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Published in:
Pharmacoepidemiology and Drug Safety

DOI:
10.1002/pds.5672

Publication date:
2023

Received: 14 March 2023 | Revised: 22 June 2023 | Accepted: 17 July 2023

DOI: 10.1002/pds.5672

ORIGINAL ARTICLE

WILEY

Sex disparities in treatment patterns after metformin initiation among patients with type 2 diabetes mellitus

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Abstract

Purpose: To assess sex differences in treatment patterns after metformin initiation among type 2 diabetes mellitus (T2D) patients.

Methods: A cohort study was conducted using the Groningen Initiative to ANalyze Type 2 diabetes Treatment (GIANTT) primary care database. Patients aged ≥18 years initiating metformin were followed 2–5 years. Markov modeling was conducted to estimate treatment transition rates and calculate adjusted hazard ratios (aHR) with 95% confidence intervals (CI) comparing men with women adjusted for age, HbA1c level at initiation, and cardiovascular disease history. Kaplan–Meier analyses and Cox proportional-hazards models were used to determine the time to and likelihood of getting treatment intensification. HbA1c levels at initiation and intensification were compared using Mann–Whitney *U* tests.

Results: In total, 11 508 metformin initiators were included (50.1% women). The most common transition after initiation was a dose increase (probability women 0.52, men 0.59, no significant difference). Women were more likely than men to switch to any other non-insulin hypoglycemic agent after initiation (aHR 1.66; 95% CI 1.31–2.12), after dose increase (aHR 1.48; 95% CI 1.10–1.98) and after dose decrease (aHR 2.64; 95% CI 1.28–5.46). Time to intensification was longer, time to switching was shorter, and HbA1c levels at initiation and intensification were lower for women than men.

Conclusions: Sex disparities were observed in treatment transitions after metformin initiation. Women more often switched treatment than men, which suggest that prescribers acknowledge more tolerance or other problems for metformin in women. Men intensified treatment earlier and at higher HbA1c levels, indicative of a higher need for treatment intensification.

KEYWORDS

longitudinal cohort study, sex disparities, treatment pattern, treatment prescribing, type 2 diabetes mellitus

Key Points

- After initiating metformin, more than half of the type 2 diabetes mellitus (T2D) patients had a metformin dose increase.

- Sex disparities were seen in treatment patterns among T2D patients.
- Women more often switched medication after metformin initiation, after dose increase and dose decrease, while men were more likely to receive addition of any other non-insulin hypoglycemic agent with the same or a higher metformin dose.
- Time to switching was shorter for women, whereas time to intensification was shorter for men.
- Women had slightly lower HbA1c levels than men at metformin initiation and treatment intensification.

Plain Language Summary

The current guidelines of type 2 diabetes mellitus treatment do not differentiate between men and women. However, previous studies have shown that men and women may receive different medication treatment and dosages. This study looked at whether there are differences in how men and women with type 2 diabetes mellitus are treated after starting metformin by using a database of primary care patients. The results showed that women were more likely than men to switch to a different type of diabetes medication after starting metformin, which suggests that more tolerance or other problems for metformin occurred in women. Men were more likely to receive treatment intensification than women. The study highlights potential disparities in diabetes treatment between men and women, for which the reasons and consequences should be examined.

1 | INTRODUCTION

The treatment of type 2 diabetes mellitus (T2D) includes monitoring and managing of glycated hemoglobin (HbA1c) levels. Guidelines recommend a stepwise approach starting with lifestyle advice, initiating a non-insulin hypoglycemic agent, intensifying non-insulin hypoglycemic agent treatment, and eventually initiating insulin.[1] Metformin is considered the guideline-recommended first choice of treatment for most T2D patients, with possibilities to change doses, add, or switch to other medications. The guidelines recommend a personalized treatment approach based on a patient's clinical characteristics, such as age and HbA1c level, but do not differentiate between men and women.[1]

Given these recommendations, various treatment paths among patients with T2D can be expected. A previous study showed that patients initiating with metformin remained on average on this monotherapy for more than 2 years, with the most common next step being an addition (19%) or a switch to a sulfonylurea derivative (8%).[2] Although no clinically significant differences in paths between men and women were shown in that study,[2] there are indications of sex disparities in treatment patterns and dose modification after metformin initiation. De Vries et al. observed that women were generally prescribed lower doses of metformin than men over time, and this dose difference was significant at 9-month assessment.[3] In other studies it was observed that men were prescribed more intensive treatment at initiation as well as during follow-up (e.g., higher doses), and received more often treatment intensification after failure of metformin monotherapy than women.[4,5]

Timely and well-controlled HbA1c levels are important in both men and women to reduce the risk of diabetes-related complications. However, cross-sectional studies among patients being prescribed hypoglycemic agents have shown that women in general had higher HbA1c levels when treated or were less likely to attain HbA1c targets than men.[6,7] Women had a higher probability of having elevated HbA1c levels despite being on insulin treatment, although it was also observed that men had a higher probability of not being treated with insulin while having elevated HbA1c levels.[8]

To gain better insight in sex disparities in treatment patterns among patients with T2D, longitudinal studies are needed focusing on treatment changes and related HbA1c levels. Therefore, this study aimed to assess sex differences among patients with T2D in (1) treatment patterns after metformin initiation, (2) the time between metformin initiation and treatment intensification, and (3) the HbA1c level at treatment initiation and intensification.

2 | METHODS

2.1 | Study design and population

A longitudinal cohort study was conducted using the Groningen Initiative to Analyze Type 2 diabetes Treatment (GIANTT) database.[9,10] The GIANTT database contains anonymized information from primary care electronic medical records about a dynamic cohort of patients with T2D in the northern part of the Netherlands. This includes information about prescriptions with the date, the substance, the daily quantity, and the estimated duration of the medication.

Included in this study were patients aged 18 years or older, who initiated metformin in the period January 1, 2004, and December 31, 2012. Patients should have at least 1 year of medical history and 2 years of follow-up data to enable the application of various definitions of treatment transition states (see 2.2 and Table S1). Metformin initiation was defined as a first prescription of metformin monotherapy without a prescription of any hypoglycemic agent in the preceding

365 days, and no prescription of any other hypoglycemic agent on the same day or within 7 days of the first metformin prescription. Index date was the date of this first prescription, and the patients were followed for 2 to 5 years, or follow-up was stopped if the patient reached one of the end-states of intensification (see 2.2). Patients were excluded when (1) initiating on a combination of hypoglycemic agents, (2) starting a second hypoglycemic agent within 7 days after the index date, (3) the initial metformin dose was more than 1000 mg/day or the first metformin prescription duration was more than 90 days, indicative of patients who are likely to have received metformin before,[11] (4) the dose or the duration of their first metformin prescription was missing, or (5) the first metformin prescription was for less than 5 days, indicative of an error in the collected prescription.

