Lipid-lowering treatment intensity, persistence, adherence and goal attainment in patients with coronary heart disease

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Abstract

Background To examine patterns of lipid-lowering therapy (LLT) use, and persistence and adherence among patients with coronary heart disease and their associations with lipoprotein cholesterol (LDL-C) goal attainment.

Methods Observational study among 26,768 patients who had suffered a myocardial infarction or had been revascularized in Stockholm during 2012 to 2018, and followed up through 2019. Outcomes included initiation of LLT, discontinuation, re-initiation, adherence to treatment and LDL-C goal attainment according to the European dyslipidaemia guidelines from 2011 and 2016 (mainly LDL-C <1.8 mmol/L).

Results 82% of patients commenced or continued LLT within 90 days after discharge. Of those, 71% were dispensed an LLT prescription within 30 days (62% of them for high-intensity LLT). High-intensity LLT prescribing increased over time, from 12% in 2012 to 78% in 2018. During a median follow-up of 3 (IQR 2-5) years 73% continued to fill prescriptions for a statin, 26.3% temporarily or permanently discontinued, and 0.5% changed to non-statin LLT. Only 1.3% discontinued statin treatment permanently. Throughout observation, about 80% of patients showed good statin adherence (proportion of days covered $\geq$80%). LDL-C target attainment was 52% the first year and $<$50% during subsequent years. LDL-C goal attainment was highest among patients receiving high-intensity statin treatment and showing good treatment adherence.

Conclusion In secondary prevention for patients with established coronary heart disease, the proportion of LDL-C target attainment was low throughout the time period of the study, despite increasing use of high-intensity LLT and good treatment persistence and adherence. (Am Heart J 2022;251:78–90.)

Lipid-lowering therapy (LLT) is a cornerstone in the secondary prevention of atherosclerotic cardiovascular disease. Guidelines[1,2] recommend the use of high-intensity LLT for patients with coronary heart disease (CHD) if this is tolerated, with statins as first-line therapy. Despite the unquestionable benefits of statin treatment[3] and the rare occurrence of serious side effects,[4,5] long-term persistence and adherence to statin treatment are suboptimal in routine clinical practice worldwide,[6] and low adherence is associated with a greater risk of death and new cardiovascular events.[7]

Reports from the nationwide Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) register show a steady increase in the use of statins at high-intensity dosages over recent years in survivors of myocardial infarction (MI). However, up to 50 % of patients do not attain low-density lipoprotein cholesterol (LDL-C) targets during the first weeks of therapy.[8–10] This is problematic because effective reductions of LDL-C by high-intensity LLT during the first 6 to 8 weeks post- MI are highly predictive of better outcomes.[9] A lack of effectiveness in attaining lipid targets may be explained by poor adherence and/or persistence, [8,11] aspects of LLT that are insufficiently characterized. Previous attempts to evaluate persistence and adherence to statin treatment have focused on the first year of therapy[12,13] when patients are likely to be well motivated to follow the prescription, but long-term

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Submitted March 2, 2022; accepted May 25, 2022

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https://doi.org/10.1016/j.ahj.2022.05.021

adherence is less explored. Approximately 30% of patients in secondary cardiovascular disease prevention have been reported to stop LLT during the first year of treatment,[14] but information on long-term discontinuation rates could inform policy decisions on strategies to ensure continued use of this lifesaving therapy.

To address these issues, we investigated LLT use and treatment changes among survivors of MI or following coronary revascularization in the region of Stockholm, Sweden. We explored predictors of receiving high-intensity LLT, and we quantified long-term treatment adherence and persistence in relation to the attainment of LDL-C goals.

Materials and methods

Study population

We used data from the Stockholm CREAtinine Measurements project, a health care utilization database of residents in Stockholm, Sweden, which captures the complete health care use (including primary health care and laboratory data) and is described in detail elsewhere.[15] We included adult patients (≥18 years old) admitted for a first or recurrent CHD event, including hospitalisation for acute MI and/or coronary revascularisation (coronary artery bypass graft surgery or percutaneous coronary intervention) between January 2012 and December 2018. The date of the CHD event constituted our index date. Defining algorithms can be found in Supplementary methods. Exclusion criteria included death, emigration or loss to follow-up within 30 days from hospital discharge. Patients were followed until death, emigration or study end (December 31, 2019), whichever occurred first (Figure S1). The Regional Ethical Review Board in Stockholm approved the study (EPN 2017/793-31) and waived the need for informed consent, because data made available to researchers was de-identified.

Study exposure

Our first study exposure is LLT use, which included statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and ezetimibe. Because users of PCSK9 inhibitors proved to be very few, subsequent analyses for treatment persistence, adherence and LDL-C goal attainment are based solely on statins or statin/ezetimibe combinations. LLT use was ascertained through dispensations at Swedish Pharmacies, which are registered in the national Dispensed Drugs Register.[16] High-intensity LLT is defined as regimens that lower LDL-C on average by ≥50% (definitions in Supplementary material, Table S1).

Outcome measures

Initiation of high-intensity LLT: We evaluated the proportion of patients who received an LLT dispensation (and the type of LLT) during the first 90 days and up to 1 year after the CHD event. For prevalent LLT users, we quantified changes in the prescribed dose that occurred (eg, switching from low- or moderate- to high-intensity LLT).

