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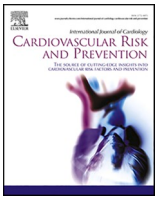

Ethnicity based differences in statin use and hypercholesterolemia control among patients with premature coronary artery disease-results of I-PAD study

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ABSTRACT

Background: Statins use is the most important treatment for high LDL cholesterol in patients with premature coronary artery disease (CAD). Previous reports have shown racial and gender differences in statin use in the general population, but this wasn't studied in premature CAD based on different ethnicities.
Methods and results: Our study includes 1917 men and women with confirmed diagnosis of premature CAD. Logistic regression model was used to evaluate the high LDL cholesterol control in the groups and the OR with 95% confidence interval (CI) was reported as the effect size. After adjustment for confounders, the odds of controlling LDL in women taking Lovastatin, Rosuvastatin, and Simvastatin were 0.27 (0.03, 0.45) lower in comparison with men. Also, in participant who took 3 types of statins, the odds of controlling LDL were significantly different between Lor and Arab compared with Fars ethnicity. After adjustment to all confounders

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(full model), the odds of controlling LDL were lower for Gilak in Lovastatin, Rosuvastatin, and Simvastatin by 0.64 (0.47, 0.75); 0.61 (0.43, 0.73); 0.63 (0.46, 0.74) respectively and higher for Arab in Lovastatin, Rosuvastatin, and Simvastatin by 4.63 (18.28, 0.73); 4.67 (17.47, 0.74); 4.55 (17.03, 0.71) respectively compared to Fars.

Conclusions: Major differences in different gender and ethnicities may have had led to disparities in statin use and LDL control. Awareness of the statins impact on high LDL cholesterol based on different ethnicities can help health decision-makers to close the observed gaps in statin use and control LDL to prevent CAD problems.

1. Introduction

Coronary Artery Disease (CAD) is one of the most common diseases that seriously causes an increase in the mortality rate all around the world [1]. It is also the cause of 33% of deaths in people under 70 years old [2,3]. CAD is a frequently recurrent phenomenon among men and women in Iran similar to some other countries; however, the exposure of young adults to it makes it more alarming [4]. A thorough examination of the causes and the prevention of premature CAD, which occurs in men under the age of 60 and in women under the age of 70, have gained significance due to its impact on individuals and their corresponding community. In addition to the factor of family history, many other risk factors may be involved in the development of this disease, one of which is high cholesterol levels. Epidemiological studies have shown that cholesterol levels, especially Low-Density Lipoproteins (LDL), are strongly associated with CAD [5,6]. Lowering LDL levels can be a great help in reducing the chance of coronary heart disease, and statins are one of the most well-known drugs. Some clinical trial studies have reported the effect of statin on reducing the LDL level depending on ethnicity or race [7,8]. In this regard, the current study attempted to investigate the relationship between statin usage and LDL control in people with premature CAD, considering both sex and ethnicity factors.

2. Materials and methods

The methodology of I-PAD study was previously reported [9] according to which the multicenter control case study included men and women with premature CAD (women $\leq$70 and men $\leq$60 years). The mean age of patients was 53.51 $\pm$ 7.52; out of these, 934 (45.09%) were women. Patients of different ethnicities were recruited from different cardiac catheterization and coronary angiography units in different cities of Iran. All patients who had underwent coronary angiography were included in the case group in case of the obstruction equal to or above 75% in at least a single coronary artery or left main $\geq$50%, while patients with normal coronary arteries were included in the control group.

The entire sample comprised 3033 men and women aged $\leq$60 or $\leq$70 years regardless of their angiography results. The two inclusion criteria for participants included a) those diagnosed with CAD using coronary angiography and b) those taking statin drugs such as Atorvastatin, Lovastatin, Rosuvastatin, and Simvastatin (n = 1917). In this context, two main factors were taken into consideration namely sex (women and men) and ethnic groups (Fars, Kurd, Arab, Lor, and Gilak). The outcome was LDL-C control, defined as LDL-C<100 mg/dl among those taking statins. Statin usage was determined through the patients' self-reports, and the LDL levels were recorded using blood tests presented in two categories of controlled-LDL (<100 mg/dl) and uncontrolled-LDL (>100 mg/dl). Other variables including age, physical activity, smoking, history of underlying diseases, history of heart attack or stroke, family history of heart disease, body mass index (BMI), high-density lipoprotein (HDL), serum total cholesterol (TC), and serum triglyceride (TG) were extracted from the subjects under study to evaluate their effect on the findings.

