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急性冠脉综合征合并低密度脂蛋白胆固醇基线低水平患者短期中等强度阿托伐他汀治疗的冠脉斑块消退效应*

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摘要 目的：评估短期中等剂量序贯长期低剂量阿托伐他汀治疗急性冠脉综合征（Acute Coronary Syndrome，ACS）合并低密度脂蛋白胆固醇（Low-density Lipoprotein Cholesterol, LDL-C）基线低水平患者冠脉斑块消退效应，使用血管内超声（Intravascular Ultrasound, IVUS）为斑块消退评估依据。**方法：**2014年1月至2016年12月在昆明医科大学附属延安医院接受IVUS指导下经皮冠脉介入治疗（Percutaneous Coronary Intervention，PCI）的ACS合并LDL-C基线低水平患者随机分组为中等剂量阿托伐他汀（20 mg/d）治疗3个月序贯低剂量阿托伐他汀（10 mg/d）治疗9月组与初始低剂量阿托伐他汀（10 mg/d）治疗12月组。分别测定基线、治疗后1、3、6、12月血脂，术后1年复查冠脉造影及IVUS，选取中度非罪犯冠脉斑块进行消退效应研究，并收集相关临床数据进行定量分析。**结果：**研究入选56例患者，51例患者完成研究。2组患者年龄、性别、LDL-C等基线资料无统计学差异。治疗1、3、6、12月，两组（Total Cholesterol，TC）、LDL-C均有不同程度下降（P＜0.05），（High Density Lipoprotein Cholesterol，HDL-C）不同程度升高（P＜0.05），TC、HDL-C组间无差异，3月后序贯治疗组LDL-C水平明显低于单一治疗组（P＜0.05）。序贯治疗组（Triglyceride，TG）治疗12月出现有统计学意义降低（P＜0.05），单一治疗组TG降低无统计学差异。序贯治疗组冠脉斑块容积减少明显优于单一治疗组（P＜0.05），斑块容积减少及斑块容积减少百分比分别为2.68± 2.25&1.14± 1.99（mm^3）、34.60± 30.37&11.73± 20.71（%）。Logistic回归显示LDL-C降低与阿托伐他汀序贯治疗是斑块消退的重要决定因素。**结论：**短期中等强度序贯长期低强度阿托伐他汀治疗和长期低强度阿托伐他汀治疗均可导致ACS合并LDL-C低基线水平患者冠状动脉斑块消退，而前者效果优于后者。

关键词：急性冠脉综合征（ACS）；低密度脂蛋白胆固醇（LDL-C）；血管内超声导管（IVUS）；阿托伐他汀；斑块消退

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Efficacy of Short-term Moderate-intensity Atorvastatin on Coronary Plaque Regression in Acute Coronary Syndrome patients with Low Baseline Low-density Lipoprotein Cholesterol Level*

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ABSTRACT Objective: To detect effects of short-term moderate-intensity followed by long-term low-intensity atorvastatin on regression of coronary plaque using intravascular ultrasound (IVUS) in patients with acute coronary syndrome (ACS) and low baseline Low-density Lipoprotein Cholesterol (LDL-C) level. **Methods:** The ACS patients with low baseline LDL-C level who underwent percutaneous coronary intervention (PCI) under IVUS guidance were randomized to receive moderate-intensity atorvastatin (20 mg/d) for 3 months followed by low-intensity atorvastatin (10 mg/d) for 9 months group or the initial low-intensity atorvastatin (10 mg/d) for 12 months group during the period from January 2014 to December 2016 in the Affiliated Yan'an Hospital of Kunming Medical University. Lipid levels were measured at baseline, 1, 3, 6, and 12 months after treatment, meanwhile coronary angiography and IVUS were performed again 1 year after PCI. The regression effect was conducted on the moderate non-culprit coronary plaques. The clinical data were entirely collected and quantitatively analyzed. **Results:** 56 patients were overall enrolled and randomly assigned to the sequential therapy group and the monotherapy group, 51 cases finally completed the study. None of statistical differences in baseline data such as age, sex, LDL-C, was found between the two groups. After treatment of 1, 3, 6, 12 months, total cholesterol (TC) and LDL-C differently decreased in both groups (P<0.05), high- density lipoprotein cholesterol(HDL-C) differently raised (P<0.05). No statistical difference existed in TC and HDL-C between two groups. The LDL-C level of the sequential therapy group was significantly lower than that of the monotherapy group 3 months later (P<0.05). The decrease of triglyceride in the sequential therapy group had statistical difference after 12 months of

