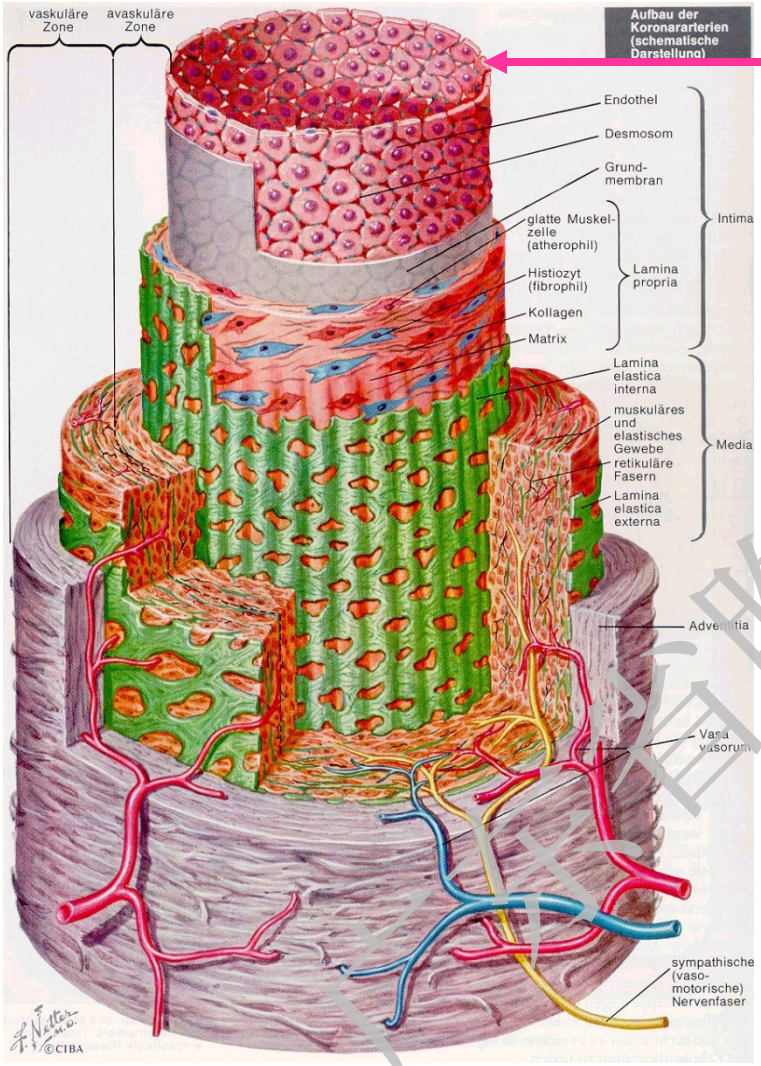
不同类型动脉粥样硬化的影像学特征和他汀治疗策略

刘金来

中山大学附属第三医院心内科

目 录

动脉结构示意图



动脉解剖图

内皮细胞
Endothelial Cell

血液

组织

天然屏障

分泌器官

内分泌

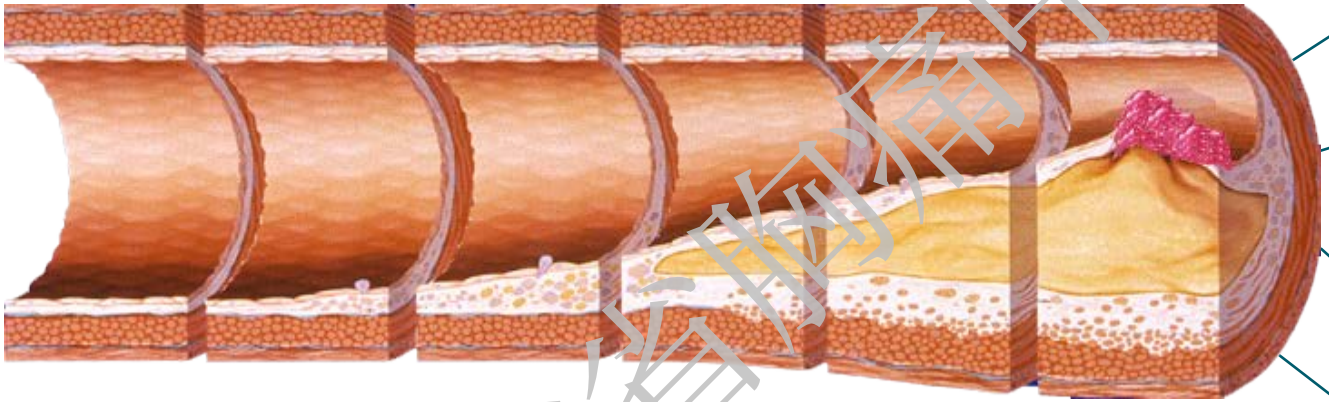
旁分泌

产生和分泌生物活性物质

调控血管舒缩、生长

斑块是动脉粥样硬化进展的重要表现

泡沫细胞[1] | 脂质条纹[1] | 内膜损伤[1] | 动脉粥样硬化形成[1] | 纤维斑块[1] | 复杂病变/斑块破裂[1]

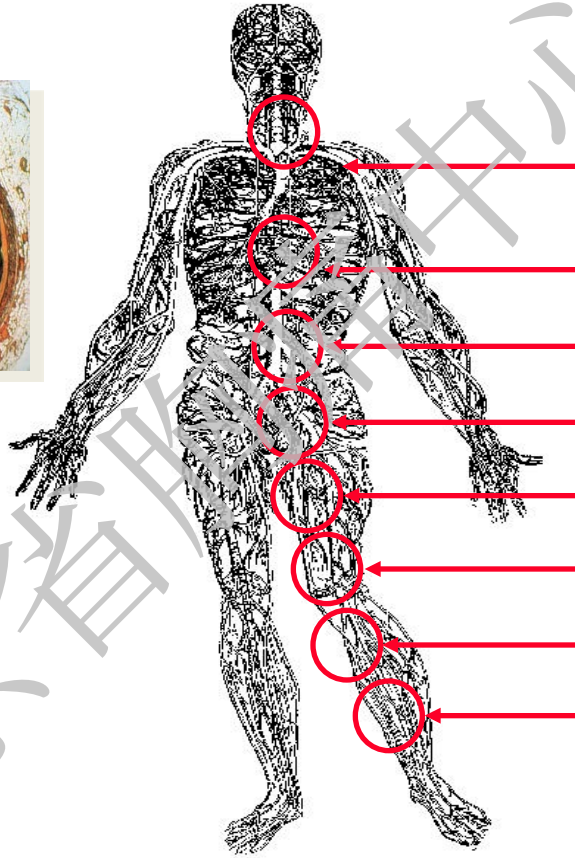


- 卒中[2]
- TIA[2]
- MI[2]
- 心绞痛[2]
- 肾动脉粥样硬化性狭窄[2]
- PAD[2]

1. Pepine CJ. Am J Cardiol. 1998;82:23S-27S
2. Stone NJ, et al. J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2889-934

全身动脉血管床

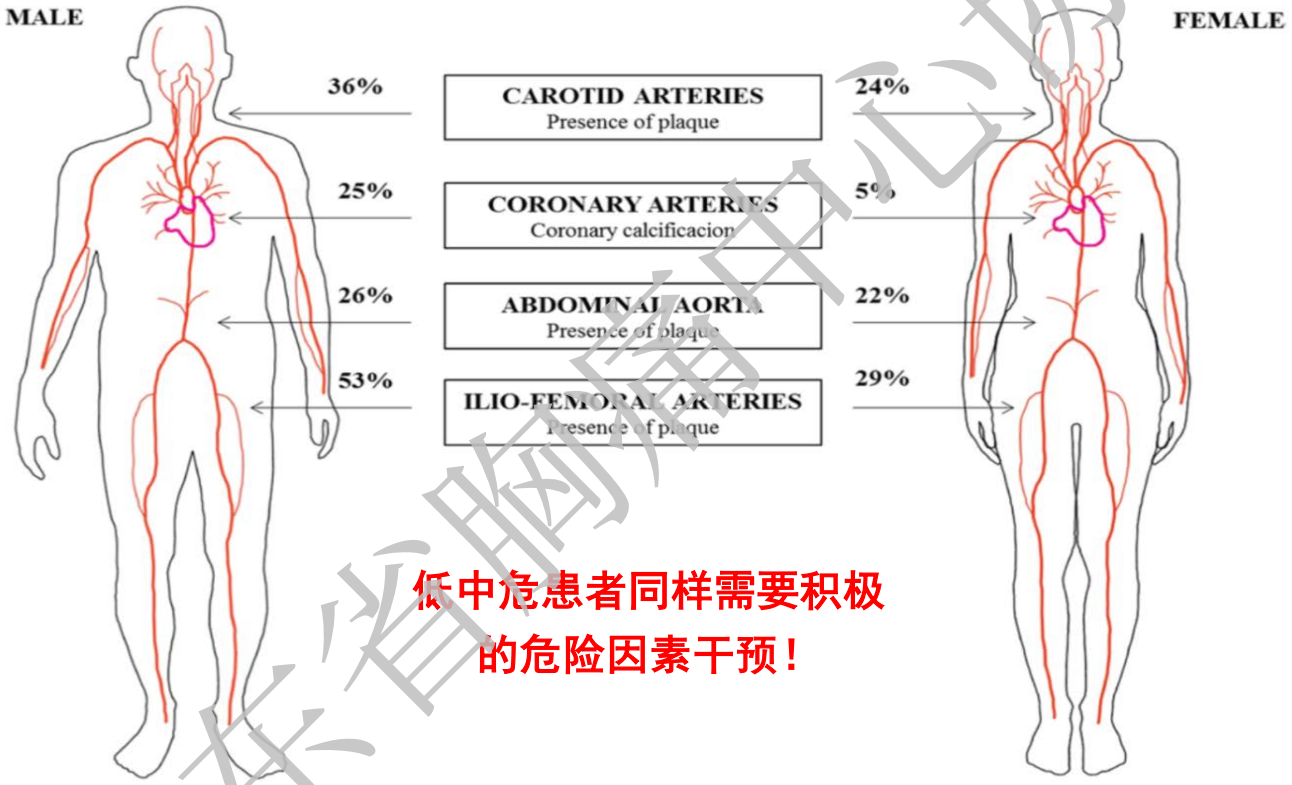
- 22 Meters of large vessels in the body
- Atherosclerosis is a diffuse disease
- Plaque mass may be
- 1 Kg or more