2.1. Statistical methods

The characteristics of the participants were compared in terms of their sex and ethnicities. While some characteristics were categorical, some others were continuous. Except for age, other quantitative variables were classified and their frequency and percentage were reported. Chi-squared test was employed to determine the frequency distribution of variables between the two groups of sex and ethnicity. In addition, the frequencies of statin use and LDL control were compared between the two groups (sex and ethnicities). Finally, the p-value from Chi-squared test was reported in each table. Logistic regression was also conducted to examine the relationship between the statin use and LDL control in both groups. Moreover, two main logistic regression models were employed: one focusing on sex and the other on ethnicity as the main cases of exposure. All four types of statins were examined as independent variables, and the model was separately repeated for each of them. In all models, the LDL control (<100: controlled and $\geq$100 uncontrolled) was considered a dependent variable among the participants treated with statins. The models were fitted step by step in the form of four adjusted models: Model 1 considered age; Model 2 added smoking and activity; Model 3 added ethnicities, cornice disease, family history of stroke or heart attack, and history of CAD; and Model 4 (full adjusted) incorporated HDL, TC, TG, and BMI. The p-values were reported for all the models. The required analyses were carried out using SPSS.26.

2.2. Result

Tables 1 and 2 present the baseline characteristics for both sex and ethnicity groups composed of 1917 participants. The information on the statin use and LDL control for the sex group is shown in Table 3 and Fig. 1 and for the ethnicity group in Tables 4–7 and Fig. 2. As observed, the mean ages of women and men were 60.83 $\pm$ 7.17 and 54.48 $\pm$ 6.16 years old, respectively (Table 1). The majority of people in this case study were Fars in ethnicity (Persian) including 750 men and 328 women, and the least number of participants belonged to Arabs including 33 men and 36 women (Table 2). The frequency of taking statins was almost the same between men and women in all four statins groups. In both groups, Atorvastatin (27%) and Simvastatin (99%) were the least and the most frequently taken drugs, respectively, and the rates of taking the other two drugs of Rosuvastatin and Lovastatin were 92% and 97%, respectively (Table 1). In the ethnicity group, the highest and lowest frequencies of taking statin were attributed to Simvastatin (above 99%) and Atorvastatin (20–73%), respectively (Table 2). Unlike the same amounts of statins taken by men and women, the proportion of controlled LDL varied. Among the participants who took Lovastatin, Rosuvastatin, and Simvastatin, women had lower controlled LDL levels than men (above 70% vs. below 70%). They only had the same controlled LDL level in the case of Atorvastatin in both groups (Fig. 1). Among different ethnicities, Arab and Gilak patients had the highest and lowest proportions of the controlled LDL in all four types of statins, respectively, compared with Fars participants (Fig. 2).

The results from the fitting models OR (95% CI) in the cases of Lovastatin, Rosuvastatin, and Simvastatin were significantly different between women and men. However, no significant difference was observed in any of the models in the case of Atorvastatin (Table 3). After adjustment for age (Model 1), the odds of controlling LDL in women

Table 1
Baseline characteristics of I-PAD participants with diagnosed premature CAD and taking statins across Sex groups, n = 1917.

		Female	Male	P-value
Age		60.83 ± 7.17	54.48 ± 6.16	<0.001
Ethnicity	Fars	325 (48.7)	744 (59.9)	<0.001
	Tork	43 (6.4)	108 (8.7)	
	Gilak	89 (13.3)	86 (6.9)	
	Kord	93 (13.9)	105 (8.4)	
	Arab	36 (5.4)	33 (2.6)	
	Lor	82 (12.2)	166 (13.3)	
Activity [I]	Yes	471 (70.4)	788 (63.1)	0.001
Smoking	Yes	59 (8.8)	769 (61.6)	<0.001
History of disease [II]	Yes	553 (82.7)	637 (51)	<0.001
History of heart attack and stroke	Yes	18 (2.7)	28 (2.2)	0.974
History of CVD	≤2 year	351 (52.5)	654 (52.4)	
	>2 year	318 (47.5)	594 (47.6)	
Family history of CVD	Yes	327 (48.9)	594 (47.6)	0.592
BMI	<25	136 (20.3)	375 (30.1)	<0.001
	30–25	275 (41.1)	578 (46.3)	
	>30	258 (38.6)	295 (23.6)	
HDL (mg/dl)	≥35	579 (86.5)	909 (72.8)	<0.001
	<35	90 (13.5)	339 (27.2)	
TC (mg/dl)	<240	636 (95.1)	1201 (96.2)	0.202
	≥240	33 (4.9)	47 (3.8)	
TG (mg/dl)	<200	533 (79.7)	1010 (80.9)	0.562
	≥200	136 (20.3)	238 (19.1)	
LDL (mg/dl)	<100	468 (70)	946 (75.8)	0.006
	≥100	201 [30]	302 (24.2)	

