华中科技大学同济医学院附属 TONGJI HOSPITAL
同济医院 TONGJI MEDICAL COLLEGE
HUAZHONG UNIVERSITY OF SCIENCE & TECHNOLOGY

Clopidogrel is optimal for Chinese patients with coronary heart disease after percutaneous coronary intervention

---- a multicenter study

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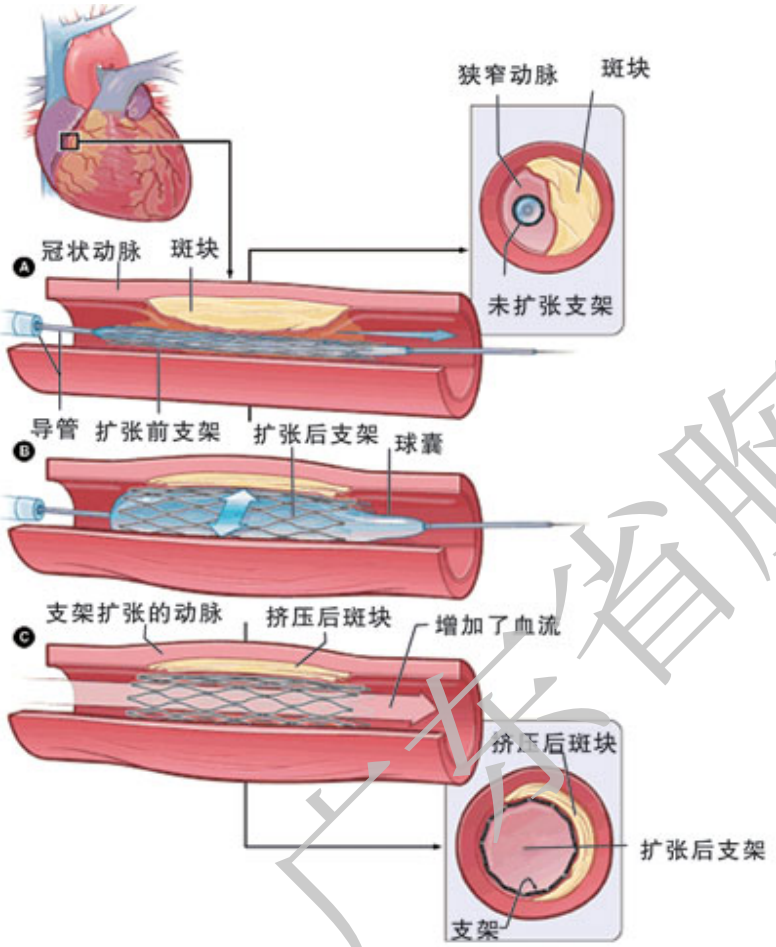
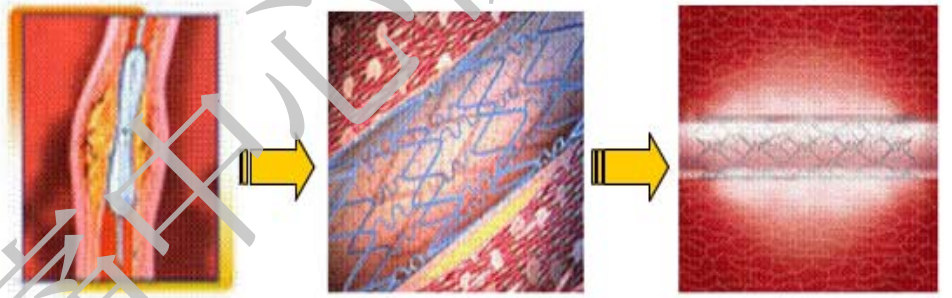
Dual antiplatelet therapy after PCI

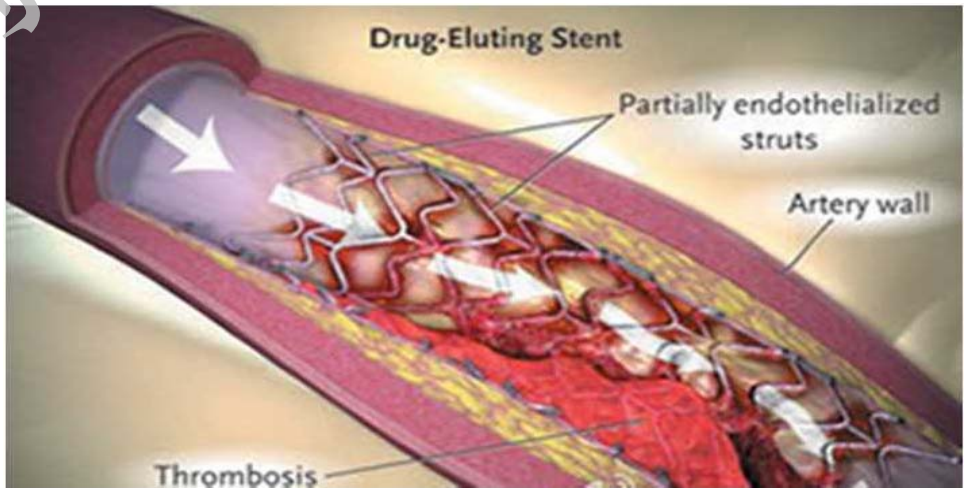




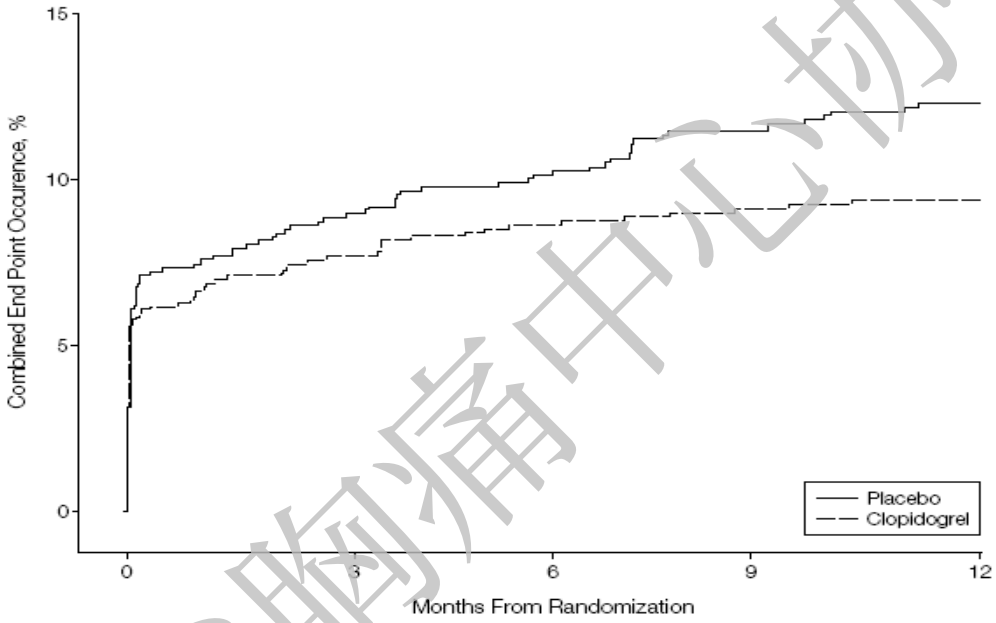
单纯球囊扩张术：
再狭窄发生率高达50%

金属裸支架植入术：
再狭窄发生率约为30%

药物洗脱支架：
再狭窄发生率仅为5%



Combined End Point Results at 1 Year for Clopidogrel vs Placebo



No. at Risk					
Clopidogrel	1053	931	920	909	901
Placebo	1053	929	910	881	863

Data are shown as occurrence of death, myocardial infarction, or stroke at 1 year. The relative risk reduction for clopidogrel compared with placebo is 26.9% (95% confidence interval, 3.9%-44.4%; *P*=.02).

Numerous clinical trials (CATS, TASS, ISAR, CAPRIE, CHARISMA, MATCH, CURE, COMMIT, PCICURE) have demonstrated that the use of clopidogrel could decrease the incidence of major adverse cardiac events.

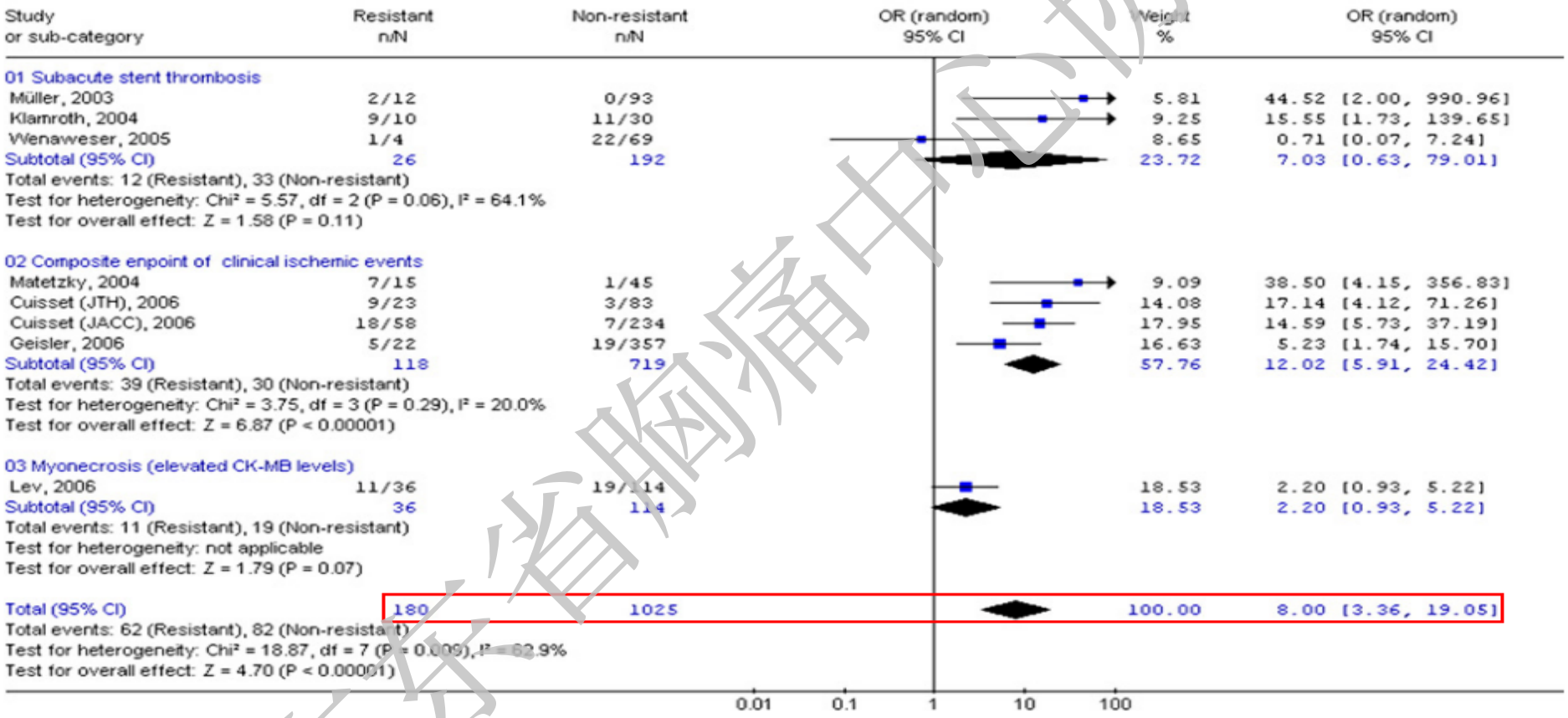
JAMA. 2002;288(19):2411-20.

