Original article

Adherence to standard-dose or low-dose statin treatment and low-density lipoprotein cholesterol response in type 2 diabetes patients

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Abstract

Objective:
To determine the association between adherence, dose and low-density lipoprotein (LDL) cholesterol response in patients with type 2 diabetes initiating statin treatment.

Research design and methods:
This cohort study was performed using data for 2007–2012 from the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT) database. The association between adherence to a standard-dose statin and LDL cholesterol response was assessed using linear regression, adjusting for covariates. The effect of low-dose versus standard-dose was assessed in a propensity-score matched cohort. Adherence rates, defined as the proportion of days covered (PDC), were estimated between statin initiation and LDL outcome measurement.

Main outcome measure:
LDL cholesterol level at follow-up.

Results:
The effect of adherence on LDL cholesterol response, measured in 2160 patients, was dependent on the baseline LDL cholesterol level. For patients with a baseline LDL cholesterol of 3.7 mmol/l and an adherence rate of 80%, a 40% reduction in LDL cholesterol was predicted. In the matched sample of 1144 patients, the treatment dose showed a difference in impact on the outcome for adherence rates higher than 50%. It was estimated that a patient with a baseline LDL cholesterol of 3.7 mmol/l will need an adherence rate of at least 76% on low-dose and 63% on standard-dose treatment to reach the LDL cholesterol target of 2.5 mmol/l.

Limitations:
Adherence was measured as the PDC, which is known to overestimate actual adherence. Also, we were not able to adjust for lifestyle factors.

Conclusions:
We determined the concurrent effect of treatment adherence and dose on LDL cholesterol outcomes. Given the adherence levels seen in clinical practice, diabetes patients initiating statin treatment are at high risk of not reaching the recommended cholesterol target, especially when they start on a low-dose statin.

Introduction

Patients with type 2 diabetes are at high risk for developing cardiovascular disease (CVD), and the use of statins is associated with a reduction in the risk of cardiovascular events.1,2 Clinical guidelines recommend statin treatment for
almost all diabetes patients unless they have a very low cardiovascular risk\textsuperscript{3,5}. Dutch guidelines recommend starting with a standard-dose statin for both primary and secondary prevention, and aim for an LDL cholesterol level of \( <2.5 \text{mmol/l} \) (\(<97 \text{mg/dl}\)), which is considered the most cost-effective strategy\textsuperscript{1}. It is expected that not all patients will achieve the lipid targets on standard-dose treatment, depending on their LDL cholesterol level at initiation, in which case they should switch to a high-dose statin. In case of low LDL cholesterol levels, one may start with a low-dose statin\textsuperscript{3}.

Observational studies show that lipid targets are not met in at least a third of patients\textsuperscript{6,7}. Insufficient treatment response could be due to prescribing low-dose treatment\textsuperscript{6,8} or non-adherence to treatment\textsuperscript{9–12}. In the last decade, the prescribed daily dose of statins has increased but on average patients receive less than the recommended standard dose\textsuperscript{3,13}. Adherence to statins has also improved but remains sub-optimal with up to 30\% of patients being non-adherent in the first year after initiation\textsuperscript{14}. It is not clear, however, what the concurrent impact of statin dose and non-adherence is on treatment response in clinical practice.

Several studies have assessed the association between non-adherence and LDL cholesterol response in statin initiators but most used arbitrary cut-off points for adherence\textsuperscript{9–12}. This makes it difficult to determine what level of non-adherence may lead to a clinically relevant decrease in treatment response. Moreover, few studies differentiated between the choice or dose of statins\textsuperscript{9,11}. One study observed LDL cholesterol outcomes decreasing from \( 3.6 \text{mmol/l} \) (\( 140 \text{mg/dl}\)) to \( 2.4 \text{mmol/l} \) (\( 95 \text{mg/dl}\)) with adherence levels increasing from 20\% to 100\%, and also observed differences between statins, not taking account of dose\textsuperscript{3}. Another study showed that high risk patients on low-dose statins were less likely to achieve the LDL cholesterol target across several adherence categories\textsuperscript{11}. For clinical practice it is important to gain better insight in the impact of the level of non-adherence in relation to the dose of statin on treatment response.

