# Ticagrelor with Aspirin on Platelet Reactivity in Acute Non-disabling Cerebrovascular Events (PRINCE) Trial

## Final Analysis (NCT02506140)

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**Presenting on behalf of Yongjun Wang, MD**
**and all the PRINCE trial Investigators**

INTERNATIONAL STROKE CONFERENCE 2018

American Heart Association | American Stroke Association
life is why

# Disclosures

**Study Sponsors**

- National Natural Science Foundation of China (81322019)
- Beijing Institute for Brain Disorders (BIBD- 600004)
- Beijing Municipal Science & Technology Commission of Cerebral Vascular Disease (D15110700200000)
- AstraZeneca
  - Provided study drugs
  - No role in design, analysis of presentation

# Background

- **Minor stroke and TIA have a high risk of recurrent stroke**
- **Combination of clopidogrel and aspirin was superior to aspirin alone in reducing the recurrence of stroke in noncardioembolic minor stroke or high risk TIA**
- ***CYP2C19*2 or *3* LoF alleles (more common in Asians) did not benefit from clopidogrel and aspirin compared with those using aspirin alone**

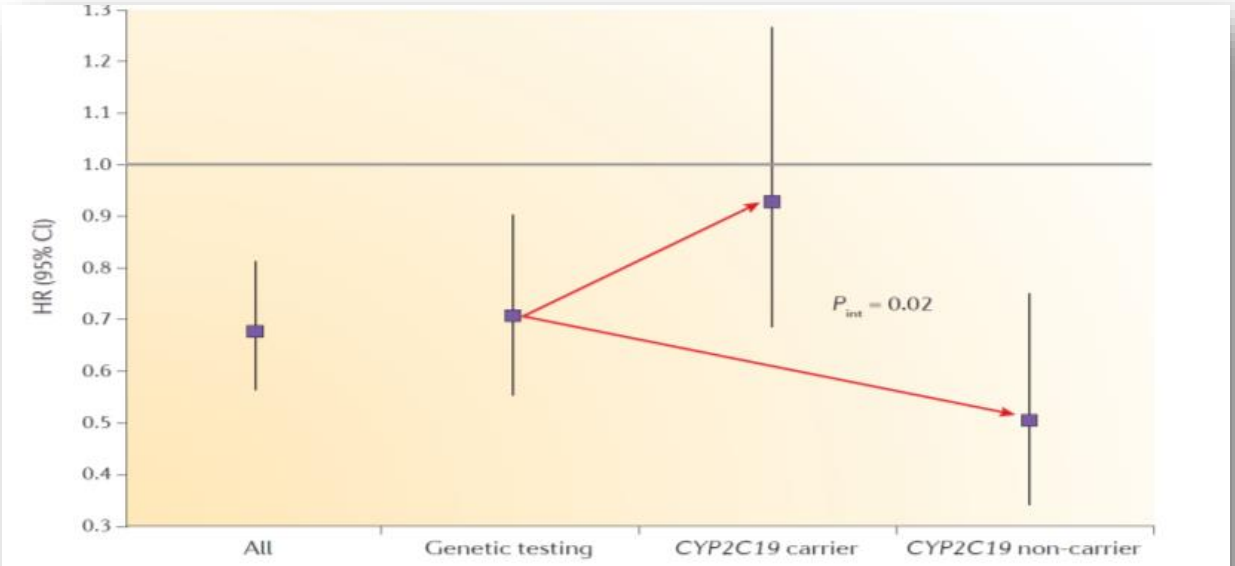
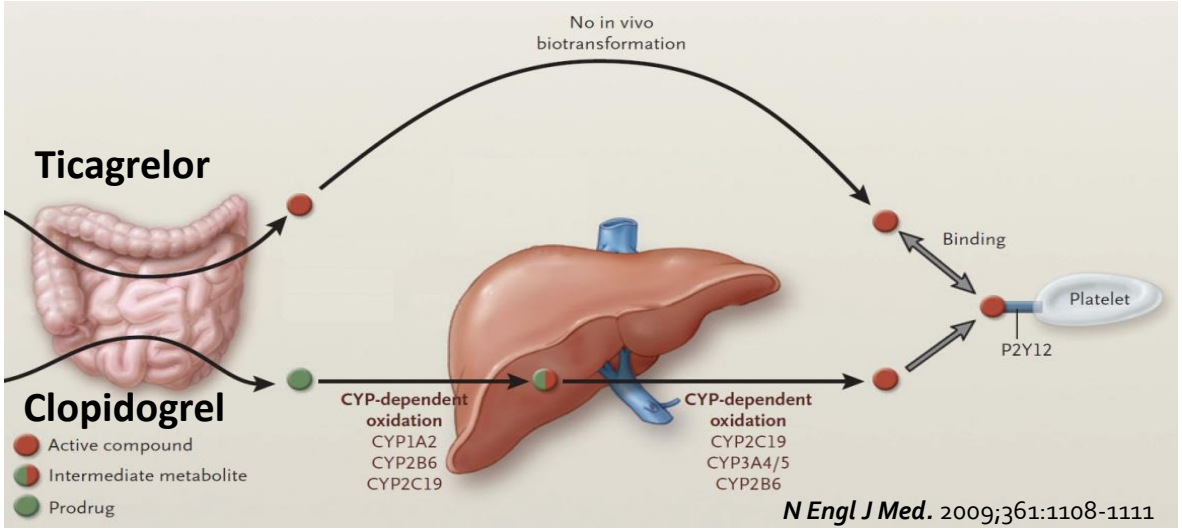


