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Duration and effectiveness of glucose-lowering regimens in the real world management of diabetes: Data from the Australian EXTEND45 Linked Cohort Study

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ABSTRACT

Background: Diabetes is a common condition that often requires increasing intensity of glucose lowering regimens. We describe the population trends in the intensity of regimens, and associations of achieved HbA1c and treatment persistence.
Methods: We performed an episode-based analysis of the EXTEND-45 dataset, assessing trends in glucose lowering therapy and the associated outcomes of HbA1c and treatment persistence. Trends from 2009 to 2014 were assessed for each intensity level of a glucose lowering therapy regimen, according to the year prescribed. Episodes were defined as the length of time that an individual adhered to a regimen through ongoing prescription, and this was used as to define persistence. Mean HbA1c were calculated for each episode. Persistence and HbA1c were compared across the different regimens of treatment intensity.
Results: The intensity of glucose lowering therapy remained stable over time with around one third of episodes utilising a single glucose lowering agent. Mean HbA1c was higher for insulin-based treatment (mean 7.9 % SD = 1.3 %), and lowest for episodes of no glucose lowering treatment (mean 6.3 % (SD = 0.8 %). Around half of participants achieved glycemic targets of 7 %. While there was considerable variation in persistence, the median persistence was around 3 months (94 days, IQR 51–201 days).
Conclusions: Therapeutic intensity for diabetes has remained stable over 9 years. Whilst there was considerable variability in persistence with glucose lowering regimens, the mean duration of all regimens was less than a year. Requirement for higher intensity treatment with insulin was related to poorer glycemic control.

1. Introduction

An estimated 1.2 million Australian adults were living with type 2 diabetes mellitus in 2014–2015 (AIHW, 2018). This highly prevalent, chronic disease is a progressive disorder, attributed to a decline in beta cell function, and is associated with a range of micro- and macrovascular complications, including nephropathy, retinopathy and peripheral neuropathy (Chatterjee et al., 2017). Optimal control of blood glucose levels with glucose lowering treatment control is a major component of complication prevention and treatment in diabetes management (National Institute for Healthcare Excellence (NICE), 2015; Buse et al., 2019). Whilst lifestyle modification is recommended for the initial management of diabetes, commencement of pharmacological treatment is often required to achieve relevant clinical glycaemic targets. Guidelines recommend initiating glucose-lowering treatment with a single glucose lowering agent and when clinical targets are not met, progressively uptitrating existing agents or adding additional agents and, ultimately, insulin to a patient's regimen,

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in order to achieve these targets (*General Practice Management of Type 2 Diabetes*: 2016–18, 2018; American Diabetes, A, 2018; Colagiuri, 2012).

Whilst diabetes therapy is directed towards achieving acceptable glycaemia, several factors influence prescribing practice in the real-world. Patient factors such as age, comorbidities and contraindications associated with level of renal function can all determine the optimal glucose-lowering therapy for an individual (DUSC, 2017). In an Australian context, the availability of novel agents and their recommendations and subsidy status on the Pharmaceutical Benefits Scheme (PBS) for example with the introduction of novel agents such as dipeptidyl peptidase-4 (DPP4) inhibitors, and subsequent approval for PBS listing as dual therapy in 2009 directs clinician choices when considering optimal pharmacotherapy for patients with diabetes. This is relevant when considering uptitration of intensity of glucose lowering agents.