Treatment discontinuation, re-initiation, and adherence. For this part of the analysis, we focused on statins users only. Among patients who were dispensed statins within 30 days from hospital discharge, we evaluated treatment changes compared with any previous statin treatment, defined as 90 days before index classifying them as intensification or de-intensification. Treatment discontinuation was defined as the first period of 90 days or more without any statin coverage. The number of days on a statin was calculated according to prescribed dosage. If patients had a supply of the same statin available from a prior prescription (ie, stockpiling), we added that to the supply of the following prescription. Patients who switched to a different type of statin were classified as persisting on statin therapy. Re-initiation was defined as the first occurrence of a statin dispensation between discontinuation and the end of the follow-up period. Changes in statin intensity on re-initiation were defined by comparing the intensity of the last statin filled before the period of ≥90 days without statin coverage, with the intensity of the statin filled on re-initiation. We estimated adherence to statin treatment every 6 months through the proportion of days covered (PDC), calculated by dividing the number of statin pills dispensed by the number of days during the period. To calculate days covered, we assumed an intake of 1 tablet/capsule per day. The PDC was categorized into good (≥80%), moderate (20-79%), and poor (<20%) adherence.[17]

LDL-C goal attainment and maintenance: We extracted all LDL-C measurements performed at all sources of Stockholm care (primary, outpatient-specialist and hospital care), which in most cases was assessed indirectly, by the Friedewald equation. We evaluated whether patients attained the LDL-C goals recommended by European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) guidelines of 2011[18] (LDL-C < 1.8 mmol/L or ≥50% LDL-C reduction) or 2016[19] (LDL-C <1.8 mmol/L and ≥50% LDL-C reduction). We evaluated goal attainment within distinct windows of treatment, using the mean of all tests encountered within the specific time window.

Study covariates

Patient data prior to and during the hospitalization were used to define covariates, which included demographic factors, comorbidity, estimated glomerular filtration rate (eGFR) and ongoing medications (details and definitions in Supplementary material, Table S2).

Statistical analyses

We used descriptive statistics to assess baseline characteristics at the time of the qualifying CHD event. Contin-

uous variables are summarized using means and standard deviations or medians and interquartile ranges, while categorical variables are presented using absolute and relative frequencies.

We first described time trends regarding the dispensation of LLT and the intensity of LLT dispensed across the study period. Multivariable logistic regression was performed to identify independent predictors of receiving high-intensity LLT (for details Supplementary Methods). LLT management over time and calendar period was visualized through Sankey plots, separately for the periods 2012 to 2015 and 2016 to 2018, and absolute percentage frequencies are presented.

Kaplan-Meier curves were generated to reflect the time until discontinuation (defined as ≥90 days – the grace period, or admissible interval - without a dispensation) and, when pertinent, re-initiation of statin. Sensitivity analyses were performed using alternative grace periods of 120 and 180 days to define treatment discontinuation.

For the analysis of persistence and adherence, only patients who survived ≥1 year were included. For analyses evaluating LDL-C targets, patients were included if there was ≥1 LDL-C measurement during the follow-up and were classified as meeting a target if they achieved it at any stage during the follow-up. The mean PDC was calculated and categorized for each interval. Similarly, we assessed the proportion of the patients at 12 months after discharge who attained LDL-C targets according to the clinical guidelines that applied at the time (2011 guidelines applied until August 2016 and thereafter 2016 guidelines). The combined continuous measure of treatment intensity and adherence was created and plotted against the percent change in LDL-C to visualize how the changes in adherence and treatment intensity after 1-year of therapy were associated with LDL-C goal attainment (for details Supplementary Methods and Table S3).

We assessed the long-term maintenance/attainment of LDL-C goal every 6-months and up to 60 months of follow-up. Multivariable generalized linear models for repeated measures were used to estimate the probability that a patient had ≥80% of days covered with their medication in each interval, ie, good adherence. Subgroup analyses were performed for filling a high-intensity LLT prescription over time and treatment adherence. These subgroups include: Age categories (18-49; 50-64; 65-79; ≥80 years), Sex, and eGFR categories (<30, 30-59, and ≥60 mL/min/1.73 m^2). Summary statistics, analyses, and graphs were performed with R, version 4.1.2. Sankey bar plots were created by using the SAS %SANKEY macro.[20]

Patient and public involvement

Patients or the public were not involved in the design or conduct or reporting or dissemination plans of our research.

Results

Baseline characteristics

A total of 26,768 patients met the inclusion criteria and were included in our analysis (Figure S2). Their median (IQR) age was 71 [62-79] years (Table), 69% were ≥65 years old, and 69% were men. The most frequent comorbidity was hypertension (71%), followed by diabetes (28%), congestive heart failure (26%) and chronic kidney disease (CKD) (26%, defined as eGFR<60 mL/min/1.73 m^2). Most of the patients (60%) had not been dispensed LLT before the index CHD event. Regarding education, 28% of the patients had undergone compulsory school, 41% high-school and 29% university education.

Initiation of lipid-lowering therapy

Overall, 82% of patients commenced or continued LLT within 90 days after discharge. Of those, 71% were dispensed an LLT prescription within 30 days after discharge and were included in our analysis. Of these, 62% were dispensations of high-intensity LLT, mainly with atorvastatin 40 or 80 mg (Table S4, left panel). Among patients with at least 365 days of follow-up, 86% were on statin therapy, and 60% filled a high-intensity LLT prescription at any time within the post-discharge period (Table S4, right panel).

Among patients who had not been dispensed LLT before the index CHD, 42% filled a high-intensity statin within 30 days (36% within 1 year). Prevalent users of low- or moderate-intensity LLT, patients older than 80 years of age, women, those with a previous history of CHD, and those with eGFR <30 mL/min/1.73 m^2 were less likely to be dispensed high-intensity LLT (Table S5). Patients with discharge LDL-C levels <1.8 mmol/L and those without recorded LDL-C measurements were less likely to be dispensed high-intensity LLT. Results were similar when these data were stratified by calendar years (Table S6).

The pattern of LLT use differed across calendar years as there was a progressive increase in the proportion of patients who were dispensed high-intensity LLT, from 12% in 2012 to 78% in 2018 (Figure 1A). This was primarily explained by greater use of atorvastatin (Figure 1B). Patterns of LLT use over time also differed across categories of kidney function, with the uptake of high-intensity LLT being lower in patients with CKD (Figure S3). During the first 3 years of LLT therapy, a growing proportion of patients switched to high-intensity LLT, particularly during 2016 to 2018 (Figure 2A and B).

