Lp-PLA2-冠心病的生物标志物

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主要内容

1.Lp-PLA2的基本介绍、作用机制和特异性

2.Lp-PLA2致动脉粥样硬化的机理

3.Lp-PLA2与冠心病的相关性

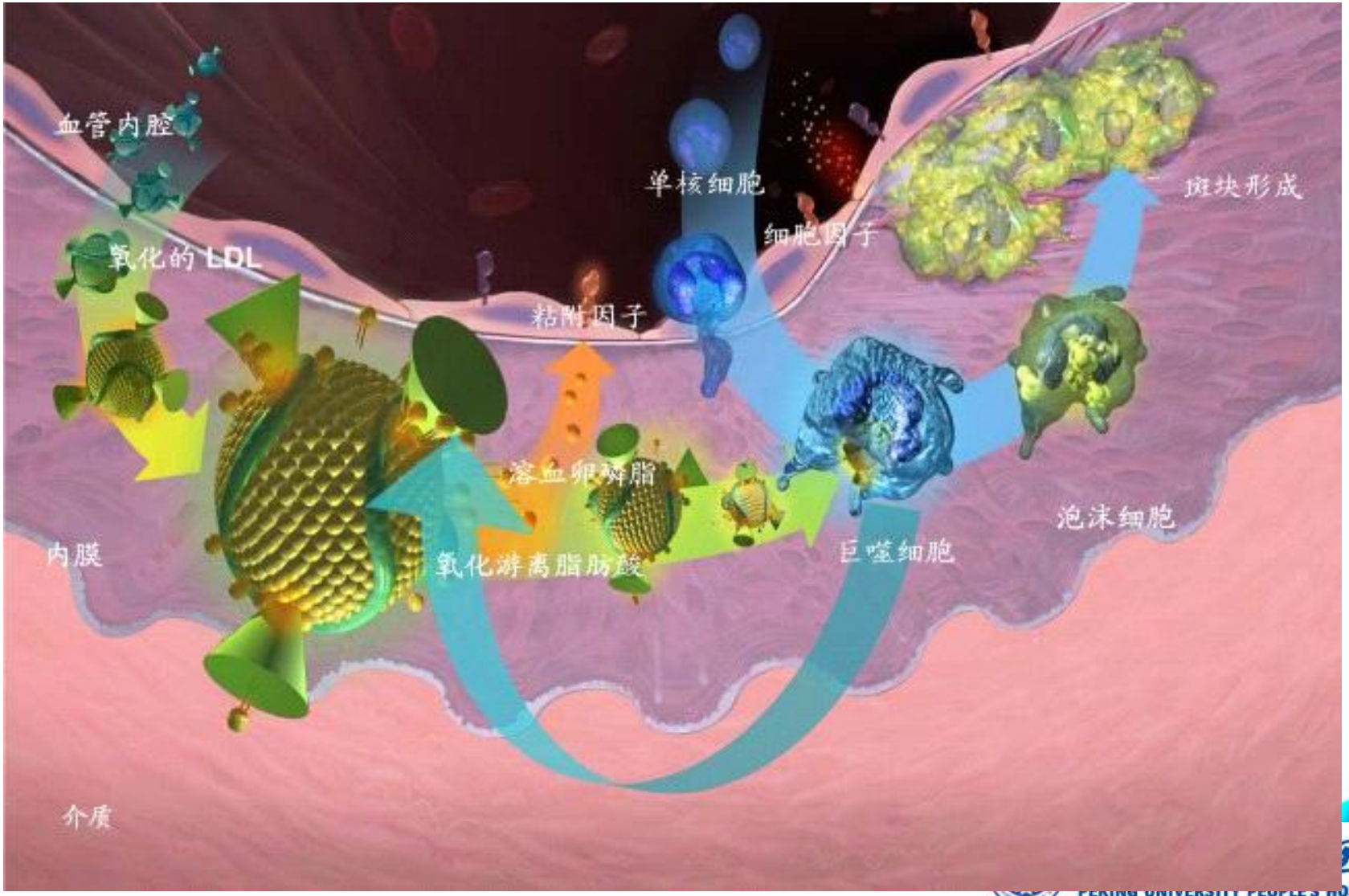
4.Lp-PLA2与降脂药物相关性

5.Lp-PLA2的抑制剂-Darapladib

Lp-PLA2的基本介绍

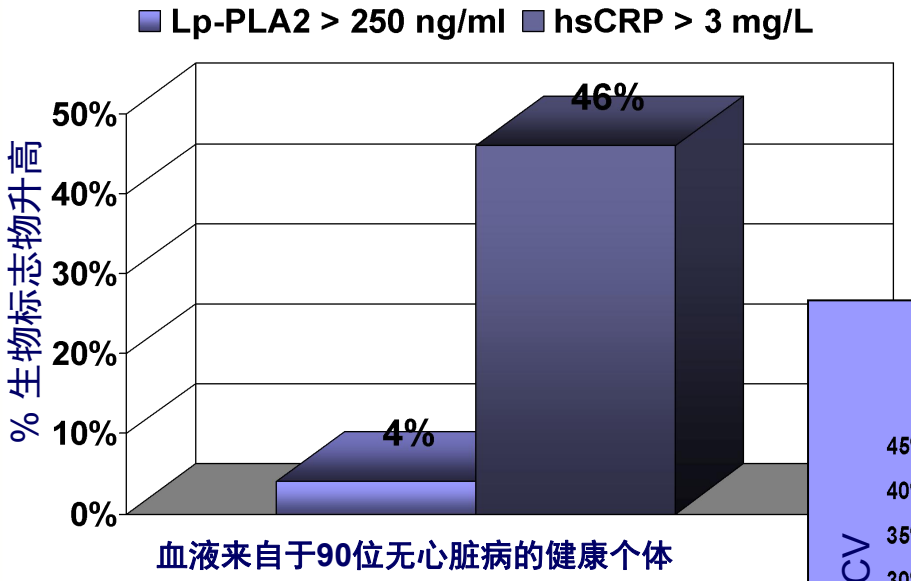
- 同义词:
  - **Lp-PLA$_2$**
  - **PAF-AH** (血小板激活因子乙酰水解酶)
- 由动脉粥样硬化斑块中的炎症细胞表达
- 主要由巨噬细胞/单核细胞，T细胞和肥大细胞生成
- 与LDL颗粒中载脂蛋白B的负电荷区域结合在循环系统中运输

