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ORIGINAL ARTICLE

Statins Are Underutilized in Patients with Nonalcoholic Fatty Liver Disease and Dyslipidemia

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Abstract
Background Cardiovascular disease provides the greatest mortality risk in patients with nonalcoholic fatty liver disease (NAFLD). Clinical practice guidelines recommend statins to treat dyslipidemia in patients with NAFLD; however, the extent to which such patients receive statins has not been studied.
Methods We conducted a structured medical record review to assess for appropriate statin use in patients in a Veterans Administration facility with dyslipidemia and NAFLD as well as a parallel cohort without NAFLD. Appropriate statin use was defined as receipt of statins without a clinically significant, unjustified dose change during the study period.
Results Of 255 patients with NAFLD and dyslipidemia, 152 (59.6 %) patients received appropriate statin care. Primary care providers (PCPs) recognized the presence of NAFLD in 106 patients (41.6 %). Among the 63 of 106 (59.4 %) patients who were on a statin at the time of detection, 24 (38.1 %) received a clinically significant dose reduction or discontinuation. Patients whose PCPs recognized the presence of NAFLD (adjusted OR = 0.34, 95 % CI = 0.18–0.64) were less likely to receive appropriate statin care than patients with undetected NAFLD. Also, patients with detected NAFLD were less likely than dyslipidemic patients without NAFLD to receive appropriate statin care (OR = 0.45, 95 % CI = 0.25–0.79).
Conclusion Statins are underused in patients with NAFLD and dyslipidemia. The most important determinant for inappropriate statin use was PCP recognition of NAFLD. While these results need to be confirmed in non-VA healthcare systems, they highlight the need for efforts to enhance PCP knowledge of existing guidelines regarding statin use in NAFLD.

Keywords Nonalcoholic fatty liver disease · Statin · Cirrhosis · Veterans Administration · Automated data · Ethnicity

Background

Nonalcoholic fatty liver disease (NAFLD) represents a sequela of the metabolic syndrome. As such, cardiovascular disease remains the leading cause of death in patients with NAFLD [1]. Observational studies have implicated NAFLD as an independent risk factor for developing cardiovascular disease independent of the effect of coincident obesity or diabetes [2]. Thus, reduction in overall cardiovascular risk by controlling concomitant manifestations of the metabolic syndrome such as hypertension, insulin resistance, and dyslipidemia should be a central component of the care of patients with NAFLD.

Current clinical practice guidelines [3, 4] support the use of statins for treatment of dyslipidemia and secondary prevention of myocardial infarctions in patients with NAFLD. The literature is now extensive regarding the safety profile of statins in the context of chronic liver

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disease [5] including NAFLD [6] and cirrhosis [7]. While statins have long been associated with harmless, moderate, and non-progressive elevations of transaminase levels [8], patients with dyslipidemia may have myriad other reasons for presenting with such abnormal laboratory values, most notably NAFLD [4]. Overall, neither epidemiologic [9] nor histopathologic [10] studies have shown an association between transaminase elevation and progressive or chronic liver dysfunction in patients on statins.

Patients with NAFLD and an indication for statin use should be treated as long as their transaminases remain below three times the upper limit of normal (ULN) [4]. However, concern persists regarding the inappropriate discontinuation or withholding of statins for patients who present to their primary care providers (PCPs) with elevated liver function tests (LFTs) [11]. However, the extent and determinants of this potential gap in care remain undefined. There have been no studies to characterize the processes of care for patients with both NAFLD and dyslipidemia. Using our established cohort of patients with NAFLD at a single Veterans Administration (VA) medical center [12], we sought to evaluate the rates of dyslipidemia, statin use, and statin discontinuation.

Materials and Methods

Study Sample

We designed an observational cohort study in order to follow patients with NAFLD and the processes of care relating to their prescribed statin use over time. We used a pre-established algorithm to identify patients with NAFLD who sought care at the Michael E DeBakey VA Medical Center in Houston, Texas, between 2001 and 2011 [13]. Using structured automated data from the VA Corporate Data Warehouse, we selected patients based on the following criteria: (a) $\geq$2 alanine transaminase (ALT) values >40 IU/ml >6 months apart; (b) no positive results for hepatitis C RNA or hepatitis B surface antigen; and (c) negative screening for alcohol abuse, defined as an AUDIT-C score <4 in the 12 months prior to or after the first elevated ALT. AUDIT-C is a questionnaire used to screen Veterans for alcohol use disorders; over 80 % of VA outpatients nationwide are tested annually.