The threshold for optimal glycaemia is defined in major clinical guidelines currently as a glycated haemoglobin (HbA1c) level between 6.5 and 7 % (National Institute for Healthcare Excellence (NICE), 2015; *General Practice Management of Type 2 Diabetes*: 2016–18, 2018; American Diabetes, A, 2018; Draznin et al., 2022). These targets are based on evidence derived from large-scale clinical trials and, initially, an analysis of a seminal observational study comparing the effect of HbA1c level on complication risk (Tandon et al., 2012; Stratton et al., 2000; UK Prospective Diabetes Study (UKPDS) Group, 1998; Duckworth et al., 2009; Group, T.A.t.C.C.R.i.D.S, 2008; Group, T.A.C, 2008). However, when considering a reduction in cardiovascular complications, in the 3 major studies that were designed to evaluate the effect of tight glycaemic in older patients with diabetes and high cardiovascular risk there was no observed reduction in all-cause or cardiovascular mortality (Duckworth et al., 2009; Group, T.A.t.C.C.R.i.D.S, 2008; Group, T.A.C, 2008). A large meta-analysis of 4 major glucose lowering trial did demonstrate a reduction in clinical kidney events and eye complications over a 5-year period (Zoungas et al., 2017). Furthermore, an analysis of outcomes from the ACCORD trial where participants randomised to receive intensive management with a target HBA1c of 6 % resulted in a delay in onset of some microvascular complications such as macroalbuminuria, eye complications and peripheral neuropathy; excess cardiovascular mortality, hypoglycaemic and weight gain was noted in this group (Ismail-Beigi et al., 2010). Therefore, a patient centred approach, allowing for individualisation of targets is now also incorporated into guidelines, particularly when considering the implications of comorbidities, prognosis and complications such as hypoglycaemia in an older patient (Draznin et al., 2022; Inzucchi et al., 2015; Inzucchi et al., 2014).

Different glucose-lowering drugs have consistently led to a similar reduction in HbA1c of around 0.7–1.0 percentage points compared with placebo (Bennett et al., 2011). The average HbA1c achieved in these clinical trials is generally reported as the outcome, however the time scale for achieving this in a real-world setting is less defined. Additionally, evidence is limited for direct comparisons of effectiveness between different intensities of pharmacotherapy (e.g., monotherapy versus dual therapy), although intensification of therapy has been demonstrated to maintain glycaemic control in a patient group with an expected increase in treatment requirements (Colagiuri, 2012; Bennett et al., 2011; Best et al., 2012). Similarly, evidence for real world tolerability of glucose lowering treatments is limited, particularly in the context of achieving optimal glycaemia. Persistence with therapy is a proxy for tolerability and has been utilised as an outcome in other real-world analyses (Flory et al., 2018; Iglay et al., 2015). Knowledge of persistence of pharmacotherapies of varying intensity in the community may assist in determining their real-world tolerability, in the context of current prescribing patterns and level of treatment intensity.

The EXamining ouTcomEs in chroNic Diseases in the 45 and Up Study (EXTEND45) Study is a longitudinal large administrative data set of linked sources that combines information from the 45 and Up Study – a population-based cohort study of healthy ageing – with various routinely-collected datasets (Foote et al., 2020; Banks et al., 2008). Through linking pharmaceutical dispensing data with biochemical pathology and hospital data, it provides a comprehensive overview of contemporary prescribing practice in Australia and then links this to other parameters such as glycaemic control and persistence. The unique data linkage ensuring complete follow up of participants in this study differs to other diabetes cohorts such as the National Health and Nutrition Survey (NHANES), which used repeated cross-sectional cohorts of adults over a 20-year period and the Australian Diabetes, Obesity and Lifestyle Study (AusDiab), which followed a longitudinal cohort of adults over 25 years and were limited by steadily declining response rates (Stephanie, 2013; Fang et al., 2021).

In this analysis, we examined real-world prescribing patterns of glucose-lowering therapy regimens for diabetes between 2006 and 2014, according to the intensity of therapy (mono-, dual-, triple therapy, and insulin). We then compared the persistence and achieved HbA1c for each intensity of treatment.

2. Methods

2.1. Overview of the EXTEND45 study

The EXTEND45 Study is a population-based longitudinal linked data study built on the Sax Institute's 45 and Up Study of residents aged 45 years and older in the state of New South Wales (NSW), Australia (n = 267,153) (Foote et al., 2020). Detailed descriptions of the 45 and Up Study, have been published elsewhere (Inzucchi et al., 2014). Briefly, between 2006 and 2009, potential participants were randomly sampled from the Services Australia (formerly Australian Government Department of Human Services (DHS)) enrolment database (Banks et al., 2008), invited to join the study, complete a baseline study questionnaire and consent to data linkage to health databases. The EXTEND45 Study combines information from the 45 and Up Study baseline questionnaire via data linkage to administrative and routinely collected health datasets including the Pharmaceutical Benefits Scheme (PBS) (https://www.pbs.gov.au/info/about-the-pbs#What_is_the_PBS, 2022) and Medicare Benefits Schedule (MBS) (Schedule, M.B, 2017), both held by Services Australia, and community pathology provider databases (Foote et al., 2020). The PBS data includes claims for all subsidised pharmaceutical products nationwide while the MBS data includes all claims for subsidised medical and diagnostic services provided by medical and other health service providers. MBS and PBS data were provided by Services Australia and linked to 45 and Up Study by the Sax Institute. All other data sources were linked by the Centre for Health Record Linkage (CHeReL) (https://www.cherel.org.au/) (Lawrence et al., 2008). Diagnostic information was coded according to ICD-10-Australian Modification, and was sourced from the Admitted Patient Data Collection database (APDC), which captures inpatient separations from all public, private and repatriation hospitals as well as day procedure centres and aged care facilities. All data was housed in a Secure Unified Research Environment (SURE) for provision of secure data access.

