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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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SUMMARY

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 vs. 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 vs. 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 with 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 with those starting on standard-dose treatment, which calls for a closer look at the rationale of starting patients on low-dose statin treatment.

What's known

Statins are associated with a reduction in risk of cardiovascular disease and recommended for almost all diabetes patients. Statins are not optimally used in clinical practice and lipid targets are not reached in a third to half of the patients. This lack of treatment response could be because of being prescribed low-dose treatment, lack of treatment intensification and/or non-adherence to treatment, which are well-known problems in clinical practice.

What's new

The study provides insight in treatment modifications, adherence levels and cholesterol response in patients with type 2 diabetes during 2-year follow-up after initiating low-dose vs. standard-dose statin treatment. Treatment intensification was uncommon in patients on a low dose. Discontinuation rates were higher and adherence levels were lower in patients starting on low-dose. Discontinuations, inadequate adherence levels and lack of treatment intensification were common in those who had inadequate LDL-cholesterol response.

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 a third to half of the patients (4,5).

This lack of treatment response could be because of being prescribed low-dose treatment (4,6,7), lack of treatment intensification (8–10) 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 (8–10). Suspicion of non-adherence to treatment could be reason for the physician not to modify treatment, however, the ability of physicians in recognising

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 vs. 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 vs. 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 vs. 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 anonymised 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 included patients with a statin initiation date up to 180 days before the documented date of type 2 diabetes diagnosis. 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 because of being institutionalised, 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 preprocessed to correct for, amongst others, stockpiling, erroneous prescription durations because of 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 2 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 intensive-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

Table 1 Dose-classification of different types and dosings of lipid-lowering treatment

Lipid-lowering drug	Low-dose	Standard-dose	Intensive-dose
Fluvastatin	All doses	–	–
Pravastatin	≤ 40 mg	> 40 mg	–
Simvastatin	≤ 20 mg	> 20 mg to ≤ 60 mg	> 60 mg
Atorvastatin	≤ 10 mg	> 10 mg to ≤ 30 mg	> 30 mg
Rosuvastatin	–	≤ 10 mg	> 10 mg

Lipid-lowering drugs other than statins were classified in the low-dose treatment group.

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 × 100%.

Adherence measurement

Adherence was estimated over the 2 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 2 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 (i) proportion of first treatment modifications and discontinuation, (ii) treatment adherence and turbulence during 2 years of follow-up, and (iii) LDL-cholesterol response after 2 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 vs. a standard-dose was determined using log-rank tests.

Results

In total 7772 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 1776 patients initiated on a low dose compared with 5842 that initiated on a standard dose. Patients that initiated on low-dose treatment were, for example older (*t*-test; p < 0.001), more often female patients (chi-square test; p < 0.001), had a longer diabetes duration (chi-square test; p < 0.001), and better glucose regulation (*t*-test; p < 0.001) compared with patients initiating on standard-dose treatment. The LDL-cholesterol level at baseline was normally distributed with an average of 3.8 mmol/l and 28% had a level of 4.2 mmol/l or higher, indicating that in 72% of the patients we could expect adequate treatment response. There was no difference in LDL-cholesterol at baseline (*t*-tests; p = 0.703), nor in the proportion of patients with a baseline LDL-cholesterol level at target (chi-square test; p = 0.131) (Table 2).

