ESC European Society of Cardiology

European Heart Journal Open (2022) **2**, 1–9
https://doi.org/10.1093/ehjopen/oeac070

ORIGINAL ARTICLE
Epidemiology and prevention

Gaps and discontinuation of statin treatment in Norway: potential for optimizing management of lipid lowering drugs

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Received 1 July 2022; revised 3 October 2022; online publish-ahead-of-print 27 October 2022

Handling Editor: Maciej Banach

Editorial for this article: Eur Heart J Open 2022; https://doi.org/10.1093/ehjopen/oeac071

Aims In clinical practice, many patients do not reach the recommended treatment targets for LDL-cholesterol levels. We aimed to examine treatment patterns and adherence for patients on lipid lowering drugs in Norway to inform future strategies to improve therapies.

Methods and results We obtained information on all dispensed statins, ezetimibe, and proprotein convertase subtilisin/-kexin 9 (PCSK9) inhibitors 2010–2019 from the Norwegian Prescription Database. Treatment gaps were assessed assuming patients take one tablet per day and were defined to occur if a patient did not refill a prescription when the previous one should have been depleted. Treatment was defined as discontinued when the preceding prescription would have been used and no new subsequent prescription was filled. The mean proportion of days covered (PDC) was calculated by aggregating the total number of tablets dispensed during each calendar year and dividing by 365. Patients 80 years were excluded. A considerable proportion of statin users in Norway had long treatment gaps or discontinuation in treatment. The 19.6% of the patients had treatment gaps of 180 days or more, and 10.8% had gaps or greater than 365 days. Similar results were found for patients on antidiabetics and hypertensives. PDC ranged from 84.9% for simvastatin to 72.2% for ezetimibe (2019). The most common lipid lowering drugs in 2019 were atorvastatin, simvastatin, and ezetimibe.

Conclusion There is a great potential for improving drug adherence and optimizing lipid lowering therapy by switching to more effective statins in greater doses, and more often add ezetimibe and PCSK9 inhibitors to treatment.

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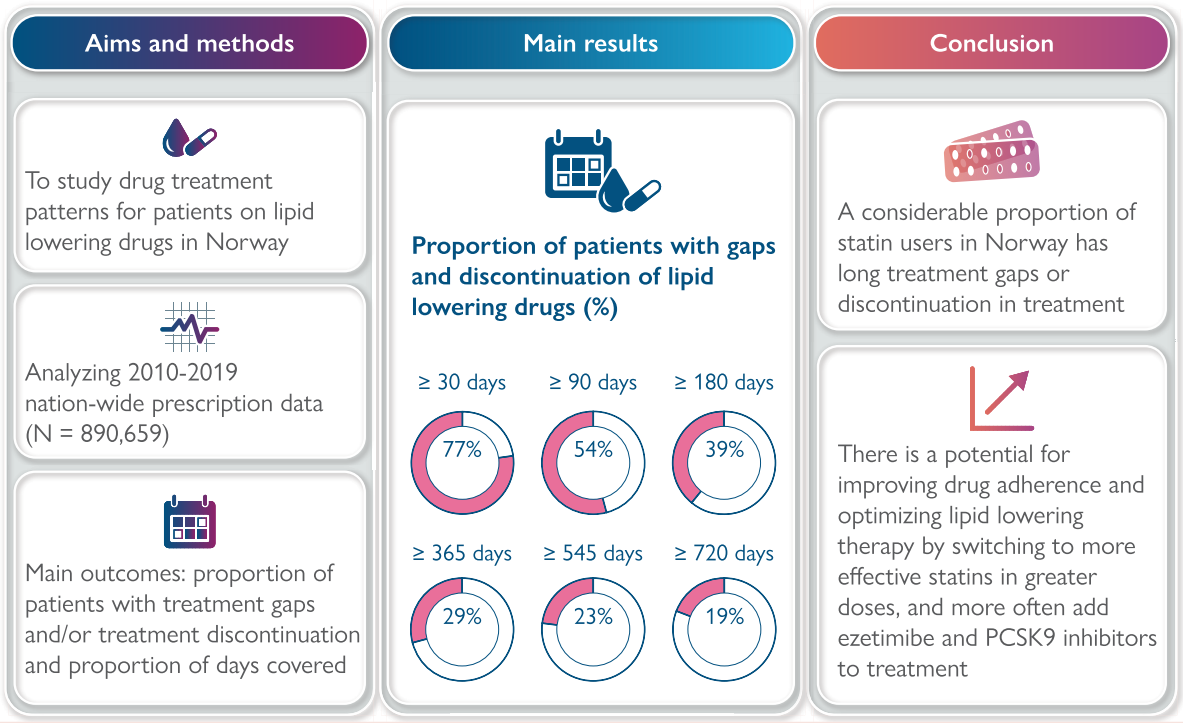
Graphical Abstract



Keywords Lipid lowering drugs • Drug adherence • The Norwegian Prescription Database