Treatment discontinuation, re-initiation of statin treatment

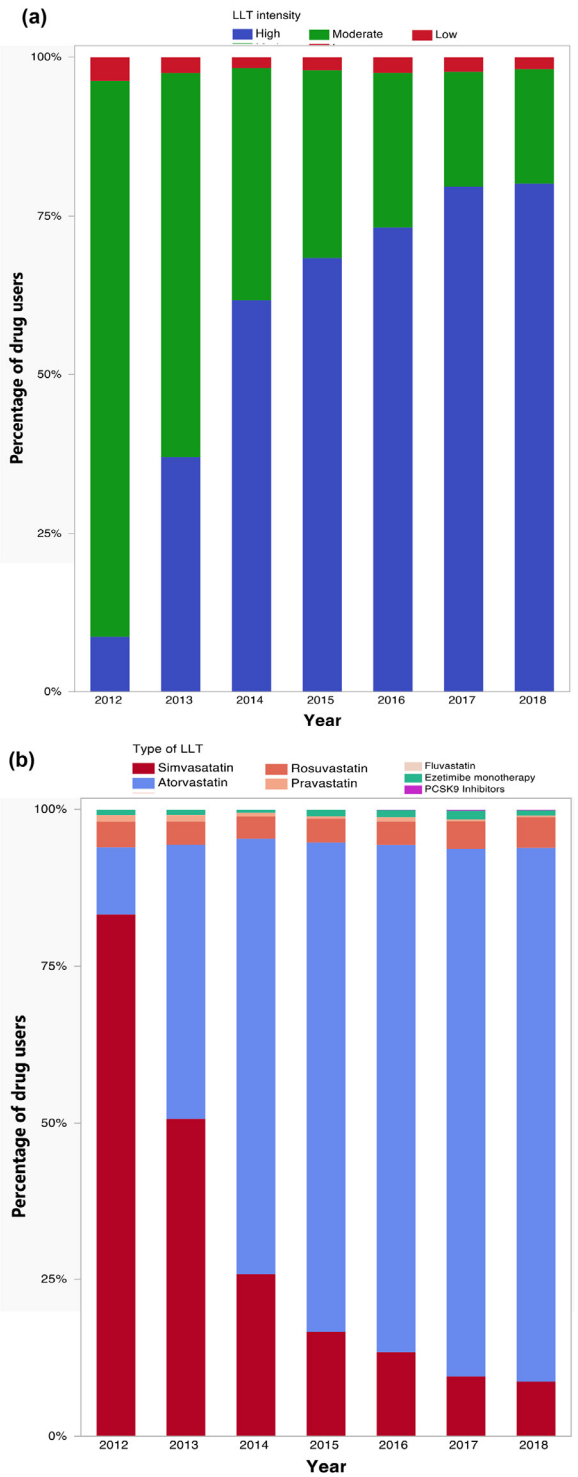
The majority (68%) of patients who initiated LLT with statins had at least 1 year of follow-up (see Figure S2 for exclusion). These patients were followed for a median (IQR) of 3 (2-5) years. Overall, statin use was rather

Table. Characteristics of study patients at the discharge of their index CHD event

	$N = 26,768$
Case qualifying event, *n* (%)	
Acute myocardial infarction	19,814 (74%)
Stable coronary heart disease receiving revascularization*	6,954 (26%)
Age (in y), median [IQR]	71 [62-79]
Age category (y), *n* (%)	
18-49 y	263 (1%)
50-64 y	8,228 (31%)
65-79 y	11,705(44%)
≥80 y	6,572 (25%)
Women, *n* (%)	8,286 (31%)
eGFR (in mL/min/1.73 m^2), mean [SD] ($n = 26,536$)	73 [23]
eGFR categories, *n* (%)	
≥60 mL/min/1.73 m^2	19,564 (73%)
30-59 mL/min/1.73 m^2	5,558 (21%)
<30 mL/min/1.73 m^2	1,414 (5%)
Unknown	232 (1%)
Smoking status	
Never smoked	5,943 (20%)
Previous smoker >1 mo	4,769 (18%)
Current smoker	3,268 (12%)
Unknown	12,788 (47%)
BMI category (kg/m^2), *n* (%)	
<25 kg/m^2	4,940 (18%)
25-29 kg/m^2	7,204 (27%)
≥ 30 kg/m^2	4,040 (15%)
missing	10,584 (40%)
Total cholesterol (in mmol/L), mean [SD] ($n = 22,972$)	5.0 [2.0]
LDL-cholesterol (in mmol/L), mean [SD] ($n = 22,111$)	2.8 [1.1]
HDL-cholesterol (in mmol/L), mean [SD] ($n = 22,383$)	1.2 [0.4]
Triglycerides (in mmol/L), mean [SD] ($n = 22,545$)	1.6 [0.9]
Type of myocardial infarction, *n* (%)	
STEMI	5,227 (20%)
NSTEMI	11,230 (42%)
No infarct	6,766 (25%)
unknown	3,545 (13%)
Comorbidities, *n* (%)	
Hypertension	18,945 (71%)
Previous myocardial infarction	10,348 (39%)
Diabetes mellitus	7,529 (28%)
Congestive heart failure	6,996 (26%)
Atrial fibrillation	5,178 (19%)
Chronic respiratory disease	5,083 (19%)
Stroke	2,526 (9%)
Peripheral arterial disease	2,072 (8%)
Transient ischemic attack	1,801 (7%)
Cancer	1,064 (4%)
Previous lipid-lowering therapy, *n* (%)	
no LLT	16,008 (60%)
Prevalent LLT user; High-intensity	2,642 (10%)
Prevalent LLT user; Moderate-intensity	7,411 (28%)
Prevalent LLT user; Low-intensity	707 (3%)
Highest attained education, *n* (%)	
Compulsory school	7,366 (28%)
Secondary school	11,066 (41%)
University	7,708 (29%)
Missing	628 (2%)

