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Original Article

Statin therapy/lipid lowering therapy among Indian adults with first acute coronary event: The dyslipidemia Residual and Mixed Abnormalities IN spite of Statin therapy (REMAINS) study

Salgaonkar V. Jaywant [a,*], *A.K. Singh* [b], *Mundkur S. Prabhu* [c], *R. Ranjan* [d]

[a] *Associate Director, Medical Affairs, MSD, India*
[b] *Senior Specialist, MSD, India*
[c] *Ex-Senior Specialist, MSD, India*
[d] *Associate Manager, Medical Affairs, MSD, India*

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ABSTRACT

Objective: The primary objective was to evaluate the effect of statin therapy/lipid lowering therapy (LLT) on lipid profile, in adults presenting with first acute coronary event.

Methods and material: A multicentre, observational, prospective cohort study of lipid profiles pre- and post-statin therapy/LLT, among adult patients with confirmed diagnosis of first acute coronary event. The primary outcome measures were low-density lipoprotein cholesterol (LDL-C) in mg/dl, high-density lipoprotein cholesterol (HDL-C) in mg/dl and triglycerides (TG) in mg/dl at baseline and end of study (EOS, 12 weeks [mean: 13.5 weeks]).

Results: Totally 474 patients completed the study. Number of patients with any LDL-C abnormality (LDL-C [all; LDL was abnormal, either alone or along with other lipid parameter(s)]) decreased from 118 (24.9%) to 27 (5.7%), and for LDL-C (only; only the LDL was abnormal), from 46 (9.7%) to 13 (2.7%), both from baseline to EOS. Of 118 patients with high LDL-C (all) at baseline, 91 (77.1%) had reduction in LDL-C to <100 mg/dl, of which 54 (45.8%) had LDL-C <70 mg/dl at EOS. The patients with LDL-C fraction abnormalities decreased, while HDL-C abnormalities increased at EOS from baseline. No major difference was observed at baseline and EOS in levels of TG (all [TG was abnormal, either alone or along with other lipid parameter(s)]) and TG (only [only the TG was abnormal]). Six (1.3%) had seven serious adverse events.

Conclusions: Though statin therapy is effective in lowering LDL-C, there still remains residual dyslipidemia, which probably should be tackled with therapeutic and non-therapeutic options.

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* *Corresponding author.*
E-mail address: viraj.salgaonkar@merck.com (S.V. Jaywant).

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1. Introduction

Several large trials have demonstrated the efficacy of statins in the primary prevention of cardiovascular events, including first acute major coronary event in adults with average triglycerides (TG) and low-density lipoprotein-cholesterol (LDL-C) and below average high-density lipoprotein-cholesterol (HDL-C) levels.[1–4] Further, trials on statin therapy such as Scandinavian Simvastatin Survival Study (4S)[5] and Cholesterol and Recurrent Events Trial (CARE)[6] also established their role in reducing coronary events such as stroke risk, fatal coronary artery disease (CAD) and nonfatal myocardial infarction (MI). For secondary prevention of acute coronary events, high levels of LDL-C, carotid artery remodeling, morbid obesity and low levels of HDL-C are important prognostic indicators to evaluate the efficacy of aggressive lipid therapy strategies.[7]

The prevalence of dyslipidemia is increased in diabetic patients, which contributes to the higher incidence of cardiovascular diseases (CVDs), resulting in higher morbidity and mortality.[8] The American Diabetes Association recommends the use of statins by diabetic patients with overt CVD and by patients without CVD who are older than 40 years of age and have one or more CVD risk factors, regardless of baseline lipid levels.[9]

At present, statins are the gold-standard treatment options for lowering LDL-C. Additionally statins are also known for their ability to reduce the risk of cardiovascular events and their excellent safety profile.[10–12] Besides LDL-C, other lipid parameters, such as high TG[13,14] and low HDL-C levels[15,16] also play a role in the causation and progression of coronary heart disease (CHD).

One of the Cholesterol Treatment Trialists' Collaboration (CCT) meta-analyses states that statin therapy can safely reduce the 5-year incidence of major coronary events, coronary revascularization, and stroke by about one fifth per mmol/L reduction in LDL cholesterol, largely irrespective of the initial lipid profile or other presenting characteristics.[17]

Management of lipid parameters beyond LDL-C may require additional therapeutic or non-therapeutic options to statin therapy, to likely benefit the patients with residual risks.[18,19] In clinical practice, there is scarce information about the extent to which CHD patients on lipid therapy achieve control of HDL-C, LDL-C, and TG. Further, there is paucity of data regarding occurrence of cardiovascular events among patients with mixed dyslipidemia (at least 2 lipid abnormalities) compared to patients with LDL-C abnormalities alone. There is also a lack of understanding in the use of comprehensive lipid management therapies to target dyslipidemia beyond LDL-C as a secondary prevention measure subsequent to a CHD event.

