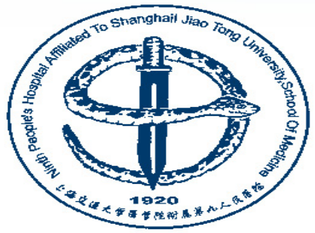
2020 AHA EVINACUMAB Study

上海交通大学医学院附属第九人民医院心内科

范虞琪



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Shanghai Ninth People's Hospital affiliated to Shanghai JiaoTong University, School of Medicine

研究背景及目的

- 高胆固醇血症患者尽管接受了最大耐受剂量下的其他降脂疗法（如他汀、PCSK9i等），若没有达到指南推荐的LDL-C目标水平，仍增加了ASCVD的风险。存在严重的高胆固醇血症的患者中，多数患有杂合子家族性高胆固醇血症（HeFH），此类患者ASCVD风险更高。

- 本研究的目的旨在评价应用Evinacumab静脉注射（IV）/皮下注射（SC）两种方式下治疗的有效性和安全性。

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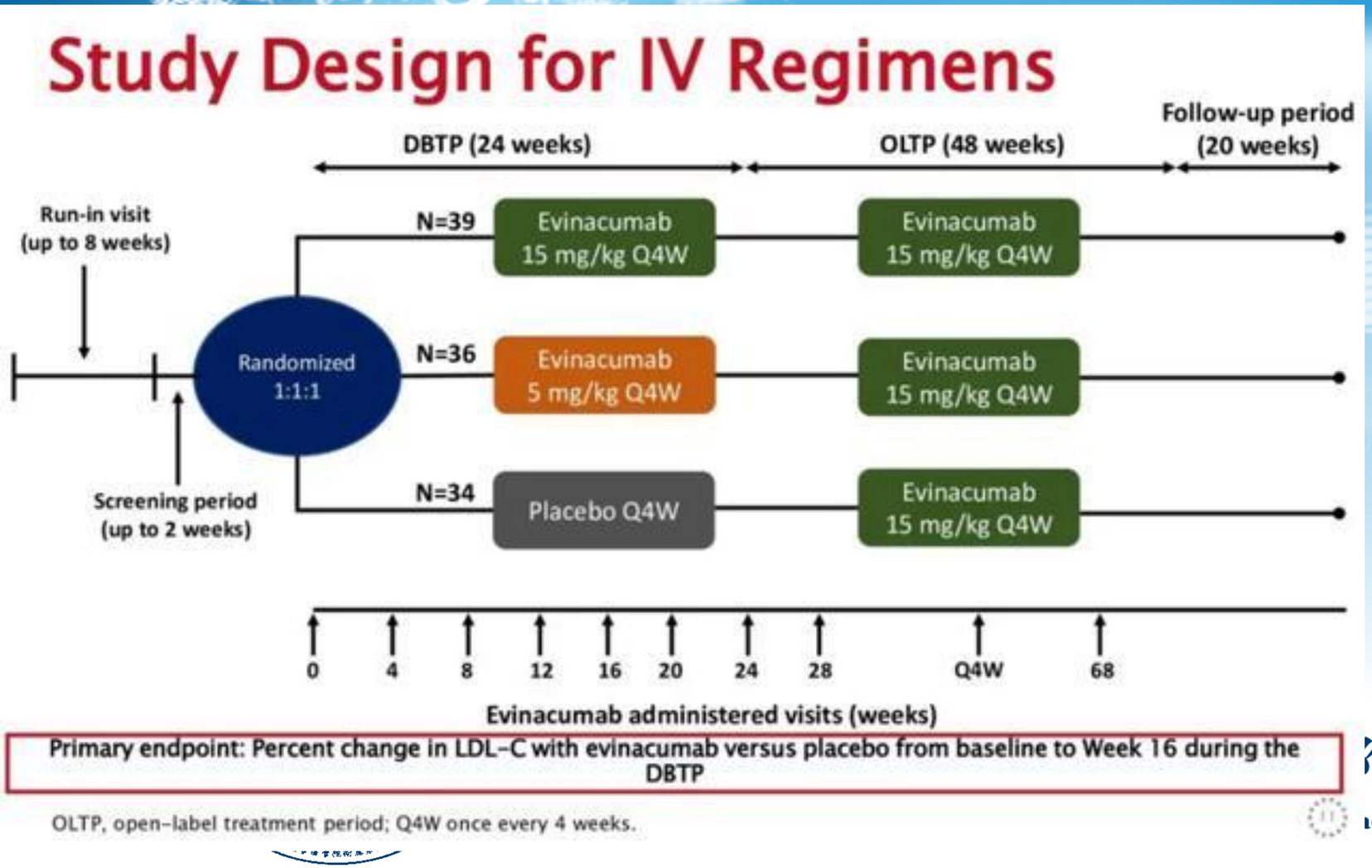
研究方法