The aim of this study is to determine the association between statin adherence and LDL cholesterol response in type 2 diabetes patients initiating on the recommended standard-dose statin treatment, and to assess the effect of low-dose versus standard-dose on this association.

### Patients and methods

#### Study design

A retrospective cohort study was performed in patients with type 2 diabetes initiating lipid-lowering treatment between January 2007 and December 2012. First, the association between adherence to statin treatment and LDL cholesterol response was determined in patients on standard-dose statin treatment. Second, the effect of low-dose versus standard-dose statin treatment on this association was determined in a propensity-score matched cohort.

#### Setting

This study was performed in the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT) database. The GIANTT database contains anonymized longitudinal information retrieved from electronic medical records of general practitioners and is maintained by the University Medical Centre Groningen\textsuperscript{15}. These records include medical history, prescription data, routine laboratory test results and physical examinations of type 2 diabetes patients from the northern part of the Netherlands that are managed in primary care. Medical history consists of date of diabetes diagnosis and comorbidity data, which is based on the International Classification of Primary Care (ICPC)\textsuperscript{16} or text descriptions that are coded manually.

#### Patient selection

Patients managed in general practice for type 2 diabetes initiating statin treatment were included (Anatomical Therapeutic Chemical [ATC] code C10AA)\textsuperscript{17}. Since the documented date of diagnosis is not always exact in our database, we allowed for a grace period of up to 180 days before the documented diagnosis in which the statin might be initiated. Statin initiation was defined as having no prescription for any lipid lowering medication (ATC code C10) in the preceding 360 days. Patients needed to have sufficient medical history to be classified as initiators, and a follow-up period of at least 270 days. Patients with temporary absence from the database, for example due to being institutionalized, as identified by long-term gaps in all prescribed medication, were not included as initiators.

Patients were included in the standard-dose treatment group when they were prescribed simvastatin 40 mg, atorvastatin 20 mg, or rosuvastatin 5 or 10 mg from statin initiation till the LDL cholesterol measurement at follow-up. These doses are recommended in the first steps of the Dutch guideline and expected to reduce the LDL cholesterol on average by 37\% to 43\%\textsuperscript{3,18,19}. Patients were included in the low-dose group when they were prescribed pravastatin 40 mg, simvastatin 20 mg or atorvastatin 10 mg from statin initiation till the LDL cholesterol measurement at follow-up. Such low-dose treatment is expected to reduce the LDL cholesterol on average by 32\% to 38\%\textsuperscript{3,18,19}.

For assessing LDL cholesterol response, which was calculated using the Friedewald equation, patients without an LDL cholesterol measurement at baseline or follow-up, or with triglyceride levels \( >4.5 \text{mmol/l} \) which may result in
unreliable LDL cholesterol calculations, or who used co-medications that interact with statin treatment were excluded. We included as interacting medication: (1) medication causing an increase of the statin concentration (amiodarone, amlodipine, diltiazem, verapamil, ciclosporin, imatinib, ticagrelor, danazol, and colchicine), and (2) medication causing a decrease of the statin concentration (bosentan, carbamazepin, phenobarbital, phenytoin, and primidone).

Adherence measurement

Adherence was estimated over a period from statin initiation till the LDL cholesterol measurement at follow-up. It was calculated as the proportion of days covered (PDC), which expresses the proportion of days for which a patient has received medication in the study period. Patients receiving treatment in daily packages or with single prescription durations longer than 270 days or with missing prescription data were excluded, since the PDC cannot be reliably calculated in such cases.