* patients undergoing CABG and PCI without register diagnosis of MI.HDL, high-density lipid; LLT, lipid-lowering treatment; LDL, low-density lipoprotein; NSTEMI, non st-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

Figure 1



Time trends showing the first LLT filled after CHD hospitalization by (A) intensity of LLT and (B) type of lipid-lowering drug.

constant, with most changes in dose occurring during the first year of treatment (Figure S4). For example, after 6 months of statin therapy, 5% had de-intensified, 9% had intensified and 0.5% permanently discontinued treatment; after 1-year of treatment, 19% had switched to different intensity statin (8% de-intensification and 11% intensification). The majority of patients persisted on statin treatment: 0.5% changed to non-statin LLT (ezetimibe monotherapy or PCSK9 inhibition), and only 1.3% of patients permanently discontinued, conditional on being alive.

Overall, 25% of patients discontinued statin treatment at some point, of whom 95% restarted therapy. The median number of months to treatment discontinuation was 25 (IQR 16-56) months, and the median time from discontinuation to re-initiation was 5 months (IQR 4-9) (Figures S5a and S5b). Using larger grace periods to define treatment discontinuation provided rates consistent with our main analysis (Figures S6). For patients who restarted statin therapy, the majority (76%) did so with the same statin intensity as before, 13% of patients with reduced and 11% with increased statin intensity (Figure S7).

Adherence to statin treatment

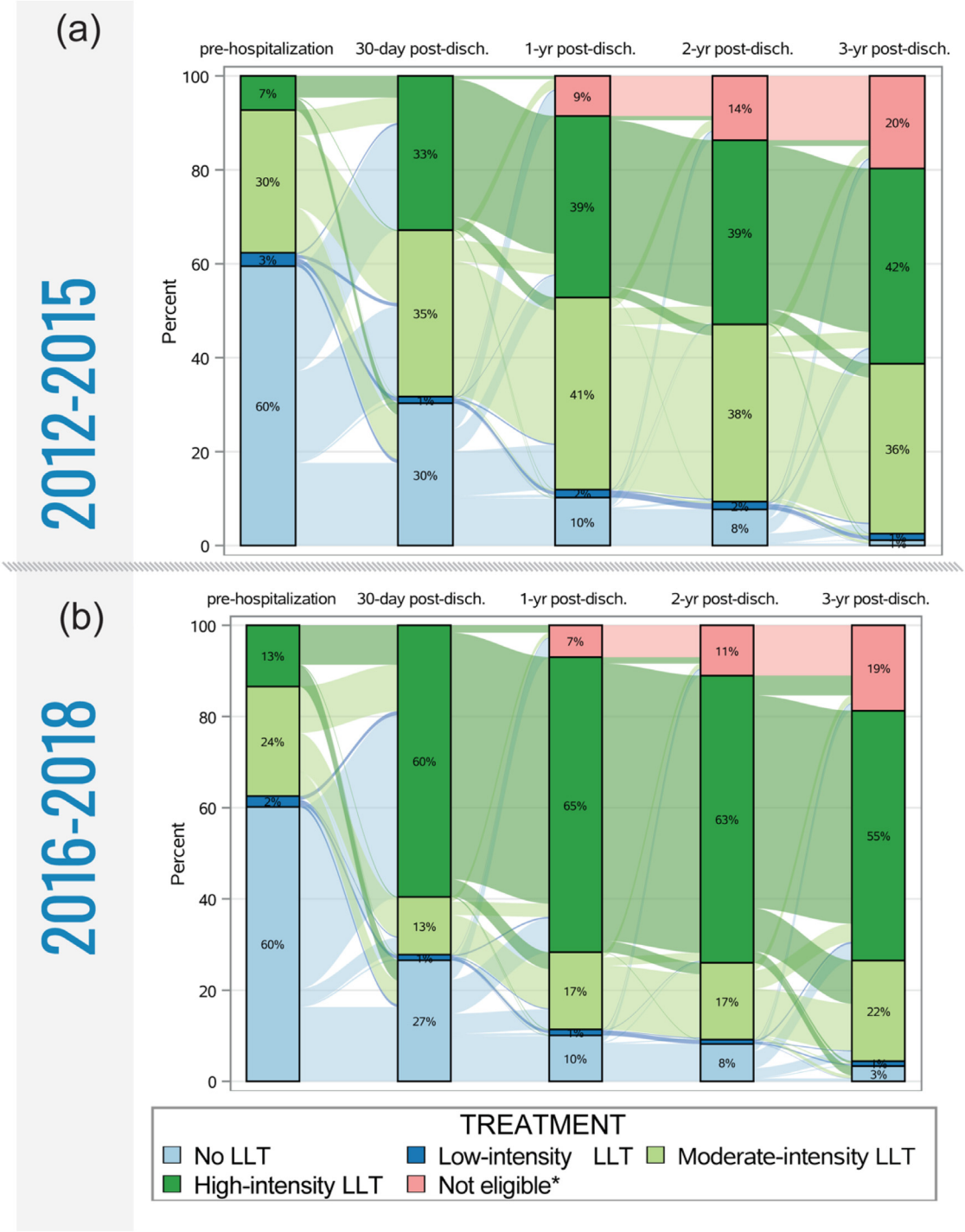
Statin adherence was highest during the first follow-up months and then decreased to approximately 80% at 5-years (Figure 3A). After multivariable adjustment, patients on high-intensity statin therapy were more likely to be adherent to treatment than patients on low-moderate intensity treatment (OR 1.07, 95%CI 1.05-1.09) (Table S7). In addition, patients with ages 65 to 79, or ≥80 years, eGFR <30, and eGFR 30-59 mL/min were more likely to have high adherence, each compared with their counterparts age 50 to 64 years and eGFR ≥60 mL/min, respectively (Table S7 and Figure S8a–e).