In India, there is a wide gap in translation of evidence to practice. Though there is evidence[20] to suggest that in patients with diabetes, low HDL-C levels are stronger predictor of mortality from CHD than LDL-C, further quantification of protocol based treatment regimen as well as residual abnormality and risk has never been studied.

The primary objective of our observational study was to evaluate the effect of statin therapy/LLT on lipid profile, in Indian adults presenting with first acute coronary event. The prevalence of mixed dyslipidemia, the need to address low HDL-C and/or high TG in addition to, or in the absence of high LDL-C post statin therapy/LLT, and the various risk subgroups (including individuals with prevalent diabetes mellitus) were also assessed.

2. Materials and methods

2.1. Study design

We conducted a multicenter, observational, prospective cohort study in 19 tertiary care centers of India in patients with first acute coronary event. The study was planned for 12 weeks from the onset of first acute coronary event. However, all patients who were on statin therapy/LLT (as per the discretion of their respective investigators) for an average of 13.5 weeks were analyzed in this study. This was taken as the end of study (EOS) period.

2.2. Setting

The study was initiated on 23rd April 2010 and was completed at all the centers by 15th December 2012. The patients were enrolled at the time of their first acute coronary event presentation (Index Date), information about demographics; current medical treatment, family history and acute coronary event were collected by interviewing the patients. Physical examination was conducted of all the patients prior to discharge. At baseline and EOS visits, investigations and lipid assessments were performed. The study flow chart is presented in Fig. 1. The required study data was collected and entered into a case record form (CRF). The final protocol and informed consent form (ICF) were reviewed and approved by the Institutional Ethics Committees/Institutional Review Boards, at each trial sites, participating in the study. Prior to initiation of the study, a written informed consent was obtained from the patients, who participated in this study. Each participating tertiary care center with dedicated cardiac/coronary care facility was responsible for recording and maintaining the data in source documents in compliance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) – Good Clinical Practice (GCP) and institutional requirements for the protection of confidentiality of patients.

2.3. Study population

Men and women aged ≥35 years with a confirmed diagnosis of first acute coronary event (STEMI [ST elevation myocardial infarction]/NSTEMI [non-ST elevation myocardial infarction]/unstable angina) were included in the study. Other inclusion criteria were: access to medical records covering the entire study period, potential to collect (8 h) fasting blood sample within 24 h of onset for symptoms; considered for initiation/maintenance/modification of statin therapy before discharge from hospital; availability of core data set and willing to comply with the study requirements. Patients who were already participating in a clinical trial or any other type of

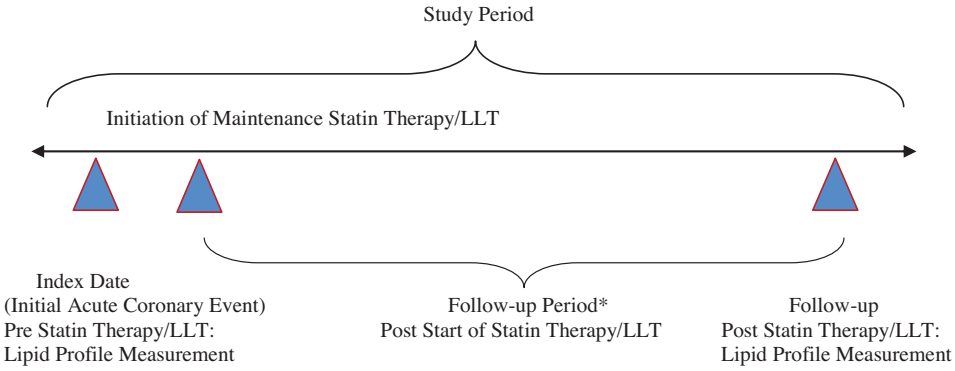

Fig. 1 – Study flow chart. *12 weeks [Mean (SD) of 13.5 (1.8) weeks].

clinical study which involved therapeutic intervention or otherwise failed to consent to interview; patients with known inherited disorder of lipoprotein metabolism; and with history of hypothyroidism, nephrotic syndrome, chronic alcoholism, or Cushing's syndrome were excluded. Patients were discontinued from the study if they experienced any major cardiovascular event (fatal, non-fatal) during the follow-up period e.g. MI, stroke, angina, transient ischemic attacks or acute worsening of congestive heart failure or if they withdrew informed consent.

