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High-density lipoprotein cholesterol as a predictor of clinical outcomes in patients achieving low lipoprotein cholesterol targets after elective percutaneous coronary intervention

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Abstract

Objective

To investigate the significance of high-density lipoprotein (HDL) cholesterol after statin therapy on the outcomes of patients with coronary artery disease (CAD) who underwent elective percutaneous coronary intervention (PCI).

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Materials and methods

One hundred patients with CAD were included in this prospective study. All patients had elective PCI with their baseline LDL cholesterol less than 100 mg/dL. Patients were classified according to baseline HDL cholesterol into two groups: group I with normal HDL cholesterol levels (> 40 mg/dL for men or >50 mg/dL for women) and group II with low HDL cholesterol levels. Major adverse cardiac events (MACE) were reported in both groups at 6-month follow-up.

Results

During the follow-up, the low HDL cholesterol group had insignificantly higher rates of composite MACE. HDL cholesterol levels were inversely related to the occurrence of composite MACE (odds ratio for MACE: 0.3697, 95% CI: 0.1421 to 0.9619; P=0.0414). Low HDL cholesterol on follow-up was a significant predictor of target vessel revascularization (TVR) (P=0.009).

Conclusion

Low HDL cholesterol was associated with high MACE after elective PCI and thus clearly influenced the prognosis.

Keywords

Coronary intervention, high-density lipoprotein, low-density lipoprotein

Introduction

Lowering low-density lipoprotein (LDL) cholesterol is considered to be the primary target in lipid modification for treatment and prevention of atherosclerosis in the majority of current guidelines [1]. Lipid-lowering treatment with hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has achieved significant reductions in cardiovascular events [2]. However, despite attaining optimal LDL cholesterol targets in all the statin trials, there is still a substantial residual risk in the active treatment arms. The Framingham Heart Study showed that low high-density lipoprotein (HDL) cholesterol (defined as <40 mg/dL for men and <50 mg/dL for women) was sufficient to qualify as a risk factor for coronary artery disease (CAD) [3,4]. Low HDL cholesterol levels continue to be inversely associated with cardiovascular events among those on statins with well controlled LDL cholesterol levels, including those with LDL cholesterol <70 mg/dL [5,6]. Moreover, moderate increases in HDL cholesterol in statin-treated patients are correlated with regression of coronary atherosclerosis. These findings support the hypothesis that HDL cholesterol is a potent atheroprotective factor; it is considered to be a therapeutic target independent of LDL cholesterol lowering. However, there is a limited data regarding the impact of HDL cholesterol levels after statin therapy on clinical outcome in patients, who have undergone percutaneous coronary intervention (PCI) [7]. Accordingly, we sought to investigate the significance of HDL cholesterol levels after statin therapy on cardiovascular events in CAD patients undergoing elective PCI. This study was designed to assess clinical significance of HDL cholesterol as a predictor of major adverse cardiac events (MACE) up to 6-month follow-up after elective PCI in patients who were already on statin therapy with LDL cholesterol levels <100 mg/dL.

Materials and methods

Study population

This prospective study was carried out at the catheterization laboratory of the Al Ahrar Teaching Hospital and the catheterization laboratory of the Benha University Hospital, from October 2013 to March 2014. Patients with CAD, who underwent elective PCI during this period, were screened for baseline lipid profile and were followed up 6 months after PCI.

Key inclusion criteria

Patients with baseline LDL cholesterol <100 mg/dL who already were on statin therapy before PCI, continued using statins up to 6 months after PCI and maintained their LDL cholesterol levels <100 mg/dL at the end of the follow-up period. One hundred patients who met the inclusion criteria were classified into two groups:

GROUP I: Fifty patients with normal HDL cholesterol levels (>40 mg/dL for men or >50 mg/dL for women) at baseline;

GROUP II: Fifty patients with low HDL cholesterol levels (<40 mg/dL for men or <50 mg/dL for women) at baseline.

Each patient was given information about the purpose of the study and signed an informed consent form.

Exclusion criteria

It included discontinuation of statins during first 6 months after PCI, loss of follow-up lipid panels,

patients with initial or follow up LDL cholesterol <100 mg/dL.