LDL cholesterol response

The primary outcome measure was the LDL cholesterol level (mmol/l) at least 270 days and not more than 540 days after statin initiation. For patients with multiple LDL cholesterol measurements in this period, the one nearest to 360 days after statin initiation was selected. As secondary outcome, percentages of patients achieving the LDL cholesterol target of 2.5 mmol/l were estimated.

Confounders

The association between statin adherence and LDL cholesterol response may be confounded by patient characteristics. In addition to baseline LDL cholesterol level, the following baseline characteristics possibly related to cardiometabolic treatment were considered: (1) age, gender, and diabetes duration; (2) HDL cholesterol, total cholesterol, triglycerides, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, HbA1c, creatinine, potassium, hemoglobin, albuminuria, body mass index (BMI) and smoking status; (3) comorbidity, including lipid disorders (ICPC code T93), high blood pressure (K85/K86/K87), stroke/cerebrovascular accident (K89), transient ischemic attack (K90), atherosclerosis (K91), myocardial infarction/ischemic heart disease (K75/K76), angina pectoris (K74), heart failure (K77), bypass/angioplasty (including: coronary artery bypass grafting [CABG], percutaneous transluminal coronary angioplasty [PTCA], peripheral bypass and percutaneous transluminal angioplasty [PTA]) and microvascular complications including: proteinuria (U98/U90), diabetic neuropathy (N94.2), diabetic foot, retinopathy (F83) and blindness.

Statistical analyses

Descriptive statistics are presented for patients on low-dose and standard-dose treatment who persisted on the same dose up to the LDL cholesterol measurement at follow-up, and they were compared on baseline characteristics and adherence rates using chi-square tests, independent sample t-tests and Wilcoxon rank-sum tests.

To determine the association between adherence and LDL cholesterol response in patients on standard-dose statin treatment, we first used a multivariate linear regression model adjusted for baseline LDL cholesterol and possible confounders. Confounders were selected via forward selection and included with a p-value of 0.05. Missing data on SBP, DBP, HbA1c, fasting glucose, HDL cholesterol, triglycerides, total cholesterol, creatinine, potassium, hemoglobin, albuminuria, and BMI were imputed using multiple imputation. Patients who had no data on SBP and DBP and HbA1c and BMI were excluded from this analysis, since imputation was considered unreliable for these patients.

Next, to determine the effect of low-dose versus standard-dose statin treatment on the association between adherence and LDL cholesterol response a propensity-score matched cohort was formed. Since patients initiating low-dose treatment may differ from patients initiating standard-dose treatment, confounding by indication can be expected. Propensity-score matching is a method that is recommended to balance treatment groups and reduce indication bias. Within the matched sample, the association between adherence, baseline LDL cholesterol and treatment dose (low-dose versus standard-dose) and the interaction terms adherence/baseline LDL cholesterol and adherence/treatment dose were determined using a multivariate linear regression model adjusted for baseline LDL cholesterol.

The propensity scores were calculated using logistic regression based on all available demographic and clinical characteristics and comorbidity data (see Confounders). Patients on low-dose and standard-dose treatment were matched 1:1 on the propensity score using a nearest neighbor matching algorithm with a caliper width equal to 0.01. The standardized differences of characteristics between the low-dose and standard-dose group were calculated, and variables with a standardized difference of ≤0.10 were assumed to be balanced. We adjusted variable selection of the propensity score generating model until all baseline variables were sufficiently balanced in the matched cohort.

Robustness of the regression models was verified by examining normality and homoscedasticity of residuals.
and collinearity of the model. This resulted in log transforming the outcome variable and centering the variables adherence and LDL cholesterol at baseline. The analyses were performed with Stata version 13 (Stata Corp., College Station, TX, USA).

Sensitivity analysis
To examine whether the period of follow-up may affect the results, we conducted two additional analyses with more restricted follow-up periods of 270–450 days (around 1 year ± 90 days) and 315–405 days (around 1 year ± 45 days) after statin initiation.

