Real-world treatment patterns among patients with atherosclerotic cardiovascular disease (ASCVD) using lipid-lowering therapy in the HealthCore Integrated Research Database (HIRD)

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Purpose

- Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in the US[1] and includes coronary heart diseases such as myocardial infarction, ischemic stroke, and peripheral artery disease.
- Low-density lipoprotein cholesterol (LDL-C) is one of the primary causes of ASCVD.[2,3]
- The American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines recommend lipid-lowering therapies (LLTs) to reduce LDL-C by 50% and recommend that patients should be treated to an LDL-C <70 mg/dL.[2]
- Statins are the preferred first-line LLT; however, around 80% of patients on statins do not achieve recommended LDL-C goals.[4]
- Other treatments, including ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitor monoclonal antibodies (PCSK9is), are recommended as next line of treatment. With these newer treatments, the knowledge regarding adherence, persistence, and discontinuation among LLTs remains limited.

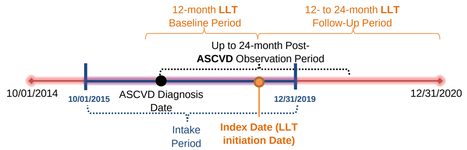
Objective

- This study examined real-world treatment patterns of LLTs including statins, ezetimibe, and PCSK9is as well as LDL-C goal attainment among patients with ASCVD using a large claims-based database. Treatment patterns included: adherence, persistence, and temporary and permanent discontinuation for LLTs, measured over 12 and 24 months from the first LLT claim after the first outpatient ASCVD visit during the predefined study period.

Methods

Study Design & Data Source

Figure 1. Illustration of Study Design



- The research questions were addressed using a retrospective, observational study including claims, eligibility, and outpatient lab data from the HealthCore Integrated Research Database (HIRD®) during October 1, 2014 – December 31, 2020.
- The HIRD is an integrated, longitudinal database with data on over 70 million lives across health plans in 14 geographically-diverse states dating back to 2006.
- LDL-C values were obtained from the HIRD integrated electronic labs reported by national outpatient laboratories.
- Index date was the earliest LLT fill date for patients during their 12- or 24-month post-ASCVD diagnosis observation period. All analyses were anchored to the index date (LLT initiation).
- Combination therapy were assigned based on other LLTs used within 30 days from start of the first LLT (i.e., index date; see cohort definitions below). Starting a second LLT >30 days after index date was considered augmentation and not a combination therapy.

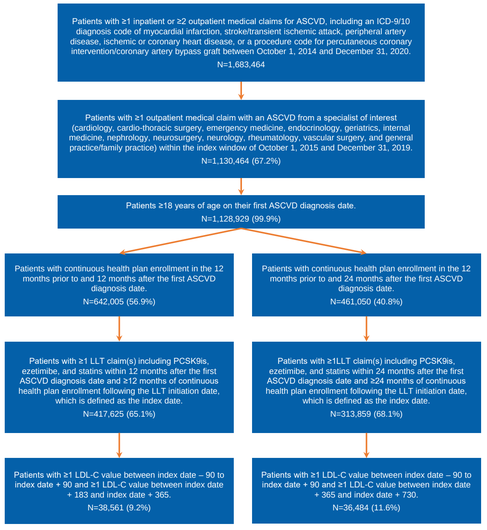
Study Population

- Patients with an ASCVD diagnosis and ≥1 claim(s) of LLT.
- Detailed inclusion/exclusion criteria are shown in Figure 2.

Cohort Definitions

- Statin monotherapy: ≥1 claim for statins and without any other LLTs within 30 days from index date.
- Ezetimibe monotherapy: ≥1 claim for ezetimibe and without any other LLTs within 30 days from index date.
- PCSK9is monotherapy: ≥1 claim for PCSK9is and without any other LLTs within 30 days from index date.
- Ezetimibe + statin combination therapy: ≥1 claim for ezetimibe and ≥1 claim for statins without PCSK9is within 30 days from the index date.
- PCSK9is + statin combination therapy: ≥1 claim for PCSK9is and ≥1 claim for statins without ezetimibe within 30 days from the index date.
- PCSK9is + ezetimibe combination therapy: ≥1 claim for PCSK9is and ≥1 claim for ezetimibe without statins within 30 days from the index date.
- PCSK9is + ezetimibe + statin combination therapy: ≥1 claim for PCSK9is and ≥1 claim for ezetimibe and ≥1 claim for statins within 30 days from the index date.