All patients were subjected to the following:

1. Baseline evaluation

All patients underwent baseline evaluation at index PCI, including a full history focusing on cardiovascular risk factors; complete physical examination focusing on the cardiovascular system; lipid panel that included total cholesterol (TC), HDL cholesterol, LDL cholesterol, and triglycerides (TG); electrocardiography (ECG) to detect ischaemia; and echocardiography (Echo) to assess left ventricular function by measuring ejection fraction (EF).

2. PCI procedure

All patients received statins before and after PCI. Each physician reported a type of statin and its doses. The choice of other drugs for dyslipidaemia was at each physician's discretion. Before the PCI, all patients received 150 mg of aspirin daily. Clopidogrel (300 mg of loading dose) was given at least one day before the procedure. The procedure was performed through the femoral or radial artery after administration of unfractionated heparin (100 U/kg). The choice of stent was at each physician's discretion.

A successful PCI procedure was defined as a decrease in minimum stenosis diameter to <30%. After the procedure, aspirin 150 mg/d was continued for lifelong. Clopidogrel (75 mg/d) was administered for a period of 3 months after bare metal stent (BMS) implantation and at least for 12 months after implantation of drug eluting stents (DES). For all the patients, 12-lead ECG was obtained prior and following intervention to detect procedure-related ischemic changes.

3. Follow-up lipid profile at 6 months

All patients underwent laboratory lipid profile testing at baseline and at 6-month follow-up. Each test included: TC, HDL cholesterol, LDL cholesterol, and TG using fasting blood samples in the morning after fasting for 12 hours.

4. Clinical follow-up at 6 months

All patients were followed up for any symptoms of ischaemia. ECG was done to any complaining patient and if standard ECG was positive for new ischaemia with elevated cardiac biomarkers, the patients were referred to coronary angiography examination to detect possible complications. In addition, patients with recurrent ischaemic pain at a persistent level that was not controlled by medication since stent implantation were referred for coronary angiography examination to detect possible complications.

Study endpoints

Composite MACE, including cardiac deaths after the exclusion of non-cholesterol cardiac deaths and non-fatal myocardial infarction, defined as chest pain with new ST-segment changes and elevation of cardiac markers, which reflected myocardial necrosis to at least twice the upper limit of normal. Target lesion revascularization (TLR) defined as revascularization either by PCI or by coronary artery bypass grafting (CABG) of the target lesion resulting from restenosis or reocclusion within the stent or in the 5 mm distal or proximal segments adjacent. Target vessel revascularization (TVR) defined as revascularization either by PCI or by CABG of any segment of the epicardial coronary artery containing the target lesion [8].

Statistical analysis

Data were entered, checked, and analysed using Epi-Info version 6 and SPP version for Windows. Data were summarised using arithmetic mean, Student's t-test, χ^2 (chi-squared), test of significance, and level of significance were done for all of the above mentioned statistical tests. The threshold of significance was fixed at 5% level (*P*-value). The results were considered significant when the probability of error was less than 5% ($P<0.05$), non-significant when the probability of error was more than 5% ($P>0.05$), and highly significant when the probability of error was less than 0.1% ($P<0.001$). The smaller the *P*-value was obtained, the more significant were the results. An odds ratio was used to assess the relation among levels of HDL cholesterol with morbidity and mortality outcomes after PCI.

Results

Study population

Baseline demographic, clinical, laboratory, and angiographic characteristics of the two groups showed statistically non-significant differences in almost all parameters. Group II (low HDL cholesterol group) had statistically non-significant fewer males. Group II had statistically non-significant lower left ventricular EF, and statistically non-significant higher prevalence of hypertension, diabetes mellitus (DM), and previous ACS. There was no significant difference between the two groups in angiographic characteristics regarding the number of vessels affected, the number and type of stents in each group, the mean stent diameter, and

mean stent length. Group II had higher total number of implanted stents with statistically non-significant difference and had non-significant higher number of implanted DES in comparison with Group I (Table 1).