- 本研究为随机双盲实验，

- 入组患者需满足如下条件：
  ①LDL-C≥70mg/dL且合并有ASCVD或者LDL-C≥100mg/dL不合并ASCVD的HeFH患者/非HeFH患者；
  ②所有患者需接受能耐受最大剂量下他汀（或联合依折麦布）治疗4周；
  ③接受PCSK9i治疗的患者，需预先降脂治疗至少8周。

试验设计



静脉注射方案（如下图）：共纳入109名患者，随机以1:1:1比例根据Evinacumab用量分为3组（15 mg/kg Q4W, 5 mg/kg Q4W, 安慰剂组 Q4W）。首先进行24周双盲治疗，后进行48周开放标签治疗且后续Evinacumab用量调整为15 mg/kg Q4W。

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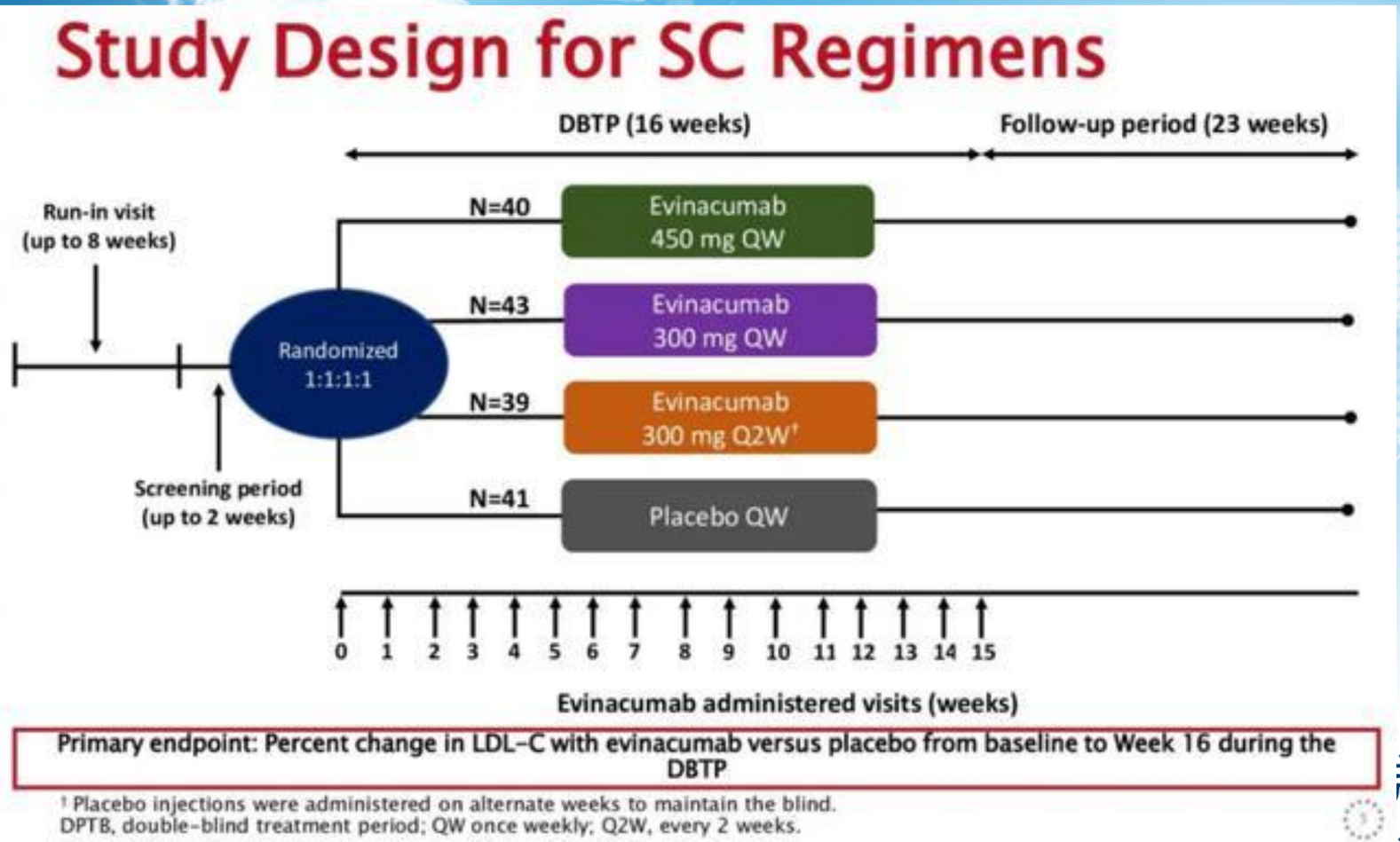
试验设计