2.4. *Treatment*

There was no protocol specified treatment or intervention that was given to the patient, however as per the eligibility, the trial patients were considered for initiation/maintenance/modification of statin therapy before discharge from hospital. Statin therapies prescribed in all the trial sites as per the institutional regimen included atorvastatin (10, 20, 40, 80 mg), rosuvastatin (10, 20 and 40 mg), simvastatin (40 mg) and other LLT, such as fenofibric acid/fenofibrate (145 and 160 mg).

2.5. *End-points*

The primary end-points described the lipid profile and quantified the inadequacy/under treatment with statins among all patients and various risk subgroups (including individuals with prevalent diabetes mellitus) experiencing their first acute coronary event. The secondary end-points were the prevalence of mixed dyslipidemia and the need to address low HDL-C and/or high TG in addition to, or in the absence of high LDL-C, at EOS, post statin therapy/LLT subsequent to the first acute coronary event among all patients, as well as to assess the risk subgroups (including individuals with prevalent diabetes mellitus).

2.6. *Statistical methods*

The study was not based on a hypothesized effect size; hence, a formal estimation of statistical power was not applicable. All statistical analyses were performed using SAS® for Windows Version 9.2. The $p \leq 0.05$ was considered as statistically significant. The full analysis set (FAS) included all those patients treated with statin therapy/LLT and who completed the study as per protocol. The primary and secondary efficacy analyses were performed on patients in FAS population. The safety population (SAF) included all enrolled patients who satisfied all inclusion and exclusion criteria. The analysis of all safety end-points was based on SAF. Safety analysis included the analysis of vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP], pulse rate [beats/min] and respiratory rate [breaths/min]), and laboratory variables (LDL-C, HDL-C, TG, lipoprotein [a], apoprotein A1, apoprotein B, hs-CRP and random blood glucose [all in mg/dl] and HbA1c [%]). Blood pressure was measured minimum of 2 times and an average of SBP and DBP was used; if measured more than twice. Multiple logistic analyses were used to obtain association between risk factors and for sub-group analysis in diabetic and non-diabetic patients. Descriptive statistics of observed values and changes from baseline were provided for all above vital signs and laboratory parameters. No formal inferential statistical analysis was performed for these parameters.

3. Results

A total of 635 patients were enrolled in the study, of which 514 (80.9%) had completed data. Of these 514 patients with completed data, 40 (6.3%) patients discontinued from the study. Four hundred and seventy four (74.6%) patients completed the study and were included in the FAS dataset. All the 635 enrolled patients were included in the SAF dataset. A summary of patient's demographic characteristics is as shown in Table 1. The mean (SD) age of the patients was 54.2 (10.60) years and the mean (SD) BMI (kg/m^2) was 25.56 (3.649). Of 474 patients who completed the study, 80.2% were male patients ($n = 380$) whereas female patients comprising only 19.8% ($n = 94$), with majority of female patients being in post-menopausal phase (83/94 [88.3%]). Among the completers, 195 (41.1%) patients had history of hypertension and 137 (28.9%) patients had history of diabetes mellitus. At baseline, 453 (95.6%) patients were not on statin therapy and only 21 (4.4%) patients were taking statins, for a median duration of one week, at the time of enrolment (there was an outlier, one subject who was on statin therapy since 381 weeks). All the patients at baseline ($n = 635$) as well as at EOS ($n = 474$)

Table 1 – Summary of patient demographic characteristics.