Table 1. **Baseline demographic characteristics, risk factors, clinical presentation, and angiographic characteristics before PCI in the two groups**

Variable	Group I N=50	Group II N=50	*P* value
Age, years, mean ± SD	54±8	57±7	1.0
Male	35	34	0.8
Female	15	16	0.83
DM	19	22	1.0
HTN	31	37	0.2
Smoking	11	15	0.69
EF	57.1	54.02	0.68
SVD	32	22	0.73
2VD	17	27	0.57
MVD	1	1	–
One BMS	19	13	0.57
Two BMS	10	17	0.43
Three BMS	1	1	–
One DES	13	10	0.74
Two DES	6	8	0.78
Mixed BMS and DES	1	1	–
Total number of BMS	43	60	0.34
Total No. of DES	26	27	0.43
Previous STEMI	22	28	0.32
Previous UA/NSTEMI	16	23	0.34
Stable angina	4	7	0.54

DM – diabetes mellitus; HTN – hypertension; SVD – single vessel disease; 2VD – two vessels disease; MVD – multi-vessel disease; BMS – bare metal stent; DES – drug eluting stent; STEMI – ST segment elevation myocardial infarction; UA – unstable angina; NSTEMI – non-ST segment elevation myocardial infarction

Lipid panel at baseline in the two groups

It showed statistically non-significant differences in mean TC and LDL cholesterol levels in both groups (147.98 mg vs. 155.7 mg, *P*=0.15) and (80.14 mg vs. 81.1 mg, *P*=0.51), respectively. Group II had significant lower level of HDL cholesterol compared with group I (37.48 mg vs. 50.2 mg, *P*=0.001), while it had significant higher level of mean TG compared with group I (141.6mg vs. 128.52 mg, *P*=0.002) which related to suspected inverse relation between HDL cholesterol and TG levels (Table 2).

Lipid panel in the two groups after 6-month follow-up

Mean TC and LDL cholesterol levels in both groups showed statistically non-significant differences (122.5 mg vs. 129.7 mg, *P*=0.2), (62.06 mg vs. 64.94 mg, *P*=0.55), respectively. After 6-month follow-up, group II maintained a significant lower level of HDL cholesterol compared with group I (37.48 mg vs. 52.74 mg, *P*=0.001) and significant higher level of mean TG compared with group I (121.54 mg vs. 111.32 mg, *P*=0.002) (Table 3).

Table 2. **Lipid panel in the two groups at baseline**

	Group I	Group II	*P* value
Mean TC	147.98	155.7	0.15
Mean LDL cholesterol	80.14	81.1	0.51
Mean HDL cholesterol	50.2	37.48	0.001
Mean TG	128.52	141.6	0.002

TC – total cholesterol; TG – triglycerides; HDL cholesterol – high-density lipoprotein cholesterol; LDL cholesterol – low-density lipoprotein cholesterol

Table 3. **Lipid panel in the two groups after 6-month follow-up**

	Group I	Group II	P value
Mean TC	122.5	129.7	0.2
Mean LDL cholesterol	62.06	64.94	0.55
Mean HDL cholesterol	52.74	37.48	0.001
Mean TG	111.32	121.54	0.002

TC – total cholesterol; TG – triglycerides; HDL cholesterol – high-density lipoprotein cholesterol; LDL cholesterol – low-density lipoprotein cholesterol

Effect of statins on lipid panel after 6-month follow-up in both groups

Statin therapy significantly reduced the levels of TC and LDL cholesterol in both groups especially in Group I (17.21% in group I vs. 16.69% in group II) and decreased LDL cholesterol levels by (22.5% in group I and 19.8% in group II). Statin therapy significantly decreased TG levels in both groups especially in Group II (13.38% in group I and 14.16% in group II). Statin therapy increased HDL cholesterol only by 4.8% in group I and 8.3% in group II. In conclusion, statin therapy markedly reduced levels of both LDL cholesterol and TC. In comparison, statin therapy was less effective to elevate the level of HDL cholesterol.

Clinical outcomes for the study population

During the follow-up, 17 patients (34%) in group II and 8 patients (16%) in group I had MACE. The incidence of composite MACE was significantly higher in group II compared with group I (*P*=0.01). HDL cholesterol levels were inversely related to the occurrence of composite MACE (odds ratio for MACE: 0.3697, 95% CI: 0.1421 to 0.9619; *P*=0.0414). Although both groups had comparable incidences of cardiac death or non-fatal myocardial infarction, group II had a statistically significant higher incidence of TLR (12 patients (24%) vs. 5 patient (10%), *P*=0.04) and TVR (14 patients (28%) vs. 6 patients (12%), *P*=0.009) (Table 4, Figure 1).