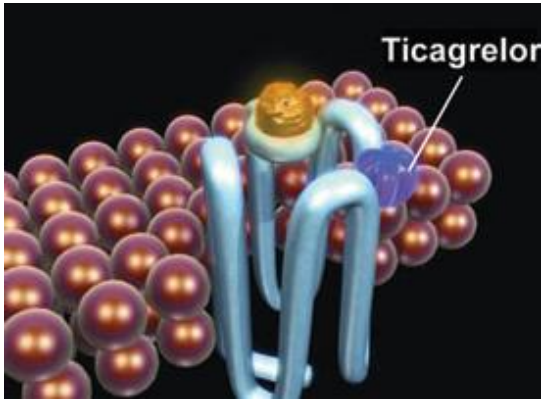

Figure 1 | **The CHANCE trial substudy.** The graph shows the hazard ratios (HRs) and 95% confidence intervals for 90-day stroke recurrence in patients treated with aspirin plus clopidogrel versus aspirin monotherapy. Data are shown for the whole CHANCE cohort[6], the subset of patients who underwent genetic testing for three *CYP2C19* major alleles[7], and the two subgroups who did and did not carry *CYP2C19* mutations that reduced the ability to metabolize clopidogrel. $P_{int}$, *P*-value for statistical interaction between the two *CYP2C19* carrier subgroups.

Nature Reviews Neurology2016
NEJM. 2016;374:1533-1542
NEJM. 2013;369:11-19
JAMA. 2016;316:70-78

# Background

- **Ticagrelor was more efficacious in acute coronary syndromes compared with clopidogrel, irrespective of *CYP2C19* genotype, with increased risk of bleeding in pts having history of stroke.**
- **SOCRATES Trial in Asian substudy: there was a trend of better efficacy in reducing risk of the vascular events in the ticagrelor than aspirin group.**
- **Limited data are available on the safety and efficacy of ticagrelor, compared with clopidogrel on the background of aspirin in stroke pts.**




Lancet. 2010;376:1320-1328
Lancet. 2013;382:614-623
Stroke. 2017;48:167-173

# Purpose and Design

- Determine safety and efficacy of ticagrelor plus aspirin in pts with minor stroke and high risk TIA, especially for carriers of CYP2C19 loss-of-function allele.

- **Multicenter (n=26), PROBE, open-label with blinded assessments :**
  1. Platelet Function Tests, PFT
  2. Imaging (CT/MR)
  3. 90-day clinical endpoint