2.2 | Outcomes

The first outcome was the treatment pattern after the index date expressed by transition rates between treatment states. We distinguished the following states (A) beginning state: initiation of metformin, (B) intermediate states: dose increase, dose decrease, metformin discontinuation, metformin re-initiation after discontinuation, no change of metformin treatment in 730 days, and (C) end-states: addition of any other non-insulin hypoglycemic agent (OHA) to metformin with the same or a higher metformin dose ("addition+") or with a lower metformin dose ("addition−"), switching from metformin to any OHA, OHA initiation after metformin discontinuation, and insulin initiation (Table S1). Gaps of at least 270 days were used in these definitions to distinguish between the states, allowing for gaps that are introduced by delayed or long-duration prescriptions. The end-states "addition+" and "insulin initiation" were considered as true intensification states. Treatment switches to any OHA, OHA initiation, and "addition−" states were considered as potential intensification states. For the "potential intensification" it is uncertain whether the start of any OHA was intended to increase the effect or because of metformin-related problems requiring the start of any OHA while discontinuing or decreasing the dose of metformin. The second outcome was the time between metformin initiation and true as well as potential intensification. The third outcome was the HbA1c level at the time of initiation and treatment intensification. We included the most recent HbA1c measurement in the period 365 days before or up to 7 days after the index date, and 120 days before or up to 7 days after the treatment intensification date, respectively. The time window of 120 days before this date was chosen to allow for actions taken at a next regular diabetes visit, whereas a grace period of 7 days after this date was chosen to allow for delays in entering the results of these tests in the medical records.

2.3 | Determinant

The determinant in all analyses was the sex of the patients as documented in the database. This was a binary variable (men and women), and men were used as the reference.

2.4 | Statistical analyses

Baseline characteristics of included patients are reported descriptively as mean with standard deviation (SD), or median with interquartile range (IQR) for continuous variables. For categorical variables, the number and percentage of patients are reported. Sex differences in characteristics were tested using independent-samples *t*-tests, Mann–Whitney *U* tests, and Chi-Squared tests depending on the type of the data and data distribution (Table S2 for definitions and time windows details).

We fitted continuous-time Markov models to estimate transition rates from metformin initiation to intermediate subsequent treatment states, and from those intermediate states to the end-states. A Markov model stratified by sex was fitted to obtain the probabilities of going from state A to state B, given that someone is leaving state A. Missing doses of metformin prescriptions were imputed using last-observation-carried-forward when the dose before and after the missing were available. Medication treatment decisions can be influenced by various patient factors, and based on guideline recommendations HbA1c level, age, and cardiovascular disease (CVD) history can be justifiable factors guiding these decisions. Therefore, a complete case Markov model was used to estimate adjusted hazard ratios (aHR) for the transitions, which are displayed in a forest plot. This model included sex as determinant, and HbA1c level, age, and CVD history all at baseline as covariates. The time-to-event between metformin initiation and intensification end-states were analyzed using Kaplan–Meier analyses, with the log-rank test to test for differences between sexes. Cox proportional hazards regression models were used to estimate the aHRs for reaching the true intensification and potential intensification, adjusted for age, HbA1c level, and CVD history all at baseline. Complete case analysis was first conducted for the Cox models, and multiple imputation was applied to overcome missing data in baseline HbA1c as additional analysis. Finally, HbA1c levels at the time of treatment initiation and intensification were compared between sexes using Mann–Whitney *U* tests.

A *p*-value <0.05 was considered statistically significant for the aHR Markov model and Cox regression. The Markov modeling and Cox regression analyses were conducted using R (version 4.0.3; R Foundation for Statistical Computing Platform).[12] The other analyses and Kaplan–Meier figures were conducted using SPSS (version 23.0; IBM, Armonk, NY). Network plots were generated using CorelDRAW Graphic-Suite 2019. The forest plot was generated using Microsoft Excel 2010.

3 | RESULTS

3.1 | Patient selection and baseline characteristics

Of the 19 212 T2D patients identified as metformin initiators, 11 508 met the inclusion criteria (Figure 1). The mean age of the patients was 62.5 years (SD: 11.6), most had their diabetes diagnosed less than 2 years ago, the median HbA1c level at the time of metformin initiation was 7.2% (IQR: 6.7%–8.2%), and about half were women (50.1%) (Table 1). Women were older, had higher cholesterol levels,

