抗血小板治疗的临床检测与监测

中国医学科学院 阜外医院
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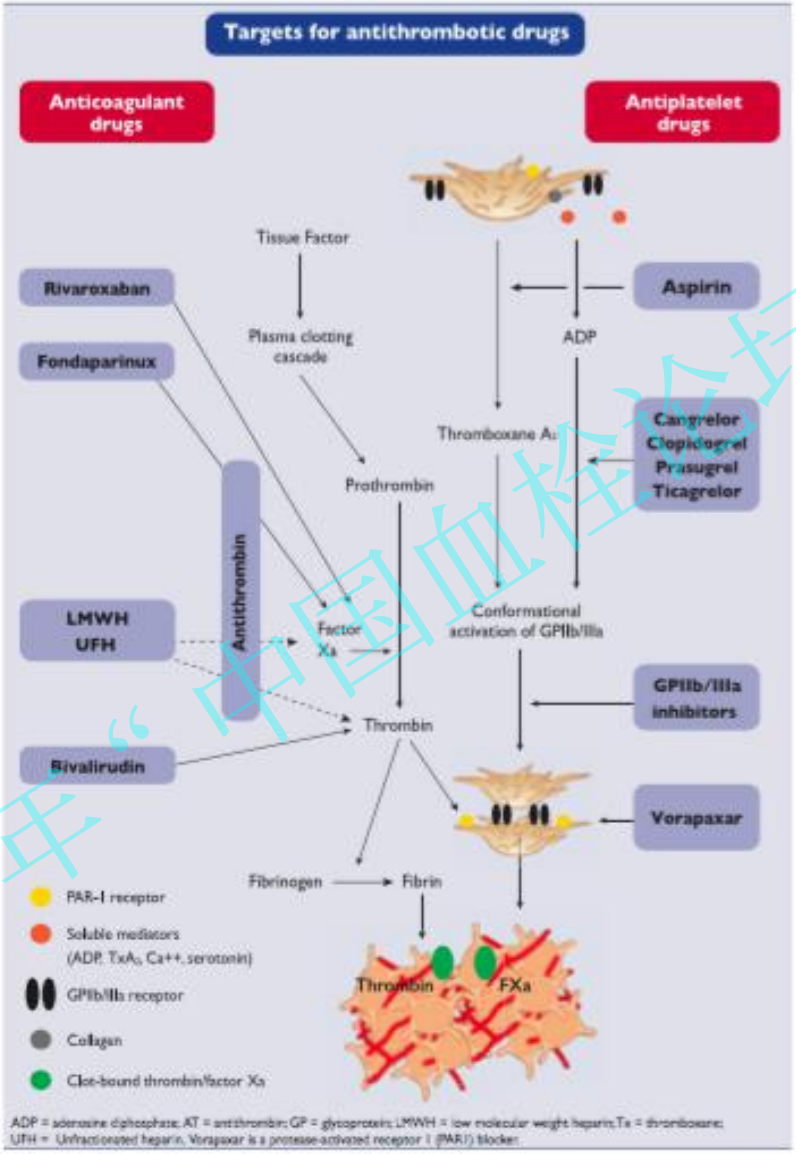
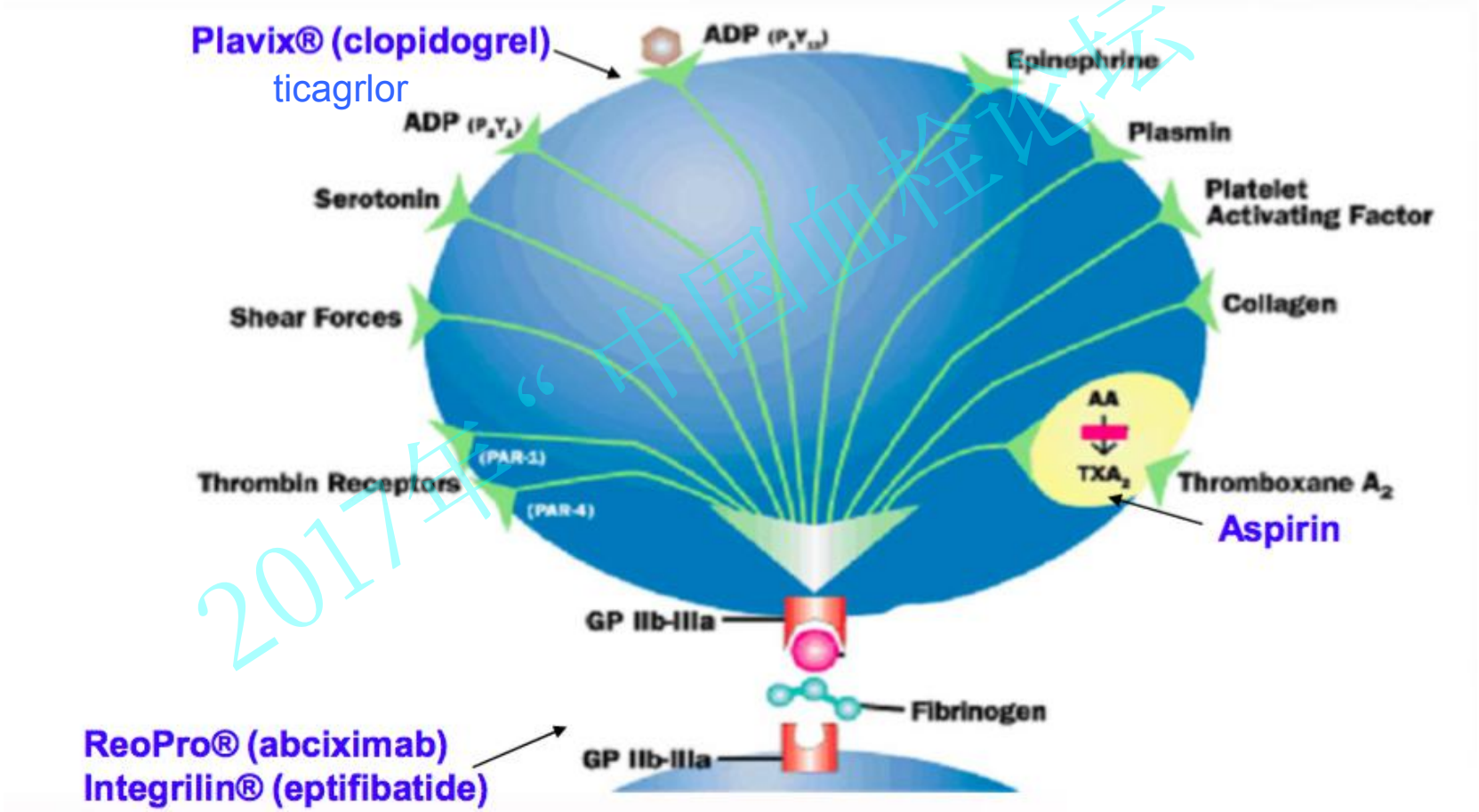
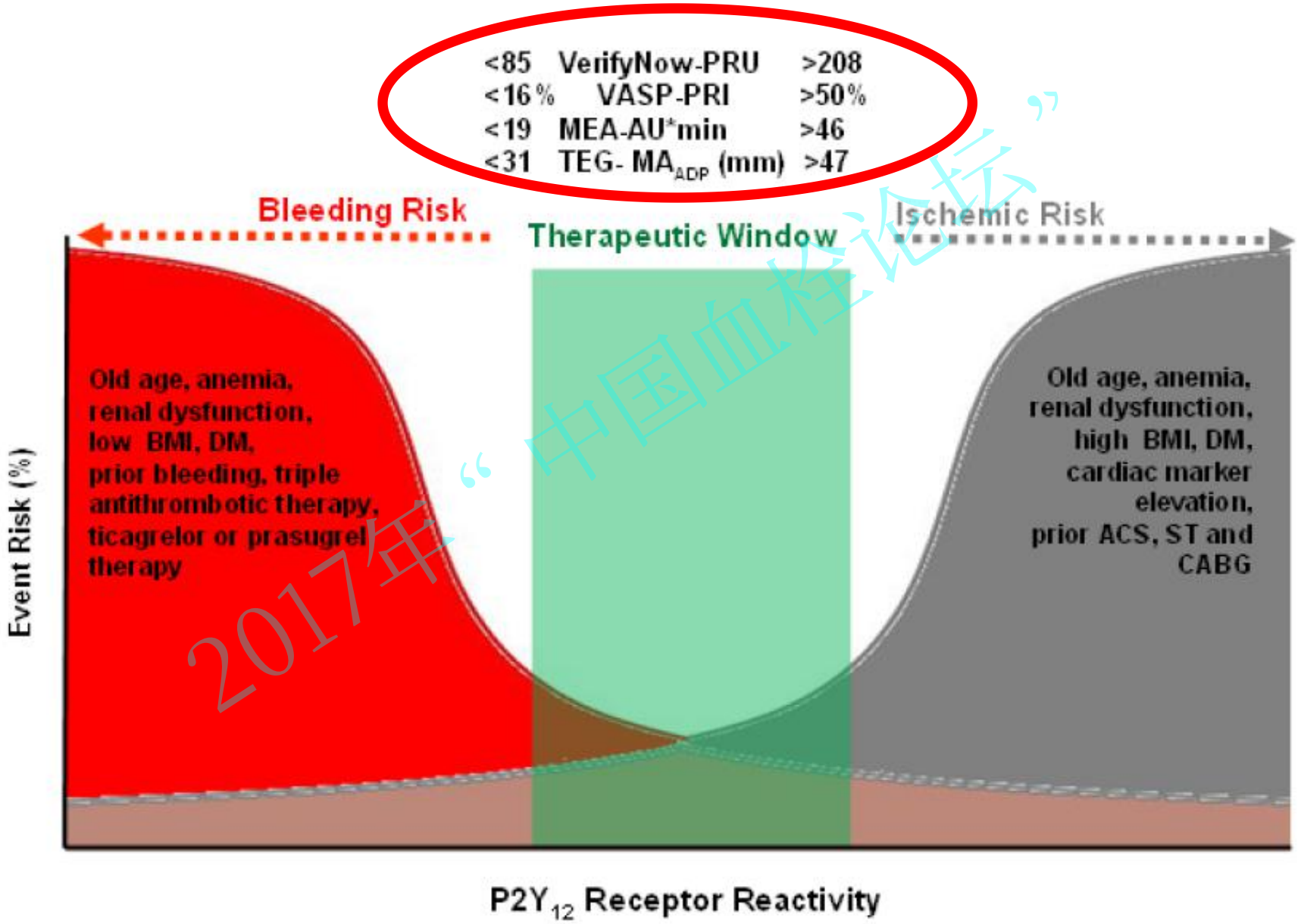


Figure 4 Antithrombotic drugs for non-ST-elevation acute coronary syndromes. The figure depicts the targets of available antithrombotic drugs that can be used to inhibit blood coagulation and platelet aggregation during and after thrombus formation.

2015 ESC guidelines for non ST-ACS

不同抗血小板药物作用靶点





The NEW ENGLAND JOURNAL of MEDICINE

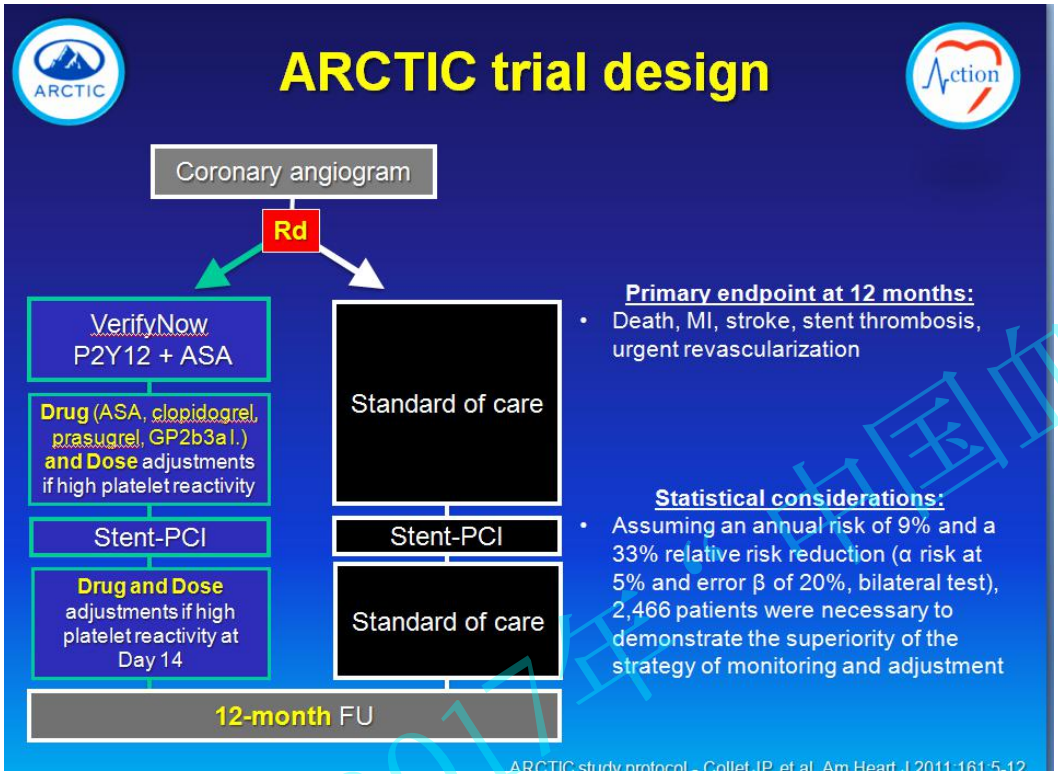
2012.11.04

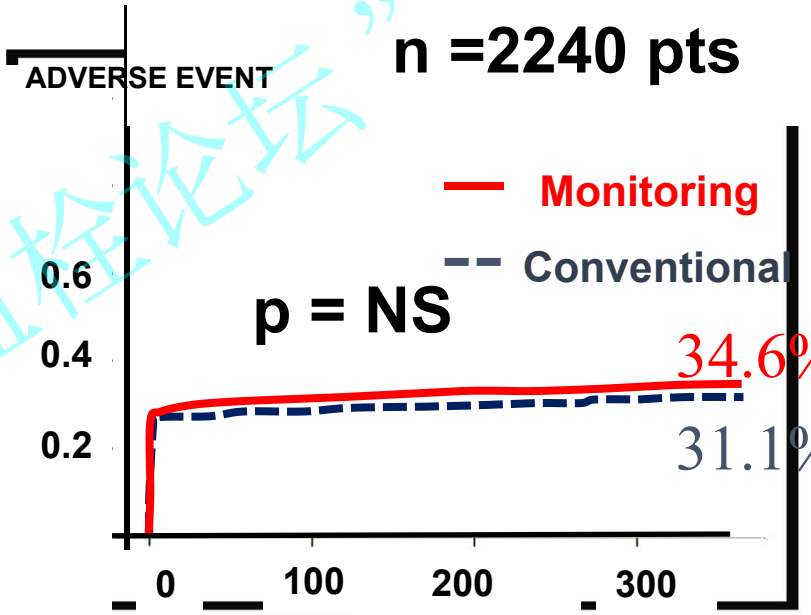
ORIGINAL ARTICLE

Bedside Monitoring to Adjust Antiplatelet Therapy for Coronary Stenting

Jean-Philippe Collet, M.D., Ph.D., Thomas Cuisset, M.D., Ph.D., Grégoire Rangé, M.D., Guillaume Cayla, M.D., Ph.D., Simon Elhadad, M.D., Christophe Pouillot, M.D., Patrick Henry, M.D., Ph.D., Pascal Motreff, M.D., Ph.D., Didier Carrié, M.D., Ziad Boueri, M.D., Ph.D., Loic Belle, M.D., Eric Van Belle, M.D., Ph.D., Hélène Rousseau, Ph.D., Pierre Aubry, M.D., Jacques Monsegu, M.D., Pierre Sabouret, M.D., Stephen A. O'Connor, M.B., B.Ch., Jérémie Abtan, M.D., Mathieu Kerneis, M.D., Christophe Saint-Etienne, M.D., Olivier Barthélémy, M.D., Farzin Beygui, M.D., Ph.D., Johanne Silvain, M.D., Ph.D., Eric Vicaut M.D., Ph.D., and Gilles Montalescot, M.D., Ph.D., for the ARCTIC Investigators*