Attainment of LDL-C target attainment and maintenance

Overall, 52% of patients attained LDL-C targets. The proportion attaining the LDL-C goal was higher (56%) for patients receiving high-intensity statin treatment and showing good adherence (Figure 4A and Figure S9), followed by patients with low-moderate intensity statin treatment and good adherence (40%). Goal attainment was lower in patients with moderate/poor treatment adherence.

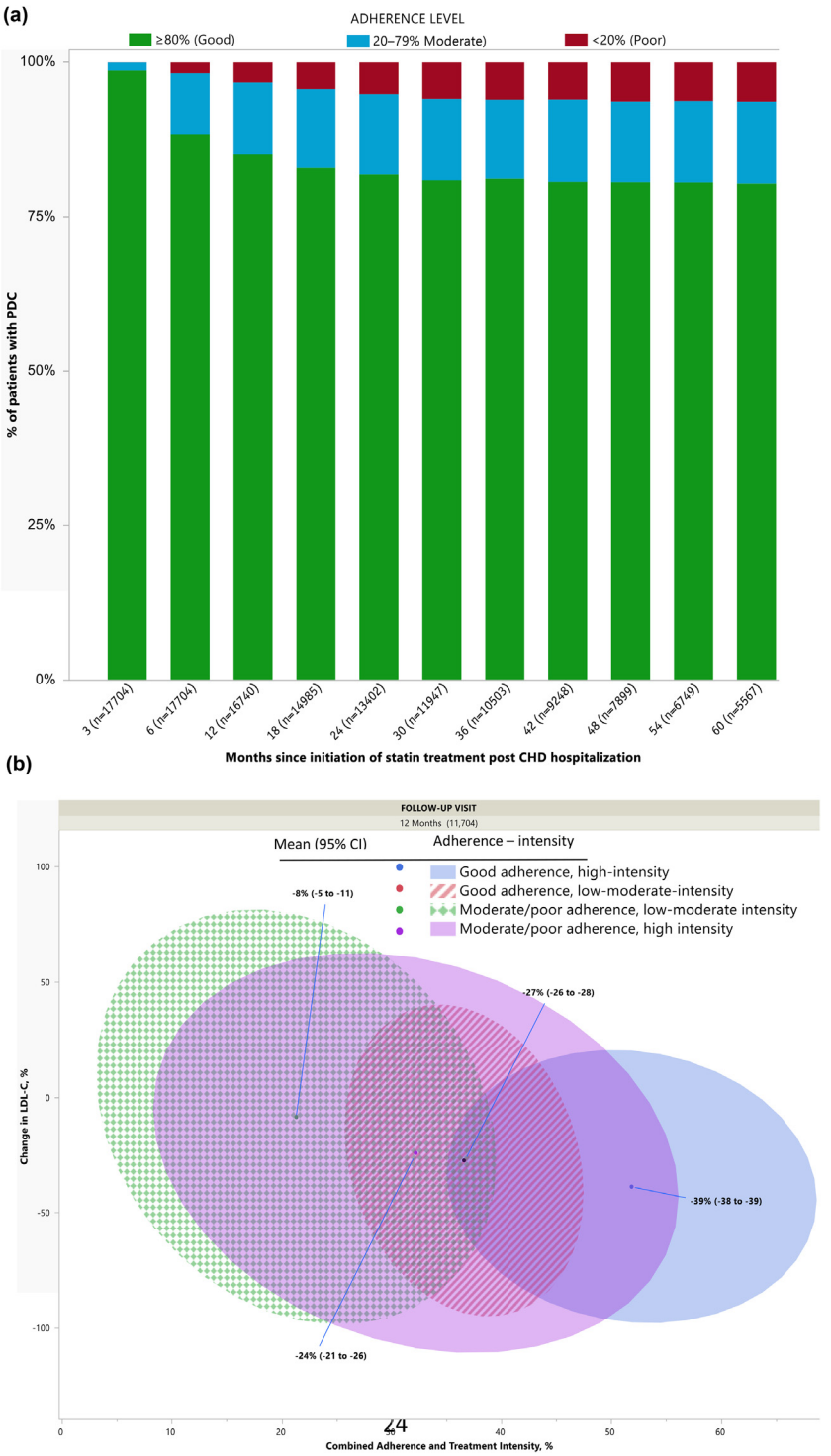
Patients receiving high-intensity statins and having good adherence showed, on average, the greatest reduction of LDL-C (mean 39% reduction; Figure 3B). In contrast, the LDL-C reduction among patients receiving statins of the same intensity but with moderate/poor treatment adherence was lower (24%). The average % LDL-C reduction for patients receiving low-moderate intensity and showing good adherence was 27% but went down to 8% if adherence was moderate/poor. The majority (59%) of patients close to LDL-C cholesterol targets