Comprehensive Risk Reduction for Patients With Coronary and Other Vascular Disease After PCI

2005 PCI Recommendations	2007 PCI Recommendations	2007 COR and LOE	Comments
	Antiplatelet Agents/Anticoagulants: Clopidogrel		
For post-PCI stented patients, clopidogrel 75 mg per day should be given for at least 1 month after BMS implantation, 3 months after sirolimus stent implantation, and 6 months after paclitaxel stent implantation, after which clopidogrel should ideally be continued for up to 12 months in all stented patients who are not at high risk of bleeding.	1. For all post-PCI patients who receive a DES, clopidogrel 75 mg daily should be given for *at least 12 months* if patients are not at high risk of bleeding. For post-PCI patients receiving a BMS, clopidogrel should be given for a minimum of 1 month and *ideally up to 12 months* (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks).	*I (B)*	Modified recommendation (changed text)
	2. For all post-PCI non-stented STEMI patients, treatment with clopidogrel should continue for at least 14 days.	*I (B)*	New recommendation
	3. Long-term maintenance therapy (e.g., 1 year) with clopidogrel (75 mg per day orally) is reasonable in STEMI and non-STEMI patients who undergo PCI without reperfusion therapy.	*IIa (C)*	New recommendation

J Am Coll Cardiol, 2008;51:172–209

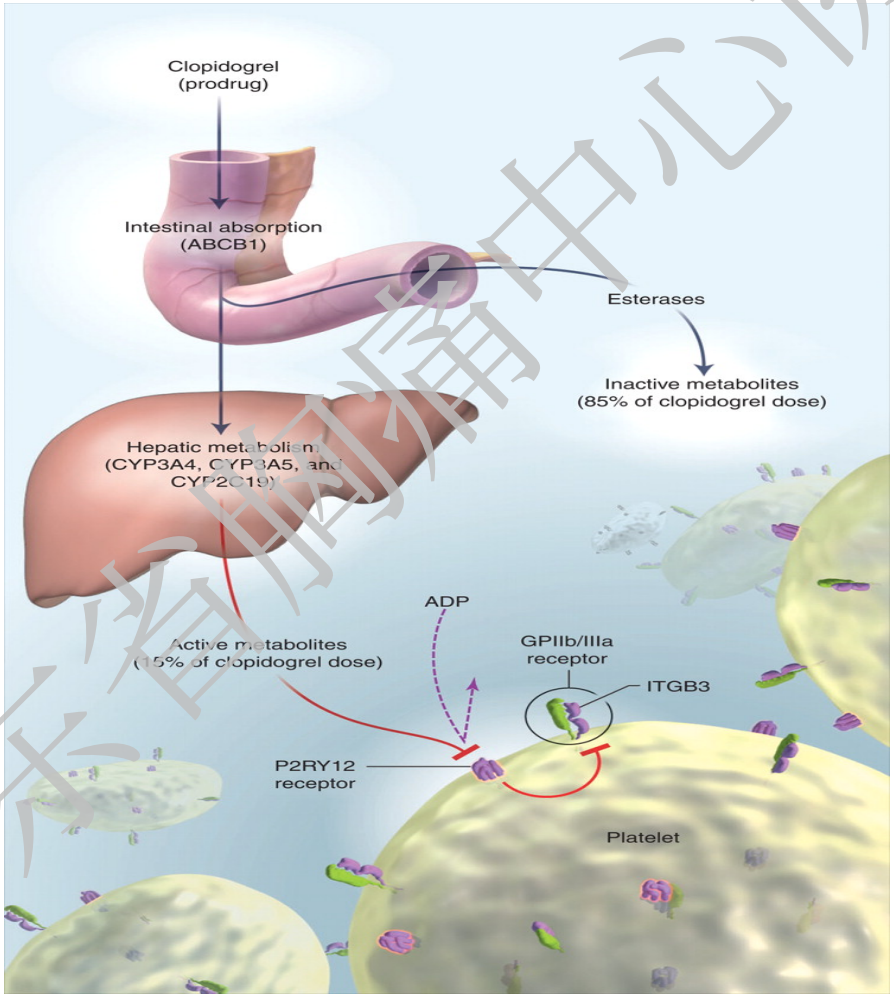
Forest plot of ORs of cardiovascular outcome for clopidogrel nonresponsiveness from eligible studies.

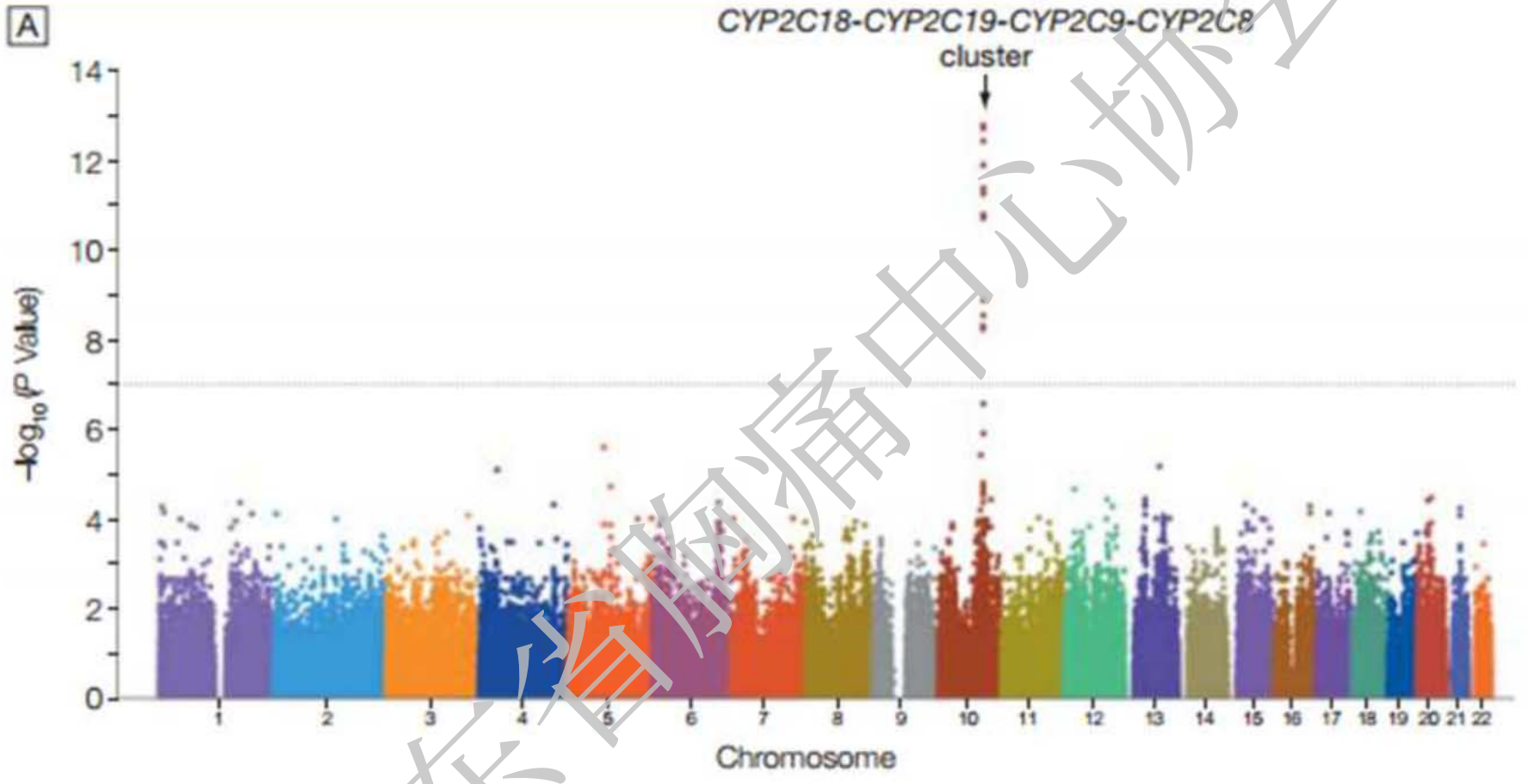


Nearly thirty percent of patients with clopidogrel treatments can't reflect enough platelet inhibition effect，and part of patients even present with clopidogrel resistance.

