Characteristics Associated with Inclisiran Initiation in Outpatient Physician Clinics

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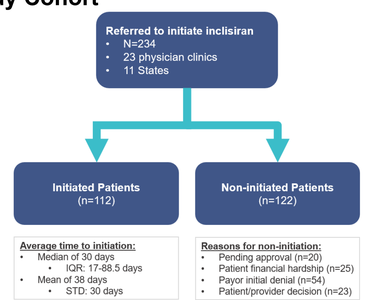
Introduction

- Inclisiran is a novel small interfering ribonucleic acid (siRNA) based inhibitor of PCSK9 production, effectively promoting low-density lipoprotein cholesterol (LDL-C) reabsorption in the liver.
- Inclisiran is indicated in the US as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of LDL-C [1].
- Inclisiran is administered as a subcutaneous injection by a healthcare provider at three months and then twice yearly after the initial injection [1]. This convenient treatment schedule potentially reduces patient burden and improves adherence.
- In two phase 3 ORION-10 and ORION-11 trials, inclisiran was shown to reduce LDL-C by 49.9 - 52.2% [2].. Prior authorization requirements, however, can complicate inclisiran initiation in the outpatient setting [3].
- The objective of this study was to identify characteristics associated with successful initiation of inclisiran in outpatient physician clinics.

Methods

- This was a retrospective, longitudinal, multicenter cohort study of all patients referred for treatment with inclisiran between January and July of 2022 at outpatient physician clinics nationally. Eligible patients were identified from a central electronic medical record.
- Patients were followed from the date of treatment referral until the day they received their initial injection, or the order was discontinued. Patients awaiting treatment on 11/28/2022 were censored.
- Variables collected included demographics, clinical covariates, diagnosis, baseline LDL-C, and time to inclisiran initiation. Prior therapy with anti-PCSK9 monoclonal antibodies (anti-PCSK9 mABs) and statins were collected in addition to concurrent statin and ezetimibe use.
- The Cox proportional hazards model was used to identify characteristics associated with successful initiation of inclisiran.

Study Cohort



Results

- Overall, 234 patients were referred to initiate treatment with inclisiran between January and July of 2022 at 23 outpatient physician clinics in 11 states.

