MR STEPHEN WOOD (Orcid ID : 0000-0002-9256-2216)

Article type : Research Article

Diabetic Medicine

Article type: Research Article

Article number: DME-2019-00264

Copy editor: Maria Hale

Proofs to: Stephen.Wood@monash.edu

Figures: 0; Tables: 2; Equations: 0; References: 27

Author running head: S. J. Wood *et al*.

Short title running head: Type 2 diabetes treatment initiation in Australia

Research Article: Epidemiology

Pharmacological treatment initiation for type 2 diabetes in Australia: are the guidelines being followed?

S. J. Wood[1], D. J. Magliano[2,3], J. S. Bell[1,4,5], J. E. Shaw[3], C. S. Keen[1] and J. Ilomäki[1,2]

[1]Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences and [2]Department of Epidemiology and Preventative Medicine, Monash University, and [3]Baker Heart and Diabetes Institute, Melbourne, [4]NHMRC Cognitive Decline Partnership Centre, Hornsby Ku-ring-gai Hospital, Hornsby, and [5]Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia

Correspondence to: Stephen J. Wood. E-mail: Stephen.Wood@monash.edu

What's new?

- Metformin or sulfonylurea monotherapy are guideline-recommended initial treatments for type 2 diabetes in Australia.
- Some 86% of Australians with type 2 diabetes received metformin monotherapy, 5% sulfonylurea monotherapy, 2% other monotherapy and 8% combination therapy as initial pharmacotherapy.
- Initial sulfonylurea monotherapy prescribing has become less frequent in recent years.
- People initiating combination therapy were more likely to be men and to have fewer comorbidities.
- Prescribing patterns for type 2 diabetes medications in Australia indicate a high level of concordance with clinical practice guidelines.

Abstract

Aim To determine the patterns and predictors of pharmacological treatment initiation for type 2 diabetes and whether treatment initiation is consistent with Australian clinical practice guidelines that recommend metformin monotherapy.

Methods Individuals aged 40–99 years initiating a non-insulin type 2 diabetes medication between July 2013 and February 2018 were identified from a 10% random national sample of pharmacy dispensing data. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the predictors of initiating sulfonylurea monotherapy, non-guideline monotherapy and combination therapy compared with metformin monotherapy. Predictors included age, sex, initiation year and comorbidities determined using the Rx-Risk comorbidity index.

Results Of the 47 860 initiators, [47% women, mean age 60.7 (SD 12.1) years], 85.8%, 4.6%, 1.9% and 7.7% received metformin monotherapy, sulfonylurea monotherapy, non-guideline

monotherapy and combination therapy, respectively. Increasing age was associated with increasing odds of initiating sulfonylurea monotherapy and non-guideline monotherapy. Combination therapy initiation was less likely in women (OR 0.74, 95% CI 0.69–0.79) and people with more comorbidities (e.g. OR 0.36, 95% CI 0.29–0.44 for seven or more comorbidities vs. no comorbidities) but more likely in congestive heart failure (OR 1.42, 95% CI 1.22–1.65), cerebrovascular disease (OR 1.50, 95% CI 1.32–1.69) and dyslipidaemia (OR 1.29, 95% CI 1.19–1.40).

Conclusion Treatment initiation in Australia is largely consistent with clinical practice guidelines, with 86% of individuals initiating metformin monotherapy. Initiation on combination therapy was more common in men and in those with fewer comorbidities.

<H1>Introduction

In recent years, there has been a rapid increase in the use and cost of dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium–glucose cotransporter-2 (SGLT-2) inhibitors and glucagon like peptide-1 (GLP-1) agonists [1]. Currently, it is unclear to what extent these treatments are prescribed, either alone or in combination with other anti-hyperglycaemic agents, as initial treatment for type 2 diabetes. The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) advise that dual therapy should be initiated if HbA_{1c} > 58 mmol/mol (7.5%) [2,3], whereas the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) advise that treatment should be initiated with two type 2 diabetes medications concurrently if HbA_{1c} ≥ 75 mmol/mol (9.0%) [4]. Conversely, Australia's general practice guidelines and Therapeutic Guidelines (TG) make no recommendations about initiating treatment with combination anti-hyperglycaemic agents, regardless of HbA_{1c} levels [5,6]. Australian guidelines also recommend that patients initially trial either metformin or sulfonylurea monotherapy, with progression to other type 2 diabetes therapies reserved for those who cannot tolerate or do not respond sufficiently to initial therapy [5,6].