Results
In total 6046 of the type 2 diabetes patients initiating statin treatment between 2007 and 2012 received a standard-dose statin, and 1525 patients received a low-dose statin during the first year of treatment (Figure 1). More females (chi-square test; \( p < 0.001 \)), older patients, and those with a longer diabetes duration and lower glucose levels (t-tests; \( p < 0.001 \)) were on low-dose treatment compared to standard-dose treatment (Table 1). The average baseline LDL cholesterol levels were 3.7 mmol/l and 3.8 mmol/l for patients initiating low-dose and standard-dose treatment respectively (t-test; \( p = 0.029 \)). More patients were above the LDL cholesterol target

Figure 1. Selection of standard-dose and low-dose patients. BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; LDL cholesterol, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
level at baseline in the low-dose treatment group than in the standard-dose treatment group (66% vs. 62%; chi-square test: \( p = 0.007 \)). In the standard-dose group more patients had missing LDL cholesterol measurement at baseline (29% vs. 32%; chi-square test: \( p = 0.016 \)).

There were small differences in history of angina pectoris and myocardial infarction or ischemic heart disease between the groups (Table 1).

Fewer patients in the low-dose treatment group reached the target in comparison to the standard-dose group (Table 2). The median adherence was 85% in the low-dose group (interquartile range [IQR]: 47%–99%) and 89% in the standard-dose group (IQR: 55%–99%) (Wilcoxon rank-sum test; \( p = 0.014 \)) (Figure 2).

Table 1. Characteristics of baseline populations on low-dose and standard-dose statin treatment.

| Variable                      | Low-dose (n = 1525) | Standard-dose (n = 6046) | \( p \) Value |
|-------------------------------|---------------------|--------------------------|--------------|
| Age, mean (SD)                | 64.6 (11.6)         | 62.3 (12.1)              | <0.001       |
| Male sex                      | 46.5%               | 52.4%                    | <0.001       |
| SBP, mmHg (SD)                | 143.7 (19.3)        | 144.5 (20.1)             | 0.171        |
| DBP, mmHg (SD)                | 82.0 (10.5)         | 82.7 (10.6)              | 0.036        |
| Diabetes duration (IQR)       | 2 (0–6)             | 1 (0–5)                  | <0.001       |
| Fasting glucose, mmol/l       | 7.9 (2.4)           | 8.2 (2.9)                | <0.001       |
| HbA1c (%)                     | 7.0 (1.2)           | 7.3 (1.6)                | <0.001       |
| LDL cholesterol, mmol/l       | 3.68 (0.8)          | 3.75 (1.0)               | 0.029        |
| HDL cholesterol, mmol/l       | 1.2 (0.3)           | 1.2 (0.3)                | <0.001       |
| Triglycerides, mmol/l         | 2.1 (1.8)           | 2.3 (1.7)                | <0.001       |
| Total cholesterol, mmol/l     | 5.6 (1.0)           | 5.7 (1.2)                | <0.001       |
| Creatinine, μmol/l            | 82.6 (22.5)         | 82.6 (21.6)              | 0.993        |
| Potassium, mmol/l             | 4.3 (0.42)          | 4.2 (0.42)               | 0.053        |
| Hemoglobin, mmol/l            | 8.9 (0.9)           | 9.0 (0.9)                | 0.022        |
| Body mass index               | 30.6 (5.6)          | 30.6 (5.8)               | 0.997        |
| Smoking                       | 22.9%               | 28.5%                    | 0.006        |

Comorbidity:

- Hypertension: 37.4% vs. 36.2% \((p = 0.396)\)
- Angina pectoris: 4.7% vs. 3.4% \((p = 0.020)\)
- Myocardial infarction/IHD: 5.1% vs. 4.1% \((p = 0.071)\)
- Heart failure: 1.7% vs. 2.3% \((p = 0.189)\)
- Bypass/angioplasty: 2.6% vs. 2.6% \((p = 0.925)\)
- Lipid disorder: 7.8% vs. 7.5% \((p = 0.682)\)
- Stroke/CVA/TIA/atherosclerosis: 4.6% vs. 4.5% \((p = 0.856)\)
- Microvascular complications: 4.1% vs. 3.6% \((p = 0.301)\)

CVA, cerebrovascular accident; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IHD, ischemic heart disease; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischemic attack.