Figure 2. Patient Selection Diagram



Outcomes Definitions

- The outcomes of interest included LLT adherence, persistence, temporary discontinuation, permanent discontinuation, and LDL-C change during 12 and 24 months of follow-up.
- Adherence was defined as having the proportion of days covered (PDC) ≥ 80%. PDC was calculated as days covered by a drug (or overlap days for combinations) divided by number of days during the entire follow-up period (i.e., 12 or 24 months). Stockpiling was used such that early fills were added to the end of the preceding fill.
- Persistence was defined as the number of days from index date until temporary or permanent LLT discontinuation (≤60 days allowed gap) or end of follow-up. Patients who discontinued ≥1 LLT of a combination were considered not persistent.
  - Temporary discontinuation was defined as having a gap in LLT days supplied >60 days with ≥1 additional claim for the same LLT over the remainder of the follow-up period.
  - Permanent discontinuation was defined as having a gap in LLT days supplied >60 days without additional claims for the same LLT over the remainder of follow-up period.
- Augmentation occurred when the first treatment continues unchanged, and a new medication is added to the regimen.
- Treatment switching occurs when index medications were discontinued (>60 days without medication), and a new treatment was initiated within 60 days of discontinuation.
- All LDL-C outcomes were evaluated among a subset of ASCVD patients who had at least 2 LDL-C values in linked outpatient laboratory data.
  - One baseline LDL-C measurement at index LLT date ± 90 days.
  - For 12 months cohort: one or more subsequent LDL-C measurement at index LLT date + 183 days to index LLT date + 365 days.
  - For 24 months cohort: one or more subsequent LDL-C measurement at index LLT date + 365 days to index LLT date + 730 days.

Statistical Analyses

- Descriptive statistics including means, standard deviations (SD), medians, interquartile range (IQR), and absolute/relative frequencies for continuous and categorical data, respectively, were generated. No statistical testing was performed. Cell sizes with ≤10 patients were blinded for privacy in results.

Results

Table 1. Patient demographic and clinical characteristics at index/baseline

	Any LLT Treated (n=417,625)	Statin monotherapy (n=398,295)	Ezetimibe monotherapy (n=6,747)	PCSK9i monotherapy (n=1,237)	Ezetimibe + statin (n=11,011)	PCSK9i + statin (n=177)	PCSK9i + ezetimibe (n=88)	PCSK9i + ezetimibe + statin (n=70)
Male	63.8%	63.7%	59.2%	54.9%	71.2%	65.5%	63.6%	68.6%
Age, mean (SD)	66.5 (11.90)	66.5 (11.95)	68.1 (10.80)	69.3 (9.75)	66.2 (10.53)	60.2 (9.83)	62.7 (9.26)	57.1 (10.29)
Geographic region,[1] %								
Midwest	25.7%	26.2%	18.2%	16.7%	16.7%	14.1%	19.3%	21.4%
Northeast	15.6%	15.7%	13.5%	10.9%	13.9%	14.7%	14.8%	15.7%
South	30.1%	30.2%	29.6%	32.0%	30.0%	29.4%	29.5%	34.3%
West	25.2%	24.7%	34.9%	36.9%	35.6%	37.9%	33.0%	22.9%
Unknown	3.3%	3.2%	3.9%	3.4%	3.9%	≤10	≤10	≤10
Health plan type,[2] %								
HMO	22.7%	23.1%	15.1%	14.8%	13.3%	15.8%	14.8%	18.6%
PPO	66.8%	66.4%	76.2%	73.1%	76.3%	71.8%	69.3%	67.1%
CDHP	10.4%	10.4%	8.6%	12.1%	10.4%	11.9%	15.9%	≤10
Medicare Advantage								
%	19.1%	19.6%	12.0%	7.9%	7.8%	≤10	≤10	≤10
Index year,[3] %								
2015	19.9%	19.6%	24.1%	5.4%	31.1%	14.7%	15.9%	17.1%
2016	40.9%	40.9%	42.1%	37.8%	43.7%	25.4%	25.0%	27.1%
2017	15.4%	15.6%	13.1%	15.4%	10.3%	11.9%	15.9%	≤10
2018	12.3%	12.5%	10.2%	17.5%	7.6%	15.8%	21.6%	17.1%
2019 & 2020	11.4%	11.5%	10.5%	23.8%	7.4%	32.2%	21.6%	27.1%
Baseline cardiovascular disease risk factors,[4] %								
At least 1 risk factor	97.3%	97.2%	98.7%	99.5%	98.1%	98.3%	100.0%	98.6%
Baseline Medication utilization,[5] %								
At least 1 medication utilized	78.7%	78.6%	78.7%	72.9%	81.0%	75.7%	77.3%	74.3%
Baseline LLT utilization, %								
No LLT	16.3%	16.5%	16.9%	50.4%	4.7%	15.8%	13.6%	≤10
Any LLT	83.7%	83.5%	83.1%	49.6%	95.3%	84.2%	86.4%	85.7%
Statin	82.8%	83.4%	42.1%	30.9%	93.1%	79.1%	46.6%	82.9%
Ezetimibe	4.5%	1.1%	71.1%	11.6%	84.5%	22.0%	77.3%	75.7%
PCSK9i	0.1%	0.0%	0.2%	22.6%	≤10	32.8%	22.7%	24.3%
LLT Provider Specialty at LLT index date								
Cardiology	30.8%	30.3%	35.9%	63.9%	42.7%	72.3%	58.0%	61.4%
Primary Care Physician (PCP)	46.6%	46.8%	40.9%	15.5%	45.0%	31.1%	40.9%	31.4%