Variable	Statistics	Total
Number of patients enrolled	*n*	635
Number of patients who completed the study	*n* (%)	474 (74.6)[a]
Number of patients who discontinued from the study	*n* (%)	161 (25.4)[a]
Primary reason for discontinuation:		
Patient not fulfilling selection criteria	*n* (%)	1 (0.2)[a]
Clinical trial was terminated at this site	*n* (%)	0 (0.0)[a]
Clinical trial was terminated by Sponsor	*n* (%)	0 (0.0)[a]
Other reasons	*n* (%)	160 (25.2)[a]
Number of patients in safety population (SAF)	*n* (%)	635 (100.0)[a]
Number of patients in full analysis set (FAS)	*n* (%)	474 (74.6)[a]
Data of patients who completed the study (*n* = 474)		
Age (in years)	Mean (SD)	54.2 (10.60)[b]
Gender: Female	*n* (%)	94 (19.8)[b]
Gender: Male	*n* (%)	380 (80.2)[b]
If female, menopausal[c]		
Yes	*n* (%)	83 (88.3)[b]
No	*n* (%)	11 (11.7)[b]
Patients with hypertension	*n* (%)	195 (41.1)[b]
Patients with diabetes mellitus	*n* (%)	137 (28.9)[b]
Patients on statin therapy at baseline	*n* (%)	21 (4.4)[b]
Duration on statin therapy (weeks)[d]	Mean (SD)	21.5 (83.11)[b]
Patients not on statin therapy at baseline	*n* (%)	453 (95.6)[b]
BMI (kg/m^2) at baseline (*n* = 473)	Mean (SD)	25.56 (3.649)

[a] Percentages were based on number of patients enrolled.
[b] Percentages were based on number of patients in full analysis set (FAS).
[c] Percentages were based on total number of female patients in FAS.
[d] Duration on statin therapy (weeks) = Date of first dose of statin therapy – Date of baseline visit.

belonged to the National Cholesterol Education Program – Adult Treatment Panel III (NCEP ATP III) high risk group.

The details of prevalence of dyslipidemia at baseline and at EOS are presented in Table 2. The number of patients with LDL-C (all) abnormality decreased from 24.9% (*n* = 118) at visit 1 to 5.7% (*n* = 27) at EOS. Similar trend was also seen in patients with LDL-C (only) abnormality wherein the values decreased from 9.7% (*n* = 46) at baseline to 2.7% (*n* = 13) at EOS. However, an inverse trend was observed in the number of patients with HDL fraction abnormality, namely HDL-C (all), HDL-C (only),

Table 2 – Prevalence of dyslipidemia (FAS population).

Lipid abnormality	Total (*n* = 474)			
	At baseline, *n* (%)	At EOS, *n* (%)	At EOS LDL < 70, *n* (%)	At EOS LDL < 100, *n* (%)
LDL-C (all)	118 (24.9)	27 (5.7)	54 (45.8)[a]	91 (77.1)[a]
HDL-C	234 (49.4)	258 (54.4)		
TG	83 (17.5)	81 (17.1)		
LDL-C (only)	46 (9.7)	13 (2.7)		
HDL-C only	133 (28.1)	192 (40.5)		
TG only	19 (4.0)	18 (3.8)		
LDL-C (all) + HDL-C but not TG	44 (9.3)	6 (1.3)		
LDL-C (all) + TG but not HDL-C	7 (1.5)	3 (0.6)		
HDL-C + TG but not LDL-C (all)	36 (7.6)	55 (11.6)		
HDL-C + TG + LDL-C (all)	21 (4.4)	5 (1.1)		
Number (%) of patients with mixed dyslipidemia	108 (22.8)	69 (14.6)		

Percentages were based on number of patients in full analysis set (FAS).
[a] Indicates percentages were based on number of LDL-C (all) patients at baseline.
Mixed dyslipidemia was defined as the presence of at least 2 abnormal lipid values.
(all): LDL/TG was abnormal, either alone or along with other lipid parameter(s).
(only): only the LDL/TG was abnormal.
Elevated LDL-C: ≥RF (risk factors) or CVD or DM: LDL ≥ 100 mg/dl (i.e. 2.6 mmol/L).
≥2RF: LDLv130 mg/dl (i.e. 3.3 mmol/L).
<2RF: LDL ≥ 160 mg/dl (i.e. 4.1 mmol/L).
Low HDL-C: HDL < 40 mg/dl (1.0 mmol/L) for men and HDL-C < 50 mg/dl (1.3 mmol/L) for women.
Elevated TG: TG ≥ 200 mg/dl (i.e. 2.3 mmol/L); however normal TG is <150 mg/dl (i.e. 1.7 mmol/L).

Table 3 – Summary of lipid lowering agents by dose (FAS population).