Table 2. LDL cholesterol outcomes at follow-up.

| LDL cholesterol at follow-up | Low-dose | Standard-dose | \( p \) Value |
|------------------------------|----------|---------------|--------------|
| LDL cholesterol missing, n (%) | 494 (32.4) | 1951 (32.3) | 0.926        |
| Mean LDL cholesterol level, mmol/l (SD) | 2.63 (0.87) | 2.44 (0.95) | <0.001       |
| LDL cholesterol at target, n (%) | 566 (37.1) | 2627 (43.5) | <0.001       |
| LDL cholesterol above target, n (%) | 465 (30.5) | 1468 (24.3) | <0.001       |

Figure 2. Boxplots showing the proportion of days covered (PDC) till the follow-up LDL cholesterol measurement for patients on standard-dose and low-dose treatment.

Adherence and LDL cholesterol response

A total of 2160 patients were included in the standard-dose treatment group for analyzing the association between adherence and LDL cholesterol response (Figure 1). Most patients were excluded because of missing LDL cholesterol.
measurements. Excluded patients had a slightly longer duration of diabetes (Supplemental Table S1). The multivariate linear model included adherence, LDL cholesterol at baseline, age, lipid disorder, fasting glucose, hypertension and diabetic neuropathy (Figure 3). Adherence was significantly associated with LDL cholesterol at follow-up, with every 10% increase in adherence resulting in an expected decrease in LDL cholesterol of 0.068 mmol/l (adjusted coefficient $-0.0068$, $p<0.001$). For patients with a baseline LDL cholesterol value of 3.7 mmol/l, an adherence rate of 100% was associated with a 48% reduction in LDL cholesterol; an adherence rate of 80% was associated with a reduction of 40%; and an adherence rate of 60% was associated with a reduction of 31% in LDL cholesterol. In this range, a 10% decrease in adherence was associated with 4% less reduction in LDL cholesterol.

### Sensitivity analysis

Restricting the follow-up period to 270–450 days resulted in the inclusion of 1595 patients; with a follow-up period of 315–405 days only 941 patients could be included.

| Variable                          | Coefficient ($\beta$) | Standard error | $p$-value |
|----------------------------------|-----------------------|----------------|-----------|
| Adherence (PDC) (%)              | −0.0068               | 0.00025        | <0.001    |
| LDL cholesterol at baseline (mmol/l) | 0.1594               | 0.00660        | <0.001    |
| Age (years)                      | −0.0026               | 0.00055        | <0.001    |
| Lipid disorder (yes/no)          | 0.0808                | 0.02464        | 0.001     |
| Fasting glucose (mmol/l)         | −0.0107               | 0.00247        | <0.001    |
| Hypertension (yes/no)            | −0.0266               | 0.01323        | 0.044     |
| Diabetic neuropathy (yes/no)     | −0.2636               | 0.12583        | 0.036     |
| Constant                         | 1.001                 | 0.05218        | <0.001    |

$R^2 = 0.384$, $p < 0.001$.  

LDL-c, LDL cholesterol; PDC, proportion of days covered.

Figure 3. Predicted LDL cholesterol response in patients ($n=2160$) on standard-dose treatment for different adherence rates using a multivariate linear model.
Using these restrictions the observed associations between adherence and LDL cholesterol response were similar (Supplemental Figures S1 and S2).