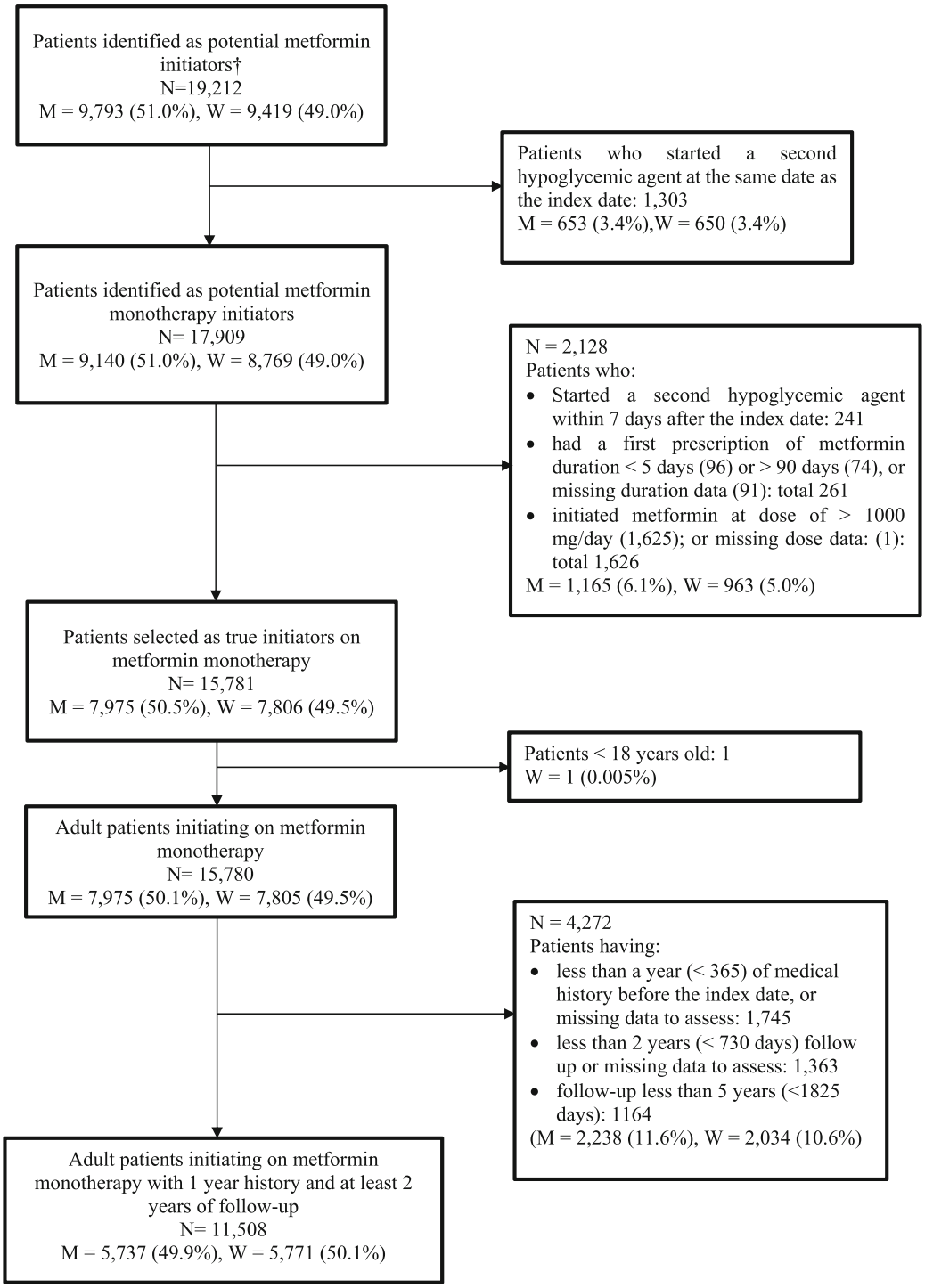


FIGURE 1 Flow chart of included patients. †Patients with a metformin prescription without any hypoglycemic agent prescription in the preceding 365 days. GIANTT: Groningen Initiative to ANalyze Type 2 diabetes Treatment; M: Men, W: Women. Denominator for all exclusion percentages is total number in initial cohort of potential metformin initiators.

systolic blood pressure levels, and body mass index. Women were prescribed a higher number of chronic medication and antihypertensive medication than men at metformin initiation. Men had higher glycemic levels, higher diastolic blood pressure levels, and more often a history of a CVD, were prescribed more lipid-lowering medication, and started on a higher dose of metformin at initiation than women (Table 1).

3.2 | Treatment patterns

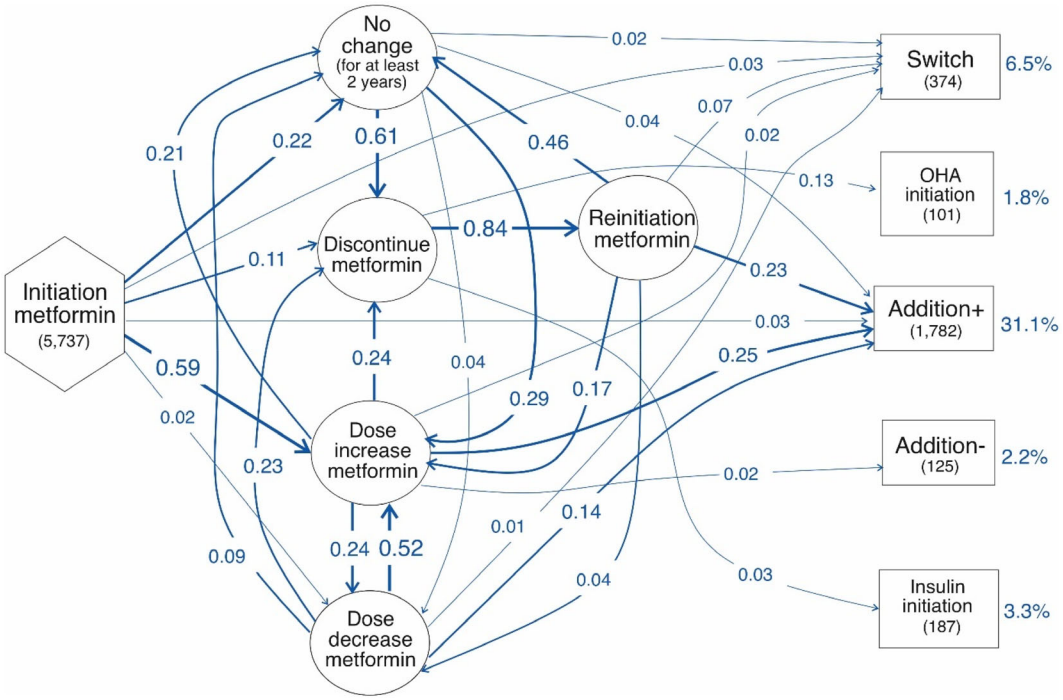
The patients were followed for a median duration of 1147 days (Table 1). The most common end-states reached were addition+ in 26.1% of women and 31.1% of men, and switch to any OHA in 9.5% of women and 6.5% of men (Figure 2A,B). The adjusted Markov model

TABLE 1 Baseline characteristics of patients with type 2 diabetes mellitus initiating metformin monotherapy in 2004–2012.