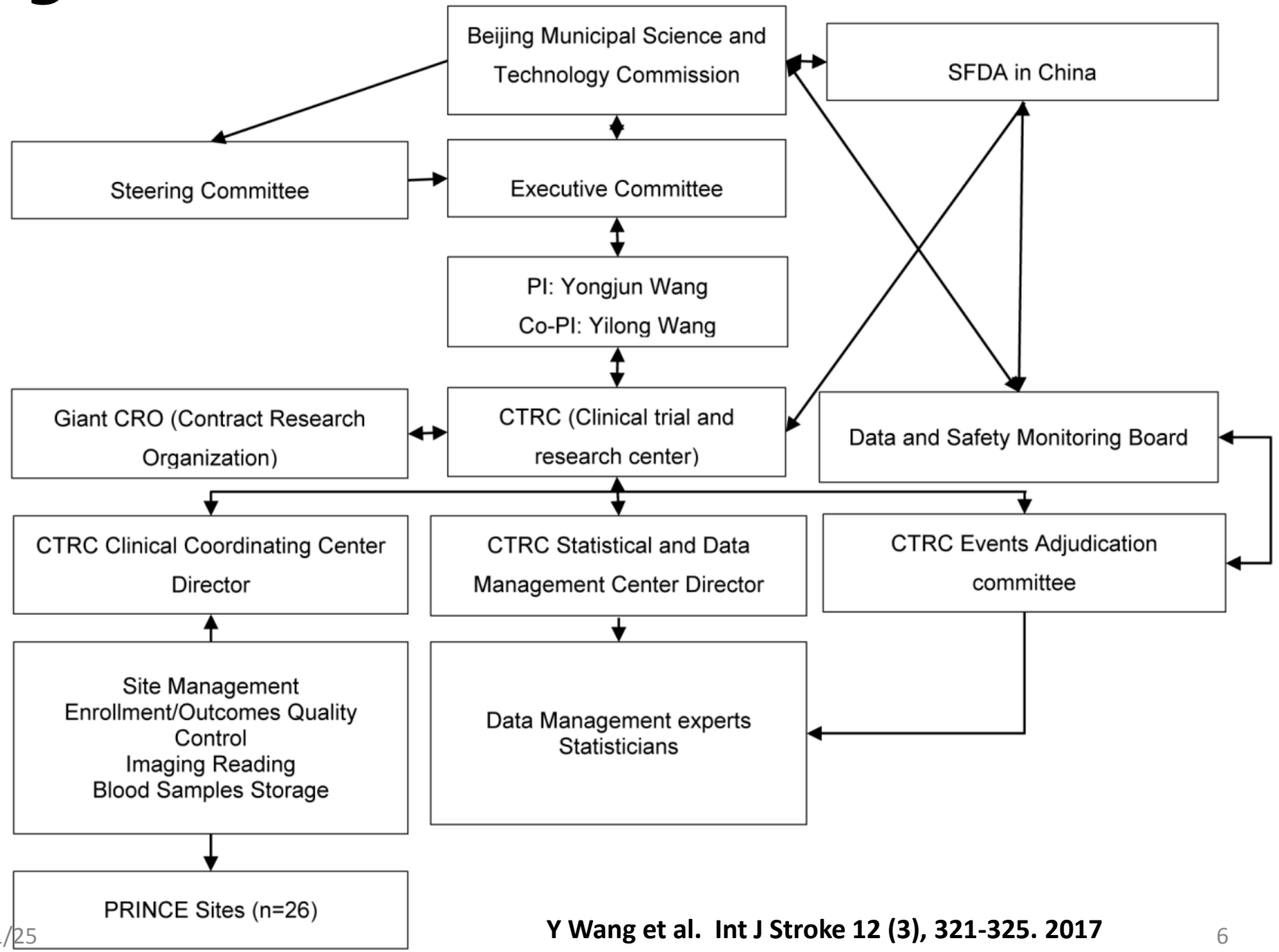
- **Independent Safety Monitor /DSMB (Interim analysis)：**

  Terminate if the interim analysis reached a prespecified statistical significance level ($p < 0.005$).



**Y Wang et al. Int J Stroke 12 (3), 321-325. 2017**

# Organization




Y Wang et al. Int J Stroke 12 (3), 321-325. 2017

# Design

- **Efficacy outcomes**
  - **Primary: 90-day PRU and high on-treatment platelet reactivity (HOPR)**
  - **Secondary:**
    - **stroke during 90 days**
    - **composite vascular events : any stroke, myocardial infarction, and vascular death during 90 days**
- **Safety outcomes**
  - **Primary: major bleeding (PLATO definition), including fatal/life-threatening and other, or minor bleeding**
  - **Secondary: Intracranial hemorrhage; total mortality**