Lp-PLA2作用机制


血管内腔
单核细胞
斑块形成
细胞因子
氧化的LDL
粘附因子
溶血卵磷脂
泡沫细胞
内膜
氧化游离脂肪酸
巨噬细胞
介质

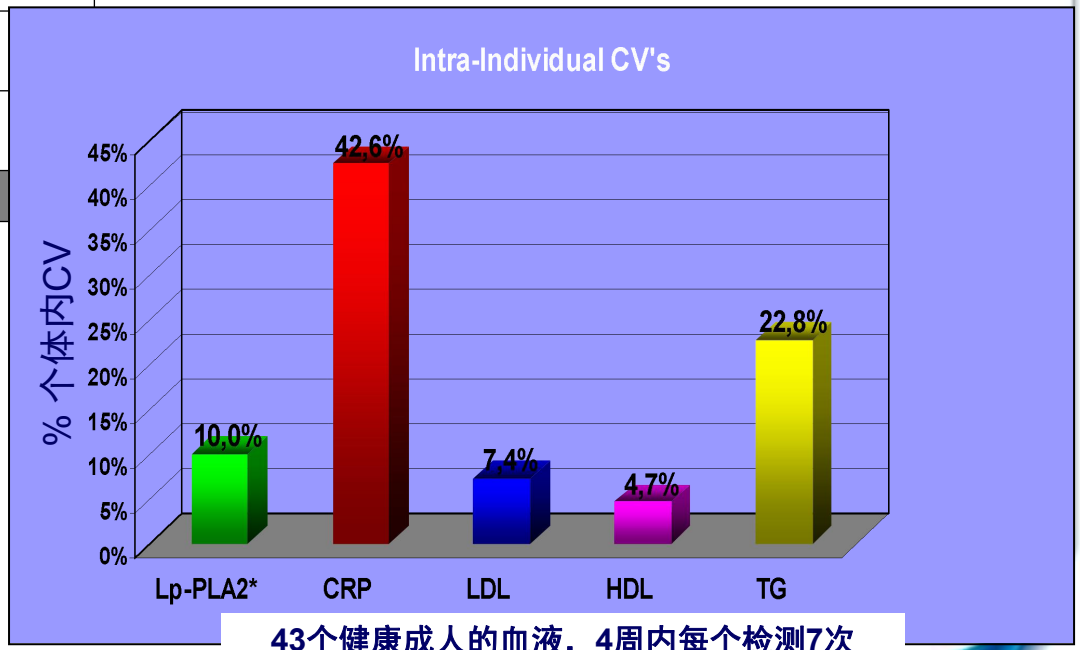
Lp-PLA2的特异性

健康个体的Lp-PLA$_2$ 升高不明显



血液来自于90位无心脏病的健康个体

Lp-PLA$_2$生物变异性低



43个健康成人的血液，4周内每个检测7次

Wolfert RL et al. (2004), *Circulation*.