Introduction

Pharmacological treatment with statins to reduce hypercholesterolaemia is crucial for primary and secondary prevention of atherosclerotic cardiovascular and cerebrovascular disease (CVD).[1,2] The addition of non-statin lipid-modifying drugs, in particular ezetimibe, and more recently proprotein convertase subtilisin/-kexin 9 (PCSK9) inhibitors, are recommended in patients who do not reach their individual treatment goal despite highest tolerated statin dose.[1,2] The beneficial effects of lipid lowering drugs on CVD outcomes are mainly mediated through the reduction of low-density lipoprotein cholesterol and other apo-B-containing serum lipoproteins.[3] However, they likely also improve clinical outcomes by reducing chronic subclinical inflammation.[4] Therefore, statins, alone or in combination with ezetimibe and/or a PCSK-9 inhibitors, were given high scientific recommendation in the current European guidelines for CVD prevention[1] and dyslipidemia.[2] The recommended LDL-cholesterol treatment goal was recently reduced from 1.8 to <1.4 mmol/L for patients with established ASCVD or a very-high CVD risk, and recent studies indicate that even lower treatment targets may be associated with a further risk reduction for subsequent cardiovascular events.[5]

National and international studies indicate that a majority of patients in clinical practice fails to achieve the recommended lipid goals[6,7] which in turn increase their risk of CVD events[6]. Furthermore, many patients are treated with suboptimal statin doses and rarely are prescribed combination therapy with non-statin drugs.[8,9] It is a prerequisite for treatment effects that patients are prescribed the optimal lipid lowering drugs and then use them as prescribed by their physician. Today, poor drug adherence (i.e. patients do not take their drugs as prescribed) remains a major challenge in lipid management globally, contributing substantially to adverse clinical outcomes.[10,11]

The concept of drug adherence includes the initiation, implementation, and discontinuation phases,[12] with persistence, defined as the 'time from initiation to discontinuation', representing a quantitative concept. It is well known that estimates of adherence are strongly influenced by the applied definition of adherence,[13] as well as the measurement method.[14] Pharmacy prescription data currently provide the best opportunity for assessing population-wide drug adherence.[12,14] Recent international registry-based studies [15,16] and meta-analyses [10] have documented that poor statin adherence is common in the real-world setting, and it is associated with adverse outcomes in terms of cardiovascular disease events and mortality.

Knowledge about temporal trends in treatment practice and adherence to lipid lowering drugs are lacking in Norway. Such information may enhance clinical and public awareness, potentially paving the way for more optimized lipid management in clinical practice. This observational study aims to evaluate treatment patterns (dispensed drugs and doses) and adherence for patients on lipid lowering drugs in Norway during 2010 and 2019 using nation-wide prescription data.

Methods

Data

We received patient-level data from the Norwegian Prescription Database (NorPD) for all pharmacy dispensed statins (ATC code C10AA), ezetimibe

(C10AX09), combination of statins and ezetimibe (C10BA02, C10BA05, and C10BA06), and PCSK9 inhibitors (C10AX13 and C10AX14) for the period 2010–2019. For patients with at least one such dispensing, we obtained information on their use of pharmacy dispensed diabetes drugs (ATC-code A10), diuretics (C03), beta-blockers (C07), calcium channel blockers (C08), and renin-angiotensin modulating drugs (C9) during the period 2010–2019.

For each dispensing, we received information on patient characteristics (age, sex, and month of death if applicable), dispensing date, ATC code of drug, number of defined daily doses (DDDs), and number of tablets or milligram active substance. The dataset encompassed 890 659 patients and 72 664 529 prescription fills. There were no missing data. Norway has flexible reimbursement rules for statins (except rosuvastatin), ezetimibe, less flexible rules for rosuvastatin and ezetimibe combinations while PCSK9 inhibitors have very strict rules. Approximately 99% of all prescription fills for lipid lowering drugs are reimbursed

Sample selection

We excluded prescription fills for patients greater than 80 years of age [n = 17 769 161 (24.5%)]. For example, prescriptions for patients born in 1935 were excluded from analysis from 1 January 2016. The exclusion was motivated by weak evidence of statin benefit among older people, especially for primary prevention.[17] Furthermore, physicians may discontinue treatment in older people due to comorbidity or severe health state.

We also excluded patients with one or more prescription fills of pitavastatin (102 patients), prescription fills with a negative number of tablets (two prescription fills); and prescription fills with more than 20 000 tablets on one prescription (one prescription fill). A total of 804 904 patients remained for analysis. Descriptive statistics and patient characteristics for the total population (extracted raw data) and the study population are provided in Supplementary material online, *Table S1 and S2*.

Analyses of treatment practice

We present frequencies of patients and prescription fills, as well as their distributions by type of drug and drug dose, during the period 2010–2019. Patients at high CVD risk have lower LDL-cholesterol targets than others, and their drug use, doses, and adherence are particularly important.[1,2] Because NorPD does not hold valid information on diagnoses or risk levels, we performed separate analyses for patients with at least one anti-diabetes and one anti-hypertension drug prescription during the study period (diuretics, beta blockers, calcium channel blockers, and renin-angiotensin modulating drugs).