动脉粥样硬化通常发现于一处以上的动脉血管床

中低危患者普遍存在亚临床动脉粥样硬化

N=4184，40-55yr

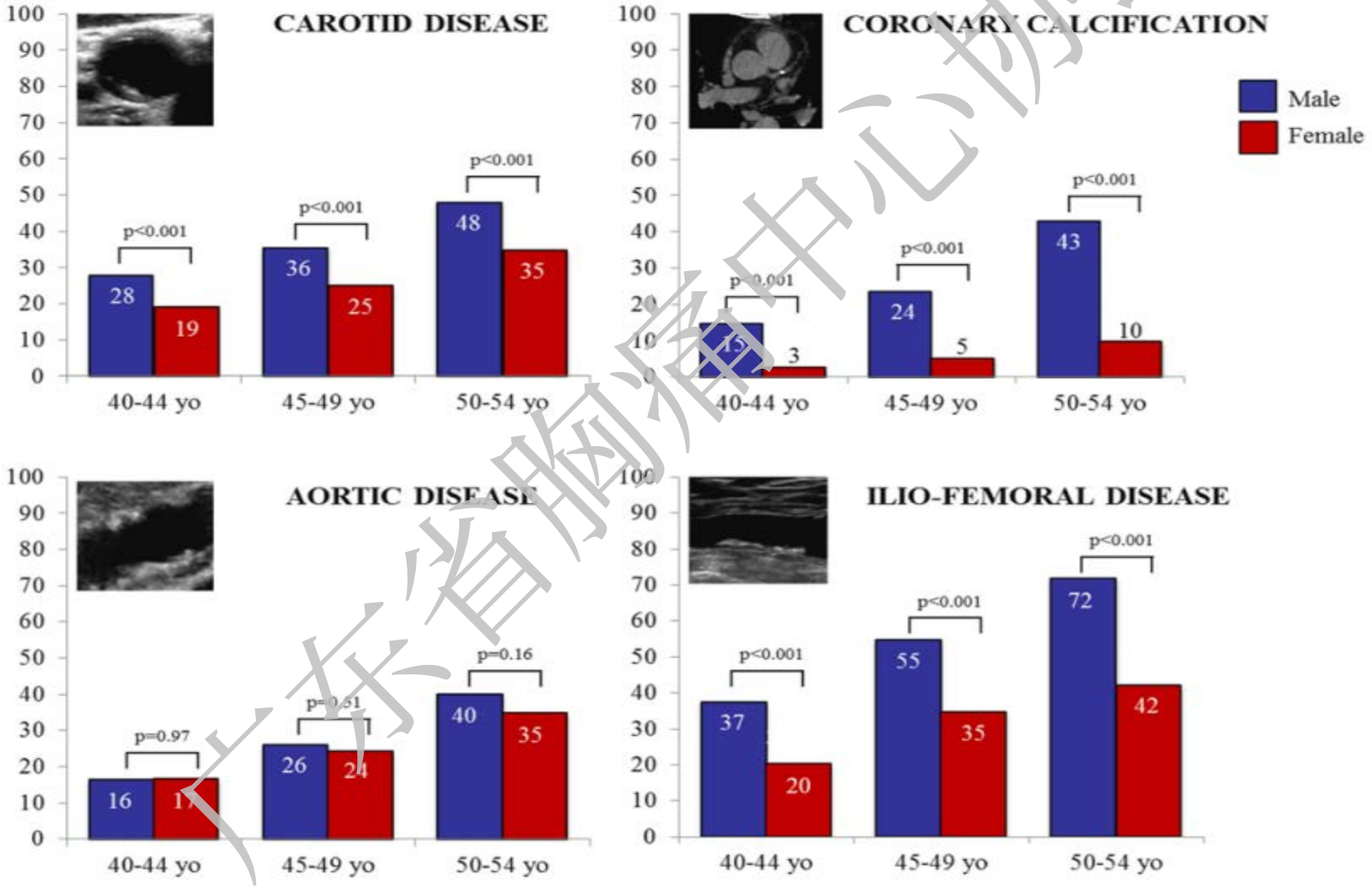


低中危患者同样需要积极的危险因素干预！

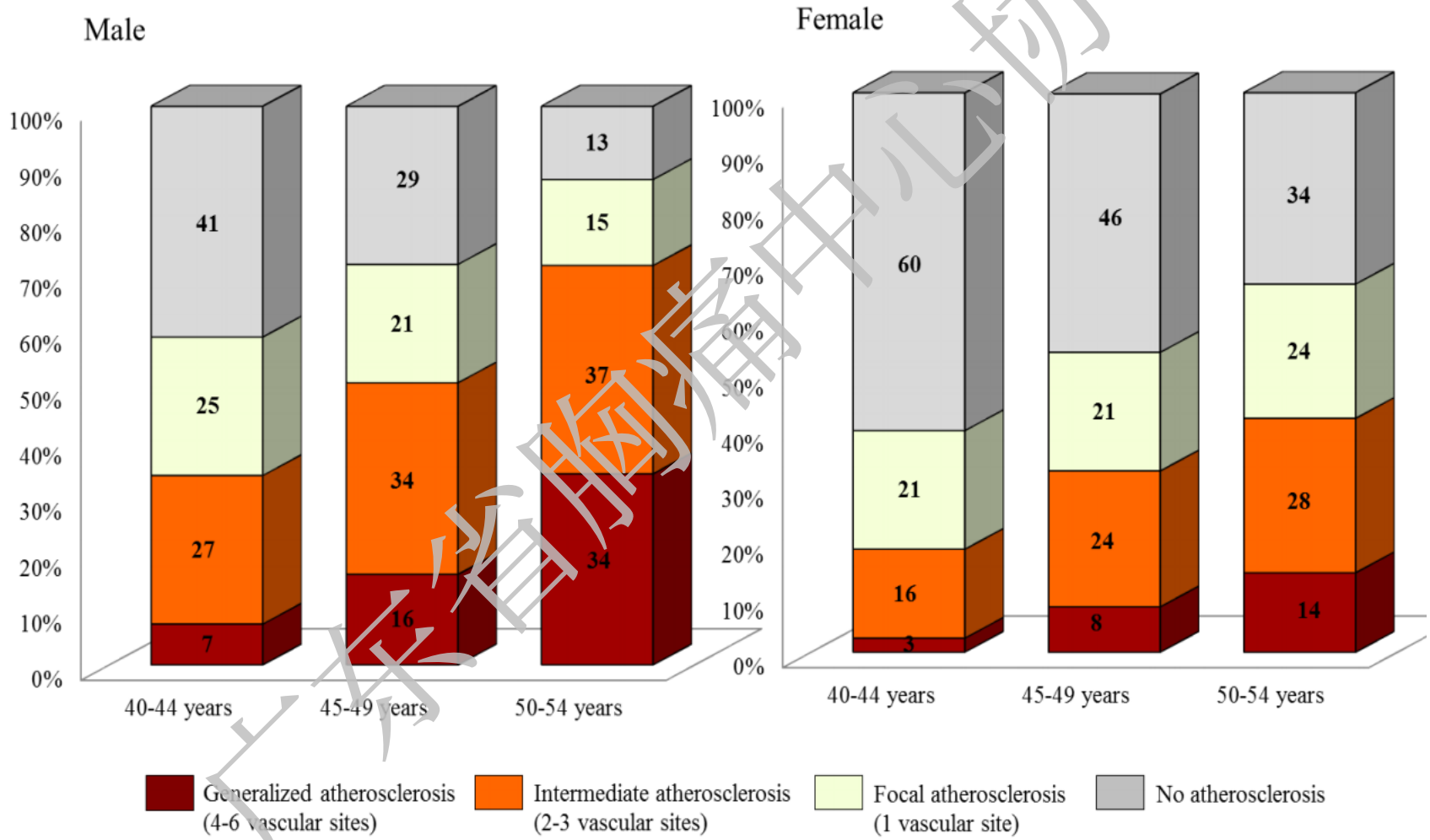
PESA研究：纳入4184名无症状受试者，平均年龄45.8(40-54)岁，其中99%为Framingham评分低中危患者，利用2/3 D超声检查颈动脉、腹主动脉、髂股动脉动脉粥样硬化情况。

Fernández-Friera Let al. Circulation. 2015 Jun 16;131(24):2104-13.

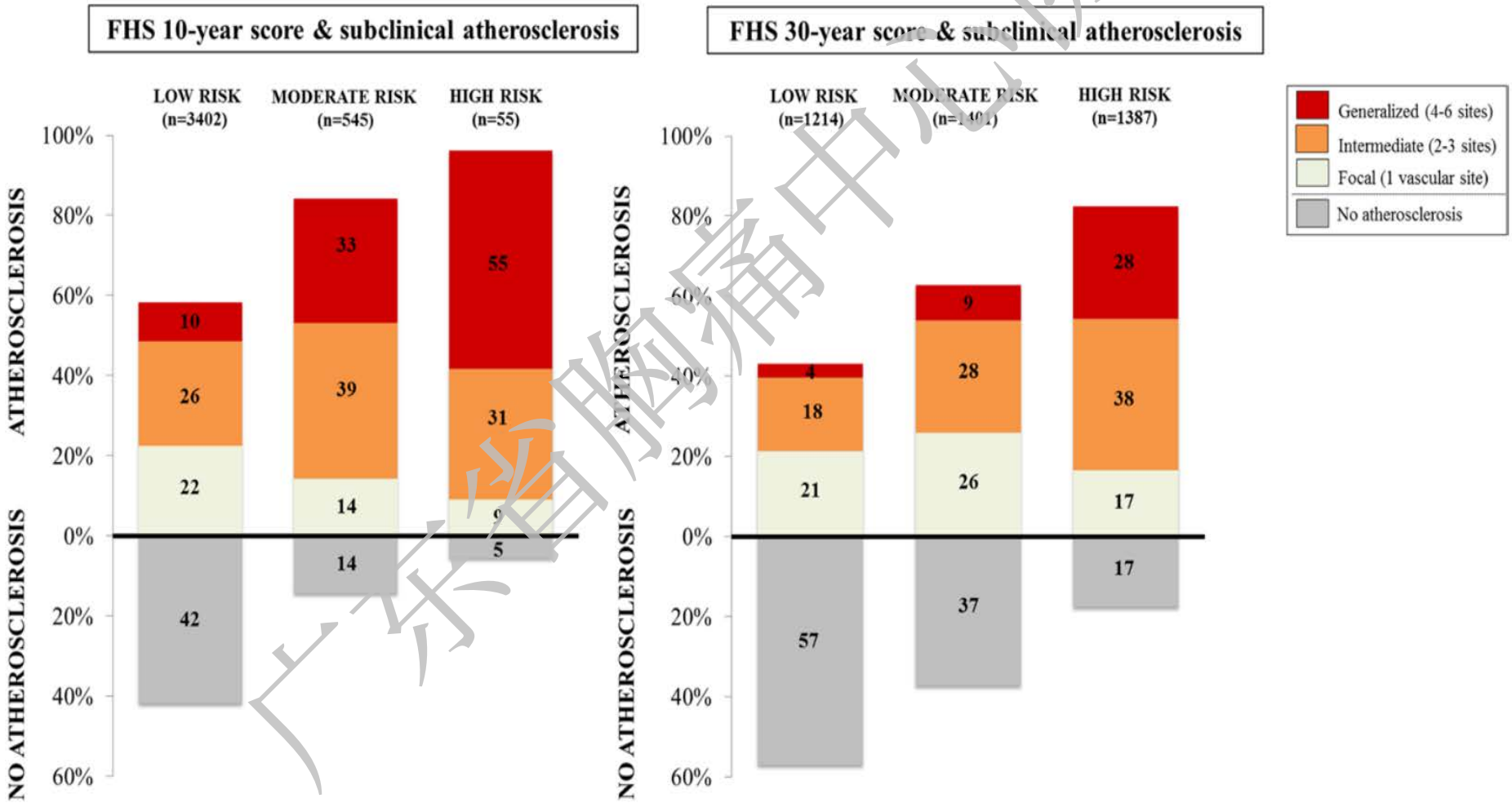
Prevalence of subclinical atherosclerosis by age and sex in each vascular territory



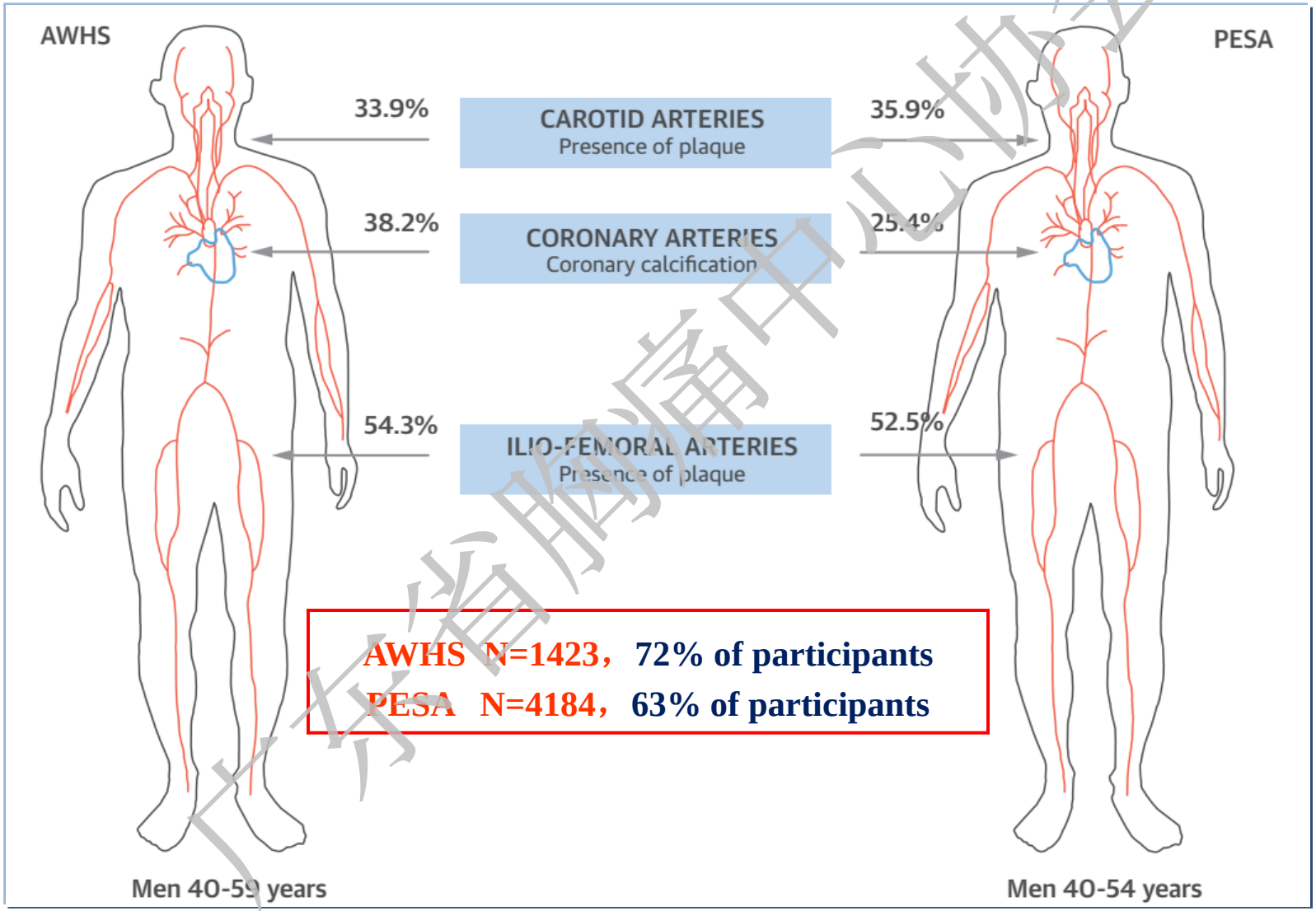
Distribution of multi-territorial extent of subclinical atherosclerosis



Distribution of subclinical atherosclerosis detected by noninvasive imaging according to FHS risk score

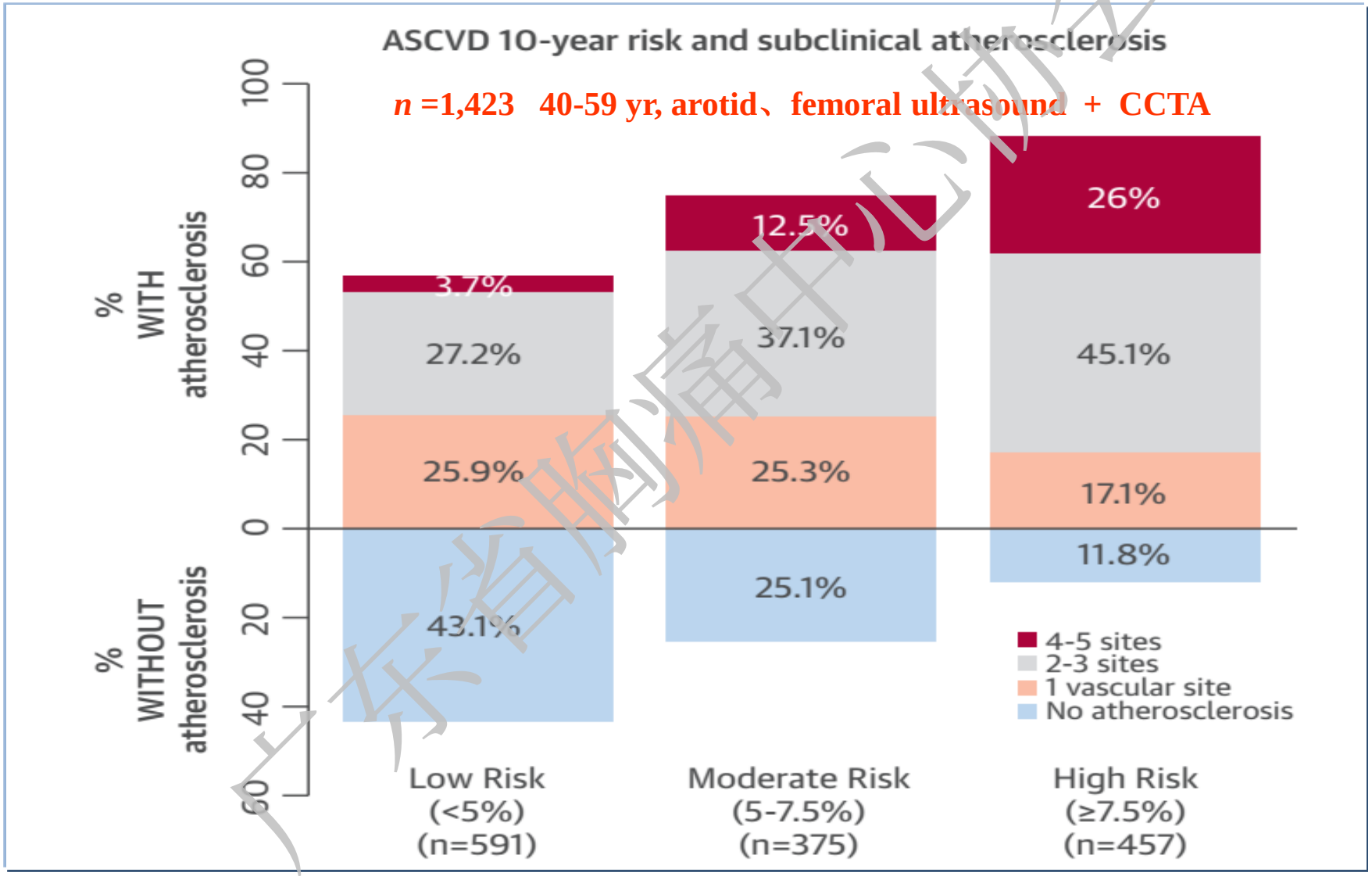


Prevalence of Subclinical Atherosclerosis in 2 Contemporaneous Cohort Studies: AWHS and PESA