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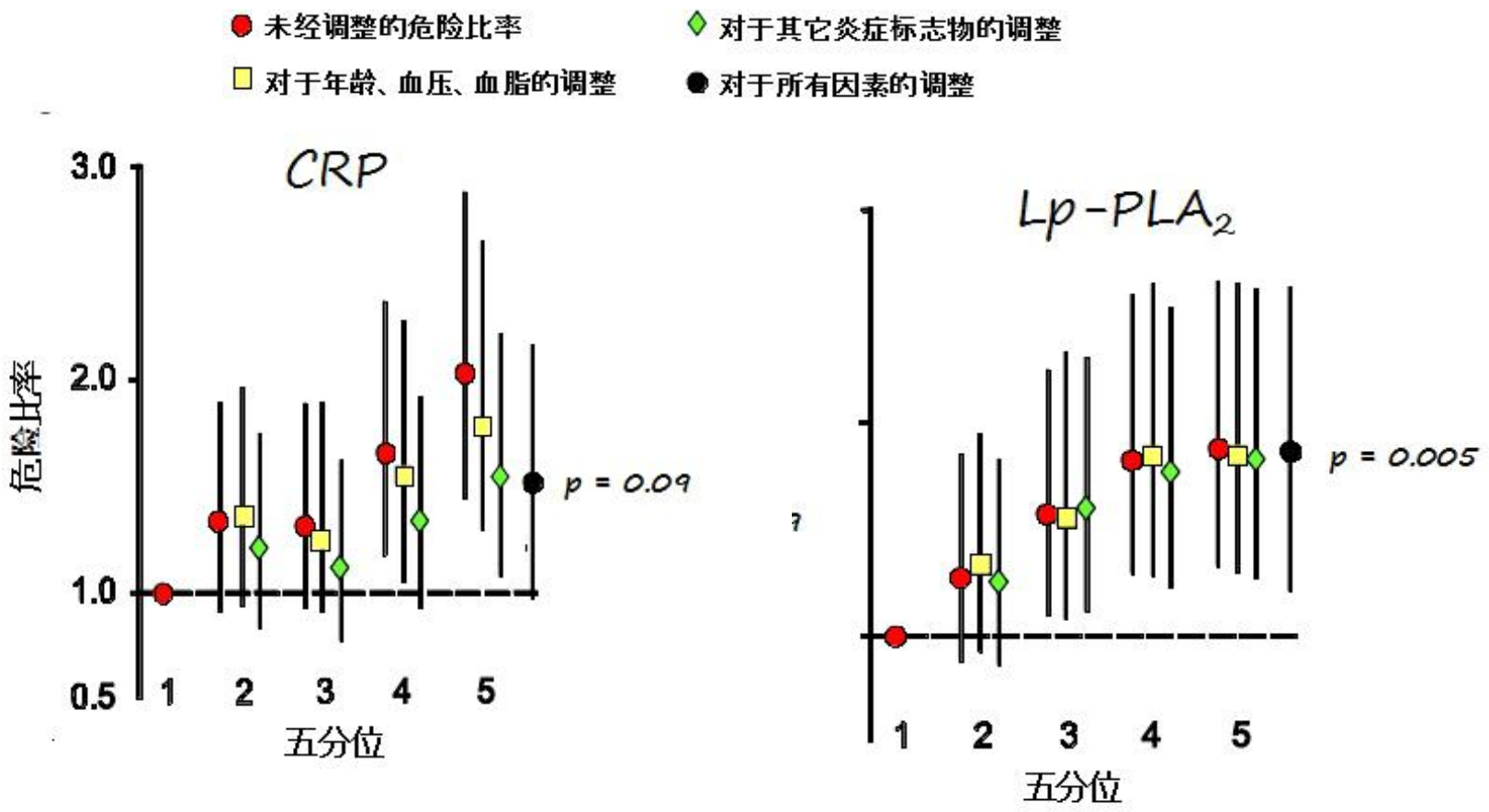
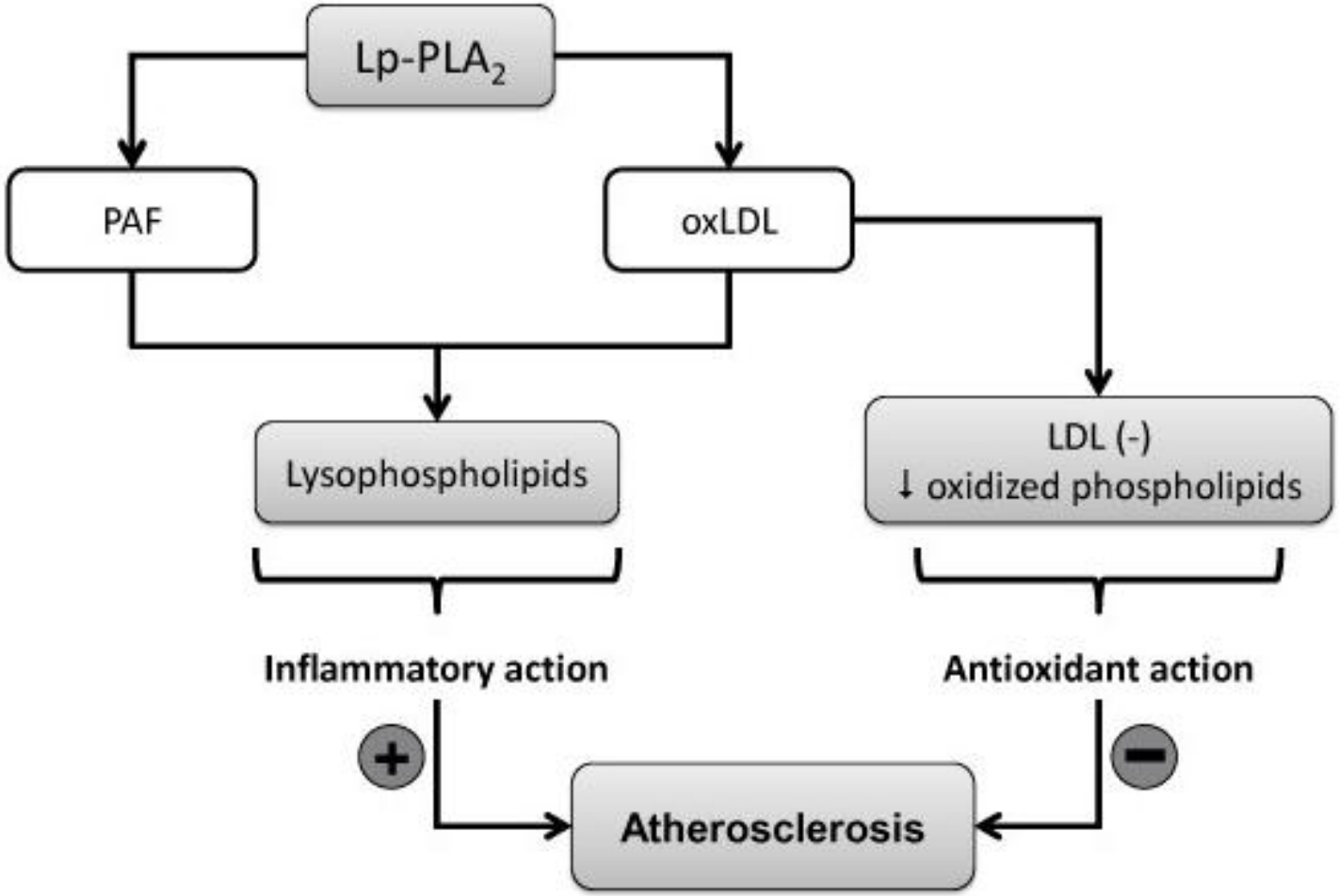
Lp-PLA2的特异性



Lp-PLA$_2$的价值并没有被多变量调整而削弱

Packard CJ, et al. *N Engl J Med* 2000.