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treatment (P<0.05), however that in the monotherapy group had no statistical difference. The reduction of plaque volume induced by the sequential therapy group was significantly larger than the monotherapy group (P<0.05). Mean change in plaque volume and mean percentage change in plaque volume were 2.68± 2.25&1.14± 1.99(mm^3), 34.60± 30.37&11.73± 20.71(%) in both groups respectively. Logistic regression indicated that LDL-C reduction and atorvastatin sequential therapy were significant determinants of coronary regression. **Conclusions:** The sequential therapy of short-term moderate-intensity followed by long-term low-intensity atorvastatin and the monotherapy of long-term low-intensity atorvastatin can induce regression of coronary plaque in ACS patients with low baseline LDL-C level, whereas the former is superior to the latter.

Key words: Acute coronary syndrome; Low-density lipoprotein cholesterol; Intravascular ultrasound; Atorvastatin; Plaque regression
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前言

他汀治疗不仅可以降低血脂，而且能够稳定易损斑块，减少急性心血管事件风险和改善长期临床预后结局，是目前冠心病标准化治疗方案之一，被诸多指南推荐为一线治疗[1-6]。对于ACS合并LDL-C低基线水平患者，国内指南建议及早使用他汀药物，但未给出具体剂量及使用方法[1-3]。众所周知，他汀治疗效果依赖于胆固醇基线水平高低。因此临床实践中，不在少数医师争议LDL-C已在目标值以下ACS患者他汀治疗强度，关注LDL-C低水平患者他汀治疗方法及疗效。目前IVUS检测斑块进展变量已经被作为冠心病临床事件的有效替代指标[7,8]。本研究旨在通过不同剂量、方式的他汀治疗合并LDL-C低基线水平ACS患者，并用IVUS评价冠状动脉斑块消退效应，提供一种新药物治疗模式。

1 材料和方法

1.1 研究对象

2014年1月至2016年12月在昆明医科大学附属延安医院接受IVUS指导下经皮冠脉介入治疗的ACS患者。纳入标准：75岁≤ 年龄≥ 18岁；LDL-C≤ 70 mg/dL；1月内未服用中等强度他汀类药物（阿托伐他汀≥ 20 mg/d或相当于此剂量其他他汀）；IVUS检查研究斑块距离PCI部位＞5 mm（近端或远端，除外左主干）；研究节段狭窄程度＜70 %；斑块负荷≥ 50 %，病变节段长度≥ 10 mm[8]。排除标准：左主干病变，血栓病变，研究节段钙化病变或曾行PCI治疗，正在服用非诺贝特等类型降脂药物，纽约心功能分级Ⅲ-Ⅳ级。本研究实施前经医院医学伦理委员会讨论通过并备案，受试者签署知情同意书。

1.2 研究方法

手术操作：先行冠脉造影，罪犯病变接受PCI治疗后，同一血管行IVUS检查，血管超声仪为波科公司（Boston scientific Corporation, California, USA）生产，机械传感探头频率40 MHz。传感器探头至最远端，以0.5 mm/s速度自动回撤至冠状动脉开口，期间连续记录，所有参数测量依据指南标准进行[7]。术中常规肝素抗凝，IVUS检查前予以硝酸甘油200 μg冠脉内注射。

1.3 患者分组及干预

患者随机分组进入阿托伐他汀（辉瑞）20 mg/d治疗3月后减量为阿托伐他汀（辉瑞）10 mg/d治疗9月的序贯治疗组与阿托伐他汀（辉瑞）10 mg/d持续治疗12月的单一治疗组。术后1、3、6、12月，复查血脂、肝肾功能，术后12月复查冠脉造影及IVUS。研究者同期继续服用阿司匹林、氯吡格雷等其他冠心病二级预防药物。患者出现包括急性心肌梗死、靶血管血运重建、肝功能损伤及死亡等主要不良心血管事件（major adverse cardiovascular event，MACE）则终止研究。

1.4 统计学处理

采用SPSS 22.0统计软件进行数据分析。计量资料以 $\bar{x}\pm s$ 表示，比较使用ANOVA及t检验；计数资料比较用 χ^2 检验或Fisher确切概率法，Logistic回归总结斑块消退影响因素，以P＜0.05为差异有统计学意义。