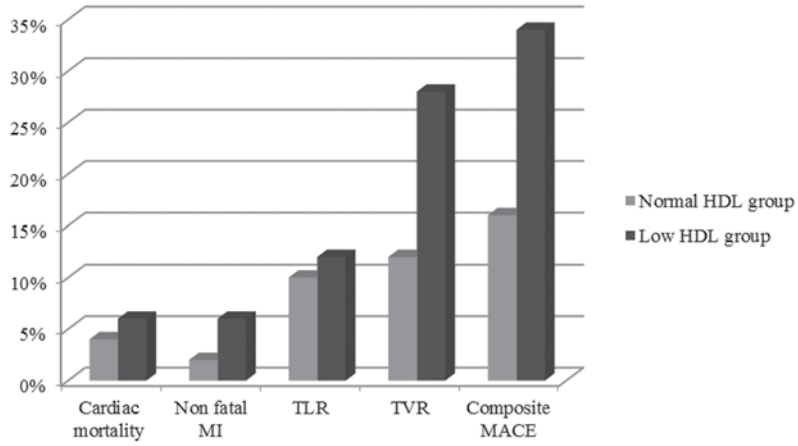

Figure 1. Major adverse cardiovascular events in both groups

Table 4. **Major adverse cardiovascular events in both groups**

Event	Group I N = 50	Group II N= 50	χ^2 test	*P* value
Cardiac mortality	2 (4%)	3 (6%)	0.21	1.0
Non-fatal MI	1 (2%)	3 (6%)	1.3	0.62
TLR	5 (10%)	12 (24%)	8.95	0.04
TVR	6 (12%)	14 (28%)	11.31	0.009
Composite MACE	8 (16%)	17 (34%)	10.15	0.01

MI – myocardial infarction; TLR – target lesion revascularization; TVR – target vessel revascularization; MACE – major adverse cardiac events

Subgroup analysis

Incidence of MACE among diabetics in group II was significantly higher in comparison with diabetics in group I. Among hypertensive patients, incidence of MACE was significantly higher among hypertensive patients from group II. Among smokers, smokers in group II had significantly higher MACE (45.45% vs. 26.31%, 32.25% vs. 15.62%, 46.66% vs. 27.27%, *P*=0.005, 0.04, 0.01, respectively). According to stent type, the incidence of MACE was significantly higher in patients from group II received BMS vs. group I (32.25% vs. 15.62%) and significantly higher in patients from group II received DES vs. group I (26.3% vs. 10%, *P*=0.04) (Table 5).

Table 5. **Incidence of MACE in relation to a stent type in both groups**

	Normal HDL cholesterol group	Low HDL cholesterol group	*P* value
Complicated patients with BMS	5/31 (15.62%)	10/31 (32.25%)	0.04
Complicated patients with DES	2/20 (10%)	5/19 (26.3%)	0.04

BMS – bare metal stent; DES – drug eluting stent

Discussion

However, only few randomized trials tested the effect of HDL cholesterol level on elective PCI outcome. This non-randomized prospective study showed that low HDL cholesterol levels after statin therapy in all patients targeting LDL cholesterol levels <100 mg/dL is inversely related to the occurence of MACE after elective PCI [odds ratio for MACE: 0.3697, 95% CI: 0.1421 to 0.9619, *P*=0.0414) up to 6-month follow-up. Although both groups had comparable incidences of cardiac death and non-fatal myocardial infarction, the low HDL cholesterol group (group II) had a significantly higher incidence of TLR and TVR (*P*=0.009). Our results, in line with other studies, strenghthen the notion of the importance of HDL cholesterol levels for cardiovascular outcome at any stage of the disease with higher incidence of long-term mortality and adverse cardiac events. In support of our observations of patients who underwent elective PCI with history of either stable CAD or ACS, previous studies like the MIRACL trial (that assessed the effect of HDL cholesterol) showed a marked reduction in cardiovascular adverse events, namely about 1.4% for each increment of HDL cholesterol by 1 mg/dL, and analysis of HDL cholesterol-quartiles demonstrated a significant risk reduction in quartile 4 relative to quartile 1 during a 16 week follow-up. Also, low HDL cholesterol baseline levels (<40 mg/dL in men and <45 mg/dL in women) were related to a significantly higher incidence of death, myocardial infarction, and target lesion revascularization [8,9]. An example of a small non-randomized observational trials that tested an effect of HDL cholesterol on elective PCI outcome and was in line with our study is the study conducted by Seo *et al.* They concluded that HDL cholesterol level after statin therapy was an independent risk factor

