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ABSTRACT

Objective: The aim was to assess demographic and clinical factors as predictors of short (6 months) and long term (18 months) HbA1c levels in diabetes patients initiating metformin treatment.

Research design and methods: We conducted a cohort study including type 2 diabetes patients who received their first metformin prescription between 2007 and 2013 in the Groningen Initiative to Analyze Type 2 Diabetes Treatment (GIANTT) database. The primary outcome was HbA1c level at follow-up adjusted for baseline HbA1c; the secondary outcome was failing to achieve the target HbA1c level of 53 mmol/mol. Associations were analyzed by linear and logistic regression. Multiple imputation was used for missing data. Additional analyses stratified by dose and adherence level were conducted.

Results: The cohort included 6050 patients initiating metformin. Baseline HbA1c at target consistently predicted better HbA1c outcomes. Longer diabetes duration and lower total cholesterol level at baseline were predictors for higher HbA1c levels at 6 months. At 18 months, cholesterol level was not a predictor. Longer diabetes duration was also associated with not achieving the target HbA1c at follow-up. The association for longer diabetes duration was especially seen in patients starting on low dose treatment. No consistent associations were found for comorbidity and comedication.

Conclusions: Diabetes duration was a relevant predictor of HbA1c levels after 6 and 18 months of follow-up in patients initiating metformin. Given the study design, no causal inference can be made. Our study suggests that prompt treatment intensification may be needed in patients who have a longer diabetes duration at treatment initiation.

INTRODUCTION

The wide use of metformin in the treatment of type 2 diabetes mellitus (T2DM) is a result of extensive clinical experience, its documented effects on hard clinical outcomes, its weight-neutral feature and low risk of hypoglycemia. Nevertheless, some of the patients experience treatment failure with metformin by not reaching the desired HbA1c level. A prospective study in the United Kingdom found that, after a year of metformin treatment, up to 38% of patients with baseline HbA1c of 7.0–7.9% (53–63 mmol/mol) failed to achieve the recommended target HbA1c level of 7.0% (53 mmol/mol). The incidence of failure increased to 63% in patients with higher baseline HbA1c. A Danish study showed that the percentage of glucose-lowering drug starters that failed to achieve the target HbA1c level decreased from 40% to 20% in the period from 2000 to 2012, when the pre-treatment HbA1c levels also decreased. This indicates that despite earlier diagnosis and treatment in recent years, some patients may not respond sufficiently to treatment.

It is important for clinical practice to identify patients that will or will not respond to medication treatment. Little is known about predictors of actual treatment response but several studies have looked at changes in HbA1c levels in patients initiating metformin. A recent systematic review suggested that older age, shorter diabetes duration, low baseline HbA1c and lower BMI were all predictors of lower HbA1c levels at follow-up in patients initiating metformin. The number of studies with sufficient quality evaluating the effect of multiple demographic and clinical predictors, however, was limited. Moreover, although T2DM patients often have non-diabetes-related comorbidity and use on average more than eight drugs, not much is known about the influence of these factors on HbA1c in patients starting medication treatment. Both comorbidity and comorbidity could influence HbA1c levels through direct and indirect pathways, which may include treatment conflicts and changes in lifestyle or treatment goals.

Considering the wide use of metformin in T2DM treatment, further investigation into the predictors of initial HbA1c response is needed. Therefore, this study aims to identify demographic and clinical predictors of short term (6 months) and long term (18 months) HbA1c levels in patients initiating metformin treatment.

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Supplemental data for this article can be accessed here

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Patients and methods

Study design and population

This observational cohort study involved patients participating in the Groningen Initiative to Analyze Type 2 Diabetes Treatment (GIANTT) project who were diagnosed with T2DM and managed in general practice in northern Netherlands. The GIANTT database includes prescription data, comorbidity and event data, routine laboratory test results, and physical examinations extracted from Electronic Medical Records (EMRs). According to the code of conduct for the use of data in health research, no ethics committee approval is needed for research using data from anonymous medical records in the Netherlands.