2 结果

2.1 研究完成状况

研究入组56例患者，结束无死亡病例，无心肌梗死等MACE发生。在序贯治疗组，1例退出研究，1例因肌肉疼痛副反应改为低剂量治疗后无不适，1例因肌肉疼痛伴肝酶升高停药，2例均终止研究；单一治疗组1例失访，1例因乏力、肌肉酸痛退出研究。最终完成研究51例。两组患者年龄、性别、危险因素等基线资料无差异（详见表1）。

2.2 血脂治疗状况

两组患者TC、HDL-C及TG在治疗前及治疗后1、3、6、12月组间无统计学差异。两组患者LDL-C治疗前无统计学差异，治疗后3、6、12月降低程度出现统计学意义差异（P＜0.05）。序贯治疗组患者治疗后TC、LDL-C、HDL-C及TG较基线水平均有不同程度变化（P＜0.05），LDL-C治疗1月即开始出现具有统计学意义降低，TC治疗3月出现具有统计学意义降低，TG治疗12月出现具有统计学意义降低，HDL-C治疗3月出现具有统计学意义升高。单一治疗组患者治疗后TC、LDL-C及HDL-C较基线水平亦有不同程度改变（P＜0.05），TG轻度降低但差异无统计学意义；LDL-C及TC治疗3月出现具有统计学意义降低，HDL-C治疗6月出现具有统计学意义升高（详见表2）。

2.3 IVUS检测结果

两组患者治疗前研究节段管腔面积、外弹力膜面积、斑块负荷及斑块容积无统计学差异。治疗后两组患者管腔面积无统计学意义变化（P＞0.05）；两组患者外弹力膜面积、斑块负荷及斑块容积均减少，组间及组内差异均具有统计学意义（P＜0.05）。两组患者不同程度斑块容积减少提示2种治疗方式均有斑块消退效应，斑块容积减少及斑块容积减少百分比的组间差异提示序贯治疗组斑块消退效应明显优于单一治疗组（P＜0.05，详见表3）。

表 1 患者一般临床资料

Table 1 General clinical data of overall patients

	Totality(n=51)	STG(n=25)	MG(n=26)	P
Age(year)	54.82± 7.11	54.04± 7.56	55.58± 6.71	0.446
Sex n(%)	35(68.63)	17(68.00)	18(69.23)	0.925
Risk factors n(%)				
Smoke	27(52.94)	14(56.00)	13(50.00)	0.668
Hypertention	32(62.75)	16(64.00)	16(61.54)	0.856
Diabetes	11(21.57)	6(24.00)	5(19.23)	0.679
Chronic Kidney Disease	2(3.92)	1(4.00)	1(3.85)	0.977
Treatment Status n(%)				
Aspirin	24(47.06)	12(48.00)	12(46.15)	0.895
Antihypertensive	28(54.90)	13(52.00)	15(57.69)	0.683
Hypoglycemic	9(17.65)	5(20)	4(15.38)	0.948
Systolic Pressure(mmHg)	143.63± 25.62	143.2± 27.31	143.96± 24.44	0.925
Diastolic Pressure(mmHg)	84.33± 18.35	85.36± 17.79	83.35± 19.16	0.699
Ventricular Ejection Fraction(%)	46.94± 7.08	46.76± 7.72	47.12± 6.56	0.860
NT-proBNP (pg/mL)	382.88± 300.48	403.78± 287.06	362.79± 317.21	0.631
Creatinine(umol/L)	96.53± 16.36	95.36± 16.17	97.65± 16.79	0.622
Uric Acid(umol/L)	292.75± 112.76	289.28± 115.51	296.08± 112.24	0.832
Distribution of Coronary Artery Lesion n(%)				0.843
left Anterior Descending Artery	26(50.98)	13(52.00)	13(50.00)	
Left Circumflex Artery	9(17.65)	5(20.00)	4(15.38)	
Right Coronary Artery	16(31.37)	7(28.00)	9(34.62)	
Segmental Lesions n(%)				0.904
Proximal	26(50.98)	12(48.00)	14(53.85)	
Midpiece	15(29.41)	8(32.00)	7(26.92)	
Distal	10(19.61)	5(20.00)	5(19.23)	
Vessel Diameter(mm)	3.28± 0.63	3.14± 0.54	3.42± 0.70	0.126
Stents	1.29± 0.73	1.32± 0.75	1.27± 0.72	0.807

Note: Annotation: Sequential Therapy Group, STG; Monotherapy Group, MG; NT-proBNP, N-Terminal Pro-Brain natriuretic peptide.