- The Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting (ARCTIC)





No benefit of PR monitoring in all comers PCI patients

Collet et al. NEJM 2013

Limitations of ARCTIC

1. Low risk patients (mainly stable CAD)

2. Inadequate therapeutic strategy to overcome HTPR

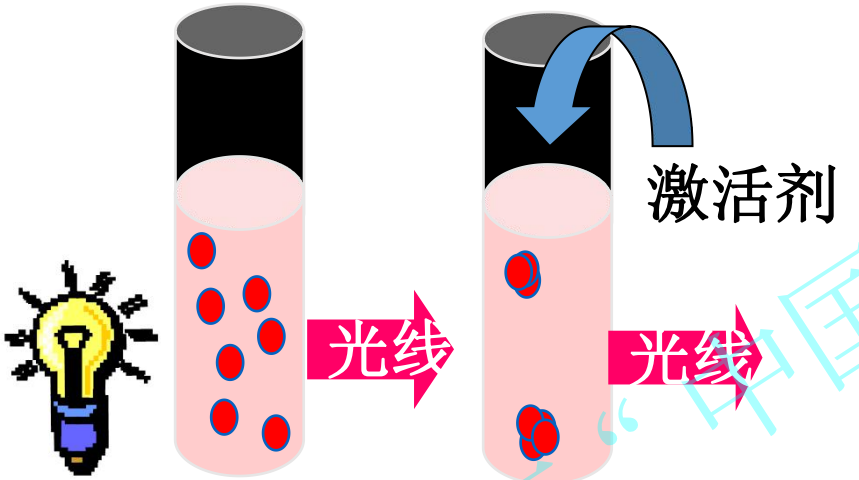
3. Primary end-point driven by peri-procedural MI (H6 troponin) which is unlikely related to PR

4. Complex design (aspirin resistance, use of clopidogrel/prasugrel…)

我们的思考

- 血小板功能检测到底有没有临床使用价值？
- 血小板高反应性的定义？
- 何种血小板功能的检测方法才是合适的？
- 可否与CYP2C19基因型检测相结合指导临床治疗？
- 是否需考虑种族差异？

1、光学比浊法血小板聚集试验（LTA）



- 1962即建立方法，
- 缺限：耗时很长

检测结果可重复性差，

血标本的需要量较大

抗血小板抵抗的定义：

受试者服用氯吡格雷后达到的最大血小板抑制率与基线相比<10%为抵抗，10－29%为半抵抗

2, VerifyNow

原理

枸橼酸抗凝全血中加入诱导剂**TRAP**，使血小板与纤维蛋白原珠凝集时的透光度增加，凝集程度与透光度增加呈正比，结果以**mV/10s**报告

优点：快速：**10’**样本稳定期，**3’**出结果，
适于床旁监测
简便：全血，无需样本预处理
操作人员无需专业培训
结果不受抗凝剂和致聚剂的影响

不足：
昂贵，目前多用于科研

3、流式细胞仪检测血小板激活的标志物

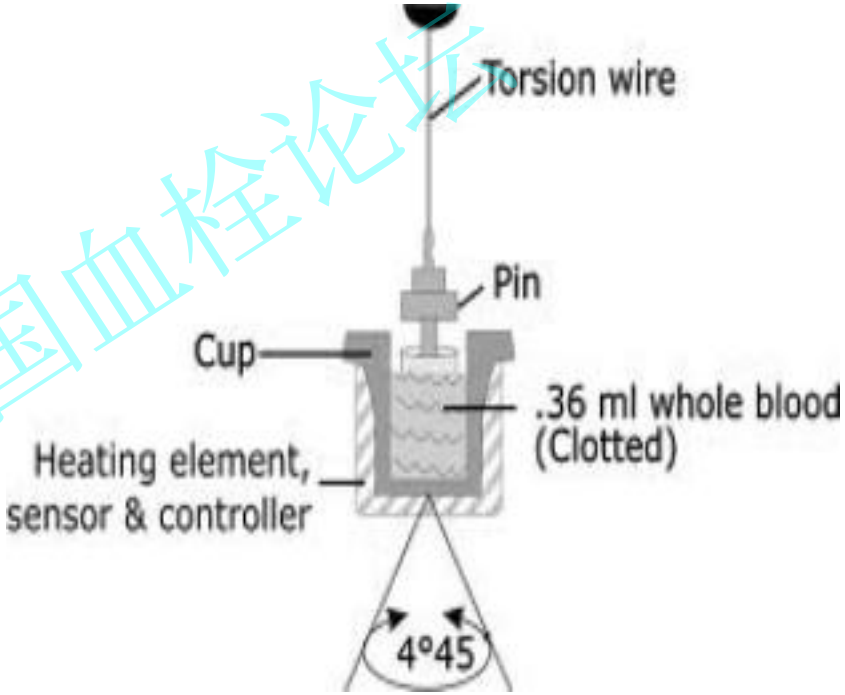
①舒血管物质磷酸蛋白（VASP）：利用VASP的磷酸化作用来评价氯吡格雷作用

Platelet surface P-selectin, platelet surface activated GP IIb/IIIa, leukocyte-platelet aggregates	Low sample volume; whole-blood assay	Sample preparation; expensive; requires flow cytometer, experienced staff	Yes	Yes*	Yes†	Yes

②P-选择蛋白（GMP-140）：用P-选择蛋白的单克隆抗体标测，分析血小板P-选择蛋白的表达。

③GP Ⅱb/Ⅲa：用GP Ⅱb/Ⅲa的单克隆抗体标测，分析血小板GP Ⅱb/Ⅲa的表达。这种方法用的不是全血，而且耗时而繁琐，所以限制了临床上的推广。

4, 血栓弹力图（Thrombelastography，TEG）



血凝块的形成源于凝血酶诱导纤维蛋白A聚集，形成三维纤维蛋白性纤维网。它具有抵抗剪切张力引起变形的性质，此特性可通过弹性指数测量，而定量监测血凝块形成的全过程。

阿司匹林无反应性与不良临床事件显著相关

阿司匹林无反应性cutoff值：EPI<193秒

ORIGINAL ARTICLE

Use of the PFA-100™ closure time to predict cardiovascular events in aspirin-treated cardiovascular patients: a systematic review and meta-analysis

15 studies, 2693 patients

Thromb Haemost 2008; 99: 1129–1131

PFA-100 closure time to predict cardiovascular events in aspirin-treated cardiovascular patients: A meta-analysis of 19 studies comprising 3,003 patients

19 studies, 3003 patients

Review Article

Response variability to aspirin as assessed by the platelet function analyzer (PFA)-100

A systematic review

53 studies, 6450 subjects

氯吡格雷低反应对临床预后的影响（早期小样本研究）

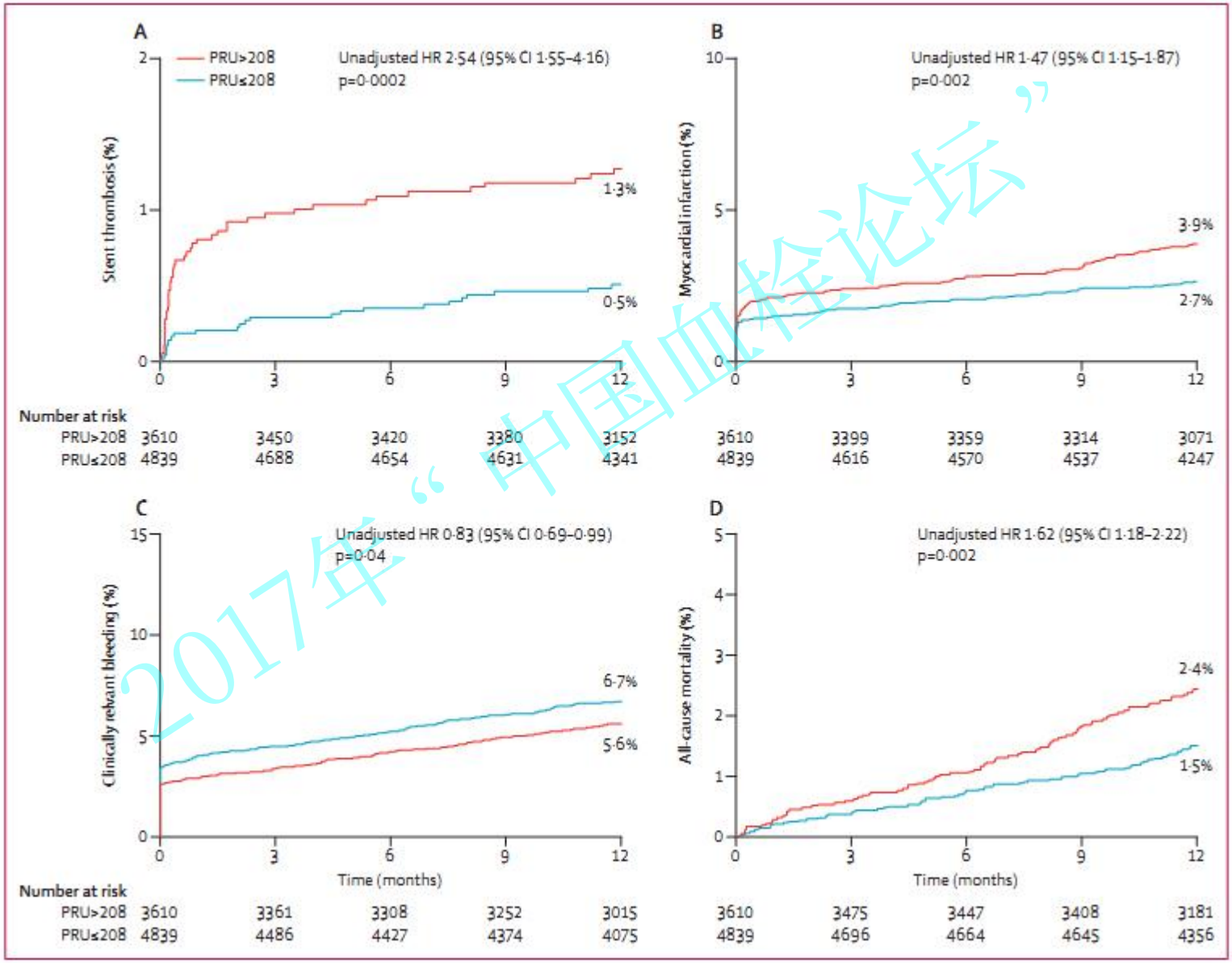
Study	Results	Clinical Relevance
1. Barragan et al. (Catheter Cardiovasc Interv. 2003;59::295)	↑ $P2Y_{12}$ reactivity ratio (VASP-P levels)	Stent Thrombosis
2. Ajzenberg et al. (J Am Coll Cardiol. 2005;45:1753)	↑ Shear- Induced platelet aggregation	Stent Thrombosis
3. Gurbel et al. (CREST Study) (J Am Coll Cardiol. 2005;46:1827)	↑ $P2Y_{12}$ reactivity ratio ↑ ADP- induced aggregation ↑ Stimulated GPIIb/IIIa expression	Stent Thrombosis
4. Matzesky et al. (Circulation.2005;109:3171)	↑ ADP-Induced platelet aggregation	Recurrent Cardiac Events (4th quartile)
5. Gurbel et al. (CLEAR PLATELETS and CLEAR PLATELETS Ib) (Circulation. 2005;111:1153, J Am Coll Cardiol;2006 (in press)	↑ Periprocedural platelet aggregation	Myonecrosis and Inflammation Marker Release
7. Gurbel et al. (J Am Coll Cardiol. 2006;47:45B)	↑ Platelet aggregation (pre-PCI) on chronic clopidogrel	Post -PCI Events
8. Cussiet et al. (J Thromb Haemost. 2005;3:1)	↑ Platelet aggregation	Recurrent Events
9. Lev et al. (J Am Coll Cardiol. 2006;47:27)	Clopidogrel/Aspirin resistant patients	Post-PCI Myonecrosis

THE LANCET 2013 Aug 17;382(9892):614-23.

Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study

*Gregg W Stone, Bernhard Witzenbichler, Giora Weisz, Michael J Rinaldi, Franz-Josef Neumann, D Christopher Metzger, Timothy D Henry, David A Cox, Peter L Duffy, Ernest Mazzaferri, Paul A Gurbel, Ke Xu, Helen Parise, Ajay J Kirtane, Bruce R Brodie, Roxana Mehran, Thomas D Stuckey, for the ADAPT-DES Investigators**

- 8583例PCI患者，随访12个月
- VerifyNow检测，PRU>208定义为血小板高反应性



血小板高反应性是PCI术后不良事件的危险因素

Adjusted Risk of PRU>208 for events in ADAPT-DES (**N=8583**)

Event	Adj HR[95%CI]	P value
ST, def/prob	2.51 [1.45, 4.37]	0.001
- Definite	3.12 [1.65, 5.90]	0.0004
MI	1.40 [1.07, 1.83]	0.01
Major bleeding	0.75 [0.62, 0.91]	0.004
Death, all-cause	1.24 [0.88, 1.75]	0.23

Stone GW et al, *Lancet* 2013; 382: 614–23

European Heart Journal (2015) **36**, 1762–1771
doi:10.1093/eurheartj/ehv104

CLINICAL RESEARCH
Thrombosis and antithrombotic therapy

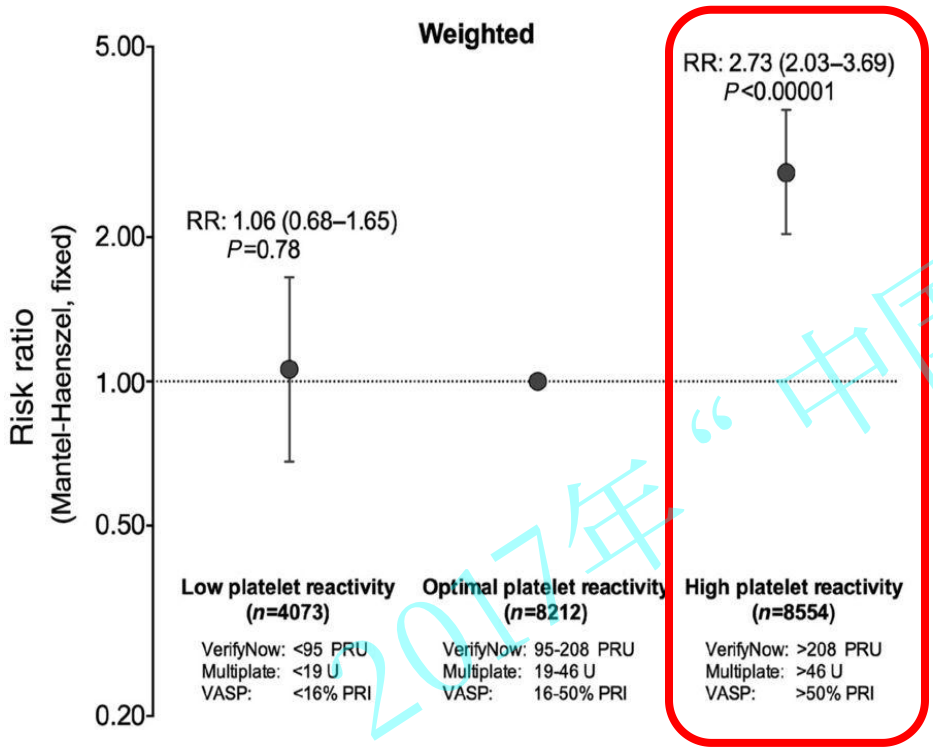
Bleeding and stent thrombosis on $P2Y_{12}$-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention

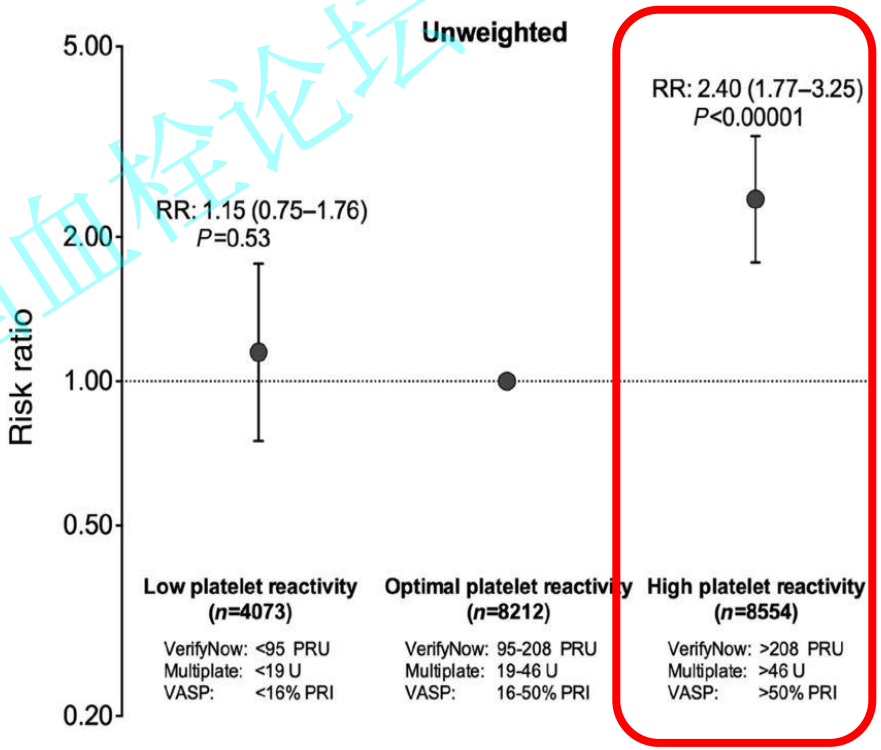
- 17项以西方人群为主的近期研究
- 标准化血小板功能检测，排除了较老的LTA检测

Table I Baseline characteristics of the 17 studies included in the collaborative analysis

First author	Acronym	Year	*n*	Expl study	Device	$P2Y_{12}$-inhibitor	Definition of bleeding
Bonello[15]	–	2012	301	Yes	VASP	Prasugrel	TIMI major
Breet[19]	POPular	2010	1052	No	VerifyNow	Clopidogrel	TIMI major
Campo[20]	–	2011	300	No	VerifyNow	Clopidogrel	TIMI major + minor
Cuisset[22]	POBA	2013	1542	No	VASP	Clopidogrel, prasugrel	BARC type ≥ 2
Freynhofer[17]	WILMAA	2011	300	No	VASP	Clopidogrel	TIMI major
Mangiacapra[23]	ARMYDA-PROVE	2012	732	No	VerifyNow	Clopidogrel	TIMI major
Marcucci[27]	–	2009	683	No	VerifyNow	Clopidogrel	TIMI major
Morel[24]	–	2011	433	No	VASP	Clopidogrel	TIMI major
Patti[26]	ARMYDA-PRO	2008	160	No	VerifyNow	Clopidogrel	TIMI major
Patti[25]	ARMYDA-BLEEDING	2011	310	No	VerifyNow	Clopidogrel	TIMI major
Palmerini[28]	GEPRESS	2014	978	No	VASP	Clopidogrel	BARC type ≥2
Price[9]	GRAVITAS	2011	1692[a]	No	VerifyNow	Clopidogrel	GUSTO mod/severe
Sibbing[13]	ISAR	2010	2533	Yes	Multiplate	Clopidogrel	TIMI major
Sibbing[21]	ISAR-REACT 4	2012	564	No	Multiplate	Clopidogrel	TIMI major
Siller-Matula[18]	MADONNA	2012	395[a]	No	Multiplate	Clopidogrel	TIMI major
Siller-Matula[16]	PEGASUS PCI	2012	416	No	Multiplate	Clopidogrel	TIMI major
Stone[12]	ADAPT-DES	2013	8,448	Yes	VerifyNow	Clopidogrel	ADAPT-defined

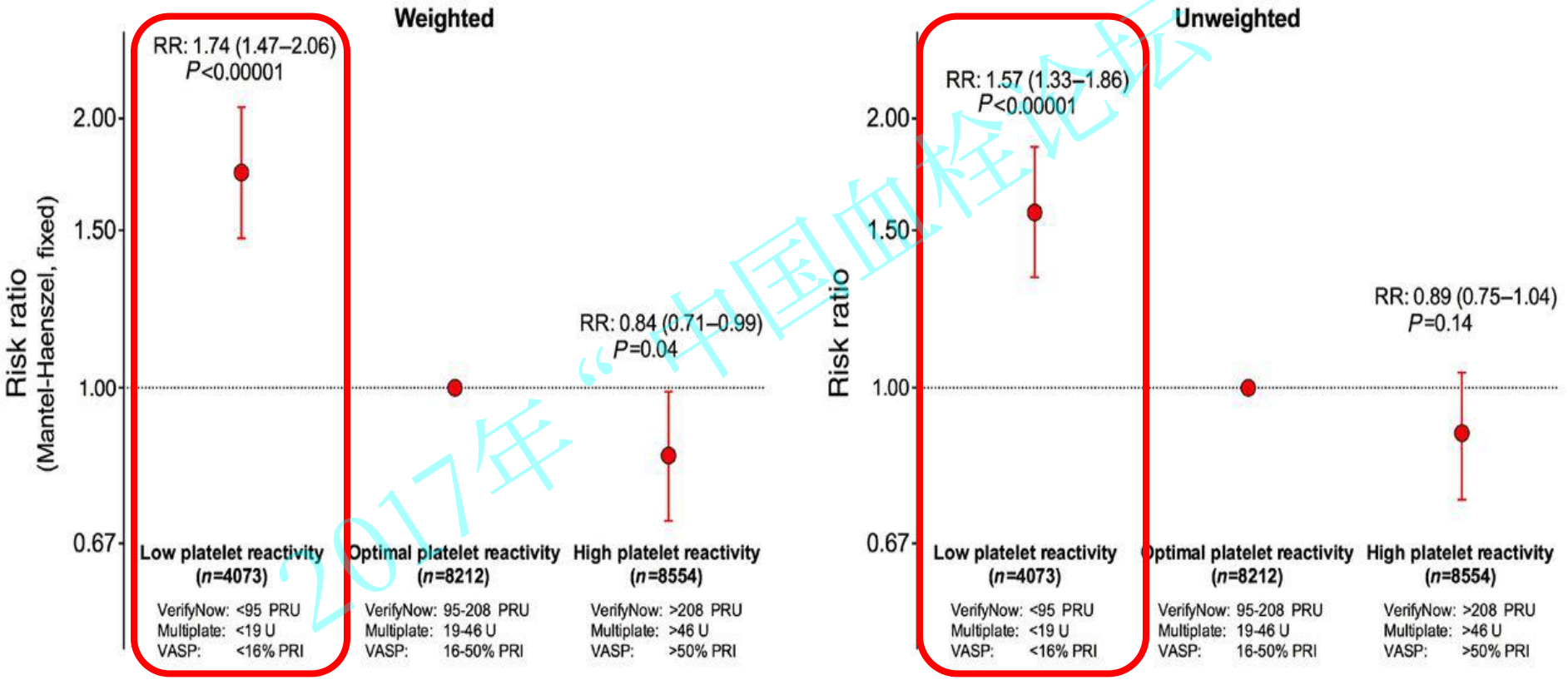
Relative risk of stent thrombosis according to platelet reactivity levels.





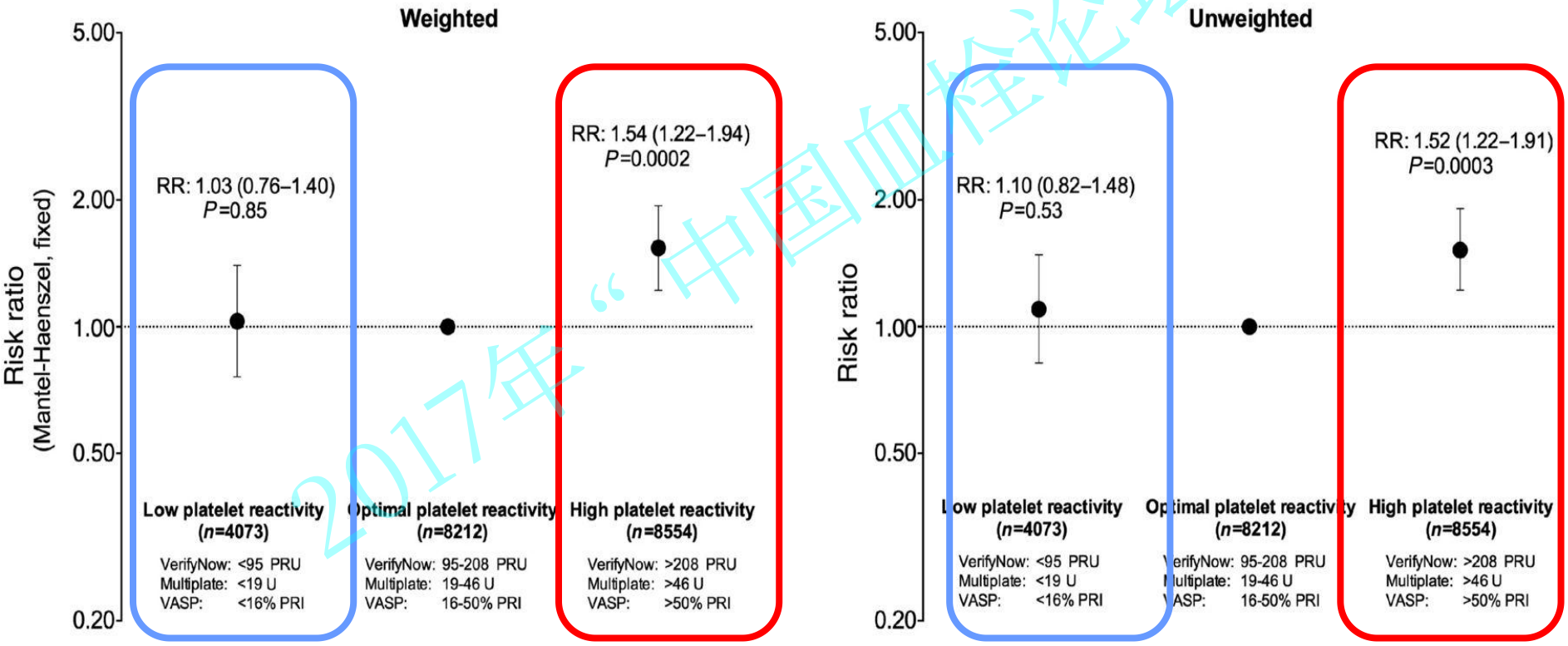
Dániel Aradi et al. Eur Heart J 2015;36:1762-1771

Relative risk of bleeding events according to platelet reactivity levels.



Dániel Aradi et al. Eur Heart J 2015;36:1762-1771

Relative risk of mortality according to platelet reactivity levels.



Dániel Aradi et al. Eur Heart J 2015;36:1762-1771

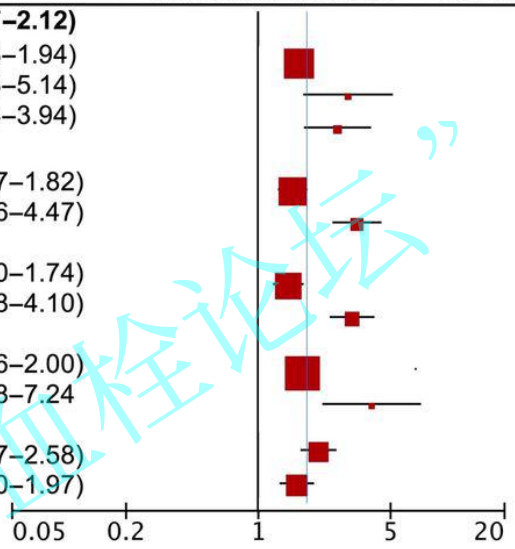
Interaction analysis according to subgroups.