*HOPR : P2Y12 reaction unit (PRU)>208 measured by VerifyNow P2Y12 assay*

**Y Wang et al. Int J Stroke 12 (3), 321-325. 2017**

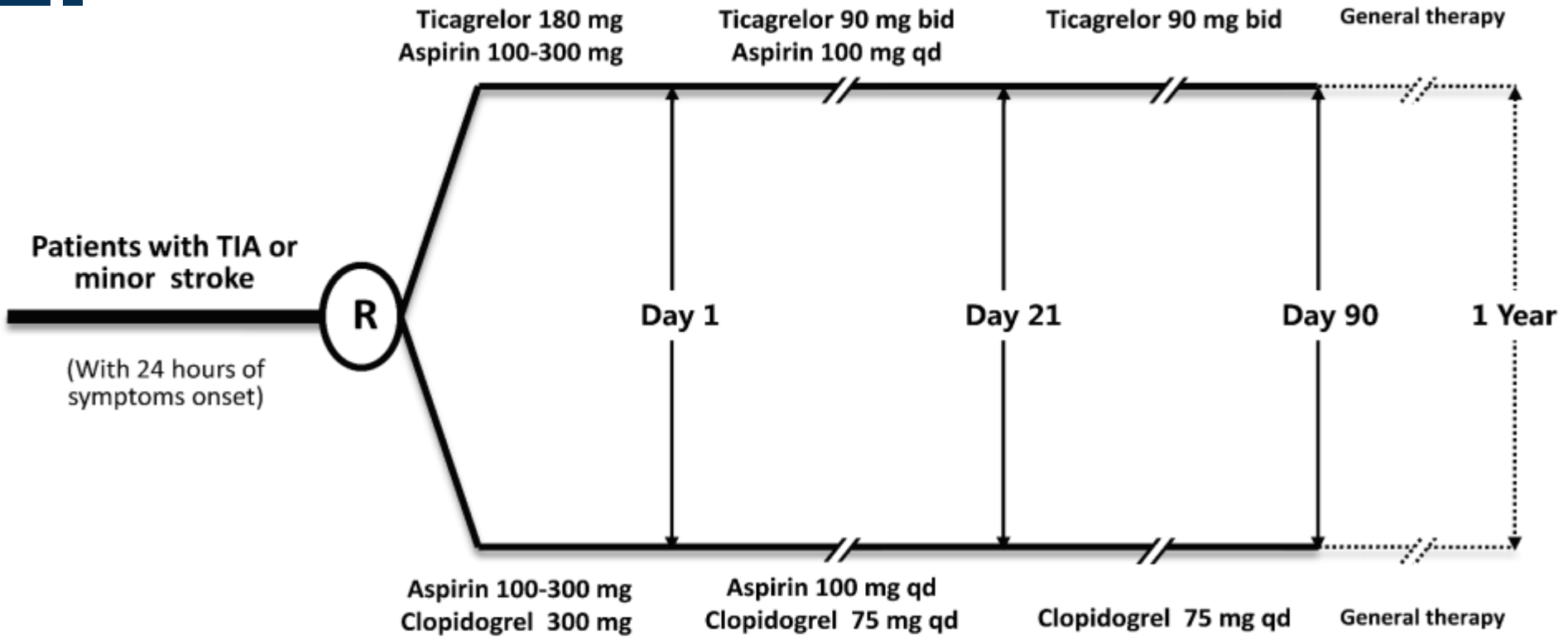
# Study population: Key Eligible Criteria

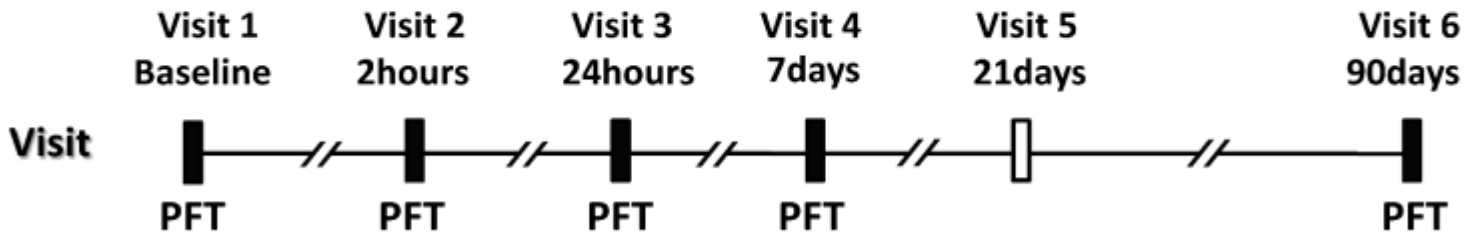
1. 40 - 80 years old.
2. Ischemic minor stroke or TIA within 24 hours ：
   - 2.1 minor stroke (NIHSS≤ 3)
   - 2.2 TIA with moderate-to-high risk of stroke ( ABCD2 score ≥ 4 or the stenosis of offending vessel ≥ 50% ).
3. No indication for anticoagulation (presumed cardiac source of embolus, e.g., AF).
4. No Contraindication to ticagrelor, clopidogrel or acetylsalicylic acid
5. IV tPA and Endovascular therapy not allowed