for TLR, TVR and MACE. So, raising the HDL cholesterol level may be a subsequent goal after achieving target LDL cholesterol levels [10]. The results of the ARBITER 6-HALTS study conducted by Taylor *et al*. implied that raising HDL cholesterol may be the next target to ameliorate the progression of coronary atherosclerosis statin therapy [11]. Importantly, although HDL cholesterol levels <40 mg/dL in men and <50 mg/dL in women are currently regarded as markers for high cardiovascular risk, which was also supported by our findings, we would nevertheless suggest that any elevation of HDL cholesterol regardless of actual levels may be important prior to PCI and has a profound beneficial influence on the occurrence of MACE over the whole range of HDL cholesterol levels [12].

Effect of HDL cholesterol level on outcome of DES patients

The subgroup analysis showed that the incidence of complications was significally higher in group II patients recieved DES (5 patients) compared with group I patients recieved DES (2 patients) (41.67 % vs. 16.67 %, *P*=0.04), putting in mind that all angiographic charachterstics including number of vessels affected and also the number of stents in both groups were nearly equal. This was in aggrement with Seo *et al*. from the Percutaneous Coronary Intervention Registry in Catholic University of Korea. They investigated the significance of HDL cholesterol levels after statin therapy on cardiovascular events in patients treated with DES implantation for CAD. A similar study was conducted which lasted 180 days, and a higher incidence of TLR, TVR, and MACE in low HDL cholesterol group compared with high HDL cholesterol group was found. They concluded that HDL cholesterol level after statin therapy was an independent risk factor for TLR, TVR, and MACE in patients who underwent PCI with DES.

Effect of HDL cholesterol level on outcome of diabetic patients

The subgroup analysis also showed that there was a significant difference between the two groups in incidence of complications in relation to DM, putting in mind that there was no significant difference between the two groups in DM at index PCI. The incidence of complications was lower among diabetic patients in group I than in diabetic patients in group II (26.31 % vs. 45.45 %). This observation confirms the value of an increase in HDL cholesterol levels in diabetics undergoing PCI. This was in aggrement with Ogita *et al.* They identified 165 patients who achieved target LDL cholesterol <100 mg/dL anmd underwent PCI. The rate of MACE was significantly higher in diabetic patients with low HDL cholesterol who achieved optimal LDL cholesterol (6.9 % vs. 17.9 %, *P*=0.030) [13].

Protective effect of HDL cholesterol

The adverse effect of low HDL cholesterol on clinical outcome after elective PCI with either BMS or DES, which was observed in our and other studies and was in aggrement, suggests the protective effect of high HDL cholesterol levels. The most acceptable explanation of the protective effects of HDL cholesterol immediatly after PCI is that high HDL cholesterol levels protect against the occurence of myocardial injury. This injury, caused by coronary microembolization which occurs during PCI-related manipulations on the plaque affecting the occurence of PCI related to MI, is defined as an elevation of cardiac troponin I (cTnI) >3 x upper normal limit (not tested in our study) but which in many other trials showed a direct inverse effect on the occurence of AMI and short- and long-term mortality after PCI. The explanation that HDL cholesterol may be cardioprotective against PCI related to MI could be described via many mechanisms, namely the more stable plaque morphology in patients with high HDL cholesterol may result in a lesser and milder microembolization in case of plaque rupture, and HDL cholesterol may additionally exert a direct cardioprotective effect.

In general, patients with normal or high levels of HDL cholesterol have a natural protective armor from adverse cardiovascular events. HDL cholesterol particles are able to remove cholesterol from artery atheroma and transport it back to the liver for excretion or re-utilization, which is the main reason why the cholesterol carried within HDL cholesterol particles is sometimes called «good cholesterol» (despite that it is exactly the same as the cholesterol in LDL cholesterol particles). People with higher levels of HDL cholesterol seem to have fewer problems with cardiovascular disease, while people with low HDL cholesterol levels (less than 40 mg/dL) have increased rates for heart disease [14]. However, emerging experimental studies have identified that HDL cholesterol modifies endothelial cell adhesion, protein expression, inhibits endothelial cell apoptosis, promotes re-endothelialisation, stimulates the production of prostacyclin, decreases platelet aggregability, inhibits LDL cholesterol oxidation, and has anti-inflammatory effects, all of which may contribute to its anti-atherosclerotic properties [15].