Patients with possible diagnosis of T2DM were selected from electronic medical records based on diagnostic coding, laboratory values, treatment and text notes, whereafter the diagnosis was confirmed by the general practitioner. Patients were included in the study when they received a first prescription of metformin between January 2007 and December 2013, i.e. without a prescription for any glucose regulating drug in the past, and had been in the GIANTT cohort in the year preceding this first prescription. Patients with a first prescription of >1000 mg metformin/day were not included, since this is highly indicative of patients entering the practice with prevalent diabetes treatment. Also patients with incomplete prescription history were not included. The date of the first metformin prescription was used as the index date. Patients were excluded when (1) they were managed by a specialist for their diabetes care, (2) the date of diagnosis was unclear, i.e. erroneous or more than 1 year after the index date, (3) they had no laboratory measurements or prescriptions for any drug recorded before the index date, indicating incomplete data collection, (4) they were deregistered within 6 months after the index date, or (5) they received a treatment switch or addition during follow-up (6 months or 18 months).

HbA1c and other study variables

The primary outcome was the HbA1c level after 6 months (short term outcome) and 18 months (long term outcome) adjusted for the baseline HbA1c level. The secondary outcome was defined by not achieving HbA1c target level of 53 mmol/mol at 6 and 18 months (binary).

As possible predictors we included the baseline variables age, gender, HbA1c, diabetes duration, systolic and diastolic blood pressure, BMI, lipids (total cholesterol, HDL cholesterol, and triglycerides), estimated glomerular filtration rate (eGFR), comorbidities and comedication. LDL cholesterol level was not included as a predictor since it is calculated from other lipid levels which were already included as predictors.

Baseline data collected was the most recent measurements available in a period of 24 months before and up to the index date, except for BMI and comorbidities where a period of up to 5 years prior to the index date was included to reduce missing data. Age and diabetes duration were calculated at the index date. Baseline eGFR was calculated by the Modification of Diet in Renal Disease Study (MDRD) equation. The presence of comorbidities at baseline was assessed for cardiovascular diseases, malignancies, mental disorders, respiratory diseases, musculoskeletal diseases, liver diseases, and diabetes complications based on the International Classification of Primary Care (ICPC-1) codes or conditions as documented in GIANTT (Supplementary Appendix 1). Comedication was defined as the number of antihypertensive, lipid-lowering, and other chronic drugs prescribed in the preceding 5 months up to 1 month after metformin treatment initiation.

Both medication adherence and dose are expected to affect change in HbA1c. Medication adherence, expressed as medication possession ratio (MPR), was calculated as percentage of total days’ supply of medication in the period of 6 or 18 months. Dose for the 6 month period was defined as average initial dose, which was calculated by dividing total metformin dose in milligrams by days’ supply from all prescriptions within 6 months after the index date. Dose for the 18 month period was defined as the final daily dose, which was the last dose prescribed between 15 and 18 months after the index date.

Statistical analyses

Missing baseline data was dealt with by multiple imputation using a chained equations (MICE) procedure, after checking missing data patterns. Baseline data for HbA1c, blood pressure, BMI, lipids and eGFR were more often missing for patients with short diabetes duration at the index date. This is indicative of missingness not being completely at random, for which complete case analysis can give biased results. The imputation model contained all baseline variables to avoid bias in the analysis models. We generated 30 imputed datasets, approximated by the highest percentage of missing data in the variables. Imputed data was checked by fit of the model and visual inspection of overlaid histograms comparing observed and imputed data. Patients with missing outcome data were excluded from the models. Also patients with extremely elevated triglycerides (>9 mmol/l) were excluded since hypertriglyceridemia may falsely increase HbA1c.

Baseline characteristics of patients who did or did not achieve HbA1c target levels at 6 or 18 months were compared with Student’s t-test or chi-square test, where appropriate. The association between each predictor and the outcomes was first assessed in univariate analyses. Predictors with a p-value ≤.15 were included in multivariate linear and logistic regression models, using backward elimination. The initial model consisted of all predictors, and variable selection was done based on the estimates over all imputed datasets using Rubin’s rules. Variable with the highest p-value was then removed from the model. This selection was repeated until all variables with p-value of <.05 were retained in the model. Overall performance for the multivariate models was assessed by their explained variance $R^2$. Model checking was performed by visual inspection of the residual plot of each imputed dataset for the multivariate models. A link test was used to check the functional form of the models. For the linear regression, a slope discontinuity was observed around the HbA1c target level of 53 mmol/mol, and model fit
improved after including a binary variable of achieving target HbA1c level at baseline. Patients causing model instability (<0.01%) were excluded (Figure 1). Consistent patterns across the residual plots indicated no further problems with the imputation models. Discriminative ability of the models with binary outcome was assessed with C-index, which was calculated as an average from each imputed dataset.