Metformin monotherapy is generally preferred as first-line treatment because it is cost-effective and does not cause hypoglycaemia or weight gain [5]. It is associated with lower cardiovascular mortality when compared with sulfonylureas and may reduce the risk of myocardial infarction, stroke and atrial fibrillation [7]. One reason for not initiating treatment with metformin is concern over metformin-induced lactic acidosis. Meta-analyses have demonstrated that metformin is not associated with substantially increased lactate concentrations in people with mild-to-moderate chronic kidney disease but acknowledge

there is insufficient evidence in severe chronic kidney disease [8]. In 2016, the US Food and Drug Administration (FDA) revised the product information to contraindicate metformin prescribing in patients with estimated glomerular filtration rate (eGFR) < 30 ml min 1.73 m^{-2}, whereas it was previously also contraindicated in mild and moderate renal impairment [9]. Both metformin and sulfonylureas are reimbursed as initial treatment through Australia's Pharmaceutical Benefits Scheme (PBS), with sulfonylureas an option when metformin is contraindicated or poorly tolerated [5]. Other classes of medications such as thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 agonists are not considered first-line. To attract government reimbursement for patients prescribed these medications, prescribers are required to confirm that either metformin or a sulfonylurea has been used and was either not tolerated or not sufficient to allow the patient to reach their glycaemic target.

In Australia, metformin-containing fixed-dose combination products with sulfonylureas, thiazolidinediones, DPP-4 inhibitors and SGLT-2 inhibitors are available. Up to 22% of metformin–glibenclamide initiations among Australian veterans were in people with no history of using either component [10]. Expert opinion in Australia and internationally is divided on whether treatment should always be initiated with metformin monotherapy in people presenting with poor glycaemic control. This is because it is unclear whether the advantages of early, aggressive treatment are outweighed by higher costs and possible adverse events [11].

No previous studies have investigated the patterns of treatment initiation for type 2 diabetes in the general Australian population. The objective of this study is to determine the patterns and predictors of treatment initiation for type 2 diabetes in Australia and whether treatment initiation is consistent with current clinical practice guidelines.

<H1>Participants and methods

<H2>Study design, data source and study population

We conducted a population-based study on predictors of type 2 diabetes medication initiation between July 2013 and February 2018. We utilized data from a 10% simple random sample of Australia's PBS. These data are considered nationally representative of dispensing for all Australia's 25 million population and have been widely used in drug utilization research [12].

Under the PBS, Australian citizens, permanent residents and people from countries with reciprocal healthcare agreements are entitled to receive a broad range of government-

subsidized medications. The data contain information about each dispensed medication's PBS item code, strength, dispensed quantity, date of prescribing and date of supply. The data contain also information on the recipients' year of birth, sex, year of death and concessional status.

The study population included adults aged between 40 and 99 years who had been dispensed a non-insulin medication for type 2 diabetes between 1 July 2013 and 28 February 2018. The former date was chosen because the 10% PBS sample does not contain records for medications priced below co-payments prior to 1 July 2012. All people who initiated with insulin were excluded because we could not exclude the possibility that these people had type 1 diabetes. We also excluded individuals under 40 years to minimize the number of people in our data who were prescribed metformin for polycystic ovarian syndrome. A study from the United Kingdom showed that the incidence rate ratio (IRR) for metformin prescribing in women with polycystic ovarian syndrome is very low in the 40–44 vs. 20–24 years age group [IRR 0.17, 95% confidence intervals (CI) 0.16–0.18] [13].

<H2>Measures and definitions

Medication initiation for type 2 diabetes was defined as the first dispensing (index date) of a medication with Anatomical Therapeutic Chemical (ATC) code A10B between 1 July 2013 and 28 February 2018 and no record of anti-diabetic medication (ATC code A10) dispensing during one year prior to the index date. Type 2 diabetes medications at initiation were classified as: (1) metformin monotherapy (A10BA); (2) sulfonylurea monotherapy (A10BB); (3) non-guideline monotherapy, acarbose (A10BF), thiazolidinediones (A10BG), DPP-4 inhibitors (A10BH), GLP-1 agonists (A10BJ) or SGLT-2 inhibitors (A10BK and A10BX), and 3) combination therapy (A10BD) and when people were dispensed more than one individual type 2 diabetes medication on their index date.