检测方法

药物

疾病状态

Subgroup	LPR: n/N	no LPR: n/N	Risk Ratio 95%CI
Overall			**1.82 (1.57–2.12)**
1. VerifyNow	172/2167	461/11210	1.64 (1.38–1.94)
Multiplate	32/1358	20/2550	2.98 (1.73–5.14)
VASP	26/548	86/3006	2.62 (1.74–3.94)
2. Exploratory studies	164/2748	404/8532	1.52 (1.27–1.82)
Validation studies	66/1325	163/8234	3.32 (2.46–4.47)
3. ADAPT-DES	140/1690	388/6758	1.44 (1.20–1.74)
Excl. ADAPT-DES	90/2383	179/10008	3.13 (2.38–4.10)
4. Clopidogrel	210/3909	549/16242	1.71 (1.46–2.00)
Prasugrel	20/164	18/524	3.97 (2.18–7.24
5. ACS	210/3909	549/16242	2.08 (1.67–2.58)
No ACS	20/164	18/524	1.60 (1.30–1.97)

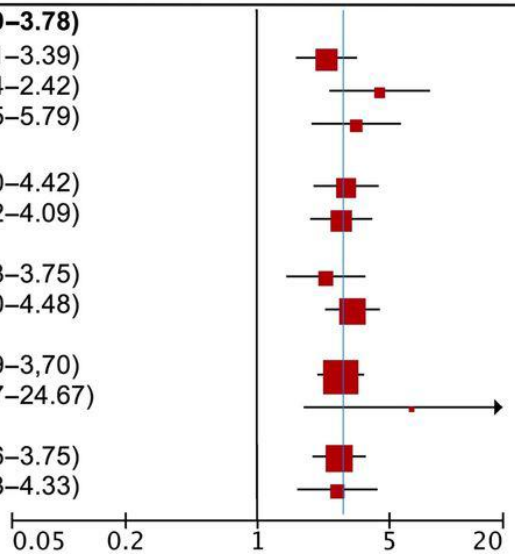


检测方法

药物

疾病状态

Subgroup	HPR: n/N	no HPR: n/N	Risk Ratio 95%CI
Overall			**2.88 (2.19–3.78)**
1. VerifyNow	81/6355	40/7022	2.34 (1.61–3.39)
Multiplate	26/927	17/2981	4.47 (8.24–2.42)
VASP	38/1272	34/2282	3.36 (1.95–5.79)
2. Exploratory studies	62/4112	38/7168	2.97 (2.00–4.42)
Validation studies	83/4442	53/5117	2.80 (1.92–4.09)
3. ADAPT-DES	45/3609	26/4839	2.32 (1.43–3.75)
Excl. ADAPT-DES	100/4945	65/7446	3.21 (2.30–4.48)
4. Clopidogrel	139/8463	84/11690	2.78 (2.09–3,70)
Prasugrel	6/92	7/596	6.60 (1.77–24.67)
5. ACS	106/4307	69/5968	2.72 (1.96–3.75)
No ACS	39/4244	22/6320	2.66 (1.63–4.33)



？？????....

患者是否应该区别对待？

不同风险患者治疗策略有所不同？

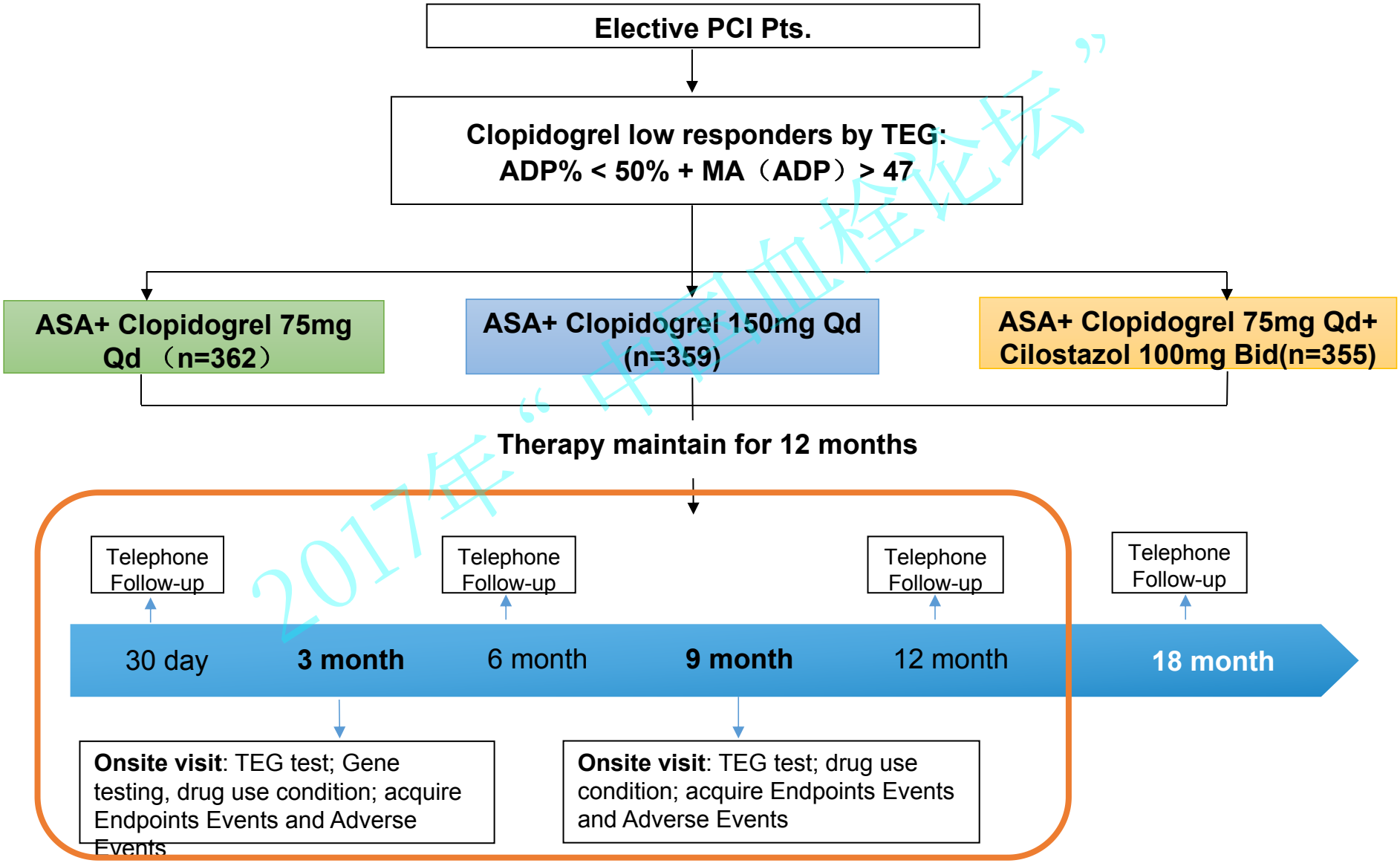
阜外医院-前瞻性干预研究

- Clopidogrel Response Evaluation And Therapeutic InterVEntion in High Risk PCI Patients

  CREATIVE study

- 根据TEG检测结果，入选1050例血栓高危患者， 随机分为标准双抗组、氯吡格雷加倍组、加用西洛他唑组。
- 随访12个月（MACCE，TEG，出血事件）

Study Flow Chart



Population Characteristics

	STANDARD N=362	DOUBLE N=359	TRIPLE N=355	P value
Gender (male)	214 (59.1%)	219 (61.0%)	211 (59.4%)	0.136
Age (year)	58.64±8.75	58.12±8.97	58.39±9.03	0.201
BMI (kg/m^2)	25.78±3.12	26.02±3.16	25.69±3.04	0.073
SBP (mmHg)	128.1±17.5	127.2±16.4	126.9±15.4	0.599
DBP (mmHg)	77.6±10.7	78.6±10.5	77.3±9.3	0.197
diabetes mellitus	121 (33.4%)	115 (32.0%)	121 (34.1%)	0.838
Hypertension	243 (67.1%)	219 (61.0%)	229 (64.5%)	0.228
Dyslipidemia	233 (64.4%)	246 (68.5%)	229 (64.5%)	0.408
Pre-stroke	39 (10.8%)	37 (10.3%)	46 (13.0%)	0.503
Smoking	124 (34.3%)	137 (38.2%)	137 (38.6%)	0.320
Pre-MI	57 (15.7%)	59 (16.4%)	44 (12.4%)	0.260
Pre-CABG	8 (2.2%)	7 (1.9%)	4 (1.1%)	0.495
Pre-PCI	72 (19.9%)	77 (21.4%)	67 (18.9%)	0.688
Atrial fibrillation	353 (97.5%)	355 (98.9%)	348 (98.0%)	0.367

Procedural Characteristics

	STANDARD N=362	DOUBLE N=359	TRIPLE N=355	P value
Presentation				0.9931
NSTEMI	43 (11.9%)	48 (13.4%)	46 (13.0%)	
STEMI	25 (6.9%)	24 (6.7%)	26 (7.3%)	
Unstable angina	148 (40.9%)	148 (41.2%)	140 (39.4%)	
Stable angina	146 (40.3%)	139 (38.7%)	143 (40.3%)	
Procedure time	26.34±16.10	29.77±21.05	28.55±20.85	0.061
No. of stents	1.65±0.75	1.73±0.85	1.73±0.84	0.215
Length of stents	31.86±16.89	32.79±18.66	31.71±17.16	0.672
Transradial approach	339 (94.4%)	338 (94.2%)	330 (93.5%)	0.635
Pre-dilatation	254 (70.2%)	264 (73.5%)	258 (72.7%)	0.578
B2/C type lesions	282 (78.8%)	297 (83.9%)	277 (78.7%)	0.128
No. of target lesions				0.064
1	274 (75.7%)	242 (67.4%)	235 (66.2%)	
≥2	88 (24.3%)	117 (32.6%)	120 (33.8%)	
CTO lesions	48 (13.4%)	56 (15.6%)	47 (13.3%)	0.741

Baseline Medication

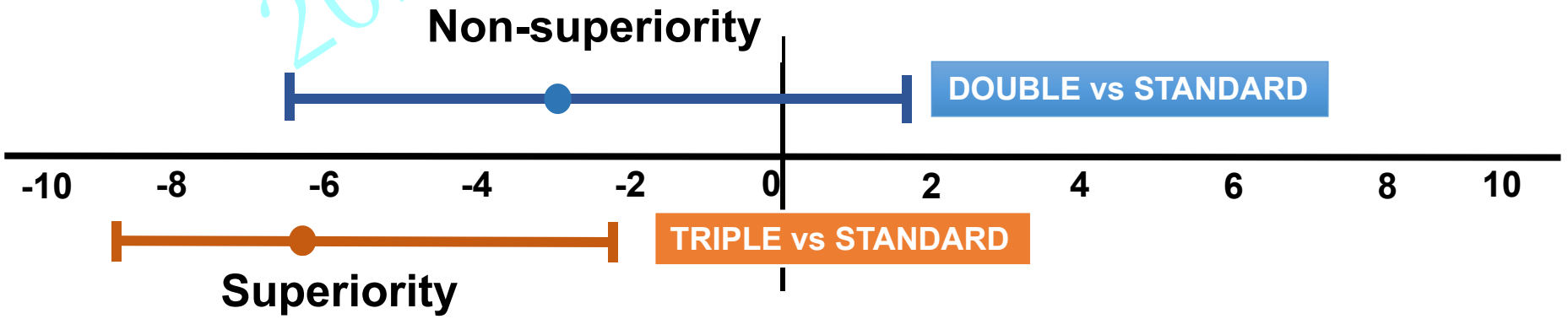
	STANDARD N=362	DOUBLE N=359	TRIPLE N=355	P value
Clopidogrel regimen				0.579
Loading dose, 300 mg	135 (37.3%)	146 (40.7%)	133 (37.5%)	
Maintenance, 75 mg＞5d	227 (62.7%)	213 (59.3%)	222 (62.5%)	
Perioperative anticoagulation				
LMWH	197 (54.4%)	192 (53.5%)	195 (54.9%)	0.925
Fondaparinux	111 (30.7%)	118 (32.9%)	107 (30.1%)	0.706
Unfractionated heparin	138 (38.1%)	134 (37.3%)	140 (39.4%)	0.843
IIb/IIIa inhibitors	44 (12.2%)	52 (14.5%)	44 (12.4%)	0.598
Statin	1818 (86.7)	1895 (89.2)	1761 (90.6)	0.625
Calcium-channel blocker	480 (22.9)	514 (24.2)	418 (21.5)	0.081
Proton pump inhibitor	41 (11.3%)	29 (8.1%)	35 (9.9%)	**0.028**

Primary Endpoint: MACCE

(CMH Chi square test)

STANDARD (n = 362)	DOUBLE (n = 359)	Difference : -3.3 95% CI : [-6.5; 1.7]	Superiority *P* value P=0.172
47 (13.0%)	35 (9.7%)		

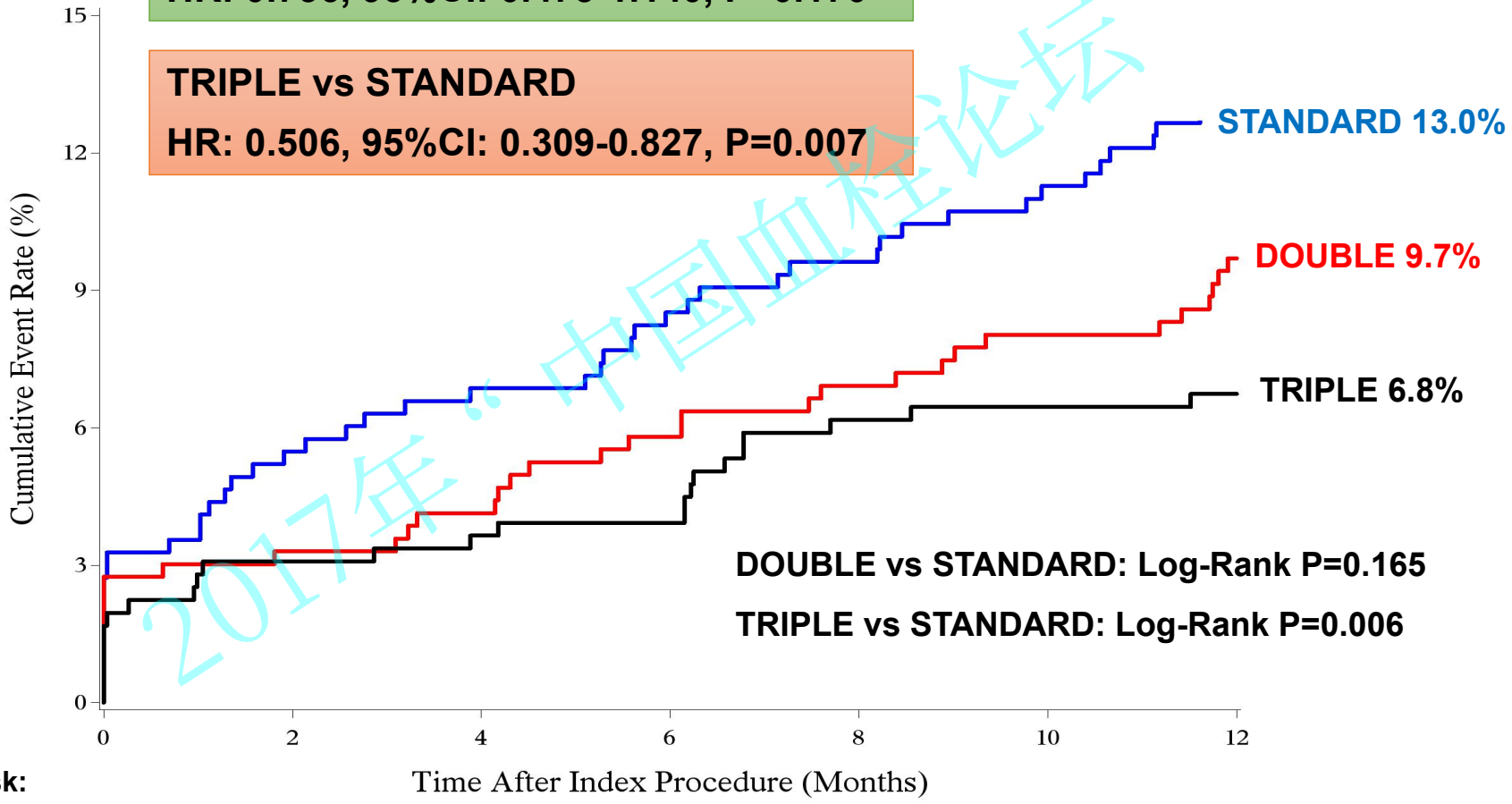
STANDARD (n = 362)	TRIPLE (n = 355)	Difference : -6.2 95% CI : [-8.8; -2.2]	Superiority *P* value P=0.005
47 (13.0%)	24 (6.8%)		