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 1776 patients that initiated on a low-dose either
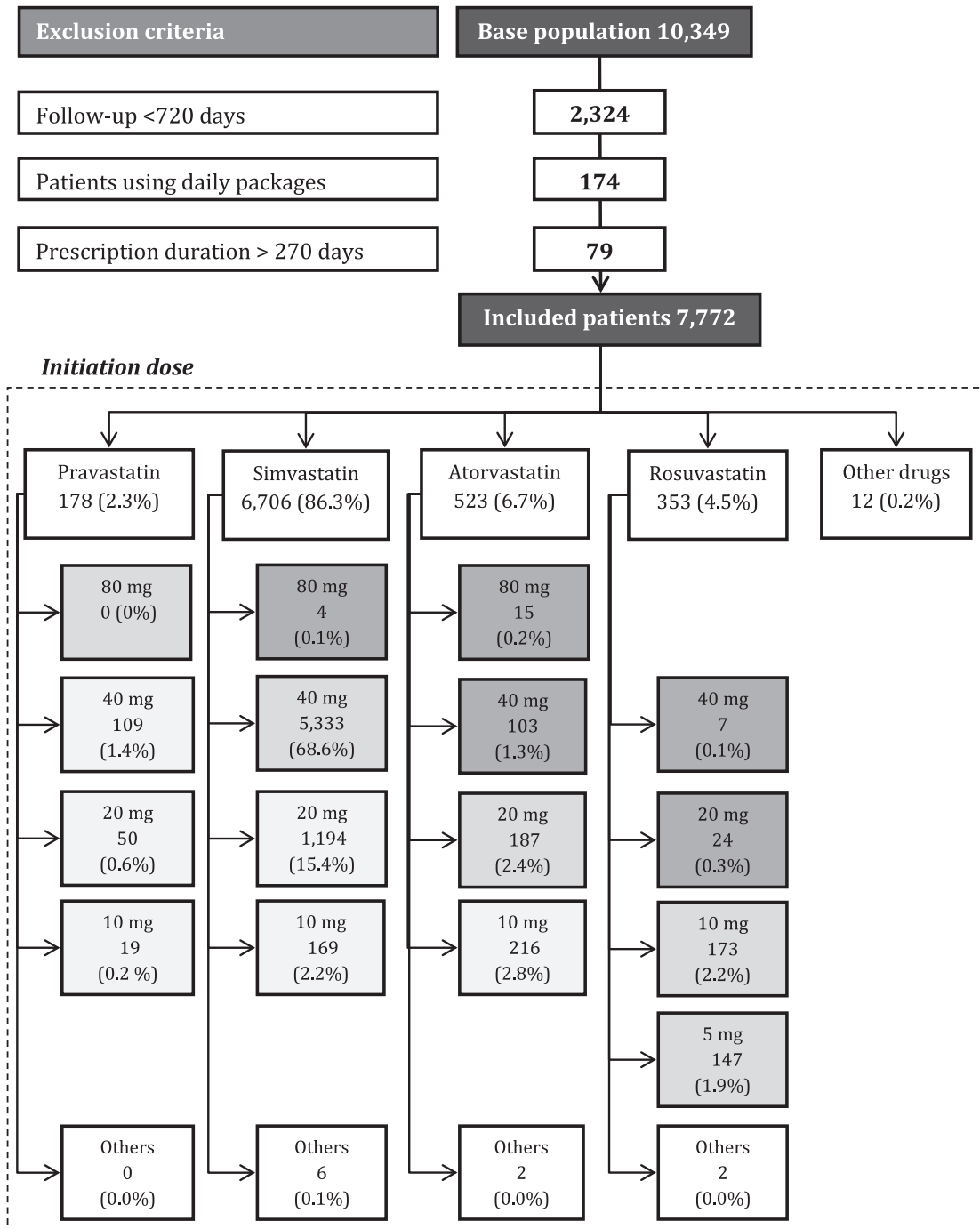
Figure 1 Flow chart of the patient selection and initiation dose of the patients. Initiation dose: dark grey = intensive-dose; grey = standard-dose; light grey = low-dose

did not have any treatment change during follow-up or did not receive a dose increase. Almost 15% received a dose increase and more than 22% discontinued treatment. Patients restarting treatment after discontinuation (10%) mostly restarted with a similar low-dose statin.

Of the 4842 patients that initiated on a standard dose, the majority did not have a treatment change or switched to a similar dose statin without subsequent change. Just over 8% received a dose decrease without subsequent dose increase, and almost 19% discontinued treatment. Patients restarting treatment after discontinuation (10%) mostly received a similar standard-dose statin or a low-dose statin.

