Statin treatment in type 2 diabetes patients

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
CHAPTER 5

Prescribing patterns, adherence and LDL-cholesterol response of type 2 diabetes patients initiating statin on low-dose versus standard-dose treatment: a descriptive study

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Submitted

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ABSTRACT

Aims: The aim of this study was to describe and compare treatment modifications and discontinuation, adherence levels, and response to treatment in patients with type 2 diabetes initiating on low-dose versus standard-dose statin treatment.

Methods: A 2-year follow-up cohort study was performed using data from the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT) database in patients with type 2 diabetes initiating statin treatment between January 2007 and December 2012. First we determined whether there were differences in treatment modifications and discontinuation after statin initiation between patients starting on a low-dose versus standard-dose. Second, we looked at differences in adherence and LDL-cholesterol response after 2 years follow-up between these groups.

Results: Around 22% of patients initiated statin treatment on a dose lower than recommended. More than half of them remained on a low dose during a 2-year follow-up period, whereas less than 15% received a dose increase. Of the patients initiating on standard-dose, also more than half remained on the same treatment during this period, whereas 8% received a dose decrease without subsequent increase. Over 25% of patients starting on low-dose or standard-dose treatment discontinued treatment, often within the first 180 days after initiation or after a first treatment change. Patients on low-dose treatment had lower adherence levels and were less likely to have adequate LDL-cholesterol response compared to patients on standard-dose after 2 years follow-up.

Conclusions: Current patterns of statin treatment in patients with type 2 diabetes are suboptimal, with discontinuation, inadequate adherence levels and lack of treatment intensification seen in those who had inadequate LDL-cholesterol response after 2 years of follow-up. Patients starting on low-dose had more treatment modifications, discontinuation and adherence problems as compared to those starting on standard-dose treatment, which calls for a closer look at the rationale of starting patients on low-dose statin treatment.
INTRODUCTION

Patients with type 2 diabetes have an increased risk of developing cardiovascular disease, therefore statin treatment is recommended for almost all type 2 diabetes patients. Statins are associated with a reduction in risk of cardiovascular disease [1,2]. Dutch guidelines recommend to start with simvastatin 40 mg for both primary and secondary prevention, and aim for an LDL-cholesterol level of ≤2.5 mmol/l (≤97 mg/dl) [3]. However, statins are not optimally used in clinical practice and lipid targets are not reached in about a third of the patients [4,5].

This lack of treatment response could be due to being prescribed low-dose treatment [4,6,7], lack of treatment intensification [8,9,10] and/or non-adherence to treatment [11,12]. In the last decade, the prescribed daily dose of statins has increased but on average patients receive less than the recommended dose [6,13], which could lead to insufficient treatment response. Also, it has been shown that at least a third of the patients with lipid levels above target do not receive treatment modifications [8,9,10]. Suspicion of non-adherence to treatment could be reason for the physician not to modify treatment, however the ability of physicians in recognizing non-adherence is poor [14]. There is evidence of redundant treatment intensification in non-adherent patients [15], but also lack of treatment intensification in adherent patients [9]. Also, the relation between adherence and LDL-cholesterol response is related to the treatment dose [7]. The initial treatment dose could have an impact on subsequent adherence and treatment modification patterns. Better insight in such patterns of statin treatment modifications and adherence is needed for the development and refinement of interventions aimed at improving outcomes of statin treatment in daily practice.

The aim of this study was to describe and compare treatment modifications and discontinuation, adherence levels, and cholesterol response in patients with type 2 diabetes initiating on low-dose versus standard-dose statin treatment.
METHODS

Study design
A 2-year follow-up cohort study was performed in patients with type 2 diabetes initiating statin treatment between January 2007 and December 2012. First we determined whether there were differences in treatment modifications and discontinuation after statin initiation between patients starting on a low-dose versus standard-dose. Second, we looked at differences in treatment modifications, discontinuation, adherence and LDL-cholesterol response after 2 years follow-up between patients starting on a low-dose versus standard-dose.

Setting
This study was performed using data from 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 Center Groningen [16]. 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. Medical history consists of date of diabetes diagnosis and comorbidity data, which is based on the International Classification of Primary Care (ICPC) [17] or text descriptions that are coded manually.