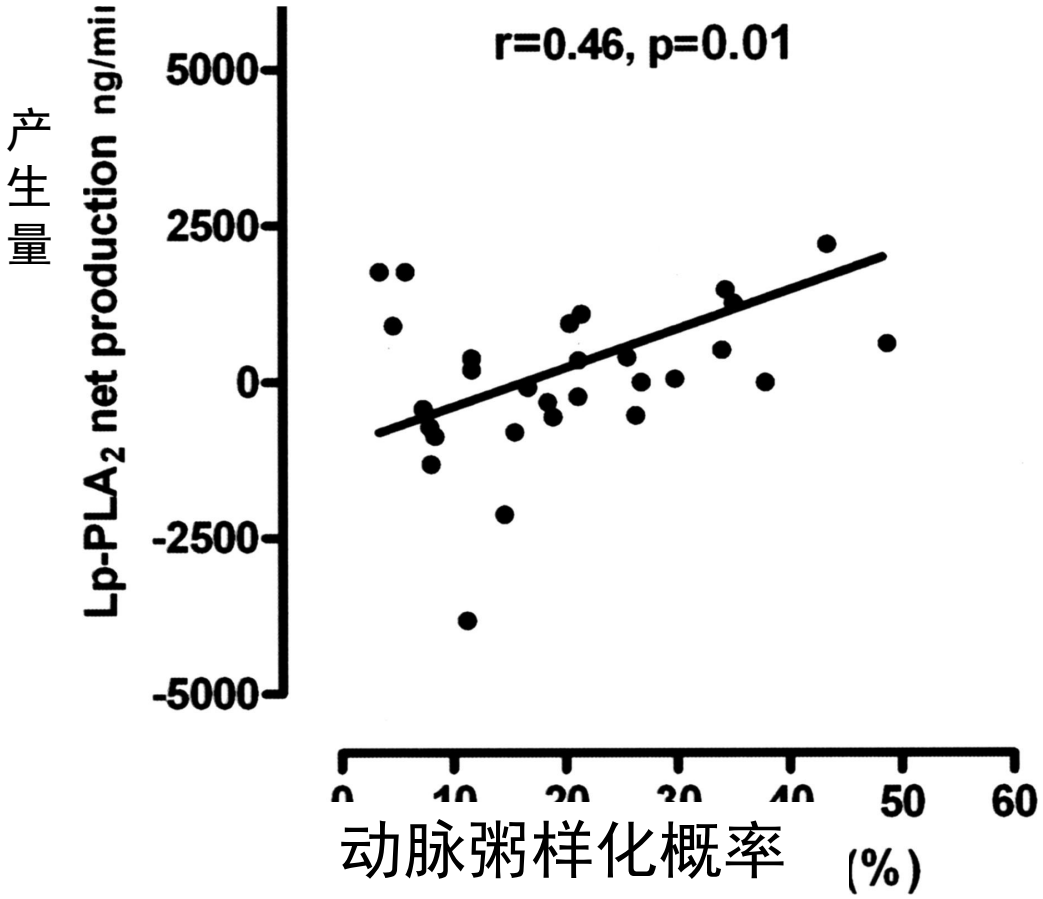
Lp-PLA2致动脉粥样硬化的作用机理



Antioxidant and inflammatory aspects of lipoprotein-associated phospholipase A2 (Lp-PLA2): 2011

Lp-PLA2与冠心病的相关性

Lp-PLA2 产生量和动脉粥样化的相关性



American Heart Association
Learn and Live

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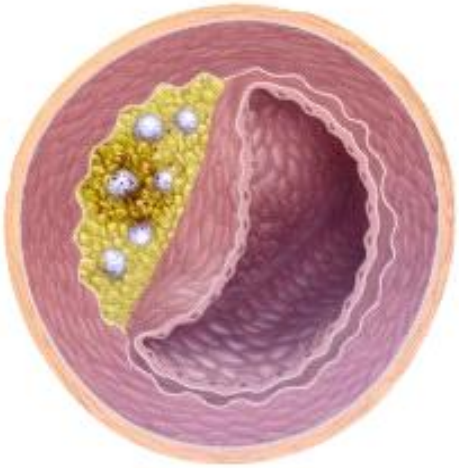
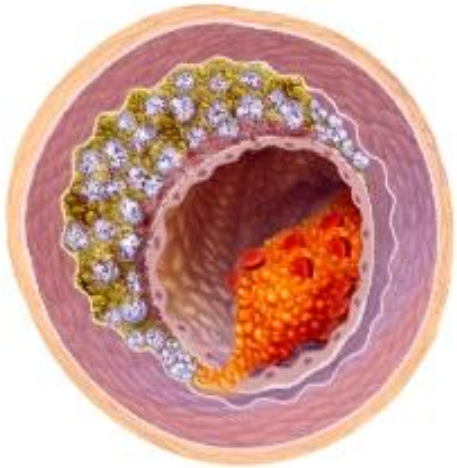
Lp-PLA2与冠心病的相关性

- Lp-PLA2的水平随着冠脉斑块的变化而变化，即动脉粥样硬化斑块恢复时，Lp-PLA2水平降低。



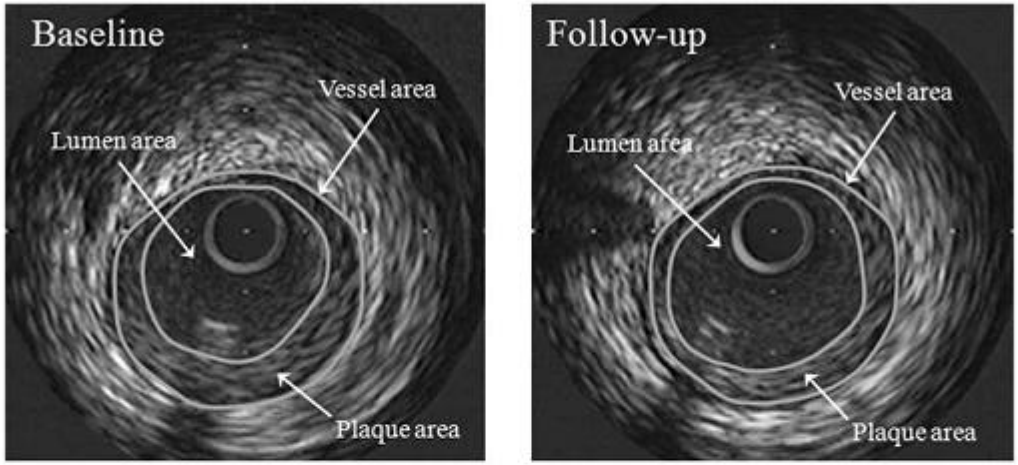
稳定粥样斑块

$Lp\text{-}PLA_2$ 含量低



不稳定粥样斑块

$Lp\text{-}PLA_2$ 含量高



	Baseline	Follow up
Plaque volume (mm^3)	100.1	89.2
Lp-LPA2 (IU/L)	502	237
LDL-C (mg/dL)	118.1	53.2
HDL-C (mg/dL)	48.1	47.8
LDL-C / HDL-C ratio	2.46	1.11

Fig. 1. Example of baseline and 6-month follow-up IVUS images and biomarkers. Eccentric plaque is observed at non-PCI proximal site in left anterior descending artery. Lumen is significantly enlarged whereas plaque and circulating Lp-PLA2 levels are reduced in patients treated with statins for six months.