皮下注射方案（如下图）：共纳入163名患者，随机以1:1:1:1比例根据Evinacumab用量分为4组（450mg QW; 300mg QW; 300mg Q2W; 安慰剂组 QW）。

Baseline Characteristic

	Evinacumab 15 mg/kg IV Q4W (n=38)	Evinacumab 5 mg/kg IV Q4W (n=35)	Placebo IV Q4W (n=33)	Total (N=106)
Age, years, mean (SD)	52.1 (12.1)	55.7 (9.6)	56.2 (10.9)	54.6 (11.0)
Female, n (%)	19 (50.0)	22 (62.9)	18 (54.5)	59 (55.7)
Race, white, n (%)	35 (92.1)	32 (91.4)	27 (81.8)	94 (88.7)
BMI, kg/m2, mean (SD)	29.3 (4.9)	28.8 (4.6)	28.8 (5.2)	29.0 (4.9)
HeFH	31 (81.6)	29 (82.9)	26 (78.8)	86 (81.1)
By genotyping	10 (26.3)	11 (31.4)	11 (33.3)	32 (30.2)
By clinical diagnosis	21 (55.3)	18 (51.4)	15 (45.5)	54 (50.9)
CHD, n (%)	21 (55.3)	20 (57.1)	25 (75.8)	66 (62.3)
LLT, n (%)				
Any statin	33 (86.8)	27 (77.1)	28 (84.8)	88 (83.0)
High-intensity statin†	23 (60.5)	17 (48.6)	15 (45.5)	55 (51.9)
Ezetimibe	13 (34.2)	15 (42.9)	12 (36.4)	40 (37.7)
PCSK9 inhibitor	37 (97.4)	33 (94.3)	32 (97.0)	102 (96.2)

Baseline Lipids for IV Regimens

	Evinacumab 15 mg/kg IV Q4W (n=38)	Evinacumab 5 mg/kg IV Q4W (n=35)	Placebo IV Q4W (n=33)	Total (N=106)
LDL-C mg/dL, mean (SD)	143.1 (54.4)	146.0 (61.0)	144.5 (46.6)	144.5 (54.0)
ApoB, mg/dL, mean (SD)	112.6 (32.4)	113.4 (33.8)	116.7 (27.0)	114.1 (31.1)
HDL-C, mg/dL, mean (SD)	51.5 (17.4)	58.2 (16.8)	55.4 (18.0)	54.9 (17.4)
Non-HDL-C, mg/dL, mean (SD)	169.4 (54.2)	170.6 (61.5)	176.2 (48.0)	171.9 (54.5)
Total cholesterol, mg/dL, mean (SD)	220.9 (56.8)	228.8 (60.2)	231.6 (50.4)	226.8 (55.7)
Fasting triglycerides, mg/dL, median (Q1:Q3)	126.5 (89.0:166.0)	102.0 (86.0:156.0)	147.0 (104.0:200.0)	122.0 (92.0:171.0)
Lp(a), nmol/L, median (Q1:Q3)	34.0 (15.0:157.0)	27.0 (18.0:80.0)	33.0 (16.0:154.0)	31.0 (17.0:127.0)