The potential effect of adherence and dose on the outcome was analyzed by stratified analysis. Patients were stratified into two groups of adherence levels (<80% and ≥80%) and three dose levels (0–500 mg, >500–1000 mg, and >1000 mg). Patients with insufficient information about dosing or duration of a prescription were excluded. Additionally, we conducted a sensitivity analysis using a binary outcome model with the inclusion of those with treatment alteration, either a switch to or addition of other glucose lowering agents, within 6 or 18 months, as those who failed achieving the target for HbA1c.

All analyses were performed using Stata version 13 (StataCorp, TX, USA).

Results

Cohort characteristics

Between the years 2007 and 2013, there were 7061 new users of metformin in the GIANTT cohort, 1040 (15%) of whom did not meet the inclusion criteria of this study (Figure 1). The final cohort of 6050 patients consisted mostly of patients in their sixties, with 60% diagnosed as T2DM patients within the preceding 3 months. There were 5202 patients with an HbA1c at 6 month follow-up, and 4661 at 18 month follow-up. Included patients at 18 months more often had short diabetes duration at the time of treatment initiation but were otherwise similar to the patients included for at 6 months (Table 1). During the first 6 months no treatment alterations were observed but within 18 months treatment alteration was observed in 263 patients. Good adherence levels (≥80%) were seen for 87% of the patients in the 6 month period and for 82% in the 18 month period. Adherence levels were higher in those who reached the target level for HbA1c (Table 2).

Predictors of HbA1c level at follow-up

Univariate associations are presented in Supplementary Appendix 2. The multivariate linear regression model predicting HbA1c levels after 6 months, which explained 30% of the variance, showed significant associations for gender, age, diabetes duration, baseline HbA1c at target, total cholesterol, and being treated with lipid-lowering drugs (Table 3). Female
gender and older age were associated with higher HbA1c levels after 6 months but not 18 months (β coefficients 0.58 and 0.02 respectively). This means that females are expected to have a 0.58 mmol/mol higher HbA1c level than males at follow-up, and for each increase in age with 1 year the HbA1c level is expected to increase with 0.02 mmol/mol at follow-up. Patients initiating metformin treatment after longer diabetes duration were more likely to have higher HbA1c levels after 6 and 18 months compared to patients initiating metformin within 3 months after diagnosis. When initiating metformin after a diabetes duration of more than a year, HbA1c levels at follow-up are expected to be around 2 mmol/mol higher (β coefficients ranging between 1.90 and 2.10). Patients with baseline HbA1c at target were more likely to have lower HbA1c levels after 6 and 18 months (β coefficients 2.74 and 3.25). Higher BMI was associated with slightly higher HbA1c levels after 6 and 18 months (β coefficients 0.06 and 0.05). Higher total cholesterol level was associated with lower HbA1c levels after 6 months (β coefficient −0.21), whereas patients already treated with a lipid-lowering drug were more likely to have higher HbA1c levels after 6 months (β coefficient 0.48). Finally, patients treated with 1–5 other chronic drugs at baseline were more likely to have lower HbA1c levels after 18 months in comparison with patients without any comedication (β coefficient −0.58).

In the complete case analysis at 6 month follow-up, the association of gender, diabetes duration, baseline HbA1c at target, and treatment with a lipid-lowering drug were retained but the effect of age, BMI and total cholesterol were no longer significant (Table 3). Most regression coefficients and significance levels in the univariate analyses were similar to those observed in the imputed analysis (Supplementary Appendix 2).