The percentage of patients that did not have any treatment change during follow-up was lower in the

Table 2 Characteristics of the total baseline population and patients classified by treatment initiation dose

Variable	Total population (n = 7772)	Standard-dose (n = 5842)	Low-dose (n = 1776)	p
Age, mean (SD)	62.1 (11.7)	61.5 (11.7)	63.9 (11.5)	< 0.001
Male sex	50.2%	51.7%	45.3%	<0.001
SBP, mmHg (SD)	144.5 (19.8)	144.5 (19.9)	144.6 (19.1)	0.969
N	6337	4734	1490	
% missing	18.5	19.0	16.1	0.006
DBP, mmHg (SD)	82.8 (10.6)	83.1 (10.6)	82.2 (10.6)	0.008
N	6336	4734	1489	
% missing	18.5	19.0	16.2	0.007
Diabetes duration				
≤ 2 years (n)	65.7% (5008)	68.8% (4020)	55.6% (988)	< 0.001
2–10 years (n)	26.8% (2039)	24.5% (1434)	34.1% (605)	
> 10 years (n)	7.5% (571)	6.6% (388)	10.3% (183)	
Fasting glucose, mmol/l (SD)	8.3 (2.9)	8.4 (3.1)	8.0 (2.5)	< 0.001
N	5601	4258	1261	
% missing	27.9	27.1	29.0	0.120
HbA1c % (SD)	7.3 (1.6)	7.4 (1.7)	7.1 (1.3)	< 0.001
N	6288	4728	1459	
% missing	19.1	19.1	17.8	0.249
LDL-cholesterol, mmol/l (SD)	3.8 (0.9)	3.8 (1.0)	3.8 (0.9)	0.703
N	5202	3904	1236	
% missing	33.1	33.2	30.4	0.029
> target (n)	91.5% (4760)	91.4% (3570)	92.8% (1147)	0.131
≤ target (n)	8.5% (442)	8.6% (334)	7.2% (89)	
HDL-cholesterol, mmol/l (SD)	1.19 (0.33)	1.18 (0.33)	1.22 (0.33)	0.002
N	5298	3995	1237	
% missing	31.8	31.6	30.3	0.313
Triglycerides, mmol/l (IQR)	1.9 (1.4–2.7)	2.0 (1.4–2.8)	1.9 (1.3–2.6)	< 0.001
N	5332	4013	1251	
% missing	31.4	31.3	29.6	0.171
Total cholesterol, mmol/l (SD)	5.9 (1.2)	5.9 (1.2)	5.9 (1.1)	0.183
N	5186	3921	1199	
% missing	33.3	32.9	32.5	0.757
Body mass index (SD)	30.6 (5.7)	30.6 (5.7)	30.6 (5.5)	0.805
N	3786	2877	849	
% missing	51.3	50.8	52.2	0.287
Comorbidity				
Macrovascular complications (n)	11.7% (911)	10.9% (634)	12.3% (219)	0.084
Microvascular complications (n)	3.6% (279)	3.3% (195)	4.3% (76)	0.061

DBP, diastolic blood pressure; IQR, inter quartile range; SBP, systolic blood pressure; SD, standard deviation.