Am Heart J. 2007 ;154:221-31

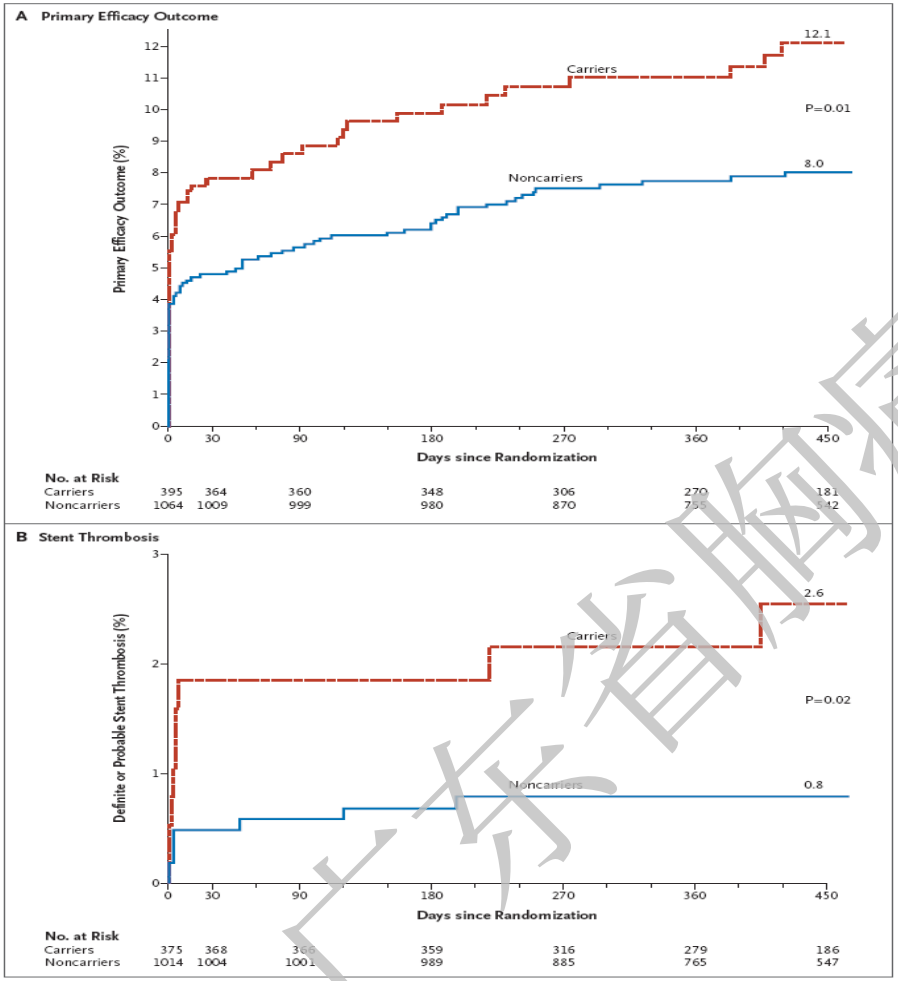
The metabolism of clopidogrel





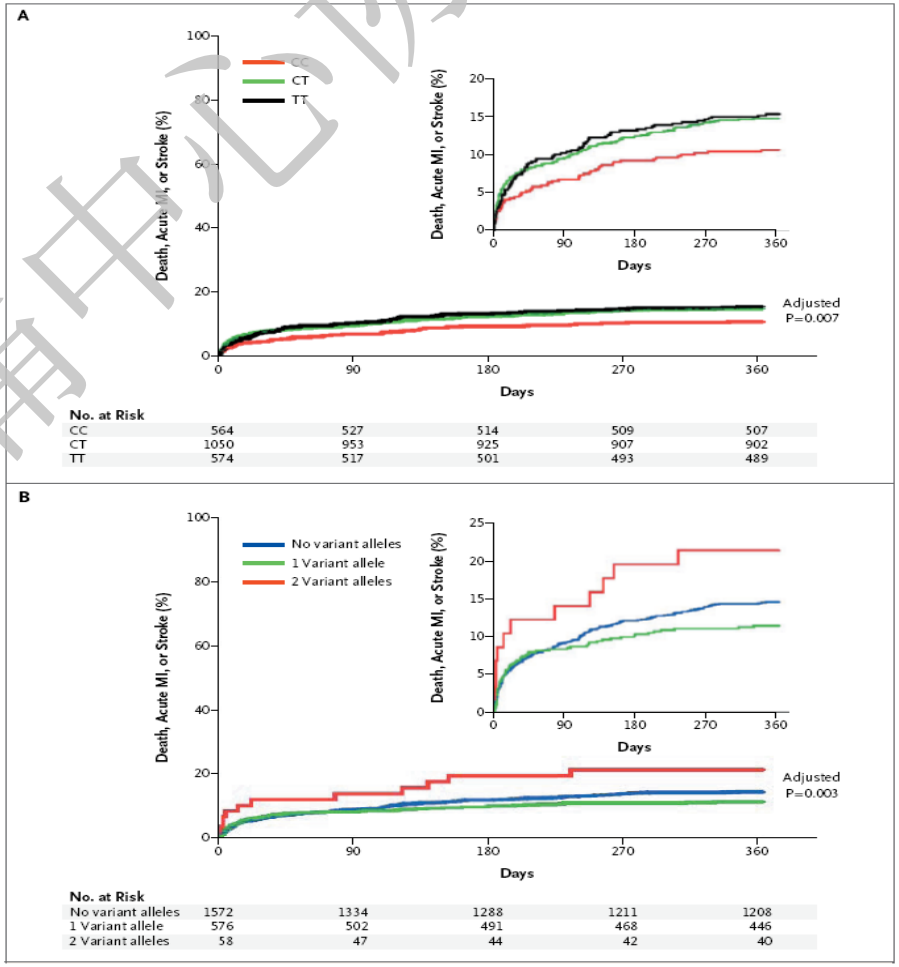
The results of GWAS showed that the strongest signal (rs12777823) was linked with CYP2C19*2 (r^2=0.87). CYP2C19*2 is the only site confirmed by GWAS that influence the platelet aggregation activity under clopidogrel treatment.

Association between Status as a Carrier of a CYP2C19 Reduced-Function Allele and the Primary Efficacy Outcome or Stent Thrombosis in Subjects Receiving Clopidogrel.

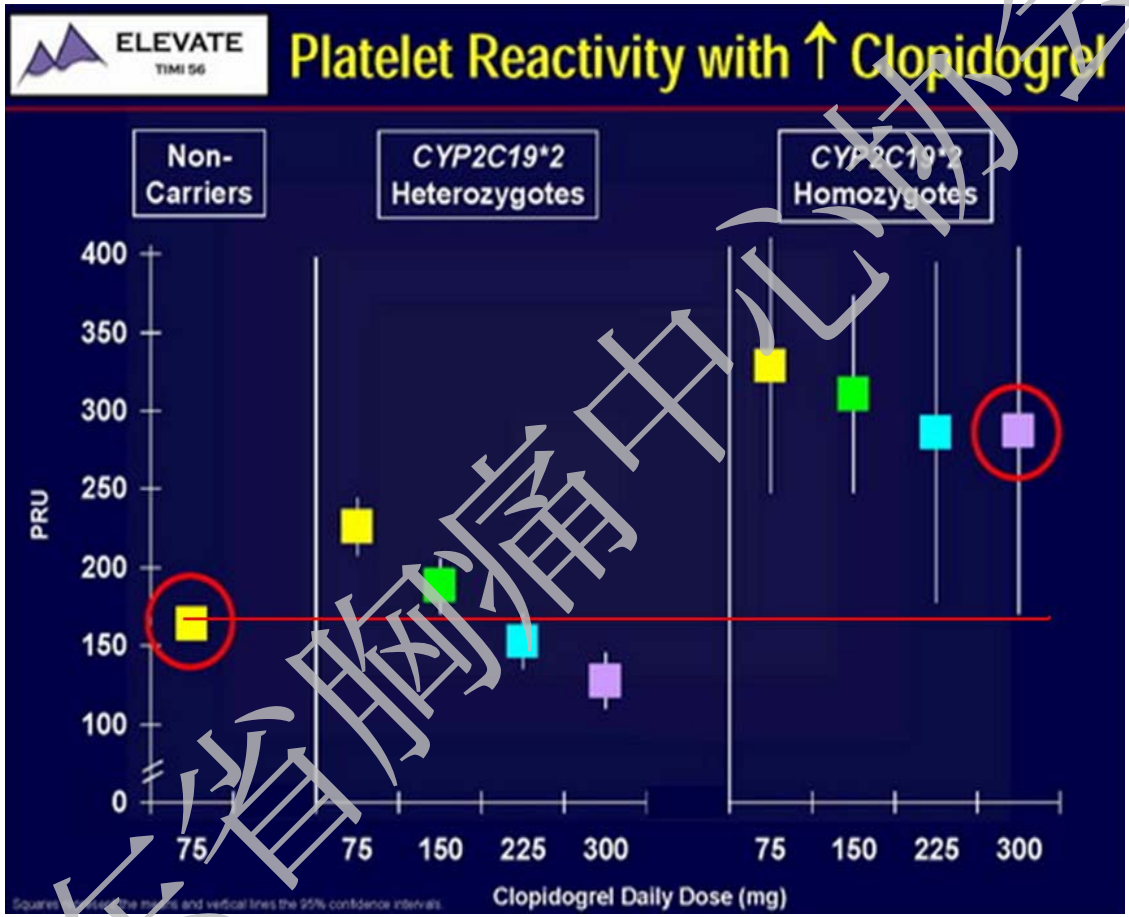


Mega et al. NEJM. 2009;360(4):354-62.

Estimated Rates of Death from Any Cause, Nonfatal Myocardial Infarction, or Stroke, According to Characteristics of Variant-Allele Polymorphisms.

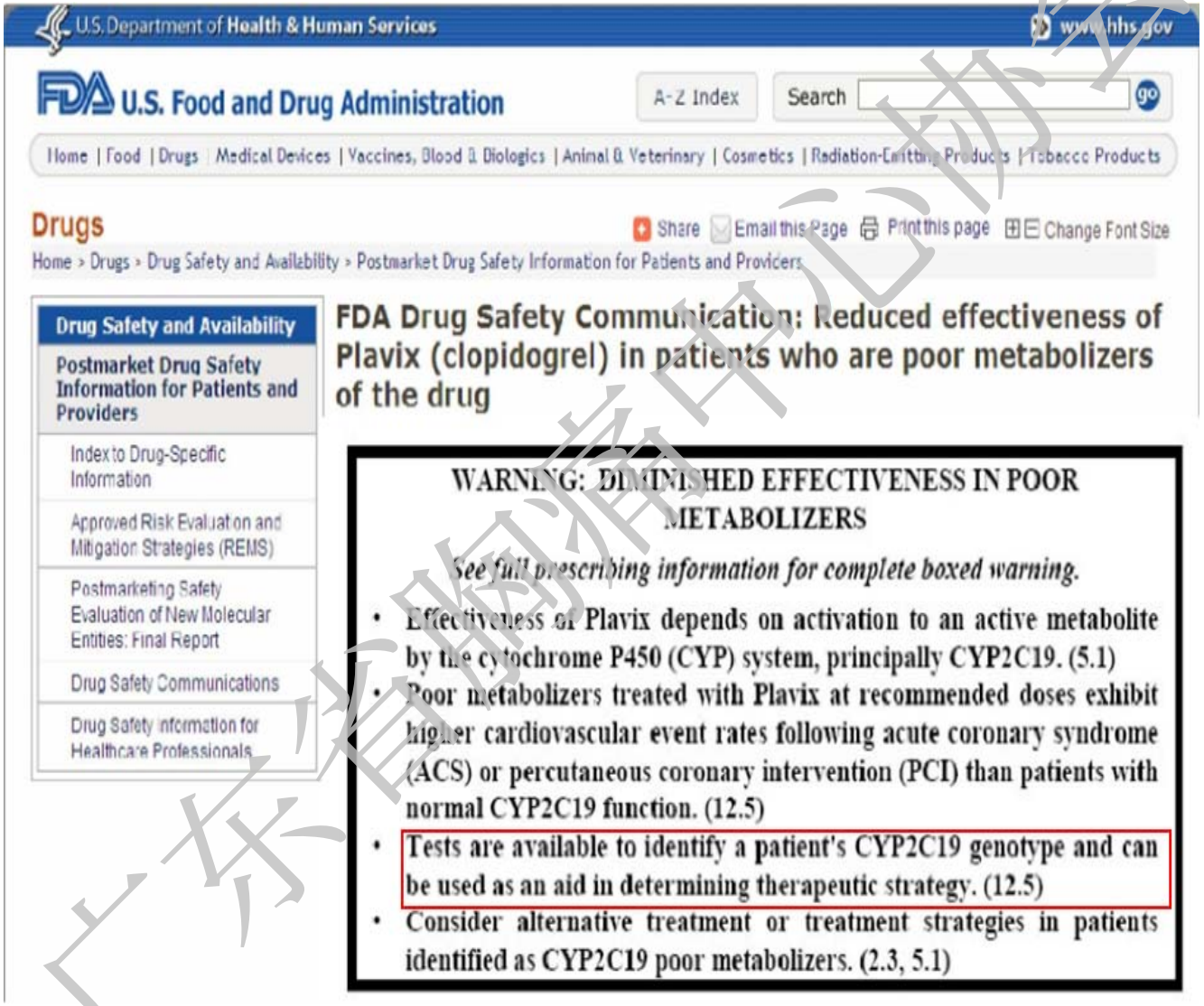


Simon et al. NEJM. 2009;360(4):363-75.



Conclusions: For CYP2C19*2 heterozygotes, increasing the dose to 225 mg per day, the activity of platelet inhibition can reach the level of non-carriers. However, even if increase to 300 mg maintenance dose, it's still difficult to achieve considerable level of platelet inhibition for CYP2C19*2 homozygotes.