2.2. Cohort selection and temporal windows

For the present study, participants were included if they had at least one pathology test in the linked pathology datasets and were identified as having incident or prevalent diabetes. Diabetes was defined according to the presence of any of five pre-specified criteria: 1) pathology record of HbA1c result ≥6.5 %, 2) fasting serum glucose >7.0 mmol/L 3) random serum glucose>11.1 mmol/L in accordance with accepted international guidelines, 4) a dispensation record of an oral glucose lowering (OGL) agent or insulin/insulin analogue within the PBS, or, 5) self-reported diabetes on the baseline questionnaire. The subtype of diabetes was not defined by using this method i.e. Type 1 or other forms of diabetes were not excluded.

The start date for participants with prevalent diabetes was their date of enrolment into the 45 and Up Study. The study start date for participants with incident diabetes was the date that they first met our pre-specified definition of diabetes, or, provided that they had met our criteria, the date on which they had received an MBS claim for diabetes education, whichever was earlier. The study end date for each participant was date of death, or the date on which their data ceased or 30th June 2014, whichever occurred sooner.

2.3. Identification of glucose-lowering treatment episodes and regimens

Prescribing patterns of glucose-lowering therapy regimens were identified for all treatment episodes among the study participants. Treatment episodes were defined as the period that a participant adhered to a particular regimen of pharmacotherapy without changes or breaks in treatment of two or more standard coverage days (SCD). SCDs relate to the number of treatment days covered by a single script and vary by drug agent. When drugs had different possible dosing possibilities a conservative approach was taken, and the longest prescription duration/lowest dose was assumed. Episodes were attributed to the calendar year in which they commenced and were categorised into six regimens of glucose-lowering treatment therapy that align with those used in the Drug Utilisation Sub-Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee (PBAC) analysis on drugs for Type 2 diabetes (DUSC, 2013), i.e.:

1. Never treated with pharmacotherapy
2. Monotherapy (one oral glucose lowering [OGL] agent)
3. Dual therapy (two OGL agents)
4. Triple or more therapy (three or more OGL agents)
5. Insulin based treatment (+/− one or more OGL agent)
6. Treatment break (previously treated but not currently treated with OGL)

Only episodes commencing before 30 June 2014 or ending before 30 June 2015 were included. Further information regarding the medication classes in each regimen is contained in Supplementary Table 2.

2.4. Outcomes of interest

The three outcomes of interest; temporal trend, achieved HbA1c and treatment persistence, were compared across the six regimens for glucose lowering treatment. Achieved HbA1c was calculated for each treatment episode and was defined as the unweighted mean of all HbA1c test results recorded in the time window lasting from 4 weeks after the beginning of an episode to 4 weeks following the conclusion of an episode. The time windows were selected to reflect biological plausibility in the attribution of an HbA1c level to a treatment regimen. For individuals never on pharmacotherapy, the achieved HbA1c was calculated as the mean of all available HbA1c results throughout their follow-up period. Treatment persistence was defined as the length of time, in days, that a patient continued with a particular regimen of pharmacotherapy without any breaks.

2.5. Statistical analysis

Treatment episode regimens were described by calendar year. Achieved mean HbA1c and persistence for each episode were analysed unadjusted and age-adjusted using *t*-tests if normally distributed, and Wilcoxon rank sum test if non-normally distributed. All statistical analyses were performed using SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC).

2.6. Ethical approval

As part of their consent to participate in the *45 and Up Study*, participants agreed to have their baseline questionnaire data linked to other health databases (Banks et al., 2008). Ethical approval for the *45 and Up Study* was obtained from the University of New South Wales Human Research Ethics Committee with the following (HC05035–26/07/2005–25/07/2010, HC10186–15/06/2010–15/06/2015). The EXTEND45 Study was granted ethical approval by the NSW Population and Health Services Research Ethics Committee (HREC/13/CIPHS/69).