Effect of statins on raising levels of HDL cholesterol

In the total cohort of our study, HDL cholesterol levels increased by an average of 5.11% in all patients (2.54% in normal HDL cholesterol group vs. 7.68% in low HDL cholesterol group) and LDL cholesterol levels decreased by an average of 21.15% in all patients (22.5% in normal HDL cholesterol group vs. 19.8% in low HDL cholesterol group) after statin therapy, respectively. Our study showed the small effect of statin monotherapy on raising HDL cholesterol levels and on avoiding the increased risk of low HDL cholesterol level. This was in aggremement with the multiple studies that tested whether very aggressive reductions in LDL cholesterol are enough to offset the increased risk associated with very low serum levels of HDL cholesterol. Previous studies indicated that the ratio of total cholesterol to HDL cholesterol could be a target for high-risk patients, which could be achieved by more aggressive LDL cholesterol lowering or potentially by increasing HDL cholesterol [16,17]. A recent meta-analysis of statin therapy reported that statin monotherapy did not alter the correlation between HDL cholesterol level and cardiovascular risk, such that low levels of HDL cholesterol remained significantly and independently associated with an increased risk despite treatment with statins [18].

Increasing HDL cholesterol level as a target

Because of the residual cardiovascular risk seen in statin monotherapy, treatment may be intensified with the use of combination therapy aimed at either further reduction of LDL cholesterol levels or increase of HDL cholesterol levels. It is an important issue because nearly 80% of statin-treated patients with low LDL cholesterol levels still have low HDL cholesterol levels [19]. Certain changes in lifestyle may have a positive impact on raising HDL cholesterol levels, including aerobic exercise, weight loss, nicotinic acid supplementation, smoking cessation, removal of trans-fatty acids from and addition of soluble fiber to the diet, consumption of omega-3 fatty acids such as fish oil or flax oil, increased intake of unsaturated fats and carbohydrates [20]. Niacin increases HDL cholesterol by selectively inhibiting hepatic diacylglycerol acyltransferase, reducing triglycerides synthesis and VLDL secretion. Pharmacologic doses of niacin (1 to 3 grams/day) increase HDL cholesterol levels by 10–30%, making it the most powerful agent to increase HDL cholesterol. However, high incidence of side effects remains a clear limitation related to that drug. A randomized clinical trial demonstrated that treatment with niacin can significantly reduce atherosclerosis progression and cardiovascular events. Most saturated fats increase HDL cholesterol to varying degrees but also raise total and LDL cholesterol. A high fat, adequate-protein, low carbohydrate diet may have similar response to niacin (lowered LDL cholesterol and increased HDL cholesterol) through beta-hydroxybutyrate coupling to niacin receptor [21]. New medications targeting reverse cholesterol metabolism pathways, such as torcetrapib, has been of interest in new trials. The increase in adverse events observed in the studies, where HDL cholesterol was considerably elevated, could be related to a mechanism of action of torcetrapib rather than to the increase in HDL cholesterol itself. Raising HDL cholesterol is a potential therapeutic goal after lowering LDL cholesterol for cardiovascular disease prevention, but effective and completely safe adjuvant therapy is still undetected [22].

Conclusion

HDL cholesterol level after achieving the target of LDL cholesterol level with statin therapy was an important risk factor for clinical outcome mainly on both TLR and TVR in patients who underwent PCI with either DES or BMS, especially in diabetic patients. Raising the HDL cholesterol level may be a subsequent goal after achieving target LDL cholesterol levels in patients with coronary artery disease and for patients undergoing elective PCI.

Limitations of the study

Our study had some limitations. Firstly, our findings were subject to selection bias and confounding factors because the study had a small sample size and was observational. Secondly, it was a two-centre study and our catheterisation laboratories were not equipped with intravascular ultrasound, which may help in further assessment of the lesions. To minimize these biases, we used propensity score matching, but hidden bias may still remain because of the influence of unmeasured confounders. Our findings should be confirmed by an adequately powered, randomized multi-centre prospective trial. Thirdly, coronary angiography was analysed quantitatively, not qualitatively. A detailed qualitative coronary analysis may be helpful in further interpreting our findings. Lastly, the name and dosage of the statins prescribed to the study population were not reported in this study as not all patients were on the same trade name of drug and not all of them were on the same dose.

Conflict of interest: None declared

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