**Y Wang et al. Int J Stroke 12 (3), 321-325. 2017**

# Design




* **PFT** : *Platelet function test*

**Y Wang et al. Int J Stroke 12 (3), 321-325. 2017**

PRINCE

**P**latelet **R**eactivity **I**n acute **N**on-disabling **C**erebrovascular **E**vents

*Protocol*

International Journal of Stroke WSO

# Effect of ticagrelor with clopidogrel on high on-treatment platelet reactivity in acute stroke or transient ischemic attack (PRINCE) trial: Rationale and design

Yilong Wang[1,2,3,4], Yi Lin[5], Xia Meng[1,2,3,4], Weiqi Chen[1,2,3,4], Guohua Chen[6], Zhimin Wang[7], Jialing Wu[8], Dali Wang[9], Jianhua Li[10], Yibin Cao[11], Yuming Xu[12], Guohua Zhang[13], Xiaobo Li[14], Yuesong Pan[1,2,3,4], Hao Li[1,2,3,4], Liping Liu[1,2,3,4], Xingquan Zhao[1,2,3,4] and Yongjun Wang[1,2,3,4];
On Behalf of The PRINCE Protocol Steering Group

International Journal of Stroke
0(0) 1–5

DOI: 10.1177/1747493017694390
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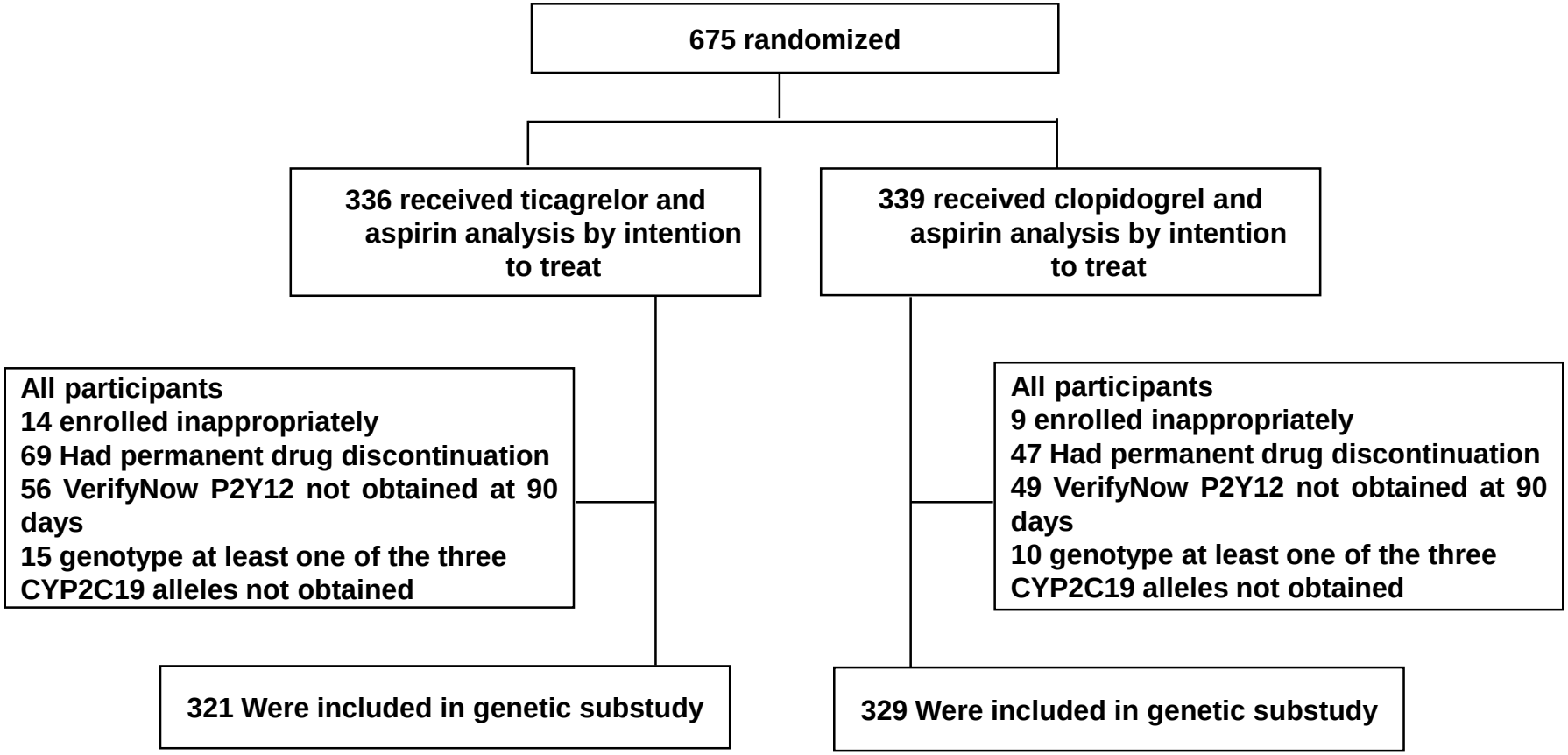
# Flow chart