[1]Geographic regions based on US Census regions.
[2]Health plans: health maintenance organization (HMO); preferred provider organization (PPO); consumer-driven health plan (CDHP).
[3]Index year for 2019 and 2020 combined since 38 patients had an index date in 2020.
[4]Baseline cardiovascular risk factors included: type 2 diabetes, hypertension, current/former smoker (from claims), chronic kidney disease stages 1-5, heart failure, hyper/dyslipidemia, atrial fibrillation, and ventricular arrhythmia.
[5]Cardiovascular medications included: anti-diabetic, anti-coagulant, anti-arrhythmic, anti-hypertensive, and anti-platelet therapies.

- Patient demographic characteristics were similar across LLT cohorts.
- Most patients had ≥1 risk factor for ASCVD and ≥1 cardiovascular medication (excluding LLTs) during baseline.
- PCPs provided the majority of medications, except for PCSK9is, for which cardiologists were the most prevalent prescribers.

Table 2. Treatment patterns during 12-month follow-up

	Any LLT Treated (n=417,625)	Statin monotherapy (n=398,295)	Ezetimibe monotherapy (n=6,747)	PCSK9i monotherapy (n=1,237)	Ezetimibe + statin (n=11,011)	PCSK9i + statin (n=177)	PCSK9i + ezetimibe (n=88)	PCSK9i + ezetimibe + statin (n=70)
Persistence over follow-up, 60-day allowed gap								
Persistent patients, %	69.1%	69.5%	61.6%	62.1%	62.2%	33.3%	46.6%	28.6%
Days of persistence, median (IQR)	366 (214-366)	366 (219-366)	366 (151-366)	366 (140-366)	366 (180-366)	145 (76-366)	276 (98-366)	114 (59-323)
Adherence over follow-up, Proportion of Days Covered (PDC)								
mean (SD)	0.79 (0.27)	0.79 (0.27)	0.73 (0.30)	0.72 (0.29)	0.72 (0.29)	0.46 (0.32)	0.56 (0.32)	0.43 (0.30)
PDC ≥ 80%, %	65.5%	66.0%	58.0%	54.9%	55.0%	22.6%	31.8%	≤10
Treatment changes over follow-up period								
No treatment changes, %	91.8%	92.3%	60.9%	86.0%	93.8%	90.4%	79.5%	98.6%
Augmentation, %	1.9%	1.3%	35.7%	11.6%	0.9%	6.8%	18.2%	0.0%
Treatment switch, %	0.2%	0.2%	3.4%	2.3%	0.3%	≤10	≤10	0.0%
Discontinuation over follow-up period								
Temporary discontinuation, %	13.1%	13.0%	13.5%	15.8%	15.1%	19.8%	12.5%	21.4%
Days from initiation to discontinuation, median (IQR)	90 (84-180)	90 (83-180)	90 (76-180)	93 (57-161)	90 (90-180)	101 (63-180)	120 (100-146)	84 (30-110)
Days from discontinuation to restart, median (IQR)	96 (76-142)	97 (76-142)	95 (75-142)	97 (75-145)	92 (74-134)	92 (78-145)	93 (64-125)	88 (68-133)