Table 1. Baseline Characteristics of All Inclisiran Referrals

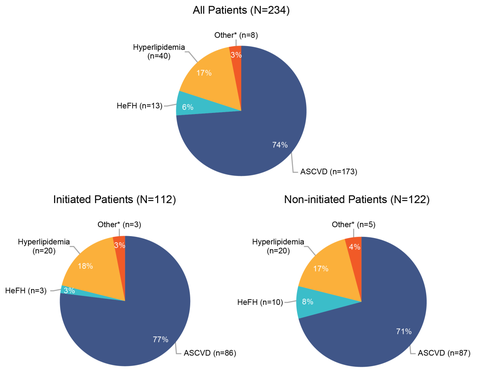
Characteristic	Initiated Patients (N=112)	Non-initiated Patients (N=122)	All Patients (N=234)	P-value
Age in years, mean±SD	70.5 (8.8)	66.2 (9.0)	68.3 (9.1)	<0.01
Age in years, median (IQR)	71 (67-75)	66 (60-72)	69 (64-74)	-
Age in years, categories, n (%)				
<65	19 (16.7)	47 (38.5)	66 (28.2)	<0.01
65-74	60 (53.6)	53 (43.4)	113 (48.3)	
75+	33 (29.5)	22 (18.0)	55 (23.5)	
Sex, n (%)				
Female	49 (43.8)	80 (65.6)	129 (55.1)	<0.01
Male	63 (56.3)	42 (34.4)	105 (44.9)	
Patient Region, n (%)				
Midwest	6 (5.4)	12 (9.8)	18 (7.7)	
Northeast	5 (4.5)	9 (7.4)	14 (6.0)	0.09
South	93 (83.0)	84 (68.9)	177 (75.6)	
West	8 (7.1)	17 (13.9)	25 (10.7)	
Body mass index, mean±SD	30 (5.8)	30 (6.3)	30 (6.0)	0.96
Body mass index, median (IQR)	30 (26-33)	29.5 (26-33)	29.7 (26-33)	-
Body mass index ≥30 mg/kg2	54 (48.2)	56 (45.9)	110 (47.0)	0.88
Payor Type, n (%)				
Commercial	21 (18.8)	53 (43.4)	74 (31.6)	
All Medicare*	91 (81.2)	67 (54.9)	158 (67.5)	<0.01
Medicare, traditional**	81 (72.3)	36 (29.5)	117 (50.0)	
Medicare Advantage	10 (8.9)	31 (25.4)	41 (17.5)	
Other†	0	2 (1.6)	2 (0.9)	
Elixhauser Comorbidity Score, median (IQR)	6 (0-24)	6 (0-14.5)	6 (0-15)	0.75
Predominant Comorbidities, n (%)	64 (57.1)	73 (59.8)	137 (58.6)	0.68
Cardiac Arrythmias	29 (25.9)	27 (22.1)	50 (23.9)	0.50
Depression	13 (11.6)	25 (20.5)	38 (16.2)	0.07
Diabetes	39 (34.8)	42 (34.4)	81 (34.6)	0.95
Hypertension	98 (87.5)	97 (79.5)	195 (83.3)	0.16
Hypothyroidism	23 (20.5)	21 (17.2)	44 (18.8)	0.52
Peripheral vascular disease	21 (18.8)	21 (17.2)	42 (18.0)	0.76
Valvular Disease	28 (25.6)	33 (26.2)	60 (25.2)	0.83
ASCVD Conditions, n (%)	103 (92.0)	109 (89.3)	212 (90.6)	0.44
Acute coronary syndrome	8 (7.1)	11 (9)	19 (8.1)	0.55
Coronary artery disease	91 (81.3)	99 (81.2)	190 (81.2)	0.88
History of myocardial infarction	28 (25)	29 (23.8)	57 (24.4)	0.50
Stable or unstable angina	31 (27.7)	29 (23.8)	60 (25.6)	0.60
Coronary or other arterial revascularization	69 (61.6)	65 (53.3)	134 (57.3)	0.13
Stroke	12 (10.7)	13 (10.7)	25 (10.7)	0.94
Transient ischemic attack	12 (10.7)	5 (4.1)	17 (7.3)	0.07
Peripheral aterial disease	8 (7.1)	16 (13.1)	24 (10.3)	0.12

Abbreviations: SD, standard deviation; IQR, interquartile range

*; all Medicare; **; Traditional Medicare; †; other included managed Medicaid (n=1), Tricare (n=1)

- A higher proportion of patients in the initiated cohort had traditional Medicare, compared to the non-initiated cohort (72% vs. 30%).
- The population was comorbid with a median Elixhauser comorbidity score of 6.0 (IQR: 0-15) overall with no observed differences between groups.
- Of the 122 who did not initiate treatment, the majority (44%) were due to payor denials. Most of the denials (39%) were due to step therapy policies requiring use of anti-PCSK9 mABs prior to inclisiran.
- There were no observed differences in the prevalence of ASCVD risk factors, cardiovascular procedural history, or cardiovascular comorbidities between patients who initiated and those that did not initiate inclisiran.

Figure 1. Primary Diagnosis of All Inclisiran Referrals



- Most patients (>70%), regardless of initiation status, had ASCVD. There was no difference in the distribution of primary diagnosis between initiated and non-initiated patients.