J Am Coll Cardiol. 2016; 67(11):1263–74

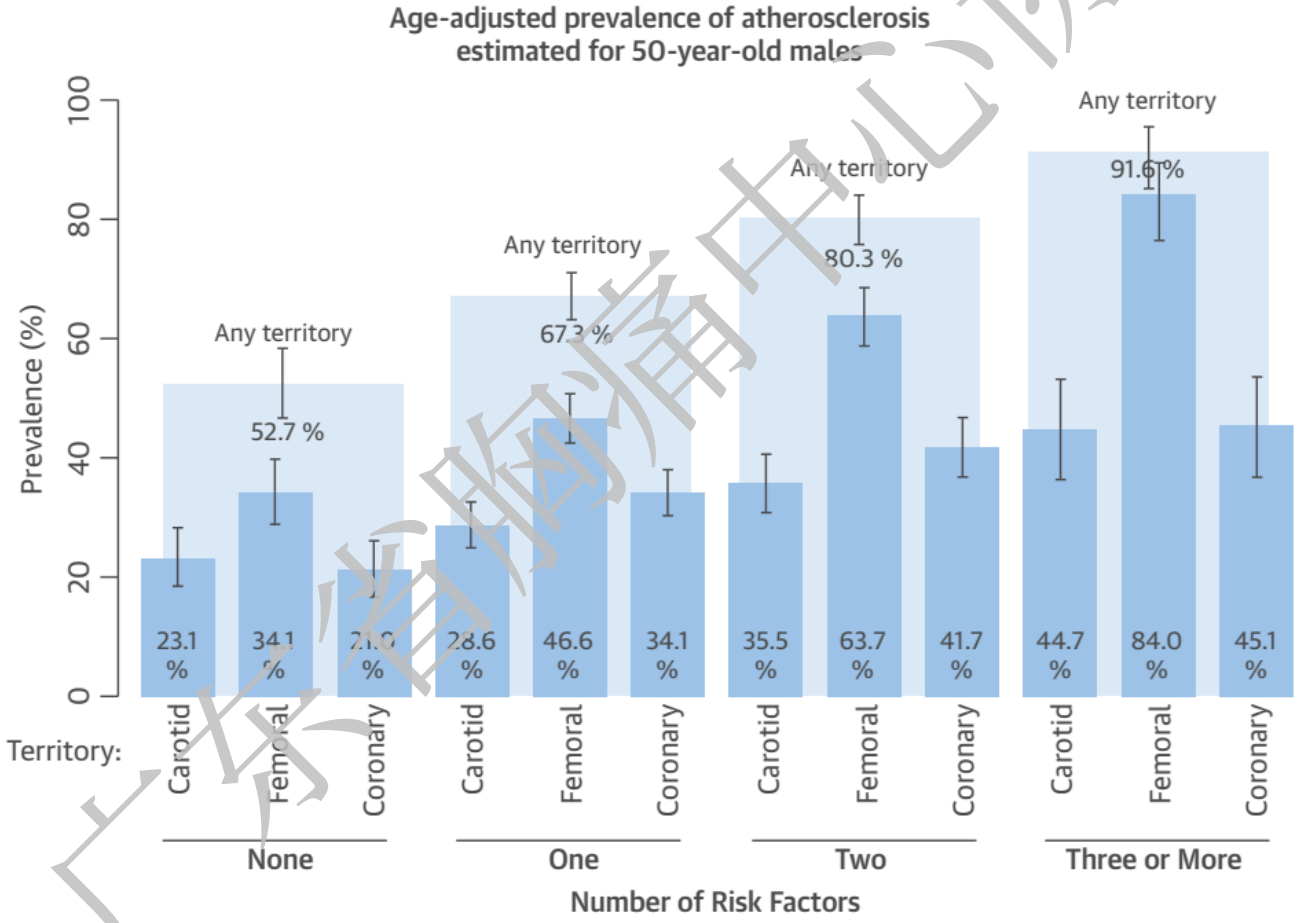
Presence of Subclinical Atherosclerosis According to Traditional Risk Equation--the AWHS study



J Am Coll Cardiol. 2016; 67(11):1263–74

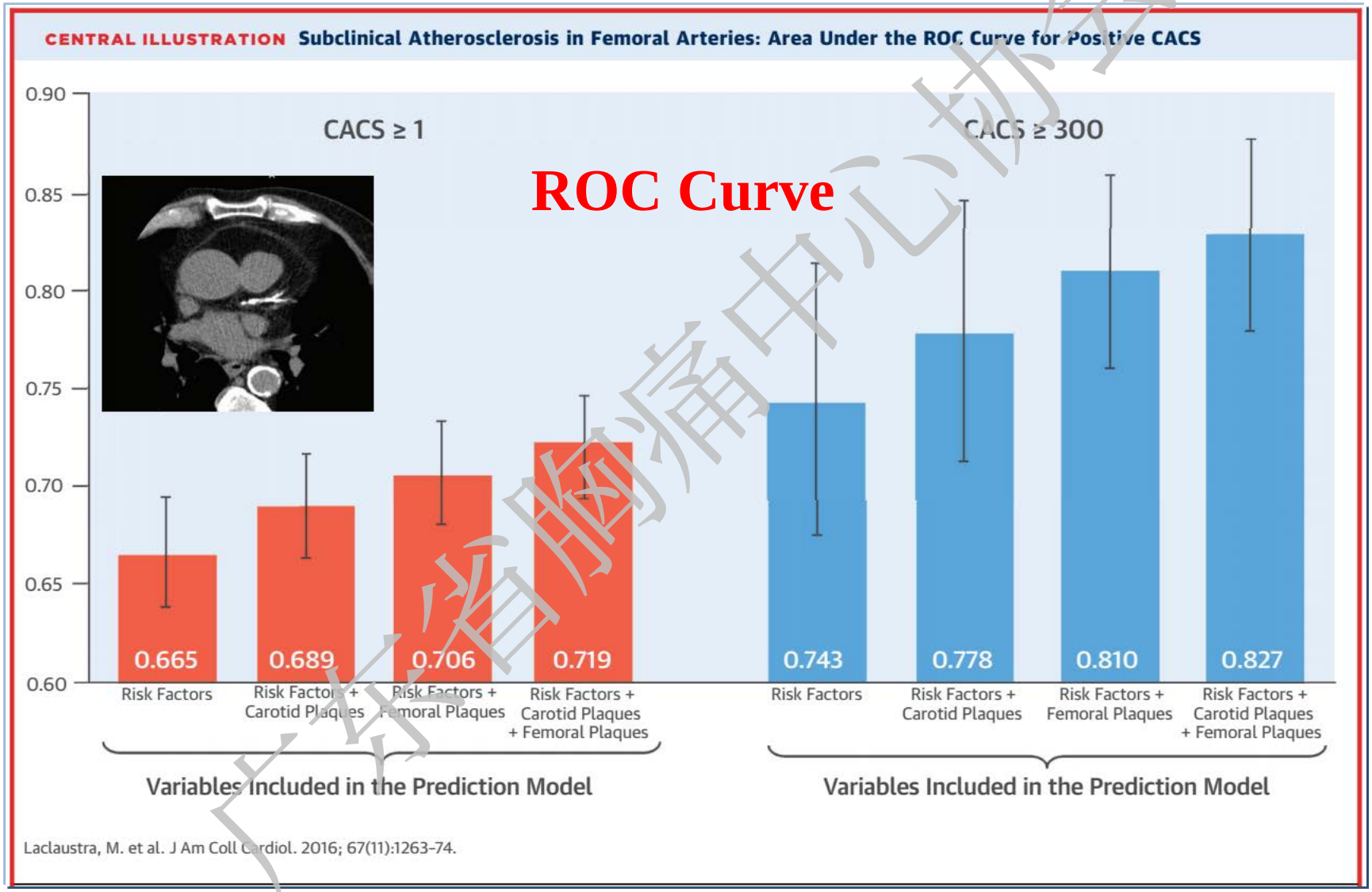
Prevalence of Subclinical Atherosclerosis in Different Vascular Territories

FIGURE 1 Prevalence of Subclinical Atherosclerosis in Different Vascular Territories



J Am Coll Cardiol. 2016; 67(11):1263–74

Prediction of coronary calcification by adding the presence of AS in different territories to classical risk factors



J Am Coll Cardiol. 2016; 67(11):1263–74

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然而，无症状性斑块难以发现

斑块是动脉粥样硬化进展的重要表现，预示着**极高的心血管疾病风险**，然而，斑块在引起心血管疾病等严重后果前常常无临床症状，该如何识别伴斑块人群？

不同动脉ASCVD的影像学诊断

- 彩色多普勒超声

  颈动脉、下肢动脉彩超等

- CTA 或MRA

  冠脉、颈动脉、颅内动脉、肾动脉等

- 造影、IVUS

更多地关注外周动脉

- 颈动脉

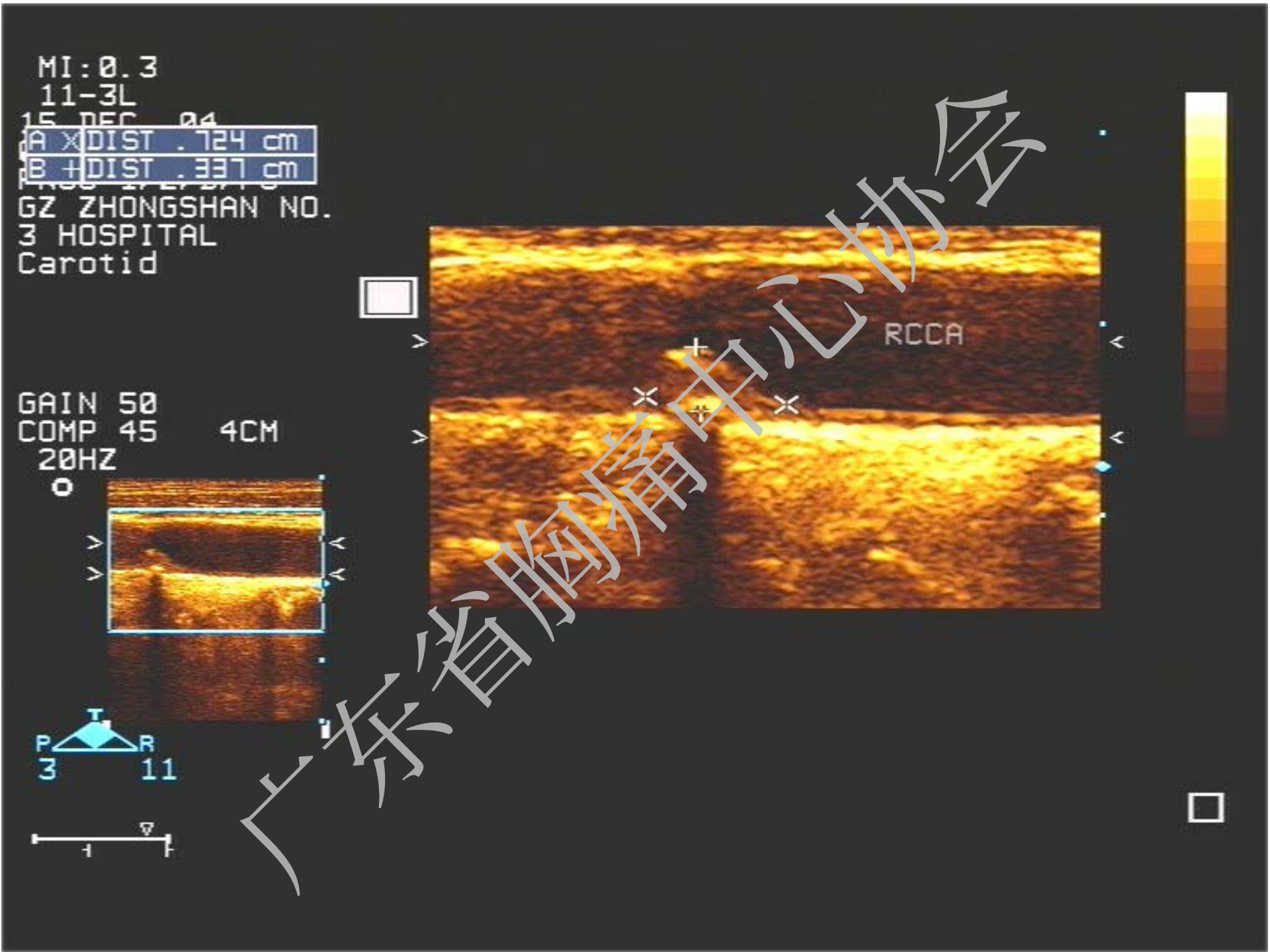
  ASCVD的“窗口”