Lipid lowering agent	During hospitalization *n* (%)[a]	Total (*n* = 474)	At EOS *n* (%)[a]
Statin			
Atorvastatin 10 mg	15 (3.2)		16 (3.4)
Atorvastatin 20 mg	49 (10.3)		73 (15.4)
Atorvastatin 40 mg	235 (49.6)		242 (51.1)
Atorvastatin 80 mg	157 (33.1)		146 (30.8)
Rosuvastatin 10 mg	8 (1.7)		21 (4.4)
Rosuvastatin 20 mg	6 (1.3)		12 (2.5)
Rosuvastatin 40 mg	9 (1.9)		9 (1.9)
Simvastatin 40 mg	1 (0.2)		0
Other			
Fenofibrate 160 mg	2 (0.4)		2 (0.4)
Fenofibric acid 145 mg	1 (0.2)		1 (0.2)

Percentages are based on number of patients in full analysis set (FAS).
[a] One patient has been counted at more than one instance in statin or other.

and HDL-C + TG but not LDL-C (all), wherein the number of patients increased at EOS as compared with baseline (234 [49.4%] to 258 [54.4%], 133 [28.1%] to 192 [40.5%] and 36 [7.6%] to 55 [11.6%], respectively). No major difference was observed between baseline and EOS in number of patients with abnormal TG fraction, namely TG (all) and TG (only) abnormality. The total number of patients with mixed dyslipidemia decreased at EOS as compared with baseline (108 [22.8%] to 69 [14.6%]).

At baseline, a majority of patients (330 [69.6%]) were non-smokers, however, they increased in number at EOS (354 [74.7%]). The median of average number of packs smoked per day by the smokers (current and former) at baseline and EOS was one, for a median duration of 15 years. At baseline, a majority of patients (390 [82.3%]) did not consume alcohol, and they increased in number at EOS (416 [87.8%]). Hence, majority of the patients were non-smokers and did not consume alcohol. A total of 273 (57.6%) patients had at least one medical history at baseline.

There were a total of 45 (9.5%) patients with at least one family history, of which 28 (5.9%) had family history of diabetes and 22 (4.6%) had family history of MI or sudden death either before the age of 55 years for males, or 65 years for females. A summary of lipid lowering agents by dose is provided in Table 3. Atorvastatin 40 mg had been prescribed to a majority of patients during hospitalization ($n = 235$). The same trend was also seen at EOS i.e. at week 12 ($n = 242$), followed by Atorvastatin 80 mg which was prescribed to 157 patients at visit 1 and 146 patients at EOS, and Atorvastatin 20 mg had been prescribed to 49 patients at visit 1 and 73 patients at EOS. Rosuvastatin (10 mg, 20 mg and 40 mg), simvastatin 40 mg and fenofibric acid (145 and 160 mg) was prescribed to a very small number of patients.

A table of multivariate analysis presenting association between dyslipidemia, statin therapy/LLT and patient characteristics is provided in Table 4. Elevated LDL-C and TG, and low HDL-C had statistically significant associations ($p < 0.05$) with patient characteristics such as age, diabetes, cigarette smoking, BMI, gender, and hypertension at baseline, and with hypertension and age at EOS. The subgroup analysis of 137 diabetic patients and 336 non-diabetic patients presenting association between dyslipidemia, statin therapy/LLT and patient characteristics are as shown in Table 5. In diabetic patients, low HDL-C and elevated TG had statistically significant associations ($p < 0.05$) with cigarette smoking, BMI, gender at baseline, and with cigarette smoking and hypertension at EOS, for elevated TG. In non-diabetic patients, elevated LDL-C, low HDL-C and elevated TG had statistically significant associations ($p \leq 0.05$) with age, cigarette smoking, BMI, gender, and hypertension at baseline, and with age at EOS, for low LDL-C and elevated TG. The median change from baseline to visit 2 (EOS) was −35 in TC (mg/dl), −33 in measured LDL-C (mg/dl), −1 in HDL-C (mg/dl), 3 in TG (mg/dl), 4 in lipoprotein (a) (NMOL/L), 7 in apoprotein A1 (mg/dl), −7.55 in hs-CRP (mg/L), and no change in HbA1c (%). The median change from baseline to visit 2 values suggests improvement in the laboratory values of TC, LDL-C and hs-CRP. However, there was marginal to no change or deterioration observed at EOS in the values of HDL-C, TG, lipoprotein (a), apoprotein A1 and HbA1c. Serious adverse events (SAEs) by system organ class (SOC) and preferred term (PT) are presented in Table 6. Of 474 patients, 6 (1.3%) patients had a total of seven SAEs. Of the seven SAEs by SOC, 5 (1.1%) belonged to cardiac disorders, 1 (0.2%) to infections and infestations, and 1 (0.2%) to nervous system disorder. No major change from baseline to EOS was observed in any of the median values of the vital signs. The physical examination findings were similar for all the parameters for both baseline and EOS visits. All the patients in SAF had at least one clinical information data, however, none had occurrence of any major event during the follow-up period. All the patients (474) had taken statin therapy/LLT during the follow-up and had taken other concomitant medication at discharge.