Analyses of treatment adherence

Mean proportion of days covered (PDC) was estimated by drug and year, by summing up the number of tablets (statins and ezetimibe) or milligrams (PCSK9) dispensed during each calendar year and dividing by 365. Patients were defined to be on a lipid lowering drug if they had at least one prescription fill of that drug during the year. One patient can therefore be present in more than one drug group. Because patients may start or discontinue drug treatment any day during the calendar year, and because some patients fill prescriptions unregularly, this simple method for estimating mean PDC, may entail bias. We explored potential bias in various sensitivity analyses, including by removing prescription filled 6 months before time of death, by prevalent and incident patients separately and by removing incident patients who had their first filling after 1st October 1st in the year of interest or patients who died during the year. In addition, we used the reverse waiting time distribution (RWD) with random index dates in a 1-year sampling window for each calendar year to estimate the days covered by a single prescription.[18] In the estimation, we included age categories, sex of the patient and categories for the number of pills as explanatory covariates to improve predictive accuracy.[19] Changes in PDC over time were tested statistically using logistic regression.

We estimated the proportion of patients with gaps in statin use of more than 90, 180, 365, 545, and 730 days duration, and of discontinuation. We assumed that patients on statins take one tablet per day. If a patient receives for example 100 tablets and fills the next prescription after 190 days, we assumed there had been a treatment gap of 90 days. Treatment was defined as discontinued when the preceding prescription would have been used (assuming one tablet per day) and no new subsequent prescription was filled. When calculating the proportion of patients with a discontinuation, individuals were censored if they were registered as dead or turned 81 years old during the study period. Analyses of adherence and treatment gaps were restricted to incident patients from 2012 (washout period 2010–2011).

Statistical software

Analyses were performed using R version 4.1.2 (2021), STATA software version 15 (College Station, TX, USA), and Microsoft Excel (2016).

Ethical approval

Approval to use data from NorPD was granted from NorPD (ref:20/13004–9) and the Regional Committees for Medical and Health Research Ethics (REK) (ref:153702).

Data availability

The data underlying this study were provided by NorPD under by permission from REK. Data will be shared on request to the corresponding author with the permission of NorPD and REK.

Results

The proportion of the Norwegian population under 80 years with at least one lipid lowering drug prescription increased from 8.9% in 2010 (n = 415 351) to 10.0% in 2019 (n = 511 124).[20] With 2010–2011 as washout period, the number of drug-naive (incident) patients on lipid lowering drug increased from 26 446 in 2012 to 32 554 in 2019. The mean age of the patients in 2019 was 65 years (SD = 10.5) and 42% of the patients were female. There were 106 532 patients who had a dispensing of both an anti-diabetes and an anti-hypertension drug in 2019. Prevalence, incidence, number of prescriptions, and more detailed patient characteristics for patients on lipid lowering drugs are provided in Supplementary material online, *Table S1 and S2*.

Choice of lipid lowering drug and prescribed doses

In 2010, 72.2% of the patients had at least one prescription fill of simvastatin, 24.1% of atorvastatin, and 3.1% of ezetimibe (*Figure 1*). In 2019, these proportions were 27.2%, 55.3%, and 11.3%, respectively. In total, 159 779 patients switched from pravastatin or simvastatin to atorvastatin during the study period, while 24 601 switched to rosuvastatin. PCSK9 inhibitors were introduced in Norway in 2015, and the number of patients on these drugs increased from 54 in 2015 to 1266 in 2019. In 2019, patients on PCSK9 inhibitors represented 0.2% of the patients on lipid lowering drugs in Norway. Of the patients with at least one prescription of anti-diabetes and one anti-hypertension drug during 2010 through 2019, 27.3% used simvastatin, 53.9% atorvastatin, 2.4% pravastatin, 5.0% rosuvastatin, 11.2% ezetimibe, and 0.2% PCSK9 inhibitors.

For all statins, prescriptions with higher doses (40 or 80 mg) represented a lower proportion of the prescription fills in 2019 compared with in 2010 (*Table 1*). For example, for atorvastatin, 23.9% of the prescription fills were 80 mg in 2010, while it was 14.5% in 2019. There was also a decrease in the proportion of 40 mg prescriptions during the study period (42.9–37.5%). Patients on antidiabetics and antihypertensives had somewhat higher doses, but the differences were small. The number of patients and prescription fills of lipid lowering drugs according to type of drug are presented in Supplementary material online, *Table S3*.