  CIMT

  粥样斑块

- 下肢动脉

  “病在腿上，险在心上”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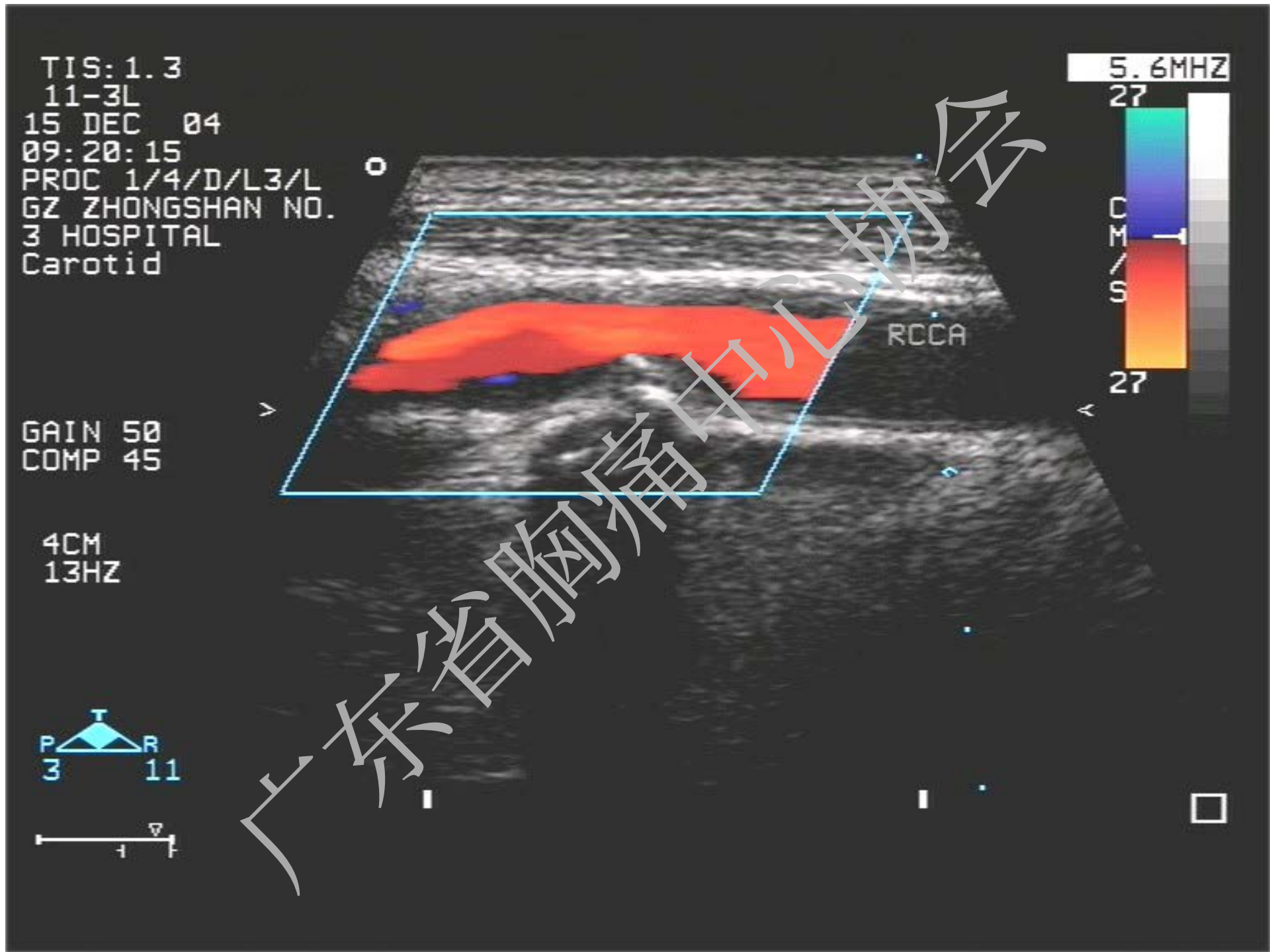
11-3L
A X DIST .724 cm
B + DIST .337 cm
GZ ZHONGSHAN NO.
3 HOSPITAL
Carotid
GAIN 50
COMP 45
4CM
20HZ
RCCA
P
R
3
11
广东省胸痛中心协会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11-3L
15 DEC 04
09:20:15
PROC 1/4/D/L3/L
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3 HOSPITAL
Carotid
GAIN 50
COMP 45
4CM
13HZ
5.6MHZ
27
CM/S
27
RCCA
P
T
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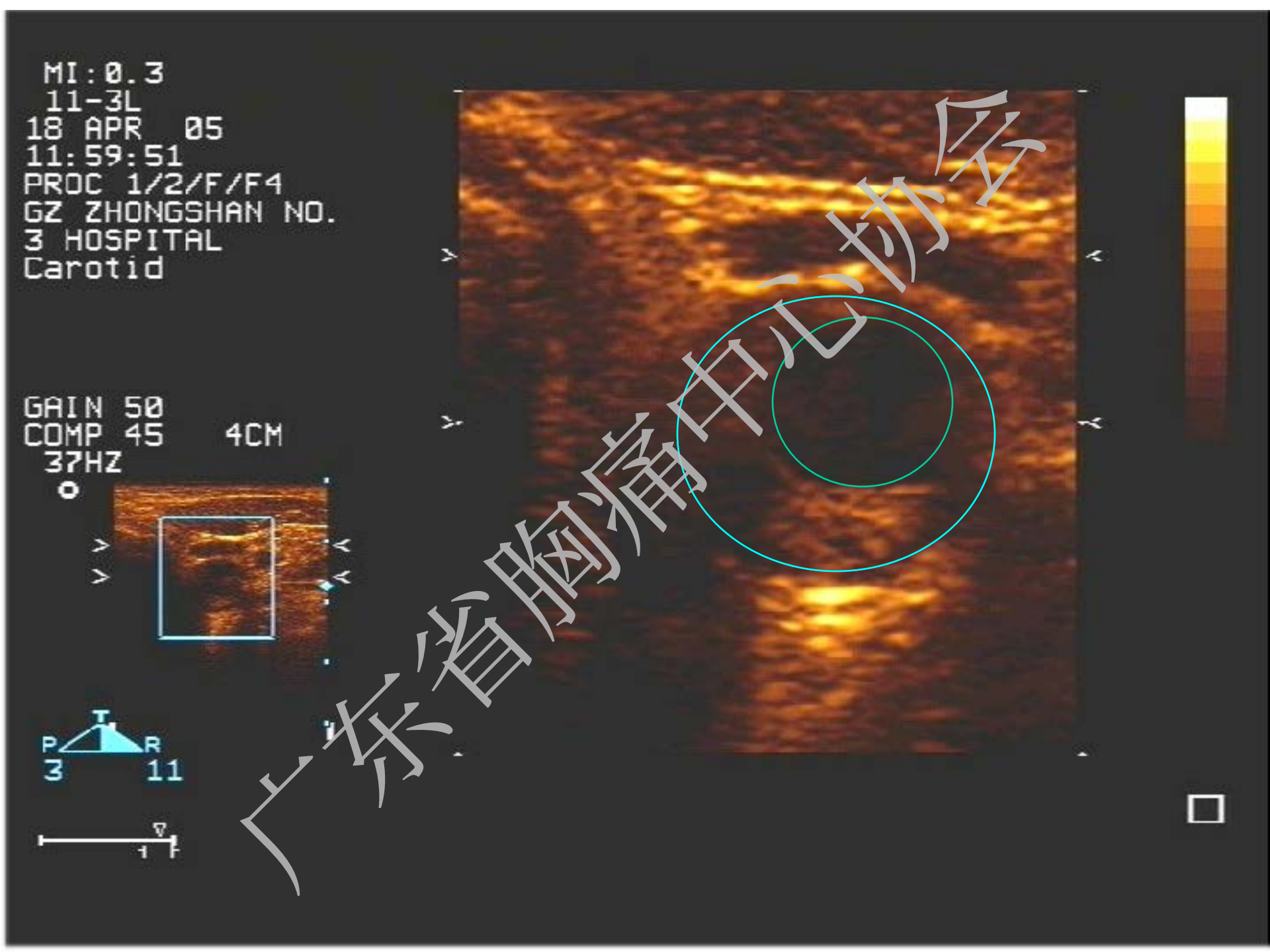
3
11
广东省胸痛中心协会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11-3L
18 APR 05
11:59:51
PROC 1/2/F/F4
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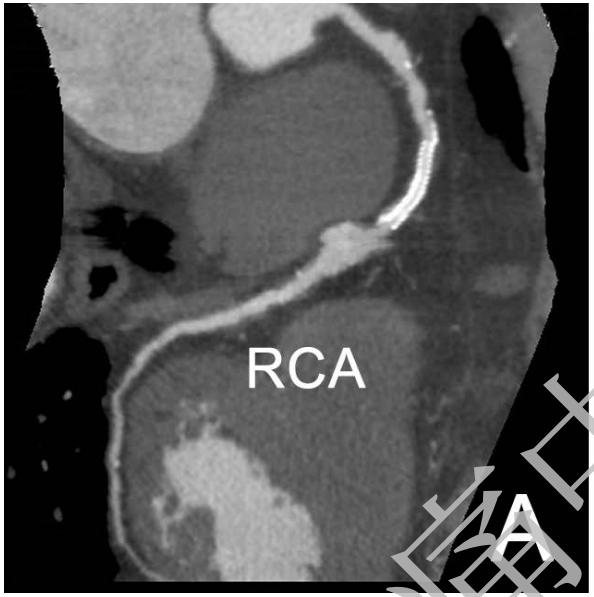
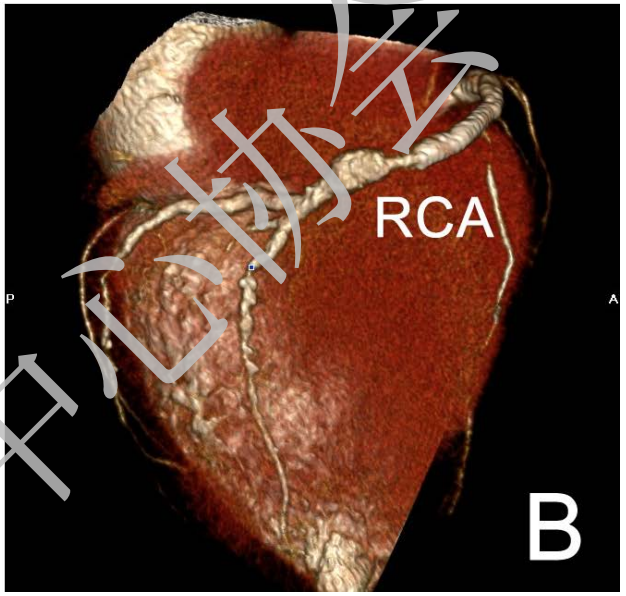
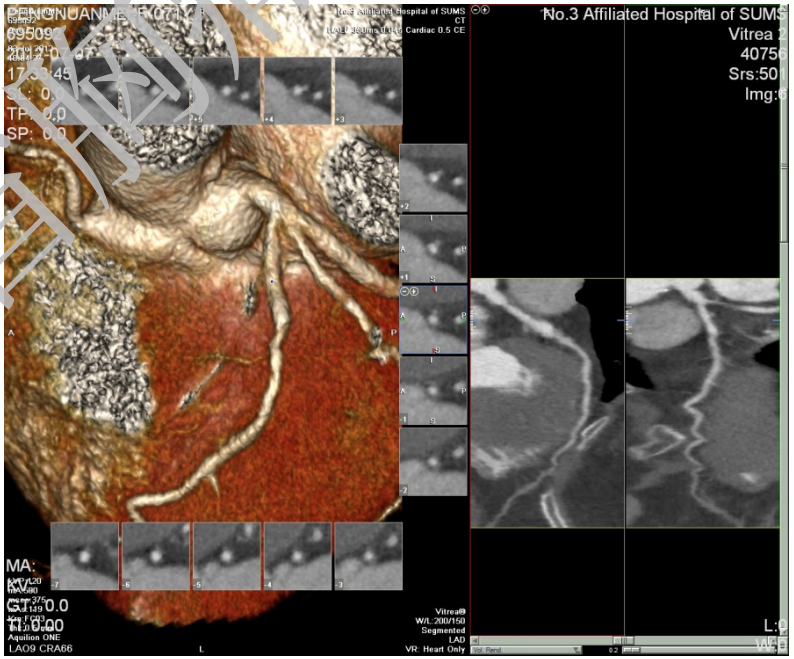
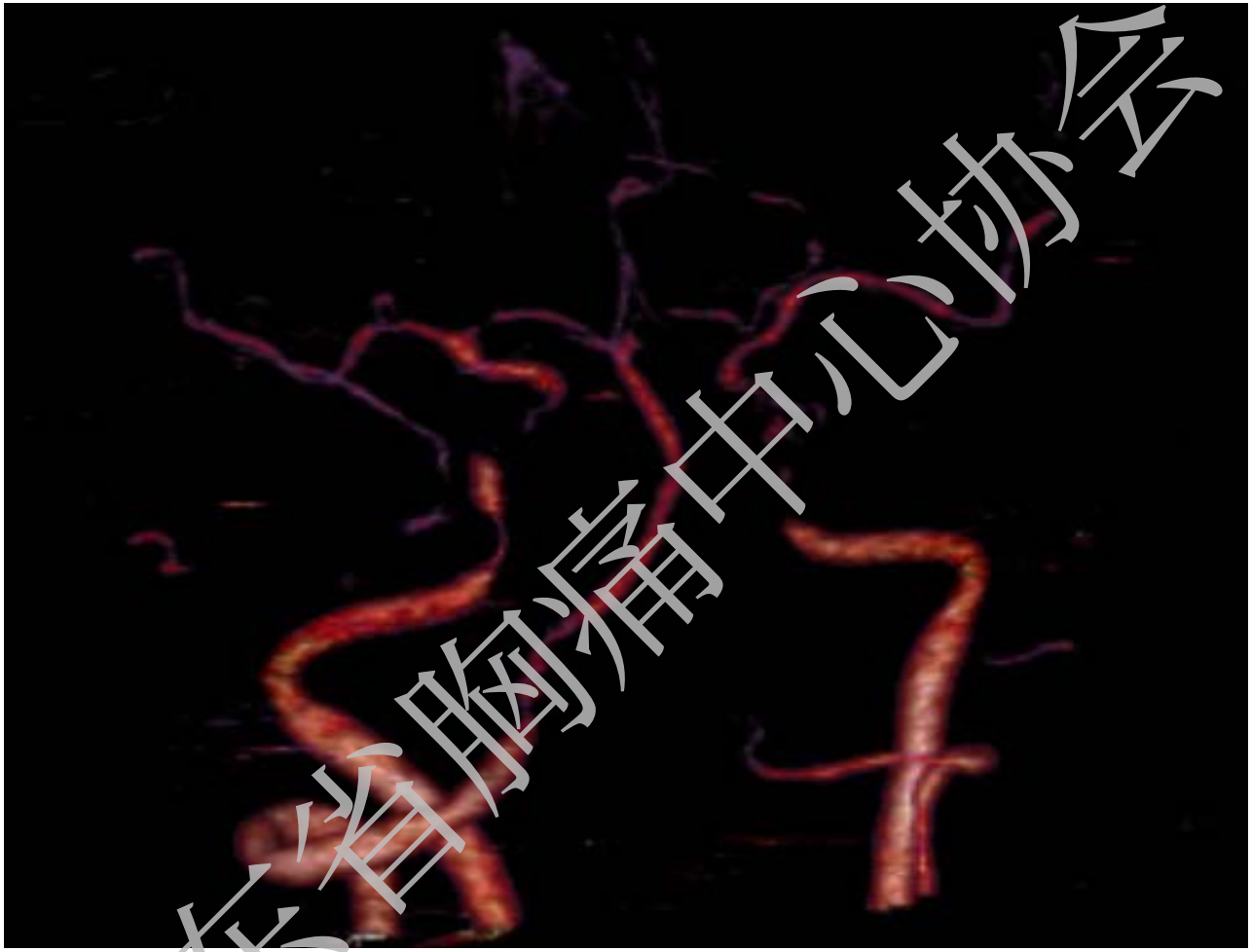
3 HOSPITAL
Carotid
GAIN 50
COMP 45
37HZ
4CM
P
R
3
11
广东省胸痛中心协会

冠脉CTA

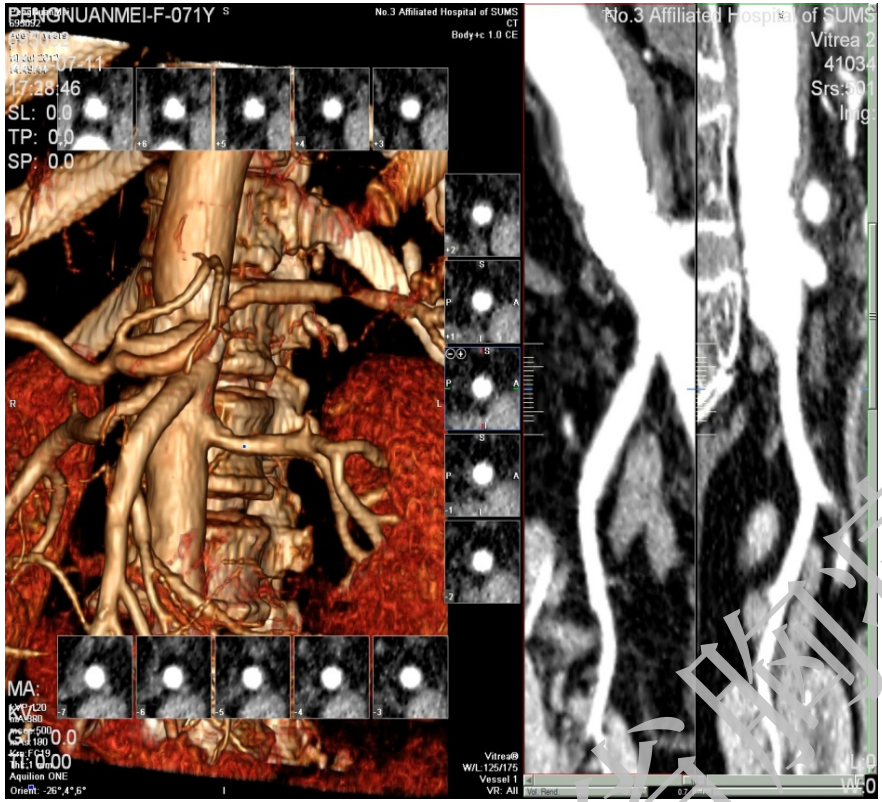








颅脑CTA示：重度脑动脉硬化，双侧颈内动脉及左侧椎动脉多发钙化斑块，右侧椎动脉纤细。



中腹部CT平扫+增强+CTA：

双肾动脉起始部粥样硬化斑块形成，管腔略狭窄；腹主动脉、脾动脉、肠系膜上动脉硬化

颈动脉造影

2016 ESC/EAS血脂异常指南
显著斑块人群属于极高危/高危人群

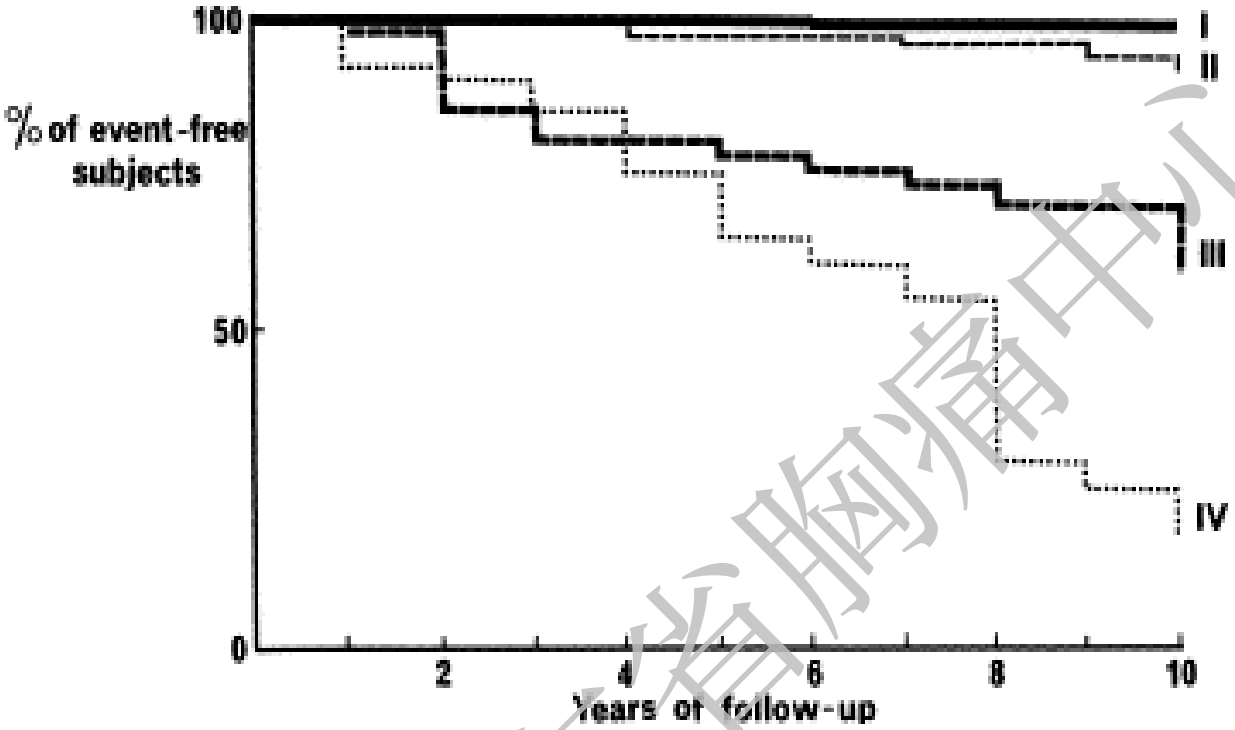
Table 4 Risk categories

Very high-risk	Subjects with any of the following: • Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia. • Severe CKD (GFR <30 mL/min/1.73 m²). • A calculated SCORE ≥10% for 10-year risk of fatal CVD.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m²). • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	SCORE is ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	SCORE <1% for 10-year risk of fatal CVD.