3. Results

We identified 24,236 individuals with diabetes, of whom 16,220 had prevalent diabetes, and 8016 developed incident diabetes between 2006 and 2014 (Supplementary Table 1). Just over one quarter of individuals (26.9 %, $n = 6523$) were never treated with pharmacotherapy during the study period (Supplementary Table 1). The mean age of participants in the study was 66.3 years (SD 10.7 years) and 44.9 % were female (Supplementary Table 1).

3.1. Prescribing patterns in NSW (2006–2014)

Between January 2006 and December 2014, 149,532 treatment episodes were identified. From those episodes, 143,009 were identified among the 17,713 individuals who had at least one PBS dispensation for a glucose-lowering agent during the study period. The most common glucose lowering regimen was monotherapy (33.1 %) followed by insulin-based therapy (21.7 %), treatment break (20.3 %) and dual therapy (17.0 %). Only 4.4 % of episodes constituted of a regimen where the individual had never received pharmacotherapy and 4.0 % involved three or more therapies (Table 1).

The relative proportions of the different glucose lowering regimens remained relatively stable over time (Fig. 1).

3.2. Levels of achieved HbA1c for different treatment regimens

In episodes involving use of glucose lowering treatment, the monotherapy regimens had the lowest mean HbA1c (mean = 6.9 % SD = 1.1 %). %). Dual therapy regimens, and triple or more regimens yielded a mean HbA1c of 7.3 % (SD = 1.1 %) and 7.4 % (SD = 1.1 %), respectively. Insulin-based regimens had the highest mean HbA1c (mean 7.9 % SD = 1.3 %) The mean HbA1c for participants who never received pharmacotherapy was 6.3 % (SD = 0.8 %) (Table 1).

3.3. Treatment persistence

Overall, the median persistence, as defined by episode duration, was <4 months, for those receiving glucose lowering pharmacotherapy. Persistence was highest for insulin based regimens (median = 108 days, IQR 51–169 days) in those receiving glucose lowering pharmacotherapy. Persistence was shortest for regimens involving three or more glucose lowering therapies (median = 54 days, IQR 29–148 days). Mean persistence for Insulin-based regimens and monotherapy regimens were similar (mean = 164 days) but differed in their median (Insulin-based median = 108 days and monotherapy median = 76 days).

4. Discussion

In a population-based cohort of 24,236 adults with diabetes mellitus, pharmacotherapy was prescribed for around three-quarters of participants. The prescribing patterns for different treatment intensities did not vary over the study period. Overall the mean HbA1c for monotherapy and dual therapies lay between 6.9 and 7.3 %, meaning that while a considerable number of patients in the real world are achieving guideline-recommended control, a considerable number appear to be exceeding these targets. Perhaps not surprisingly, glycaemic control, as assessed by HbA1c, was worse overall in those receiving an insulin-based regimen,

Table 1
Intensity of treatment regimen by number of episodes, length of persistence and achieved HbA1c.

Intensity of treatment regimen	Total number of episodes	Median number of days persistence (*IQR*)	Mean number of days persistence (*SD*)	Mean HbA1c % (*SD*)
No pharmacotherapy	6523	1996 *(1055–2157)*	1653 *(762)*	6.3 *(0.8)*
Treatment break	30,350	94 *(62–191)*	188 *(235)*	6.9 *(1.2)*
Monotherapy	49,475	76 *(51–169)*	164 *(270)*	6.9 *(1.1)*
Dual therapy	25,355	84 *(50–197)*	176 *(250)*	7.3 *(1.1)*
Triple or more therapy	6035	54 *(29–148)*	132 *(254)*	7.4 *(1.1)*
Insulin based	31,794	108 *(51–169)*	164 *(205)*	7.9 *(1.3)*
Overall	149,532	94 *(51–201)*	235 *(421)*	7.1 *(1.2)*