IV组LDL降幅

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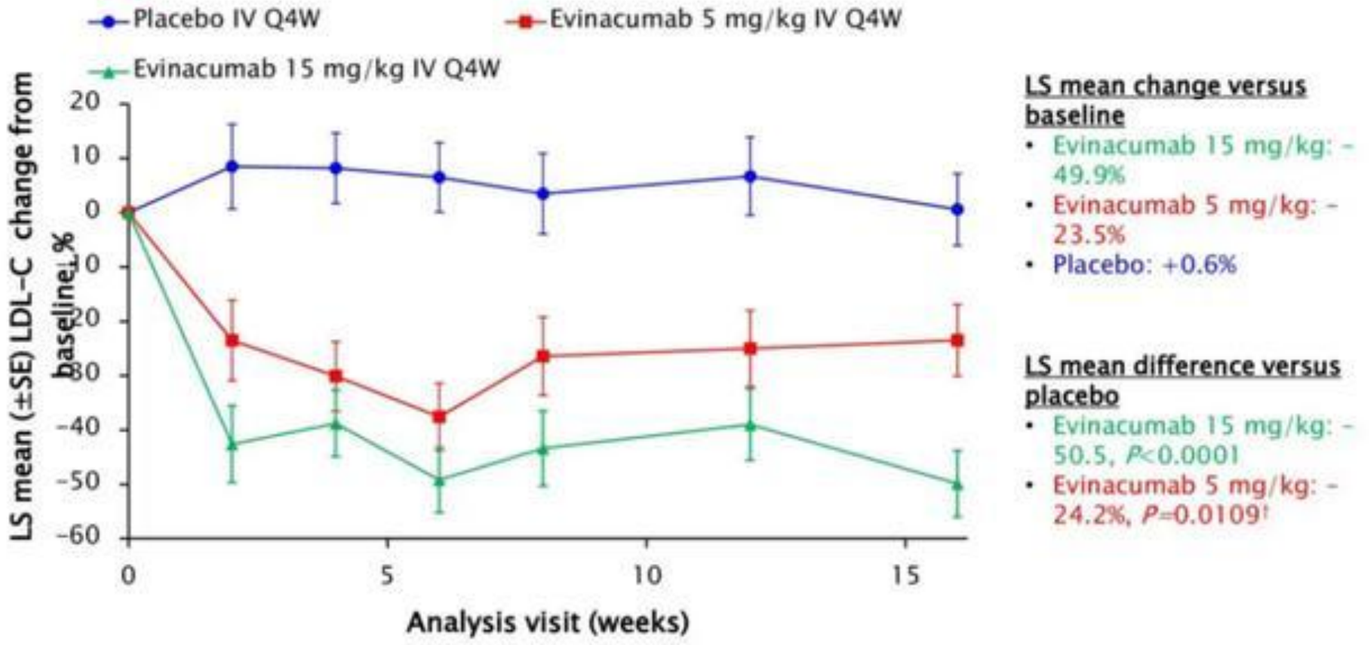
Percent Change in LDL-C with IV Regimens



静脉注射途径

- 3组患者在基线时LDL-C平均水平接近
- 患者群体以中年患者为主且女性比例略高。
- **与基线数据相比**，15 mg/kg Q4W组LDL-C水平降低了49.9%；5 mg/kg Q4W组LDL-C水平降低了23.5%。
- **与安慰剂组相比**，15 mg/kg Q4W组和5 mg/kg Q4W组LDL-C水平分别降低了50.5%、24.2%。