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BP = blood pressure; CKD = chronic kidney disease; DM = diabetes mellitus; GFR = glomerular filtration rate; PAD = peripheral artery disease; SCORE = systematic coronary risk estimation; TIA = transient ischaemic attack.

极高危	有如下任何一种情况者： • 临床或影像学明确记录的 CVD，临床 CVD 包括既往心肌梗死（MI）、急性冠脉综合征（ACS）、经皮冠脉介入治疗（PCI）、冠脉搭桥术（CABG）及其他动脉血运重建术、卒中和短暂性脑缺血发作（TIA）和外周动脉疾病（PAD），影像学明确记录的 CVD 指有强烈倾向发生临床事件的情况如冠脉造影或颈动脉超声中有明显斑块； • 糖尿病伴靶器官损伤如蛋白尿或伴主要危险因素如吸烟、高血压或血脂异常； • 严重 CKD[肾小球滤过率（GFR）＜30 ml/（min·1.73m²）]； • 10 年致死性 CVD 风险的 SCORE 评分≥10%。
高危	有如下情况者： • 单一危险因素显著升高，尤其是胆固醇水平＞8 mmol/L（如家族性高胆固醇血症）或血压≥180/110 mmHg； • 其他伴糖尿病者（一些青年 1 型糖尿病患者可能是低或中危）； • 中度 CKD（GFR 30~59 30 ml/（min·1.73m²）； • 10 年致死性 CVD 风险的 SCORE 评分≥5%，＜10%。
中危	10 年致死性 CVD 风险的 SCORE 评分≥1%，＜5%。
低危	10 年致死性 CVD 风险的 SCORE 评分＜1%。

The CAFES-CAVE study



I: normal wall
II: wall thickening
III: non-stenosing plaques
IV: stenosing plaques (>50%)

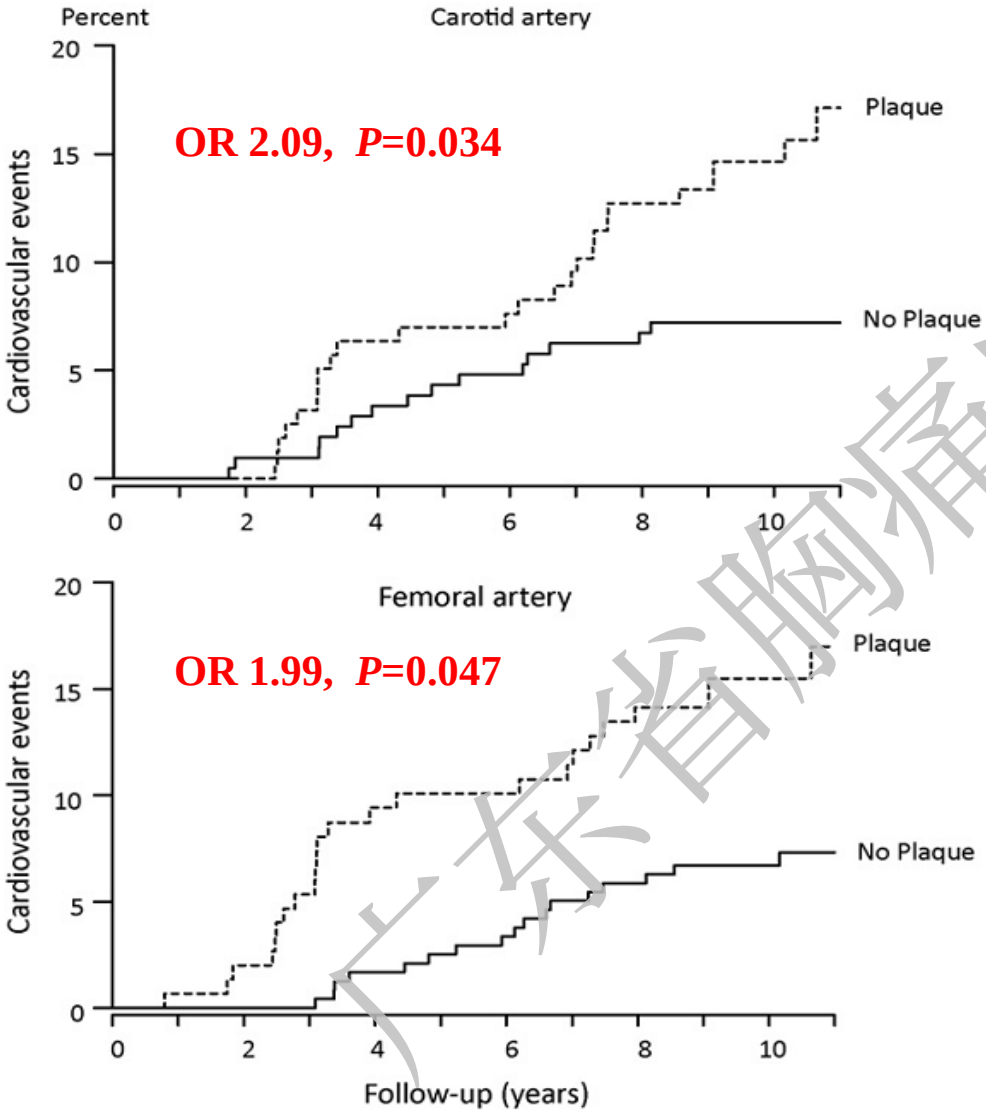
13 221 low-risk, healthy, asymptomatic individuals were included in a **10-year**, prospective, follow-up based on carotid and femoral bifurcation morphology defined by B-mode US.

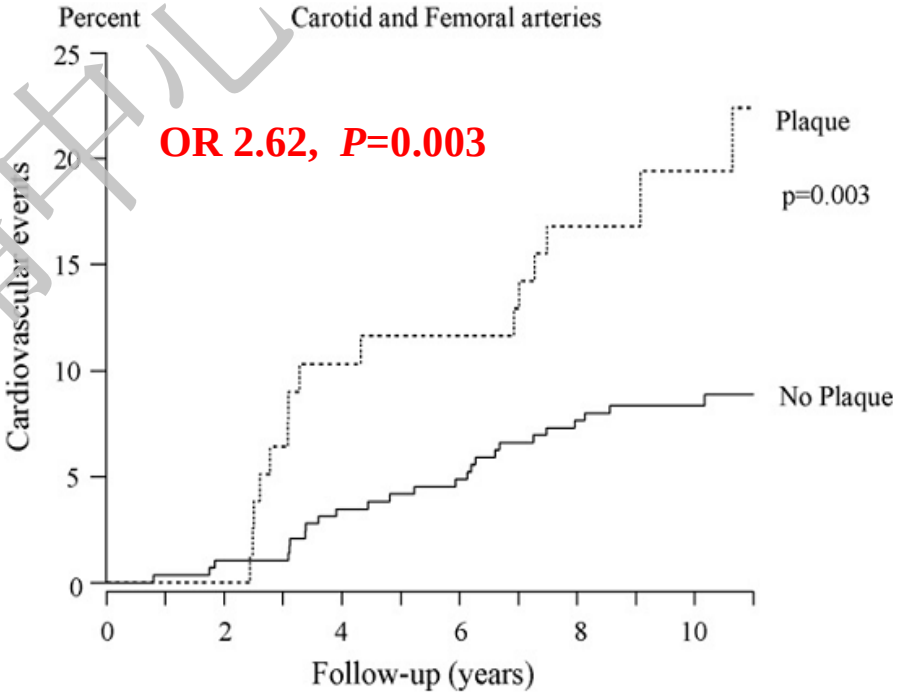
Results

I: 0.1% CVEs ,
II: 8.6% CVEs,
III:39.3% CVEs,
IV: 81.5% CVEs.
II+III+IV:
98.6% CVEs and deaths

Atherosclerosis, 2001, 156:379 -387

K-M curve for CVEs in the groups with and without plaques in the carotid and femoral arteries followed for a mean 10 yrs





Atherosclerosis, 2010, 209: 469 - 473

Tromsø研究：
颈动脉斑块增加新发MI风险

挪威Tromsø前瞻性研究，共纳入**6226**例无MI病史患者，测量其IMT，总斑块面积，斑块回声反射性，随访**6**年，记录新发MI的发生率

*斑块面积最高三分位数组vs无斑块组

Johnsen SH et al. Stroke. 2007;38:2873-80.

目 录

胆固醇理论历久弥新

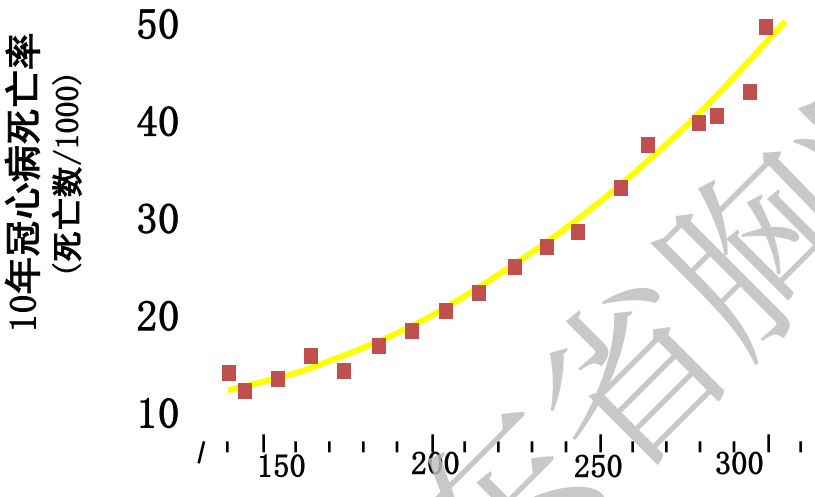
N.N.Anitschkow

Sudan-stained aorta of a rabbit fed 61 egg yolks over a 70-day period. Anitschkow recognized that the earliest lesions appeared in the arch near the orifices of branch points and then moved caudally (1913)

胆固醇与动脉粥样硬化

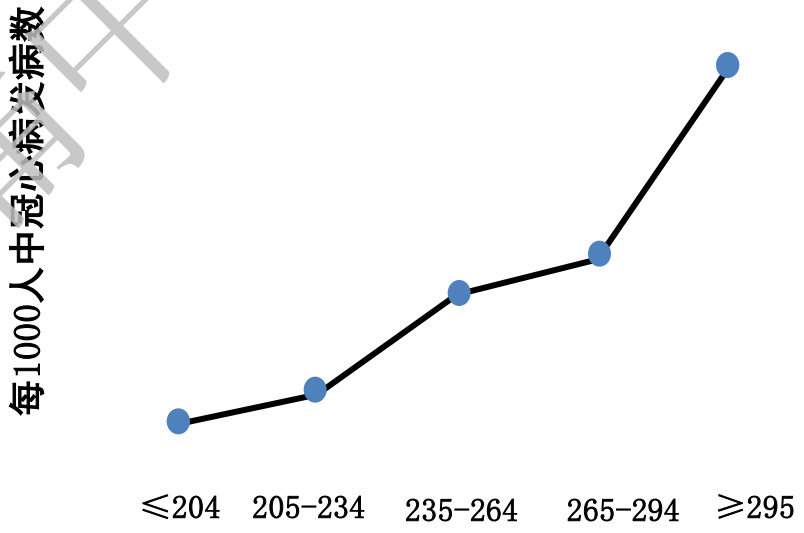
总胆固醇水平减少1%
冠心病危险性减少2%

- **多重危险因素干预试验 (MRFIT) (n=361,662)**



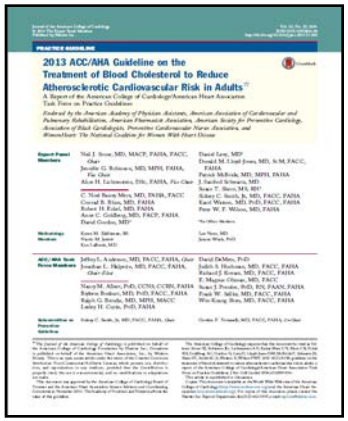
总胆固醇水平升高1%
冠心病危险性增加2%

- **Framingham 研究 (n=5209)**

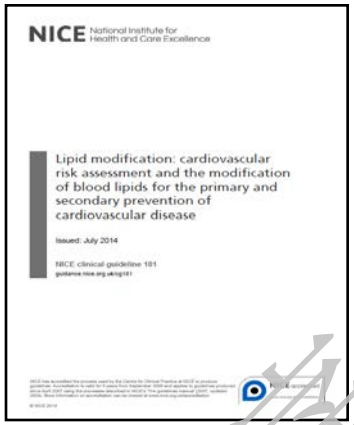


没有胆固醇，就没有动脉粥样硬化！

权威血脂指南一致指出
降低ASCVD风险，他汀是首选

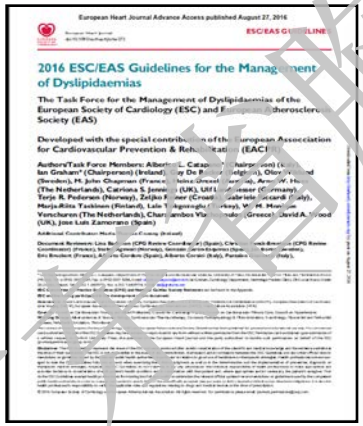


2013 ACC/AHA胆固醇管理指南[1]



2014 NICE血脂管理指南[2]

2014 NLA血脂异常管理建议[3]



2016 ESC血脂异常指南[4]

2016 中国血脂异常指南[5]