Mega et al. JAMA. 2011;306(20):2221-8.



http://www.fda.gov/Drugs/DrugSafety

Recommendations	Class[a]	Level[b]
Aspirin should be given to all patients without contraindications at an initial loading dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (*H. elicobacter pylori* infection, age ≥65 years, concurrent use of anticoagulants or steroids).	I	A
Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated.	I	C
Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins) , regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).	I	B
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.[d]	I	B
Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.	I	A
A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.	I	B
A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.	IIa	B
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
In patients pre-treated with $P2Y_{12}$ inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered.	IIa	C
Ticagrelor or clopidogrel should be considered to be (re-) started after CABG surgery as soon as considered safe.	IIa	B
The combination of aspirin with an NSAID (selective COX-2 inhibitors and non-selective NSAID) is not recommended.	III	C

Eur Heart J. 2011;32(23):2999-3054.

How about the characteristics of the metabolism of clopidogrel in Chinese patients

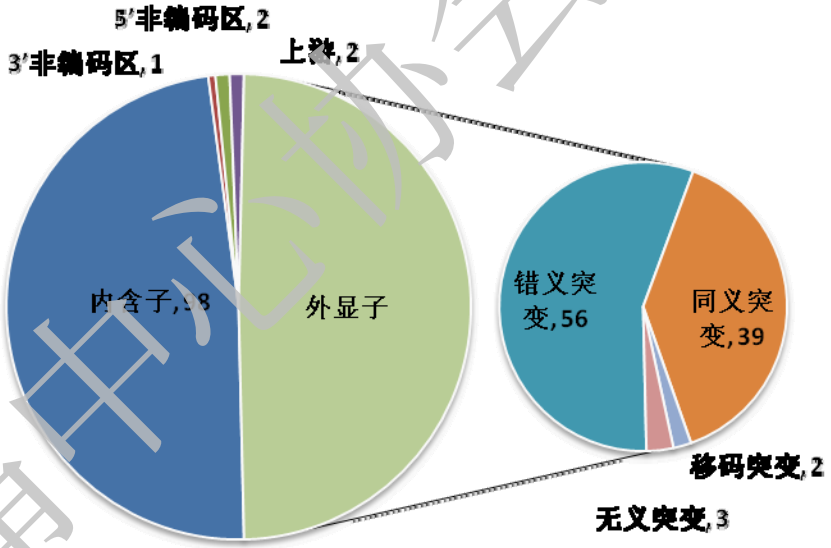
Inspiration come from 2 patients with coronary heart disease after percutaneous coronary intervention

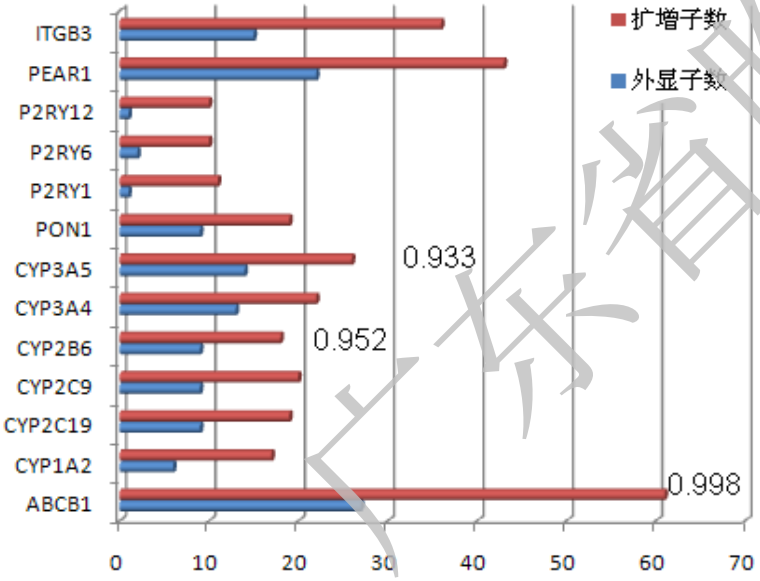
Case 1: Female; 51 years old; recurrent episodes of exertional chest pain for 1 years, and exacerbation for 1 month；coronary angiograpgy indicated 80%-90% stenosis of LAD and proximal coronary artery, and 3 stents were implanted; genetic testing showed she was a CYP2C19*2 heterozygotes. The platelet aggregation rate was 20% after administered with 75 mg bid clopidogrel for 2 weeks.

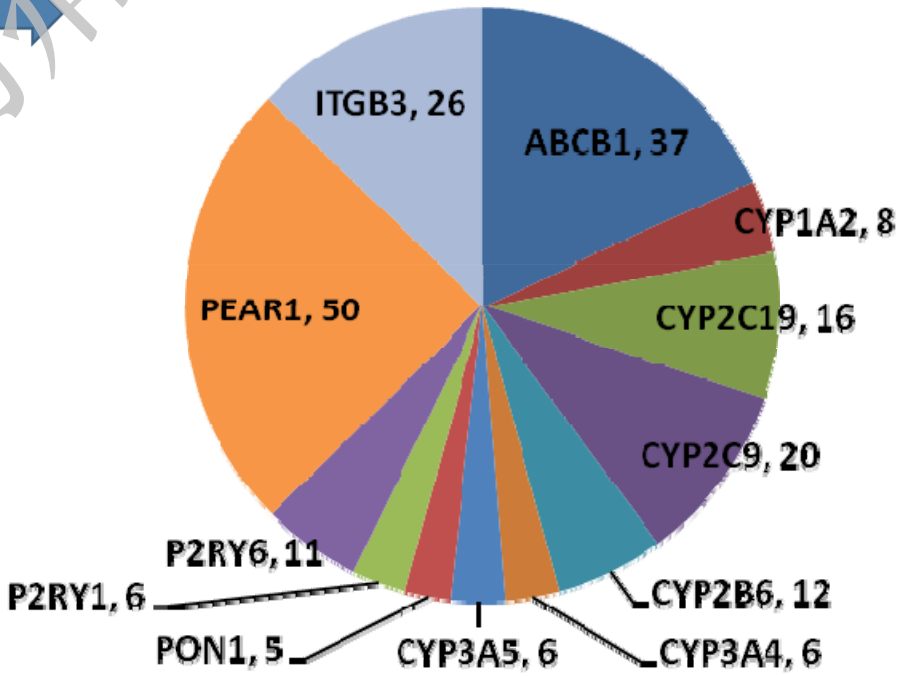
Case 2: Male; 60 years old; patient was performed PCI for acute myocardial infarction; genetic testing showed he was a CYP2C19*2 homozygotes. The platelet aggregation rate was 25% after administered with 75 mg bid clopidogrel for 2 weeks.

Questions:

- Whether the dose and the antiplatelet drug for Chinese patients are similar to Westerners?
- Do Chinese patients exist clopidogrel resistance?
- How about the incidence of cardiovascular events in Chinese patients after PCI?


5′非编码区, 2
3′非编码区, 1
上游, 2
内含子, 8
外显子
错义突变, 56
同义突变, 39
移码突变, 2
无义突变, 3


扩增子数
外显子数
ITGB3
PEAR1
P2RY12
P2RY6
P2RY1
PON1
CYP3A5
CYP3A4
CYP2B6
CYP2C9
CYP2C19
CYP1A2
ABCB1
0.933
0.952
0.998
0
10
20
30
40
50
60
70


ITGB3, 26
ABCB1, 37
CYP1A2, 8
CYP2C19, 16
PEAR1, 50
CYP2C9, 20
P2RY6, 11
P2RY1, 6
CYP2B6, 12
PON1, 5
CYP3A5, 6
CYP3A4, 6

Gene variants involve in clopidogrel absorption, metabolic activation, and antiplatelet aggregation.

Gene	SNPs	Name	Allele（M>m）[a]	Function	Chinese MAF[b]	European MAF[c]
ABCB1	rs1045642	C 3435 T	C>T	cds-synon	0.417	0.571
CYP2C19	rs4244285	CYP2C19*2	G>A	cds-synon	0.256	0.155
	rs4986893	CYP2C19*3	G>A	stop-gain	--[d]	--
	rs12248560	CYP2C19*17	C>T	nearGene-5	0.022	0.217
CYP2C9	rs1057910	CYP2C9*3	A>C	missense	0.044	0.058
CYP2B6	rs3745274	CYP2B6*9	G>T	missense	0.151	0.270
CYP3A4	rs2242480	CYP3A4*2	C>T	intron region	0.280	0.073
CYP3A5	rs776746	CYP3A5*3	G>A	intron region	0.337	0.036
P2RY12	rs6785930	c.18C>T	G>A	cds-synon	0.238	0.305
	rs6809699	c.36C>T	C>A	cds-synon	0.186	0.186
PEAR1	rs12566888		G>T	intron region	0.298	0.046
	rs12041331		G>A	intron region	0.314	0.055
ITGB3	rs5918	c.176T>C	T>C	missense	0.012	0.137

[a] M, major allele； m, minor allele（according to the Chinese frequency in Hapmap database）。

[b,c] The data come from the Hapmap database。

[d] No relevant data。

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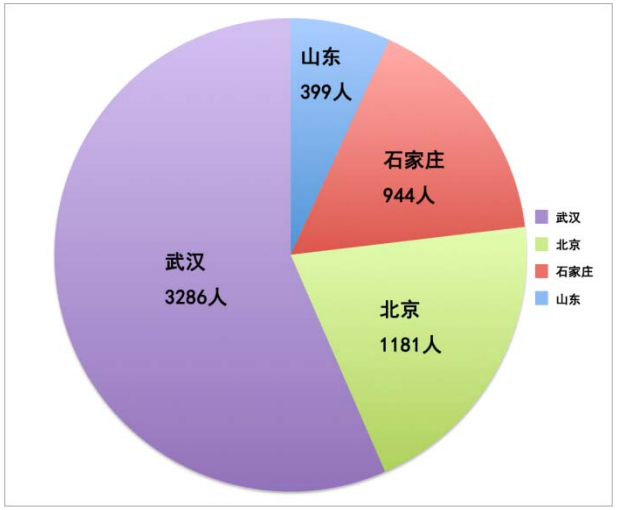
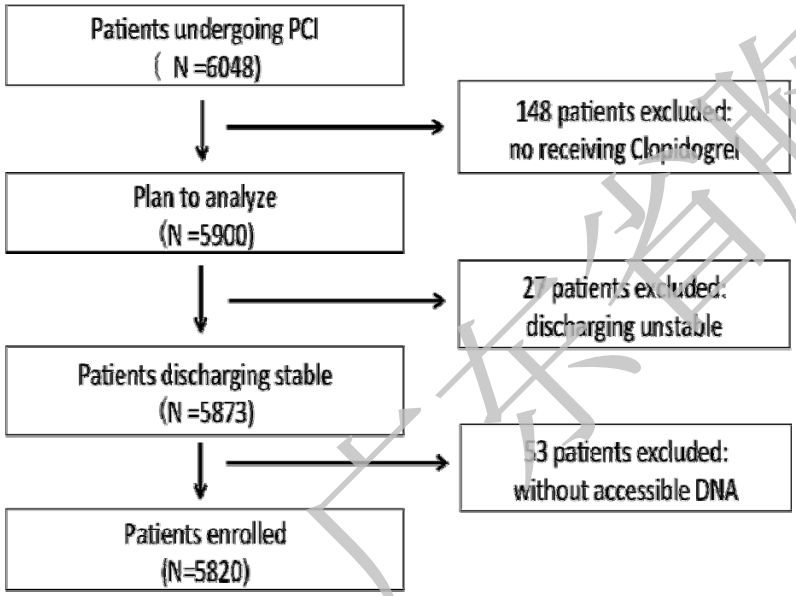
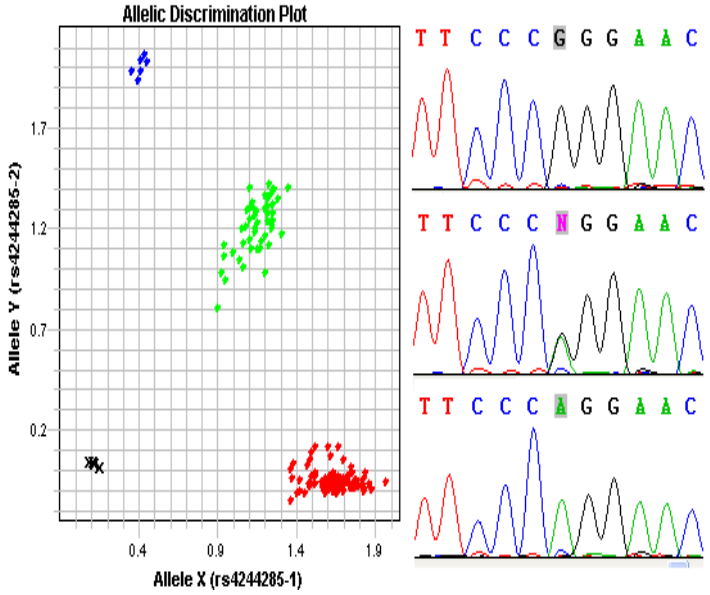