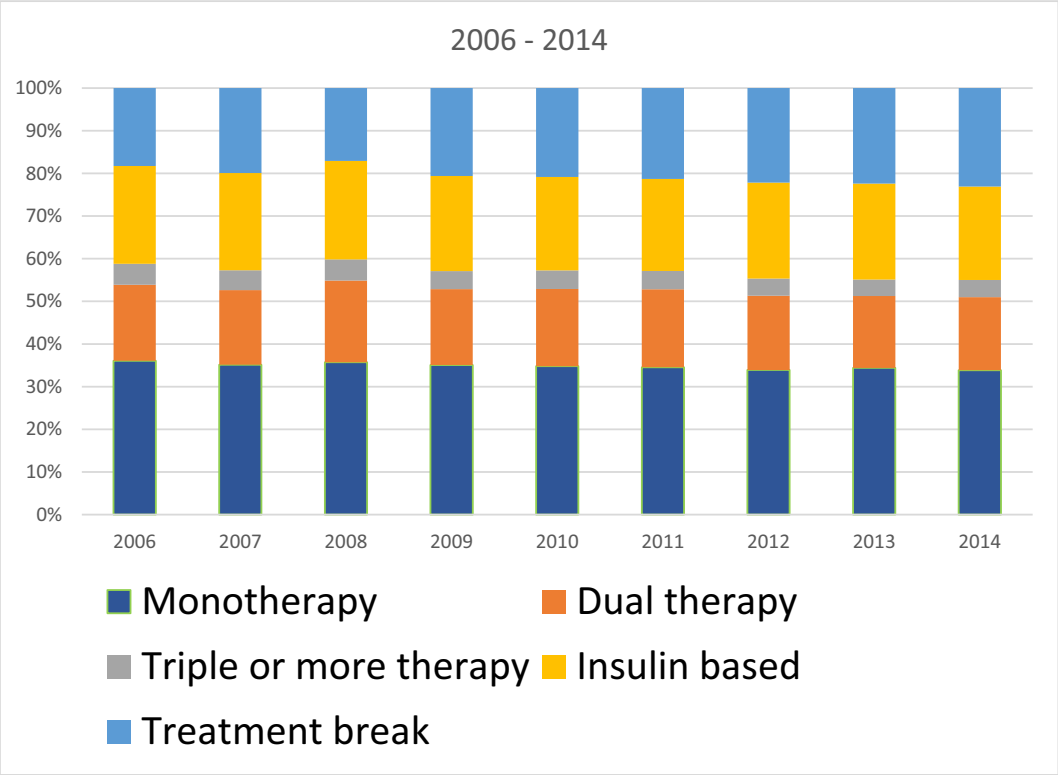

Fig. 1. Proportion of episodes for each regimen of treatment intensity by year.

the highest intensity of treatment with insulin. In this episode-based analysis, the average persistence to oral glucose-lowering regimens shortened as the intensity of treatment increased. The longest persistence for those receiving pharmacotherapy was to insulin-based regimens which do represent the most intensive regimen. However, it is clear there is a wide variation in persistence to any of the regimens. The results have a number of implications for clinical practice. When considering persistence with therapy, practitioners should consider a regimen regarding tolerability and the impact this may have on persistence with therapy, and balance this with achieved HbA1c to monitor for efficacy. Additionally, the relatively short persistence highlights that at a health systems level, treatment regimens are dynamic and careful consideration needs to be given for measures to promote adherence.

Patients who required the greatest intensity of therapy with insulin-based glucose lowering regimens had the highest mean HbA1c. This may reflect severity of disease, or be a surrogate marker for beta cell failure, and therefore the requirement for insulin (Chatterjee et al., 2017). Other explanations include patient factors such as tolerance to therapy or failure to adhere to therapy when glucose lowering therapy is insulin based particularly when the competing risk of hypoglycemia is considered against optimal glycemia.

When comparing treatment intensities, we separated patients who were never on pharmacotherapy during our study to those who were on a treatment break to differentiate these two subgroups. Whilst the mean HbA1c was lower in patients who were never on pharmacotherapy, the mean HbA1c in patients on a treatment break still reflected good control, at 6.9 %. One potential hypothesis is the de-escalation of therapy occurring due to the patient achieving acceptable control prior to the treatment break. Whilst another potential explanation for a treatment break is non-adherence with therapy, most patients in this subgroup appear to continue to achieve an acceptable HbA1c Additionally, whilst our cohort comprised of a high proportion of older participants whereby overly tight glycaemic control may be less beneficial, or even deleterious; glycemic targets appeared to be achieved for most treatment intensities.