Figure 2



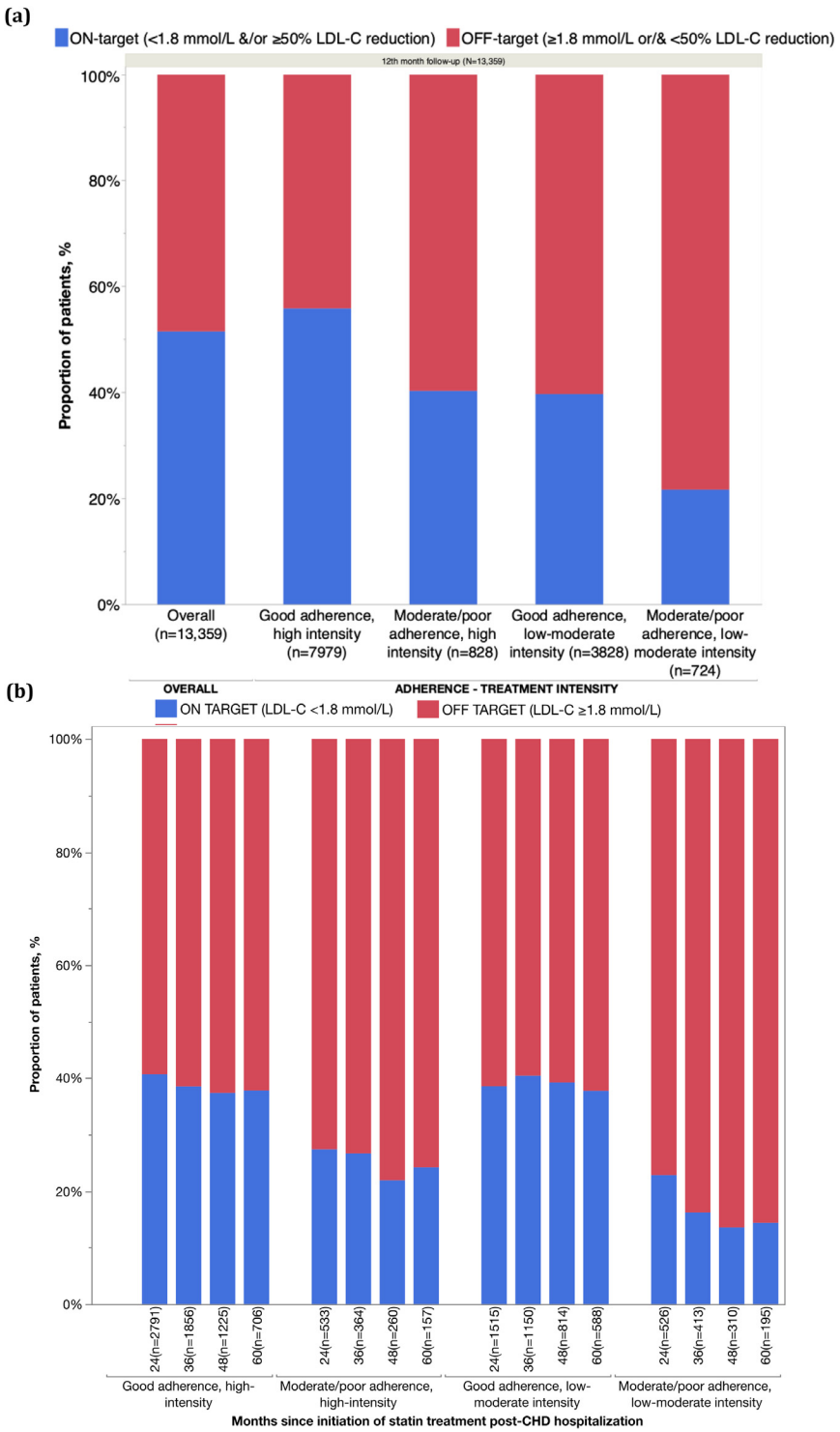
Sankey plots depicting the 3-year use of LLT after a CHD during 2 distinct periods, 2012-2015 (panel A), and 2016-2018 (panel B). Stacked bars show percentages of patients at each point in time, whereas connecting regions show the proportions that changed to a different category.*end of follow-up (emigrated/died /permanently discontinued LLT or end of data). disch disc,harge; LLT, lipid-lowering therapy.

Figure 3



(A) Proportion of patients classified as having a good (PDC> 80%), moderate (PDC=20–80%) and poor (PDC <20%) adherence during up to 60 months after CHD; (B) Ellipse plots depicting percent change in LDL-C after 1-year of statin therapy stratified by adherence-treatment intensity groups.

Figure 4



(A) LDL-C target attainment by adherence and statin treatment intensity at 12 months after CHD and (B) Long-term LDL-c target maintenance for up to 60 months of follow-up.

(LDL-C between 1.8-2.6 mmol/L) were those on high-intensity statins with good treatment adherence (Figure S10).

Beyond the first 12 months of therapy, and despite good adherence to treatment, <50% of patients attained LDL-C targets (Figure 4B). Among patients who had attained the LDL-C goal at 12 months of follow-up, >40% with adequate adherence to treatment had not maintained targets (Figure S11a). In comparison, most patients who had not achieved the LDL-C goal at 12 months of follow-up remained off-target (Figure S11b).

Good treatment adherence, use of high-intensity statins, and the presence of hypertension or diabetes mellitus were associated with higher odds of achieving and maintaining LDL-C targets (Figure 5A and B). By contrast, women, patients aged 50 to 64 years, prevalent users of statin at the time of the qualifying CHD event, and a history of revascularization had significantly lower odds of achieving and maintaining LDL-C targets LDL-C targets (Figure 5B).

Discussion

In this study of survivors of CHD in routine care, we observed an increasing use of high-intensity LLT over time, both as first-line therapy and through treatment intensifications. Persistence and adherence to statin therapy were generally high beyond the first year of use. Although about a quarter of patients discontinued statin therapy at some point, these were temporary interruptions and treatments were restarted in most cases. The use of high-intensity statins and good treatment adherence partly explained LDL-C goal attainment. However, the achievement of LDL targets was only 52% the first year of therapy and <50% during subsequent years.

The efficacy of high-intensity LLT in pivotal secondary prevention trials,[21] the strengthening of the recommendation in recent guidelines,[18,19] the patent expiry of atorvastatin in November 2011, the safety alert on simvastatin 80 mg because of potential muscle toxicity,[22] and a reportedly increasing adherence of prescribers to evidence-based recommendations in the region of Stockholm[23] may together explain the increasing use of high-intensity LLT (mainly atorvastatin 40-80 mg) in these patients. Similar trends have been reported globally.