4. Discussion

In the current observational study, statin therapy/LLT was found to be effective in reducing the number of patients with primarily abnormal LDL-C fraction and mixed dyslipidemia. Our findings are consistent with the Prospective Cardiovascular Münster (PROCAM, 2010) study, which showed that many MI survivors had high TG and/or low HDL-C versus matched controls, and CV risk associated with the dyslipidemic profile was higher despite low LDL-C levels.[21] High LDL-C had statistically significant association with age ($p = 0.0078$),

Table 4 – Multivariate analysis to obtain association between dyslipidemia, statin therapy/LLT and patient characteristics (FAS population).

Dependent variable	Variable	Total (n = 474)					
		At baseline			At EOS		
		Adjusted OR[a]	95% CI[a]	p-Value[a]	Adjusted OR[a]	95% CI[a]	p-Value[a]
Elevated LDL-C	Age (years)	2.1670	1.1955–3.9279	0.0078	2.8770	0.8163–10.1401	0.1205
	BMI (kg/m^2)				0.9200	0.8166–1.0365	0.1693
	Prior cerebro-vascular disease	4.0801	0.3522–47.2679	0.2269			
	Diabetes	2.1939	1.3674–3.5198	0.0002	1.9057	0.8184–4.4376	0.1433
	Gender	0.5616	0.2908–1.0847	0.1225	2.3737	0.8648–6.5152	0.0771
	Hypertension	1.3681	0.8663–2.1605	0.1735	2.6593	1.1068–6.3898	0.0059
	Cigarette smoking status	1.7581	1.0778–2.8679	0.0049	2.6482	1.0091–6.9494	0.1515
Low HDL-C	Age (years)	0.7816	0.5017–1.2175	0.2753	0.6256	0.4041–0.9687	0.0200
	BMI (kg/m^2)	1.0643	1.0098–1.1217	0.0178			
	Diabetes	1.7492	1.1522–2.6557	0.0091			
	Gender	2.3700	1.4491–3.8761	0.0000	1.3436	0.8400–2.1489	0.2168
Elevated TG	Age (years)				0.4954	0.2957–0.8300	0.0078
	BMI (kg/m^2)	1.0933	1.0244–1.1668	0.0091	0.9551	0.8930–1.0216	0.1797
	Hypertension	1.8516	1.1236–3.0515	0.0148			
	Cigarette Smoking Status	2.2800	1.3586–3.8265	0.0049			

[a] Was obtained by the methods of multiple logistic analysis.
EOS, end of study; FAS, full analysis set; OR, odds ratio.
An OR is a measure of association between an exposure and an outcome.
Elevated LDL-C: ≥RF (risk factors) or CVD or DM: LDL ≥ 100 mg/dl (i.e. 2.6 mmol/L).
≥2RF: LDLv130 mg/dl (i.e. 3.3 mmol/L).
<2RF: LDL ≥ 160 mg/dl (i.e. 4.1 mmol/L).
Low HDL-C: HDL < 40 mg/dl (1.0 mmol/L) for men and HDL-C < 50 mg/dl (1.3 mmol/L) for women.
Elevated TG: TG ≥ 200 mg/dl (i.e. 2.3 mmol/L); however normal TG is <150 mg/dl (i.e. 1.7 mmol/L).

diabetes (p = 0.0002), cigarette smoking (p = 0.0049) at baseline. The association of high LDL-C with age, diabetes, cigarette smoking, and hypertension highlights the importance of treating abnormal LDL-C levels in patients with such risk factors. In diabetic patients the LDL-C levels increased with hypertension. The LDL-C levels also increased with prior cerebro-vascular disease. In non-diabetic patients, the association of high LDL-C was statistically significant with age, hypertension and cigarette smoking prior to statin therapy but the association was not statistically significant post statin therapy. Our findings are similar to a period prevalence study in which it was observed that co-occurrence of diabetes mellitus, hypertension, and high LDL-C mandates comprehensive disease management strategies.[22] The EUROASPIRE IV study reported that only one-fifth of the patients on lipid-lowering medication achieved the Joint European Societies (JES) 2012 CVD prevention guidelines recommended LDL-C lowering target of ≤1.8 mmol/L. The study concluded that coronary patients require more intensive cholesterol management.[23]