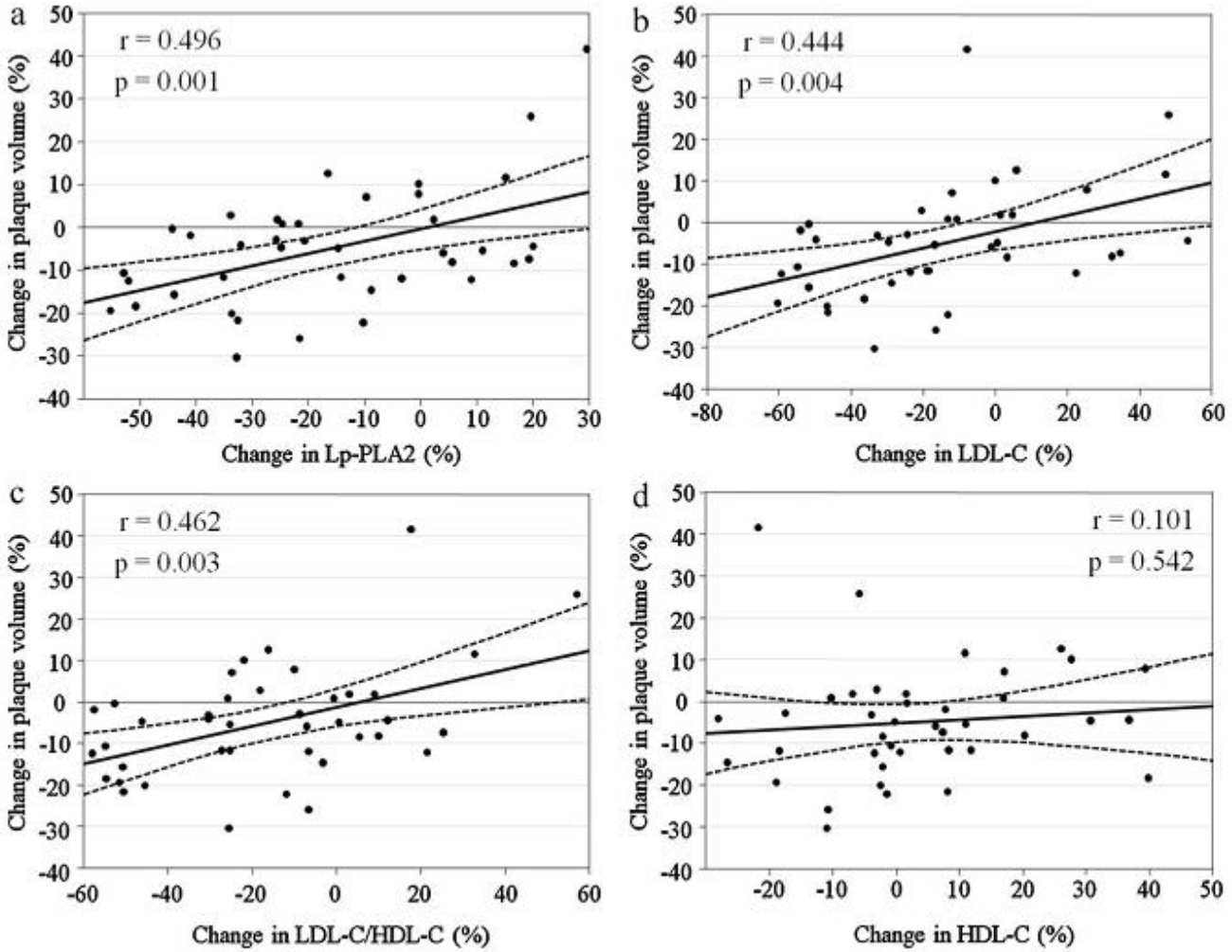


Fig. 2. Correlation between % change in plaque volume (PV) and in levels of various biomarkers in patients with ACS. Correlations were significant between % change in PV and levels of Lp-PLA2 (A) and LDL-C (B) and % change in LDL-C/HDL-C ratio (C), but not between % change in PV and HDL-C levels (D).

Lp-PLA2与降脂药物相关性

- 服用降脂药的CHD比未服用降脂药的CHD的Lp-PLA2的活性明显降低。许多他汀类药物（如阿托伐他汀、普伐他汀、氟伐他汀、瑞舒伐他汀、辛伐他汀）可以降低血浆中Lp-PLA2的水平。

- 在血浆中，Lp-PLA2 70%与LDL结合在一起，他汀类药物在降低LDL的同时，也会相应降低Lp-PLA2的水平。但是，他汀类药物在降低LDL和Lp-PLA2时，其降低的程度不同。