The Rx-Risk Index (Appendix S1), was used to identify each person's comorbidities by using medication dispensing during the year prior to the index date as a proxy for comorbidities. This index has been validated for use with Australian PBS data and permits a comorbidity score for an individual to be calculated [14]. In addition to the comorbidity score, individual comorbidities considered to be important predictors of initial type 2 diabetes treatment were considered separately. These included atrial fibrillation, cerebrovascular disease, congestive heart failure, depression, dyslipidaemia, hypertension, ischemic heart disease/angina and ischemic heart disease/hypertension. End stage renal disease was not included in the multivariate analysis because the number of individuals in this category was too low. We considered cardiovascular comorbidities because the Australian guidelines advise

consideration of cardiovascular disease when selecting a type 2 diabetes medication and recommend that metformin should be used with caution in people with cardiac disease [5]. An individual comorbidity was included in the final model if the unadjusted *P*-value associated with the odds ratio (OR) was < 0.1.

<H2>Statistical analysis

Baseline characteristics were presented as means with standard deviations (SD) or as a frequency and percentage. Predictors of treatment initiation were estimated using multinomial logistic regression. Adjusted ORs and 95% CI were estimated for predictors of sulfonylurea monotherapy, non-guideline monotherapy and combination therapy compared with metformin monotherapy. All analyses were conducted using the statistical software package SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). This study was approved by the Monash University Human Research Ethics Committee. The study protocol and final manuscript was approved by Australian Government Department of Human Services.

<H1>Results

<H2>Cohort characteristics

Of the 47 860 people who initiated type 2 diabetes medications, 85.8% initiated metformin monotherapy, 4.6% sulfonylurea monotherapy, 1.9% non-guideline monotherapy and 7.7% combination therapy. The mean age at the time of medication initiation was 60.7 (12.1) years (Table 1). The mean ages of people initiating metformin monotherapy, sulfonylurea monotherapy, non-guideline monotherapy and combination therapy were 60.3 (11.8), 67.7 (13.3), 65.1 (12.5) and 60.1 (12.1) years, respectively.

Women accounted for 47.8% of those initiating metformin monotherapy, 45.4% of sulfonylurea monotherapy, 47.5% of non-guideline monotherapy and 38.2% of combination therapy.

In the group initiating non-guideline monotherapy, DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 agonists were dispensed to 52.0%, 21.5% and 12.3% of individuals, respectively. Characteristics of people prescribed each class of non-guideline monotherapy are provided (Appendix S2) but were not included in the multinomial logistic analysis due to insufficient numbers. Gliclazide constituted 87% of all sulfonylurea monotherapy initiations. Of those who initiated a combination therapy, 54% initiated a fixed-dose combination product and 97% were combinations with metformin. Of the combination therapy initiators, 92.3% initiated with two medications, 7.2% with three medications and 0.6% with more than three medications.

The mean (SD) number of estimated comorbidities in the metformin monotherapy, sulfonylurea monotherapy, non-guideline monotherapy and combination therapy groups were 3.9 (2.5), 4.9 (3.0), 4.4 (2.9) and 3.6 (2.6), respectively.

<H2>Predictors on type 2 diabetes treatment initiation

There was a graded association between age and odds of initiating with either non-guideline monotherapy or sulfonylurea monotherapy, with people aged ≥ 80 years compared with those aged 40–49 years having more than three times the odds of initiating a non-guideline monotherapy (OR 3.37, 95% CI 2.56–4.43) and almost five times the odds of initiating sulfonylurea monotherapy (OR 4.95, 95% CI 4.15–5.91) (Table 2). The association between age and initiating combination therapy, however, was less clear. Women were less likely than men to initiate combination therapy (OR 0.74, 95% CI 0.69–0.79).

Commented [MH1]: TS: Insert Table 2 near here

Compared with people with no comorbidities, people with one to three comorbidities (OR 0.56, 95% CI 0.49–0.64), four to six comorbidities (0.39, 95% CI 0.33–0.45) and seven or more comorbidities (0.36, 95% CI 0.29–0.44) had lower odds of receiving combination therapy.