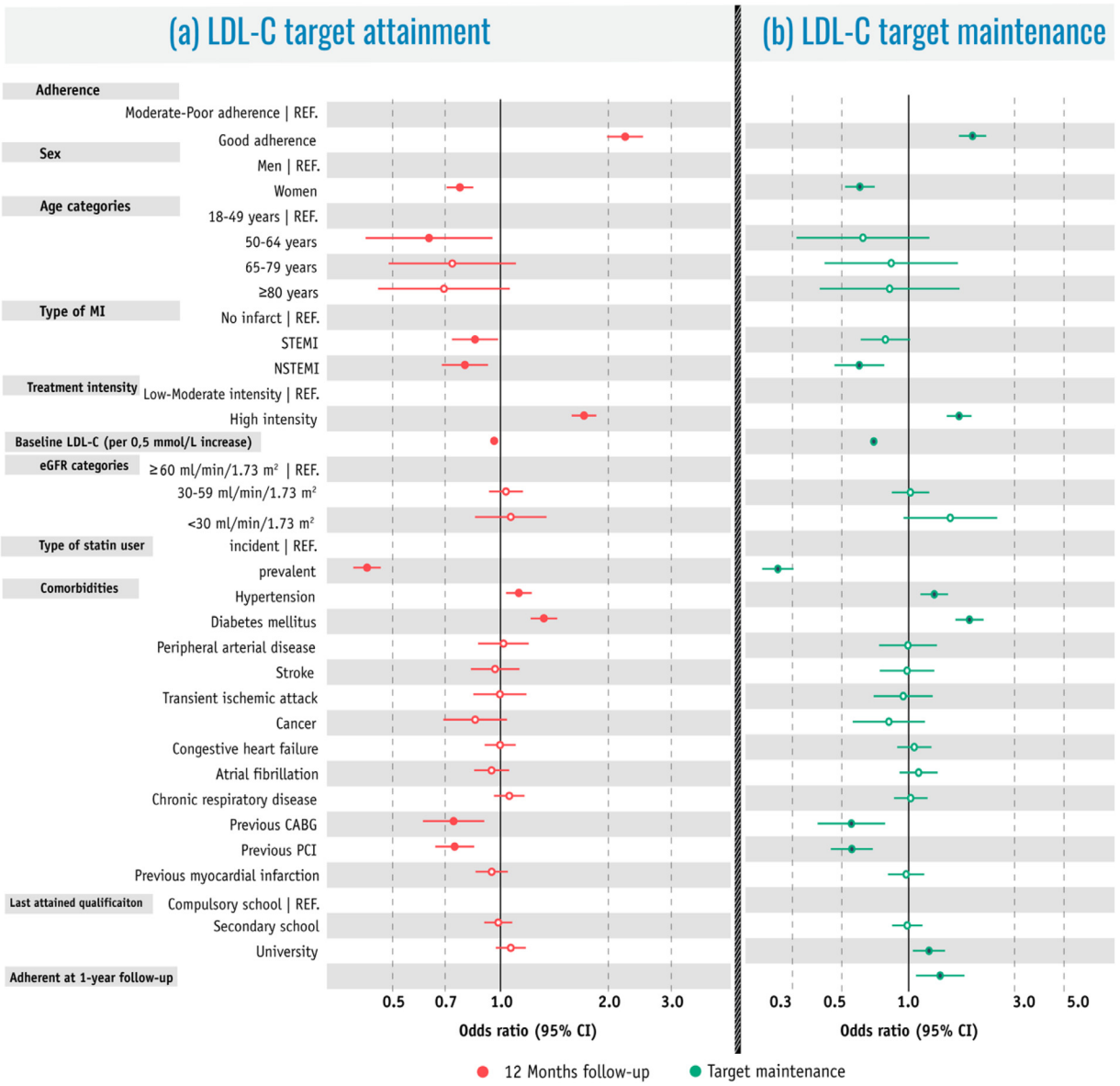
A large proportion of patients in our study (40%) were prevalent users at the time of their CHD event, and they were more likely to continue with the same statin intensity as before the event.[24] This may be simply attributed to treatment inertia. Further, clinicians may be more judicious in providing intensive statin treatment to sicker and older patients, given their higher prevalence of multiple comorbidities, potential risks for adverse drug effects, and drug interactions due to polypharmacy. Patients with advanced CKD were also less likely to received high intensity LLT in our study, perhaps reflecting therapeutic nihilism given a number of trials suggesting lack of efficacy of statins in persons with advanced CKD and dialysis,[25,26] or fear for acute kidney injury as a rare but potentially life-threatening adverse effect.[27,28] Finally, women were less likely to receive high-intensity LLT than men, possibly reflecting a greater sensitivity to adverse effects and/or a biased perception that disease is more severe (and hence requires more aggressive treatment) in men.[29]

A novelty of our study is the evaluation of treatment persistence and adherence in the long term, for which there has been considerably less epidemiological data. In a Finish study covering 1997 to 2007, 52% of patients remained adherent to therapy during the first 6 years[30]; while in the US (2007-2013), 66% patients with recent ACS were adherent after 15 months of treatment,[31] and in Scotland (2009-2016) a 53% adherence rate was observed up to 36 months after treatment initiation.[32] Compared with those studies, our study shows considerably higher adherence and persistence. Reasons behind this better performance are unknown, but may in part be related to a Universal health care access policy with the costs of medications almost subsidized in full. Further, cardiac rehabilitation is greatly valued in Swedish post-CHD care, through periodic assessments and reinforcement of lifestyle advice, including importance of medication adherence, and personalized care.[33] The SWEDEHEART registry collects nationwide indicators of post-CHD care, and shows that approximately 80% of all MI cases in our country participate in the cardiac rehabilitation program.[35] This attendance rate is higher than what reported for other similar registers such as EUROASPIRE IV,[34] which was 62%.