However, in non-diabetic patients, low HDL-C had no statistical significant association with BMI and gender (male over female); and this association either remained unchanged or decreased post statin therapy. High TG had statistically significant association ($p < 0.05$) with BMI (p = 0.0091), hypertension (p = 0.0148), and cigarette smoking (p = 0.0049) prior to statin therapy. In diabetic patients, TG levels increased with cigarette smoking and gender (male over female) both pre and post statin therapy; marginally increased with BMI prior to statin therapy and post statin therapy it either remained unchanged or decrease. However, in non-diabetic patients, high TG levels had statistically significant association with hypertension prior to therapy and no significant association with cigarette smoking. Post therapy the association either remained unchanged or decreased. The findings of HDL-C and TG abnormalities are similar to those of the Copenhagen male study, which stated that high TG-low HDL-C were powerful predictors of IHD besides isolated high LDL-C. That study inferred that prevention of IHD should emphasize on interventions targeting at high TG-low HDL-C and not just manage overall hypercholesterolemia.[24] A study of 1800 adults in India revealed a high incidence of dyslipidemia; the prevalence being higher in males.[25] It was found that high cholesterol and high TG were more prominent in adults aged 31–40 years than those under age 30. Another study investigating dyslipidemia in Asian Indians residing in India showed that the overall prevalence of dyslipidemia ranged from 10% to 73%. Specifically, prevalence of hypercholesterolemia was 28% in urban patients as compared to 22% in the rural patients.[26] High TG, low HDL-C and high LDL-C levels characterize typical lipid profile in the Indian population.

Our findings signify the need to treat high LDL-C as well as low HDL-C and high TG in diabetic population with associated risk factors such as hypertension, BMI and gender (male over female). Published literature has also reported that lipid abnormalities (high LDL-C, low HDL-C and high TG) frequently accompany both hypertension and glucose intolerance in diabetes and in the metabolic syndrome.[27,28]

Inclusion of other drugs in addition to statin therapy was suggested by Cziraky et al. to promote the cost-effective

Table 5 – Subgroup analysis of diabetic and non-diabetic patients to obtain association between dyslipidemia, statin therapy/LLT and patient characteristics (FAS population).

Diabetic patients		Total (n = 137)						Non-diabetic patients		Total (n = 336)					
Dependent variable	Variable	At baseline			At EOS			Dependent variable	Variable	At baseline			At EOS		
		Adjusted OR[a]	95% CI[a]	p-Value[a]	Adjusted OR[a]	95% CI[a]	p-Value[a]			Adjusted OR[a]	95% CI[a]	p-Value[a]	Adjusted OR[a]	95% CI[a]	p-Value[a]
High LDL-C	Prior cerebro-vascular disease	3.7873	0.3261–43.9863	0.2567				High LDL-C	Age (years)	2.5529	1.2191–5.3461	0.0083	2.2769	0.4919–10.5399	0.2503
	Gender	0.5099	0.2124–1.2237	0.1370					BMI (kg/m^2)				0.8515	0.7112–1.0196	0.0935
	Hypertension	1.8308	0.8521–3.9335	0.2232	3.8425	0.8168–18.0768	0.0698		Gender	0.4487	0.1650–1.2198	0.1088			
Low HDL-C	Age (years)	0.4991	0.1762–1.4648	0.2378	0.5457	0.2149–1.3855	0.2112		Hypertension				2.4416	0.8106–7.3545	0.0921
	Prior cerebro-vascular disease	0.2269	0.0178–2.8473	0.2188					Cigarette Smoking Status	1.7473	0.9837–3.1034	0.0119	1.7921	0.5888–5.4550	0.2991
	Gender	4.3086	1.5818–11.3031	0.0015				Low	Age (years)				0.6108	0.3733–0.9995	0.0488
	Hypertension				1.5222	0.7566–3.0624	0.2377	HDL-C	BMI (kg/m^2)	1.0650	1.0030–1.1310	0.0383			
High TG	BMI (kg/m^2)	1.1486	1.0163–1.2981	0.0090					Gender	1.9790	1.1118–3.5226	0.0154			
	Gender	2.7676	0.9024–8.4882	0.0686	4.0959	1.3278–12.6345	0.0481	High	Age (years)				0.5182	0.2864–0.9376	0.0289
	Cigarette smoking status	6.5219	2.1823–19.4911	0.0016	3.7366	1.0817–12.9077	0.0289	TG	BMI (kg/m^2)	1.0537	0.9732–1.1409	0.1955	0.9378	0.8663–1.0151	0.1103
									Hypertension	1.9475	1.0645–3.5627	0.0249			
									Cigarette smoking status	1.6373	0.8813–3.0418	0.1720			

n is number of diabetic patients & non-diabetic patients.