Congestive heart failure (OR 1.59, 95% CI 1.37–1.83), atrial fibrillation (OR 1.30, 95% CI 1.13–1.50) and cerebrovascular disease (OR 1.29, 95% CI 1.13-1.47) were associated with higher odds of initiating sulfonylurea monotherapy.

Congestive heart failure (OR 1.42, 95% CI 1.22–1.65), cerebrovascular disease (OR 1.50, 95% CI 1.32–1.69) and dyslipidaemia (OR 1.29, 95% CI 1.19–1.40) were associated with higher odds of initiating combination therapy. Depression was associated with lower odds of initiating sulfonylurea monotherapy (OR 0.81, 95% CI 0.72–0.91) and combination therapy (OR 0.86, 95% CI 0.78–0.95). Dyslipidaemia was associated with lower odds of initiating sulfonylurea monotherapy (OR 0.84, 95% CI 0.76–0.93) and non-guideline monotherapy (OR 0.83, 95% CI 0.71–0.96).

Compared with 2013/2014, the odds of initiating with sulfonylurea monotherapy were lower in 2014/2015 (OR 0.78, 95% CI 0.69–0.88), 2015/2016 (0.69, 95% CI 0.61–0.78) and 2016/2017 (0.58, 95% CI 0.50–0.66). There was no clear change in the odds of initiating non-guideline monotherapy or combination therapy over the study period.

<H1>Discussion

The main finding of our study was that 86% of people initiate treatment with metformin, suggesting a high concordance with clinical practice guidelines. This is consistent with metformin having established long-term safety, favourable adverse event profile and low risk of weight gain or hypoglycaemia [5]. The result is also likely to reflect prescribers'

familiarity with this medication because it has been the first-line treatment for type 2 diabetes for many years in Australia.

The decreasing odds of initiating with sulfonylurea monotherapy over time is consistent with research by Wilkinson *et al*. [15] that reports decreased sulfonylurea prescribing in the UK in recent years. Among those who initiated sulfonylureas, gliclazide constituted 87% of initiations. This may be because gliclazide is specifically listed in the Australian diabetes general practice guidelines as being the only sulfonylurea that does not increase cardiovascular risk when used as monotherapy compared with metformin [5]. It is also likely to reflect longstanding prescriber familiarity with this medication. There was no apparent trend in the initial prescribing of non-guideline monotherapies, although it is known to be increasing overall [1]. Data in Appendix S2 indicate that initial prescribing of SGLT-2 inhibitors is increasing, possibly demonstrating prescribers' increasing familiarity with the robust benefits of this class in preventing hospitalizations for heart failure and progression of renal disease [17].

In our study, older individuals were more likely to initiate non-guideline monotherapy and sulfonylurea monotherapy than were younger individuals. This may be explained by the higher prevalence of renal impairment in older people [18]. It may also reflect that Australian guidelines include 'cardiac disease' as a precaution for prescribing metformin and cardiac disease is more prevalent in older people [5]. The guideline recommendation is at odds with recent systematic reviews that have demonstrated metformin is associated with reduced all-cause mortality and with a lower risk of chronic heart failure readmission in people with chronic heart failure [19]. Conversely, other anti-hyperglycaemic agents, such as insulin, sulfonylureas and thiazolidinediones are associated with increased risk of mortality in patients with existing chronic heart failure [20].

There is uncertainty over the clinical and economic outcomes associated with initiating multiple type 2 diabetes medications concurrently rather than sequentially [21], although the latter approach is advised in Australian guidelines [5,6]. Further studies are required to provide evidence for which approach is superior [22]. It has been hypothesized that using medications with complementary mechanisms of action at treatment initiation in type 2 diabetes could delay disease progression [23]. The ADA/EASD recommend initiating dual therapy when $HbA_{1c} \geq 75$ mmol/mol (9.0%) but acknowledge the lack of proven advantage with this approach [4]. Similarly, AACE/ACE guidelines state dual therapy is appropriate when $HbA_{1c} > 58$ mmol/mol (7.5%), but the reference cited for this recommendation does not

discuss initial combination therapy [2,3]. Australian guidelines do not address the issue [5,6]. Proposed advantages of initiating combination treatment include rapid attainment of glycaemic targets, bypassing of clinical inertia and the preservation of β-cell function [23]. Meta-analyses have shown the relative risk of attaining HbA_{1c} < 53 mmol/mol (7.0%) on initial combination therapy vs. initial metformin monotherapy to be 1.4 [24]. A study involving initial treatment with a sitagliptin/metformin fixed-dose combination showed a relative risk of 1.7 for attaining HbA_{1c} < 48 mmol/mol (6.5%) [25].