[I] : doing any kinds of physical activity such as walking, exercise, etc in free time.
[II] : Blood pressure, Blood lipids, Diabetes. TC: Total serum cholesterol, TG: Serum triglyceride, BMI: Body mass index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, CVD: Cardiovascular disease.

taking Lovastatin, Rosuvastatin, and Simvastatin were 0.24 (0.03, 0.41), 0.25 (0.03, 0.41), and 0.24 (0.03, 0.40) less than that in men. After adjustment for other variables except HDL, TC, TG, and BMI (Model 3), the odds of LDL control in Lovastatin, Rosuvastatin, and Simvastatin were 0.73 (0.55, 0.97), 0.73 (0.55, 0.97), and 0.73 (0.55, 0.96), which remained significantly lower in women than men. However, no significant result was observed for the full model (Model 4).

Followed by adjustment for age in the ethnicity group, the odds of controlling LDL by taking Lovastatin in Gilak, Arab, and Lor were 0.52 (0.66, 0.32), 7.14 (25.2,1.53), and 0.45 (0.02,1.07), respectively (Table 5). As shown in Table 5, the odds of controlling LDL in Gilak patients were less than those in Fars patients. In addition, the same amounts in Arab and Lor patients were higher than those in Fars participants. After adjustment for other factors (full model), compared with Fars patients, the LDL control still exhibited a statistically significant decrease among Gilak 0.36 (0.25, 0.53) and a significant increase among Arab 4.63 (17.28, 0.73) patients. The odds of LDL control for the Lor community were significantly higher than those for Fars in Model 3. However, in the full-adjusted model (Model 4), the obtained result was not significant. As shown in Table 6, consumption of Rosuvastatin was high among all ethnicities (above 90%); yet, the odds of LDL control were higher in Arab 7.25 (1.56 and 25.58) and lower in Gilak 0.49 (0.28, 0.64) than those in Fars (after adjustment for age (Model 1)). Having adjusted all variables (full model), we found that the odds of controlling LDL were lower for Gilak, i.e., 0.61 (0.73, 0.43), and higher for Arab, i.e., 4.67 (17.47, 0.74), than those for Fars. The consumption of Simvastatin among all ethnicities was over 99% and the controlled LDL between ethnicities was significant (Table 7). Upon adjusting the age (model 1), the odds of LDL control for Gilak patients were 0.51 (0.32, 0.65) lower and for Arab were 7.08 (1.51 and 24.99) higher than for Fars. In the full-adjusted model (Model 4), the odds of controlling LDL for Gilak was 0.63 (0.48, 0.74) lower and for Arab was 4.55 (17.03, 0.71) higher than that for Fars. No significant difference was observed in any of the models in the case of Atorvastatin (Table 4).

2.3. Discussion

A number of studies have investigated the interracial differences of lipid-lowering drugs among Asians, Westerns, Caucasian, Hispanic, and Afro-Caribbean or African-American nations [10,11]. However, to the best of the author's knowledge, this is the first study in its kind that has examined the inter-ethnic differences of lipid-lowering drugs in Iran

Table 2
Baseline characteristics of I-PAD participants with diagnosed premature CAD and taking statins across Ethnicity groups, n = 1917.

		Ethnicity						
		lor	Arab	Kord	Gilag	Tork	Fars	P-value
Age		52.34 ± 6.44	51.28 ± 6.89	54.43 ± 6.09	53.24 ± 5.75	51.69 ± 7.40	51.49 ± 7.25	0.006
Sex	Women	82 (33.1)	36 (52.2)	93 (47)	89 (50.9)	43 (28.5)	325 (30.4)	<0.001
	Men	166 (66.9)	33 (47.8)	105 (53)	86 (49.1)	108 (71.5)	744 (69.6)	
Activity [a]	Yes	179 (72.2)	23 (33.3)	168 (84.8)	100 (57.1)	100 (66.2)	684 (64)	<0.001
Smoking	Yes	116 (46.8)	24 (34.8)	74 (37.4)	52 (29.7)	78 (51.7)	478 (44.7)	<0.001
History of disease [b]	Yes	145 (58.5)	48 (69.6)	133 (67.2)	118 (67.4)	94 (62.3)	650 (60.8)	0.143
History of heart attack and stroke	Yes	7 (2.8)	0	5 (2.5)	5 (2.9)	4 (2.6)	25 (2.3)	0.831
History of CVD	≤2 year	145 (58.5)	53 (76.8)	37 (18.7)	161 (92)	98 (64.9)	509 (47.6)	<0.001
	>2 year	103 (41.5)	16 (23.2)	161 (81.3)	14 (8)	53 (35.1)	560 (52.4)	
Family history of CVD	Yes	108 (43.5)	27 (39.1)	111 (56.1)	52 (29.7)	75 (49.7)	545 (51)	<0.001
BMI	<25	73 (29.4)	16 (23.2)	51 (25.8)	59 (33.7)	30 (19.9)	279 (26.1)	0.173
	30–25	108 (43.5)	32 (46.4)	81 (40.9)	76 (43.4)	79 (52.3)	473 (44.2)	
	>30	67 (27)	21 (30.4)	66 (33.3)	40 (22.9)	42 (27.8)	317 (29.7)	
HDL (mg/dl)	≥35	185 (74.6)	68 (98.6)	157 (79.3)	134 (76.6)	107 (70.9)	831 (77.7)	<0.001
	<35	63 (25.4)	1 (1.4)	41 (20.7)	41 (23.4)	44 (29.1)	238 (22.3)	
TC (mg/dl)	<240	241 (97.2)	69 (100)	190 (96)	168 (96)	147 (97.4)	1015 (94.9)	0.178
	≥240	7 (2.8)	0	8 (4)	7 (4)	4 (2.9)	54 (5.1)	
TG (mg/dl)	<200	202 (81.5)	69 (100)	145 (73.2)	129 (73.7)	131 (86.8)	860 (80.4)	<0.001
	≥200	46 (18.5)	0	53 (26.8)	46 (26.3)	20 (13.2)	209 (19.6)	
LDL (mg/dl)	<100	199 (80.2)	66 (95.7)	141 (71.2)	100 (57.1)	107 (70.9)	794 (74.3)	<0.001
	≥100	49 (19.8)	3 (4.3)	57 (28.8)	75 (42.9)	44 (29.1)	275 (25.7)	