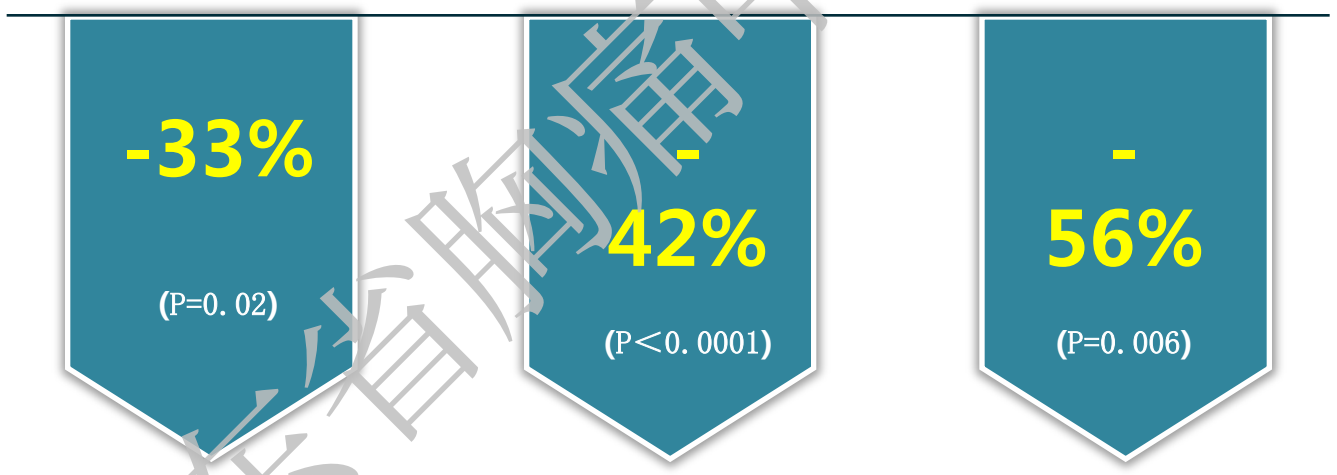
“他汀类已成为防治ASCVD这类疾病最为重要的药物。”

“为了调脂达标，临床上应首选他汀类调脂药物（I 类推荐，A 级证据）”

1. Stone NJ, et al. J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2889-934
2. Rabar S, et al. BMJ. 2014 Jul 17;349:g4356
3. Jacobson TA, et al. J Clin Lipidol. 2014;8(5):473-88
4. Catapano AL, et al. Eur Heart J. 2016 Aug 27. pii: ehw272. [Epub ahead of print]
5. 中国成人血脂异常防治指南（2016年修订版）.中国循环杂志. 2016;31(10):937-953

阿托伐他汀显著降低主要ASCVD风险

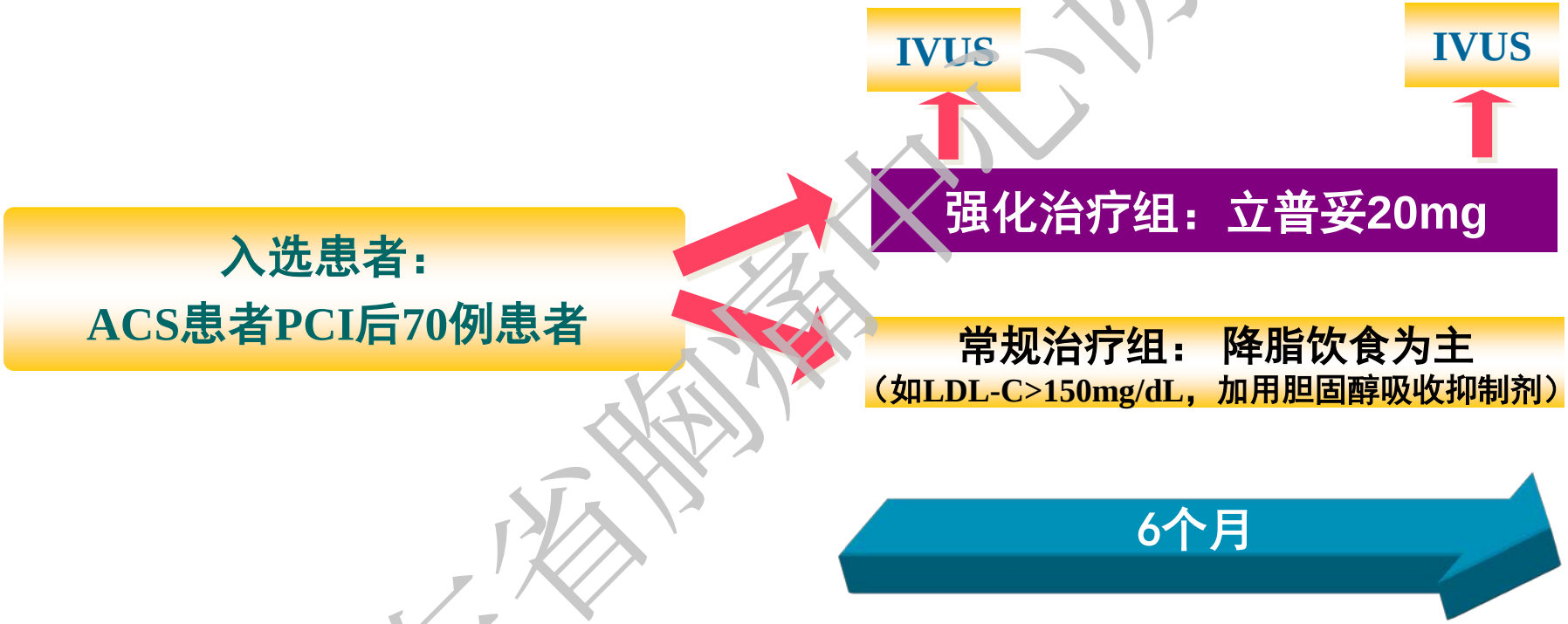
- SPARCL颈动脉狭窄亚组研究共纳入1,007例近期有卒中或TIA病史伴颈动脉狭窄患者；颈动脉平均狭窄51%



*任何心血管事件：卒中或TIA、心源性死亡、非致死性心肌梗死、心脏骤停后的复苏、不稳定性心绞痛、冠状动脉血管重建术、需紧急住院的心绞痛或心肌缺血、血管重建术（冠状动脉或颈动脉或周围动脉）、有临床意义的周围血管疾病