**Low-dose versus standard-dose treatment**

A propensity-score matched sample of 1144 patients on low dose and on standard dose was created, for which the baseline characteristics were balanced (Supplemental Table S2). The multivariate linear model included adherence, LDL cholesterol at baseline, low-dose treatment, and the interaction terms adherence/LDL cholesterol at baseline and adherence/low-dose treatment. The average LDL cholesterol level of these patients at baseline was 3.7 mmol/l. Being on low-dose treatment was significantly associated with lower LDL cholesterol response at follow-up (Figure 4). Again adherence was found to be associated with LDL cholesterol at follow-up (coefficient $-0.0067$, $p<0.001$). This association was however dependent on LDL cholesterol at baseline (coefficient $-0.0009$ for the interaction term, $p=0.013$), showing a stronger effect of adherence on LDL cholesterol at follow-up in patients with higher baseline LDL cholesterol levels. Also the treatment dose affected the relation between adherence and LDL cholesterol at follow-up (coefficient $-0.0016$ for the interaction term, $p=0.010$), showing a stronger effect of adherence on LDL cholesterol for patients on a low-dose treatment.

Following from the model presented in Figure 4, an adherence rate of 80% in patients with a baseline LDL cholesterol of 3.7 mmol/l treated with low-dose treatment was associated with a 34% reduction in LDL cholesterol compared to 40% reduction for patients treated with standard-dose statin treatment. For adherence rates higher than 50% and a baseline LDL cholesterol of 3.7 mmol/l, patients on low-dose treatment need to be at least 10% more adherent than patients on standard-dose

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**Table:**

| Variable                                                      | Coefficient ($\beta$) | Standard error | $p$-value |
|---------------------------------------------------------------|-----------------------|----------------|-----------|
| Low-dose treatment                                            | 0.0923                | 0.0159         | <0.001    |
| LDL cholesterol at baseline                                  | 0.1668                | 0.0090         | <0.001    |
| Adherence (PDC)                                               | $-0.0067$             | 0.0045         | <0.001    |
| Adherence (PDC) $\times$ LDL cholesterol at baseline         | $-0.0009$             | 0.0004         | 0.013     |
| Adherence (PDC) $\times$ low-dose treatment                  | 0.0016                | 0.0006         | 0.010     |
| Constant                                                      | 0.8154                | 0.0112         | <0.001    |

$R^2 = 0.385$, $p < 0.001$.  
CI, confidence interval; LDL-c, LDL cholesterol; PDC, proportion of days covered.

**Figure 4:** Predicted LDL cholesterol response for low-dose and standard-dose statin treatment in a propensity-score matched sample ($n=1144$). Associations are presented for a LDL cholesterol baseline level of 3.7 mmol/l.
treatment to reach the same LDL cholesterol level (Figure 4). For example, to reach the LDL cholesterol target of 2.5 mmol/l (97 mg/dl), a patient with a baseline LDL cholesterol of 3.7 mmol/l needs to have an adherence rate of at least 76% on low-dose treatment and of 63% on standard-dose treatment. In our study population, 38% in the low-dose and 28% in the standard-dose treatment group did not reach these adherence rates. Patients with a lower baseline LDL cholesterol level of, for example, 2.7 mmol/l need to have an adherence rate of at least 37% on low-dose treatment and 33% on standard-dose treatment to reach this target. With a higher baseline LDL cholesterol level of 4.7 mmol/l an adherence rate of 88% is needed on standard-dose treatment, whereas patients on low-dose treatment are not expected to reach their target even with an adherence rate of 100%.

Discussion

We determined the concurrent effect of treatment dose and adherence on LDL cholesterol outcomes in diabetes patients starting on statins, where previous research focused on adherence disregarding the statin dose (or vice versa). In patients with a baseline LDL cholesterol level of 3.7 mmol/l we estimated that a 10% reduction in adherence rate on standard-dose treatment is associated with 4% less reduction in LDL cholesterol. Such patients need to take more than 60% of their medication to reach the target level of 2.5 mmol/l. Patients on low-dose treatment need to be at least 10% more adherent than patients on standard-dose treatment to reach the same LDL cholesterol level.