- 如有实验证明阿托伐他汀降低48%的LDL而降低26%的Lp-PLA2水平；氟伐他汀降低29%的LDL而降低22.8%的Lp-PLA2水平。

Lp-PLA2与降脂药物相关性

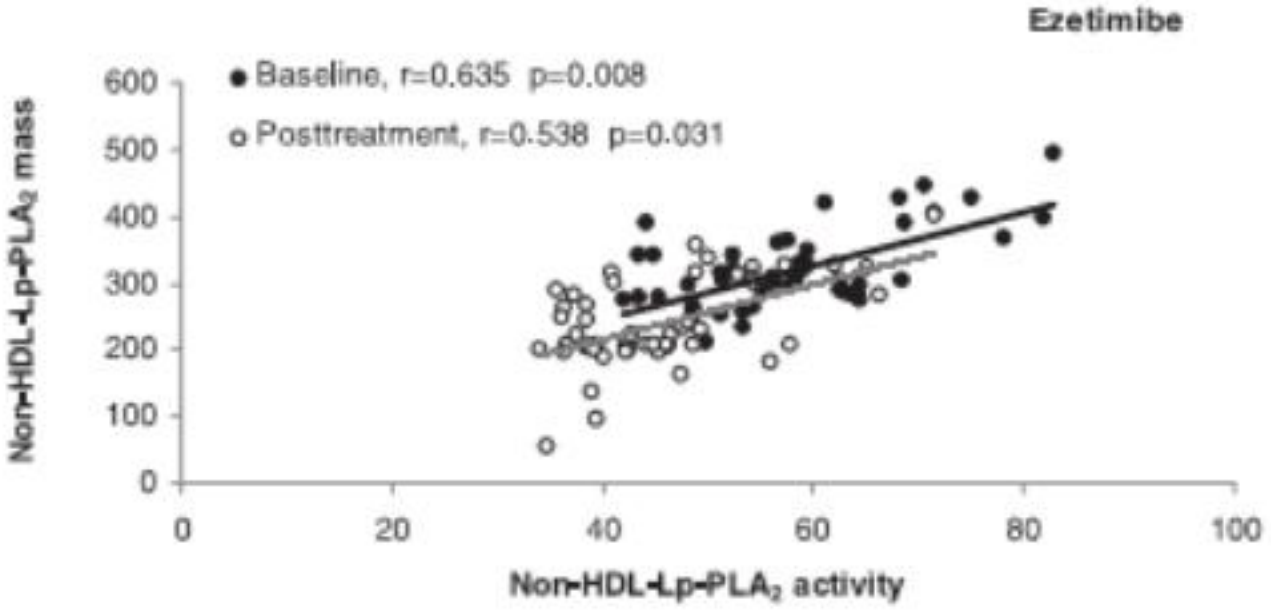
降脂药物对lp-pla2活性及浓度的影响

依替米贝　　罗素伐他汀　　非诺贝特

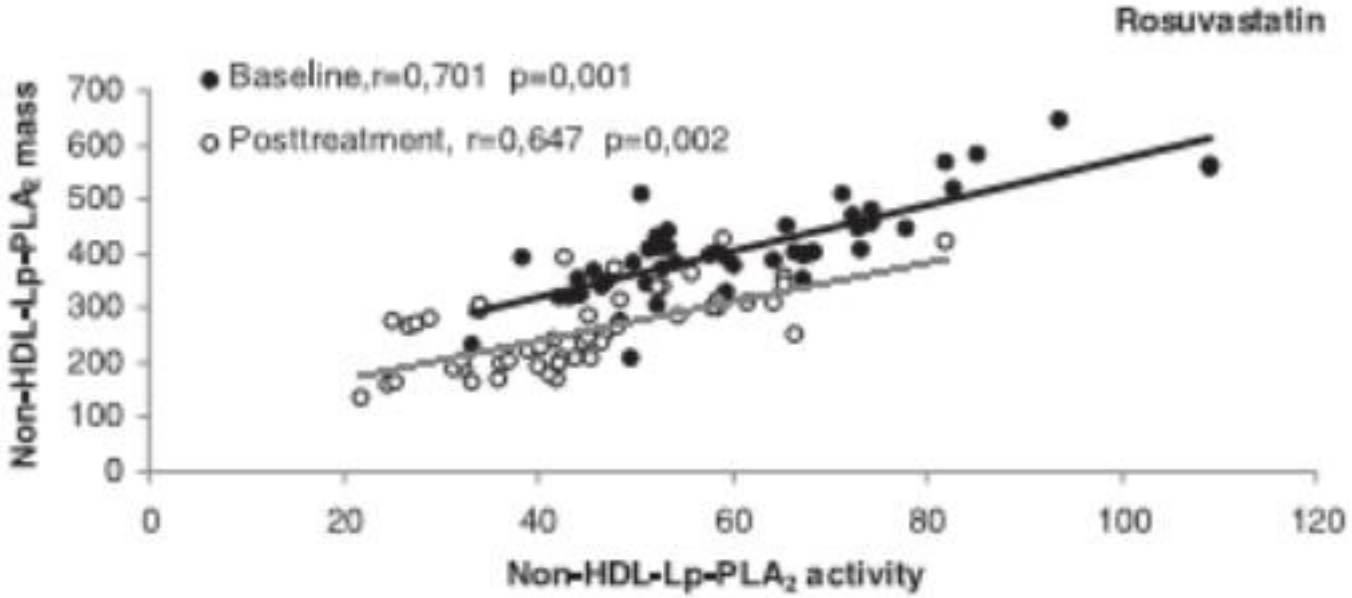
Parameter	Ezetimibe (n=50)		Rosuvastatin (n=50)		Fenofibrate (n=50)	
	Baseline	Posttreatment	Baseline	Posttreatment	Baseline	Posttreatment
Plasma Lp-PLA_2 activity, nmol/mL/min	59.7±10.5	50.7±8.9*	66.0±15.4	44.6±11.5‡	59±13.8	48.2±12.4‡
Plasma Lp-PLA_2 mass, ng/mL	397±72	325±68*	449±59	320±74‡	456±73	310.4±77.2‡
Plasma Lp-PLA_2 specific activity, nmol/ng/min	0.15±0.04	0.16±0.06	0.15±0.03	0.14±0.04	0.13±0.05	0.17±0.06†
Non-HDL-Lp-PLA_2 activity, nmol/mL/min	56.7±10.3	48.1±8.8*	63.5±21.4	42.2±16.7‡	55.7±14.0	44.9±12.8‡
Non-HDL-Lp-PLA_2 mass, ng/mL	324±71	264±54*	386±77	260±52.0‡	411±65	234±73.2‡
Non-HDL-Lp-PLA_2 specific activity, nmol/ng/min	0.17±0.05	0.18±0.08	0.16±0.04	0.16±0.05	0.13±0.06	0.17±0.08*
HDL-Lp-PLA_2 activity, nmol/mL/min	2.95±0.82	2.57±0.64*	2.41±0.72	2.40±0.61	2.10±0.80	3.23±0.74†
HDL-Lp-PLA_2 mass, ng/mL	72.7±21.5	61.1±19.8*	63.0±24.3	57.2±19.8	49.5±16.5	76.4±30.6†
HDL-Lp-PLA_2 specific activity, nmol/ng/min	0.04±0.01	0.04±0.02	0.04±0.01	0.04±0.01	0.04±0.02	0.04±0.01

Data represent the mean±SD. *$P<0.05$, †$P<0.01$, and ‡$P<0.001$ compared with baseline values.