675 patients were enrolled and included in ITT analysis before the DSMB decided to terminate the trial after reviewing the results of the interim analysis between August 2015 to March 2017.

# Baseline characteristics

| Characteristic | Ticagrelor/Aspirin (n=336) | Clopidogrel/Aspirin (n=339) | P value |
|---|---|---|---|
| Age — yr | 61.1±8.5 | 60.5±9.0 | 0.31 |
| Median | 62.0 | 61.0 | |
| Interquartile range | 55.0-67.0 | 54.0-67.0 | |
| Female sex — no. (%) | 91 (27.1) | 90 (26.5) | 0.88 |
| Systolic blood pressure (mm Hg) | 152.3±22.5 | 154.9±21.2 | 0.10 |
| Median | 150.0 | 154.0 | |
| Interquartile range | 137.5-168.0 | 140.0-170.0 | |
| Diastolic blood pressure (mm Hg) | 87.7±13.0 | 89.4±12.8 | 0.14 |
| Median | 87.5 | 88.0 | |
| Interquartile range | 80.0-96.0 | 80.0-97.0 | |
| Body-mass index ($kg/m^2$) * | 25.0±3.8 | 25.0±3.8 | 0.64 |
| Median | 24.6 | 24.8 | |
| Interquartile range | 22.6-27.0 | 22.7-27.3 | |
| Pulse rate (beats/min) | 75.1±10.1 | 76.3±11.5 | 0.36 |
| Medical history — no. (%) | | | |
| Hypertension | 203 (60.4) | 208 (61.4) | 0.80 |
| Dyslipidemia | 20 (6.0) | 21 (6.2) | 0.90 |
| Diabetes mellitus | 79 (23.5) | 85 (25.1) | 0.64 |
| Ischemic stroke | 59 (17.6) | 62 (18.3) | 0.80 |
| TIA | 8 (2.4) | 10 (2.9) | 0.65 |
| Coronary artery disease | 26 (7.7) | 25 (7.4) | 0.86 |
| Known atrial fibrillation | 0 (0.0) | 4 (1.2) | 0.13 |
| Flutter valvular heart disease | 1 (0.3) | 0 (0.0) | 0.50 |
| Pulmonary embolism | 0 (0.0) | 0 (0.0) | |