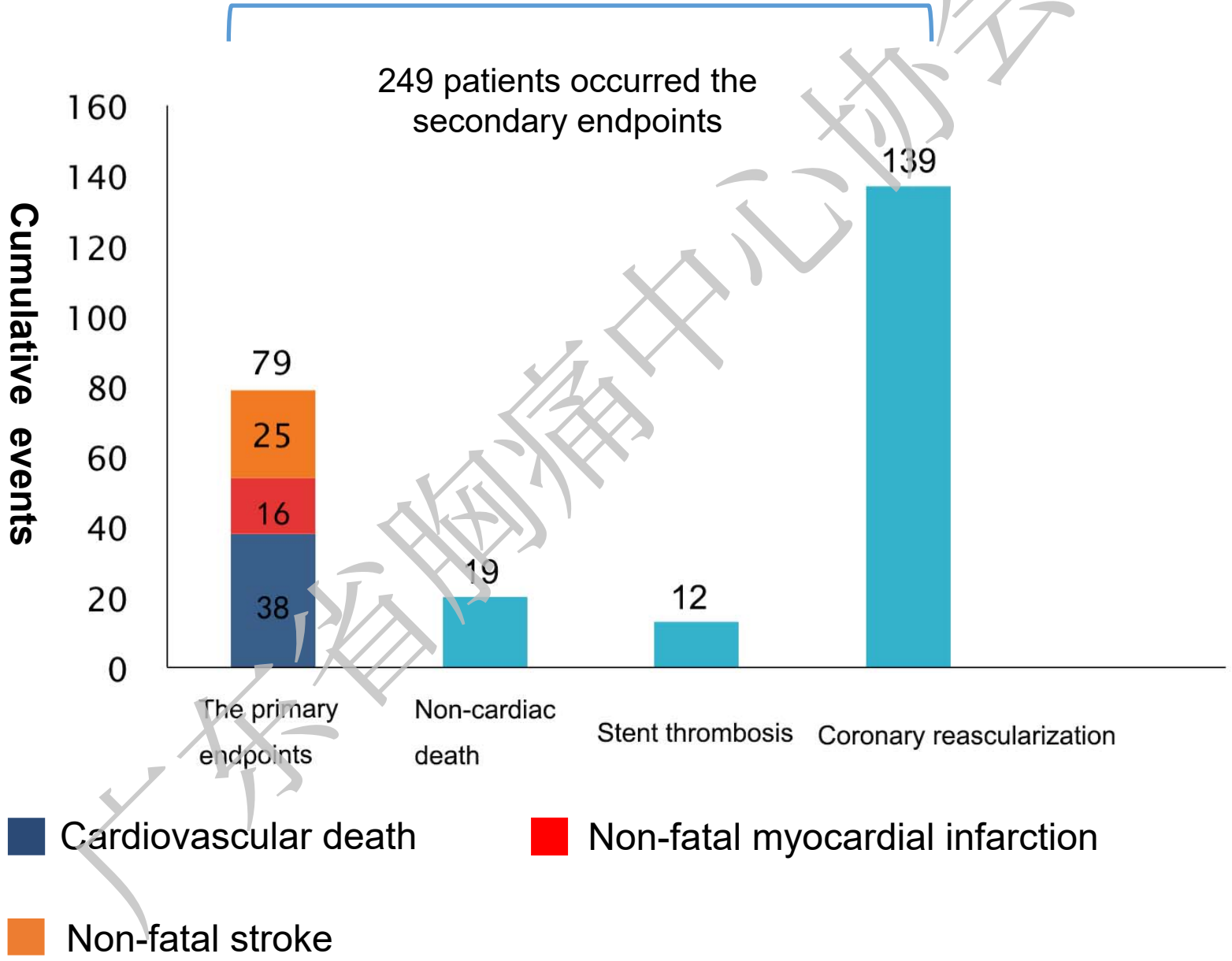
One-year follow-up

The primary endpoints:
Cardiovascular death
Non-fatal myocardial infarction
Non-fatal stroke

The secondary endpoints:
Non-cardiac death
Stent thrombosis
Coronary reascularization
The primary endpoints





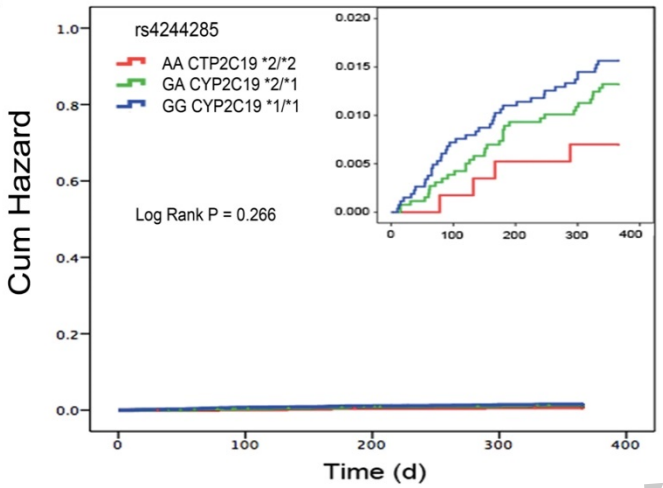

249 patients occurred the secondary endpoints
Cumulative events
160
140
120
100
80
60
40
20
0
79
25
16
38
19
12
139
The primary endpoints
Non-cardiac death
Stent thrombosis
Coronary reascularization
Cardiovascular death
Non-fatal myocardial infarction
Non-fatal stroke

SNPs	Genotype	Event group (n=79)	No event group (n=5741)	Total (N=5820)	P value
rs1045642	CC	33 (1.5%)	2163 (98.5%)	2196	0.387
	CT	38 (1.4%)	2671 (98.6%)	2709	
	TT	8 (0.9%)	898 (99.1%)	906	
rs4244285	GG	41 (1.5%)	2609 (98.5%)	2650	0.266
	GA	34 (1.3%)	2561 (98.7%)	2595	
	AA	4 (0.7%)	571 (99.3%)	575	
rs4986893	GG	71 (1.3%)	5235 (98.7%)	5306	0.809
	GA	8 (1.6%)	491 (98.4%)	499	
	AA	0 (0%)	13 (100%)	13	
rs12248560	CC	79 (1.4%)	5627 (98.6%)	5706	0.452
	CT	0 (0.0%)	93 (100%)	93	
	TT	0 (0%)	21 (100%)	21	
rs1057910	AA	70 (1.3%)	5223 (98.7%)	5293	0.311
	AC	8 (1.6%)	486 (98.4%)	494	
	CC	1 (5.0%)	19 (95.0%)	20	
rs3745274	CG	63 (1.6%)	3963 (98.4%)	4026	0.166
	GT	14 (0.9%)	1518 (99.1%)	1532	
	TT	2(1.1%)	184 (98.9%)	186	
rs2242480	CC	51 (1.6%)	3201 (98.4%)	3252	0.297
	CT	23 (1.1%)	2125 (98.9%)	2148	
	TT	5 (1.2%)	402 (98.8%)	407	
rs776746	GG	41 (1.4%)	2954 (98.6%)	2995	0.546
	GA	34 (1.5%)	2295 (98.5%)	2329	
	AA	4 (0.8%)	482 (99.2%)	486	
rs6785930	GG	45 (1.3%)	3417 (98.7%)	3462	0.856
	GA	29 (1.4%)	2014 (98.6%)	2043	
	AA	5 (1.6%)	300 (98.4%)	305	

Continued

SNPs	Genotype	Event group (n=79)	No event group (n=5741)	Total (N=5820)	P value
rs6809699	CC	63 (1.4%)	4432 (98.6%)	4495	0.236
	CA	13 (1.1%)	1201 (98.9%)	1214	
	AA	3 (3.0%)	96 (97.0%)	99	
rs12566888	GG	23 (1.1%)	2034 (98.9%)	2057	0.428
	GT	43 (1.6%)	2717 (98.4%)	2760	
	TT	13 (1.3%)	980 (98.7%)	993	
rs12041331	GG	25 (1.2%)	2132 (98.8%)	2157	0.58
	GA	40 (1.4%)	2723 (98.6%)	2763	
	AA	14(1.6%)	878 (98.4%)	890	
rs5918	TT	78 (1.4%)	5654 (98.6%)	5732	0.99
	TC	1(1.3%)	78 (98.7%)	79	
	CC	0 (0%)	1 (100%)	1	
CYP2C19 (*2, *3)	WT	34 (1.5%)	2285 (98.5%)	2319	0.205
	1 loss	40 (1.5%)	2701 (98.5%)	2741	
	≥2 loss	5 (0.7%)	753 (99.3%)	758	
CYP2C19 (*2, *3, *17)	WT/*17	34 (1.4%)	2325 (98.6%)	2359	0.204
	1 loss	40 (1.5%)	2661 (98.5%)	2701	
	≥2 loss	5 (0.7%)	753 (99.3%)	758	

A



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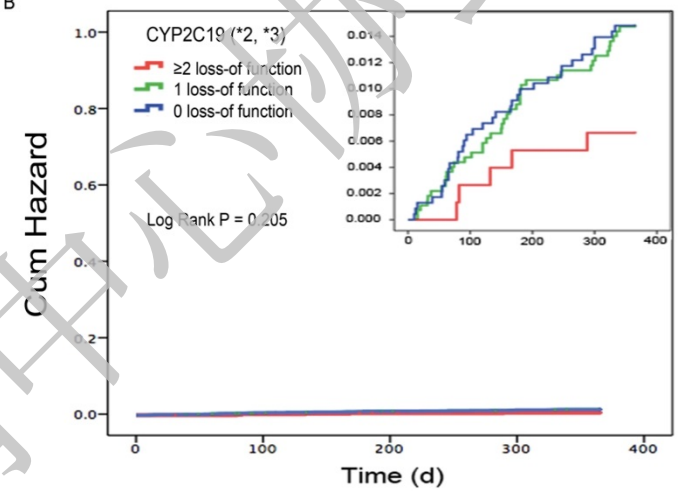