IV组其它血脂指标降幅

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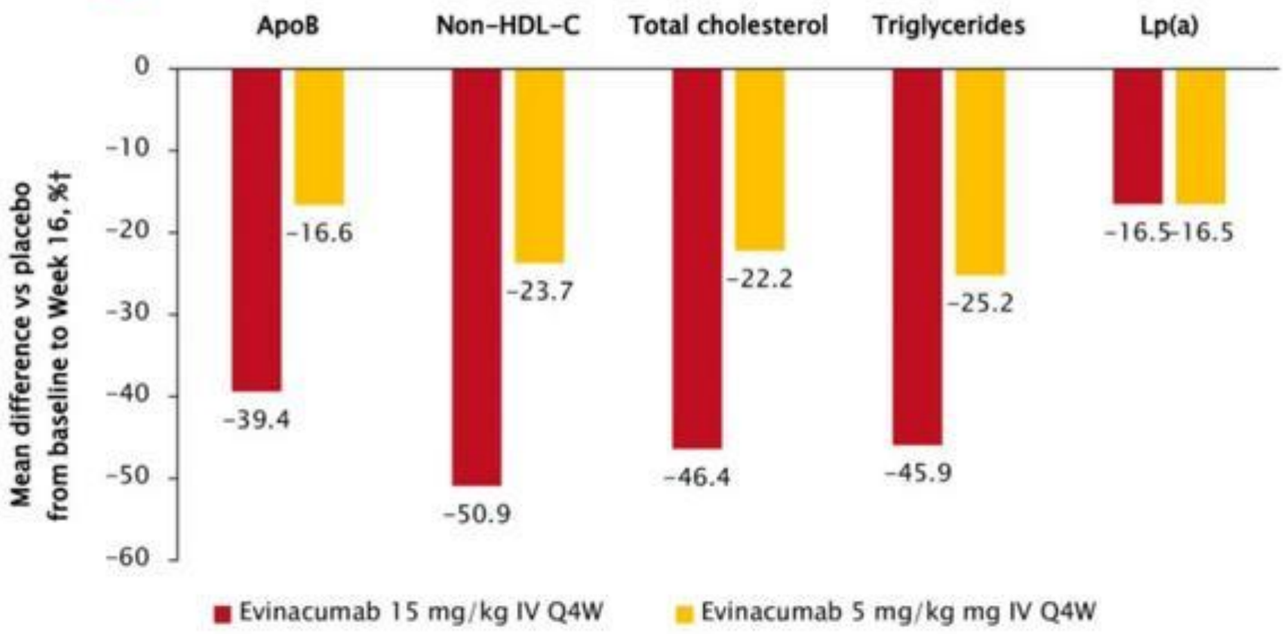
Changes in other Lipids with IV Regimens



†LS mean difference versus placebo shown for ApoB, non-HDL-C, and total cholesterol. Adjusted mean difference versus placebo shown for triglycerides and Lp(a).

对于其他血脂指标，患者在接受治疗16周后也存在不同程度的下降，且15 mg/kg Q4W组下降幅度更加明显。

IV组安全性

Safety of IV Regimens

N (%) of patients	Evinacumab 15 mg/kg IV Q4W (n=37)	Evinacumab 5 mg/kg IV Q4W (n=36)	Placebo IV Q4W (n=33)
Patients with ≥1 TEAE	31 (83.8)	27 (75.0)	23 (69.7)
Patients with ≥1 serious TEAE	6 (16.2)	2 (5.6)	1 (3.0)
Patients with ≥1 TEAE resulting in discontinuation of treatment	2 (5.4)	2 (5.6)	1 (3.0)
Patients with any TEAE resulting in death	0	0	0
TEAEs with ≥10% incidence†			
Nasopharyngitis	6 (16.2)	3 (8.3)	2 (6.1)
Headache	5 (13.5)	2 (5.6)	6 (18.2)
Myalgia	2 (5.4)	4 (11.1)	4 (12.1)
Fatigue	1 (2.7)	4 (11.1)	2 (6.1)

安全性方面，两组使用Evinacumab治疗的患者中发生的严重用药后不良事件（TEAE）分别为6例（16.2%）和2例（5.6%），两组均未发现因TEAE导致的死亡。