patients initiating on low-dose compared with standard-dose (48.7% vs. 55.4%, chi-square test p < 0.001). Patients initiating on low-dose were more likely to discontinue treatment (28.5% vs. 25.8%, chi-square test p = 0.026), and to receive a treatment intensification (14.6% vs. 2.9%, chi-square test p < 0.001) or a switch to a similar dose category (7.3% vs. 5.6%, chi-square test p = 0.009) as first treatment change. As could be expected, a reduction was more common in patients on standard-dose (10.2% vs. 0.8%, chi-square test p < 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 vs. 70.8% for standard-dose) (chi-square test p = 0.004).
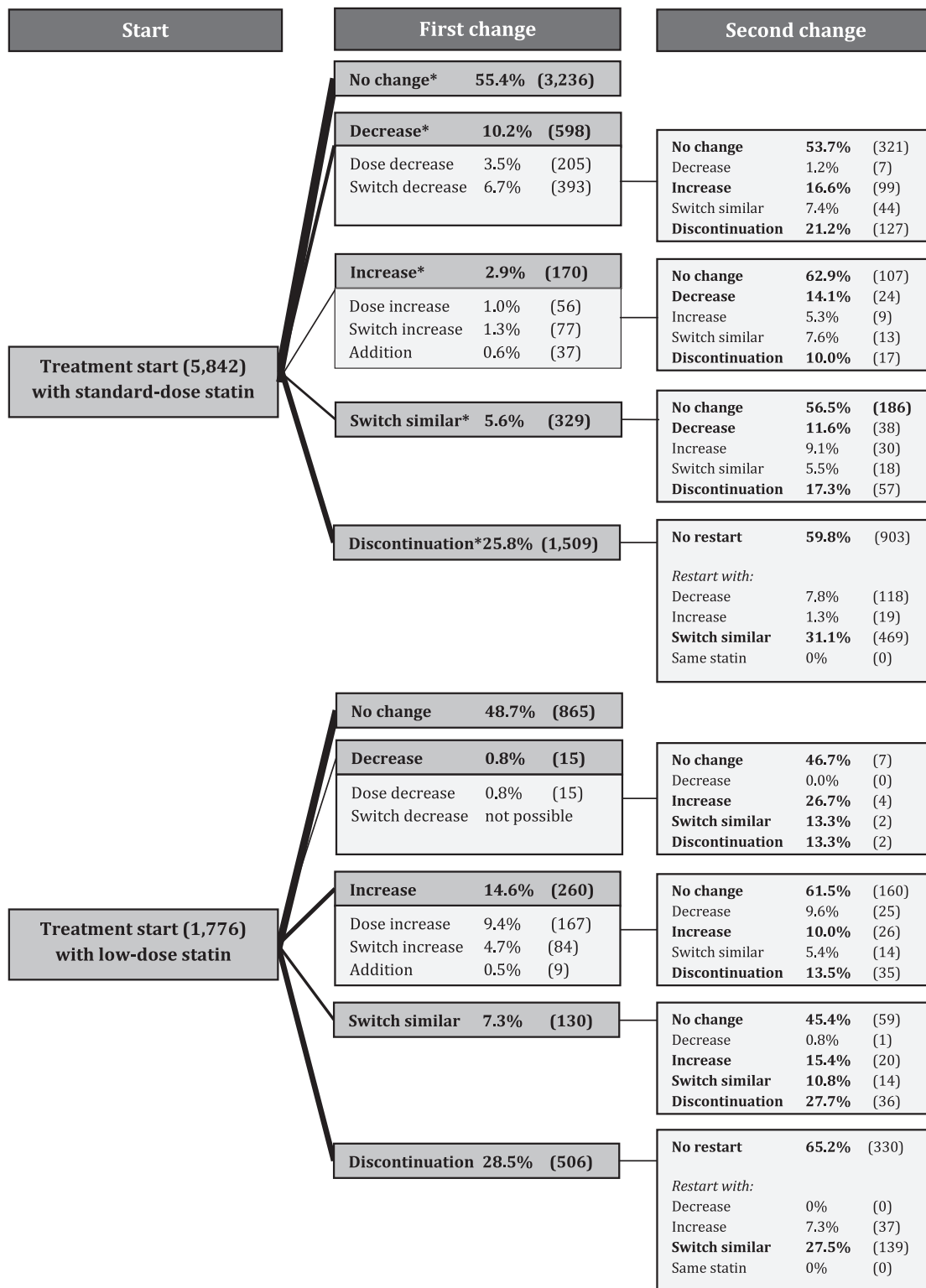
Start | **First change** | **Second change**

Treatment start (5,842) with standard-dose statin

No change* 55.4% (3,236)