In line with previous findings, we observed that reaching lipid targets was more difficult with low-dose statin treatment. Nevertheless, a substantial number of patients started on low-dose statin treatment. Remarkably, we found that these patients had a high average baseline level of 3.7 mmol/l, which was almost similar to that of patients starting on standard-dose treatment. As observed before, we found that older and female patients were more often treated with a low dose. Fear of adverse events in such patients may be the reason for initiating on a low dose but in patients with high LDL cholesterol levels up-titration to a maximally tolerated dose would be the next step. The patients in our study, however, remained on low-dose statin treatment until the end of follow-up.

The predicted LDL cholesterol reduction of 40% in patients who were 80% adherent to standard-dose treatment was similar to reductions reported in the reviews based on clinical trials. It has been acknowledged that patients may not be adherent in trials either. Regarding the association between adherence and outcomes, one small sample size study found that 10% less medication taken would correlate with 3.1% less reduction in LDL cholesterol in patients who had an average baseline LDL cholesterol of 3.9 mmol/l. Most patients in that study were on low-dose simvastatin or atorvastatin treatment. Our study provides new insights into the effect of being non-adherent on standard-dose compared to low-dose treatment. For patients on standard dose, a 10% decrease in adherence is associated with 4% less LDL cholesterol reduction. The difference in LDL cholesterol reductions seen between low-dose and standard-dose treatment becomes smaller when the adherence rate is lower. Our results suggest that for patients with less than 50% adherence there is little difference in expected outcomes regardless of the statin dose. Since most patients have higher adherence rates, physicians should preferably use standard-dose statin as initial treatment, as low-dose treatment is more sensitive to treatment non-response due to non-adherence.

Reviews and meta-analyses on the therapeutic equivalence of statins have resulted in slightly varying classifications on statin doses. We followed the classification used in the Dutch guidelines, which was based on the review of Law and provides estimates with confidence intervals. Given these partly overlapping intervals and also conflicting evidence about simvastatin compared to atorvastatin, there is some debate about the equivalence of statins but estimates based on results of more than 50 head-to-head trials conducted by the Canadian Drug Effectiveness Review Project resulted in the same classification as we used in our study.

A strength of our study is that we estimated the association between statin adherence and LDL cholesterol using adherence as a continuous variable. Often a cut-off point of 80% adherence is used to determine the effect of adherence on outcomes. Our study showed that even in patients with adherence rates above 80% relevant benefits can be achieved by increasing either the adherence or the dose, especially for patients with high baseline LDL cholesterol levels. Although patients with missing LDL cholesterol measurements could not be included, we had sufficient variation in LDL cholesterol levels for determining an association between adherence and reduction in LDL cholesterol. Also, selection by matching did not affect the observed association in the patients on standard-dose treatment, nor did restricting the time period for the outcome measurements. We did not differentiate between primary and secondary prevention patients, since the effect of statins is expected to be similar in both groups.

A limitation of our study is the use of PDC as the measure for adherence, which is known to overestimate actual adherence. This limitation is likely to result in observing a weaker association between adherence and LDL cholesterol response. Also adherence was measured over a flexible time period, which could have biased this relation.
as adherence to treatment may decrease over time. However, we conducted sensitivity analyses showing similar associations between adherence and LDL cholesterol response after restricting the maximal difference follow-up period to 180 or 90 days. Finally, we were not able to adjust for lifestyle factors that might be related to adherence and LDL cholesterol response.

Conclusion

Diabetes patients initiating statin treatment are at high risk of not reaching the recommended cholesterol target, especially when they start on a low-dose statin. Patients with high baseline LDL cholesterol levels starting on low-dose statins are not expected to reach their target even with an adherence rate of 100%. To prevent the lack of effective statin treatment more attention should be given to improving current management strategies in clinical practice.

Transparency

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Declaration of financial/other relationships

F.M.d.V., J.V., E.H., and P.D. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article. CMRO peer reviewers on this study have no relevant financial or other relationships to disclose.

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