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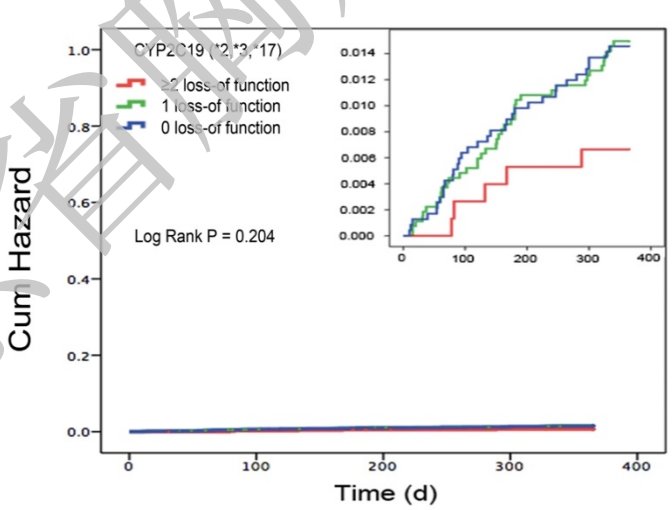

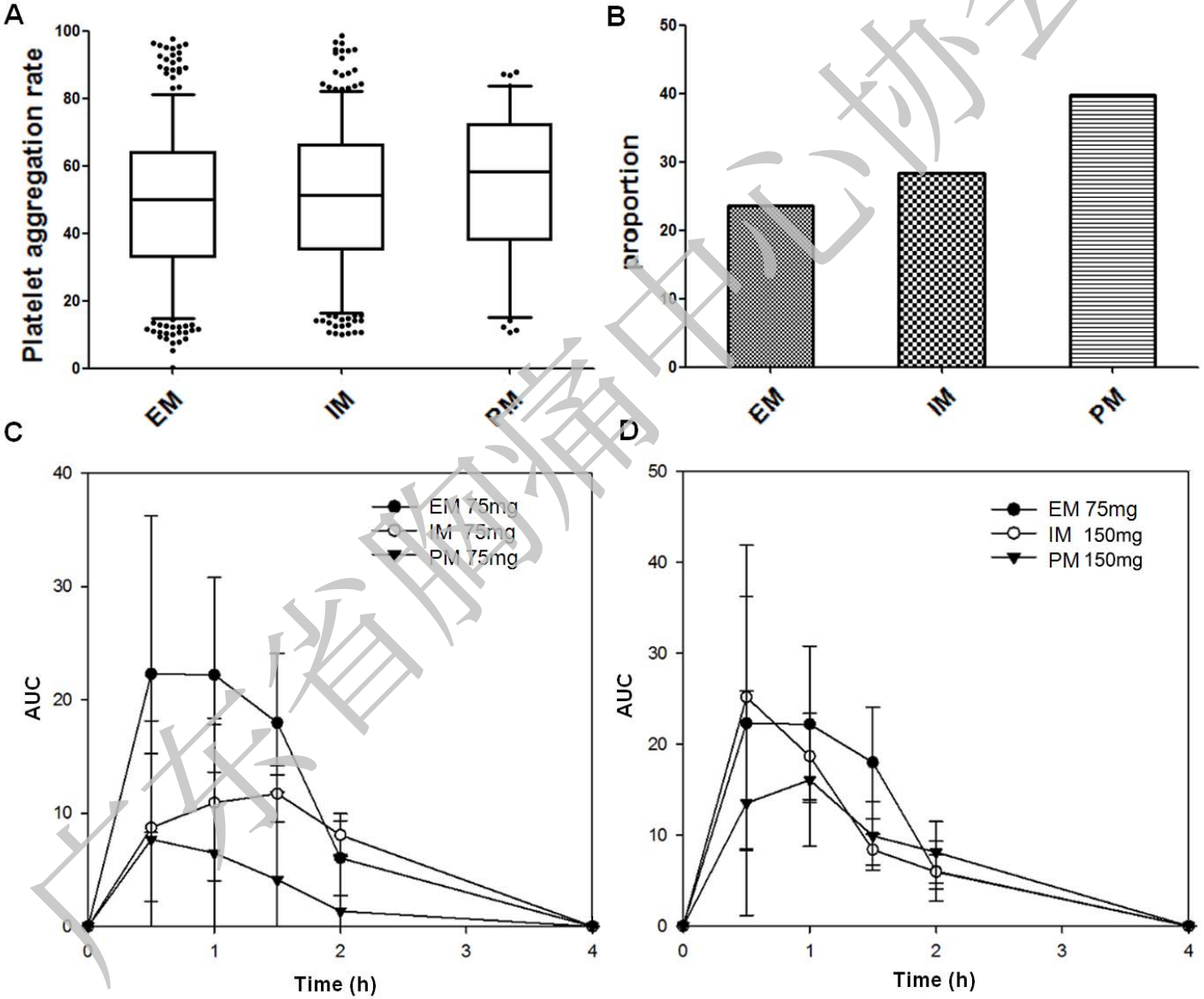

Conclusions and Perspectives

- In Chinese population, the minor allele frequency of CYP2C19*2 is 0.322;
- The rate of the primary endpoint was 1.4% , and the rate of the secondary endpoint was 4.3%. The risk of cardiovascular events was significant lower in Chinese patients with ACS after PCI than those in Whites;
- No significant associations were found between any of the tested variants and risk of cardiovascular events (P>0.05), although CYP2C19*2 carriers has slightly higher on-treatment platelet aggregation rate and lower active metabolite exposure compared with that of non-carriers. Switching from 75 mg daily clopidogrel to 150mg daily fully overcome low exposure to clopidogrel active metabolite in CYP2C19*2 carriers;
- There is no need to genotyping and adjust the dosage before administration. 75 mg daily clopidogrel is an appropriate choice for Chinese patients with ACS after PCI;
- Why are the Chinese (or east Asians) obviously different from the white? It remains to be decrypted.

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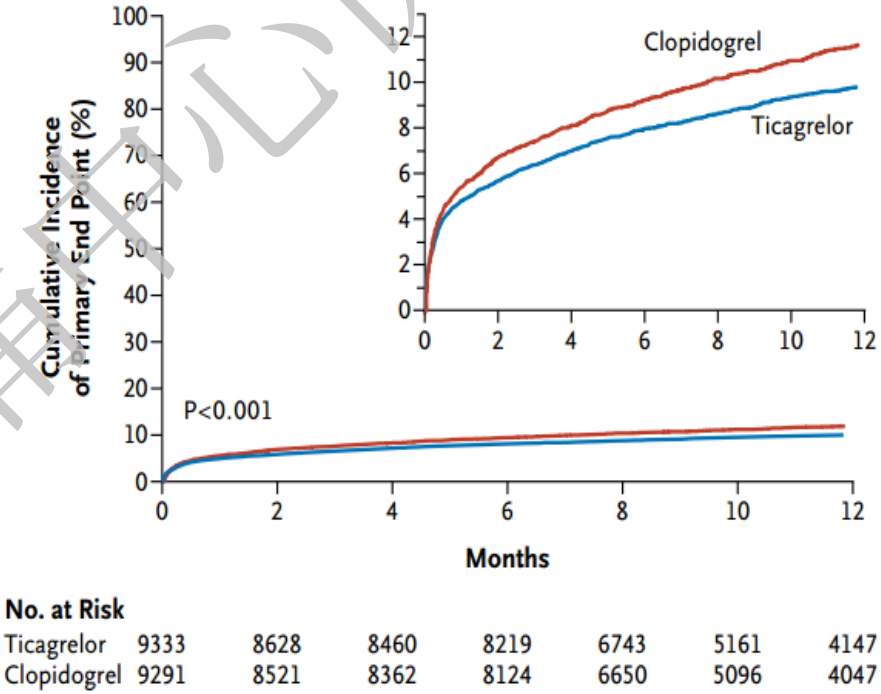
Ticagrelor increases the risk of bleeding in Chinese patients with acute coronary syndrome undergoing PCI in real practice

Background:

- Ticagrelor shows a faster, more powerful, more consistent inhibition of platelet aggregation and is not affected by genetic factors compared with clopidogrel;
- PLATO: In overall 18,624 ACS patients, the use of Ticagrelor can significantly decrease the rate of one-year cardiovascular events in ACS patients compared with clopidogrel:
  Ticagrelor group: 9.8%
  Clopidogrel group: 11.7%
- Ticagrelor didn't increase the risk of major bleeding.



N Engl J Med. 2009 ;361:1045-57.

Background

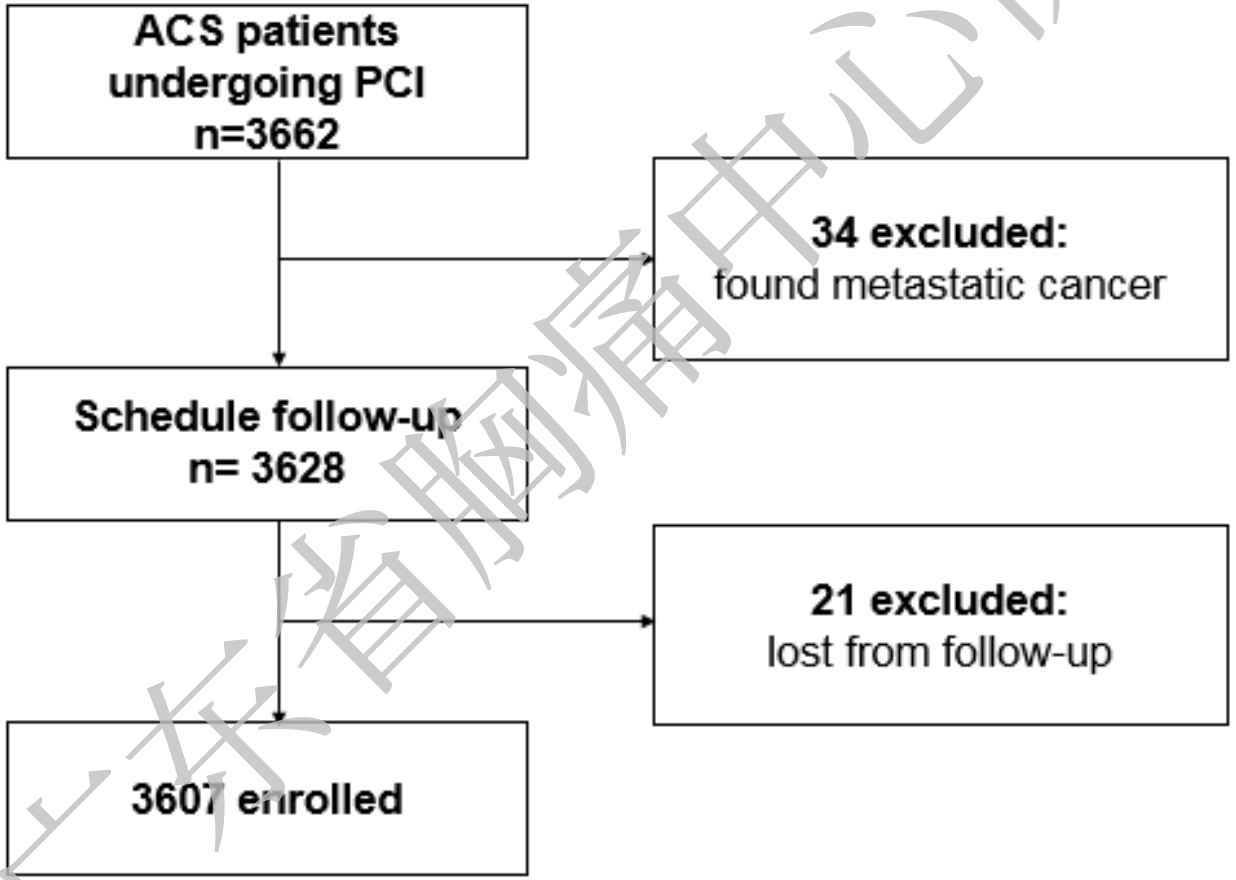
Studies conducted in Japan and South Korea found that ticagrelor did not significantly improve the prognosis of ACS patients, but increased the risk of bleeding.