Arterioscler Thromb Vasc Biol. October 2007



Arterioscler Thromb Vasc Biol. October 2007



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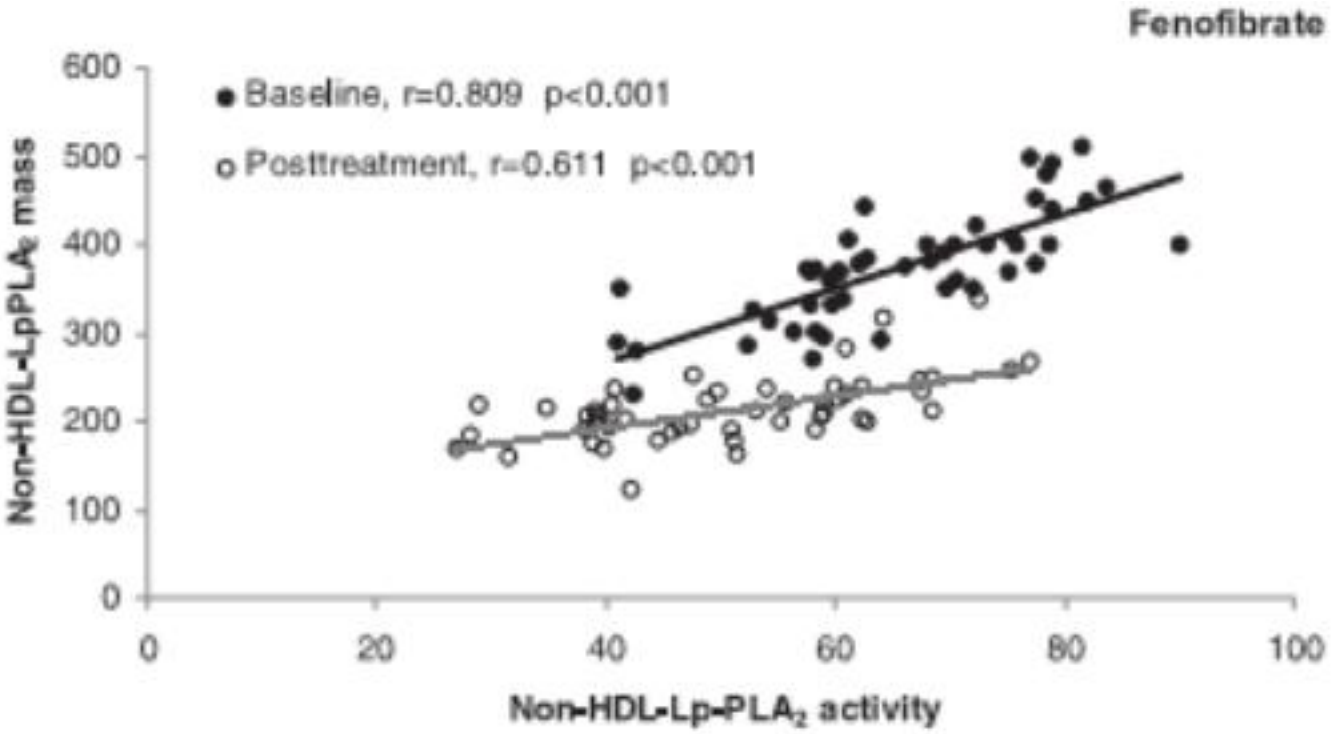

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Lp-PLA2的抑制剂-Darapladib

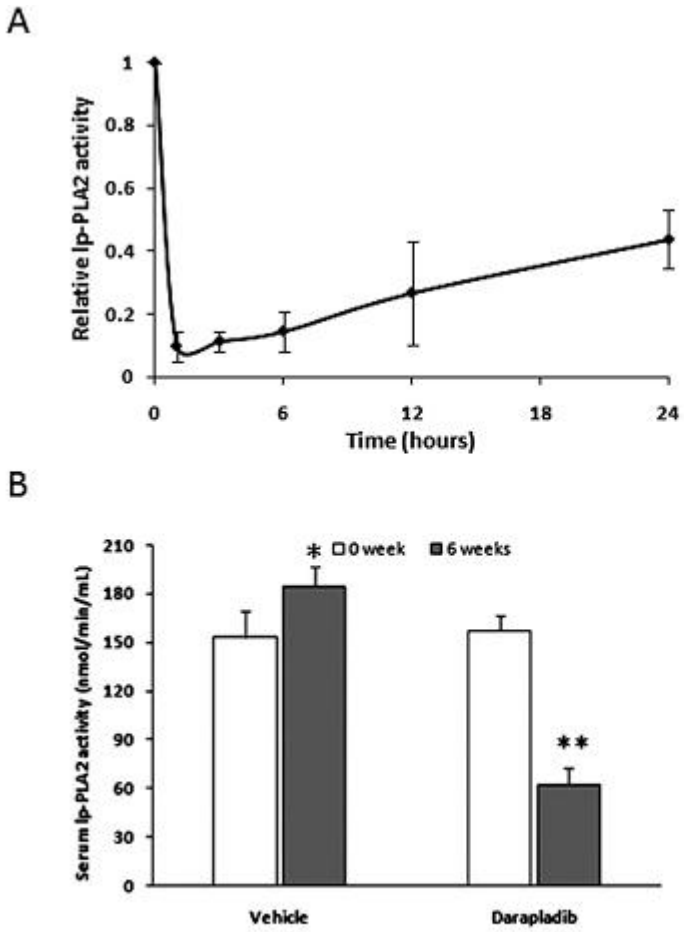

Figure 1. Darapladib significantly inhibits serum lp-PLA2 activity in ApoE-deficient mice. (A). Five apoE-deficient mice were administrated with darapladib (50 mg/kg p.o.) and serum lp-PLA2 activity before or 1, 3, 6, 12, 24 hours after administration was measured. (B). Serum lp-PLA2 activity was measured using spectrometry before and at the end of drug administration. **p<0.01 vs. vehicle at 6 weeks. and *p<0.05 vs. vehicle at 0 week.
doi:10.1371/journal.pone.0023425.g001

