costs of the medicines). Second, we did not have access to the results of HbA_{1c} tests and therefore were unable to explore the appropriateness of any change in treatment, or detect situations in which treatment should have been escalated but was not—the so-called therapeutic inertia which is increasingly causing concern internationally.¹⁷ Third, we did not have access to detailed clinical records so we were unable to determine whether people who received sulphonylurea monotherapy as a second regimen did so because of intolerance to metformin. The lack of clinical information also meant that we were solely reliant on the dispensing information to identify the therapeutic regimens used by cohort members. However, the sensitivity analyses suggest that our findings were unlikely to be an artefact of how we constructed the regimens. Fourth, we did not explore the impact of patient characteristics on treatment patterns, as the aim of the study was to provide a simple descriptive overview of treatment pathways in people who initiated metformin monotherapy as first-line treatment for type 2 diabetes. However, this could be investigated in future research. Fifth, we focused on the first exposure to unique regimens and did not look at usage patterns which included switching backwards and forwards between regimens. Future research could use sequence index plots to look at this in further detail. Finally, as this analysis did not include information about doses of medications, we are unable to comment on the possible relations between dosage and changes in treatment.

Internationally, several population-based studies have described the medications prescribed initially, and subsequently, for patients with type 2 diabetes.^{13–18–25} Some of these investigations focused on the use of individual drugs,^{13–18–20} while others, like this study, examined the use of regimens.^{21–25} However, only some of the studies

in the second group examined subsequent regimens according to the first regimen received.^{21–24} Consistent with our findings, the most common second regimen for patients who initiated treatment with metformin monotherapy in the Netherlands,^{21–24} the UK,^{23–24} Spain²⁴ and Ireland²² was metformin plus a sulphonylurea, although the proportions were lower than in our study. Conversely, different patterns were observed in France²⁴ and Italy.²⁴ However, direct comparisons between previous research and our study should be interpreted with caution because different calendar periods were examined and treatment guidelines regarding second-line and third-line therapy differed over time and between countries, as did the availability of new oral hypoglycaemic agents.

In conclusion, this study has provided a useful overview of how type 2 diabetes is being treated in New Zealand. It shows that real-world treatment patterns are complex and not always consistent with guidelines. One DPP-IV inhibitor (vildagliptin) and one SGLT2 inhibitor (empagliflozin) have recently been funded (in October 2018 and February 2021, respectively) and the methods employed in this project could be used in the future to ascertain whether the introduction of these drugs has an impact on treatment pathways in New Zealand.

Correction notice Joint authorship details has been added. "JG and LP are joint first authors."

Acknowledgements We thank Analytical Services at the Ministry of Health for providing the data for this study.

Contributors JG contributed to the design of the study, carried out the analyses, interpreted the findings and contributed to critical revision of the manuscript. LP conceived and designed the study, acquired the data, interpreted the findings and wrote the first draft of the manuscript. JZ provided statistical expertise and contributed to the design of the study, the interpretation of the findings and critical revision of the manuscript. DB provided data management expertise and programmed the study algorithm, derived the analysis dataset and contributed to critical revision of the manuscript. SH provided epidemiological expertise and contributed to the design of the study, the interpretation of the findings and critical revision of the manuscript.

Funding JG received an Otago Medical Research Foundation Summer Scholarship Award to undertake this work.

Disclaimer The funder had no role in the design of the study, or in the collection, analysis, or interpretation of the data, or in the decision to publish.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was conducted in accordance with the Declaration of Helsinki and received ethical approval from the University of Otago Human Ethics Committee (Health), reference number HD17/027.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data underlying the results presented in the study cannot be shared by the authors because of restrictions imposed by the New Zealand Ministry of Health. Researchers who meet the criteria for access to confidential data can make enquiries with the New Zealand Ministry of Health (data-enquiries@health.govt.nz).

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