表 2 不同治疗条件患者治疗前后血脂谱变化对比

Table 2 Comparison of serum lipid profile with different treatment conditions between before and after treatment

	prior treatment	1 month after treatment	3 months after treatment	6 months after treatment	12 months after treatment	P
TC(mg/dL)						
STG**	128.52± 8.38	125.18± 8.11	119.74± 6.17	115.73± 5.52	111.14± 5.05	＜0.001
MG **	127.92± 8.15	125.28± 7.32	121.56± 7.22	117.72± 6.99	114.20± 6.66	＜0.001
P	0.798	0.962	0.338	0.268	0.071	
LDL-C(mg/dL)						
STG *	65.97± 3.52	62.54± 2.66	57.37± 2.03	54.49± 1.47	51.88± 1.58	＜0.001
MG **	65.01± 4.17	63.28± 4.36	60.69± 4.14	58.33± 3.53	55.45± 3.22	＜0.001
P	0.380	0.462	0.001	＜0.001	＜0.001	
HDL-C(mg/dL)						

STG **	38.94± 3.53	40.44± 3.54	43.44± 3.27	44.73± 3.36	46.12± 3.63	＜0.001
MG ***	39.65± 4.16	40.64± 4.02	42.19± 3.99	43.18± 3.90	44.62± 3.97	＜0.001
P	0.517	0.850	0.227	0.136	0.165	
TG(mg/dL)						
STG ****	171.37± 21.54	165.81± 21.02	159.96± 17.10	157.44± 14.23	155.36± 13.67	0.012
MG	168.59± 22.76	164.34± 20.99	159.97± 16.34	157.58± 13.28	155.17± 12.57	0.053
P	0.656	0.804	0.998	0.972	0.959	

Note: Annotation: Sequential Therapy Group, STG; Monotherapy Group, MG;TG, Triglyceride;* significant change 1 month after treatment;** significant change 3 months after treatment; *** significant change 6 months after treatment;**** significant change 12 months after treatment.

表 3 不同治疗条件患者治疗前后 IVUS 变量对比

Table 3 Comparison of IVUS variables with different treatment conditions between before and after treatment

	Sequential Therapy Group	Monotherapy Group	t	P
Minimum Lumen Area (mm^2) **				
Prior treatment	7.23± 2.49	8.66± 3.77	-1.593	0.118
12 months after treatment	7.44± 2.62	8.71± 3.95	-1.357	0.182
External Elastic Membrane Area (mm^2)*				
Prior treatment	23.83± 12.08	27.22± 14.19	-0.914	0.365
12 months after treatment	15.54± 6.19	19.81± 9.55	-1.889	0.065
Plaque Burden(%)*				
Prior treatment	66.33± 9.81	66.21± 9.83	0.044	0.965
12 months after treatment	50.66± 7.01	55.34± 9.23	-2.028	0.048
Plaque Volume(mm^3)*				
Prior treatment	10.58± 5.33	14.08± 8.96	-1.704	0.096
12 months after treatment	7.91± 6.40	12.94± 9.09	-2.278	0.027
Plaque Volume Change	-2.68± 2.25	-1.14± 1.99	2.579	0.013
Percentage of Plaque Volume Change(%)	-34.60± 30.37	-11.73± 20.71	3.152	0.003

Note: Annotation:*There was significant difference before and after treatment in the group. **There was no significant difference before and after treatment in the group. -, decrease.

2.4 斑块消退影响因素

以斑块容积减少百分比＞5%为有意义斑块消退[9],进行二分类 logistic 回归分析提示 LDL-C 降低、序贯治疗与斑块消退正相关,是冠脉斑块消退的重要预测因素(详见表 4)。

表 4 影响斑块消退因素的二分类 logistic 回归

Table 4 Bivariate Logistic regression of plaque regression factors

Factors	B	S.E	Wald	P	OR	95% confidence interval
LDL-C Change	1.847	0.843	4.8	0.028	5.811	0.976-37.883
Sequential Therapy	1.565	0.604	6.719	0.010	4.781	1.465-15.608

3 讨论

LDL-C 升高是冠状动脉粥样硬化始动和维持的基本因素,其进入血管内皮形成氧化型 LDL 并被巨噬细胞吞噬形成泡沫细胞,最终构成脂质核心,是目前冠状动脉粥样硬化的主要危险评估指标之一[4,5]。阿托伐他汀是高效降脂药,通过减少合成和增加吸收,降低 LDL-C。既往 IVUS 研究发现,他汀治疗减轻斑块体积,促进斑块消退,延缓动脉粥样硬化,是目前动脉粥样硬化疾病治疗金标准之一[10-12]。