[a] : doing any kinds of physical activity such as walking, exercise, etc in free time.
[b] : Blood pressure, Blood lipids, Diabetes. TC: Serum total cholesterol, TG: Serum triglyceride, BMI: Body mass index, LDL: Low-density lipoprotein,HDL: High-density lipoprotein, CVD: Cardiovascular disease.

Table 3
Odds Ratios among those taking statins, LDL control (LDL<100) across Sex groups.

	Atorvastatin (529[a])			Lovastatin (1871[a])			Rosuvastatin (1783[a])			Simvastatin (1914[a])		
	Male	Female		Male	Female		Male	Female		Male	Female	
$N_{LDL\text{-}C\ controlled}$/ n	130/ 185	219/344	P	926/ 1221	453/650	P	871/ 1163	426/620	P	945/ 1246	467/667	P
% LDL-C controlled	63.7%	70.3%	0.126	75.8%	69.7%	0.004	74.9%	68.7%	0.05	75.8%	69.9%	0.005
% Statin use	27.4%	27.5%	0.610	97.4%	96.7%	0.549	92.7%	92.3%	0.147	99.4%	99.4%	0.556
Models		OR (95%CI)	P		OR (95%CI)	P		OR (95%CI)	P		OR (95%CI)	P
1	1 (ref)	1.19 (0.77,1.84)	0.427	1 (ref)	0.76 (0.59,0.97)	0.026	1 (ref)	0.75 (0.59,0.96)	0.024	1 (ref)	0.76 (0.60,0.97)	0.027
2	1 (ref)	1.24 (0.77,2.01)	0.377	1 (ref)	0.72 (0.55,0.96)	0.024	1 (ref)	0.72 (0.54,0.95)	0.021	1 (ref)	0.73 (0.55,0.95)	0.021
3	1 (ref)	1.07 (0.65,1.77)	0.771	1 (ref)	0.73 (0.55,0.97)	0.028	1 (ref)	0.73 (0.55,0.97)	0.029	1 (ref)	0.73 (0.55,0.96)	0.027
4	1 (ref)	1.08 (0.64,1.84)	0.761	1 (ref)	0.82 (0.60,1.11)	0.211	1 (ref)	0.81 (0.60,1.11)	0.192	1 (ref)	0.82 (0.61,1.11)	0.208

1: adjusted by age + sex.
2: model 1+ smoking and activity.
3: model 2 + cornice disease, family history of stroke or heart attack, and history of chronic heart disease (CHD).
4: model 3+ HDL, TC: Serum total cholesterol, TG: Serum triglyceride, and BMI: Body mass index.
[a] : The total patients who have used this type of statin (most of patients have taken more than one type of statin simultaneously).