Survival Analysis for MACCE
(death, MI, TVR, stroke)

DOUBLE vs STANDARD
HR: 0.736, 95%CI: 0.475-1.140, P=0.170

TRIPLE vs STANDARD
HR: 0.506, 95%CI: 0.309-0.827, P=0.007



No. at Risk:							
STANDARD	362	342	337	331	327	321	315
DOUBLE	359	347	344	338	334	330	324
TRIPLE	355	344	342	341	333	332	331

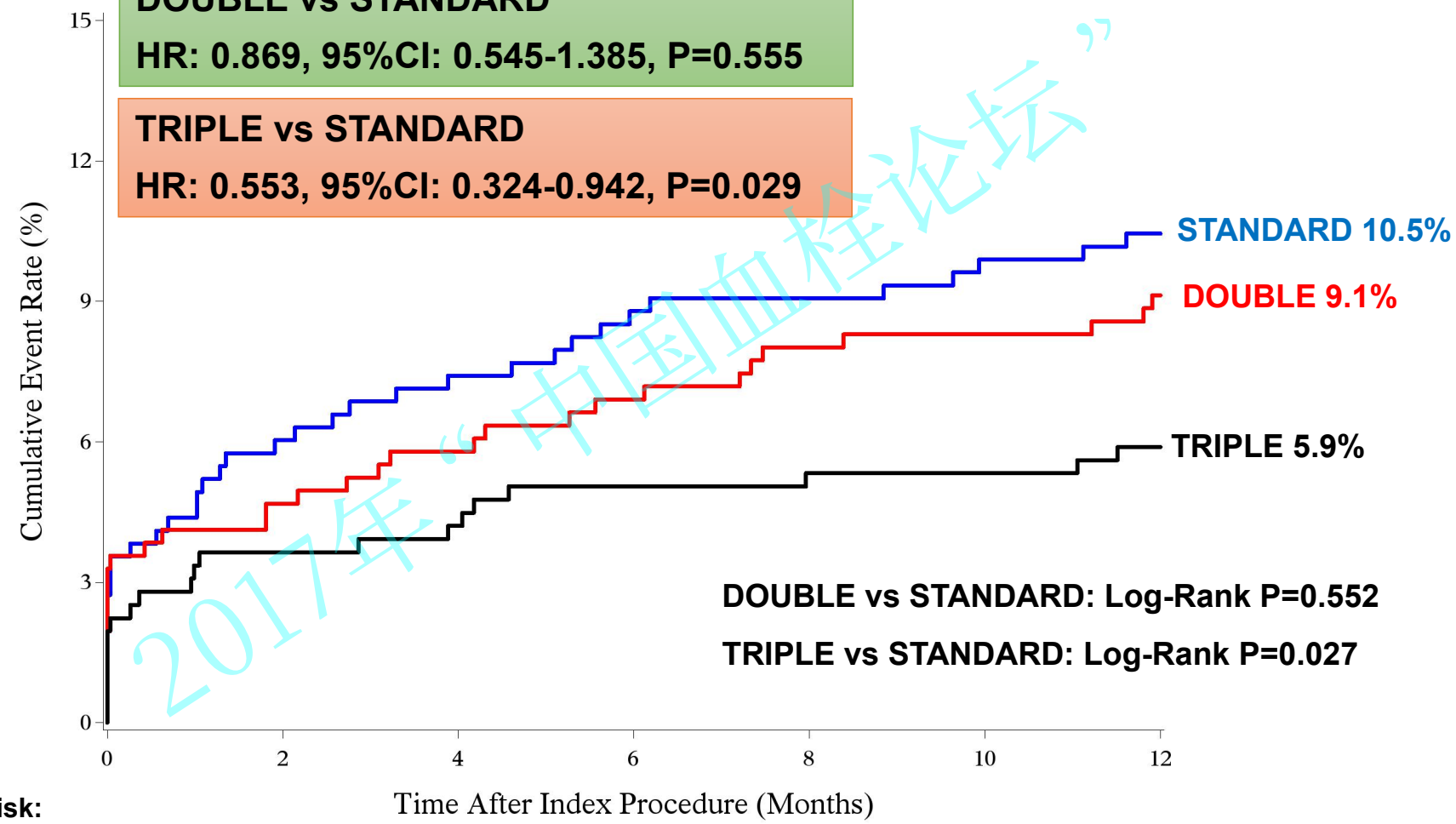
NACCE: death, MI, stroke, major bleeding

DOUBLE vs STANDARD

HR: 0.869, 95%CI: 0.545-1.385, P=0.555

TRIPLE vs STANDARD

HR: 0.553, 95%CI: 0.324-0.942, P=0.029



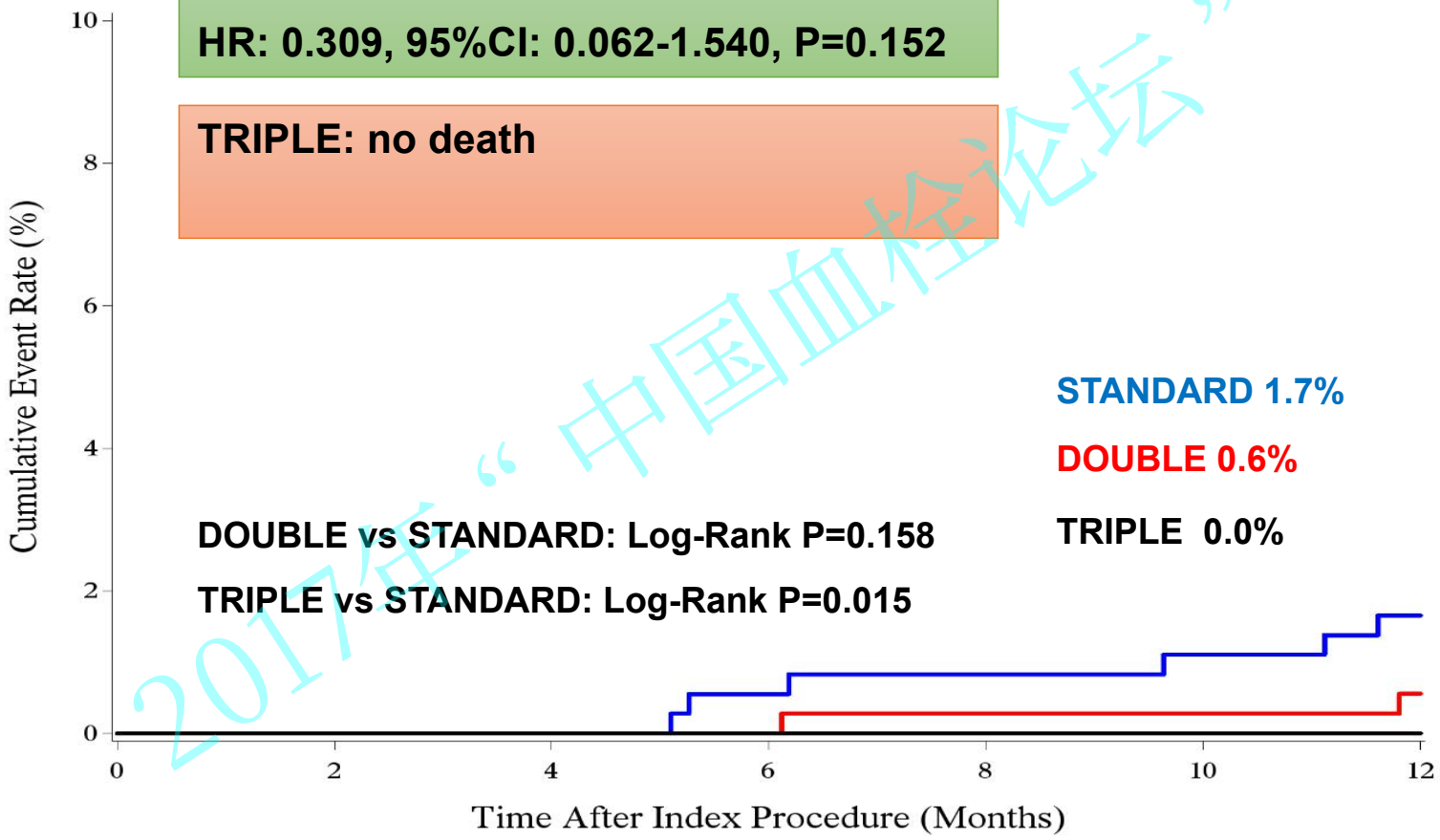
No. at Risk:							
STANDARD	362	340	335	330	329	326	324
DOUBLE	359	342	338	334	330	329	326
TRIPLE	355	342	340	337	336	336	334

All-cause Death

DOUBLE vs STANDARD

HR: 0.309, 95%CI: 0.062-1.540, P=0.152

TRIPLE: no death



STANDARD 1.7%

DOUBLE 0.6%

TRIPLE 0.0%

DOUBLE vs STANDARD: Log-Rank P=0.158

TRIPLE vs STANDARD: Log-Rank P=0.015

No. at Risk:							
STANDARD	362	362	362	360	359	358	356
DOUBLE	359	359	359	359	358	358	357
TRIPLE	355	355	355	355	355	355	355