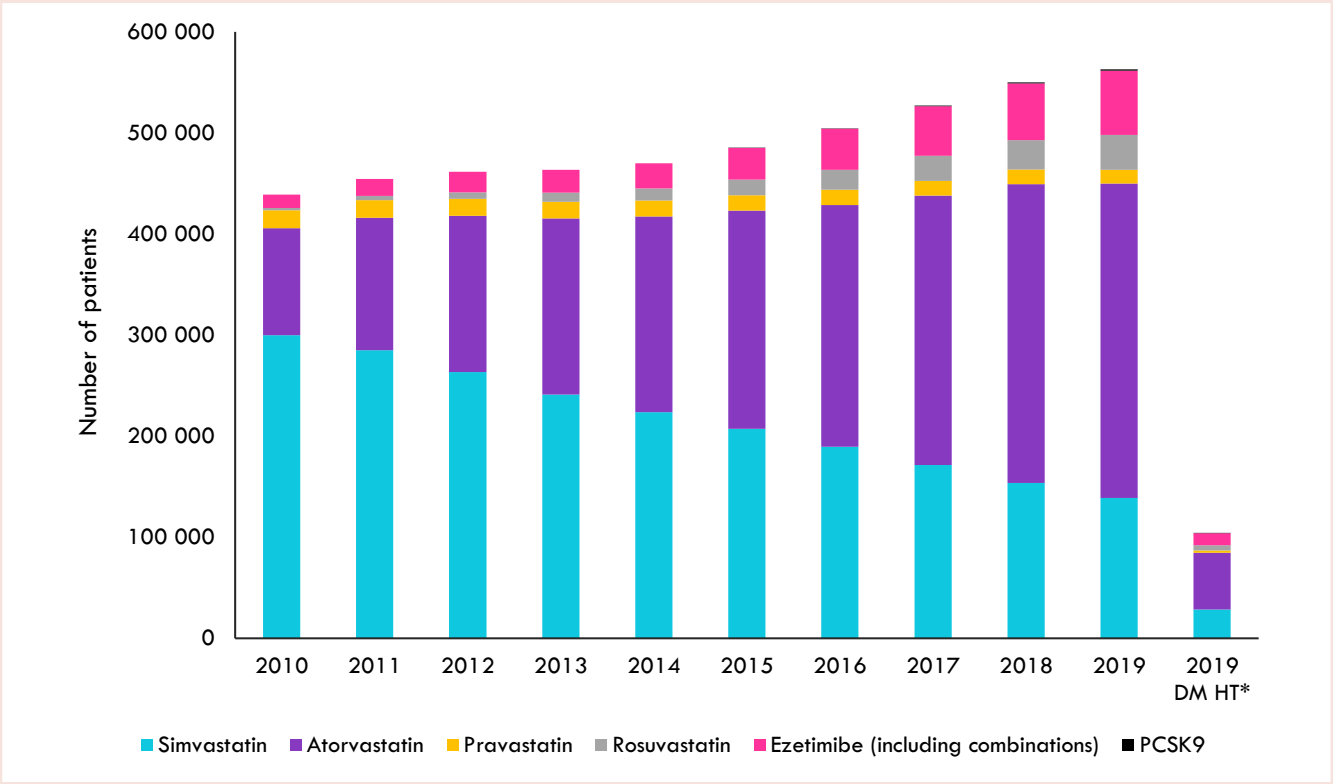


Figure 1 Number of patients on lipid lowering drugs in Norway according to type of drug and year. *Patients on both anti-diabetes and anti-hypertension drugs (diuretics, beta blockers, calcium channel blockers, and renin-angiotensin modulating drugs). Patients were defined to be on a lipid lowering drug if they had at least one prescription fill of that drug during the year. One patient can be present in more than one drug group if the patient switched drug during the year or was prescribed additional drugs (ezetimibe and/or PCSK inhibitors).

Table 1 Proportion (%) of prescription fills according to dose, by type of statin and year

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2019 Diabetes and hypertension[a]
Simvastatin											
10 mg	7.3	7.2	7.2	7.5	7.7	7.9	8.1	8.5	8.8	9.1	9.1
20 mg	40.4	40.0	39.6	39.6	39.5	39.4	40.1	40.9	41.1	41.3	40.6
40 mg	47.5	48.3	48.9	49.0	49.0	49.0	48.4	47.3	47.0	46.6	46.8
80 mg	4.7	4.5	4.2	4.0	3.8	3.7	3.4	3.2	3.0	3.0	3.6
Atorvastatin											
10mg	11.5	12.6	13.3	13.9	14.4	14.5	14.7	15.0	14.9	15.0	12.8
20mg	21.6	25.8	28.2	29.4	29.3	30.2	31.0	31.6	32.6	33.1	30.7
40mg	42.9	40.6	39.3	38.6	39.0	39.1	38.7	38.3	37.9	37.5	39.2
80mg	23.9	21.1	19.1	18.1	17.3	16.3	15.6	15.0	14.6	14.5	17.4
Pravastatin											
20 mg	38.8	40.5	39.3	40.3	40.8	41.2	42.2	43.0	43.0	43.5	38.6
40 mg	61.2	59.5	60.7	59.7	59.2	58.8	57.8	57.0	57.0	56.5	61.4
Rosuvastatin											
5 mg	23.8	23.3	24.9	25.1	27.0	26.5	29.8	31.2	30.7	29.5	28.7
10 mg	25.7	30.4	31.4	31.6	31.6	33.6	32.9	32.6	33.0	33.1	32.9
20 mg	21.4	22.8	22.4	23.4	23.4	23.5	22.6	22.5	22.6	23.0	24.2
40 mg	29.1	23.5	21.4	19.9	18.0	16.4	14.8	13.7	13.8	14.4	14.2

[a]Patients on anti-diabetes and anti-hypertension drugs (diuretics, beta blockers, calcium channel blockers, and renin-angiotensin modulating drugs).