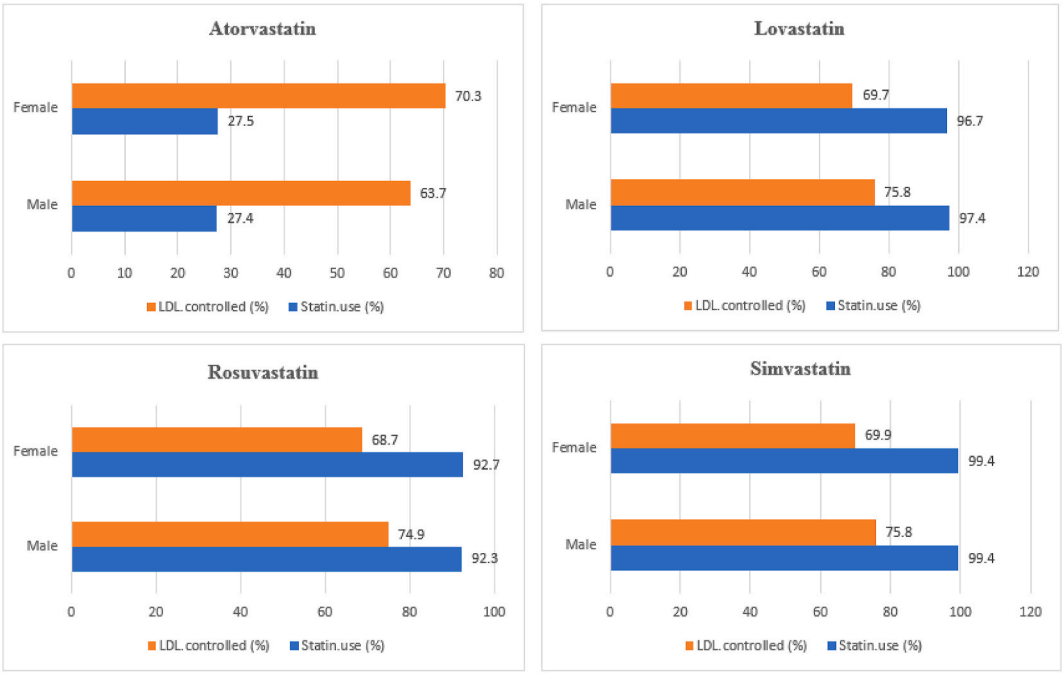

Fig. 1. Percentage of statin consumption and LDL control by Sex.

Table 4
Odds Ratios among those taking **Atorvastatin**, LDL control (LDL<100) across Race groups.

	Fars	Tork	Gilaki	Kord	Arab	Lor	
$N_{LDL\text{-}C\ controlled}$/n	140/235	20/34	19/33	49/81	50/50	69/94	**P-value**
% LDL-C controlled	59.6%	58.8%	57.6%	60.5%	100%	73.4%	<0.001
% Statin use	21.8%	22.5%	18.9%	40.9%	72.5%	37.9%	
Models		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	
1	1 (ref)	0.95 (0.46,1.99)	0.88 (0.42,1.85)	1.02 (0.61,1.72)	0	1.84 (1.09,3.13)	0.300
2	1 (ref)	0.94 (0.45,1.96)	0.88 (0.41,1.86)	1.05 (0.62,1.79)	0	1.89 (1.11,3.23)	0.271
3	1 (ref)	0.89 (0.42,1.88)	0.67 (0.30,1.51)	1.15 (0.67,1.98)	0	1.72 (0.99,2.99)	0.315
4	1 (ref)	0.73 (0.34,1.57)	0.84 (0.36,1.99)	1.13 (0.64,1)	0	1.68 (0.94,3.01)	0.433

1: adjusted by age + sex.
2: model 1+ smoking and activity.
3: model 2 + cornice disease, family history of stroke or heart attack, and history of chronic heart disease (CHD).
4: model 3+ HDL, TC: Serum total cholesterol, TG: Serum triglyceride, and BMI: Body mass index.

Table 5
Odds Ratios among those taking **lovastatin**, LDL control (LDL<100) across Race groups.

	Fars	Tork	Gilaki	Kord	Arab	Lor	P-value
$N_{LDL\text{-}C\ controlled}$/n	778/1049	105/148	97/171	139/195	66/69	187/232	
% LDL-C controlled	74.2%	70.9%	56.7%	71.3%	95.7%	80.6%	<0.001
% Statin use	97.3%	98%	97.7%	98.5%	100%	93.5%	
Models		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	
1	1 (ref)	0.84 (0.57,1.23)	0.48 (0.34,0.68)	0.91 (0.64,1.27)	8.14 (2.53,26.20)	1.45 (1.02,2.07)	<0.001
2	1 (ref)	0.85 (0.58,1.24)	0.47 (0.34,0.67)	0.93 (0.66,1.31)	7.81 (2.42,25.19)	1.48 (1.03,2.10)	<0.001
3	1 (ref)	0.78 (0.54,1.16)	0.41 (0.29,0.59)	1.03 (0.72,1.47)	7.15 (2.21,23.11)	1.44 (1,2.06)	<0.001
4	1 (ref)	0.64 (0.43,0.97)	0.36 (0.25,0.53)	1.01 (0.69,1.48)	5.63 (1.73,18.28)	1.28 (0.88,1.87)	<0.001

1: adjusted by age + sex.
2: model 1+ smoking and activity.
3: model 2 + cornice disease, family history of stroke or heart attack, and history of chronic heart disease (CHD).
4: model 3+ HDL, TC: Serum total cholesterol, TG: Serum triglyceride, and BMI: Body mass index.