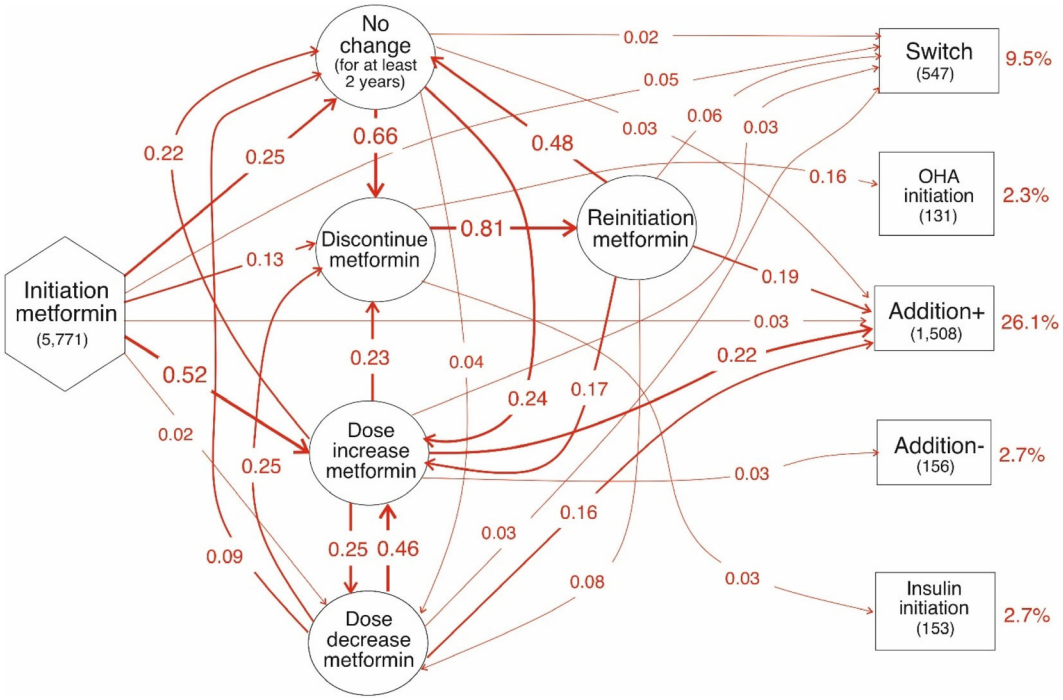
	Overall $n = 11\,508$	Men n (%) = 5737 (49.9)	Women n (%) = 5771 (50.1)	p-value[a]
Age in years, mean (± SD)	62.5 (11.6)	61.6 (11.1)	63.4 (12.0)	< 0.001
Diabetes duration group, *n* (%)				
0–1 year	9257 (80.4)	4630 (80.7)	4627 (80.2)	0.102
2–5 years	1607 (14.0)	807 (14.1)	800 (13.9)	
6–10 years	465 (4.0)	229 (4.0)	236 (4.1)	
≥ 11 years	168 (1.5)	67 (1.2)	101 (1.8)	
Missing	11 (0.1)	4 (0.1)	7 (0.1)	
Fasting glucose, median (IQR)	8.2 (7.2–9.9)	8.4 (7.3–10.4)	8.0 (7.1–9.4)	< 0.001
Missing, *n* (%)	2891 (25.1)	1445 (25.2)	1446 (25.1)	
HbA1c (%), median (IQR)	7.2 (6.7–8.2)	7.3 (6.8–8.5)	7.2 (6.7–7.9)	< 0.001
Missing, *n* (%)	2847 (24.7)	1448 (25.2)	1399 (24.2)	
SBP, median (IQR)	142 (132–159)	142 (130–157)	144 (133–160)	< 0.001
Missing, *n* (%)	2306 (20.0)	1253 (21.8)	1053 (18.2)	
DBP, median (IQR)	82 (78–90)	84 (79–90)	82 (78–90)	0.006
Missing, *n* (%)	2309 (20.1)	1256 (21.9)	1053 (18.2)	
Total cholesterol, median (IQR)	5.1 (4.4–6.0)	5.0 (4.3–5.8)	5.3 (4.6–6.1)	< 0.001
Missing, *n* (%)	4152 (36.1)	2025 (35.3)	2127 (36.9)	
LDL, median (IQR)	3.1 (2.4–3.8)	3.0 (2.3–3.7)	3.2 (2.5–3.9)	< 0.001
Missing, *n* (%)	4399 (38.2)	2174 (37.9)	2225 (38.6)	
Smoking status, *n* (%)				0.055
Yes	709 (6.2)	388 (6.8)	321 (5.6)	
No	2053 (17.8)	1037 (18.1)	1016 (17.6)	
Missing	8746 (76.5)	4312 (75.2)	4434 (76.8)	
BMI, median (IQR)	30.0 (27.0–34.0)	29.0 (27.0–33.0)	31.0 (27.0–35.0)	< 0.001
N Missing (%)	4454 (38.7)	2159 (37.6)	2295 (39.8)	
History of CVD, *N* (%)				< 0.001
Yes	2317 (20.1)	1344 (23.4)	973 (16.9)	
Chronic co-medication, *n* (%)				
0	3296 (28.6)	1883 (32.8)	1413 (24.5)	< 0.001
1–5	7385 (64.2)	3582 (62.4)	3803 (65.9)	
6–10	773 (6.7)	257 (4.5)	516 (8.9)	
11–18	54 (0.5)	15 (0.3)	39 (0.7)	
Antihypertensive medication, *n* (%)				
0	4022 (34.9)	2173 (37.9)	1849 (32.0)	< 0.001
1	2829 (24.6)	1374 (23.9)	1455 (25.2)	
2	2591 (22.5)	1213 (21.1)	1378 (23.9)	
≥ 3	2066 (18.0)	977 (17.0)	1089 (18.9)	
Lipid lowering medication, *n* (%)				
0	5473 (47.6)	2542 (44.3)	2931 (50.8)	< 0.001
≥ 1	6035 (52.4)	3195 (55.7)	2840 (49.2)	
Metformin dose at initiation, mean (SD)	643.8 (226.1)	658.8 (231.6)	628.0 (220.0)	< 0.001
Number days follow-up, median (IQR)	1147 (458–1737)	1174 (494–1737)	1125 (420–1736)	0.082

Abbreviations: BMI, body mass index; CVD, cardiovascular disease, n, number; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; IQR, interquartile range; LDL, low density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.

[a]p-values were obtained by independent t-tests (age), Mann–Whitney U test (diabetes duration, fasting glucose, HbA1c, SBP, DBP, total cholesterol, LDL, BMI, and metformin dose), Chi-square (diabetes duration group, smoking status, CVD history, and medications).