The achieved HbA1c was lower for episodes that were for no pharmacotherapy, potentially indicating stable or well controlled disease that did not require a change in therapy. Our cohort comprised of community dwelling participants, and it is possible that many patients with milder, quiescent or even resolved disease are captured in our study population due to the broad diagnostic criteria. A group of patients with milder disease is also reflected by the lower average HbA1c and high numbers of patients who were not on any pharmacotherapy. The mean HbA1c in our cohort was 7.14 %, which was lower compared to many other cohort studies or clinical trials (Forbes et al., 2018; Mathur et al., n.d.; Palmer et al., n.d.), therefore we may have captured a population including those with earlier, less severe disease.

Approximately 8 % (n = 4188) of monotherapy episodes involved agents other than metformin or a sulfonylurea. However, of these, acarbose, the only other oral agent with an unrestricted listing during this time, accounted for only a very small number episodes during our study. We noted multiple episodes of 3 or more oral agents, which were not subsidised by the PBS until after the study date, with the exception of a combination of metformin, a sulfonylurea and pioglitazone (DUSC, 2017). This implies that PBS restrictions are not always adhered to in prescribing practice.

A key strength of this study is the use of real-world, routinely collected data to examine prescribing practice. Our study design was less vulnerable to participant loss to follow up as it did not require repeat clinical review. We utilised multiple data sources using routinely collected information that was then triangulated to produce clinically relevant information.

Our cohort utilised inclusion criteria to capture individuals with diabetes who were identified using multiple data sources, thereby not restricting our analysis to individuals who self-report the condition only. PBS data captures prescriptions of pharmacotherapy subsidised for diabetes in Australia therefore we have high coverage of our main study factor. All pharmacotherapy for diabetes were above the threshold for payment so would have attracted a PBS subsidy, hence complete coverages for all available subsidised agents.

Our study also has some limitations. Firstly, the 45 and Up Study, upon which the EXTEND45 Study is built, overrepresented participants over the age of 80 and in rural areas (Up Study, 2008). Achieved HbA1c could only

be assessed in individuals with a linked pathology result, however in a previous analysis representation still appears adequate (Zhang et al., 2020). This study design has limitation common to all univariate analysis whereby causality cannot be inferred. Confounding by indication bias is likely, particular with reference to study outcomes such as achieved HbA1c.

In this real-world cohort, it is not possible to differentiate between patients with Type 1, Type 2 and other subtypes of diabetes. The cohort may therefore include some participants with Type 1 diabetes. The exact prevalence of Type 1 diabetes in Australia is not known, but estimated at 9 % of patients with diabetes, and lower prevalence in older patients (*AIHW Fact Sheet Incidence of Insulin-treated Diabetes in Australia*, 2016). Additionally, only around a quarter of episodes were for basal bolus regimens, and some of these participants may have Type 2 or other forms of diabetes. Therefore, whilst a relatively small proportion of patients requiring insulin may have Type 1 diabetes in this cohort, this remains a source of internal bias due to heterogeneity of disease when analysing outcomes.

5. Conclusions

Intensity of treatment regimens for diabetes has remained stable in NSW over a nine-year period. A high proportion of this older cohort of community dwelling participants achieved glycemic targets for diabetes. Patients requiring insulin therapy had the worst glycaemic control, and this is likely to reflect severity of disease. Persistence with therapy is heterogeneous, and not related to glycemic control or intensity of therapy and the factors driving this variation warrant further investigation.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.endmts.2023.100135.

Data availability

Data will be made available on request.

Declaration of competing interest

Professor Sophia Zoungas reports payment to her institution (Monash University) – Eli Lilly Australia Ltd, Boehringer-Ingelheim, MSD Australia, AstraZeneca, Novo Nordisk, Sanofi, Servier outside the submitted work. Professor Meg Jardine is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship; is responsible for research projects that have received unrestricted funding from Baxter, Amgen, Eli Lilly, and Merck Sharpe Dohme; serves on a Steering Committee sponsored by CSL; has served on advisory boards sponsored by Akebia, Baxter, Boehringer Ingelheim, and Vifor; and has spoken at scientific meetings sponsored by Janssen and Amgen, with any consultancy, honoraria, or travel support paid to her institution.

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