本研究拟探讨短期中等剂量序贯长期低剂量阿托伐他汀的降脂效应和斑块消退效应。他汀治疗阻滞或减轻冠心病斑块进展,尤其是高剂量、长期他汀治疗已得到国外多项研究证实,高剂量他汀治疗 6 月后斑块消退益处持续至 12 月；且与低剂量相比,高剂量导致早期斑块消退,即使 LDL-C≤ 70 mg/dL 的 ACS 患者,高剂量他汀治疗 6 月后依然存在斑块消退[12,13]。美国指南推荐高强度他汀用于冠状动脉粥样硬化二级预防,而忽视基础 LDL-C 水平；然而国人与西方人不同，基线胆固醇水平低,对他汀类药物敏感,特别是对于基线低水平患者主张小剂量开始[14]。

本研究结果再一次证明他汀药物的剂 - 效依赖关系,中等

剂量序贯治疗组降脂效应全面优于低剂量单一治疗组,降脂效应出现早,主要表现为 LDL-C 下降。IVUS 数据显示治疗前后,两组患者管腔面积无明显改变,但外弹力膜面积、斑块负荷及斑块体积减少,进而改变了血管重构,且序贯治疗组优势明显。Logistic 回归显示 LDL-C 降低和序贯治疗、斑块消退正相关,而与基线 LDL-C 无关。研究结果符合 Meta 分析及临床研究文献报道,斑块容积下降与 LDL-C 水平下降相关,他汀治疗导致斑块消退依赖于 LDL-C 水平降低[11,12,15,16,17]。本研究结果提示合并 LDL-C 基线低水平的 ACS 患者依然能够从不同强度序贯治疗中得到更多临床获益。目前各类指南提示将 ACS 患者 LDL-C 控制于≤ 70 mg/dL 水平，因此基于目标 - 治疗策略而言,基线低水平患者他汀治疗强度不是一个主要问题,然而本研究提示基线低水平者依然从序贯治疗中获得更强斑块消退效应,进而可能表现出更多临床获益。目前研究亦证实减缓斑块进展的关键因素可能是强化降脂治疗的持续时间,提示保障安全状况下尽可能延长强化治疗时限是一个优选方案,因此基于个体预计净效益治疗即个体化治疗策略可能比仅基于指南推荐目标 - 治疗 LDL-C 达标策略，在预防心血管事件更有意义[12]。因此个体化治疗是目标 - 意向治疗的重要补充,亦或不是一种行之有效的替代策略。

短期中等强度序贯低强度阿托伐他汀治疗 ACS 合并 LDL-C 基线低水平者降脂效应持续至降低治疗强度后 9 个月，且斑块消退更显著,主要得益于 LDL-C 早期降低。中等强度他汀治疗更易产生早期斑块消退,特别是在 ACS 患者,也可能在于中等强度他汀独立于降脂作用以外的多效性，包括免疫调节、平滑肌细胞迁移增值抑制等,其益处显现需要几个月时间，但是目前无斑块消退演化的最佳时间[16]。阿托伐他汀具有剂量依赖性的多效性,但最大、最快速多效性依然不清楚[18]。研究结束仅 3 人出现他汀治疗相关并发症,肌肉酸痛最常见,复查肌酶未见明显升高。序贯治疗组 12 月复查血脂接近 50 mg/dL 使人不无担忧，但有研究证实 LDL-C≤ 50 mg/dL 患者依然可以从他汀治疗中获益,未见严重不良反应[12,13,16]。且目前多部指南对 LDL-C≥ 70 mg/dL 患者的降脂治疗除接受他汀治疗外,亦推荐接受额外的降脂治疗,并不在单纯追求治疗目标值而强调最大耐受剂量，不无反证 LDL-C 低水平患者他汀治疗的安全性及必要性[19,20]。

综上所述,对于 ACS 合并 LDL-C 基线低水平患者短期中等强度序贯低强度阿托伐他汀长期治疗较初始低强度阿托伐他汀长期具有更强斑块消退效应。本研究为单中心、小样本的 ACS 合并 LDL-C 基线低水平斑块消退 IVUS 评估，罪犯血管的非罪犯斑块消退可能不能代表全部冠脉斑块的自然病史,并且支架植入的机械干预也可能改变研究斑块的进展或消退,因此需谨慎解释研究结果。

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