[a] Is obtained by the methods of multiple logistic analysis.

EOS, end of study; FAS, full analysis set; OR, odds ratio.

An OR is a measure of association between an exposure and an outcome.

Elevated LDL-C: ≥RF (risk factors) or CVD or DM: LDL ≥ 100 mg/dl (i.e. 2.6 mmol/L).

≥2RF: LDLv130 mg/dl (i.e. 3.3 mmol/L).

<2RF: LDL ≥ 160 mg/dl (i.e. 4.1 mmol/L).

Low HDL-C: HDL < 40 mg/dl (1.0 mmol/L) for men and HDL-C < 50 mg/dl (1.3 mmol/L) for women.

Elevated TG: TG ≥ 200 mg/dl (i.e. 2.3 mmol/L); however normal TG is <150 mg/dl (i.e. 1.7 mmol/L).

Table 6 – Summary of patients with SAE by SOC and PT.

System organ class preferred term	Total (n = 474) n (%)
Number of patients with at least one serious AE	6 (1.3)
Cardiac disorders	5 (1.1)
Inferior MI	1 (0.2)
Myocardial infarction	3 (0.6)
Triple vessel disease	1 (0.2)
Infections and infestations	1 (0.2)
Gastroenteritis	1 (0.2)
Nervous system disorder	1 (0.2)
Sensory disturbance	1 (0.2)

Percentages are based on the number of patients in full analysis set (FAS) in respective visit. Serious adverse events (SAE); System organ class (SOC) and preferred terms (PTs) are coded using the MedDRA version 15.0 dictionary. If a patient experienced more than one episode of an adverse event (AE), the patient is counted once for that event. If a patient had more than one AE within a SOC, the patient is counted once for each PT and once in that SOC.

achievement of optimum lipid levels in several at-risk patients.[18] A similar study conducted in France[29] demonstrated that a significant proportion of dyslipidemic patients at high CV risk did not achieve treatment goals even after statin therapy. Though statin therapy alone is not sufficient for managing lipid parameters, a study by Larsen et al. emphasized the need of statin therapy to prevent adverse clinical events, major adverse cardiac events, major bleeding unrelated to bypass surgery, and death. Absence of a discharge statin prescription after STEMI was an independent predictor of ischemic events including death in this study.[30] In daily clinical practice, almost one-third of patients with a history of coronary event have residual lipid risk including LDL-C <100 mg/dl, low HDL-C and/or high TG, known as residual lipid risk.[31] Though statin therapy is effective, a substantial proportion of patients still remain with residual dyslipidemia. Several large studies (CEPHEUS, DYSIS) have reported the need for comprehensive and intensive surveillance, awareness and treatment regimen for lowering lipids, especially in patients at a high risk for CVD.[32,33]

This observational cohort study had a few inherent limitations. The study design itself could be associated with introduction of bias at different stages. The other biases were sampling and effect size, which were not taken into consideration. Also, observation was not restricted to statin therapy alone, but other LLT were also observed and assessed.

5. Conclusion

In conclusion, management of lipid parameters beyond LDL-C would require additional therapeutic and non-therapeutic options to statin therapy/LLT, to likely benefit the patients with residual risks. The scope of comprehensive lipid management therapies may also include reducing the residual cardiovascular risks associated with low HDL-C levels and high TG levels. Future research directed toward comprehensive drug therapy regimen for the management of overall lipid abnormalities, in primary and secondary prevention of cardiovascular events is suggested.

Key messages:

(1) In our study, statin therapy/LLT was found to be effective in reducing the number of patients with primarily abnormal LDL-C fraction and mixed dyslipidemia. But statin therapy/LLT was not effective in managing HDL fraction, lipoprotein (a) and TG abnormalities.
(2) Management of lipid parameters beyond LDL-C would require additional therapeutic and non-therapeutic options to statin therapy/LLT, to likely benefit the patients with residual risks.

Conflicts of interest

The authors have none to declare.

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