Sillesen H, et al. Stroke. 2008 Dec; 39(12):3297-302

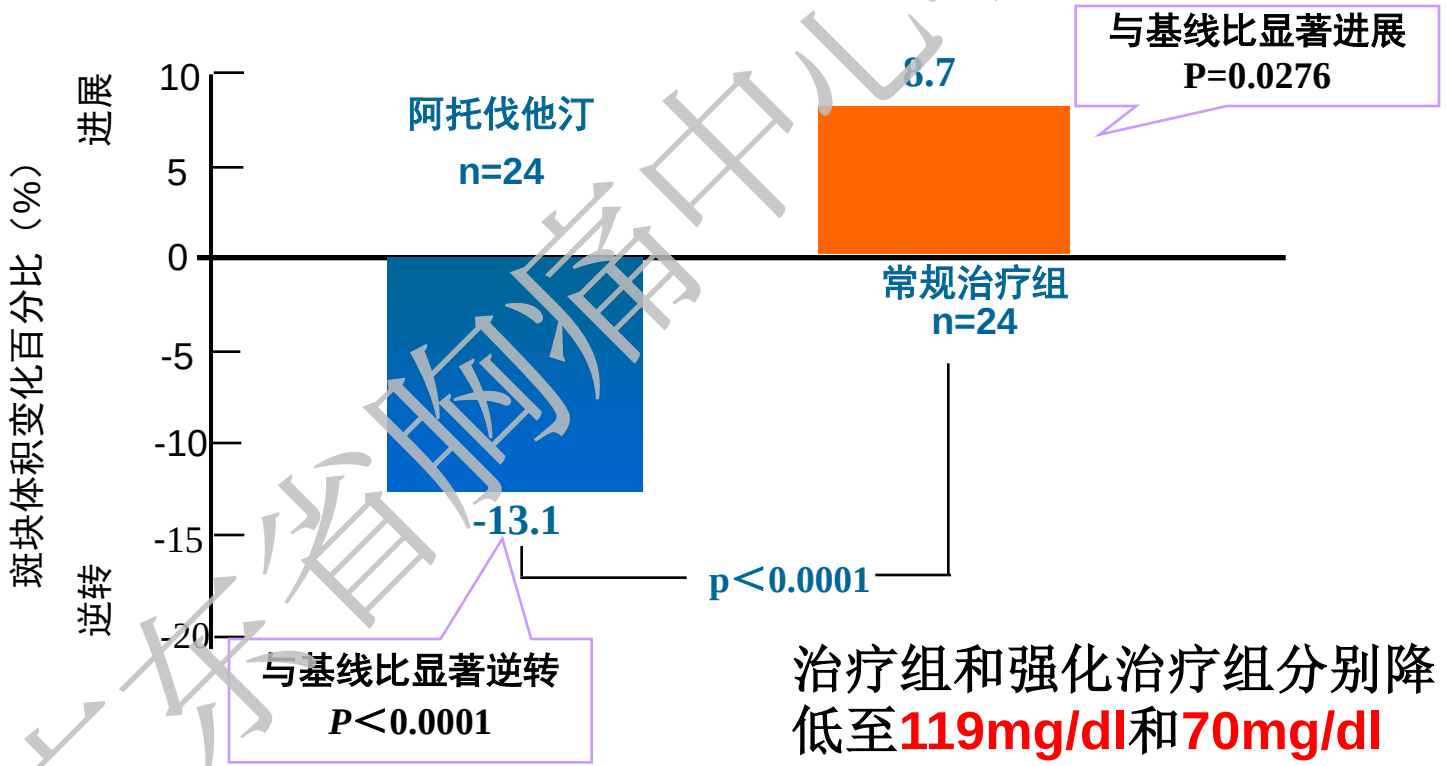
ESTABLISH:
ACS患者早期他汀治疗



主要终点:通过IVUS测定罪犯血管非PCI
部位斑块体积变化的百分数

Okazaki S, et al. Circulation. 2004; 110: 1061-68

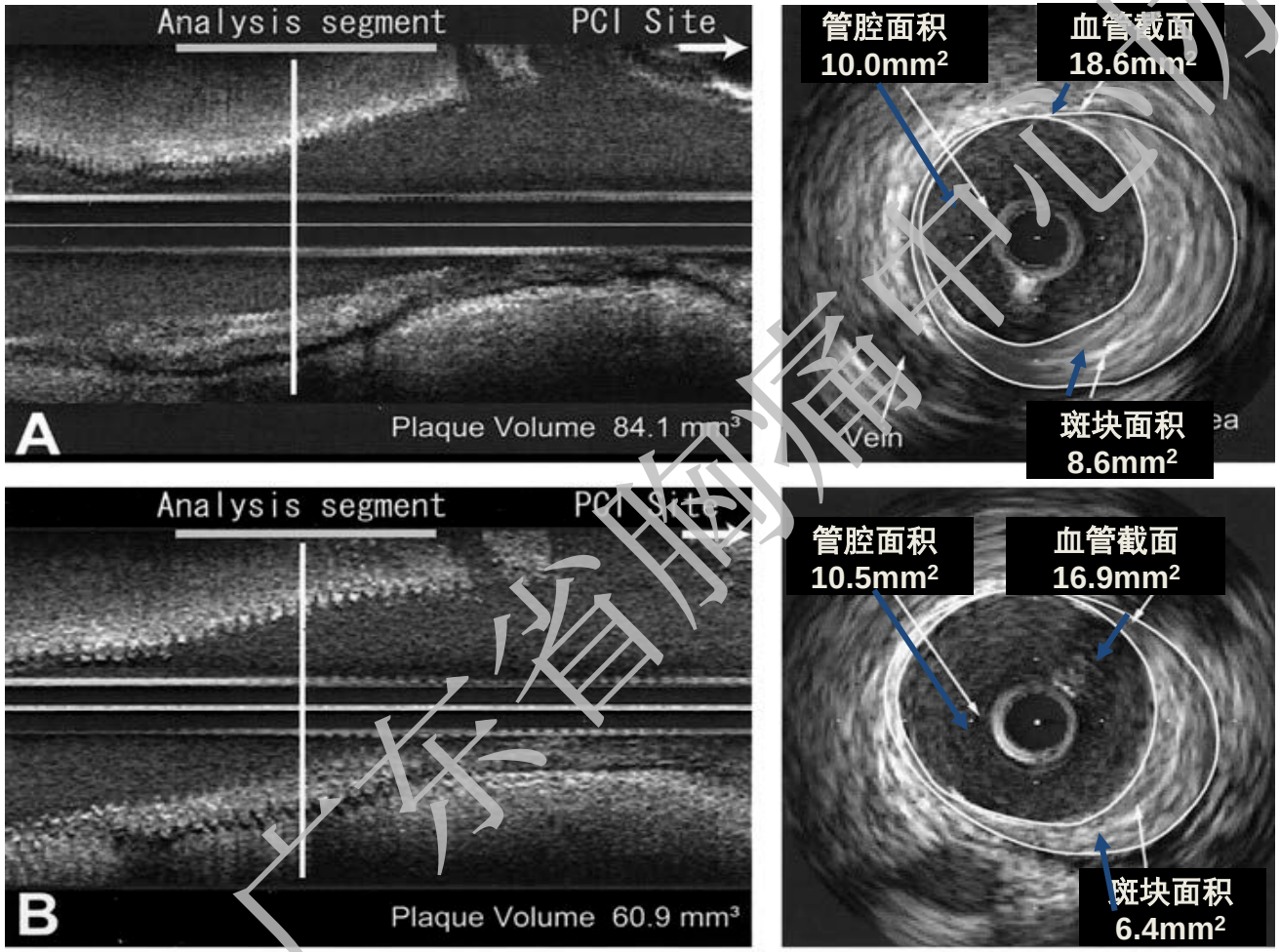
ESTABLISH：
阿托伐他汀20mg治疗，斑块出现逆转



治疗组和强化治疗组分别降低至119mg/dl和70mg/dl（P＜0.0001）

Circulation. 2004;110:1061-1068

ESTABLISH:阿托伐他汀20mg/d 6个月
逆转亚洲ACS患者动脉粥样硬化斑块



基线时

斑块面积8.6 mm^2

立普妥®治疗后

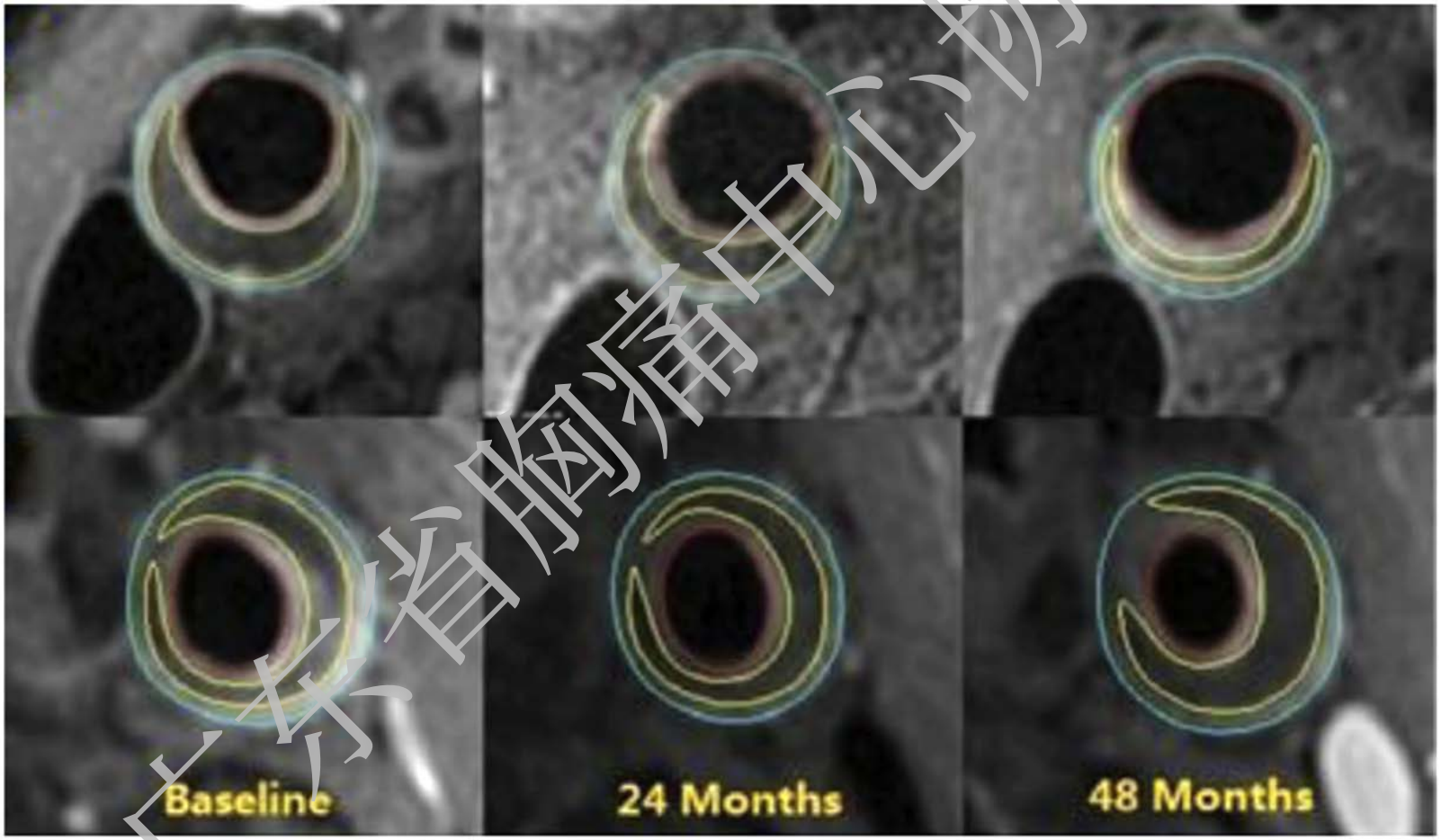
斑块面积6.4mm^2

Shinya Okazaki, et al. Circulation. 2004;110:1061-1068

REACH II研究
瑞舒伐他汀继续治疗与终止治疗影像学对比

瑞舒伐他汀继续治疗

瑞舒伐他汀终止治疗

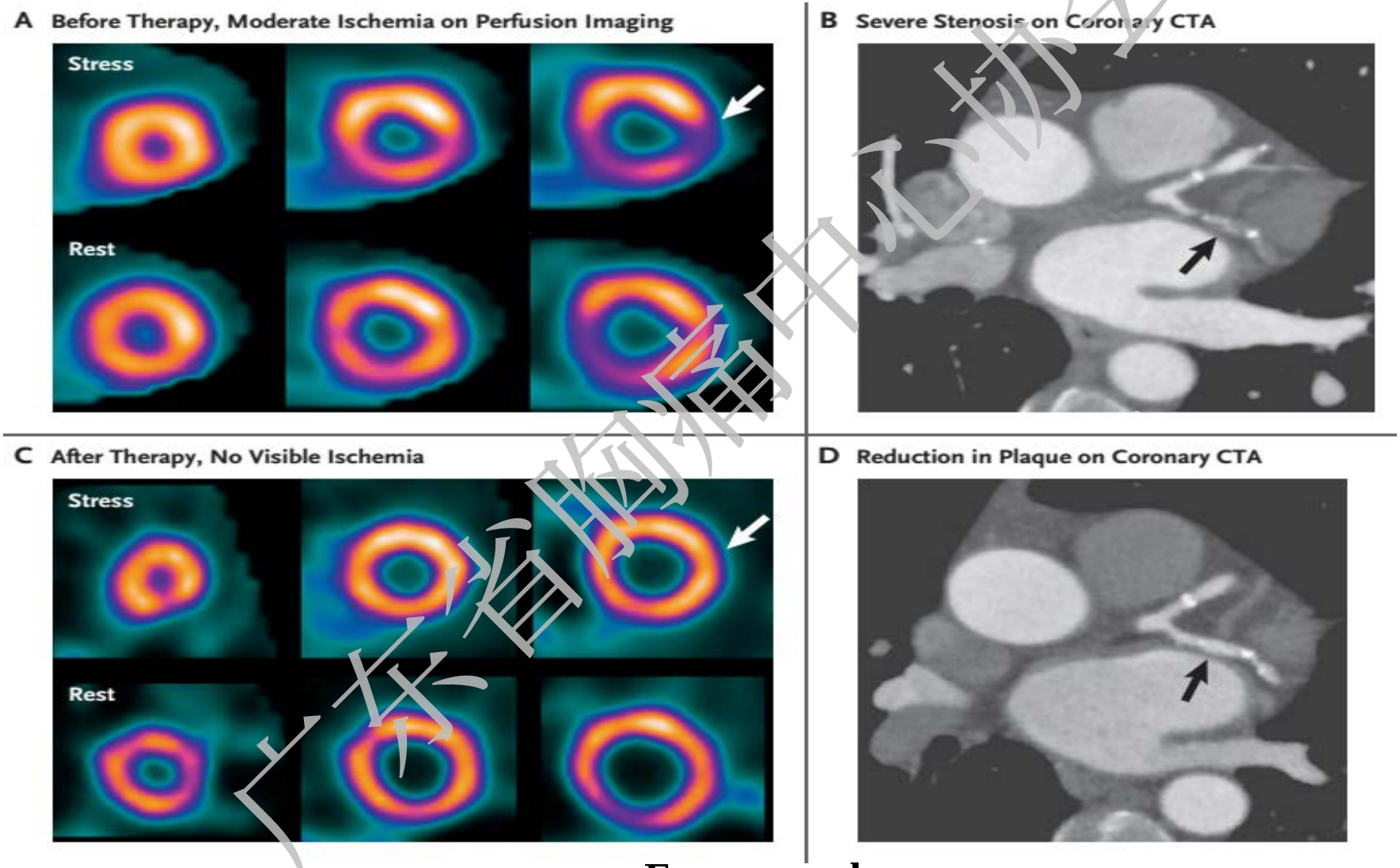


管腔为红色，外壁为蓝色，脂质内容物为黄色

Du R, et al. J Clin Lipidol. 2016 May-Jun;10(3):587-93.

The NEW ENGLAND JOURNAL of MEDICINE

IMAGES IN CLINICAL MEDICINE



Four years later

N Engl J Med. 2017 Apr 6;376(14):1370

FOURIER

Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

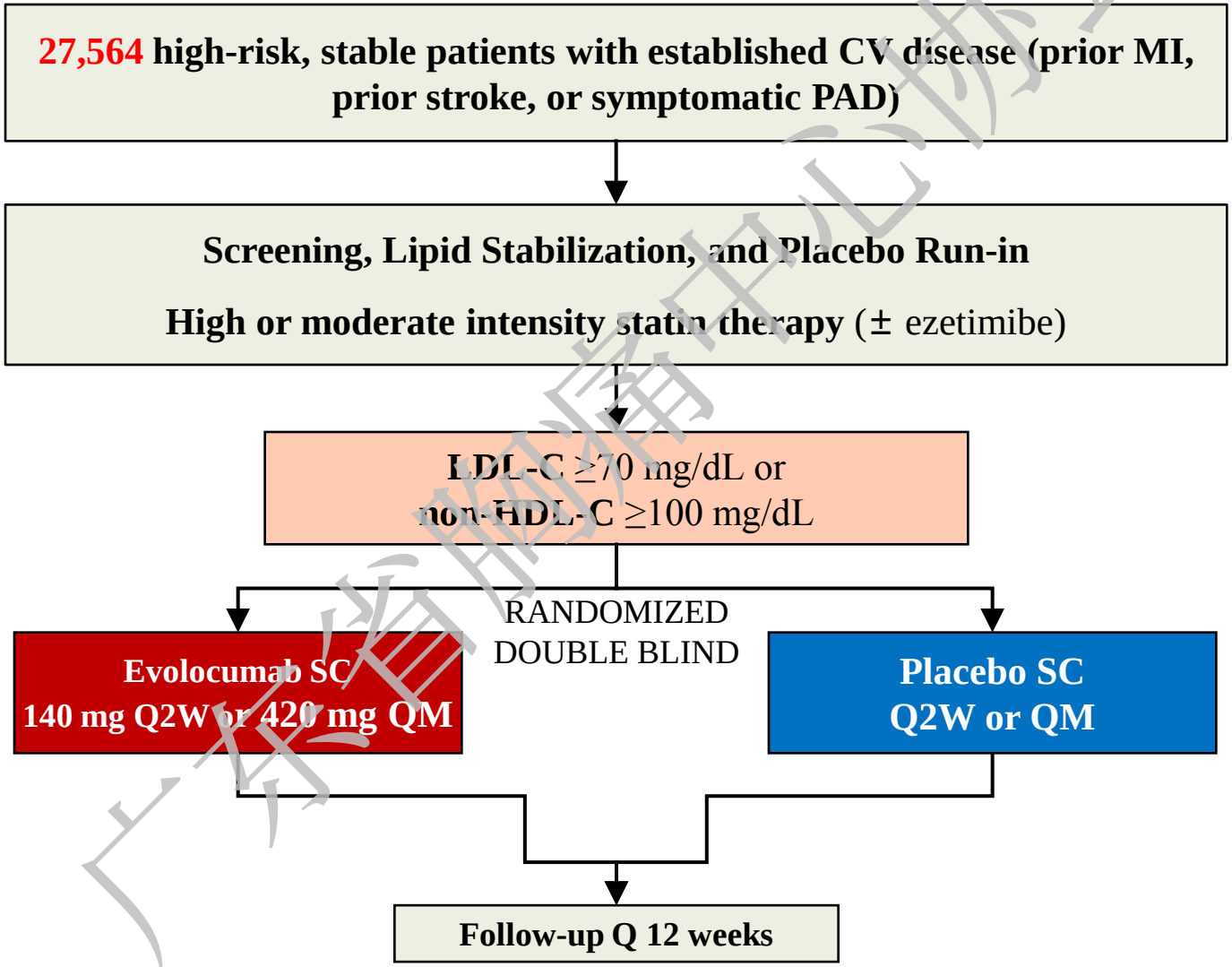
MS Sabatine, RP Giugliano, AC Keech, N Honarpour,
SM Wasserman, PS Sever, and TR Pedersen,
for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 17, 2017

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

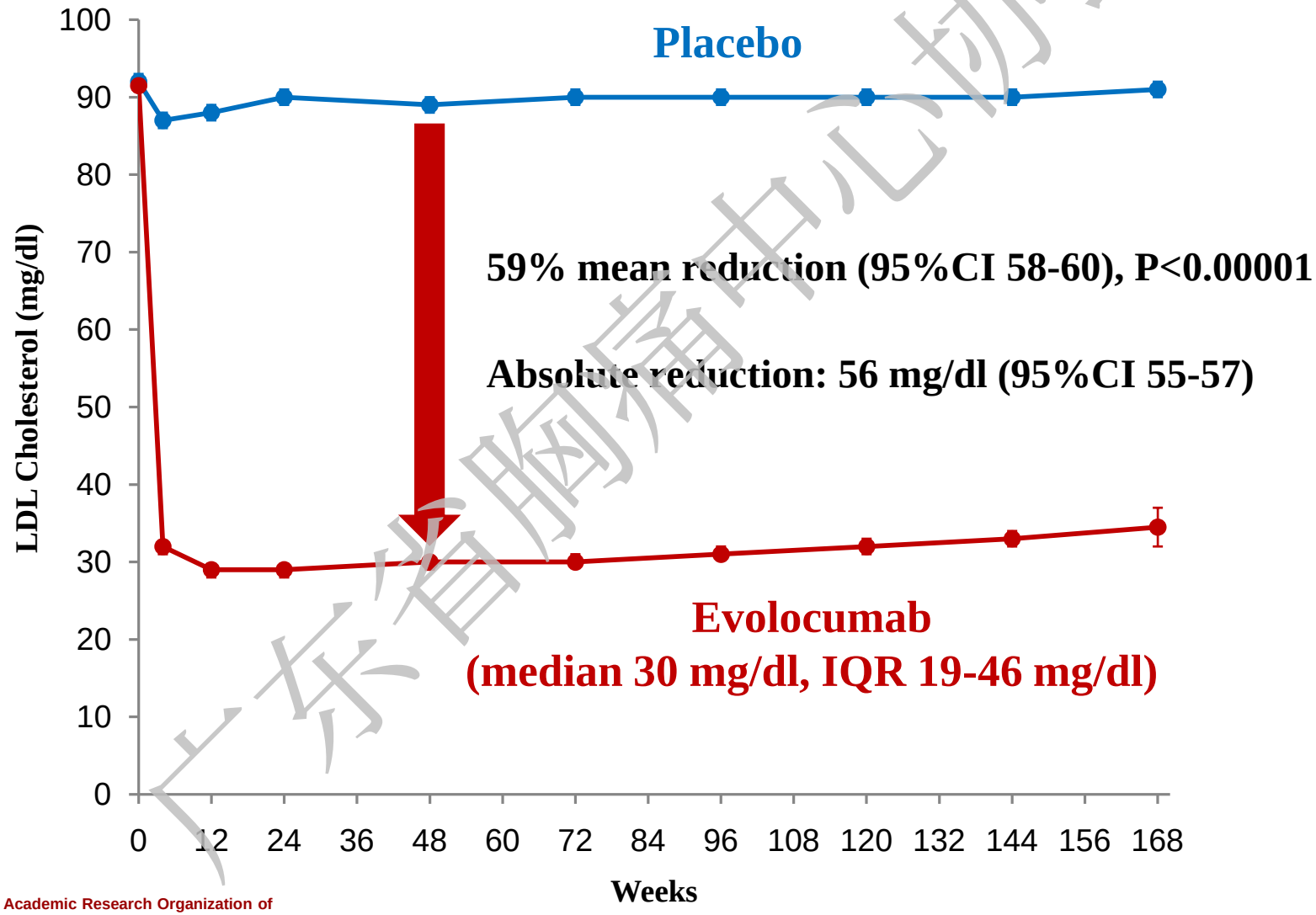
N Engl J Med. 2017 May 4;376(18):1713-1722