A quarter of patients discontinued therapy at some point, but re-initiation rates were high, above 90%. This again contrasts with previous studies from other parts of the world, where discontinuation rates vary between 15% and 75%,[14] and re-initiation ranges between 37% and 89%.[36] We acknowledge that reasons for therapy discontinuation are unknown and may explain differences across countries and studies; discontinuation could relate to patient disengagement, but also to issues of tolerability or adverse effects.[37]

Our main finding is that despite a good uptake of LLT recommendations and levels of adherence, persistence, and re-initiation rates that are high compared to other health care systems, the attainment of LDL-C target goals was low. Few studies have evaluated LDL-C goal attainment in contemporary routine care. An analysis of a convenience sample of 1,071 patients with acute coronary syndrome from 18 countries showed that only 37% had reached an LDL-C level of <1.8 mmol/L at 4 months after the event, although over 90% received statin therapy[38]; these findings were similar in analyses limited to the 439 patients from European countries.[39] In a report of 7,824 patients from 27 countries who were

Figure 5



Odds ratio (and 95% confidence intervals) for (A) LDL-C target attainment after 12 months after coronary heart disease and (B) LDL-C goal maintenance beyond 12 months.

interviewed 0.5 to 2 years after an elective coronary artery bypass graft, elective percutaneous coronary intervention, or an acute coronary syndrome, only 29% of the patients had an LDL-C level of <1.8 mmol/L when 34% received low- or moderate-intensity statins and 50% received high-intensity statins.[34] More recently, Allahyari et al[9] evaluated LDL-C goal attainment in the SWEDEHEART registry: the proportion of patients attaining the 2016 LDL-C target was only 31.6% 6 to 10 weeks after the CHD event and 31.5% after 12 to 14 months. By evaluating all LDL-C measurements performed in all sources of health care in the region, we offer goal attainment rates of high precision not subjected to attendance to a programmed study visit and that expand well beyond the first year of LLT. As such, we believe this is the largest and most comprehensive evaluation of LDL-C goal attainment in a complete routine care setting.

Contrary to our expectations, the use of low-moderate intensity statins and treatment non-adherence only partially explained the low goal attainment. However, dose escalation has a modest effect on the LDL lowering effect of statins as each doubling of the dose only reduces LDL by approximately 5 percentage points (Table S3). A recent trial demonstrated that educational sessions with patients and regular motivational telephone interviews compared to usual care, improved LLT adherence considerably in post-ACS patients, without significantly improving LDL-C goal attainment.[40] In a survey study, the failure of physicians to titrate the dose of statins and their ignorance of target LDL-C levels were factors contributing to the low achievement of LDL-C targets.[41] Patients' lifestyles, physical activity and dietary patterns could have contributed to the low target achievement level seen in our study. However, our results may also denote a lack of statin effectiveness and, as suggested by the recent 2019 ESC/EAS guidelines,[8] eligibility for expanded LLT, including add-on therapy with ezetimibe and use of PCSK9 inhibitors. The strongest predictor for not attaining or maintaining LDL-C goals in our study was prior statin use, and add-on ezetimibe therapy was not often used. Whether these are sicker patients or those in whom statins were not sufficiently effective merits further study, as they may be candidates for add-on therapies. Still, the cost-effectiveness of expensive therapy escalations remains unknown.[8]

We see as study strengths the inclusion of a more contemporary population, a longer follow-up, and the use of complete patient data (primary, secondary and tertiary health care) from an entire region, making it less susceptible to biases arising from fragmentation of care. Our findings apply to rhe Stockholm health care during a defined time period, and may not necessarily extrapolate to other countries or periods, or to non-universal health care systems. However, by evaluating the complete CHD population of Stockholm, our study offers greater generalizability than convenience samples which are selected by inclusion/exclusion criteria in registries. Our study also has limitations. Although evaluating pharmacy dispensations provides greater certainty of medication use than drug prescriptions, we cannot ensure that the patients took their pills. As in many observational studies, we can only speculate on why statins were discontinued. Adverse effects may be an important reason for stopping therapy, but more than 30 years of clinical investigation suggest that statins portend few serious adverse effects [5]. Other reasons may be deprescribing due to worsening of the patientś clinical profile, and true patient non-adherence. Goal attainment is based on LDL-C measurements in connection with health care encounters, which may underestimate the true goal attainment if healthy/adherent patients do not access health care. However, given the complete capture of laboratory data and health care for our region, this is the information physicians have had access to when making treatment decisions. LDL-C was assessed in 3 central routine laboratories in the region that may have different analyzers, but that participate in a national quality assurance program which should result in good comparability. Most measurements were indirectly estimated, as it is often the situation in routine clinical practice.

To conclude, despite a progressively increasing use of high-intensity LLT, and high rates of medication adherence and persistence, only about half of survivors of a CHD event or intervention attained LDL-C target goals. These findings reveal a clear gap between lipid guidelines and lipid management in routine clinical practice and highlight the likely challenges to be faced in attaining the even lower LDL-C goals introduced by the 2019 ESC/EAS guidelines.

Funding

The Swedish Heart and Lung Foundation (#20190587), Swedish Research Council (#2019-01059) and the Westman Foundation.

Conflict of interest

JJC received institutional funding from AstraZeneca, Astellas, and ViforPharma outside this study; CMC received consultation, advisory board membership or research funding from the Ontario Ministry of Health, Sanofi, Pfizer, Leo Pharma, Astellas, Janssen, Amgen, Boehringer-Ingelheim and Baxter. In 2018 she co-chaired a KDIGO potassium controversies conference sponsored at arm's length by Fresenius Medical Care, AstraZenec, Vifor Fresenius Medical Care, relypsa, Bayer Health Care and Boehringer Ingelheim. FM, PH KJ and TJ declare no conflict of interest.

Acknowledgments

None.

Contributors

FM and JJC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: FM, JJC and PH Acquisition, analysis, or interpretation of data: FM, PH, TJ and JJC. Drafting of the manuscript: FM, PH, JJC, CMC, KJ, TJ and JJC. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: FM, JJC. Obtained funding: JJC, PH. Supervision: JJC, PH.

Ethics approval

The Regional Ethical Review Board in Stockholm approved the study (EPN 2017/793-31).

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2022.05.021.

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