Background

- Different from Caucasian populations, genetic variants, such as CYP2C19*2, have no significant influence on clinical outcome in Chinese patients with clopidogrel treatment;
- Long-term use of ticagrelor increase the risk of minor bleeding;
- Adverse reactions, such as bleeding, could influence patients' compliance, and the compliance of P2Y12 receptor antagonist is closely related to the prognosis.

Int J Cardiol. 2017;240: 360-366.
Front Med. 2017 ;11:53-61.

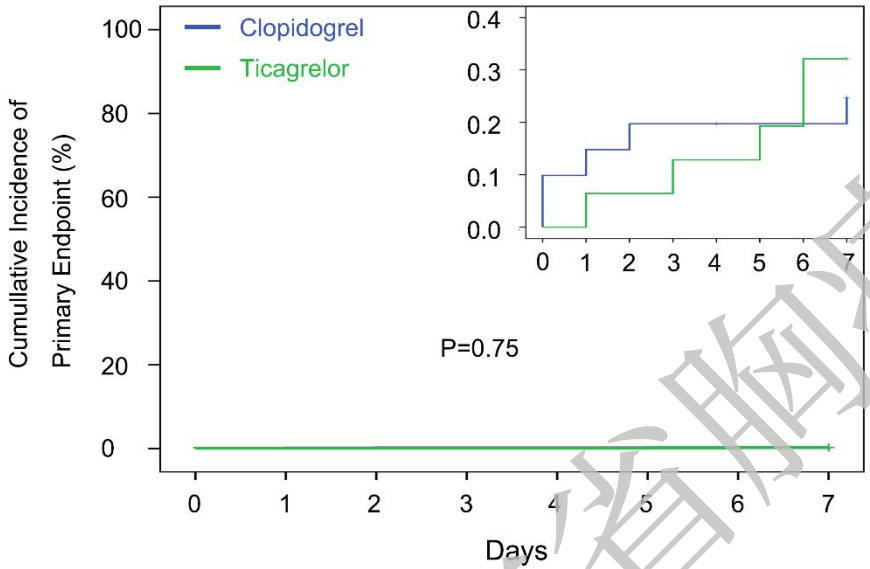
Patients enrollment



Baseline characteristics of the propensity-score matched patients

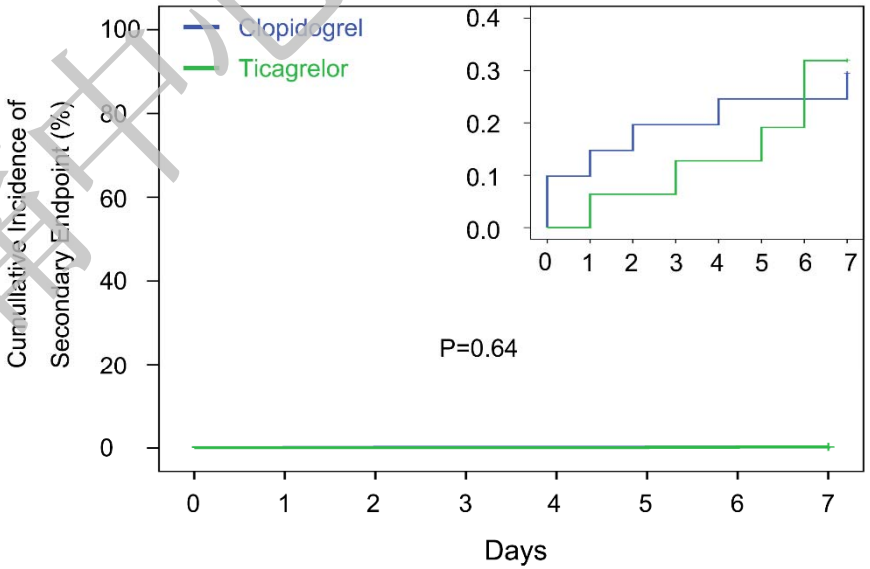
Characteristics	Clopidogrel Group	Ticagrelor Group	P value
Age	59.98±10.09	59.52±10.10	0.213
Male sex	1126 (75.0)	1148 (76.5)	0.349
Cardiovascular risk factor			
Smoker	668 (44.5)	689 (45.9)	0.441
Hypertension	911 (60.7)	902 (60.1)	0.737
Diabetes mellitus	446 (29.7)	454 (30.2)	0.75
Dyslipidemia	327 (21.8)	339 (22.6)	0.598
Other medical history			
MI	104 (6.9)	121 (8.1)	0.239
Stroke	64 (4.3)	64 (4.3)	1
Peripheral arterial disease	245 (16.3)	249 (16.6)	0.844
Chronic renal disease	56 (3.7)	69 (4.6)	0.235
Chronic obstructive pulmonary disease	22 (1.5)	18 (1.2)	0.524
Diagnosis of ACS			0.067
ST-elevation MI	323 (21.6)	371 (24.8)	
Non–ST-elevation MI	258 (17.3)	268 (18.0)	
Unstable angina	912 (61.1)	854 (57.2)	
Other discharge medication			
aspirin	1498 (99.8)	1494 (99.5)	0.205
statin	1490 (99.3)	1484 (98.9)	0.255
ACEI	1066	1078	0.628
beta blocker	1168	1178	0.659
nitrate	360	334	0.26
diuretics	111	129	0.226

Major cardiovascular events at the seventh days



NO. at Risk

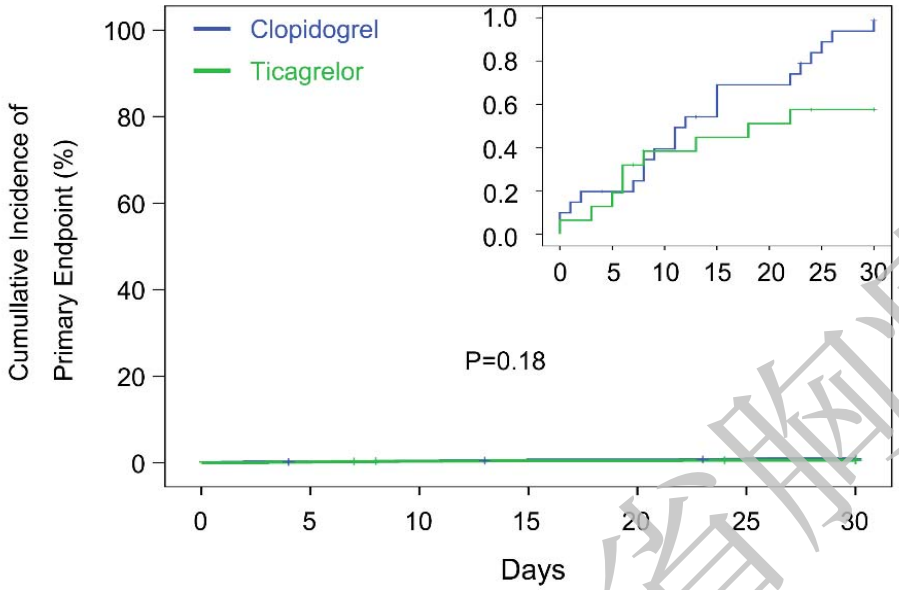
Clopidogrel	2029	2027	2026	2025	2025	2024	2024	2024
Ticagrelor	1558	1557	1557	1557	1556	1556	1555	1553

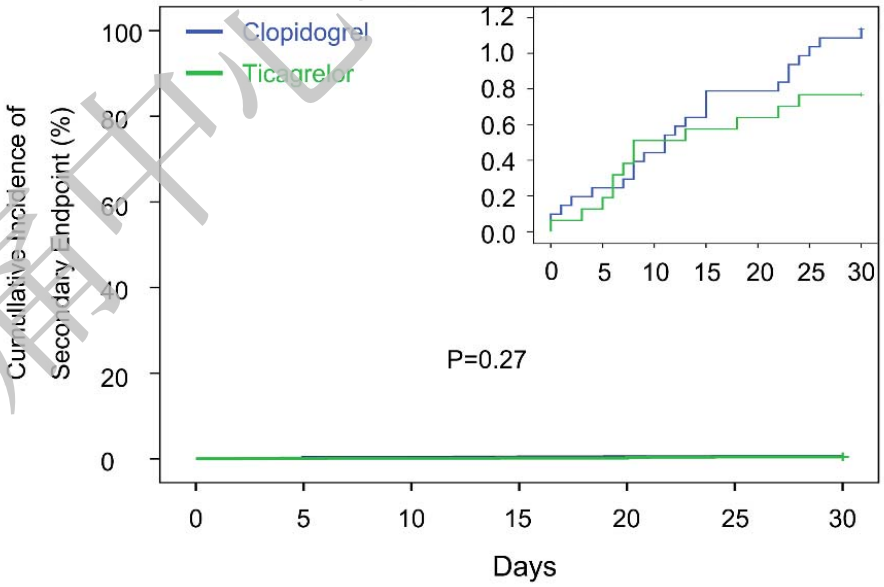


NO. at Risk

Clopidogrel	2029	2027	2026	2025	2025	2024	2024	2024
Ticagrelor	1558	1557	1557	1557	1556	1556	1555	1553