Of patients who met the criteria above, we randomly selected a subset for chart review ($n = 450$) via the Computerized Patient Record System (CPRS) (Fig. 1). CPRS is the electronic medical record system of the VA containing complete individual patient health information

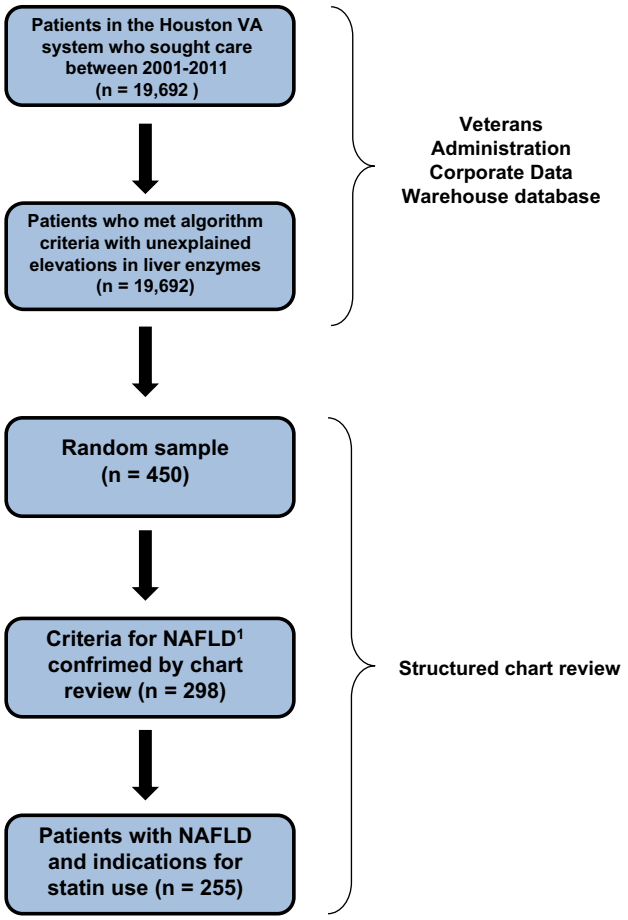

Fig. 1 Selection of patients included in the study. [1]Criteria include metabolic syndrome with no positive tests for HCV antibody, HCV RNA, or hepatitis B surface antigen, and no evidence of alcohol use based on ICD-9 codes or self-report (AUDIT-C) data. Presence of metabolic syndrome defined as BMI > 25 and two or more of the following: hypertension defined by systolic blood pressure $\geq$130 mmHg or diastolic blood pressure $\geq$85 mmHg; high-density lipoprotein (HDL) <40 g/dl; triglycerides >150 mg/dl; or presence of diabetes [hemoglobin A1c (HbA1c) >7.0]

including detailed provider progress notes as well as vital sign, laboratory, and imaging records. We defined a patient as having NAFLD if the chart review confirmed: (a) persistent transaminase elevation not secondary to viral, alcoholic, or medication-related etiologies; and (b) coinciding metabolic syndrome criteria at the time of transaminase elevation. We used a modified definition of metabolic syndrome issued by the International Diabetes Federation. We selected patients with a BMI of $\geq$25 in the presence of two of the following: hypertension denoted by systolic blood pressure >135 mmHg or diastolic blood pressure >85 mmHg; high-density lipoprotein <40 mg/dl; triglycerides >150 mg/dl; or hemoglobin A1c >7.0. We

used BMI as a surrogate for waist circumference because waist circumference data are not routinely collected as part of clinical practice. For each of these criteria, we used the value closest to the date of first elevated ALT. We considered patients actively receiving treatment for hypertension, hyperlipidemia, or hyperglycemia as having met the corresponding criterion for the metabolic syndrome.