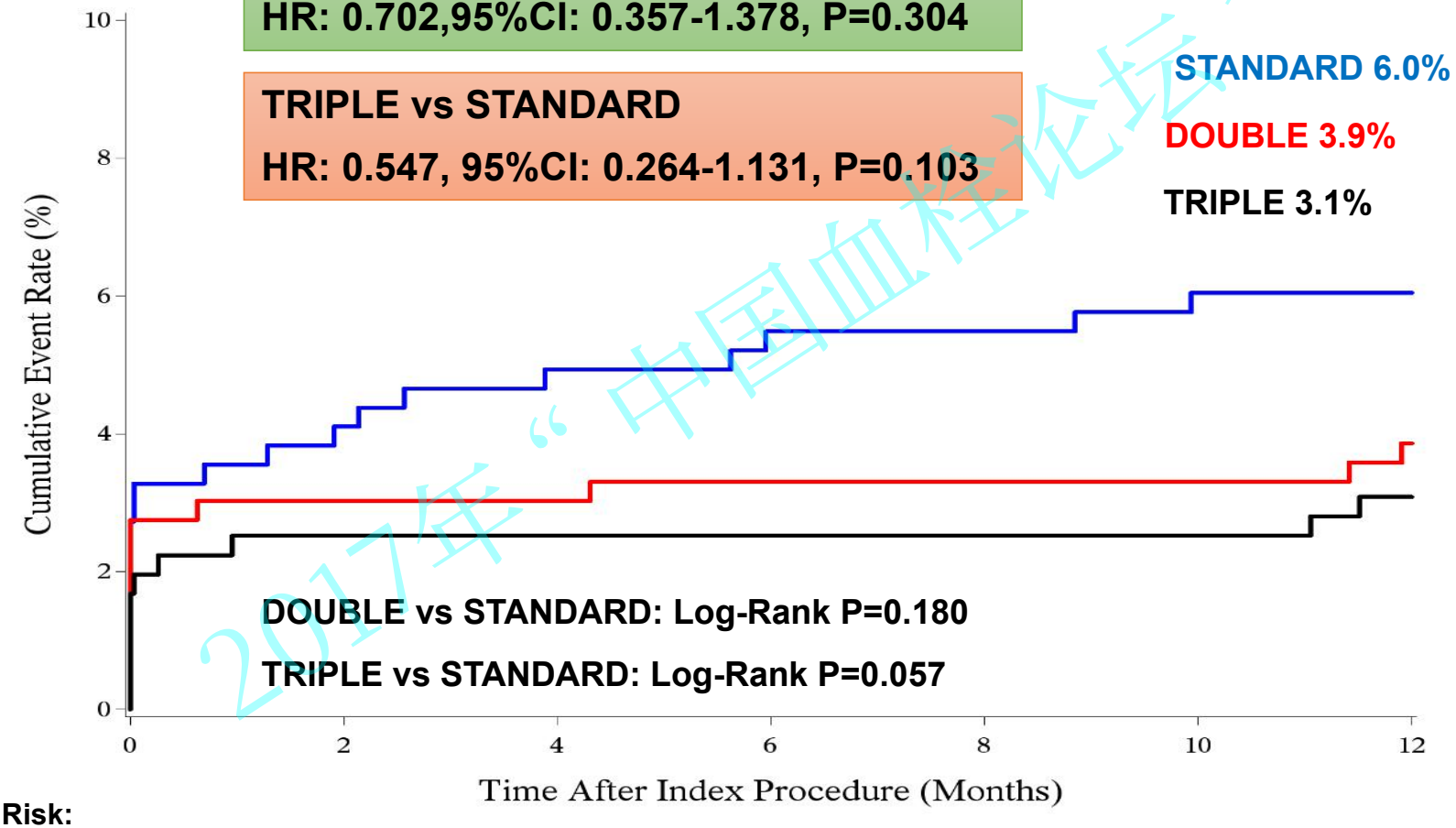
Myocardial infarction

DOUBLE vs STANDARD

HR: 0.702,95%CI: 0.357-1.378, P=0.304

TRIPLE vs STANDARD

HR: 0.547, 95%CI: 0.264-1.131, P=0.103

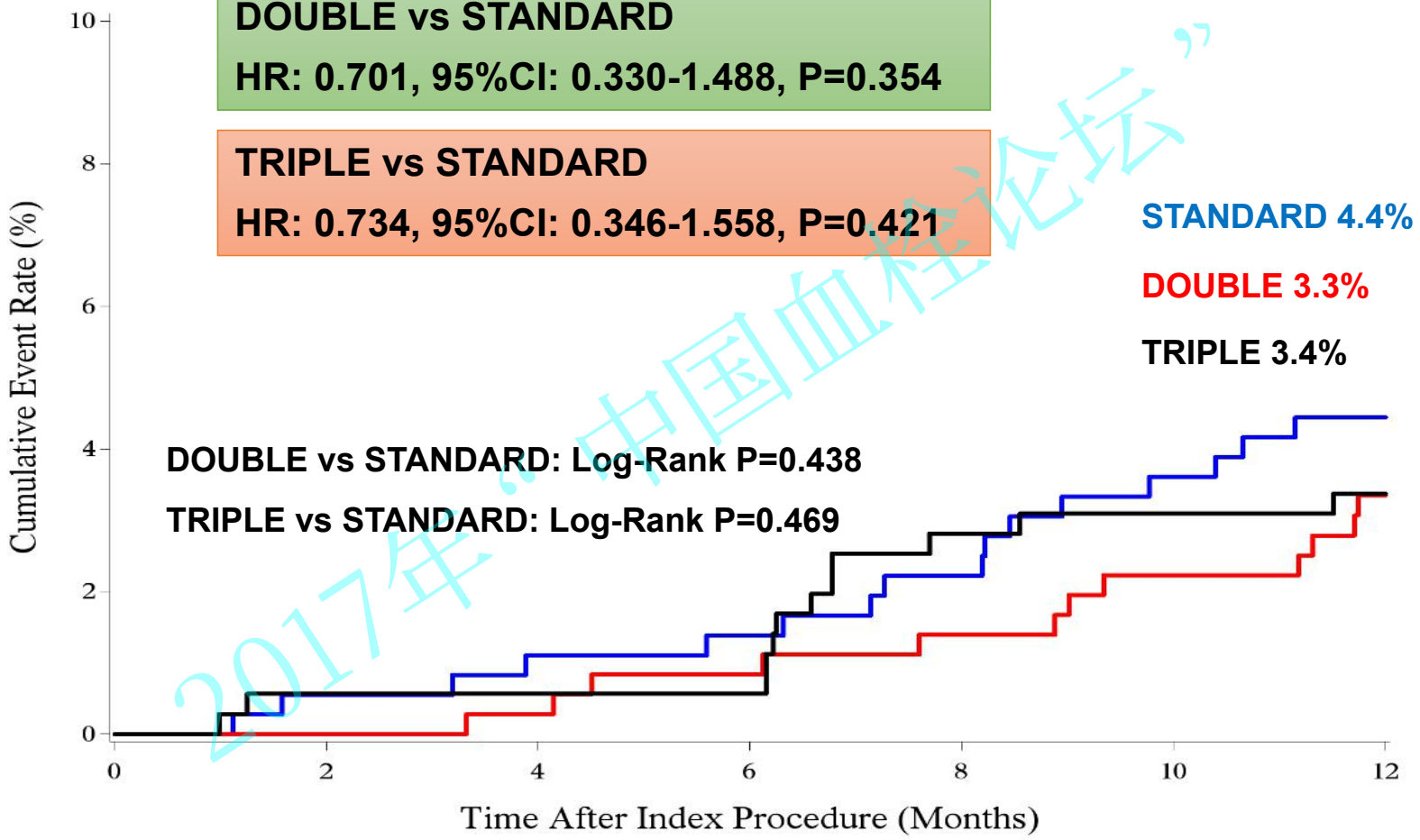


No. at Risk:							
STANDARD	362	347	344	340	339	336	334
DOUBLE	359	348	348	347	346	346	343
TRIPLE	355	346	346	346	346	346	344

Target vessel revascularization

DOUBLE vs STANDARD
HR: 0.701, 95%CI: 0.330-1.488, P=0.354

TRIPLE vs STANDARD
HR: 0.734, 95%CI: 0.346-1.558, P=0.421



No. at Risk:							
STANDARD	362	360	358	355	351	346	341
DOUBLE	359	359	358	356	353	350	345
TRIPLE	355	353	353	353	345	344	343

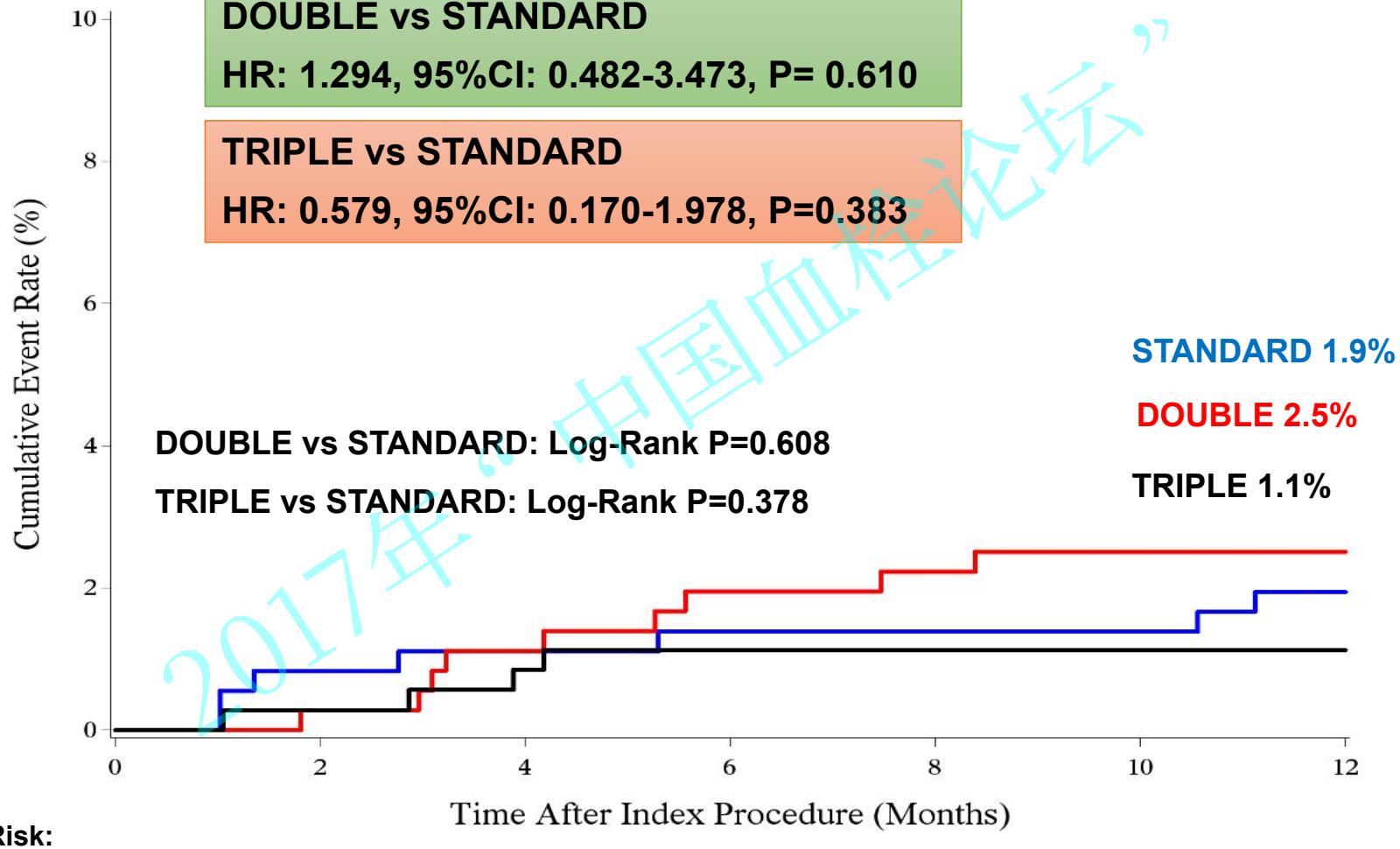
Stroke

DOUBLE vs STANDARD

HR: 1.294, 95%CI: 0.482-3.473, P= 0.610

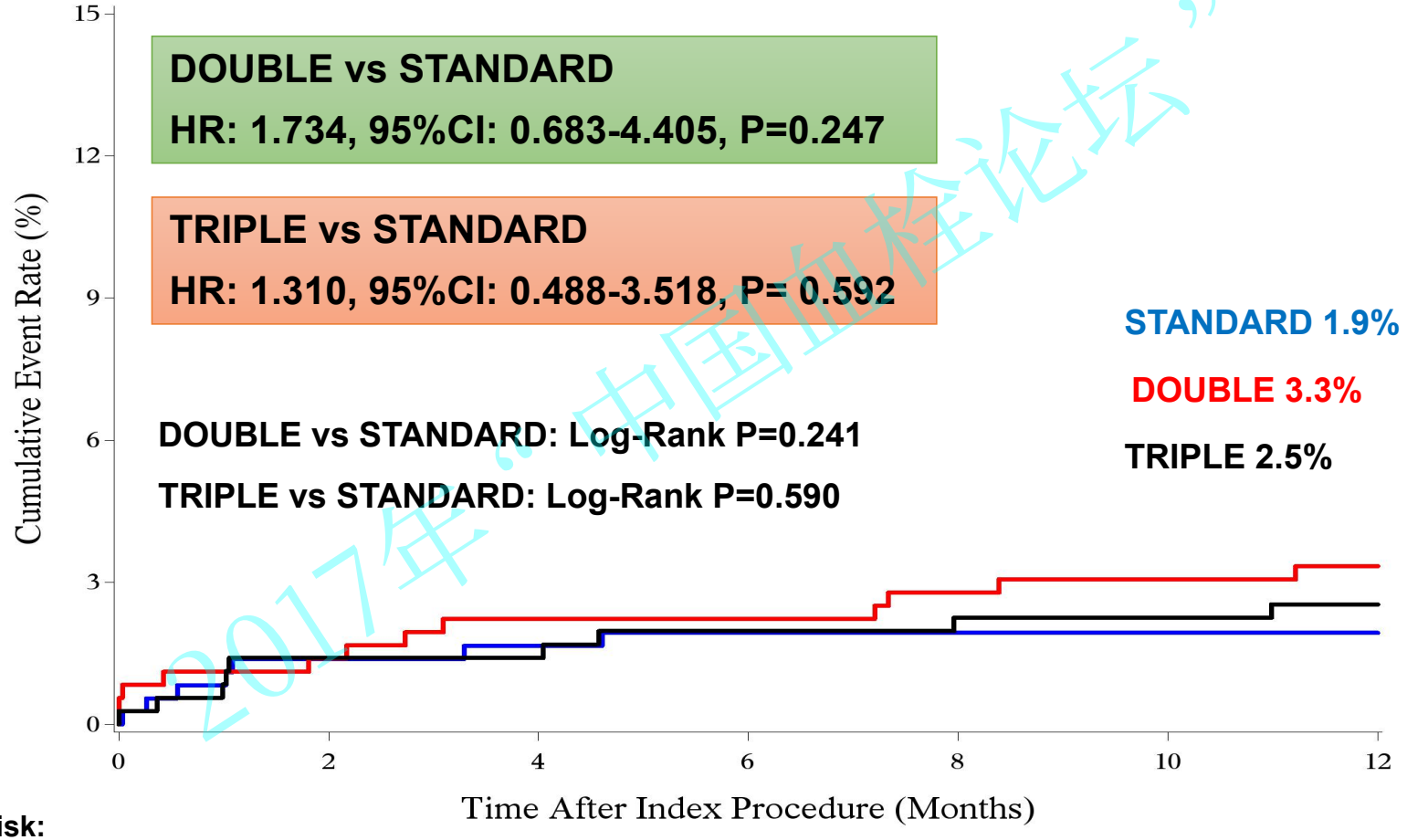
TRIPLE vs STANDARD

HR: 0.579, 95%CI: 0.170-1.978, P=0.383



No. at Risk:							
STANDARD	362	359	358	355	354	353	350
DOUBLE	359	358	355	352	350	349	348
TRIPLE	355	354	352	351	351	351	351

Major Bleeding （ BARC ≥ 3 grade ）



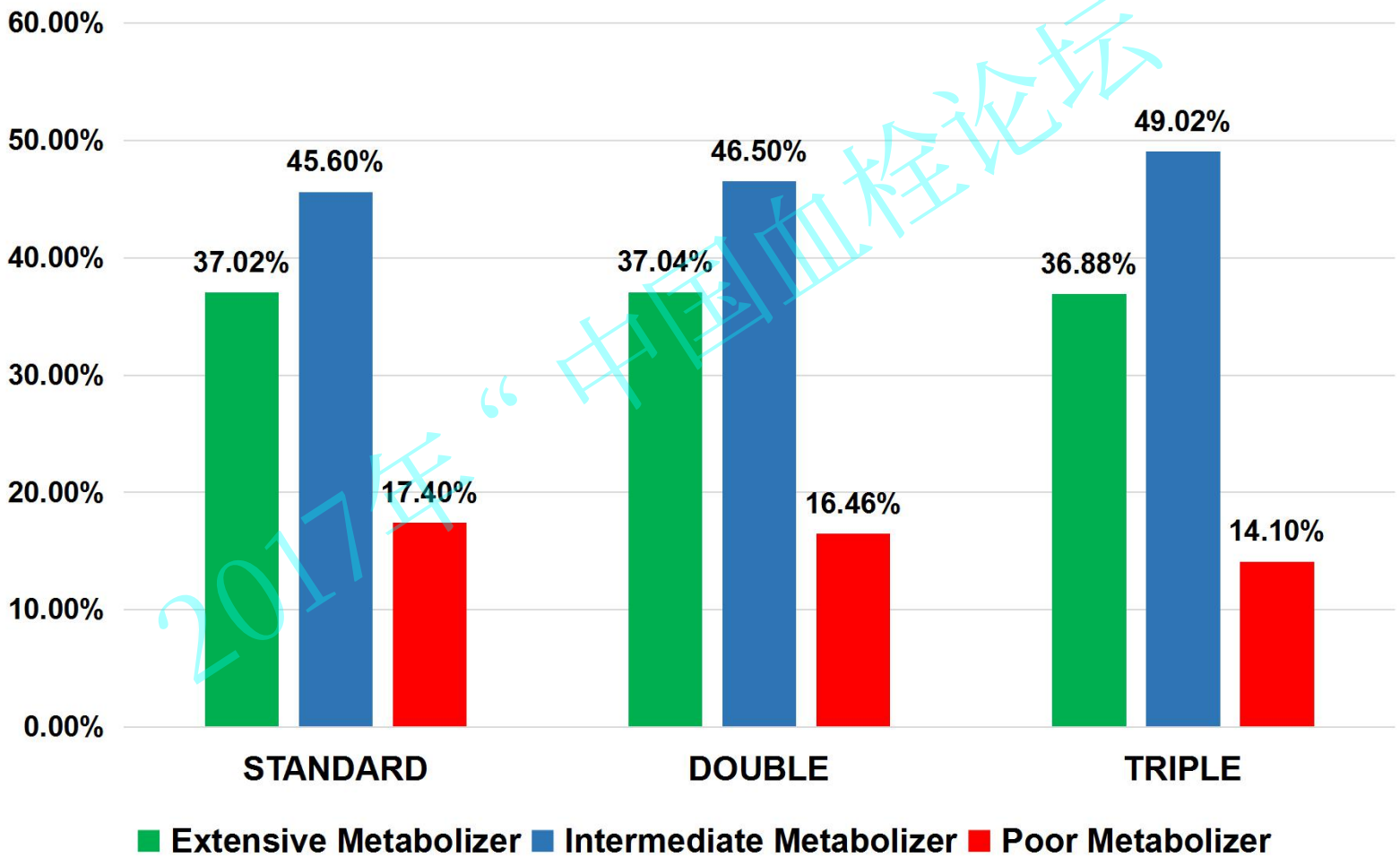
No. at Risk:							
STANDARD	362	357	356	354	353	352	350
DOUBLE	359	354	351	351	348	347	345
TRIPLE	355	350	350	348	347	347	346