Trial Design

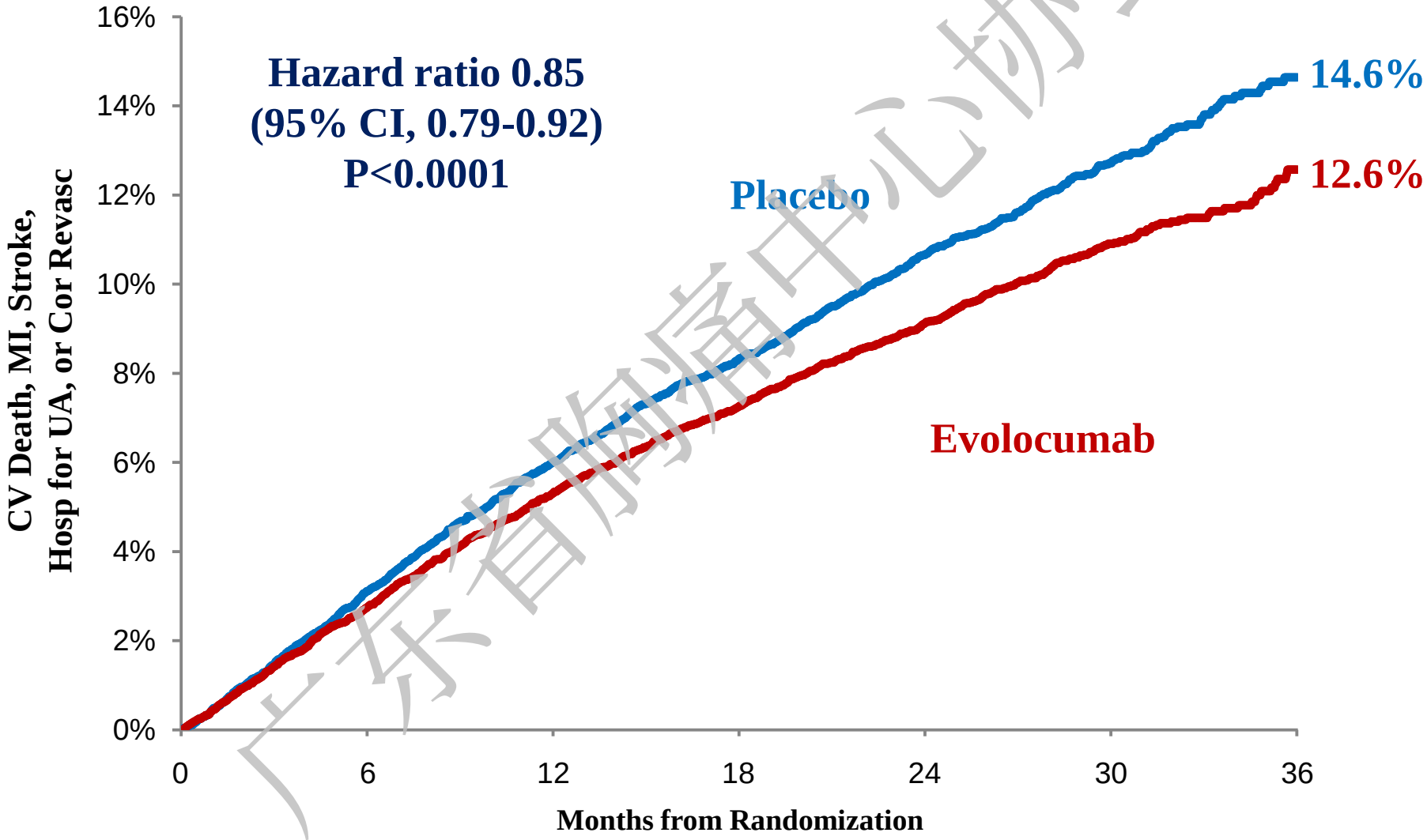


Sabatine MS et al. *Am Heart J* 2016;173:94-101

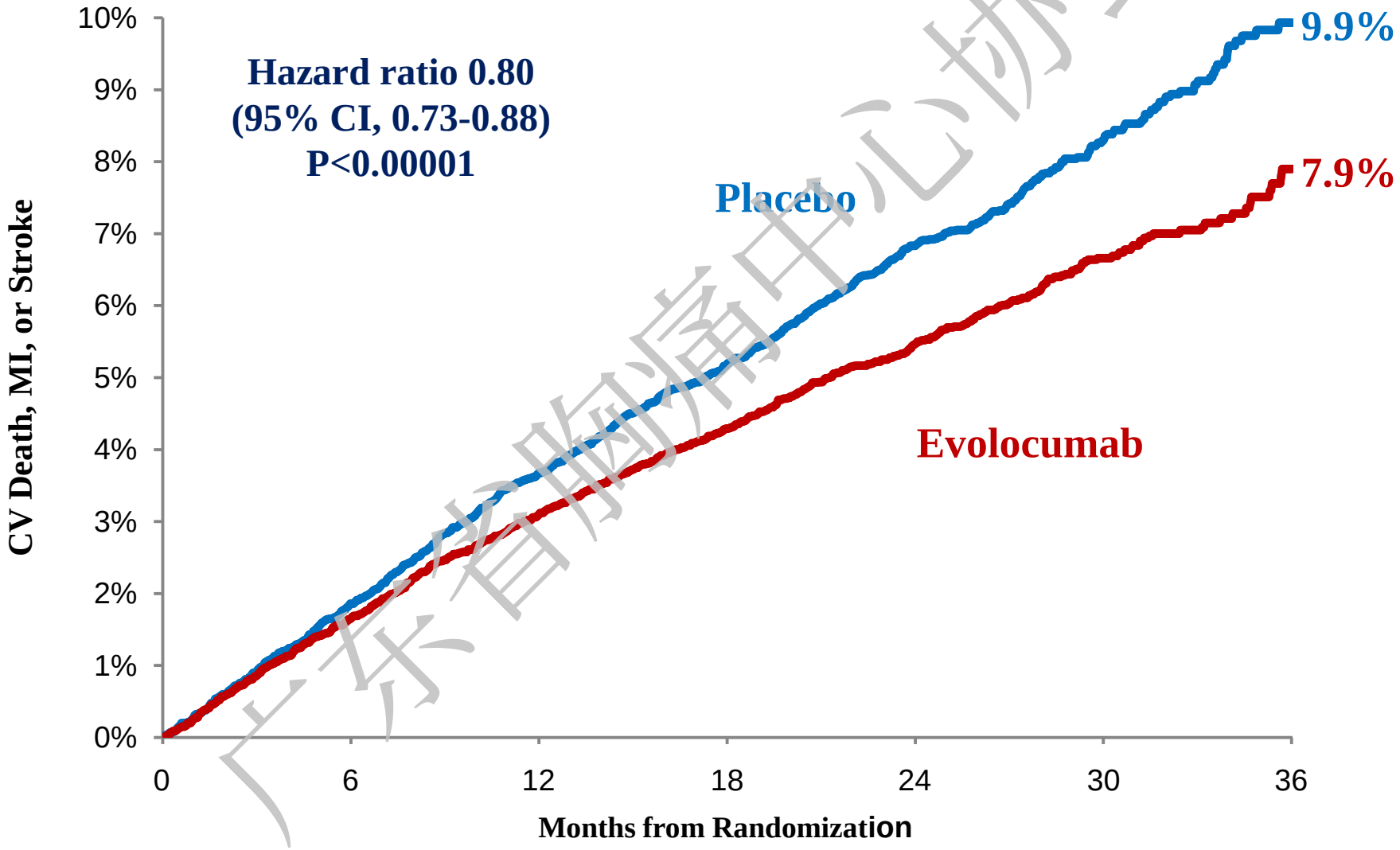
LDL Cholesterol



Primary Endpoint



Key Secondary Endpoint



Safety

	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events (%)		
Any	**77.4**	**77.4**
Serious	**24.8**	**24.7**
Allergic reaction	**3.1**	**2.9**
Injection-site reaction	**2.1**	**1.6**
Treatment-related and led to d/c of study drug	**1.6**	**1.5**
Muscle-related	**5.0**	**4.8**
Cataract	**1.7**	**1.8**
Diabetes (new-onset)	**8.1**	**7.7**
Neurocognitive	**1.6**	**1.5**
Laboratory results (%)		
Binding Ab	**0.3**	**n/a**
Neutralizing Ab	***none***	**n/a**

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC

Summary for Evolocumab

- **↓LDL-C by 59%**
  - Consistent throughout duration of trial
  - Median achieved LDL-C of 30 mg/dl (IQR **19-46** mg/dl)
- **↓CV outcomes in patients already on statin therapy**
  - **15%** ↓ broad primary endpoint; **20%** ↓ CV death, MI, or stroke
  - Consistent benefit, incl. in those on high-intensity statin, low LDL-C
  - **25%** reduction in CV death, MI, or stroke after 1st year
  - Long-term benefits consistent w/ statins per mmol/L ↓ LDL-C
- **Safe and well-tolerated**
  - Similar rates of AEs, incl DM & neurocog events w/ EvoMab & pbo
  - Rates of EvoMab discontinuation low and no greater than pbo
  - No neutralizing antibodies developed

Conclusions

In patients with known cardiovascular disease:

1.PCSK9 inhibition with evolocumab significantly & safely ↓ major cardiovascular events when added to statin therapy

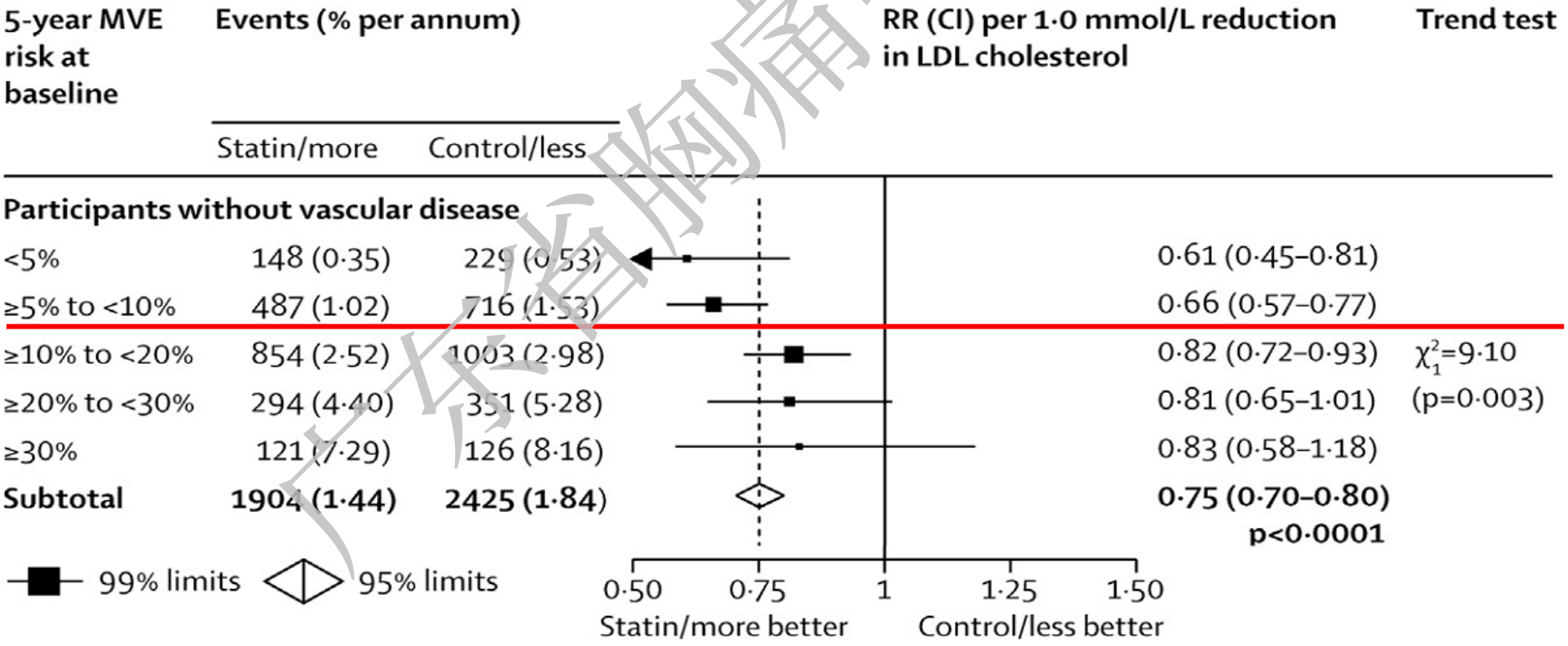
2.Benefit was achieved with lowering LDL cholesterol well below current targets

Curing Atherosclerosis Should Be the Next Major Cardiovascular Prevention Goal

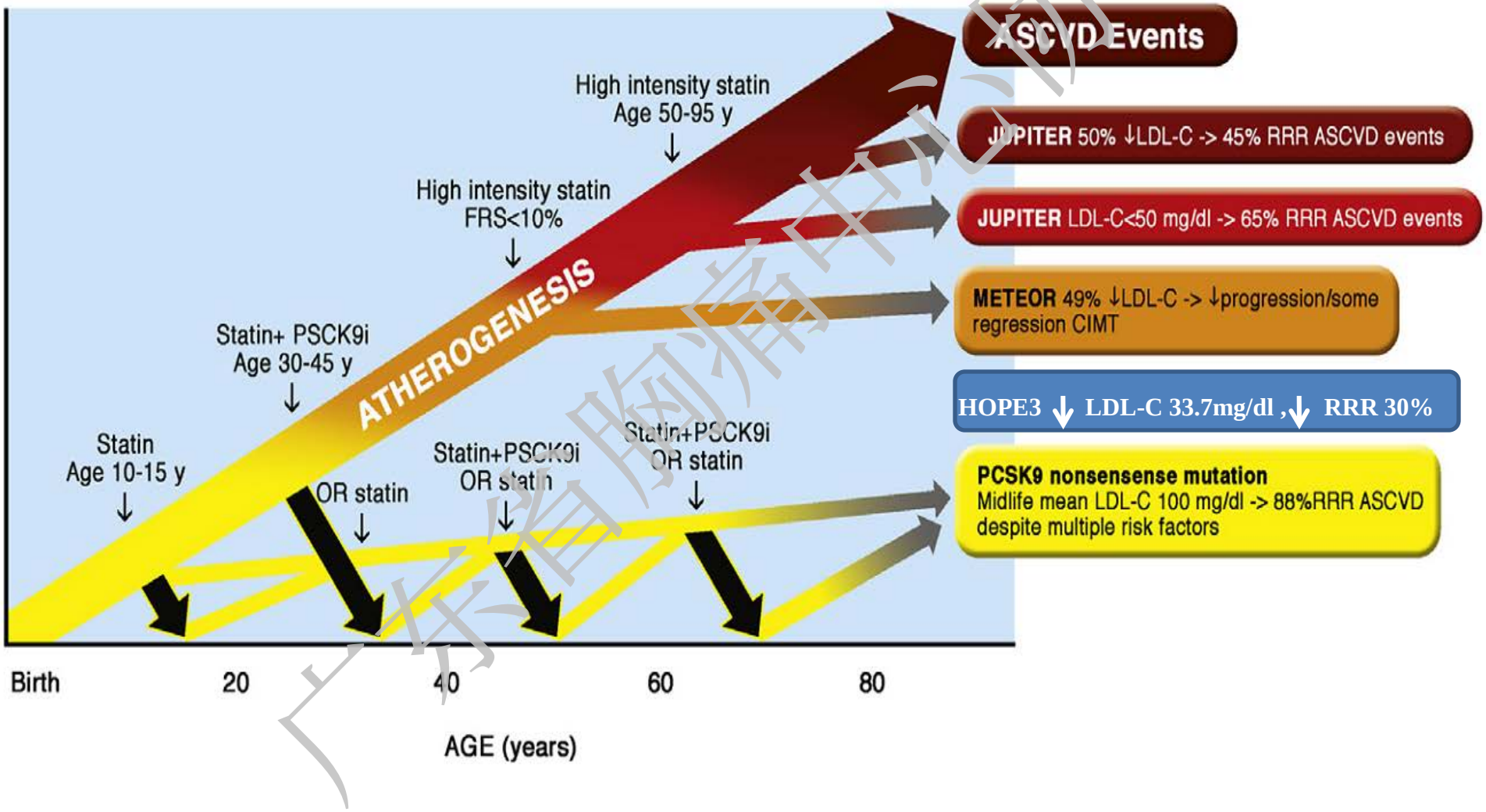
Jennifer G. Robinson, MD, MPH,* Samuel S. Gidding, MD†‡
Iowa City, Iowa; Wilmington, Delaware; and Philadelphia, Pennsylvania

J Am Coll Cardiol 2014;63:2779–85

Effects on Major ASCVD Events per 1.0-mmol/l (39mg/dl) ReductioninLDL-C



Conceptual Model for Resetting Vascular Age Clock Approach to the Primary Prevention of ASCVD



Summary

- 影像学检查发现斑块病人
- 斑块人群ASCVD风险高，属极高危人群
- 降低LDL-C降低斑块病人ASCVD风险
- 他汀药物--显著降低ASCVD风险

斑块人群启动他汀治疗，刻不容缓

Thank You !