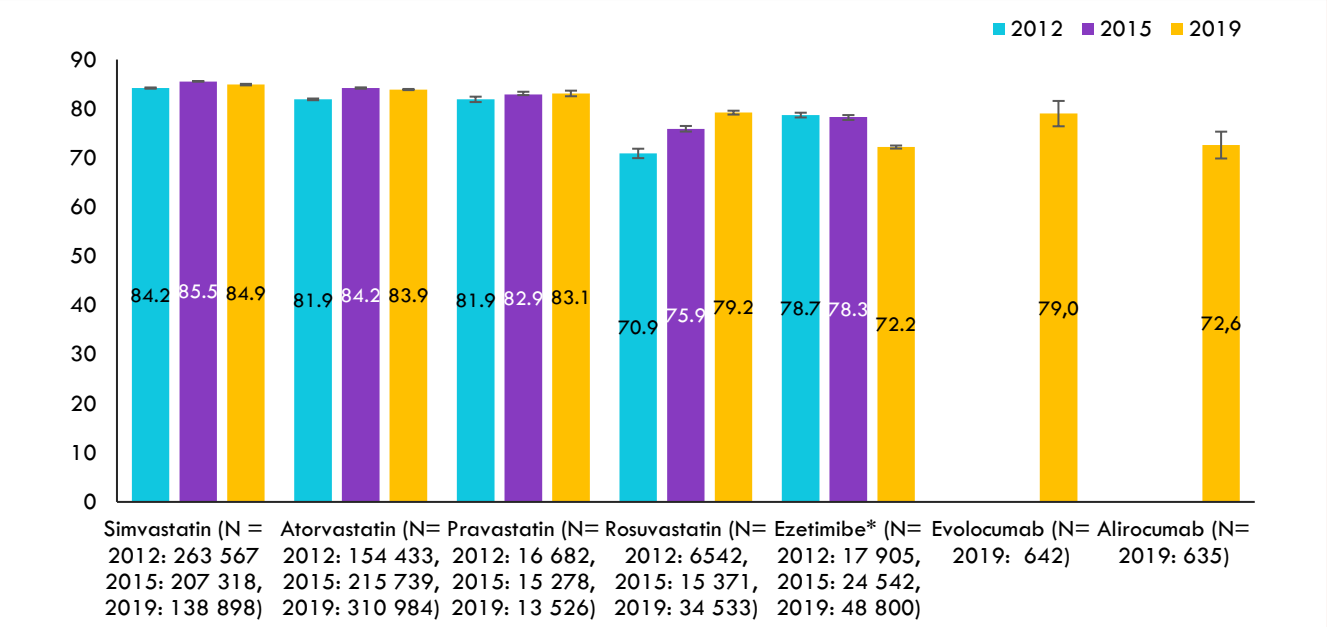


Figure 2 Mean proportion of days covered (PDC) (%)1 by lipid lowering drug in 2012, 2015, and 2019. Solid line on top of each bar shows confidence interval for mean PDC. Confidence intervals are small due to large sample size. [1]Total number of tablets dispensed in a calendar year divided by 365 and the number of patients in that year. *Ezetimibe (excluding combinations with statins).

Adherence and treatment gaps

For patients on lipid lowering drugs, adherence measured as mean PDC varied little across time and type of drug (*Figure 2*). In 2019, the mean PDC was 84.9% for simvastatin, 83.9% for atorvastatin, 83.1% for pravastatin, 79.2% for rosuvastatin, and 72.2% for ezetimibe. In 2019, the proportion of patients with PDC <80% was 37.8% for simvastatin, 21.3% for atorvastatin, 21.9% for pravastatin, 25.6% for rosuvastatin, and 31.8% for ezetimibe (data not shown). For simvastatin, atorvastatin, and pravastatin, there were only minor changes in the mean PDC from 2012 to 2019. While the mean PDC increased from 70.9 to 79.2% for Rosuvastatin from 2012 to 2019, it decreased for ezetimibe (from 78.7 to 72.2%). The estimated time trends of PDC for simvastatin, pravastatin, and atorvastatin were small, with an estimated yearly change of −0,09%, −0,15%, and 0,42%, respectively. The trends were larger in magnitude for rosuvastatin (2.7% increase per year) and ezetimibe (decrease of 1.85% per year). All time trend estimates were statistically significant. For PCSK9 inhibitors, the mean number of mg dispensed per day in 2019 was 7.9 for evolocumab (SD = 3.4) and 7.26 for alirocumab (SD = 3.5), with recommended dose 10 mg per day. This implies that a mean PDC in 2019 was 79.0% for evolocumab and 72.6% for alirocumab.

In total, 130 998 (39.2%) patients had gaps or discontinuation in statin treatment of 180 days or more (*Figure 3*). Among these patients, 65 637 had a gap of more than 180 days before they started treatment again during the period 2012–2019. These 65 637 patients had a total number of 86 174 gaps of 180 days or more. Gaps or discontinuation in statin treatment of 730 days or more were observed in 18.5% of patients (61 761 patients). The proportion of patients with gaps was similar for patients receiving diabetes drugs and those aged 61 years or younger (see Supplementary material online, *Figure S1*).