Table 6
Odds Ratios among those taking **Rosuvastatin**, LDL control (LDL<100) across Race groups.

	Fars	Tork	Gilaki	Kord	Arab	Lor	P-value
$N_{LDL\text{-}C\ controlled}$/n	742/1009	102/146	98/171	106/156	64/67	180/229	
% LDL-C controlled	73.5%	69.9%	57.3%	67.9%	95.5%	78.6%	<0.001
% Statin use	93.6%	96.7%	97.7%	78.8%	97.1%	92.3%	
Models		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	
1	1 (ref)	0.83 (0.56,1.21)	0.51 (0.36,0.72)	0.80 (0.55,1.16)	8.25 (2.56,26.58)	1.33 (0.94,1.88)	<0.001
2	1 (ref)	0.83 (0.57,1.22)	0.50 (0.36,0.70)	0.82 (0.57,1.19)	7.82 (2.42,25.25)	1.35 (0.96,1.92)	<0.001
3	1 (ref)	0.77 (0.52,1.14)	0.44 (0.31,0.63)	0.90 (0.61,1.31)	7.26 (2.24,23.51)	1.34 (0.94,1.90)	<0.001
4	1 (ref)	0.63 (0.42,0.95)	0.39 (0.27,0.57)	0.81 (0.57,1.29)	5.67 (1.74,18.47)	1.20 (0.83,1.75)	<0.001

1: adjusted by age + sex.
2: model 1+ smoking and activity.
3: model 2 + cornice disease, family history of stroke or heart attack, and history of chronic heart disease (CHD).
4: model 3+ HDL, TC: Serum total cholesterol, TG: Serum triglyceride, and BMI: Body mass index.

Table 7
Odds Ratios among those taking **Simvastatin**, LDL control (LDL<100) across Race groups.

	Fars	Tork	Gilaki	Kord	Arab	Lor	P-value
$N_{LDL\text{-}C\ controlled}$/n	794/1068	107/151	100/175	141/198	66/69	197/246	
% LDL-C controlled	74.3%	70.9%	57.1%	71.2%	95.7%	80.1%	<0.001
% Statin use	99.1%	100%	100%	100%	100%	99.2%	
Models		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	
1	1 (ref)	0.83 (0.57,1.22)	0.49 (0.35,0.68)	0.89 (0.64,1.25)	8.08 (2.51,25.99)	1.40 (0.99,1.97)	<0.001
2	1 (ref)	0.84 (0.58,1.23)	0.48 (0.34,0.67)	0.92 (0.65,1.29)	7.72 (2.40,24.91)	1.42 (1,1.99)	<0.001
3	1 (ref)	0.87 (0.53,1.15)	0.41 (0.29,0.59)	1.01 (0.71,1.43)	7.12 (2.20,23.04)	1.38 (0.98,1.95)	<0.001
4	1 (ref)	0.64 (0.43,0.95)	0.37 (0.26,0.54)	0.99 (0.68,1.44)	5.55 (1.71,18.03)	1.25 (0.87,1.81)	<0.001

1: adjusted by age + sex.
2: model 1+ smoking and activity.
3: model 2 + cornice disease, family history of stroke or heart attack, and history of chronic heart disease (CHD).
4: model 3+ HDL, TC: Serum total cholesterol, TG: Serum triglyceride, and BMI: Body mass index.

among six main ethnic groups in Iran called Fars, Kord, Lor, Tork, Gilak, and Arab. The results of the analysis in the case of Lovastatin considering ethnicity were significant for Gilak, Arab, and Lor. To be specific, Gilaki patients experienced the lower chance of controlling LDL than Fars; however, Arab and Lor patients seemed to have higher chance of control than Fars. In the cases of Rosuvastatin and Simvastatin, only the results obtained from Gilak and Arab participants were significant and the chance of controlling LDL in the Gilak and Arab patients was lower and higher than that in Fars patients, respectively. No significant difference was observed among different ethnicities in the case of Atorvastatin. The results of the present study revealed that females had lower odds of controlling LDL-C than males in the cases of Lovastatin, Rosuvastatin, and Simvastatin groups; however, no significant difference was observed regarding Atorvastatin.