For each patient meeting our definition of NAFLD, we determined indications for statin use based on the Adult Treatment Panel (ATP-III) guidelines which were in effect during the study period [14]. Only patients who met both criterion of NAFLD confirmed by chart review and indication for statin use were included in the NAFLD cohort. We also identified a group of randomly selected patients who were seen at the same facility between 2001 and 2011 and met the criteria for metabolic syndrome but not our NAFLD definition. This group served as the reference group (internal anchor) to facilitate inferences from our results.

Processes of Care

For patients who met criteria for statin use, we documented practices regarding lipid-lowering medications including (a) type, (b) dosage, (c) duration, (d) change in dose or drug, and (e) discontinuation of medications up to the end of the study (July 1, 2014). We also recorded data regarding the duration of time patients were off the lipid-lowering medications as well as the subsequent laboratory response in lipid levels.

We extracted information from PCP notes regarding recognition of transaminase elevation and used the date of first recognition as the index date from which to determine processes of statin use. For those without recognition of transaminase elevation or NAFLD, we used the time of initial transaminase elevation as our index date for determining indications for and use of statins. For all patients, we tracked subsequent LDL values and lipid-lowering medication use until the end of the study. We conducted an implicit review of PCP notes to identify justifiable reasons to withhold or discontinue statins. These included marked elevation in ALT value ($\geq 3\times$ ULN), patient refusal, or patient report of any adverse drug effect including myalgia or gastrointestinal intolerance.

Just as with the NAFLD group, we performed implicit chart review of PCP notes for our patients without NAFLD to record rates of statin use or discontinuation as well as all indications for statin discontinuation. Because no index date could be determined in this population without history of transaminase elevation, we compared rates of statin use between patients with and without NAFLD as recorded at the final clinic visit.

Statistical Analysis

Our primary outcome was appropriate use of statins, defined as any case where statins were prescribed without a clinically significant, unjustified dose change during the study period. A priori, we defined a clinically significant dose change as any change that lasted for at least 1 year and resulted in a sustained increase in LDL from <100 mg/dl to $\geq$100 mg/dl. A statin discontinuation or dose reduction was deemed justified when the PCP documented an excessive ($>3\times$ ULN) ALT, symptomatic intolerance, or patient refusal as a reason to stop statins.

We classified NAFLD patients based on appropriate and inappropriate statin use and used Chi-square tests and unpaired *t* tests to examine differences across the categorical and continuous variables, respectively. We employed a multivariate logistic regression analysis to examine the effects of demographic (age, gender, race), clinical (index ALT, index LDL and HDL level, BMI, and the presence of hypertension, hyperlipidemia, hypertriglyceridemia, and diabetes mellitus), and provider (recognition of elevated ALT) factors on appropriate statin use. Odds ratios and 95 % CI were calculated. We used Chi-square tests to compare the proportion of patients with appropriate statin use among those with and without NAFLD.

Results

Patient Characteristics of the NAFLD Cohort

We identified 298 patients who met the criteria for NAFLD based on our chart review (Fig. 1). Among these, 255 patients (85.6 %) carried an indication by ATP-III guidelines for treatment with statins. The mean age of these patients at the time of initial ALT elevation was 53.1 years (Table 1). Most ($n = 242$, 94.9 %) were male; 71.0 % ($n = 181$) were non-Hispanic whites, and 17.6 % ($n = 45$) were African American. There were 99 patients (38.8 %) with a BMI $\geq$ 35. Approximately 85.1 % of patients had hypertension, 68.2 % had hypertriglyceridemia, and 36.1 % had diabetes mellitus.

Statin Use

A total of 159 patients (62.4 %) were on statins at the time of first ALT elevation. Among these, statins were stopped or reduced in 36 patients during the study period, 28 of which were clinically significant discontinuations with an increase in LDL to $\geq$100 mg/dl for at least 1 year. Of the 96 patients not on statins at the index date, 69 remained untreated for the entire study period.