Table 2. Continued…

Discontinuation over follow-up period								
Permanent discontinuation, %	17.8%	17.5%	24.9%	22.1%	22.6%	46.9%	40.9%	50.0%
Days from initiation to permanent discontinuation, median (IQR)	120 (84-214)	121 (87-215)	90 (60-186)	105 (56-182)	120 (86-212)	90 (30-120)	90 (54-181)	84 (56-152)

- Among the 642,005 patients with 12 months of follow-up after an outpatient ASCVD visit, 65.1% used an LLT and had 12 months of follow-up after first observed LLT claim.
- Among the 461,050 patients with 24 months of follow-up after an outpatient ASCVD visit, 68.1% used an LLT and had 24 months of follow-up after the first observed LLT claim.
- Among LLT users with 12 months follow-up, 95.4% used statins, 1.6% used ezetimibe, and 0.3% used PCSK9is. Patients who used statins + ezetimibe were 2.6% of the sample, while patients on combination therapies with PCSK9is were all <1%. The LLT distribution was similar among patients with 12 and 24-month follow-up.
- Days of persistence were negatively skewed (towards end of follow-up).

Table 3. Treatment patterns during 24-month follow-up

	Any LLT Treated (n=313,859)	Statin monotherapy (n=298,586)	Ezetimibe monotherapy (n=5,444)	PCSK9i monotherapy (n=1,027)	Ezetimibe + statin (n=8,593)	PCSK9i + statin (n=106)	PCSK9i + ezetimibe (n=63)	PCSK9i + ezetimibe + statin (n=40)
Persistence over follow-up, 60-day allowed gap								
Persistent patients, %	53.5%	54.0%	44.3%	41.7%	43.8%	22.6%	27.0%	≤10
Days of persistence, median (IQR)	727 (217-731)	729 (225-731)	520 (128-731)	449 (127-731)	525 (180-731)	180 (76-522)	232 (90-727)	129 (67-326)
Adherence over follow-up, Proportion of Days Covered (PDC)								
mean (SD)	0.73 (0.30)	0.74 (0.30)	0.66 (0.33)	0.64 (0.31)	0.66 (0.31)	0.41 (0.33)	0.45 (0.35)	0.37 (0.27)
PDC ≥ 80%, %	58.8%	59.4%	49.9%	44.3%	48.1%	20.8%	28.6%	≤10
Treatment changes over follow-up period								
No treatment changes, %	88.4%	88.9%	57.5%	87.2%	90.6%	87.7%	79.4%	97.5%
Augmentation, %	2.5%	1.8%	38.6%	10.5%	1.4%	≤10	17.5%	0.0%
Treatment switch, %	0.3%	0.2%	3.9%	2.2%	0.4%	≤10	≤10	0.0%
Discontinuation over follow-up period								
Temporary discontinuation, %	25.6%	25.4%	25.2%	32.8%	28.5%	35.8%	20.6%	47.5%
Days from initiation to discontinuation, median (IQR)	180 (90-360)	180 (90-360)	180 (90-337)	164 (84-351)	180 (90-340)	171 (91-320)	240 (120-338)	141 (50-372)
Days from discontinuation to restart, median (IQR)	109 (80-184)	109 (80-184)	109 (79-183)	113 (78-196)	102 (78-170)	135 (92-211)	93 (65-95)	118 (68-185)
Permanent discontinuation, %	20.9%	20.5%	30.5%	25.5%	27.7%	41.5%	52.4%	45.0%
Days from initiation to permanent discontinuation, median (IQR)	228 (90-450)	233 (90-450)	180 (90-389)	168 (84-388)	221 (90-439)	89 (30-180)	97 (88-221)	96 (69-242)