apoe基因缺陷小鼠体内，Darapladib可以降低Lp-PLA2的活性。

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Lp-PLA2的抑制剂-Darapladib

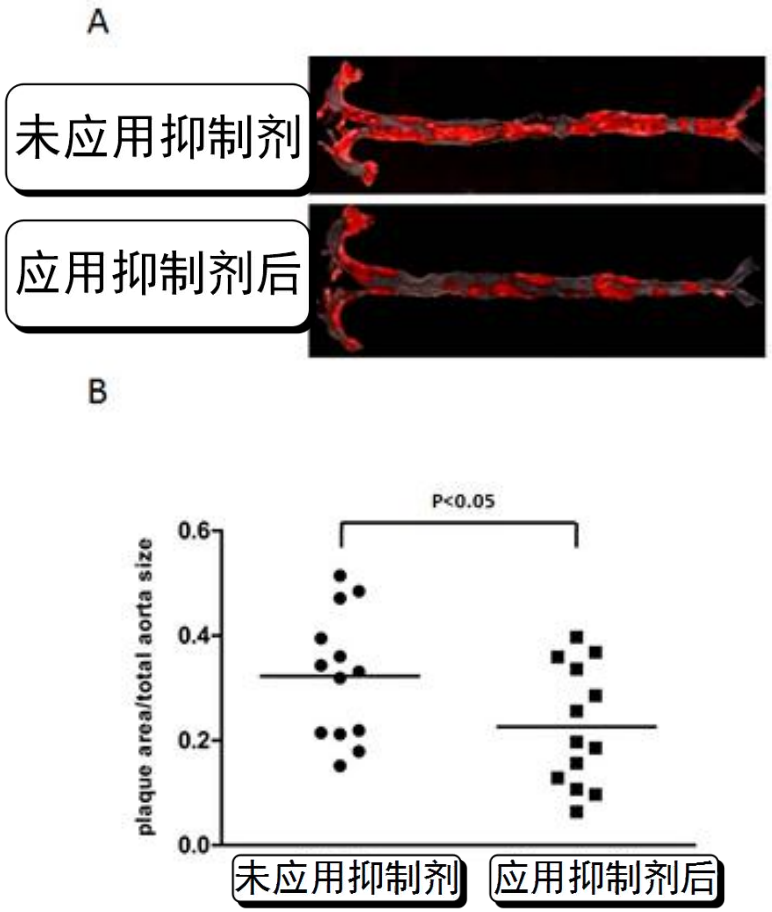

Figure 3. Inhibition of lp-PLA2 decreases the atherosclerotic area. (A). Representative en face atherosclerotic aorta preparations stained with Sudan IV. (B). Comparison of plaque sizes between the vehicle and darapladib groups (N = 13 per group). The area stained with dye is expressed as a percentage of the total surface area. The mean is depicted as a single horizontal line.
doi:10.1371/journal.pone.0023425.g003

- **在apoe基因缺陷小鼠体内，抑制剂Darapladib可以减少斑块形成。**

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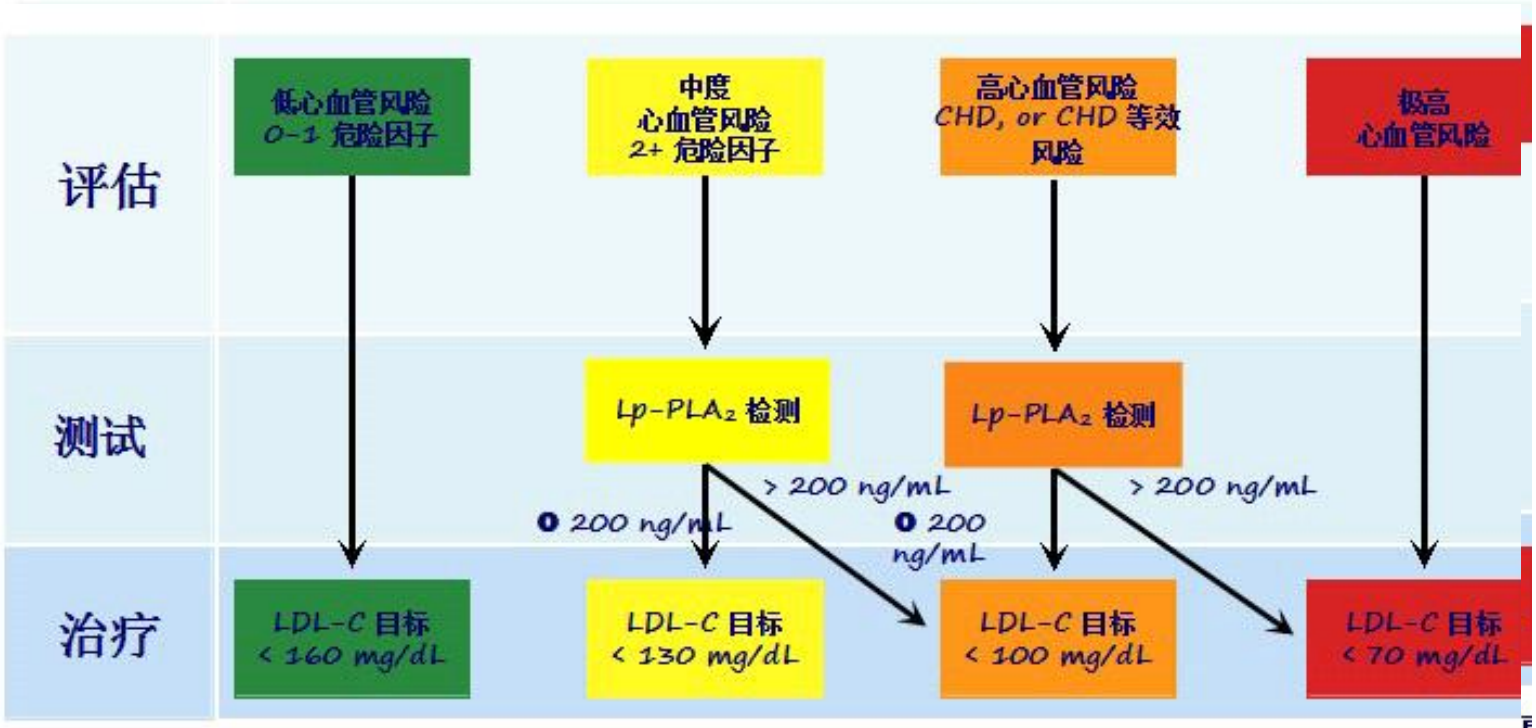
专家组一致推荐使用Lp-PLA$_2$ 检测



- 最初使用传统危险因子评估确定为中度和高度风险的个体，经PLAC 检测其心脏病和中风的风险更
- 这些个体应以更低的LDL-C水平作为治疗目标，因为已有证据表明这样可以进一步减少较高风险
心血管事件.

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Davidson MH, et al. Am J Card Suppl 2008.

谢谢！