Statins (coenzyme 3-hydroxy-3-methylglutaryl HMG-CoA reductase inhibitors) were first discovered and used in clinical practice in the 1960s [12,13]. From that time on, statins have been extensively utilized as the most effective hypolipidemic medicines accessible to doctors that help them lower cardiovascular risks and prevent disease/disability worsening in patients with secondary prevention (CVD) [14]. In response to statins, there is a wide range of inter-racial or inter-individual variances given that according to the reports, Asians and Westerners react differently to statins. With the exception of pita vastatin, variations of statins response between Asians and Westerners were observed for all statins in Ref. [15]. For instance, while the maximum Atorvastatin dose in clinical practice in Japan is 40 mg per day, it is 80 mg per day in the US. Another study demonstrated that a lower dose of statins in the Japanese people would allow for a relative reduction in the risk of contracting CVDs similar to the case of a higher dose of statins among Western people [15–17]. The detailed processes underlying the disparities in statins response between Asians and Westerners are still unknown. Several studies have found that hereditary factors might be linked to differences in how people react to statins and statins-related adverse effects, thus explaining the racial disparities between Asians and Westerners as well. Lee et al. stated that in comparison to white patients living in the same milieu, Chinese, Asian-Indian, and

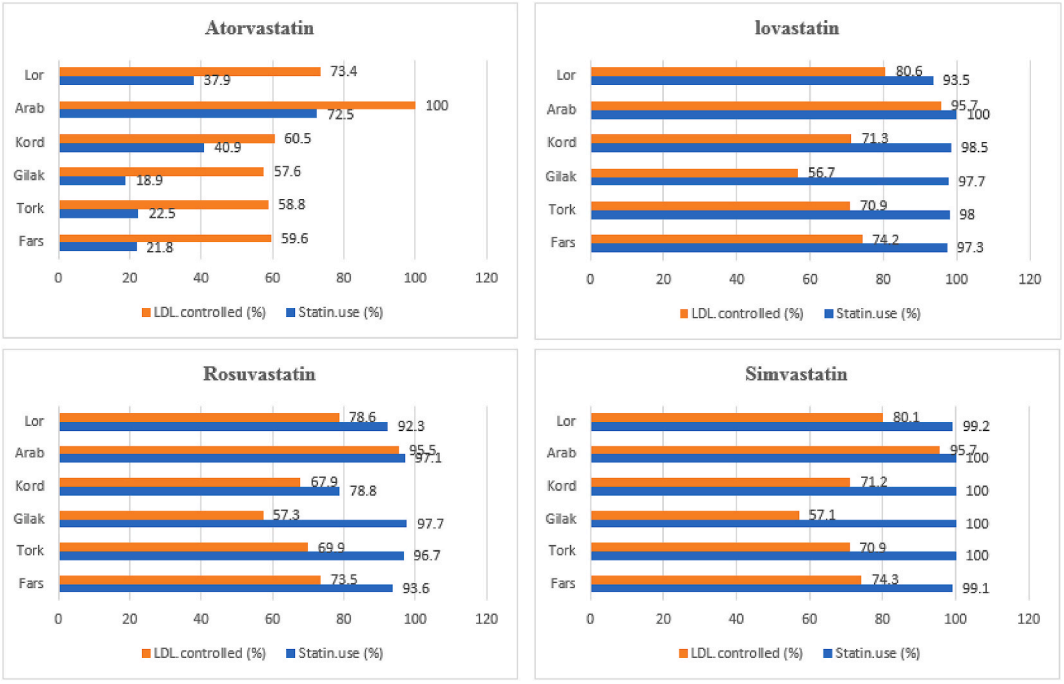

Fig. 2. Percentage of statin consumption and LDL control by Ethnicity.

Malay patients had considerably greater plasma exposure to Rosuvastatin and its metabolites [18]. In general, Asians had double Rosuvastatin plasma exposure levels compared to Caucasians [19]. A study in Turkey revealed that the percentages of patients reaching the target LDL-C level after statin therapy were 21.8%, 21.7%, 8.6%, 17.9%, and 0.8% compared to those using Atorvastatin, Rosuvastatin, Simvastatin, pravastatin, and fluvastatin, respectively [20]. A study in the case of Iranian population found that with overlapping uncertainty intervals, preference for using statins was quite similar in both rural and urban areas. In addition, healthcare practitioners and the general public [21] shared the same preferences.