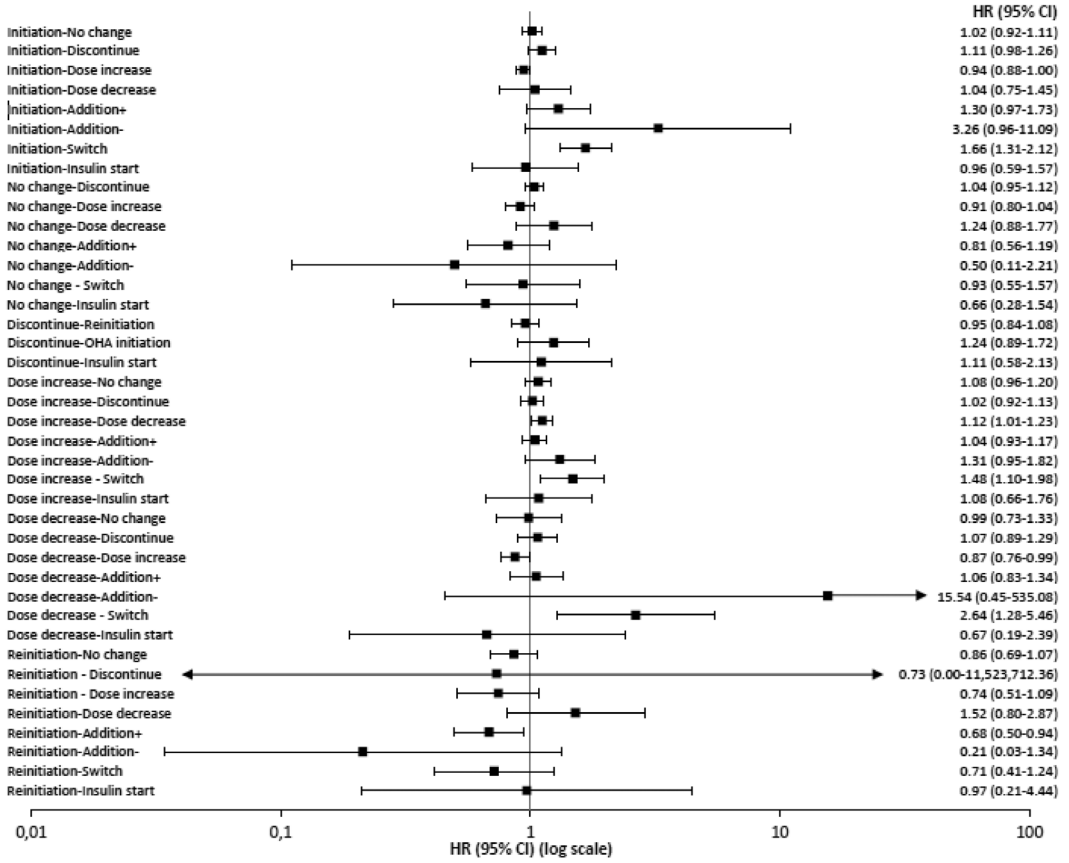
(A)



(B)

FIGURE 2 A, Transition rates for men. B, Transition rates for women. Only transition probabilities of ≥0.02 were shown in the figure. C, Adjusted hazard ratios comparing transition rates between sexes (reference class: men), adjusted for age, Hba1c level, and CVD history all at baseline. aHR, adjusted Hazard ratio; CI, confidence interval; CVD, cardiovascular disease; OHA, other non-insulin hypoglycemic agent.

included 8661 patients (missing data for HbA1c at baseline 34.7%). The most common treatment transition after metformin initiation was a dose increase for both sexes (probability women 0.52 and men 0.59, Figure 2A,B) with no significant difference (aHR 0.94, 95% CI 0.88–1.00, Figure 2C). No change in the metformin treatment for at least 2 years was also common for both sexes, with no significant



(C)

FIGURE 2 (Continued)

difference (probability women 0.25 and men 0.22; aHR 1.02, 95% CI 0.92–1.11). After a re-initiation of metformin, however, women had a lower probability than men to get an addition+ (probability women 0.19 and men 0.23; aHR 0.68, 95% CI 0.50–0.94).

Furthermore, women were more likely to switch to any OHA than men after metformin initiation (probability women 0.05 and men 0.03; aHR 1.66, 95% CI 1.31–2.12), after a metformin dose decrease (probability women 0.03 and men 0.01; aHR 2.64, 95% CI 1.28–5.46), and after a metformin dose increase (probability women 0.03 and men 0.02; aHR 1.48, 95% CI 1.10–1.98, Figure 2A–C). On the other hand, compared to men, women were less likely to have a dose increase after a dose decrease (probability women 0.46 and men 0.52; aHR 0.87, 95% CI 0.76–0.99).

3.3 | Time between initiation and treatment intensification

A total of 1661 women (28.8%) and 1969 men (34.4%) experienced a true intensification, whereas 834 women (14.5%) and 600 men (10.5%) experienced a potential intensification during follow-up. In the age, HbA1c, and CVD history adjusted Cox analysis there was no significant sex difference in reaching a true intensification end-state (aHR: 1.02, 95% CI 0.94–1.10) but women had a higher likelihood to reach a potential intensification end-state (aHR: 1.42, 95% CI 1.25–1.60). Similar results were seen in the multiple imputation analyses (Table S3). The time to true intensification was significantly longer for women than men, (Figure 3A) with a mean time to event of 1386 versus 1345 days (Log-Rank 17.7, *p*-value <0.001). On the other hand, women had a significantly shorter time to a potential intensification than men (Figure 3B), with a mean time to event of 1546 versus 1626 days (Log-Rank 28.4, *p*-value <0.001).

3.4 | HbA1c level at the time of the treatment intensification

Of the 5064 patients who had any treatment intensification during follow-up, an HbA1c measurement at the time of intensification was available for 4184 (82.6%) patients. The median HbA1c level at the time of any intensification was 7.5% (IQR: 7.1%–8.4%)