Subgroup analyses

The mean drug dose per day and/or mean PDC varied across gender, age, and whether the patients were on diabetes and hypertension drugs or not (*Table 2*). For atorvastatin, women used 24.7 mg per day in 2019, while men used 31.3 mg. The estimated gender difference in mean dose was 6.58, with a 95% confidence interval ranging from 6.4 to 6.7. Younger patients (0–59) also used a lower dose (25.8 mg/day) compared with those aged 60 and above (60–69 years: 29.6 mg/day, 70 + years: 30.0 mg/day). There was also a significant difference in mean PDC across the age groups 0–59, 60–69, and 70+, with a mean PDC of 77.8%, 85.4%, and 87.5%, respectively. There was no variation in mean PDC according to gender. Patients with at least one prescription of a diabetes and a hypertension drug used somewhat higher doses, and those in the older age cohorts had a higher mean PDC compared with the total patient population.

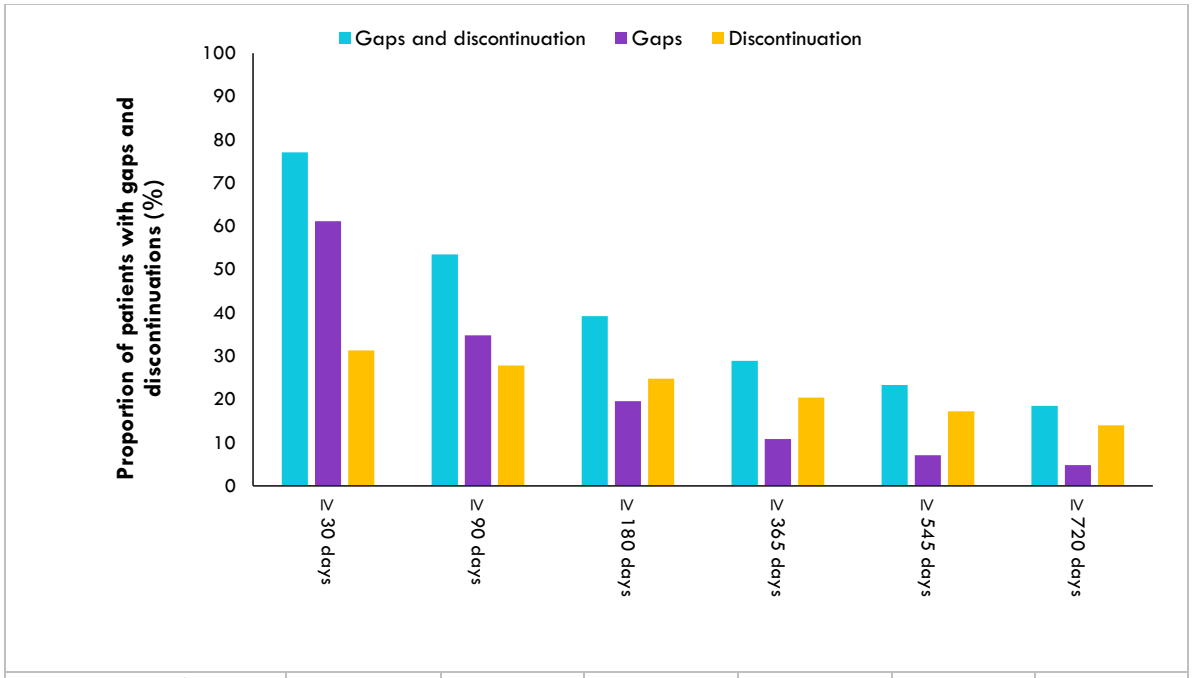
Sensitivity analysis of proportions of days covered

Our estimates of the proportions of days covered (PDC) presented above are influenced negatively by treatment gaps and initiation of treatment late in a calendar year. We tested alternative methods for estimating PDC to account for these factors, resulting in estimates means in the range 87–92% (see Supplementary material online, *Table S4*). Using the RWD, we found that younger patients (age categories < 50 years) have significantly longer prescription duration than older patients (age categories >59 years). We found no significant gender difference in prescription duration.

Discussion

Main findings

In Norway, an increasing number of patients use lipid lowering drugs. Our long-term data indicate that considerable proportions of patients have suboptimal treatment with low-intensity statins, low statin doses, modest adherence, and lengthy treatment gaps. Few patients receive ezetimibe, combination therapy with ezetimibe, or PCSK9 inhibitors.



Number of gaps[1]	548 003	191 810	86 174	40 405	25 025	16 385
Number of patients with gaps or discontinuation	257 640	178 839	130 998	97 715	77 861	61 761

Figure 3 Proportion (%) and number of patients with gaps or discontinuation in statin treatment, 2012–2019. [1]A treatment gap occurs if a patient does not refill a prescription when the previous one should have been depleted. Example: When a patient receives 100 tablets and fill the next prescription after 300 days, we define this as a 200-day gap.