Patient selection
Patients managed in general practice for type 2 diabetes initiating lipid-lowering treatment exclusively on a statin were included (Anatomical Therapeutic Chemical (ATC) code C10AA) [18]. Since the documented date of type 2 diabetes diagnosis is not always precise, we allowed for a grace period of 180 days before the documented diagnosis date for a statin initiation to be included. 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 720 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 receiving treatment in daily packages or with a single prescription duration longer than 270 days or with missing prescription attributes were excluded, since adherence cannot be reliably calculated in such cases.

Treatment changes
Statins are expected to be prescribed sequentially, but prescription information in the medical records do not necessarily reflect actual drug taking. Therefore, before
treatment changes were assessed the prescriptions were pre-processed to correct for,
amongst others, stockpiling, erroneous prescription durations due to modifications and
artefacts caused by entry errors. This approach is described in more detail elsewhere [19].

The first and second change in treatment in up to two years after statin treatment
initiation were determined. We differentiated between a treatment modification,
being a dose adjustment, treatment switch or addition, and treatment discontinuation.
Modifications in which the patient stayed on the same type of statin but changed dosing
were classified as a 'dose increase' or 'dose decrease'. Patients that started a different
lipid-lowering drug, and had a treatment stop <90 days after or before initiation of the
new lipid-lowering drug, were defined as switchers. To classify switchers (increase/
decrease/similar) all lipid-lowering drugs and dosings were classified into three dose
categories [20,21]; low-dose, standard-dose and high-dose (Table 1). Patients with a
'switch increase' switched to a lipid-lowering drug in a higher dose category, a 'switch
decrease' was a switch to a lipid-lowering drug in a lower dose category, switching to
a lipid-lowering drug in a similar dose category was defined as 'switch similar'. When
patients had a different lipid-lowering drug started without the initial lipid-lowering
drug being stopped before or in the 90 days after initiation of the new lipid-lowering
drug, the modification was defined as an 'addition'. An overlap period of at least 90 days
was used, which is the usual length of one prescription in the Netherlands. If patients
had a period of 180 days in which they had no medication available this was defined as
'discontinuation'.

Treatment turbulence during follow-up was expressed as the number of treatment
modifications divided by number of prescriptions x 100%.

<table>
<thead>
<tr>
<th>Lipid-lowering drug:</th>
<th>Low-dose</th>
<th>Standard-dose</th>
<th>Intensive-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>All doses</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>≤ 40 mg</td>
<td>&gt;40 mg</td>
<td>-</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>≤ 20 mg</td>
<td>&gt;20 mg - ≤60 mg</td>
<td>&gt;60 mg</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>≤ 10 mg</td>
<td>&gt;10 mg - ≤30 mg</td>
<td>&gt;30 mg</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td></td>
<td>≤ 10 mg</td>
<td>&gt;10 mg</td>
</tr>
</tbody>
</table>

Lipid-lowering drugs other than statins were classified in the low-dose treatment group.
Adherence measurement
Adherence was estimated over the two years of follow-up. It was calculated as Proportion of Days Covered (PDC), which expresses the proportion of days for which a patient has received medication in the study period [22]. Patients with a PDC ≥80% were classified as adherent, patients with a PDC < 80% as non-adherent [23].

LDL-cholesterol response
All LDL-cholesterol levels are based on the Friedewald equation [24]. At statin initiation (baseline) we determined whether LDL-cholesterol was at target (≤2.5 mmol/l). This was the most recent measurement in the 180 days before or at statin initiation. LDL-cholesterol response was determined after two years of follow-up, that is, using the measurement closest to 720 days after statin initiation within a period 540 and 900 days after initiation. Adequate treatment response was defined as either achieving the target LDL-cholesterol level of 2.5 mmol/l or a decrease of at least 40% from baseline LDL-cholesterol, which is the expected decrease for standard-dose treatment [20,21].