Australian general practice guidelines and the ADA guidelines advise that less stringent HbA_{1c} targets > 53 mmol/mol (> 7.0%) can be considered in people who have 'important comorbidities' or 'established cardiovascular complications' [4,5]. These guidelines are supported by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which reported that intensive glycaemic control in high-risk patients with advanced atherosclerosis was linked to higher rates of cardiovascular death [26]. In our study, people with a higher number of comorbidities had lower odds of initiating with combination therapy. Compared with people with no comorbidities, people with one to three, four to six and seven or more comorbidities had progressively lower odds of initiating combination therapy. This finding was consistent with Australian general practice recommendations related to less intensive treatment in people with 'important comorbidities'. Conversely, our study found that chronic heart failure, dyslipidaemia and cerebrovascular disease were positively associated with initiating combination treatment. Because these comorbidities are likely to be indicative of 'established vascular complications', this may reflect initial intensive treatment in patients for whom it is not guideline recommended. Finally, our study identified that women were less likely to receive initial combination therapy than men. This may be because women have more regular contact with their general practitioners and thus have less severe type 2 diabetes at the time of diagnosis [27].

<H2>Strengths and limitations

We analysed large and representative national data for a 10% random sample of the Australian population. As the Australian government's PBS provides subsidized access to prescription medications for all Australia's 25 million citizens, permanent residents and visitors from countries with reciprocal healthcare rights, the pattern of treatment initiation is largely dictated by actual or perceived clinical need rather than a person's health plan or insurance cover. Our results have implications for other countries that provide universal access to subsidized prescription medications for type 2 diabetes.

These data included records of all reimbursed medications for type 2 diabetes. However, we did not have clinical data such as renal function and HbA_{1c} results, which were likely to have been important predictors of treatment initiation. Records of in-hospital dispensing are not captured in the data and, therefore, treatment initiation that occurred in hospital was not captured. We reasoned that this would be unlikely to considerably impact our results because most patients would fill prescriptions for the same medications from a community pharmacy following hospital discharge. It is possible that some people initiated with medications other than metformin or sulfonylureas without reimbursement and, therefore, were not included in the PBS data set. However, the number of these people is likely to be small because these medications are relatively expensive. A very small number of people appear to initiate on three or more medications. This may be because they have previously accessed type 2 diabetes medication outside the PBS or in hospital during a long-term stay. The proportion of combination therapy and non-guideline monotherapy initiations may have been underestimated because people dispensed insulin on their index date were not included. However, insulin is rarely prescribed first-line treatment in type 2 diabetes [1]. Finally, the number of people commencing metformin monotherapy for type 2 diabetes may have been overestimated because metformin is occasionally used to treat polycystic ovarian syndrome in women over the age of 40 years, although other studies indicate that this number is likely to be very low [13].

<H2>Conclusion

Treatment initiation in Australia is largely consistent with clinical practice guidelines, with 86% of individuals initiating metformin monotherapy. Increasing age is associated with an increasing probability of receiving monotherapy other than metformin. Initiation with combination prescribing is more likely to occur in individuals with fewer comorbidities.

Funding sources

S.W. is supported through an Australian Government Research Training Program Scholarship. J.E.S. is supported by an NHMRC Senior Research Fellowship [APP1079438]. J.I. is supported by the NHMRC Early Career Fellowship Scheme [grant number #1072137]. J.S.B. is supported by a NHMRC Dementia Leadership Fellowship [grant number #1140298].

Competing interests

J.E.S. has received honoraria for consultancy and lectures from Astra Zeneca, Eli Lilly, Novo Nordisk, Sanofi, Novartis, Boehringer Ingelheim and Mylan. S.W., J.I., J.S.B., C.K. and D.J.M. have no competing interests to declare.

Acknowledgements

S.W. is supported through an Australian Government Research Training Program Scholarship. J.E.S. is supported by an NHMRC Senior Research Fellowship [APP1079438]. J.I. is supported by the NHMRC Early Career Fellowship Scheme [grant number #1072137]. J.S.B. is supported by a NHMRC Dementia Leadership Fellowship [grant number #1140298]. The authors would like to acknowledge the Australian Government, Department of Human Services for the provision of the data.