Table 2 Proportion of days covered[a] and mean mg drug per day for atorvastatin users in 2019, according to age, sex, and the use of diabetes drugs

	n	Mean mg/day (SD)	Proportion of days covered (%) [95% CI]
Sex			
Women	126 344	24.7[b][19.6]	83.9 [83.7, 84.1]
Men	184 640	31.3[b] [23.4]	83.9 [83.8, 84.1]
Total	310 984	28.6 [22.1]	83.9 [83.8, 84.0]
Age			
0–59	91 987	25.8 [21.6]	77.8[c][77.59, 78.04]
60–69	104 728	29.6 [22.5]	85.4[c] [85.2, 85.6]
70+	114 269	29.97 [22.0]	87.5[c] [87.3, 87.6]
On diabetes and hypertension drugs			
0–59	15 553	29.7 [23.3]	84.3 [83.8, 84.9]
60–69	19 069	33.0 [23.8]	89.2 [88.7, 89.7]
70+	21 450	32.5 [23.1]	89.8 [89.3, 90.2]

[a]Total number of tablets dispensed in a calendar year divided by 365 and the number of patients in that year.
[b]The gender difference in mean mg/day is significant at the 1%-level.
[c]An ANOVA-test shows that differences in mean PDC between all age groups are significant at the 1%-level.

Thus, there seems to be a substantial potential for improvements in patient and population health outcomes through optimized treatment with cost-effective lipid lowering drugs.

Strengths and weaknesses

The main strength of this study lies in almost complete national, longitudinal data on the use of lipid lowering drugs. Pharmacies in Norway are legally required to electronically report all prescription fills to the NorPD, thus our data cover the entire Norwegian population. Because the study was based on nationwide data rather than a sample, we remove potential selection bias and ensure generalizability. Additionally, the number of patients and prescriptions is large for almost all subgroups, reducing the uncertainty in the estimates (as confirmed by the narrow confidence intervals). Still, there are important limitations. We do not have information on prescriptions that are not redeemed by the patients, and we do not know to what extent patients use the dispensed drugs. Consequently, the dispensed drugs represent the maximum treatment patients may receive. NorPD does not hold information on prescribed dosage. For statins and ezetimibe, we assume that patients are prescribed one tablet per day.

NorPD lacks information on clinical data such as lipid parameters. Data on comorbid CVD and risk levels are also largely missing even though prescription data on drug treatment for diabetes and hypertension may serve as a proxy for these variables. Consequently, we were not able to distinguish between primary- and secondary prevention. To

investigate patients with high CVD-risk subgroup, analyses were performed for patients with at least one anti-diabetes and one anti-hypertension drug prescription during the study period. Information on medical indication for prescriptions is missing and beta blockers, diuretics, calcium channel blockers, and ARBs may have been prescribed for non-CVD reasons.

Unfortunately, our data do not allow inference on the causes of gaps and discontinuation. The occurrence of the phenomenon seems is about the same across all patient subgroups we have examined.

We used mean PDC as the measure of adherence which can be estimated in several ways.[21–23] For statins and ezetimibe, we assumed that patients are prescribed one tablet per day, and subsequently aggregated per patient per year. This allows us to present adherence by calendar year which is important with our public health approach. This method, however, results in underestimating PDC for patients who initiate or discontinue treatment during a calendar year. We explored this limitation in sensitivity analyses and observed that mean PDC is somewhat higher (between 87 and 92%) when accounting for timing of initiation and discontinuation. Because relatively few patients are prescribed lipid lowering drugs for the first time during each calendar year (see Supplementary material online, *Table S2*) and are expected to receive treatment lifelong, the bias is likely modest. The main explanation of the difference between the different PDC-methods seems to lie in the large number and magnitude of treatment gaps. We allowed for stockpiling regardless of switching between drugs. The PDC for PCSK9 inhibitors is uncertain because PDC depends on the dosing interval and prescribed doses.

Discussion of own findings

The beneficial effects of lipid lowering treatment with statins,[24] ezetimibe,[4] and PCSK9 inhibitors[25,26] on clinical outcomes are well documented. Further, high-intensity statin treatment is superior to standard-dose therapy,[24] and combination-therapy with ezetimibe and simvastatin, and likely also other statins, improve outcome compared with treatment with statins alone.[4] Statins, ezetimibe and their combinations are available as generic drugs with low prices. Thus, increasing the prescribed dosage, or the use of these drugs, has negligible costs.