Data analyses
Descriptive statistics are presented for patients initiating on a low-dose and standard-dose. Groups were compared on baseline characteristics using chi-square tests, independent sample t-tests or Wilcoxon rank-sum tests. First and second treatment changes were described for patients initiating on low-dose or standard-dose treatment. Differences between patients initiating on low-dose and standard-dose in (1) proportion of first treatment modifications and discontinuation, (2) treatment adherence and turbulence during two years of follow-up, and (3) LDL-cholesterol response after two years follow-up were tested using chi-square tests, Wilcoxon rank-sum tests, or independent sample t-tests. Kaplan-Meier curves were used to present the time till the first treatment modification, separate for treatment intensification, reduction, switch similar, and discontinuation. Significance of differences between patients initiating on a low-dose versus a standard-dose was determined using log-rank tests.

RESULTS
In total 7,772 type 2 diabetes patients who initiated statin treatment between 2007 and 2012 were included in the analyses. Of these 86% started on simvastatin treatment; 69% started on simvastatin 40 mg which is the recommended dose in Dutch guidelines [3] (Figure 1). In total 1,776 patients initiated on a low dose compared to 5,842 that initiated on a standard dose. Patients that initiated on low-dose treatment were for example older (t-test; p-value <0.001), more often female (chi-square test; p-value
Statin prescribing patterns, adherence and LDL-cholesterol response in diabetes

<0.001), had a longer diabetes duration (chi-square test; p-value <0.001), and better glucose regulation (t-test; p-value <0.001) compared to patients initiating on standard-dose treatment. There was no difference in LDL-cholesterol at baseline (t-tests; p-value 0.703), nor in the proportion of patients with a baseline LDL-cholesterol level at target (chi-square test; p-value 0.131) (Table 2).

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**Exclusion criteria**

- Follow-up <720 days
- Patients using daily packages
- Prescription duration >270 days

**Base population 10,349**

- 2,324
- 174
- 79

**Included patients 7,772**

**Initiation dose**

- Pravastatin
  - 80 mg: 178 (2.3%)
  - 40 mg: 109 (1.4%)
  - 20 mg: 50 (0.6%)
  - 10 mg: 19 (0.2%)
  - Others: 0 (0.0%)
- Simvastatin
  - 80 mg: 6,706 (86.3%)
  - 40 mg: 5,333 (68.6%)
  - 20 mg: 1,194 (15.4%)
  - 10 mg: 169 (2.2%)
  - Others: 6 (0.1%)
- Atorvastatin
  - 80 mg: 523 (6.7%)
  - 40 mg: 103 (1.3%)
  - 20 mg: 187 (2.4%)
  - 10 mg: 216 (2.8%)
  - Others: 2 (0.0%)
- Rosuvastatin
  - 40 mg: 353 (4.5%)
- Other drugs
  - 40 mg: 7 (0.1%)
  - 20 mg: 24 (0.3%)
  - 10 mg: 173 (2.2%)
  - 5 mg: 147 (1.9%)