References

1 Drug Utilisation Sub Committee. *Medicines for the Treatment of Diabetes*. XXX: Australian Government Department of Health, 2017.

2 Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA *et al*. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm – 2018 Executive summary. *Endocr Pract* 2018; **24**: 91–120.

3 Cornell S. Comparison of the diabetes guidelines from the ADA/EASD and the AACE/ACE. *J Am Pharm Assoc* 2017; **57**: 261–265.

4 Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M *et al*. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015; **38**: 140.

5 Royal Australian College of General Practitioners (RACGP). *General Practice Management of Type 2 Diabetes 2016–2018*. East Melbourne, VIC: RACGP, 2016.

6 *Therapeutic Guidelines: Endocrinology*. Melbourne: Therapeutic Guidelines, 2013.

7 Varjabedian L, Bourji M, Pourafkari L, Nader MD. Cardioprotection by metformin: beneficial effects beyond glucose reduction. *Am J Cardiovasc Drugs* 2018; **18**: 181–193.

8 Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA* 2014; **312**: 2668–2675.

9 Crowley MJ, Diamantidis CJ, McDuffie JR, Cameron B, Stanifer J, Mock CK *et al*. Appendix A, FDA safety announcements for metformin. In: *Metformin Use in Patients with Historical Contraindications or Precautions*. Washington, DC: Department of Veterans Affairs (US), 2016.

10 Gadzhanova S, Gillies M, Roughead E, Zuo Y. Fixed dose combination diabetes medicines usage in the Australian veteran population. *Aust Fam Physician* 2011; **40**: 811–815.

11 Cahn A, Cefalu WT. Clinical considerations for use of initial combination therapy in type 2 diabetes. *Diabetes Care* 2016; **39**: S137.

12 Pearson SA, Pesa N, Langton JM, Drew A, Faedo M, Robertson J. Studies using Australia's Pharmaceutical Benefits Scheme data for pharmacoepidemiological research: a systematic review of the published literature (1987–2013). *Pharmacoepidemiol Drug Saf* 2015; **24**: 447–455.

13 Ding T, Baio G, hardiman PJ, Petersen I, Sammon C. Diagnosis and management of polycystic ovary syndrome in the UK (2004–2014): a retrospective cohort study. *BMJ Open* 2016; **6**: e012461.

14 Pratt NL, Kerr M, Barratt JD, Kemp-Casey A, Kalisch Ellett LM *et al*. The validity of the Rx-Risk Comorbidity Index using medicines mapped to the Anatomical Therapeutic Chemical (ATC) Classification System, *BMJ Open* 2018; **8**: e021122.

15 Wilkinson S, Douglas I, Stirnadel-Farrant H, Fogarty D, Pokrajac A, Smeeth L *et al*. Changing use of antidiabetic drugs in the UK: trends in prescribing 2000–2017. *BMJ Open* 2018; **8**: e022768.

16 Singh AK, Singh R. Is gliclazide a sulfonylurea with difference? A review in 2016. *Expert Rev Clin Pharmacol* 2016; **9**: 839–851.

17 Custodio JS Jr, Duraes AR, Abreu M, Albuquerque Rocha N, Roever L. SGLT2 inhibition and heart failure-current concepts. *Heart Fail Rev* 2018; **23**: 409–418.

18 Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. *Adv Chron Kidney Dis* 2016; **23**: 19–28.

19 Crowley MJ. *Metformin Use in Patients with Historical Contraindications or Precautions*. Washington, DC: US Department of Veterans Affairs (US), 2016.

20 Packer M. Is metformin beneficial for heart failure in patients with type 2 diabetes? *Diabetes Res Clin Pract* 2018; **136**: 168–170.

21 Bianchi C, Daniele G, Dardano A, Miccoli R, Del Prato S. Early combination therapy with oral glucose-lowering agents in type 2 diabetes. *Drugs* 2017; **77**: 247–264.

22 Cersosimo E, Johnson EL, Chovanes C, Skolnik N. Initiating therapy in patients newly diagnosed with type 2 diabetes: combination therapy vs a stepwise approach. *Diabetes Obes Metab* 2018; **20**: 497–507.