Our results indicate that, despite excellent evidence on effectiveness, strong recommendations[1,27], and modest drug costs, considerable proportions of patients use low-intensity statins, low doses, and relatively few are using ezetimibe. The modest use of rosuvastatin may be a consequence of higher generic prices and more strict reimbursement rules in Norway than for simvastatin and atorvastatin. Furthermore, reimbursement rules for PCSK9 inhibitors have been very strict and the utilization accordingly very low. Even though we in this study do not have information on LDL-cholesterol levels, other Norwegian studies find clear association between lipid lowering treatment, LDL-cholesterol levels and CVD risk.[6,28,29] In line with this, a large European study shows that a significant number of patients do not achieve the guideline-recommended treatment targets for LDL-cholesterol in daily clinical practice and that few are using combination with non-statin lipid lowering drugs.[30] Immediate, combination therapy with statins and ezetimibe, at least to high-risk patients, has therefore recently been recommended by a European Position document.[27] Even though several patients have switched from simvastatin and pravastatin from 2010 to 2019, there are few signs that adherence has improved over time. Even more disappointing is the finding that mean PDC or doses is not higher among patients on anti-diabetes and anti-hypertension drugs, and that a substantial proportion of these patients are observed to have long gaps in their statin treatment. International data [10,11] and data from Norway[31] show that statin non-adherence is associated with a greater than two-fold increased rate of subsequent cardiovascular events, more than four-fold increased risk of stroke and almost a four-fold increased risk of death. Non-adherence also contributes to significant healthcare expenditures.[32] It is concerning that younger patients, who benefit most from lipid lowering, have the lowest adherence.

The disappointing findings cannot be explained by strict reimbursement rules except for PCSK9 inhibitors, nor can they be explained by patient co-payments which are modest in Norway (approximately €200 in total per year for any drug or medical treatment). In fact, a recent report indicates that treatment of CVD disease related to hypercholesterolaemia cost approximately €1 billion, while the cost of lipid lowering drugs is less than €50 million.[33]

Findings in other studies

Several other studies have investigated patterns of statin use in the real-world setting.[28,34–37] In line with our results, previous studies indicate that there is an underutilization of high-intensity statin therapy[35,36] and that patients at high risk for CV events have high rates of discontinuation and poor adherence.[31,36] While many studies of adherence to lipid lowering treatment have focused on individual patients and specific lipid lowering drugs, we explore all three drug groups with a public health approach.

Clinical and policy implications

Optimizing lipid lowering drug treatment represents a potential for considerable health benefits at small additional costs and possibly cost savings elsewhere in the health care system. A Cochrane review suggests 'electronic reminders, pharmacist-led interventions, and healthcare professional education to help people better remember to take their medications'.[38] The problem is greater than these findings may indicate. When people have treatment gaps of months or years duration, the problem is more than lack of memory. Statin intolerance, in particular self-perceived statin intolerance, is a leading cause of treatment gaps and discontinuations. A recent study utilizing data from more than four million patients finds a prevalence estimate of statin intolerance of 9.1%.[39] A meta-analysis of randomized double-blinded statin trials report only a weak tendency towards more muscle symptoms among statin users compared with those who received placebo (12.6 vs. 12.4%), with no difference between the groups in proportion who discontinued statins.[40] Furthermore, when patients with self-perceived muscle symptoms on statins are randomized to high-intensity statin treatment and placebo in a crossover design, the intensity of muscle symptoms is similar in statin and placebo.[41] Other causes such as cultural reasons, lack of information from the healthcare provider, lack of education or awareness of the disease, and the silent aspect of CVD diseases also contribute to the observed non-adherence.[42]

In order to improve adherence to lipid lowering treatment in general, counselling and education, self-monitoring reminders, and pharmacist-led interventions are documented cost-effective[43] and recommended measures.[2] Electronic patient record systems with reminders to inform physicians about the prescribed amounts for individual patients and to detect potential treatment gaps are now available and should be implemented in the healthcare system.[38]

Conclusion

These prescription data on lipid lowering treatment indicate that Norway has considerable potential for better CVD health at modest costs.

Author biography

I.E. holds a master's degree in economics from the University of Oslo, with a specialization in data analysis and statistics. She is employed at Oslo Economics where she primarily works with health economic analyses, using registry data from national health registries. Her fields of interest include cardiovascular diseases, neuromuscular diseases, and cancer.

Data availability

No new data were generated in support of the article.

Supplementary data

Supplementary data can be accessed through the online publication. The supplementary data include a description of patient characteristics (see Supplementary material online, *Table S1 and S2*), number of patients and doses by lipid lowering drugs and year (2010–2019) (see Supplementary material online, *Table S3*), subgroup analyses of patients receiving diabetes drugs and patients 61 years or younger (see Supplementary material online, *Figure S1*), and sensitivity analyses of different methods to estimate mean PDC (see Supplementary material online, *Table S4*).

Access to study protocol, data application, approvals, programming code, etc. can be requested by contacting one of the listed authors on this publication. Access to raw data must be obtained from the Norwegian Prescription Database.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Acknowledgements

Data from the Norwegian Prescription Database have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the register is intended nor should be inferred.

Funding

The study was financed by Novartis Norway.

Conflict of interest: I.E. is employed at Oslo Economics AS. Oslo Economics has performed projects financed by Novartis and several other public and private organizations. J.M. has received lecture fees outside the submitted work from Sanofi, Amgen, Novartis, and Bayer. C.B. is employed at Oslo Economics AS. Oslo Economics has performed projects financed by Novartis and several other public and private organizations. S.H. has no conflicts to declare. Ødegaard is a PhD-student at the University of Oslo and an employee at Novartis Norway AS. H.S. is affiliated with Oslo Economics AS and has received honorarium from Novartis and several other public and private organizations. I.S.V. is affiliated with Oslo Economics AS and has received honorarium from Novartis and several other public and private organizations.

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