When stratified by adherence level, most predictors identified in the full cohort were retained in those who were adherent (MPR of >80%) whereas diabetes duration and baseline HbA1c at target remained significant predictors for non-adherent patients (Supplementary Appendix 3). Due to small numbers other associations had large confidence.
Table 2. Treatment alteration, adherence, dose and HbA1c outcomes after 6 and 18 months, presented as mean ± standard deviation or count (%).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Missing (%)</th>
<th>6 months</th>
<th>18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>HbA1c &lt;53 mmol/mol</td>
<td>HbA1c ≥53 mmol/mol</td>
</tr>
<tr>
<td>Metformin monotherapy</td>
<td>5202</td>
<td>3782 (73)</td>
<td>1420 (27)</td>
</tr>
<tr>
<td>Treatment alteration</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Switch of therapy</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Addition of therapy</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MPR in 6 months</td>
<td>5.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–80%</td>
<td>614 (13)</td>
<td>404 (11)</td>
<td>210 (16)</td>
</tr>
<tr>
<td>MPR in 18 months</td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–80%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Average initial dose</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–500 mg</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&gt;500–1000 mg</td>
<td>1706 (33)</td>
<td>1153 (31)</td>
<td>553 (39)</td>
</tr>
<tr>
<td>&gt;1000–1500 mg</td>
<td>439 (8)</td>
<td>242 (6)</td>
<td>197 (14)</td>
</tr>
<tr>
<td>&gt;1500 mg</td>
<td>168 (3)</td>
<td>101 (3)</td>
<td>67 (5)</td>
</tr>
<tr>
<td>Final daily dose</td>
<td>20.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–500 mg</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&gt;500–1000 mg</td>
<td>1272 (34)</td>
<td>961 (34)</td>
<td>311 (36)</td>
</tr>
<tr>
<td>&gt;1000–1500 mg</td>
<td>524 (14)</td>
<td>345 (12)</td>
<td>179 (21)</td>
</tr>
<tr>
<td>&gt;1500 mg</td>
<td>440 (12)</td>
<td>262 (9)</td>
<td>178 (21)</td>
</tr>
<tr>
<td>HbA1c at 6 months (mmol/mol)</td>
<td>—</td>
<td>49.6 ± 7.5</td>
<td>46.4 ± 4.0</td>
</tr>
<tr>
<td>HbA1c at 18 months (mmol/mol)</td>
<td>—</td>
<td>48.6 ± 6.9</td>
<td>46.0 ± 4.2</td>
</tr>
</tbody>
</table>

Significant differences (p < .05) were found between those who did and did not reach the HbA1c target at 6 months (*) and 18 months (**).

MPR, medication possession ratio.

Table 3. Multivariate analyses of baseline predictors of HbA1c level after 6 and 18 months of metformin treatment adjusted for baseline HbA1c (linear regression).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete case N = 3417</th>
<th>Imputed N = 5165</th>
<th>Complete case N = 3771</th>
<th>Imputed N = 4661</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI) p</td>
<td>β (95% CI) p</td>
<td>β (95% CI) p</td>
<td>β (95% CI) p</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.61 (0.24; 0.98) .001</td>
<td>0.58 (0.21; 0.94) .002</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age</td>
<td>—</td>
<td>0.02 (0.01; 0.04) .007</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diabetes duration (months)</td>
<td>0–3</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>4–12</td>
<td>1.59 (1.03; 2.15) .001</td>
<td>1.43 (0.87; 1.99) .001</td>
<td>1.66 (1.05; 2.27) .001</td>
<td>1.56 (0.94; 2.17) .001</td>
</tr>
<tr>
<td>13–36</td>
<td>1.96 (1.47; 2.46) .001</td>
<td>1.90 (1.39; 2.40) .001</td>
<td>1.88 (1.33; 2.44) .001</td>
<td>1.93 (1.36; 2.50) .001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.06 (0.01; 0.10) .013</td>
<td>—</td>
<td>0.05 (0.01; 0.09) .012</td>
<td>—</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>—</td>
<td>−0.21 (−0.40; −0.01) .037</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Number of lipid-lowering drugs</td>
<td>None</td>
<td>0.00</td>
<td>0.00</td>
<td>—</td>
</tr>
<tr>
<td>1 drug</td>
<td>0.60 (0.23; 0.99) .002</td>
<td>0.48 (0.11; 0.85) .011</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>&gt;1 drug</td>
<td>0.81 (−0.28; 1.91) .146</td>
<td>0.21 (−0.90; 1.32) .711</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Number of other chronic drugs</td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>0.00</td>
</tr>
<tr>
<td>1–5 drugs</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>−0.46 (−0.91; −0.01) .044</td>
</tr>
<tr>
<td>6–10 drugs</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.36 (0.39; 1.11) .348</td>
</tr>
<tr>
<td>&gt;10 drugs</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.19 (1.69; 2.06) .846</td>
</tr>
</tbody>
</table>

R² (%) | 31 | 30 | 15 | 12 |

In intervals. In both average initial and final daily dose stratification, the effect of baseline HbA1c at target was seen across most dose levels (Supplementary Appendix 4). Stratifying by average initial dose and final daily dose showed that the effects of diabetes duration were not observed in those prescribed on average more than 1000 mg of metformin in the first 6 months of treatment (Supplementary Appendix 4).

Predictors of failing to achieve HbA1c target level

After 6 months, 27% of patients did not achieve the HbA1c target of <53 mmol/mol, while this was 22% after 18 months. Comparing metformin users who did or did not reach the target HbA1c level, poorer achievement was seen for males, and patients with higher baseline HbA1c and eGFR levels (Table 1). BMI was slightly higher for those not reaching the target HbA1c level, and around 6 mmol/mol in those who did not reach the target level (Table 2). Treatment alterations were more common in patients who did not reach the target after 18 months (14%) compared to those reaching the target (3%).