Table 1 Patient characteristics by appropriate statin use

	Total cohort *n* (%)	Statin use appropriate ($n = 152$)	Statin use inappropriate ($n = 103$)	*p* value
Age				
Mean (year ± SD)	53.1 ± 11.9	56.3 ± 10.8	49.2 ± 12.8	<0.001
Range	24–86	25–86	24–79	
Gender [no. (%)]				
Male	242 (94.9)	146 (96.1)	96 (93.2)	0.31
Female	13 (5.1)	6 (3.9)	7 (6.8)	
Race/ethnicity [no. (%)]				
Caucasian	181 (71.0)	114 (75.0)	67 (65.0)	0.16
African American	45 (17.6)	21 (13.8)	24 (23.3)	
Hispanic	24 (9.4)	13 (8.6)	11 (10.7)	
Other	5 (2.0)	4 (2.6)	1 (1.0)	
Body mass index (mean ± SD)	34.2 ± 5.4	35.1 ± 6.1	33.0 ± 4.1	<0.01
Metabolic syndrome [no. (%)]				
Diabetes mellitus	92 (36.1)	68 (44.7)	24 (23.3)	<0.01
Hypertension	217 (85.1)	124 (81.6)	93 (90.3)	0.06
Hypertriglyceridemia	174 (68.2)	110 (72.4)	64 (62.1)	0.09
Laboratories at the index date ± SD[a]				
ALT	59.1 ± 27.4	58.1 ± 30.8	60.5 ± 21.4	0.71
AST	37.3 ± 19.0	37.4 ± 22.5	37.1 ± 12.3	0.86
LDL	120 ± 39.5	112.9 ± 42.7	131.5 ± 31.1	<0.01
HDL	36.5 ± 9.2	36.6 ± 8.6	36.2 ± 10.0	0.66
NAFLD fibrosis score[†]				
Low	102 (40.0)	59 (38.8)	43 (41.7)	0.33
Indeterminate	124 (48.6)	72 (47.4)	52 (50.5)	
High	29 (11.4)	21 (13.8)	8 (7.8)	
PCP recognition of LFT elevation	106 (41.6)	49 (32.2)	57 (55.3)	<0.001

SD standard deviation, *ALT* alanine transaminase, *AST* aspartate transaminase, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *PCP* primary care provider, *LFT* liver function test

[†] The NAFLD fibrosis scoring system was derived from aforementioned sources, with values <−0.1455 deemed negative for significant fibrosis, values >0.675 counted as positive, and values in between being indeterminate

[a] Index date defined as the date during which elevated liver enzymes first occurred or were detected, if they were detected at all

PCPs detected NAFLD in 106 patients (41.6 %), among whom 63 (59.4 %) were on a statin at the time of detection (Fig. 2). Within this group, PCPs discontinued the statin in 29 cases and decreased the dose in three more; thus, a total of 32 patients (50.8 %) had a decrease or discontinuation of statins. None of these patients demonstrated an ALT level that was greater than 3× ULN. Of the 43 (40.6 %) patients not on statins at the index date, 10 patients (23.3 %) had a justifiable reason for withholding the medication: three patients had marked elevation in ALT, three experienced intolerance to statins, and four patients refused. We found no justifiable reason for withholding statins in the remaining patients.

In contrast, among the 149 patients with unrecognized NAFLD and indications for statin use, 96 patients (64.4 %) were prescribed a statin at the time of initial transaminase elevation (Fig. 2). All continued treatment except for four patients who later stopped due to adverse symptoms during the study period. Among the 53 patients (35.6 %) not on statins, five recorded prior intolerance to statins, two refused, and the remaining 46 had no justification documented in the charts.

Collectively, we found that 69.1 % of patients with NAFLD that remained unrecognized were treated appropriately with statins, whereas only 46.2 % of patients with clinically recognized NAFLD received appropriate statin care.

Determinants of Appropriate Statin Use in Patients with NAFLD

Older patients, those who were obese, those with lower index LDL levels, and those with diabetes had higher odds