IC组LDL降幅

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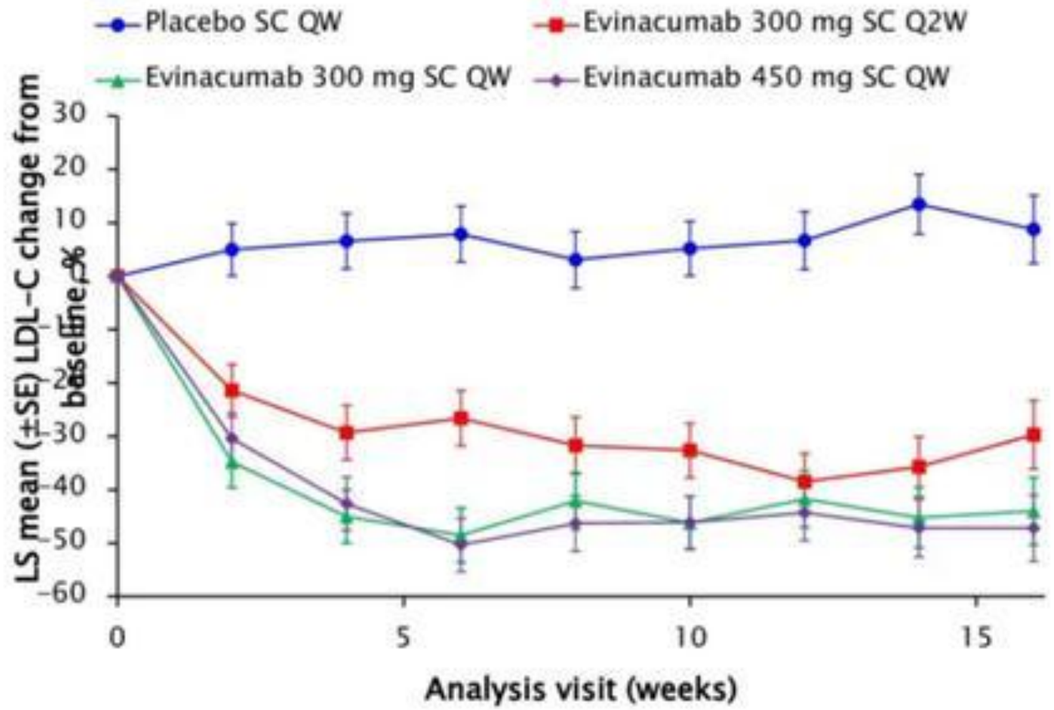
Percent Change in LDL-C with SC Regimens



LS mean change versus baseline

- Evinacumab 450 mg QW: -47.2%
- Evinacumab 300 mg QW: -44.0%
- Evinacumab 300 mg Q2W: -29.7%
- Placebo: +8.8%

LS mean difference versus placebo

- Evinacumab 450 mg QW: -56.0%, *P*<0.0001
- Evinacumab 300 mg QW: -52.9%, *P*<0.0001
- Evinacumab 300 mg Q2W: -38.5%, *P*<0.0001

- 4组患者在基线时LDL-C平均水平接近
- 患者群体以中年患者为主且女性比例略高
- 每组中HeFH患者比例均＞70%。
- 与基线数据相比，450mg QW组LDL-C水平降低了47.2%；300mg QW组LDL-C水平降低了44%；300mg Q2W组LDL-C水平降低了29.7%。
- 与安慰剂组相比，450mg QW组LDL-C水平降低了56%；300mg QW组LDL-C水平降低了52.9%；300mg Q2W组LDL-C水平降低了38.5%。