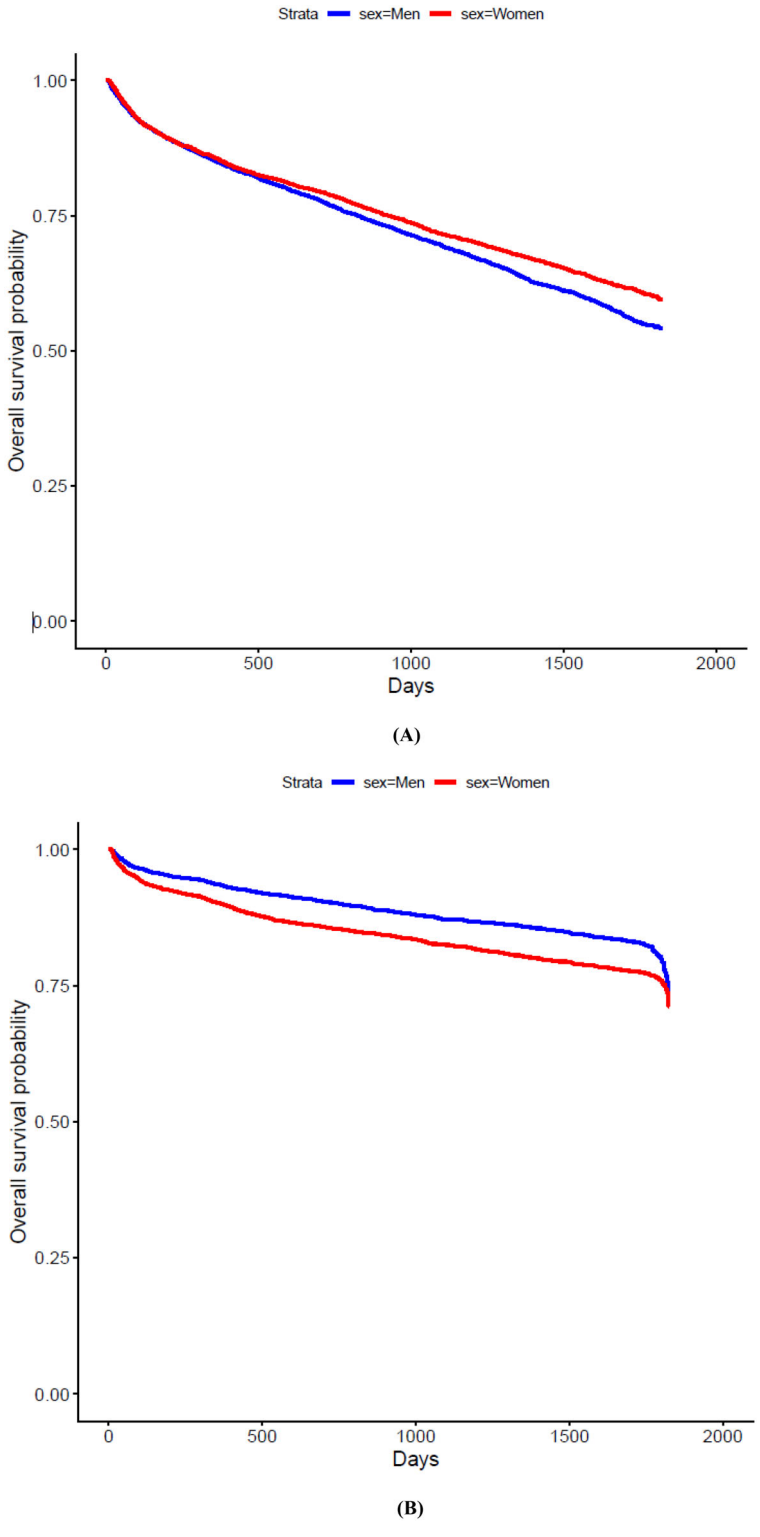


FIGURE 3 A, Kaplan–Meier analysis for time to true intensification (end-states). Men: Estimated mean time to event: 1345.3 days; Standard error: 9.3, 95% CI: 1327.0–1363.6. Women: Estimated mean time to event: 1386.3 days; Standard error: 9.5; 95% CI: 1367.8–1404.9. Overall: Estimated mean survival time: 1365.3 days; Standard error: 6.7; 95% CI: 1352.2–1378.3. Log rank: 17.7 (p-value <0.001). B, Kaplan–Meier analysis for time to potential intensification (end-states). Men: Estimated mean survival time: 1626.0 days; Standard error: 8.2; 95% CI: 1610.0–1642.1. Women: Estimated mean survival time: 1546.3 days; Standard error: 9.2, 95% CI: 1528.3–1564.4. Overall: Estimated mean survival time: 1584.5 days; Standard error: 6.2; 95% CI: 1572.4–1596.7. Log rank: 28.4 (p-value <0.001).

(Table 2), with slightly lower HbA1c levels for women than men (7.5% vs 7.6%, p-value <0.001). In addition+ and addition− states, women also had slightly lower HbA1c levels at this time of OHA addition than men (7.6% vs. 7.7%, p-value <0.001, 7.5% vs. 7.7%, p-value 0.01, respectively, Table 2). When patients switched to any OHA, the HbA1c level was 7.2% with no statistically significant sex differences (Table 2).

4 | DISCUSSION

4.1 | Principal findings and their relationship with the literature

After initiating metformin, more than half of the T2D patients (both sexes) had a metformin dose increase, whereas one-fifth remained on

TABLE 2 HbA1c levels[a] at the time of treatment intensification.

	Overall	Men	Women	*p*-value[b]
Any intensification, *n* (%)	4184 (82.6)	2155 (51.5)	2029 (48.5)	
%, median (IQR)	7.5 (7.1–8.4)	7.6 (7.2–8.6)	7.5 (7.0–8.2)	**< 0.001**
Switch to OHA, *n* (%)	760 (18.2)	308 (14.3)	452 (22.3)	
%, median (IQR)	7.2 (6.7–7.8)	7.3 (6.7–7.9)	7.2 (6.7–7.8)	0.127
OHA initiation, *n* (%)	165 (3.9)	71 (3.3)	94 (4.6)	
%, median (IQR)	6.8 (6.4–7.5)	6.8 (6.4–7.4)	6.9 (6.4–7.5)	0.485
Addition+, *n* (%)	2783 (66.5)	1527 (70.9)	1256 (61.9)	
%, median (IQR)	7.7 (7.2–8.6)	7.7 (7.2–8.8)	7.6 (7.2–8.4)	**< 0.001**
Addition-, *n* (%)	249 (6.0)	113 (5.2)	136 (6.7)	
%, median (IQR)	7.6 (7.1–8.4)	7.7 (7.2–8.8)	7.5 (7.0–8.0)	**0.011**
Insulin initiation, *n* (%)	227 (5.4)	136 (6.3)	91 (4.5)	
%, median (IQR)	7.9 (6.9–9.7)	8.0 (7.0–10.3)	7.9 (6.8–9.5)	0.324

Abbreviations: HbA1c: glycated hemoglobin A1c; *n* = number; IQR: interquartile range; OHA: other non-insulin hypoglycemic agent.
[a]Last value of HbA1c 120 days before up to 7 days after date of intensification, *n* = 414 (19.2%) missing for men and *n* = 466 (23.0%) missing for women.
[b]*p*-values were obtained by Mann–Whitney *U* tests.

metformin monotherapy for at least 2 years without any changes. Sex disparities were observed in the treatment patterns after metformin initiation. Women were more likely to switch to any OHA, while men were more likely to receive addition of any OHA with the same or a higher metformin dose. Time to switching was shorter for women, whereas time to intensification was shorter for men. Women had slightly lower HbA1c levels than men at metformin initiation and treatment intensification.