**Initiation dose: dark grey = intensive-dose; grey = standard-dose; light grey = low-dose**

**FIGURE 1.** Flow chart of the patient selection and initiation dose of the patients
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total population (n=7,772)</th>
<th>Standard-dose (n=5,842)</th>
<th>Low-dose (n=1,776)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>62.1 (11.7)</td>
<td>61.5 (11.7)</td>
<td>63.9 (11.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>50.2%</td>
<td>51.7%</td>
<td>45.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP, mmHg (SD)</td>
<td>144.5 (19.8)</td>
<td>144.5 (19.9)</td>
<td>144.6 (19.1)</td>
<td>0.969</td>
</tr>
<tr>
<td>% missing</td>
<td>18.5</td>
<td>19.0</td>
<td>16.1</td>
<td></td>
</tr>
<tr>
<td>DBP, mmHg (SD)</td>
<td>82.8 (10.6)</td>
<td>83.1 (10.6)</td>
<td>82.2 (10.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>% missing</td>
<td>18.5</td>
<td>19.0</td>
<td>16.2</td>
<td>0.007</td>
</tr>
<tr>
<td>Diabetes duration:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 years (n)</td>
<td>65.7% (5,008)</td>
<td>68.8% (4,020)</td>
<td>55.6% (988)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-10 years (n)</td>
<td>26.8% (2,039)</td>
<td>24.5% (1,434)</td>
<td>34.1% (605)</td>
<td></td>
</tr>
<tr>
<td>&gt;10 years (n)</td>
<td>7.5% (571)</td>
<td>6.6% (388)</td>
<td>10.3% (183)</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose, mmol/l (SD)</td>
<td>8.3 (2.9)</td>
<td>8.4 (3.1)</td>
<td>8.0 (2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% missing</td>
<td>27.9</td>
<td>27.1</td>
<td>29.0</td>
<td>0.120</td>
</tr>
<tr>
<td>HbA1c % (SD)</td>
<td>7.3 (1.6)</td>
<td>7.4 (1.7)</td>
<td>7.1 (1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% missing</td>
<td>19.1</td>
<td>19.1</td>
<td>17.8</td>
<td>0.249</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/l (SD)</td>
<td>3.8 (0.9)</td>
<td>3.8 (1.0)</td>
<td>3.8 (0.9)</td>
<td>0.703</td>
</tr>
<tr>
<td>% missing</td>
<td>33.1</td>
<td>33.2</td>
<td>30.4</td>
<td></td>
</tr>
<tr>
<td>&gt; target (n)</td>
<td>91.5% (4,760)</td>
<td>91.4% (3,570)</td>
<td>92.8% (1,147)</td>
<td>0.131</td>
</tr>
<tr>
<td>&lt;= target (n)</td>
<td>8.5% (442)</td>
<td>8.6% (334)</td>
<td>7.2% (89)</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l (SD)</td>
<td>1.19 (0.33)</td>
<td>1.18 (0.33)</td>
<td>1.22 (0.33)</td>
<td>0.002</td>
</tr>
<tr>
<td>% missing</td>
<td>31.8</td>
<td>31.6</td>
<td>30.3</td>
<td>0.313</td>
</tr>
<tr>
<td>Triglycerides, mmol/l (IQR)</td>
<td>1.9 (1.4-2.7)</td>
<td>2.0 (1.4-2.8)</td>
<td>1.9 (1.3-2.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% missing</td>
<td>31.4</td>
<td>31.3</td>
<td>29.6</td>
<td>0.171</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l (SD)</td>
<td>5.9 (1.2)</td>
<td>5.9 (1.2)</td>
<td>5.9 (1.1)</td>
<td>0.183</td>
</tr>
<tr>
<td>% missing</td>
<td>33.3</td>
<td>32.9</td>
<td>32.5</td>
<td>0.757</td>
</tr>
<tr>
<td>Body mass index (SD)</td>
<td>30.6 (5.7)</td>
<td>30.6 (5.7)</td>
<td>30.6 (5.5)</td>
<td>0.805</td>
</tr>
<tr>
<td>% missing</td>
<td>51.3</td>
<td>50.8</td>
<td>52.2</td>
<td>0.287</td>
</tr>
<tr>
<td>Comorbidity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrovascular complications (n)</td>
<td>11.7% (911)</td>
<td>10.9% (634)</td>
<td>12.3% (219)</td>
<td>0.084</td>
</tr>
<tr>
<td>Microvascular complications (n)</td>
<td>3.6% (279)</td>
<td>3.3% (195)</td>
<td>4.3% (76)</td>
<td>0.061</td>
</tr>
</tbody>
</table>

DBP: diastolic blood pressure; IQR: inter quartile range; SBP: systolic blood pressure; SD: standard deviation.
Treatment changes
The first two treatment changes during follow-up for patients initiating on low-dose and standard-dose treatment are shown in Figure 2. More than half of the patients that initiated on a low-dose either did not have any treatment change during follow-up (n=865, 48.7%) or did not receive a dose increase (n=110, switch similar without dose increase; n=11, dose decrease without dose increase). Almost 15% received a dose increase, including around 9.0% without further change (n=160) and 2.3% with a subsequent switch or second dose increase (n=40). Furthermore, more than 22% discontinued treatment either without a restart (n=330, 18.6%) or after a switch to a similar low-dose statin (n=36, 2.0%) or a dose increase (n=35, 2.0%). Patients restarting treatment after discontinuation (n=176, 9.9%) mostly restarted with a similar low-dose statin (n=139).