IC组其它血指标降幅

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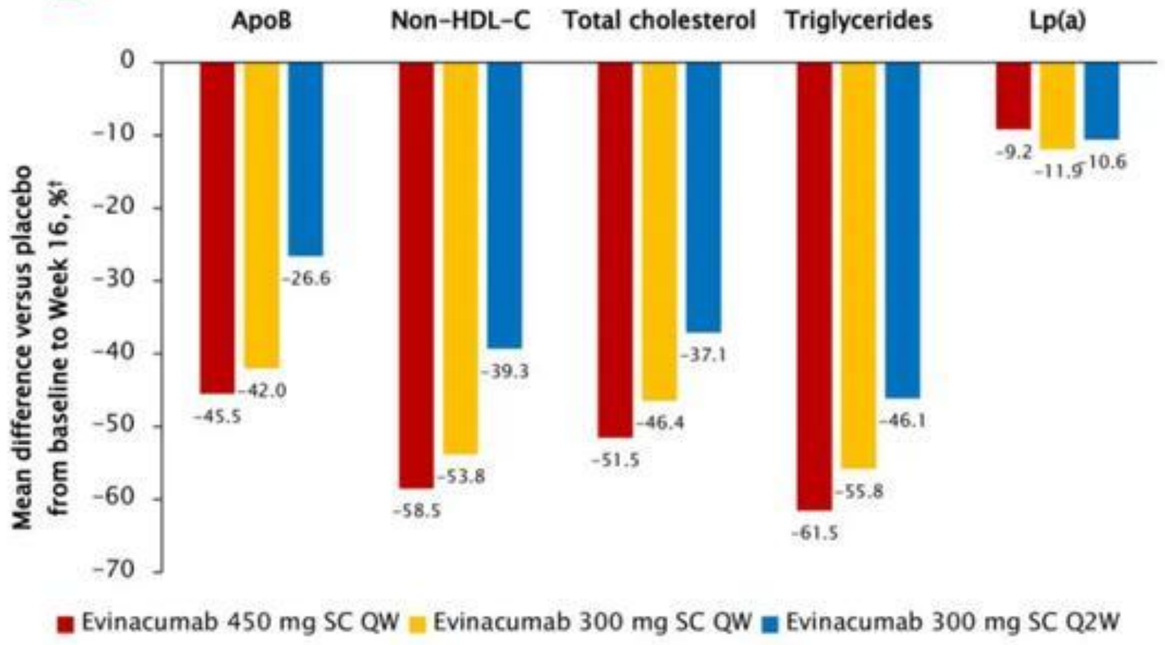
Changes in other Lipids with SC Regimens



†LS mean difference versus placebo shown for ApoB, non-HDL-C, and total cholesterol. Adjusted mean difference versus placebo shown for triglycerides and Lp(a).

- 对于其他血脂指标，患者在接受治疗16周后存在不同程度的下降，除Lp(a)在300mg QW组下降明显外，其余各指标以450mg QW组下降幅度最为显著。
- 同时研究者推测，载脂蛋白B、非HDL胆固醇、总胆固醇和甘油三酸酯的剂量或呈依赖性降低，而脂蛋白(a)呈非剂量依赖性减少。

IC组安全性研究

Safety of SC Regimens

N (%) of patients	Evinacumab 450 mg SC QW (n=40)	Evinacumab 300 mg SC QW (n=42)	Evinacumab 300 mg SC Q2W (n=39)	Placebo SC QW (n=39)
Patients with ≥1 TEAE	27 (67.5)	28 (66.7)	32 (82.1)	21 (53.8)
Patients with ≥1 serious TEAE	3 (7.5)	3 (7.1)	2 (5.1)	3 (7.7)
Patients with ≥1 TEAE resulting in discontinuation of treatment	0	0	2 (5.1)	2 (5.1)
Patients with any TEAE resulting in death	0	1 (2.4)	1 (2.6)	0
TEAEs with ≥10% incidence[†]				
Nausea	4 (10.0)	1 (2.4)	4 (10.3)	3 (7.7)
Constipation	0	0	4 (10.3)	1 (2.6)
Abdominal pain	0	0	1 (2.6)	4 (10.3)
Injection site erythema	4 (10.0)	1 (2.4)	2 (5.1)	1 (2.6)
Fatigue	4 (10.0)	1 (2.4)	0	3 (7.7)
Urinary tract infection	4 (10.0)	4 (9.5)	5 (12.8)	3 (7.7)
Nasopharyngitis	4 (10.0)	4 (9.5)	4 (10.3)	6 (15.4)
Back pain	2 (5.0)	4 (9.5)	3 (7.7)	5 (12.8)
Headache	4 (10.0)	3 (7.1)	2 (5.1)	4 (10.3)
Dizziness	1 (2.5)	2 (4.8)	1 (2.6)	5 (12.8)

[†]TEAEs occurring in ≥10% of patients in any group for each MedDRA preferred term.
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