Decrease* 10.2% (598)
Dose decrease 3.5% (205)
Switch decrease 6.7% (393)

No change	53.7%	(321)
Decrease	1.2%	(7)
Increase	16.6%	(99)
Switch similar	7.4%	(44)
Discontinuation	21.2%	(127)

Increase* 2.9% (170)
Dose increase 1.0% (56)
Switch increase 1.3% (77)
Addition 0.6% (37)

No change	62.9%	(107)
Decrease	14.1%	(24)
Increase	5.3%	(9)
Switch similar	7.6%	(13)
Discontinuation	10.0%	(17)

Switch similar* 5.6% (329)

No change	56.5%	(186)
Decrease	11.6%	(38)
Increase	9.1%	(30)
Switch similar	5.5%	(18)
Discontinuation	17.3%	(57)

Discontinuation* 25.8% (1,509)

No restart	59.8%	(903)
Restart with:		
Decrease	7.8%	(118)
Increase	1.3%	(19)
Switch similar	31.1%	(469)
Same statin	0%	(0)

Treatment start (1,776) with low-dose statin

No change 48.7% (865)

Decrease 0.8% (15)
Dose decrease 0.8% (15)
Switch decrease not possible

No change	46.7%	(7)
Decrease	0.0%	(0)
Increase	26.7%	(4)
Switch similar	13.3%	(2)
Discontinuation	13.3%	(2)

Increase 14.6% (260)
Dose increase 9.4% (167)
Switch increase 4.7% (84)
Addition 0.5% (9)

No change	61.5%	(160)
Decrease	9.6%	(25)
Increase	10.0%	(26)
Switch similar	5.4%	(14)
Discontinuation	13.5%	(35)

Switch similar 7.3% (130)

No change	45.4%	(59)
Decrease	0.8%	(1)
Increase	15.4%	(20)
Switch similar	10.8%	(14)
Discontinuation	27.7%	(36)

Discontinuation 28.5% (506)

No restart	65.2%	(330)
Restart with:		
Decrease	0%	(0)
Increase	7.3%	(37)
Switch similar	27.5%	(139)
Same statin	0%	(0)

Figure 2 First and second treatment changes for patients initiating on low-dose and standard-dose statin treatment