Our study confirms findings from previous studies showing T2D men receive more treatment intensification, such as dose increase or treatment addition, than T2D women within a similar time frame.[5,13] It could be that men have a higher need to intensify treatment given their higher glucose and HbA1c levels at the time of metformin initiation. Higher index HbA1c levels are expected to be associated with higher rates of intensification.[14] At the time of metformin initiation, men also more often had a history of CVD and received more often lipid-lowering medication. Although these factors, according to the prevailing guideline recommendations, should not be considered for the decision to intensify glucose lowering treatment, they may actually influence the general practitioner's decisions for treatment intensification.

Women were more likely to switch to any OHA than men at relatively low HbA1c levels. Although no direct information from the medical record about the switching intention, the possibility of incurring adverse drug events (ADEs) in women may occur. Previous studies have shown that women more often experience ADEs from hypoglycemic agents,[15,16] including metformin.[3,17] Women generally report ADEs more often than men after metformin initiation.[3] Experiencing ADEs when treated with metformin are likely to result into switching to another drug or decreasing the metformin dose while adding another OHA. This is in line with a previous study showing that women received less treatment with metformin as the second step in combination with an sulfonylurea derivative than men.[13] Men received treatment intensification around 40 days earlier than women, whereas women received potential intensification around 80 days earlier than men. A previous study found that men had earlier treatment additions than women in a period of 12–24 months after they progressed to uncontrolled HbA1c levels.[18] Although this might suggest that there is more clinical inertia among women, our study illustrates that this may not be the case. Women receive different treatment changes than men, particularly switching to another drug, which is often not considered as action in studies looking at clinical inertia.[19] Actually, we observed that men had slightly higher levels of HbA1c than women both at treatment initiation and intensification, indicating that—if anything—men may have experienced a bit more clinical inertia. This may seem surprising given the higher HbA1c levels seen among women treated with hypoglycemic agents and the lower likelihood to attain HbA1c targets than men seen in cross-sectional studies.[6,7] Assessing HbA1c levels at one moment in time, however, cannot reveal possible differences in HbA1c levels when decisions about treatment changes are made.

4.2 | Strengths and limitations

A strength of this study is the inclusion of a large, real-world cohort of patients with T2D with medication prescriptions and clinical data. The GIANTT cohort is representative and comparable with populations of T2D in the Netherlands.[20] Given the detailed information on dates and doses of prescriptions, we were able to model treatment transitions, including dose increases and decreases as well as addition with any OHA while decreasing the dose of metformin. In this way, the distinction between true and potential intensifications of treatment can be seen. In addition, the dates and levels of HbA1c measurements enabled us to compare these levels between the sexes at the time of treatment intensification.

Issues with incomplete data or data errors are common in any research using medical record data. Data checking and cleaning was conducted to delete duplicate prescriptions and out of range measurements (e.g., unlikely metformin initiators or error in the collected prescription). In the models, we adjusted for factors that are relevant for the initiation and intensification of medication treatment as based on the Dutch guideline recommendations. Given the guideline changes over time regarding target values in relation to age and diabetes duration, we adjusted for age. We did not adjust for diabetes duration because its collinearity with age. Furthermore, we only adjusted for baseline characteristics to prevent loss of patients due to missing data during follow-up. Particularly, HbA1c changes over time and the occurrence of ADEs or cardiovascular events can be expected to influence treatment decisions. The cross-sectional comparison illustrated that men had slightly higher HbA1c levels before treatment initiation and intensification but given the small differences of 0.1% observed this is expected to be a minor limitation. Unfortunately, data on ADEs and validated data about cardiovascular events during follow-up were not available. Additionally, since the GIANTT database includes a dynamic cohort, there is a possibility that some of the metformin initiations were not the first initiation, despite our inclusion/exclusion criteria. People may have used metformin in earlier periods or have moved into the GIANTT cohort being on low dose metformin treatment that was started at an earlier time. There is also a possibility of misclassification of the "discontinuation state," which may include patients who had left the database before the official end period as provided by their general practitioner. Patients with less than 2 years of follow-up data were excluded to enable application of our transition state definitions, which led to the exclusion of 1363 patients (Figure 1) of whom 649 women and 714 men. Usually, this happens when patients leave the practice because they moved. A final limitation is that we had no information about reasons for treatment changes, such as ADEs or medication taking problems.

4.3 | Future perspectives

It is relevant to assess the clinical impact of the observed sex differences in treatment patterns. Previously, it was found that patients intensifying monotherapy early (within 12 months) had a higher likelihood to attain glycemic control than patients intensifying later.[18] Furthermore, it was found that a one-year delay in initiating additional hypoglycemic medication among those with consistently elevated HbA1c levels was associated with an increased risk of cardiovascular events.[21] The sex differences in HbA1c levels at initiation and intensification were, however, small and thus not that clinically relevant. So far, it is not clear what the consequences are of the earlier switching of women to any OHA, as observed in our study.

Further research is needed to assess the underlying reasons for the sex differences in treatment patterns. Gaining more insight in potential sex differences of metformin dose and experiencing ADEs, with information on changes in HbA1c level over time would be helpful to better understand differences in treatment changes and their implications. Investigating the next treatment steps after the intensification states as defined in our study is important to gain a comprehensive overview of treatment patterns in T2D patients. Finally, new guideline recommendations were published in 2021 recommending to initiate treatment with sodium glucose co-transporter-2 inhibitors in non-frail patients with very high cardiovascular or renal risks.[1,22] It is of interest whether initiation with this new drug class and subsequent treatment patterns differ between the sexes. On the other hand, initiation with metformin treatment remains the mainstay for the majority of T2D patients in primary care.

5 | CONCLUSION

Sex disparities were observed in the treatment patterns among T2D patients after metformin initiation. Particularly, women more often switched medication treatment than men, which suggests that prescribers acknowledge more tolerance or other problems for metformin in women. Furthermore, men appeared to intensify treatment earlier and at slightly higher HbA1c levels than women, indicative of a higher need for treatment intensification.

AUTHOR CONTRIBUTIONS

Monika P. Oktora conceptualized the study, analyzed and interpreted the data, drafted and revised the manuscript. Stijn de Vos analyzed and interpreted the data, and reviewed and edited the manuscript. Sieta T. de Vries conceptualized the study, extracted the data, supervised the research, and reviewed the manuscript. Eelko Haksupervised the research and reviewed the manuscript. Petra Denig conceptualized the research, acquisition of data, validated data research, supervised the research, and reviewed the manuscript. All authors read the final version and approved submission. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGMENTS

Monika P. Oktora would like to thank the Indonesia Endowment Fund for Education (LPDP) for their support of her PhD program. Financial support from LPDP has helped many Indonesian students to obtain higher education in order to build Indonesia development.

FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

All authors have nothing to disclose.

DATA AVAILABILITY STATEMENT

The data sets used during this study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

An exemption letter for full ethical approval for this study was obtained from the University Medical Center Groningen Medical Ethics Review Board (reference number M21.267429).

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REFERENCES

1. American Diabetes Association Professional Practice Committee, Draznin B, Aroda VR, et al. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S125-S143. doi:10.2337/dc22-S009
2. van den Heuvel JM, Farzan N, van Hoek M, Maitland-van der Zee AH, Ahmadizar F. Mining treatment patterns of glucose-lowering medications for type 2 diabetes in The Netherlands. *BMJ Open Diabetes Res Care*. 2020;8(1):e000767. doi:10.1136/bmjdrc-2019-000767
3. de Vries ST, Denig P, Ekhart C, Mol PGM, van Puijenbroek EP. Sex differences in adverse drug reactions of metformin: a longitudinal survey study. *Drug Saf*. 2020;43(5):489-495. doi:10.1007/s40264-020-00913-8
4. Fu AZ, Qiu Y, Davies MJ, Radican L, Engel SS. Treatment intensification in patients with type 2 diabetes who failed metformin monotherapy. *Diabetes Obes Metab*. 2011;13(8):765-769. doi:10.1111/j.1463-1326.2011.01405.x
5. Xu Y, Yang Z, Lin H, Shen P, Wang H, Zhan S. Long-term patterns of antidiabetic medication use in patients with type 2 diabetes. *Med Sci Monit*. 2018;24:8707-8715. doi:10.12659/MSM.913603
6. Wexler DJ, Grant RW, Meigs JB, Nathan DM, Cagliero E. Sex disparities in treatment of cardiac risk factors in patients with type 2 diabetes. *Diabetes Care*. 2005;28(3):514-520. doi:10.2337/diacare.28.3.514
7. de Jong M, Oskam MJ, Sep SJS, et al. Sex differences in cardiometabolic risk factors, pharmacological treatment and risk factor control in type 2 diabetes: findings from the Dutch diabetes pearl cohort. *BMJ Open Diabetes Res Care*. 2020;8(1):e001365. doi:10.1136/bmjdrc-2020-001365
8. Rossi MC, Cristofaro MR, Gentile S, et al. Sex disparities in the quality of diabetes care: biological and cultural factors may play a different role for different outcomes: a cross-sectional observational study from the AMD annals initiative. *Diabetes Care*. 2013;36(10):3162-3168. doi:10.2337/dc13-0184
9. *Groningen Initiative to ANalyse Type 2 diabetes Treatment (GIANTT)*. Universitair Medisch Centrum Groningen; 2020 www.giantt.nl
10. Voorham J, Haaijer-Ruskamp FM, van der Meer K, et al. Identifying targets to improve treatment in type 2 diabetes; the Groningen initiative to ANalyse type 2 diabetes treatment (GIANTT) observational study. *Pharmacoepidemiol Drug Saf*. 2010;19(10):1078-1086. doi:10.1002/pds.2023
11. Martono DP, Hak E, Lambers Heerspink H, Wilffert B, Denig P. Predictors of HbA1c levels in patients initiating metformin. *Curr Med Res Opin*. 2016;32(12):2021-2028. doi:10.1080/03007995.2016.1227774
12. Jackson C. Multi-state models for panel data: the msm package for R. *J Stat Softw*. 2011;38(8):1-12. doi:10.18637/jss.v038.i08
13. Ambroz M, Geelink M, Smits KPJ, de Vries ST, Denig P. Sex disparities in medication prescribing amongst patients with type 2 diabetes mellitus managed in primary care. *Diabet Med*. 2022;40:e14987. doi:10.1111/dme.14987
14. Gilstrap LG, Mehrotra A, Bai B, Rose S, Blair RA, Chernew ME. National rates of initiation and intensification of antidiabetic therapy among patients with commercial insurance. *Diabetes Care*. 2018;41(8):1776-1782. doi:10.2337/dc17-2585
15. Joung KI, Jung GW, Park HH, Lee H, Park SH, Shin JY. Gender differences in adverse event reports associated with antidiabetic drugs. *Sci Rep*. 2020;10(1):17545. doi:10.1038/s41598-020-74000-4
16. de Vries ST, Denig P, Ekhart C, et al. Sex differences in adverse drug reactions reported to the National Pharmacovigilance Centre in The Netherlands: an explorative observational study. *Br J Clin Pharmacol*. 2019;85(7):1507-1515. doi:10.1111/bcp.13923
17. de Jong L, Harmark L, van Puijenbroek E. Time course, outcome and management of adverse drug reactions associated with metformin from patient's perspective: a prospective, observational cohort study in The Netherlands. *Eur J Clin Pharmacol*. 2016;72(5):615-622. doi:10.1007/s00228-016-2019-z
18. Desai U, Kirson NY, Kim J, et al. Time to treatment intensification after monotherapy failure and its association with subsequent glycemic control among 93,515 patients with type 2 diabetes. *Diabetes Care*. 2018;41(10):2096-2104. doi:10.2337/dc17-0662
19. Khunti K, Gomes MB, Pocock S, et al. Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: a systematic review. *Diabetes Obes Metab*. 2018;20(2):427-437. doi:10.1111/dom.13088
20. van Hateren KJ, Drion I, Kleefstra N, et al. A prospective observational study of quality of diabetes care in a shared care setting: trends and age differences (ZODIAC-19). *BMJ Open*. 2012;2(4):e001387. doi:10.1136/bmjopen-2012-001387
21. Paul SK, Klein K, Thorsted BL, Wolden ML, Khunti K. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. *Cardiovasc Diabetol*. 2015;14:100. doi:10.1186/s12933-015-0260-x
22. Barents ESE, Bilo HJG, Bouma M, et al. NHG standard diabetes mellitus type 2 (fourth review). 2022. Accessed June 29, 2020 https://www.nhg.org/standaarden/volledig/nhg-standaard-diabetes-mellitus-type-2

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Oktora MP, de Vos S, de Vries ST, Hak E, Denig P. Sex disparities in treatment patterns after metformin initiation among patients with type 2 diabetes mellitus. *Pharmacoepidemiol Drug Saf*. 2023;32(12):1395-1405. doi:10.1002/pds.5672