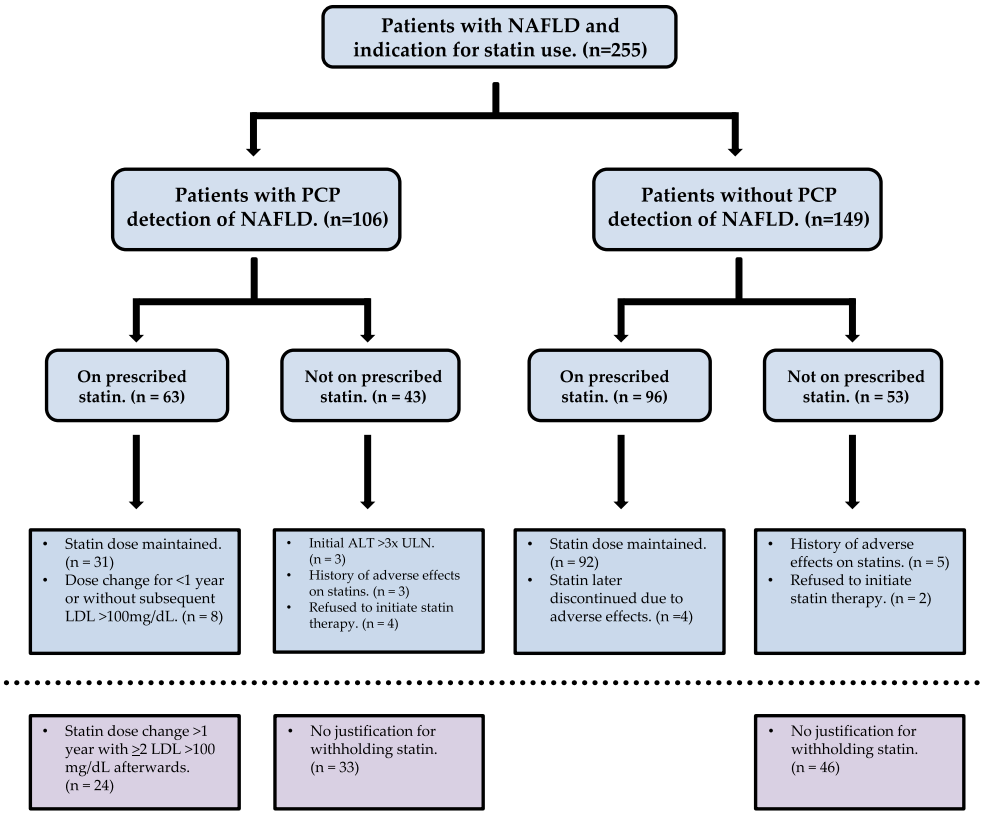

Fig. 2 Primary care processes for patients with NAFLD and an indication to receive statins. *PCP* primary care provider, *ULN* upper limit of normal, *LDL* low-density lipoprotein

of receiving appropriate statin care than the corresponding groups in bivariate analyses (Table 1). Conversely, PCP recognition of abnormal liver enzymes was associated with lower odds of receiving appropriate statin care. After adjustment for patient demographic and clinical factors, older age (adjusted OR 1.04, 95 % CI 1.01–1.07), index LDL value (adjusted OR 0.99, 95 % CI 0.98–0.99), and NAFLD recognition by the PCP (adjusted OR 0.34, 95 % CI 0.18–0.64) retained statistical significance in their association with appropriate statin use (Table 2).

Comparison with the Non-NAFLD Cohort

We selected a random sample of 100 patients with metabolic syndrome but without NAFLD to serve as potential controls. Of these, 8 lacked an indication for statin use based on chart review. Of the 92 remaining patients, a total of 52 (57.1 %) were on statins by the final PCP visit, compared to 131 (51.3 %) of all patients with NAFLD. Statins were withheld or discontinued among 9 patients (9.9 %): six for adverse drug effects, two for resolution of dyslipidemia with weight loss and appropriate improvements in lipid profile numbers, and one for increases in transaminase levels to above 3× ULN.

Table 2 Multivariate analysis of predictors for appropriate statin use

	Adjusted OR (95 % CI)	*p* value
Age	1.04 (1.01–1.07)	0.02
Gender		
Male versus female	0.40 (0.10–1.67)	0.21
Race (vs. Caucasian)		
African American	0.55 (0.24–1.26)	0.16
Hispanic	1.29 (0.45–3.72)	0.63
Other	7.43 (0.56–99.3)	0.13
Body mass index	1.06 (0.99–1.12)	0.12
Diabetes mellitus	1.82 (0.90–3.68)	0.10
Hypertension	0.39 (0.15–1.01)	0.05
Hypertriglyceridemia	1.33 (0.64–2.78)	0.45
Index ALT	1.01 (0.99–1.02)	0.25
Index LDL	0.99 (0.98–0.99)	0.01
Index HDL	0.99 (0.94–1.04)	0.62
NAFLD fibrosis score		
High versus low	1.34 (0.45–3.95)	0.60
Indeterminate versus low	0.63 (0.32–1.24)	0.18
Elevated ALT detected	0.34 (0.18–0.64)	<0.001