Adherence and LDL-cholesterol response

The adherence rate during follow-up was slightly lower in the low-dose group (PDC: median 83%; IQR 46-96) compared with the standard-dose group (PDC: median 86%; IQR 52–97) (Wilcoxon-test; $p < 0.001$) (Figure 4). More than 80% of adherent
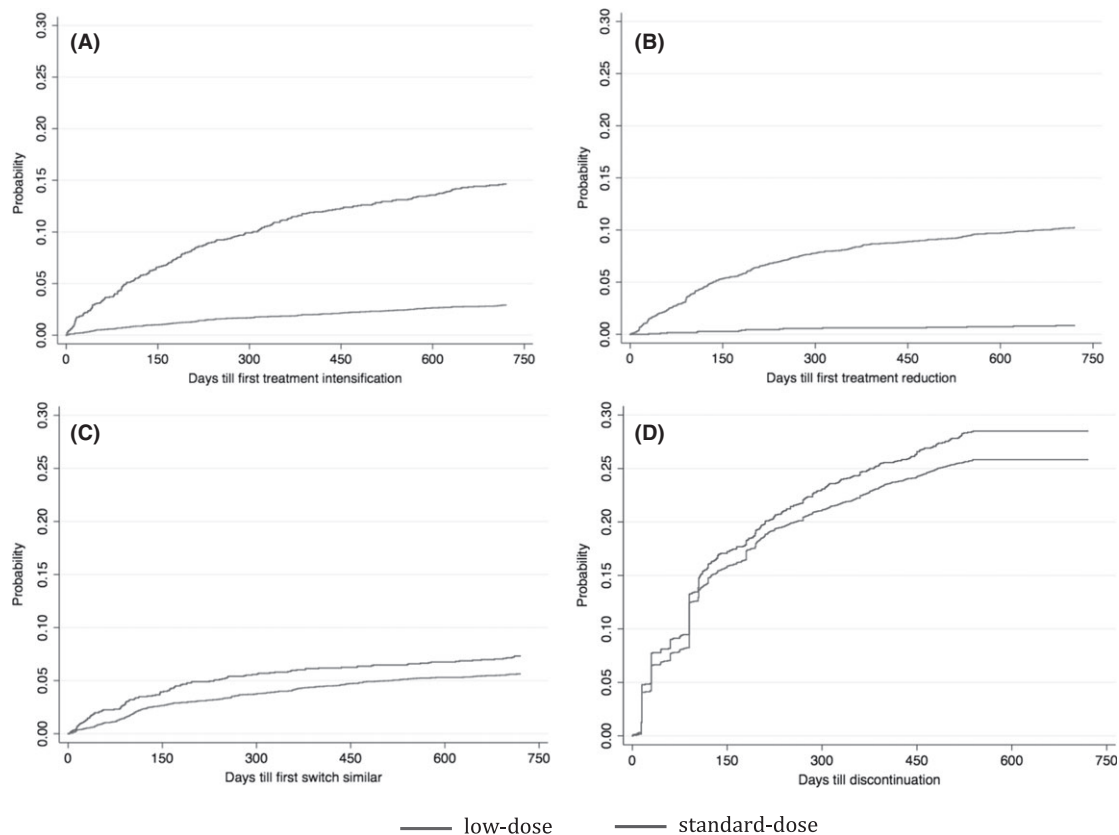
Figure 3 Days till first treatment modification or discontinuation according to the treatment initiation dose. (a) shows results when the first modification is an intensification; (b) when the first modification is a reduction; (c) when the first modification is a switch to a similar dose; (d) shows the time till discontinuation

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).
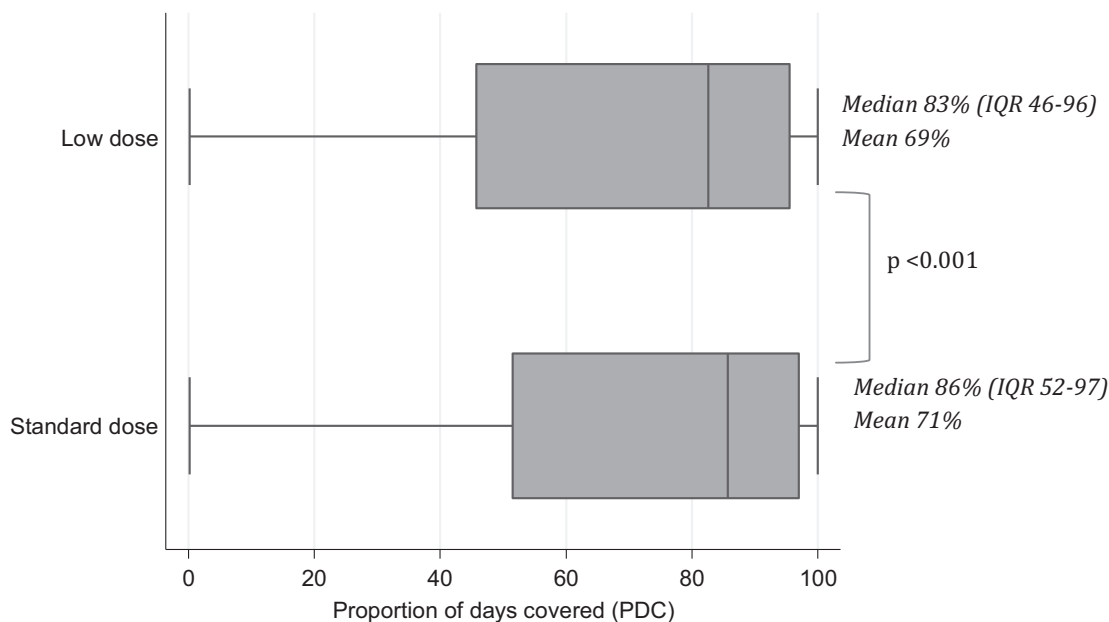
Overall, of the 502 patients initiating on low-dose treatment without an adequate LDL-cholesterol response after 2 years, 209 (42%) had a discontinuation and 128 (26%) showed poor adherence rates, whereas 108 (21%) had remained on a low dose while showing an adequate adherence rate and 57

(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.