Of the patients that initiated on a standard dose, the majority did not have a treatment change (n=3,236, 55.4%) or switched to a similar dose statin without subsequent change (n=186, 3.2%). More than 8% received a dose decrease without subsequent dose increase (n=499, 8.5%). Less than 3% received a dose increase, either as first change without subsequent decrease or discontinuation (n=129, 2.2%) or after a switch to a similar statin (n=30, 0.5%). Furthermore, almost 19% discontinued treatment either without a restart (n=903, 15.5%) or after a dose decrease (n=127, 2.2%) or switch similar or dose increase (n=74, 1.3%). Patients restarting treatment after discontinuation (n=606, 10.4%) mostly received a similar standard-dose statin (n=469) or a low-dose statin (n=118).

The percentage of patients that did not have any treatment change during follow-up was lower in the patients initiating on low-dose compared to standard-dose (48.7% versus 55.4%, chi-square test p-value <0.001). Patients initiating on low-dose were more likely to discontinue treatment (28.5% versus 25.8%, chi-square test p-value 0.026), and to receive a treatment intensification (14.6% versus 2.9%, chi-square test p-value <0.001) or a switch to a similar dose category (7.3% versus 5.6%, chi-square test p-value 0.009) as first treatment change. As could be expected, a reduction was more common in patients on standard-dose (10.2% versus 0.8%, chi-square test p-value <0.001). Also, the time to first treatment reduction was shorter for patients starting on standard-dose treatment, whereas the time to treatment intensification was shorter for patients initiating on low-dose (Figure 3a/b). The time to the first switch or to discontinuation were significantly shorter in the low-dose group (Figure 3c/d). In both groups, most switches and discontinuations occurred within the first 180 days after treatment initiation. Furthermore, there was significantly more treatment turbulence for patients initiating on low-dose during follow-up, which was mainly caused by the difference in
the amount of patients with no treatment change (67.3% for low-dose versus 70.8% for standard-dose) (chi-square test p-value 0.004).

**FIGURE 2.** First and second treatment changes for patients initiating on low-dose and standard-dose statin treatment
Adherence and LDL-cholesterol achievement

The adherence rate during follow-up was slightly lower in the low-dose group (PDC: median 83%; IQR 46-96) compared to the standard-dose group (PDC: median 86%; IQR 52-97) (Wilcoxon-test; p-value <0.001) (Figure 4). More than 80% of adherent patients without a change in treatment had an adequate LDL-cholesterol response, whereas this was just over 70% for adherent patients with a treatment change (Table 3). For patients without treatment change, regardless of the adherence level, the LDL-cholesterol response was significantly better for the standard-dose group in comparison to low-dose group (Table 3). For adherent patients with a treatment change, the LDL-cholesterol was similar for both groups. The poorest response was seen for non-adherent patients with at least one treatment change during follow-up, with only 40% of patients initiating on low-dose and 52% initiating on standard-dose treatment having an adequate LDL-cholesterol response (Table 3). Of the patients with a discontinuation as first treatment change, almost half had an adequate LDL-cholesterol response after 2 years (44.0% for low-dose and 49.8% for standard-dose).
Overall, of the 502 patients initiating on low-dose treatment without an adequate LDL-cholesterol response after 2 years, 209 (42%) had a discontinuation and 128 (26%) showed poor adherence rates, whereas 108 (21%) had remained on a low dose while showing an adequate adherence rate and 57 (11%) had a change in treatment with adequate adherence (Table 3). In comparison, of the 1179 patients initiating on standard-dose treatment without an adequate LDL-cholesterol response, 543 (46%) had a discontinuation, 284 (24%) showed poor adherence rates, 217 (18%) had remained on the same dose and 135 (11%) had a change in treatment with adequate adherence.