Table 4. LDC-C patterns during 12- or 24-month follow-up period after LLT index date

	All Patients		Adherent Patients (PDC ≥ 80%)	
	12-month follow-up (n=38,561)	24-month follow-up (n=36,484)	12-month follow-up (n=24,725)	24-month follow-up (n=20,508)
LDL-C test result closest to index date				
median (IQR)	82.0 (64.0-107.0)	82.0 (64.0-109.0)	78.0 (62.0-99.0)	77.0 (62.0-98.0)
LDL-C test result closest to end of follow-up				
median (IQR)	77.0 (62.0-98.0)	79.0 (62.0-99.0)	73.0 (59.0-90.0)	74.0 (60.0-89.0)
Patients at goal at baseline (LDL-C <70 mg/dL)				
%	32.5%	31.9%	36.6%	37.3%
Months on LDL-C goal (< 70 mg/dL), mean (SD)	10.4 (2.59)	18.0 (7.32)	10.7 (2.46)	18.8 (7.12)
Patients stayed on LDL-C goal (< 70 mg/dL) %	63.4%	50.2%	68.7%	56.4%
Patients with elevated LDL-C at baseline (LDL-C ≥70 mg/dL)				
%	67.5%	68.1%	63.4%	62.7%
Patients attaining LDL-C goal, for last LDL-C value				
<70 mg/dL, %	21.9%	22.3%	25.0%	25.7%
Attaining a ≥50% reduction relative to baseline LDL-C, %	7.9%	8.0%	8.3%	7.9%
Meeting LDL-C goal (<70 mg/dL) AND a ≥50% reduction relative to baseline LDL-C, %	6.0%	6.1%	6.4%	6.2%

- Median (IQR) LDL-C closest to LLT index date, 77 (62-98) and 79 (62-99) was similar between 12- and 24-month follow-up groups, with both above goal LDL-C (<70 mg/dL).
- Only a third of all patients were already at LDL-C goal (<70 mg/dL) within 90 days of LLT index date.

Discussion

- It was observed that 27.7 – 32.0% of patients did not use any LLT after their ASCVD diagnosis. Some patients used an LLT but did not have the required follow-up and were excluded.
- Adherence and persistence were similar across drug classes but declined over a 24-month period relative to the 12-month period across all LLTs.
- Persistence across drug classes was found to be longer among monotherapies than combination therapies.
- About one third of ezetimibe and a quarter of PCSK9is users permanently discontinued treatment during 24-months of follow-up.
- The treatment patterns and LDL-C results were relatively consistent across 12- and 24-months of follow-up.
- Median LDL-C closest to the end of follow-up remained above 70 mg/dL and was similar between 12- and 24-month cohorts.
- Of patients already at goal at LLT index date, 63% maintained goal at 12 months, and 50% maintained goal at 24 months.
- Among patients not at LDL-C goal at LLT index date, 22% of patients reached the goal (<70 mg/dL) and <10% of patients achieved a ≥50% reduction in LDL-C from index.

Limitations

- This study included patients with continuous enrollment in commercial health insurance only, which could limit the generalizability of the results.
- Only 9.2% and 11.6% of patients in the 12- and 24-month follow-up cohorts, respectively, had LDL-C values; therefore, results should be interpreted carefully. Differences between patients with and without LDL-C values were not assessed.
- The study design included incident and prevalent LLT users, which did not allow for determination of line of therapy. Incident and prevalent patients may differ in their utilization patterns or LDL-C values.
- We did not assess for other classes of lipid control medications.
- All results were descriptive, with no formal comparisons and no adjustments made for confounding variables.

Conclusions

- Despite having a preceding ASCVD diagnosis, a substantial portion of patient remained untreated.
- Among the treated patients, statins are the most common treatment by a wide margin.
- The adherence and persistence of existing LLTs were found to be suboptimal at both 12 and 24 months.
- Relatively few patients reached LDL-C goals at the end of follow-up, even among patients considered adherent, which aligns with previous literature on statin users.
- Given the nature of the chronic condition that spans a patient's lifetime, there is a large unmet need for novel lipid-lowering therapies that can circumvent adherence and discontinuation challenges in patients with ASCVD.

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Disclosures

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