药物安全性方面，皮下注射发生的用药后不良事件各组比例低于静脉注射，分别在300 mg QW和300 mg Q2W组各发生1例因TEAE导致的死亡

IC/IV组LDL降幅比较

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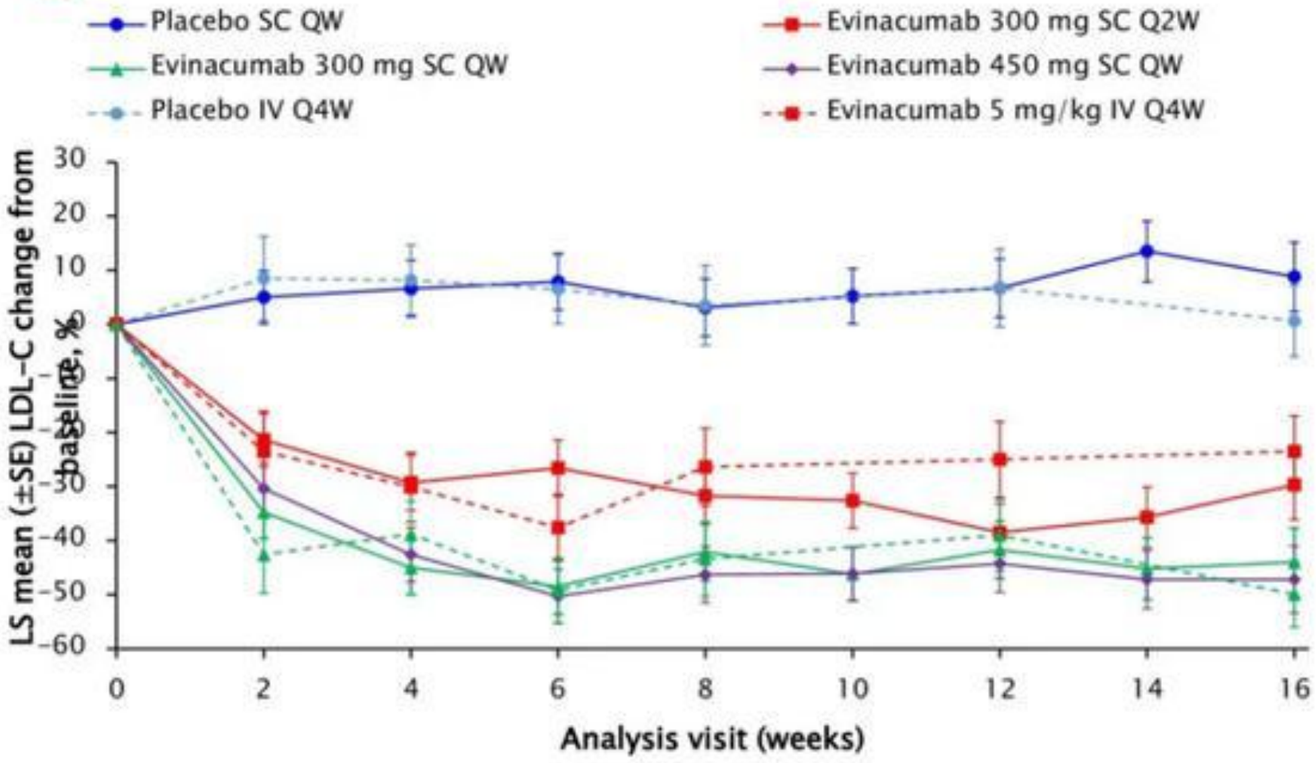
Change in LDL-C with SC and IV Regimens

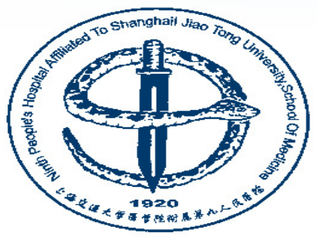


对各类用药方案集合比较可以发现，Evinacumab相较于安慰剂可明显降低LDL-C的水平，皮下注射效果或优于静脉注射。

结论

- 本研究的第2阶段结果显示，Evinacumab可降低LDL-C以及其他可导致粥样硬化斑块的脂蛋白的水平，且具有良好的耐受性。

- 对于那些接受了标准降脂治疗的难治性高胆固醇血症患者，加用Evinacumab可更好地实现指南推荐的LDL-C目标水平，可降低心血管事件风险及全因死亡率。



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