**TABLE 3.** LDL-cholesterol level and response 2 years after treatment initiation for adherent and non-adherent patients starting on low-dose or standard-dose treatment, and categorized by receiving no treatment change, treatment change or discontinuation

<table>
<thead>
<tr>
<th></th>
<th>Adherent</th>
<th></th>
<th>Non-adherent</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-dose</td>
<td>Standard-dose</td>
<td>Low-dose</td>
<td>Standard-dose</td>
</tr>
<tr>
<td>No change:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-c missing (n)</td>
<td>23.5% (167)</td>
<td>21.8% (579)</td>
<td>28.1% (43)</td>
<td>24.2% (139)</td>
</tr>
<tr>
<td>Mean LDL-c [SD] (n)</td>
<td>2.3 [0.7] (545)</td>
<td>2.1 [0.7] (2,082)</td>
<td>2.7 [0.9] (110)</td>
<td>2.4 [0.9] (436)</td>
</tr>
<tr>
<td>LDL-c response + (n)</td>
<td>80.2%* (437)</td>
<td>89.6% (1,865)</td>
<td>63.6%* (70)</td>
<td>77.3% (337)</td>
</tr>
<tr>
<td>LDL-c response – (n)</td>
<td>19.8% (108)</td>
<td>10.4% (217)</td>
<td>36.4% (40)</td>
<td>22.7% (99)</td>
</tr>
<tr>
<td>Change:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-c missing (n)</td>
<td>13.1% (30)</td>
<td>17.7% (110)</td>
<td>16.5% (29)</td>
<td>19.3% (92)</td>
</tr>
<tr>
<td>Mean LDL-c [SD] (n)</td>
<td>2.6 [0.9] (199)</td>
<td>2.4 [0.9] (511)</td>
<td>3.3 [1.1] (147)</td>
<td>3.1 [1.1] (384)</td>
</tr>
<tr>
<td>LDL-c response + (n)</td>
<td>71.4% (142)</td>
<td>73.6% (376)</td>
<td>40.1%* (59)</td>
<td>51.8% (199)</td>
</tr>
<tr>
<td>LDL-c response – (n)</td>
<td>28.6% (57)</td>
<td>26.4% (135)</td>
<td>59.9% (88)</td>
<td>48.2% (185)</td>
</tr>
<tr>
<td>Discontinuation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-c missing (n)</td>
<td>-</td>
<td>-</td>
<td>26.3% (133)</td>
<td>28.4% (428)</td>
</tr>
<tr>
<td>Mean LDL-c [SD] (n)</td>
<td>-</td>
<td>-</td>
<td>3.2 [1.0] (373)</td>
<td>3.1 [1.0] (1,081)</td>
</tr>
<tr>
<td>LDL-c response + (n)</td>
<td>-</td>
<td>-</td>
<td>44.0% (164)</td>
<td>49.8% (538)</td>
</tr>
<tr>
<td>LDL-c response – (n)</td>
<td>-</td>
<td>-</td>
<td>56.0% (209)</td>
<td>50.2% (543)</td>
</tr>
</tbody>
</table>

*significant difference between low-dose and standard-dose treatment.

LDL-c: Low-density lipoprotein cholesterol; SD: standard deviation
DISCUSSION

Around 22% of type 2 diabetes patients initiated statin treatment on a dose lower than recommended. More than half of them remained on a low dose during a 2-year follow-up period, whereas less than 15% received a dose increase. Of the patients initiating on standard-dose, more than half remained on the same treatment during this period, whereas 8% received a dose decrease without subsequent increase. More than 25% of patients starting on low-dose or on standard-dose treatment discontinued treatment, often within the first 180 days after initiation or after a first treatment change. On the other hand, 35-40% of them restarted treatment within 720 days, often with a similar dose statin. Patients that initiated on low-dose were older and more often female than patients initiating on standard-dose treatment. There was no difference in baseline LDL-cholesterol level. Patients that initiated on low-dose showed a higher treatment turbulence and received treatment changes earlier than patients initiating on standard-dose treatment. Patients on low-dose treatment had lower adherence levels and were less likely to have adequate LDL-cholesterol response compared to patients on standard-dose after 2 years follow-up. Discontinuation or poor adherence accounted for 68-70% of inadequate response, whereas no treatment change in adherent patients accounted for 18-21% of inadequate LDL-cholesterol response after 2 years follow-up.