Univariate associations are presented in Supplementary Appendix 2. Multivariate logistic regression models showed an
association of longer diabetes duration (OR ranging from 1.23 to 1.58), and baseline HbA1c at target (OR 0.10 after 6 months and 0.22 after 18 months) with failing to achieve the HbA1c target level at follow-up (Table 4). These effects were retained in the sensitivity analysis including those with treatment alteration as failing the target (Supplementary Appendix 3). Patients with higher triglycerides, higher eGFR, and on 6–10 other chronic drugs were more likely to fail the target HbA1c after 6 months (OR 1.08, 1.01, and 1.42 respectively). Finally, an increase in BMI resulted in a slightly higher chance of failing to achieve the target after 18 months (OR 1.02).

When stratified by adherence and dose, the associations of diabetes duration and baseline HbA1c at target with failure to achieve target at follow-up were seen for adherent patients and across all final dose strata (Supplementary Appendices 3 and 4). The association for diabetes duration was not observed in patients prescribed on average more than 1000 mg of metformin in the first 6 months of treatment.

**Discussion**

This study examined the demographic and clinical predictors of HbA1c level after short (6 months) and long term (18 months) follow-up in patients initiating metformin. A longer diabetes duration at treatment initiation was a clear predictor for poorer short and long term outcomes. Also, patients with their baseline HbA1c at target were more likely to have better HbA1c levels up to 18 month follow-up. Furthermore, we found that higher total cholesterol level at baseline was associated with lower HbA1c level after 6 months.

The negative effect of longer diabetes duration at initiation of treatment is in line with previous studies, and might indicate lower β-cell function. In another Dutch cohort study, patients with a longer diabetes duration also showed a more unfavorable course of HbA1c levels. Our study showed that when stratified by dose, the effect of diabetes duration remained relevant in the cohorts with an average initial dose up to 1000 mg/day. In patients prescribed higher doses in the first 6 months, the impact of a longer diabetes duration on HbA1c levels at follow-up was attenuated. This finding suggests that the impact of diabetes duration is related to the dose response of metformin, and metformin should thus be promptly up-titrated to at least 1000 mg per day in patients who initiate treatment after a longer diabetes duration. Diabetes guidelines recommend treating to target but no specific recommendations are made for patients who initiate treatment after longer diabetes duration. In general, lack of treatment intensification in patients not reaching targets is common. The Dutch guideline for general practice mentions that metformin can be up-titrated to 3000 mg per day but this may be limited by the occurrence of side effects.

Previous studies have shown that patients with lower baseline HbA1c levels had less reduction in their HbA1c after 6 months, and patients with higher baseline HbA1c levels were less likely to achieve the HbA1c targets after 1 year. Such associations are to be expected, but after adjustment for baseline HbA1c levels, we still observed that patients with their baseline HbA1c not at target showed poorer HbA1c levels up to 18 months after metformin initiation. This was seen regardless of the final daily dose or adherence level. These findings suggest that patients who do not reach the target in the first 6 months of treatment require attention. Previously, another Dutch cohort study identified four distinct HbA1c trajectories over time. They observed that the majority of patients can achieve or maintain HbA1c levels at target, but that there is a small (8%) group of patients with a delayed or poor HbA1c response who do not reach the HbA1c target even after a mean follow-up of more than 5 years. Whether this is because of poor treatment response, lack of treatment intensification or medication adherence was not clear.

We observed an association between higher total cholesterol levels at baseline and lower HbA1c levels after 6 months of follow-up. Furthermore, patients already treated with a lipid-lowering drug had higher HbA1c levels after 6 months. There is a growing body of literature on the interplay between lipids, adiposity, and glycemia.
Especially low LDL-cholesterol levels and treatment with high-dose statins were previously associated with higher glucose levels and diabetes risk. Our study adds to these findings, showing that in patients recently diagnosed with diabetes both low total cholesterol level and treatment with lipid-lowering drugs were associated with less short-term improvement in HbA1c levels after treatment initiation. Further research is needed to clarify the underlying mechanism. Notably, previous studies found no significant association of lipid levels with reaching HbA1c targets. These studies, however, conducted complete case analysis which is vulnerable to selection bias, and can lead to underestimating the association with lipid levels. Indeed, we observed selection bias and did not see effects of total cholesterol in our complete case analysis. Also, for BMI complete case analyses may be biased due to the fact the BMI data are often not missing completely at random. In our primary analysis we observed an association between BMI and HbA1c levels at follow-up, indicating that a lower BMI at baseline is associated with better short and long term outcomes, but no such association was seen in the complete case analysis. Previous studies using complete case analysis indicated that there may be a small effect of BMI on HbA1c change in metformin users but the HbA1c reduction was not significantly smaller in obese compared to non-obese patients.