Major cardiovascular events at the first month

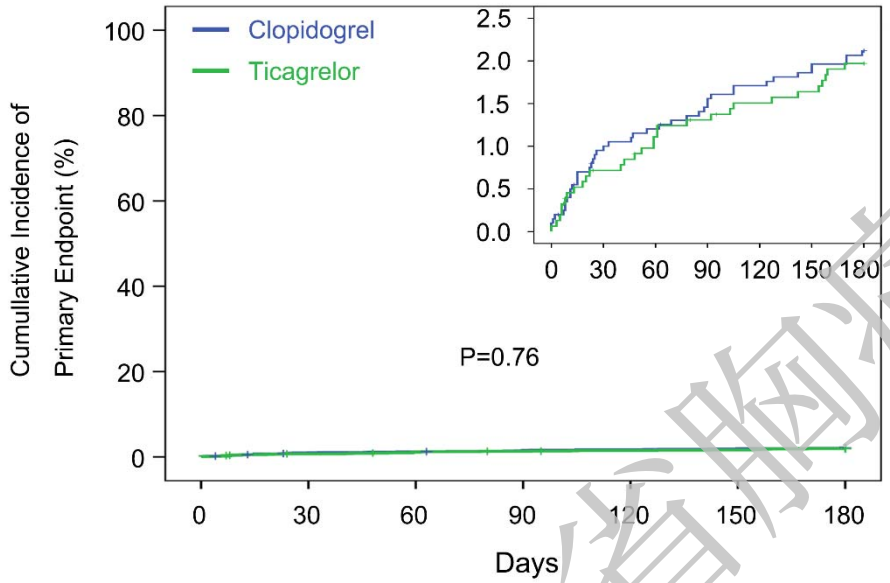




NO. at Risk							
Clopidogrel	2029	2024	2020	2016	2013	2009	2007
Ticagrelor	1558	1556	1550	1549	1548	1547	1547

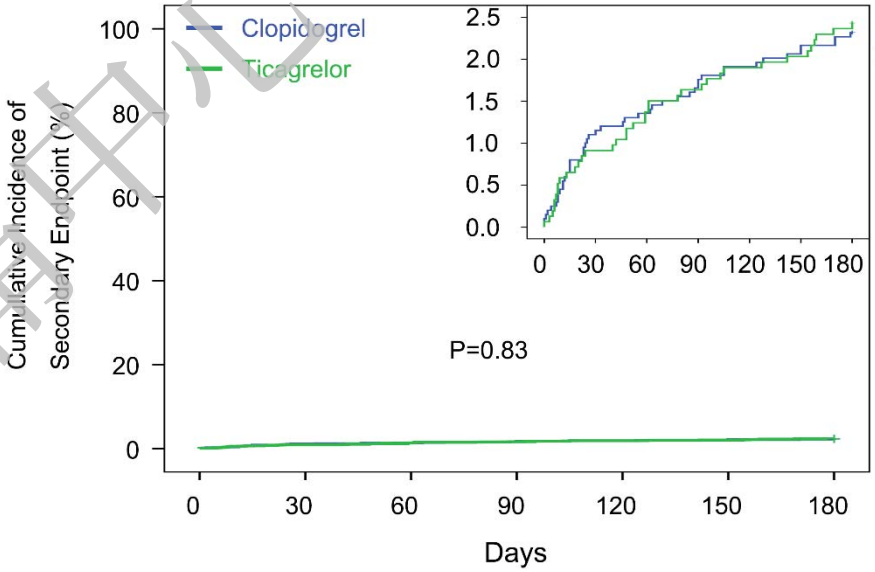
NO. at Risk							
Clopidogrel	2029	2024	2020	2016	2013	2009	2007
Ticagrelor	1558	1556	1550	1549	1548	1547	1547

Major cardiovascular events at the sixth month



NO. at Risk

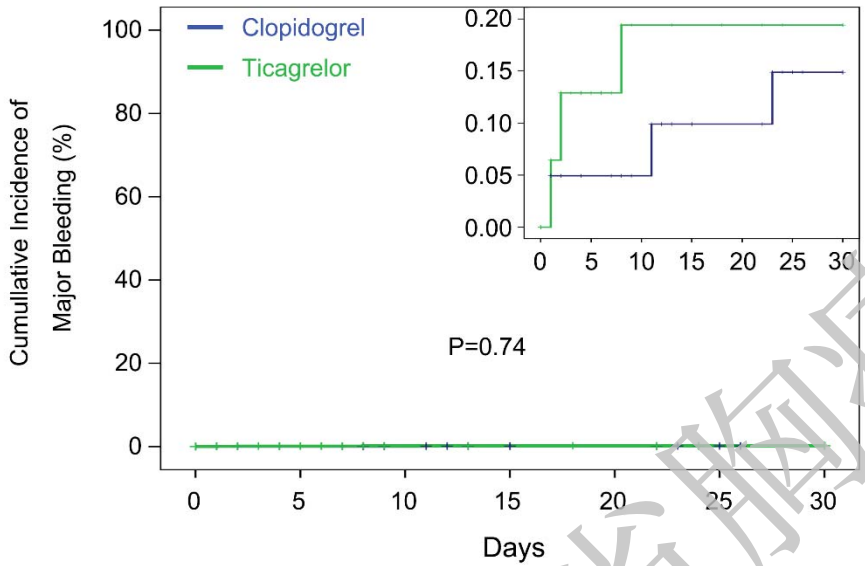
Clopidogrel	2008	1986	1981	1975	1970	1967	1962
Ticagrelor	1541	1527	1520	1516	1512	1510	1505



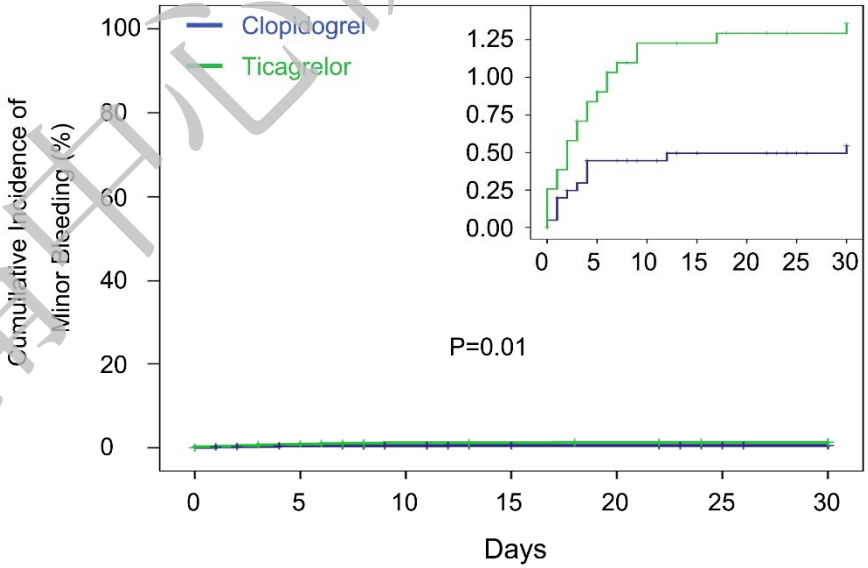
NO. at Risk

Clopidogrel	2008	1986	1981	1975	1970	1967	1962
Ticagrelor	1541	1527	1520	1516	1512	1510	1505

Bleeding at the first month

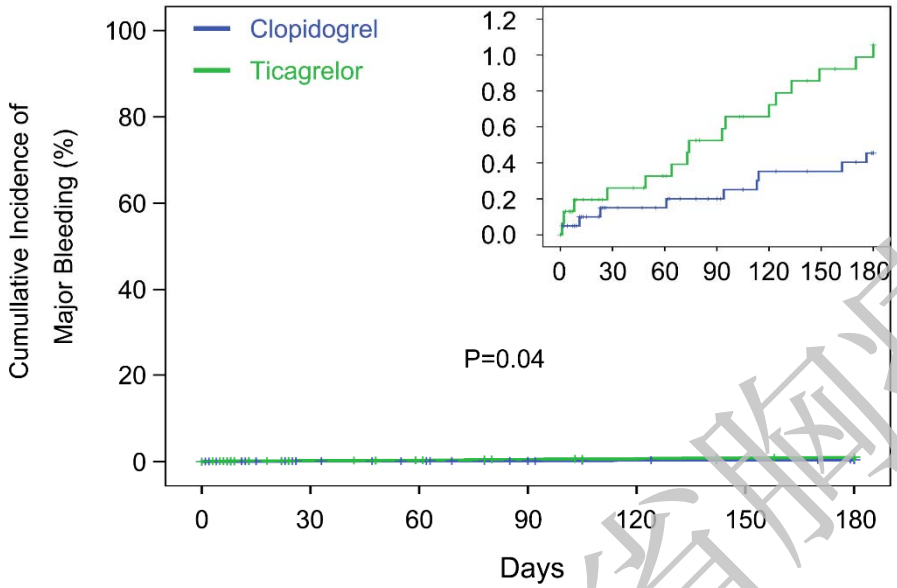


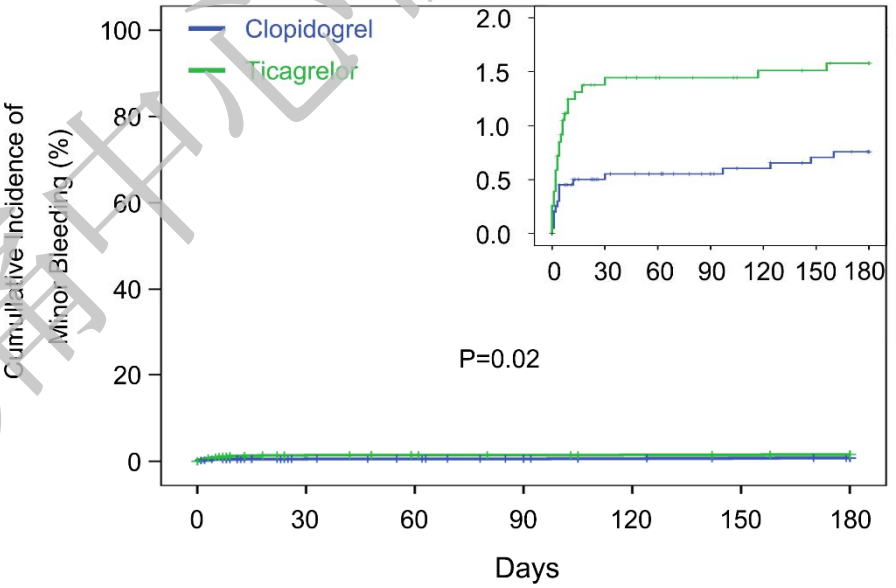
NO. at Risk							
Clopidogrel	2029	2020	2016	2012	2010	2006	2004
Ticagrelor	1558	1542	1533	1532	1531	1529	1529



NO. at Risk							
Clopidogrel	2029	2015	2011	2006	2004	2000	1998
Ticagrelor	1558	1543	1532	1531	1529	1527	1527

Bleeding at the sixth month





NO. at Risk							
Clopidogrel	2008	1986	1983	1977	1969	1967	1963
Ticagrelor	1541	1525	1519	1513	1508	1504	1502

NO. at Risk							
Clopidogrel	2000	1969	1965	1960	1954	1950	1947
Ticagrelor	1537	1504	1498	1496	1493	1492	1490

Summary

- Ticagrelor can not significantly decrease the risk of major cardiovascular events;
- Ticagrelor increases the rate of bleeding;
- Ticagrelor increases the incidence of pant or dyspnea.

Conclusion

- East Asian had a lower risk of ischemia, but a higher risk of bleeding;
- The incidence of cardiovascular events in ACS patients after PCI is lower than those in Whites (the rate of the primary endpoint is 1.4% in Chinese patients), and the clinical outcome is not associated with the genetic variants, such as CYP2C19*2;
- Compared with clopidogrel, ticagrelor did not improve the prognosis of Chinese patients with ACS, but increased the risk of bleeding.

Clopidogrel is one of the most appropriate dual antiplatelet therapy for Chinese patients undergoing PCI

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Thanks for attention