23 Abdul-Ghani M, DeFronzo RA. Is it time to change the type 2 diabetes treatment paradigm? Yes! GLP-1 RAs should replace metformin in the type 2 diabetes algorithm. *Diabetes Care* 2017; 40: 1121–1127.

24 Phung OJ, Sobieraj DM, Engel SS, Rajpathak SN. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. *Diabetes Obes Metab* 2013; **16**: 410–417.

25 Olansky L, Reasner C, Seck TL, Williams-Herman DE, Chen M, Terranella L. A treatment strategy implementing combination therapy with sitagliptin and metformin results in superior glycaemic control versus metformin monotherapy due to a low rate of addition of antihyperglycaemic agents. *Diabetes Obes Metab* 2011; **13**: 841–849.

26 Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB *et al*. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545–2559.

27 Australian Bureau of Statistics. *Patient Experiences in Australia: Summary of Findings, 2014-15*. cat. no. 4839.0. Available at https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/4839.02014-15 Last accessed 20 December 2018.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. RxRisk-V categories.

Appendix S2. Demographic characteristics of people prescribed initial non-guideline monotherapy for type 2 diabetes by medication class.

Table 1. Demographic and clinical characteristics of people by type 2 diabetes medication at treatment initiation

Demographic characteristic	Total (n = 47 860)	Metformin monotherapy (n = 41 060)	Sulfonylurea monotherapy (n = 2212)	Non-guideline monotherapy (n = 917)	Combination therapy (n = 3671)	P-value
Mean age, years	60.7 ± 12.1	60.3± 11.8	67.7 ± 13.3	65.1 ± 12.5	60.1± 12.1	< 0.0001
Age, years						
40–49	9849 (20.6)	8682 (21.1)	234 (10.6)	120 (13.1)	813 (22.1)	
50–59	13 170 (27.5)	11 521 (28.1)	400 (18.1)	184 (20.1)	1065 (29.0)	
60–69	13 371 (27.9)	11 552 (28.1)	555 (25.1)	271 (29.6)	993 (27.0)	
70–79	8045 (16.8)	6751 (16.4)	548 (24.8)	214 (23.3)	532 (14.5)	
80+	3425 (7.2)	2554 (6.2)	475 (21.5)	128 (14.0)	268 (7.3)	< 0.0001
Sex, female	22 475 (47.0)	19 632 (47.8)	1004 (45.4)	436 (47.5)	1403 (38.2)	< 0.0001
Index year						
7/2013 to 6/2014	11 504 (24.0)	9671 (23.6)	713 (32.2)	198 (21.6)	922 (25.1)	
7/2014 to 6/2015	10 438 (21.8)	8950 (21.8)	519 (23.5)	157 (17.1)	812 (22.1)	
7/2015 to 6/2016	9641 (20.1)	8319 (20.3)	423 (19.1)	207 (22.6)	692 (18.9)	
7/2016 to 6/2017	9917 (20.7)	8580 (20.9)	361 (16.3)	202 (22.0)	774 (21.1)	
7/2017 to 2/2018*	6360 (13.3)	5540 (13.5)	196 (8.9)	153 (16.7)	471 (12.8)	<0.0001
Mean comorbidity score	3.9 ± 2.5	3.9 ± 2.5	4.9 ± 3.0	4.4 ± 2.9	3.6 ± 2.6	< 0.0001
Number of comorbidities†						
0	2685 (5.6)	2165 (5.3)	109 (4.9)	71 (7.7)	340 (9.3)	
1–3	20 923 (43.7)	18 171 (44.3)	692 (31.3)	321 (35.0)	1739 (47.4)	
4–6	16 657 (34.8)	14 545 (35.4)	735 (33.2)	295 (32.2)	1082 (29.5)	
7+	7595 (15.9)	6179 (15.0)	676 (30.6)	230 (25.1)	510 (13.9)	< 0.0001
Atrial fibrillation	3589 (7.5)	2879 (7.0)	349 (15.8)	105 (11.5)	256 (7.0)	< 0.0001
Cerebrovascular disease	4719 (9.9)	3737 (9.1)	415 (18.8)	124 (13.5)	443 (12.1)	< 0.0001
Congestive heart failure	2924 (6.1)	2250 (5.5)	331 (15.0)	83 (9.1)	260 (7.1)	< 0.0001
Depression	11 047 (23.1)	9669 (23.5)	502 (22.7)	229 (25.0)	647 (17.6)	< 0.0001
Dyslipidaemia	23 135 (48.3)	19 638 (47.8)	1197 (54.1)	451 (49.2)	1849 (50.4)	< 0.0001
End stage renal disease	126 (0.3)	26 (0.1)	85 (3.8)	9 (1.0)	6 (0.2)	< 0.0001
Hypertension	23 081 (48.2)	19 694 (48.0)	1239 (56.0)	464 (50.6)	1684 (45.9)	< 0.0001
Ischaemic heart disease/angina	2136 (4.5)	1727 (4.2)	198 (9.0)	54 (5.9)	157 (4.3)	< 0.0001
Ischaemic heart	14 692 (30.7)	12 419 (30.2)	872 (39.4)	317 (34.6)	1084 (29.5)	< 0.0001