Figure 2: Baseline LDL-C of Inclisiran Referrals

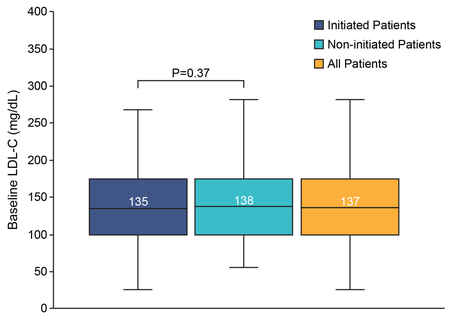
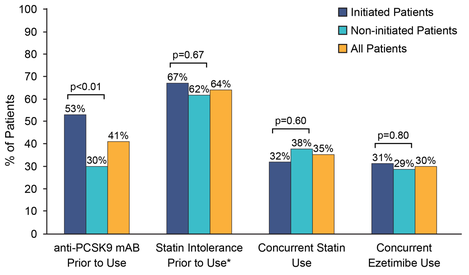


Table 2: Baseline LDL-C by Category

Baseline LDL-C (mg/dl)	Initiated Patients (N=112) n (%)	Non-initiated Patients (N=122) n (%)	All Patients (N=234) n (%)	P-value
LDL-C, median	135	137.5	136.5	0.37
LDL-C, categories, n (%)				
LDL-C <100 mg/dl	29 (25.9)	34 (27.9)	63 (26.9)	
LDL-C 100-159 mg/dl	47 (42.0)	44 (36.1)	91 (38.9)	0.65
LDL-C ≥160 mg/dl	36 (32.1)	44 (36.1)	80 (34.2)	

Figure 3. History of Lipid-Lowering Therapy



*Defined by provider-documented statin intolerance with discontinuation of statin therapy prior to initiation of inclisiran

- In total, 41% of all patients, 53% of those initiated, and 30% of the non-initiated had anti-PCSK9 mAB use prior to inclisiran (P<0.01).
- In this cohort, 24% of all patients were on high-intensity statins at the time of referral and 11% on low to moderate intensity statins with no differences between groups (data not shown).
- The median time to inclisiran initiation was 30 days (IQR: 17-88.5).

Table 3: Factors Associated with Inclisiran Initiation

Characteristic	aHR	95% CI	P-value
Age			
Less than 65 years	Ref.	Ref.	Ref.
65-74 years	1.15	0.58-2.31	0.69
75 years or above	1.12	0.52-2.4	0.77
Gender			
Female	Ref.	Ref.	Ref.
Male	1.92	1.29-2.83	**<0.01**
Payor			
Commercial	Ref.	Ref.	Ref.
Medicare, traditional	3.54	1.81-6.93	**<0.01**
Medicare Advantage	0.96	0.41-2.24	0.93
Hypertension	1.36	0.77-2.41	0.29
Diabetes	1.03	0.68-1.55	0.90
LDL-C			
< 100 mg/dL	Ref.	Ref.	Ref.
100-159 mg/dL	1.06	0.63-1.71	0.29
>160 mg/dL	1.14	0.69-1.90	0.61
Prior anti-PCSK9 mAB Use			
No prior use	Ref.	Ref.	Ref.
Prior use	1.8	1.23-2.63	**<0.01**
Statin Use	1.08	0.70-1.66	0.74

- Male sex, patients with traditional Medicare and prior use of anti-PCSK9 mABs were all associated with successful initiation of inclisiran.
- Traditional Medicare and prior use of anti-PCSK9 mABs were associated with a shorter time from referral to initiation.

Conclusions:

Inclisiran is an accessible treatment option for patients with ASCVD and elevated LDL-C.

- Inclisiran was successfully initiated in about half of patients referred. Initiated and non-initiated patients had a similar history of diagnoses and LDL-C at the time of the inclisiran referral.
- The following were associated with successful initiation of inclisiran:
  - Medicare beneficiaries
  - Prior anti-PCSK9 mAB treatment history
  - Male sex
- Male sex was associated with successful initiation potentially due to the predominance of cardiovascular disease in men which has been shown to influence treatment rates [4].
- Limitations of this study include the site of care, restricted to only physician clinics and the study timeframe starting immediately post-launch which affected initiation due to payors.
- Future directions include measuring adherence to inclisiran and real-world effectiveness among those who successfully initiate therapy.

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