OR odds ratio, *CI* confidence interval, *ALT* alanine transaminase, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein

Those without NAFLD were more likely than those with NAFLD to receive appropriate care with regards to statins (67.0 vs. 59.6 %, $p = 0.26$). This difference reached statistical significance when we restricted the comparison to the subgroup of patients with detected NAFLD (67.0 vs. 46.2 %, $p < 0.01$; OR 0.45, 95 % CI 0.25–0.79). On the other hand, we did not find any significant differences in any appropriate statin use between patients with undetected NAFLD (69.1 %) and those without NAFLD (67.0 %, $p = 0.65$).

Discussion

Our data show that, among all patients with NAFLD and an indication for statin use, only 59.6 % ($n = 152$) were treated appropriately. A large proportion of these patients ($n = 79$) were never prescribed statins during the study period; most had no justifiable reason to be without statins. Another subset, however, were patients who were on statins but received a clinically significant cessation or dose reduction in an otherwise indicated treatment ($n = 24$). For all causes of inappropriate statin use, we found that the most important determinant was PCP recognition of underlying abnormal liver enzymes. Based on our implicit review, this often reflected a response by the PCP to attempt correction of elevated liver enzymes by reducing or discontinuing the statin in an otherwise asymptomatic patient.

Among other patient factors, older age and lower index LDL also demonstrated a small but significant association with appropriate statin use. Rather than aiming to treat patients with elevated LDL values, PCPs appeared more likely to be influenced by elevated LFTs in guiding their decision-making regarding statin use. Of note, factors such as the degree of ALT elevation and NAFLD fibrosis score were not found to have any association with appropriate statin use, indicating that recognition rather than severity of NAFLD is the operative factor defining statin care. This is further supported by the higher rate of appropriate statin use found in our non-NAFLD cohort compared to those with detected NAFLD (67.0 vs. 46.2 %, respectively).

Recently the FDA removed the recommendation for periodic evaluation of LFTs in patients on long-term statin therapy [15]. This would suggest that experts are already aware of the risk for suboptimal statin practices incurred by such mild laboratory abnormalities. All studies to date indicate that statins are safe to use in the setting of chronic liver disease including NAFLD [5–7]. Statins have been the subject of clinical trials for the primary treatment of NAFLD [16–18]. A recent trial even concluded that statins lowered portal pressures in patients with cirrhosis and portal hypertension [19].

Given its strong association with the diagnosis of metabolic syndrome, NAFLD and any accompanying transaminase elevations should serve as clinical cues to sway providers toward, and not away from, the use of statins. All of our patients were by definition at a high risk for cardiovascular morbidity and mortality. Our finding—that transaminase elevation recognition was the strongest predictor of inappropriate statin use—affirms expert opinion that routine measurement of LFTs in patients on statins may lead to suboptimal treatment practices in the primary care setting.

Our study is limited by its retrospective nature and inability to quantify any harm incurred from non-adherence to statin use. We did not power our study to measure differences in rates of cardiovascular events or overall mortality. Secondly, most patients did not have imaging or biopsy data to confirm NAFLD status. Nonetheless, in a recent study, our automated selection process demonstrated a 92 % specificity and 81 % positive predictive value for the diagnosis of NAFLD [13]. Primary care practices may vary between different VA and non-VA primary care settings, limiting the generalizability of our results. Finally, we did not have information on waist circumference or fasting blood glucose and instead used BMI and hemoglobin A1c, respectively, as surrogate markers. However, several studies have employed this approach to account for limitations of preexisting clinical data [13, 20].

Notwithstanding these limitations, our data underline the pervasiveness of the longstanding perception regarding the potential hepatotoxicity of statins. Updated practice guidelines recommending continuation of statins through low-grade transaminase elevations may help, but continued efforts at provider education are likely necessary before any improvements at the primary care level can be expected. Our results highlight the need for efforts targeted at enhancing PCP knowledge of existing treatment guidelines regarding statin use in NAFLD.

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Compliance with ethical standards

Conflict of interest None.

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