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

Figure 4 Overall adherence calculated as proportion of days covered over the first 2 years of treatment, for patients initiating on low-dose and standard-dose

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 categorised by receiving no treatment change, treatment change or discontinuation

	Adherent		Non-adherent	
	Low-dose	Standard-dose	Low-dose	Standard-dose
No change				
LDL-c missing (*n*)	23.5% (167)	21.8% (579)	28.1% (43)	24.2% (139)
Mean LDL-c, [SD] (*n*)	2.3 [0.7] (545)	2.1 [0.7] (2082)	2.7 [0.9] (110)	2.4 [0.9] (436)
LDL-c response + (*n*)	80.2%* (437)	89.6% (1865)	63.6%* (70)	77.3% (337)
	19.8% (108)	10.4% (217)	36.4% (40)	22.7% (99)
LDL-c response — (*n*)				
Change				
LDL-c missing (*n*)	13.1% (30)	17.7% (110)	16.5% (29)	19.3% (92)
Mean LDL-c [SD] (*n*)	2.6 [0.9] (199)	2.4 [0.9] (511)	3.3 [1.1] (147)	3.1 [1.1] (384)
LDL-c response + (*n*)	71.4% (142)	73.6% (376)	40.1%* (59)	51.8% (199)
	28.6% (57)	26.4% (135)	59.9% (88)	48.2% (185)
LDL-c response — (*n*)				
Discontinuation				
LDL-c missing (*n*)	–	–	26.3% (133)	28.4% (428)
Mean LDL-c [SD] (*n*)	–	–	3.2 [1.0] (373)	3.1 [1.0] (1081)
LDL-c response + (*n*)	–	–	44.0% (164)	49.8% (538)
	–	–	56.0% (209)	50.2% (543)
LDL-c response — (*n*)				

*Significant difference between low-dose and standard-dose treatment. LDL-c, LDL-cholesterol; SD, standard deviation

with a similar dose statin. Patients that initiated on low-dose were older and more often female patients 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 with 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 (25,26). In our population of diabetes patients this proportion was considerably lower but still substantial with 22%. This suggests that there is an improvement over time. 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 may be suboptimal. This strategy can delay effective treatment with 18 months or more (28). Although 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 or experience with adverse events in the past 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 (31–33). With higher doses there is an increased risk for statin-induced adverse events (31–33). Patients initiating on a low dose in our study were older and more often female patients. Especially in patients vulnerable for adverse events, such as elderly people, 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 with 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. One would expect that especially in patients with high baseline LDL-cholesterol levels, treatment intensification is needed to get an adequate response (7). 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 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 short-term 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 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. Furthermore, only patients were included that had not used lipid-lowering treatment in the previous year. Some could have used statins before that year.

Such previous experiences can influence the decision for statin type and dosing, although they can also restart on the same statin even after experiencing a statin-related event (37). Patients with insufficient follow-up were excluded. Around 20% had moved or died, whereas for the other patients not enough time had elapsed since their statin initiation. The excluded patients were on average older but there was no difference in gender or baseline LDL-cholesterol level. For adherence measurement, we used the PDC which is known to overestimate actual adherence (38). 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 with 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.

Acknowledgements

Author contributions

FMdV, JV and PD designed the study. FMdV and JV performed the data analysis. FMdV, JV, EH and PD interpreted the results. FMdV and PD drafted the manuscript, which was critically reviewed by JV and EH. All authors read and approved the final version of the manuscript.

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