Stent Thrombosis

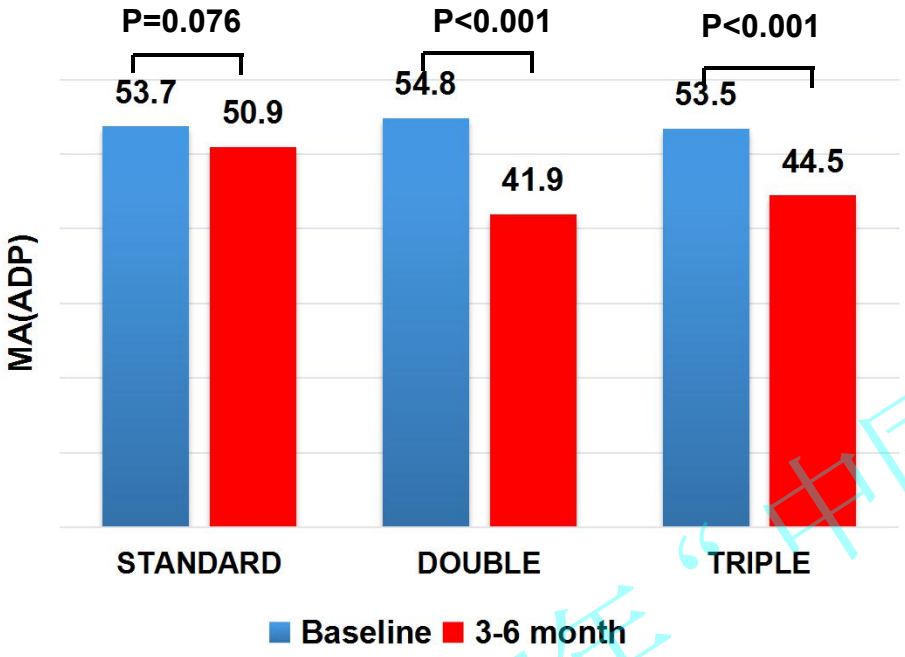
	Time to event (day)	Classification	Asprin	Clopidorel	Cilotazol	Outcomes
Standard	0	Definite	Continued	Continued		MI, TLR
	0	Definite	Continued	Continued		MI, TLR
	21	Definite	Continued	Continued		MI, TLR
	67	Probable	Continued	Continued		MI, cardiac death
	93	Probable	Continued	0		MI, TLR
	242	Probable	Continued	Continued		MI, cardiac death
Double	18	Probable	Continued	75mg		MI
	146	Probable	0	Continued		MI, cardiac death
Triple	0	Definite	Continued	Continued	Continued	MI, TLR
	5	Probable	Continued	Continued	0	MI
	27	Probable	Continued	Continued	0	MI
	62	Probable	Continued	Continued	Continued	MI

Clopidogrel Response Evaluation and AnTi-platelet InterVEntion in High Thrombotic Risk PCI Patients

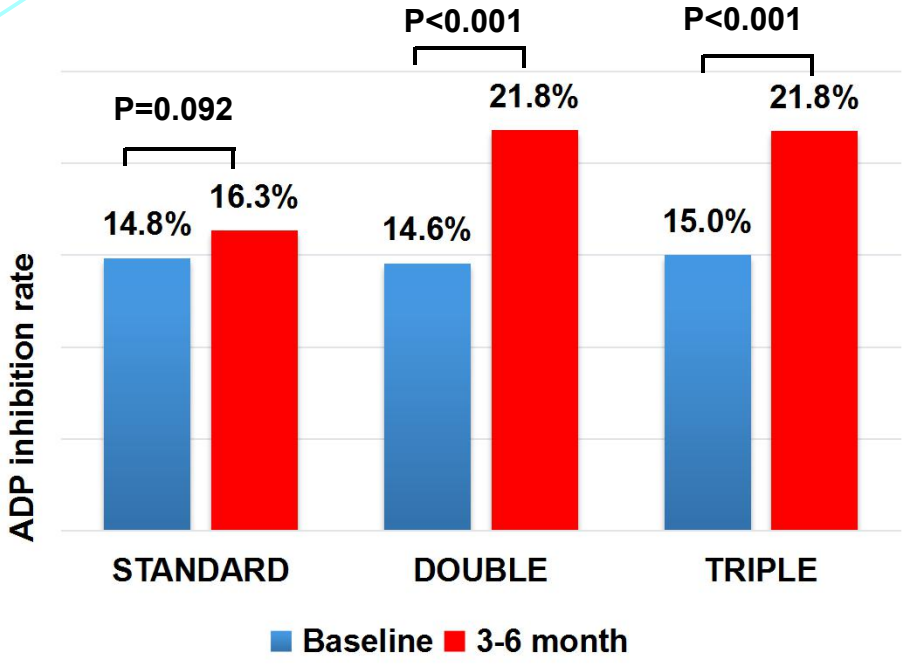
Distribution of CYP2C19 Genotype



Change of Platelet Function



- 论是双倍氯吡格雷还是加用西洛他唑的三联方案，均可改善血小板功能学指标。**两种强化治疗方案在改善血小板功能学指标方面均优于传统治疗组，但两者之间并没有显著差异。**



Conclusions

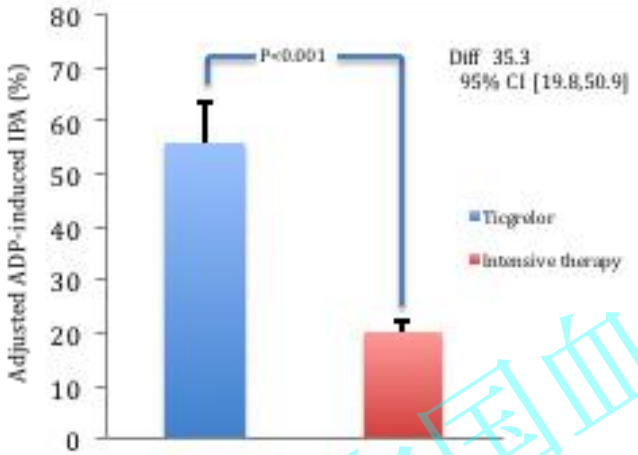
- The platelet function monitoring and treatment adjustment could improve the clinical outcomes of high risk elective PCI patients
- In patients with low responsiveness to clopidogrel, the intensified antiplatelet strategies (the additional cilostazol or double-dose clopidogrel) significantly reduced platelet reactivity and the MACCE without increasing the risk of major bleeding.

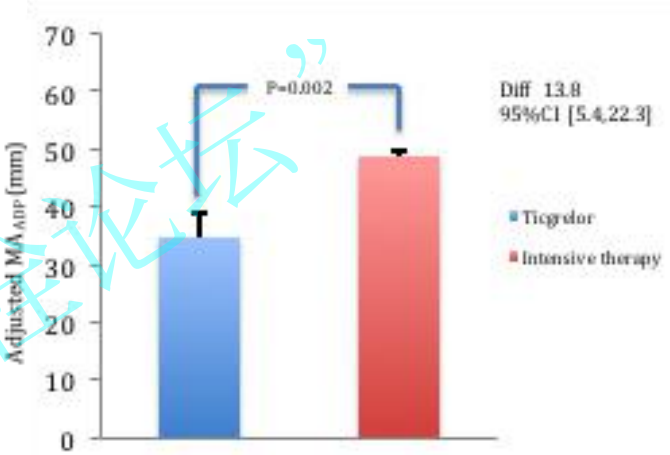
传统强化方案vs 新型药物（替格瑞洛）

- 共收集205例患者，其中有10例（4.88%）转服替格瑞洛。
- 转服替格瑞洛前平均接受强化治疗2.2个月。

患者基线临床资料的比较

	替格瑞洛 N=10	强化抗血小板 N=195	P值
年龄(岁)	54.9(8.7)	57.1（9.70）	0.492
男性[例(%)]	8（80）	132（67.7）	0.640
冠心病类型[例(%)]			0.716
STEMI	1(10)	10(5.1)	
NSTEMI	1(10)	32(16.4)	
不稳定型心绞痛	0	4(2.1)	
稳定型心绞痛	8(80)	149(76.4)	
合并症[例(%)]			
糖尿病	5(50)	67(34.4)	0.502
高脂血症	8(80)	122(62.6)	0.435
高血压	5(50)	116(59.5)	0.791
生活方式[例(%)]			
吸烟	5(50)	95(48.7)	>0.999
饮酒	2(20)	43(22.1)	>0.999
CYP2C19 基因型[例(%)]			0.122
快代谢型	1(11.1)	49(29.5)	
中代谢型	4(44.4)	90(54.2)	
慢代谢型	4(44.4)	27(16.3)	



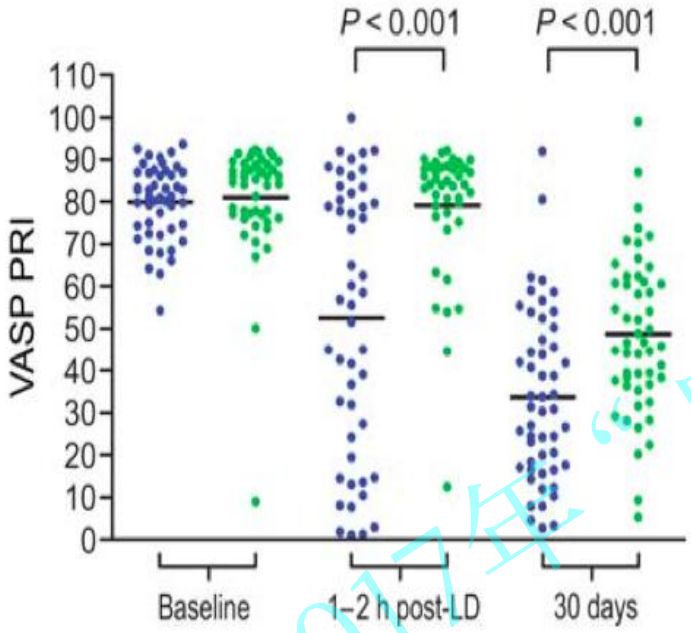


TEG 结果		替格瑞洛 N=10	强化抗血小板 N=195	P值
基线	ADP抑制率	8.35±9.29	11.33±9.16	0.323
	MA_{ADP}	54.3±7.2	55.6±5.7	0.519
随访3个月 *	ADP抑制率	52.25±35.91	20.26±20.94	0.002
	MA_{ADP}	36.0±19.0	48.9±11.7	0.028
变化值	ADP抑制率	43.9±37.06	8.94±21.86	0.003
	MA_{ADP}	-18.28±18.47	-6.68±12.18	0.028

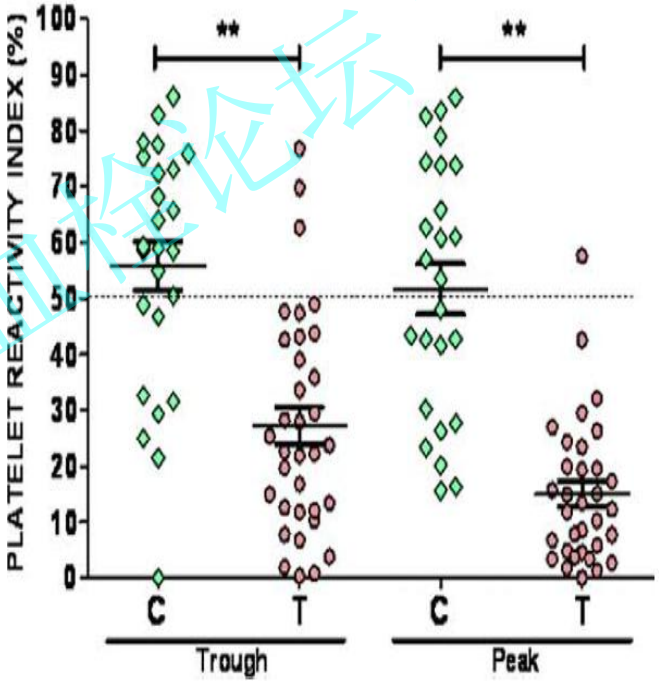
*转服替格瑞洛前，接受强化抗血小板治疗时间平均为2.2个月。

在3个月随访时，替格瑞洛组ADP抑制率及MA_{ADP}改善情况优于传统强化治疗组

新型P2Y12-ADP 受体抑制剂的血小板反应性



Prasugrel vs clopidogrel



Ticagrelor vs clopidogrel

个体差异减少了，但并未消失!

Storey. JACC 2010 Michelson AD. EHJ 2009

指南对血小板功能检测怎么说?

Platelet function testing or genetic testing may be considered in specific high-risk situations (e.g. history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk).	IIb	C
Routine platelet function testing or genetic testing (clopidogrel and ASA) to adjust antiplatelet therapy before or after elective stenting is not recommended.	III	A

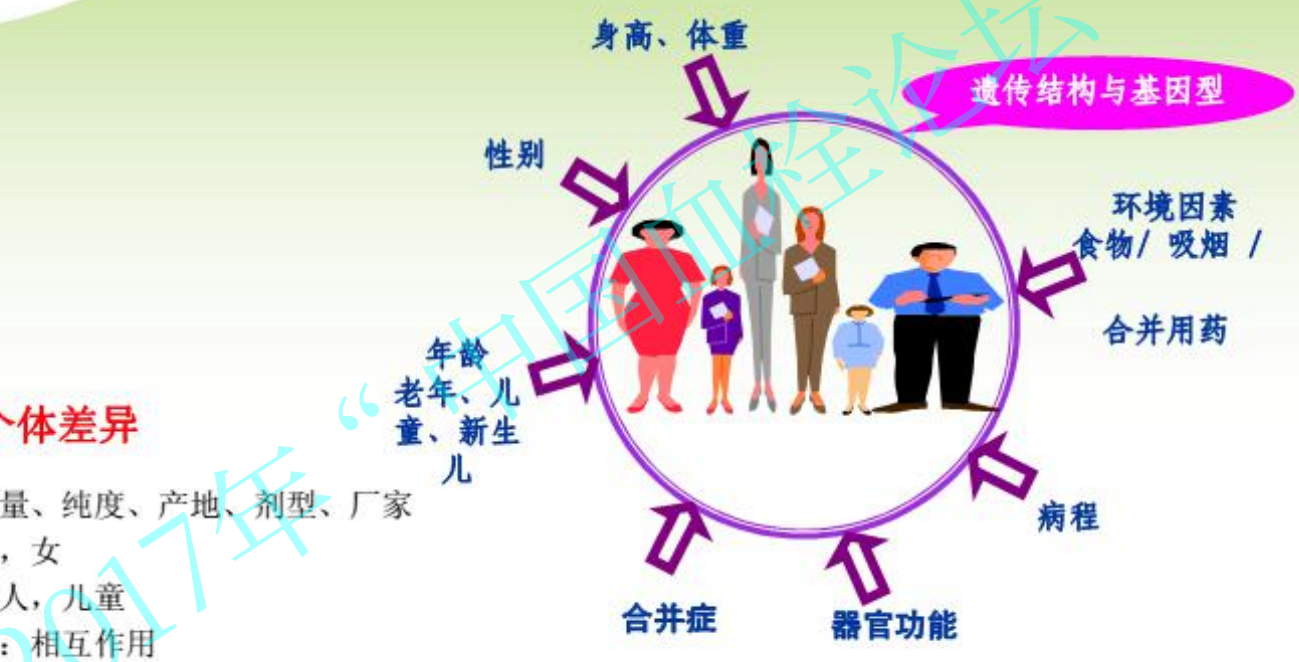
Platelet function testing should be used to guide antiplatelet therapy interruption rather than arbitrary use of a specified period of delay in patients undergoing CABG surgery.	IIa	C