Previous studies showed that more than half of the patients started statin treatment on a low dose\textsuperscript{[25,26]}. In our population of diabetes patients this proportion was considerably lower but still substantial with 22%. Having only a moderately increased LDL-cholesterol
level could be a reason to start on a low-dose. However, we observed no difference in baseline LDL-cholesterol between patients initiating on low-dose and standard-dose statin treatment. With an average baseline LDL-cholesterol level of 3.8 mmol/l, it can be expected that many of the patients will not reach the LDL-cholesterol target of 2.5 mmol/l on low-dose treatment [20,21]. After initiation on a low-dose upward titration should be the next step but this occurred in less than 15% of such patients. Others also reported that treatment intensification was uncommon in clinical practice [26,27]. The strategy to start with low-dose statin treatment and titrate treatment till the LDL-cholesterol target has been reached might be suboptimal. This strategy can delay effective treatment with 18 months or more [28]. Whereas a previous study found that treatment changes and discontinuation were not influenced by the initial statin potency [26], we found that initiating on a low dose was associated with higher treatment turbulence, including more and earlier treatment changes. Such increased treatment turbulence needed for dose titration could contribute to poorer patient adherence [29,30]. This is in accordance with the higher discontinuation and lower adherence rates we observed for patients starting on a low dose. Future studies using longitudinal modelling are needed to get better insight in the relationship between dosing, treatment turbulence and adherence, as well as interpersonal variation in treatment response.

Fear for adverse events could be another reason to initiate on low-dose statin. Muscle toxicity and effects on liver enzymes are well-acknowledged adverse events associated with statin treatment [31,32,33]. With higher doses there is an increased risk for statin-induced adverse events [31,32,33]. Patients initiating on a low dose in our study were older and more often female. Especially in patients vulnerable for adverse events, such as the elderly, physicians might be inclined to start on a low dose statin. However, patients up to the age of 80 years have been included in clinical trials, showing a safety profile that was generally similar to that of younger adults [31,34,35]. Experiencing adverse events during treatment can be a reason to become non-adherent or discontinue treatment [36]. We did not have information about adverse events but observed a lower adherence rate and higher discontinuation rate in patients that initiated on low-dose as compared to standard-dose treatment. This suggests that starting on a low dose did not prevent patients becoming non-adherent.

Treatment dosing and adherence affect the likelihood of reaching lipid targets [4,6,7]. This was also seen in our study. In addition, we observed that LDL-cholesterol response was worse for patients with treatment changes than for patients without treatment changes, regardless of the initial dose or adherence level. Treatment changes are more likely in patients that have not yet reached the LDL-cholesterol target level [26], but can also be made to reduce adverse events. Our study shows that such changes, especially in
patients who were non-adherent, did not lead to adequate LDL-cholesterol response in around half of the patients after 2-year follow-up.

Initiation on low-dose statin is a problem that is common in clinical practice \[^{25,26}\] but little was known about the subsequent treatment modifications and outcomes. Our study is one of the first providing insight in differences in treatment patterns and LDL-cholesterol response during 2 years of follow-up between patients that initiated on low-dose and standard-dose statin treatment. We had detailed information about statin dosing and subsequent changes in treatment, enabling to describe various trajectories such as discontinuations after treatment changes and restart of treatment after discontinuation.

Our descriptive approach is a limitation, since we cannot draw conclusions about possible causal relationships. We defined LDL-cholesterol response as adequate when the LDL-cholesterol target was reached or when a reduction in LDL-cholesterol of 40% was achieved, thereby allowing for patients with very high baseline LDL-cholesterol levels to have a response considered to be adequate. Around 23% of the patients, however, did not have an LDL-cholesterol measurement with no difference for patients starting on low-dose or standard-dose. For adherence measurement, we used the PDC which is known to overestimate actual adherence \[^{37}\]. Finally, we did not have information about actual adverse event rates in our study population.

In conclusion, our study illustrates that current patterns of statin treatment in patients with type 2 diabetes are suboptimal, with discontinuations followed by inadequate adherence levels and lack of treatment intensification seen in those who do not have adequate LDL-cholesterol response. Adherence levels are lower and discontinuation rates are higher in patients starting on low-dose as compared to standard-dose treatment, and when restarting patients often do so on similar low-dose statins. These findings call for a closer look at the rationale of initiating patients with type 2 diabetes on low-dose statins.
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