A genome-wide investigation of patients taking Simvastatin discovered a link between Single-Nucleotide Polymorphisms (SNPs) in the SLCO1B1 gene and their adverse effects on Chromosome 12 and statin-induced muscle. SLCO1B1 gene expressed an organic anion transporting polypeptide 1B1 (OATP1B1) found on the basolateral membrane of hepatocytes which facilitated hepatic uptake of medications like statins. Two SNPs (388 A > G, 521 T > G) and four haplotypes (SLCO1B1*1a, SLCO1B1*1 b, SLOCO1B1*5, and SLCO1B1*15) were found in the SLCO1B1 gene. The wild types including SLCO1B1*1a and SLCO1B1*1 b have one SNP (388 A > G) while SLCO1B1*5 has the other SNP; and SLCO1B1*15 has both SNPs. People with SLCO1B1*1 b had more transport activities on hepatic cells than those with SLCO1B1*5. Transport activity was dramatically reduced in patients with SLCO1B1*15. The frequency of these four key haplotypes varied depending on their race, indicating why there are racial differences in statins response among different ethnicities in Iran. In this respect, more extensive molecular research in this area clarifies whether or not there is a difference among various races in Iran in terms of this gene and its polymorphism [22–24].

Our findings revealed that in the Lovastatin, Rosuvastatin, and Simvastatin groups, females had a lower chance of managing LDL-C than men; however, there was no significant difference in the Atorvastatin group. According to different animal investigations, the metabolism rate for Simvastatin was shown to be significantly higher in males than that in females [25–27]. As a result, there is a possibility that statins have a larger clinical effect in men. On the contrary, some researchers have found that statins taken by women, compared to by men, would result in a significant reduction in both LDL-C and TC [28,29]. Vree et al. stated that the hydrolysis of Lovastatin was greater than that of Simvastatin. Despite subject-dependent hydrolysis of Lovastatin/Simvastatin to the active metabolite, males are subject to hydrolysis more than females according to this study. Due to steric hindrance, the additional methyl group in Simvastatin caused lower hydrolysis [28]. Given that cytochrome P450 system enzymes are required for the clearance of lipid-soluble statins, another possibility of the difference in the statin effect could be sex-dependent drug clearance (CYP) [30,31]. In other words, the CYP expression was changed in the case of sex factor [32]. This, in turn, could result in differences in the clearance rates, bioavailability, and therapeutic effects received with the same dose of the medicine between men and women. According to the findings, females would experience more serious side effects of statins [33,34]. The reason that no difference between ethnicity and gender was observed for Atorvastatin compared to other statins is probably because a fixed dose of statins can create different concentrations in different races and this is due to differences in genes and as a result of drug metabolism, excretion and absorption. Also, polymorphism gene can affect the effect of statins and express their effects differently [35,36].

Our study has limitations that require consideration. First, the small sample size in the Arab ethnicity which may affect the results. Therefore, a study with a larger sample size is needed in this ethnic group. Second, all the patients were using more than one type of statin at the same time and thus, it was not possible to investigate the effect of each of the statins separately. So, it seems that it is necessary to be conducted a study to investigate the effect of each type of statin on LDL control based on gender and ethnicity. Finally, due to the fact that all the patient's information was recorded through a questionnaire, we had a lot of missing data about the dosage of statin and the duration of the usage, so we could not use this information in the analysis.

2.3.1. Conclusion

There are a variety of inter-racial and sex-dependent variables in response to different categories of statin therapy except for Atorvastatin. Females had lower chance of LDL-C management by statins than males regarding the Lovastatin, Rosuvastatin, and Simvastatin groups, except for Atorvastatin. In the case of Lovastatin, the Gilak ethnicity had the

highest chance of controlling LDL-C than others. In the case of Rosuvastatin and Simvastatin, Arab ethnicity had the highest chance of controlling LDL-C than others.

Credit author statement

Raheleh Karimi: Creation of models and data analysis, Software, Writing – original draft, Ehsan Zarepur: Helped to design and administer the questionnaire and improve the manuscript Alireza Khosravi: Helped to design and administer the questionnaire and improve the manuscript Noushin Mohammadifard: Investigation and Validation Fereidoon Nouhi: Investigation and Validation Hasan Alikhasi: Investigation and Validation Shima Nasirian: Contributed to design the study Masoumeh Sadeghi: Contributed to design the study Hamidreza Roohafza: Contributed to design the study Seyed Ali Moezi Bady: Contributed to design the study Parisa janjani: Investigation Kamal Solati: Investigation Masoud Lotfizadeh; Investigation Samad Ghaffari: Data Curation Elmira Javanmardi: Data Curation Mahboobeh Gholipour: Writing - Review & Editing Mostafa dehghani: Writing - Review & Editing Mostafa Cheraghi: Writing - Review & Editing Ahmadreza Assareh: Writing - Review & Editing and Visualization Habib Haybar: Writing - Review & Editing and Visualization Seyedeh Mahdieh Namayandeh: Visualization Reza madadi: Writing - Review & Editing and Visualization Javad Kojuri: Visualization Marjan Mansourian: Supervised all phases of study, design, data analysis and manuscript development. Nizal Sarrafzadegan: Conducted the study, data collecting and designing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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