The influence of diabetes-related comorbidity has been explored in one previous study, showing no association between achieving HbA1c target levels and cardiovascular diseases or diabetes complications in metformin users. We also found no such association. In addition, we did not find any significant association with other comorbidities at baseline. We observed a negative association between the use of 1–5 other chronic drugs and HbA1c level after 18 months of follow-up, but no such associations after 6 months, nor was there an association in patients using more than five other drugs. This could be a chance finding. Looking at single drugs or diseases might reveal associations we could not detect since we used aggregated groups of drugs and diseases. A recent study showed higher odds of elevated HbA1c levels for diabetes patients with respiratory and joint disorders who were taking NSAIDs. Effects were mainly seen for patients on insulin, and may be due to competing demands. Our study indicates that comorbidity and comedication in general do not influence HbA1c levels at follow-up in patients initiating metformin.

Patients not achieving the HbA1c targets at 6 or 18 months were on higher doses metformin and showed lower adherence levels. Metformin is known to have a linear dose–response relationship. The higher doses were likely due to the prescribers’ efforts in increasing the dose for patients with higher baseline HbA1c who did not yet reach the target HbA1c. Also, in patients being non-adherent less treatment response is to be expected. The analyses stratified for adherence showed that the effects of diabetes duration, gender and total cholesterol were mainly significant in the cohort of patients with good adherence levels. The cohorts with lower adherence levels, however, were relatively small and had less statistical power.

### Strengths and limitations

This study used an observational study design and real world data in an unrestricted population of type 2 diabetes patients. The patients included were followed up by their general practitioner in a setting where adherence to diabetes care recommendations is generally high. The database includes all prescription data and test results conducted in routine practice extracted from EMRs using validated procedures which makes it particularly suitable for detailed analysis of outcomes. Missing data, however, is to be expected and was not completely at random. Most missing data was seen for baseline BMI (24–26%) and lipid levels (25–28%). Patients with missing data had a short diabetes duration, and apparently initiated metformin treatment before a full risk factor screening was conducted. It is reasonable to assume that these patients had high glucose levels but also higher levels of the other risk factors. The use of complete case analysis thus leads to selection bias, which results in underestimation of the effect of these other risk factors. Looking at the complete case analysis at 6 months, we lost more than a third of the patients, and BMI and total cholesterol were no longer included as predictors in the model. To avoid selection bias, multiple imputation by chained equation was applied in this study. This method creates multiple predictions for each missing value based on all available information about a patient. This is considered superior to complete case analysis.

For the analyses, we excluded 14% and 18% of patients without HbA1c outcome data after 6 and 18 months, respectively. Furthermore, some misclassification of metformin initiators may occur. We tried to minimize misclassification by excluding patients with an apparent erroneous diagnosis date, or who had been prescribed a glucose-lowering drug in the past, or who appeared to have entered the practice with prevalent diabetes treatment.

We studied predictors of HbA1c levels in patients initiating metformin treatment. Therefore the findings cannot be interpreted as predictors of metformin treatment response. We conducted stratified analyses to assess whether associations between patient characteristics and outcomes found were consistent for patients with different dose and adherence levels. For adherence, we used a classification based on MPR, which is considered an estimate of actual adherence. However, the MPR estimate may be less precise for the 6 month period than for the 18 month period. We did not include genetic factors, race, socioeconomic status or lifestyle factors such as smoking and diet, since such data was not available. While these may be of importance, previous studies showed no associations of race, socioeconomic status and lifestyle with HbA1c response in metformin initiators. Associations have been found between some gene variants and response to metformin.

To conclude, despite including more clinical variables this study confirmed that only a few demographic or clinical factors can predict HbA1c response in diabetes patients initiating metformin treatment. In addition to previous studies, our study showed that diabetes duration in particular was associated with HbA1c levels in patients treated with low dose.
metformin in the first 6 months of treatment. Prompt treatment intensification in such cases may thus be sensible. Further studies are needed to identify predictors of metformin treatment response, especially focusing on lipid levels and genetic factors.

**References**

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