disease/hypertensio
n

*Data were recorded until the end of February 2018, therefore the final index year is incomplete with respect to number of initiations.

†A score of 1 was deducted from the total RxRisk-V score, as the whole cohort had type 2 diabetes medications prescribed at baseline.

Table 2. Predictors of initiation on different type 2 diabetes therapies, among those initiating a non-insulin type 2 diabetes medication

Demographic characteristic	Sulfonylurea monotherapy (n = 2212)		Non-guideline monotherapy (n = 917)		Combination therapy (n = 3671)	
	OR	95% CI	OR	95% CI	OR	95% CI
Age, years						
40–49	1.00	Reference	1.00	Reference	1.00	Reference
50–59	1.26	1.07–1.49	1.20	0.95–1.51	0.96	0.88–1.06
60–69	1.65	1.41–1.94	1.78	1.42–2.23	0.89	0.80–0.98
70–79	2.53	2.14–2.99	2.30	1.81–2.94	0.82	0.73–0.93
80+	4.95	4.15–5.91	3.37	2.56–4.43	1.10	0.94–1.28
Sex, female	0.93	0.85–1.02	1.00	0.87–1.14	0.74	0.69–0.79
Index year						
7/2013 to 6/2014	1.00	Reference	1.00	Reference	1.00	Reference
7/2014 to 6/2015	0.78	0.69–0.88	0.85	0.69–1.05	0.96	0.87–1.06
7/2015 to 6/2016	0.69	0.61–0.78	1.21	0.99–1.47	0.89	0.80–0.98
7/2016 to 6/2017	0.58	0.50–0.66	1.15	0.94–1.41	0.97	0.88–1.07
7/2017 to 2/2018*	0.48	0.41–0.57	1.35	1.09–1.67	0.92	0.82–1.03
Number of comorbidities†						
0	1.00	Reference	1.00	Reference	1.00	Reference
1–3	0.74	0.60–0.92	0.55	0.42–0.72	0.56	0.49–0.64
4–6	0.79	0.62–1.00	0.57	0.41–0.77	0.39	0.33–0.45
7+	1.21	0.92–1.59	0.90	0.62–1.32	0.36	0.29–0.44
Atrial fibrillation	1.30	1.13–1.50	1.12	0.89–1.42	1.09	0.94–1.26
Cerebrovascular disease	1.29	1.13–1.47	1.19	0.96–1.49	1.50	1.32–1.69
Congestive heart failure	1.59	1.37–1.83	1.08	0.84–1.40	1.42	1.22–1.65
Depression	0.81	0.72–0.91	0.97	0.82–1.16	0.86	0.78–0.95
Dyslipidaemia	0.84	0.76–0.93	0.83	0.71–0.96	1.29	1.19–1.40
Hypertension	1.03	0.94–1.14	0.94	0.81–1.09	1.05	0.97–1.14

Ischaemic heart disease/angina	1.02	0.86–1.22	0.89	0.65–1.20	0.86	0.71–1.03
Ischaemic heart disease/hypertension	0.99	0.90–1.10	0.95	0.81–1.11	1.08	0.99–1.18

CI, confidence interval; OR, adjusted odds ratio.

*Data were recorded until the end of February 2018, therefore the final index year is incomplete with respect to number of initiations.

†A score of 1 was deducted from the total RxRisk-V score, as the whole cohort had type 2 diabetes medications prescribed at baseline.