Revascularization ESC 2014

Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.	IIb	B
Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used.	IIb	B

可结合基因型，选择性用于高危患者，辅助临床，指导个体化的抗血小板治疗。

血小板功能学检测+氯吡格雷代谢基因型

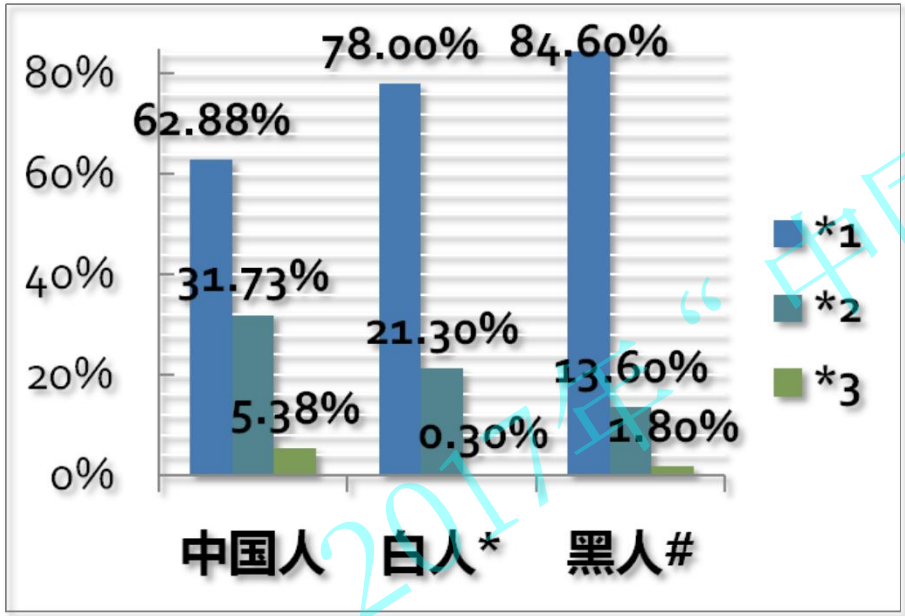


药物反应个体差异

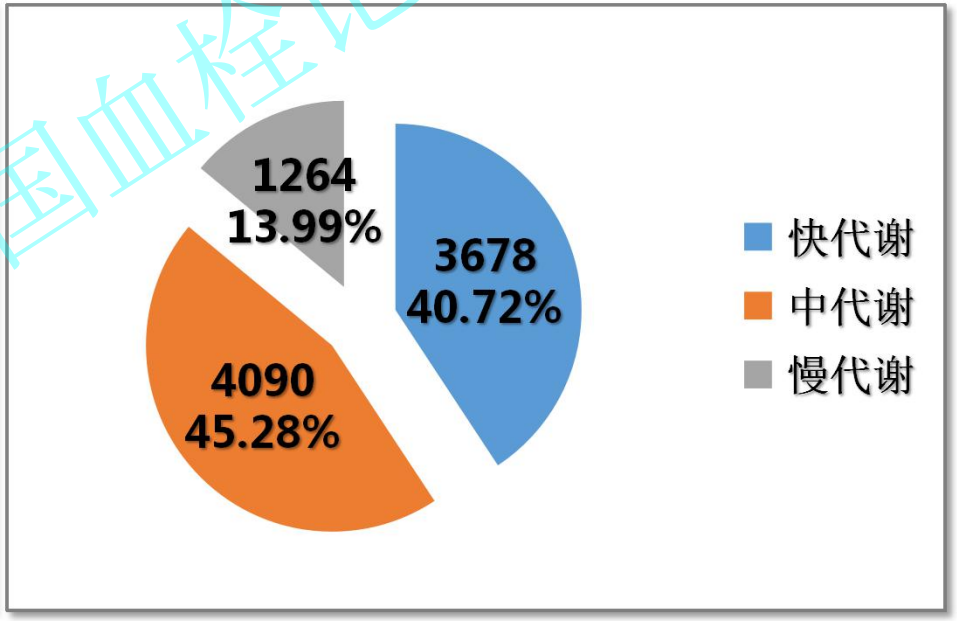
- 药物的质量、纯度、产地、剂型、厂家
- 性别：男，女
- 年龄：成人，儿童
- 其他疾病：相互作用
- 其他药物：药物相互作用及基因表达
- 生理状态：怀孕？
- 饮食状况，生活环境
- 疾病分类：不同亚型
- **遗传因素**：基因多态性/基因转录/基因突变

阜外医院研究结果（2012-10至今）

等位基因频率分布



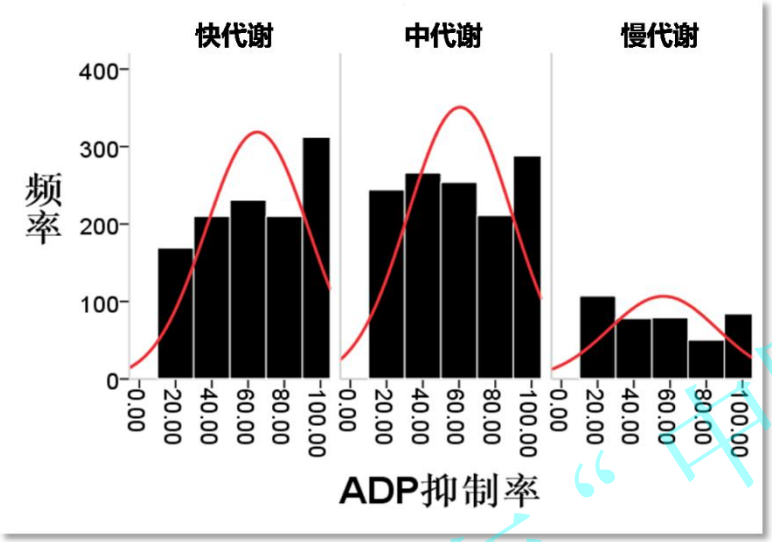
代谢型分布

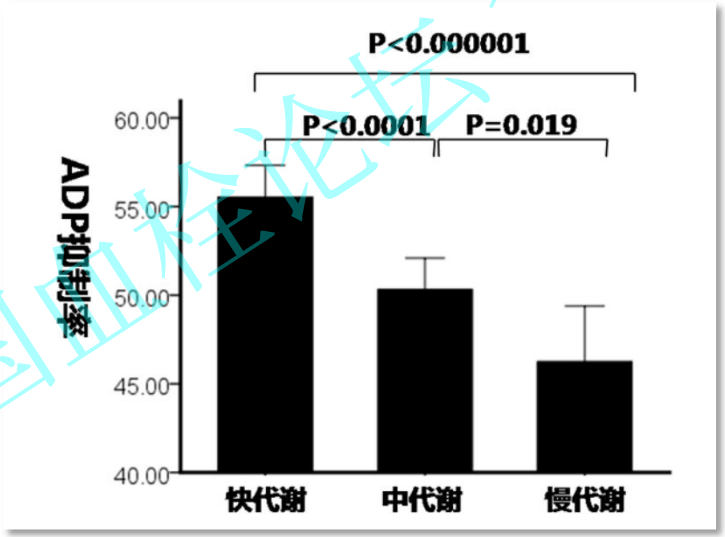


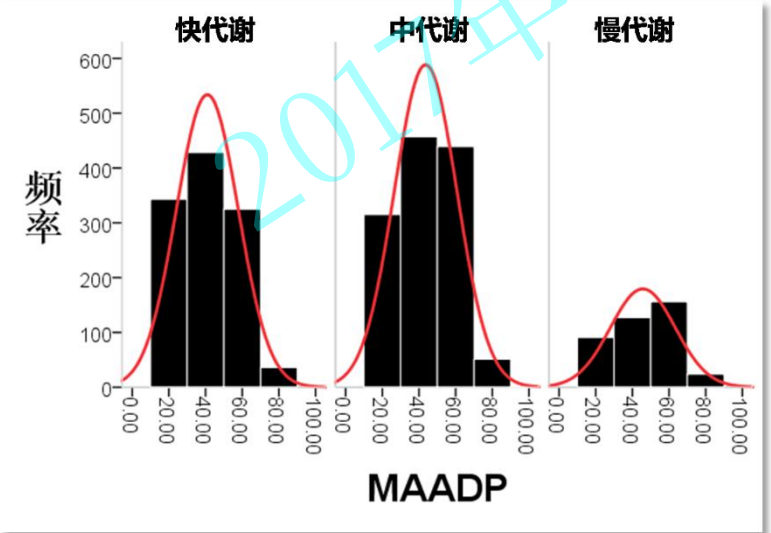
* Chang M, Dahl ML, Tybring G (1996) Use of omeprazole as a probe drug for *CYP2C19* phenotype in Swedish Caucasians: comparison with S-mephenytoin hydroxylation phenotype and *CYP2C19* genotype. Pharmacogenetics 5:358–363

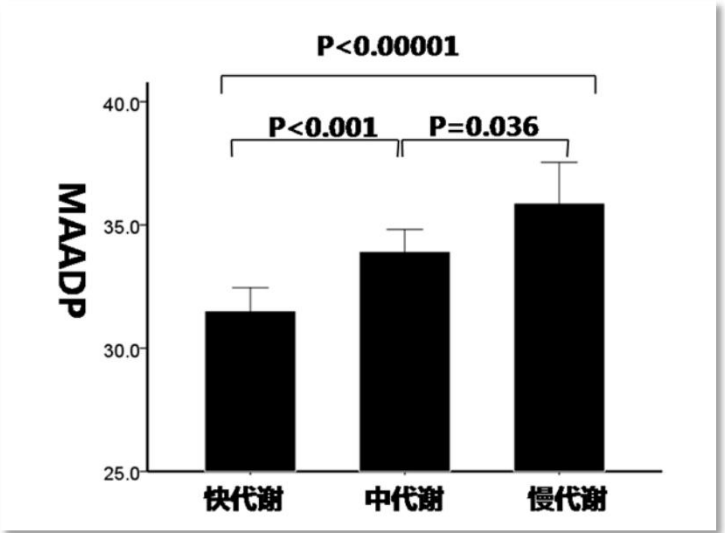
Persson I, Aklillu E, Rodrigues F (1996) S-mephenytoin hydroxylation phenotype and *CYP2C19* genotype among Ethiopians. Pharmacogenetics 6:521–526

基因型-血小板功能学检测（5933例）









患者的对抗血小板药物的反应性存在种族差异吗？

新型P2Y12受体抑制剂主要基于欧美人群的研究，而针对东亚人群的临床证据非常有限

研究	东亚患者数(%)	东亚亚组结果
氯吡格雷 vs 普拉格雷/替格瑞洛，ACS		
TRITON-TIMI 38	**<1%**	**N/A**
TRILOGY-ACS	**571 例东亚患者(8.1%)**	**HR 1.19 (0.75-1.89)**
PLATO	**1096例亚洲患者 (5.9%)，其中东亚患者644例**	**HR 0.87 (0.62-1.21)**
氯吡格雷 vs 安慰剂，ACS或PCI		
CURE	0	N/A
CURE-PCI	0	N/A
CREDO	0	N/A
COMMIT/CCS-2	**45852例中国患者（100%）**	**OR 0.91 (0.86-0.97)**
CLARITY	0	N/A
PCI-CLARITY	0	N/A
双联抗血小板治疗，冠状动脉支架置入		
ISAR	0	N/A
STARS	0	N/A
标准剂量 vs 高剂量氯吡格雷，PCI治疗的ACS		
CURRENT-OASIS 7	**2363例东亚患者（13.7%）**	**HR 0.81（0.54-1.21）**
血小板功能检测指导治疗		
GRAVITAS	0	N/A
ARCTIC	0	N/A

东亚ACS/PCI患者具有不同于欧美人群的自身特点

东亚ACS患者存在高血小板反应性 (HPR) 和低缺血风险的“东亚悖论”现象

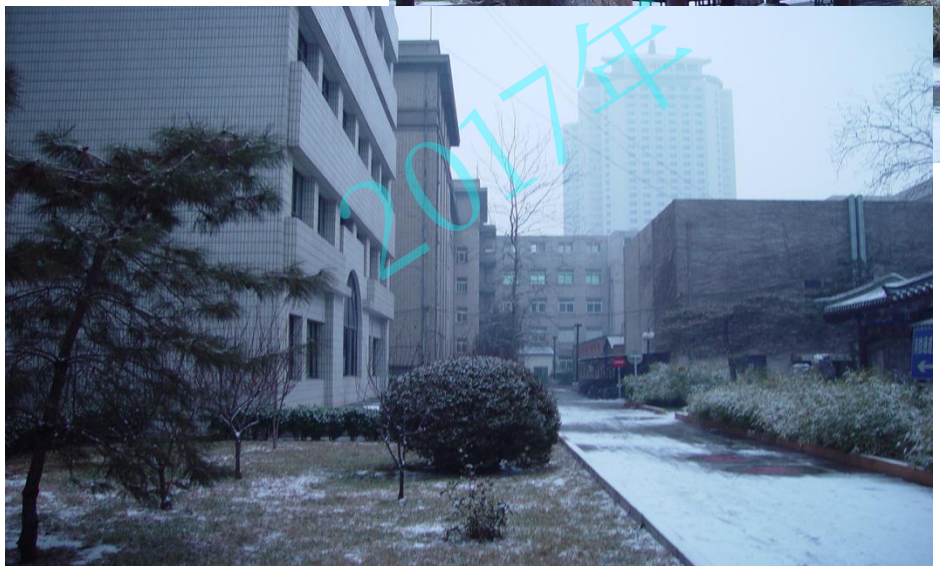
“This finding of a higher prevalence of high on-treatment platelet reactivity, but a thrombotic event rate after PCI that is similar or lower in East Asian patients than in white patients, has been called the ‘East Asian paradox’.”

研究发现，东亚患者在PCI术后双联抗血小板治疗时，虽然具有高血小板反应性，但是缺血事件发生风险与白人相似甚至更低。——这就是“东亚悖论”现象。

Levine GN, Glob Heart. 2014;9(4):457-67.

总结与展望

- 血小板功能学指标是预测PCI患者不良预后与出血风险的独立危险因素，这一点在近期的大规模临床研究和荟萃分析中得以验证。
- 血小板功能检测和药物代谢基因型是指导PCI术后个体化抗血小板治疗的重要手段，两者相结合的方式或许是未来的发展方向。
- 东亚/中国人群中，氯吡格雷慢代谢型较多，药物反应性差异大，因此需要寻找更合适的检测界值。我们前期的研究探索了适用于中国人群的检测指标，后续将在干预性研究中进行确认。
- 推荐对患者行血小板功能学检测，平衡获益/出血风险，从而进行个体化抗血小板治疗。



谢谢！