# Baseline characteristics

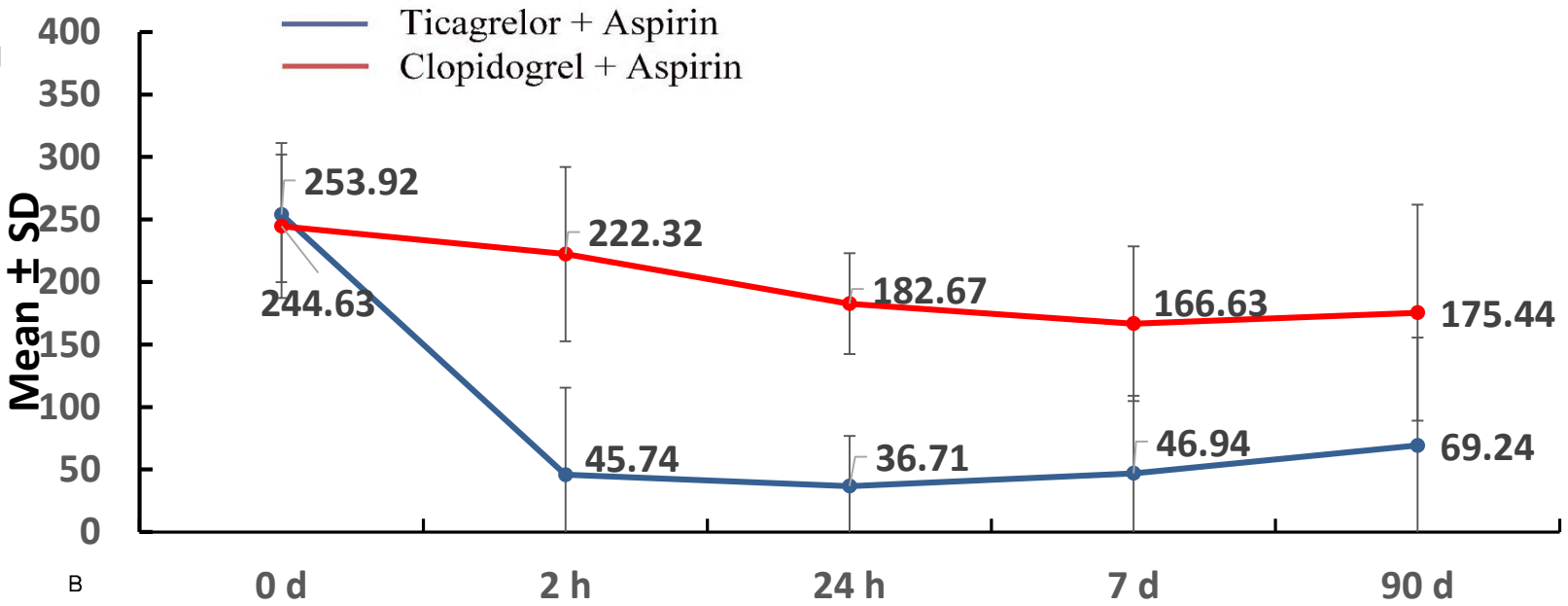
| Characteristic | Ticagrelor/Aspirin (n=336) | Clopidogrel/Aspirin (n=339) | P value |
|---|---|---|---|
| Smoking status — no. (%) | | | 0.96 |
| Non-smoker | 150 (44.6) | 155 (45.7) | |
| Current smoker | 160 (47.6) | 159 (46.9) | |
| Ex-smoker | 26 (7.7) | 25 (7.4) | |
| Drug use before randomization — no. (%) | | | |
| Proton-pump inhibitor | 2 (0.6) | 3 (0.9) | 1.00 |
| Statin | 36 (10.7) | 30 (8.8) | 0.41 |
| Aspirin | 77 ( 22.9) | 69 (20.4) | 0.42 |
| Clopidogrel | 5 (1.5) | 10 (2.9) | 0.20 |
| Ticagrelor | 0 (0.0) | 0 (0.0) | |
| Mean time to randomization after onset of symptoms-hr | 14.0 (8.3-20.6) | 13.8 (8.0-20.8) | 0.82 |
| Time to randomization after onset of symptoms — no. (%) | | | |
| <12 hr | 139 ( 41.4) | 144 ( 42.5) | 0.77 |
| ≥12 hr | 197 ( 58.6) | 195 ( 57.5) | |
| Qualifying event — no. (%) | | | |
| Minor stroke | 275 ( 81.8) | 289 ( 85.3) | 0.27 |
| TIA † | 61 ( 18.2) | 50 ( 14.7) | |
| Baseline ABCD$^2$ score among patients with TIA as qualifying event ‡ | | | 0.83 |
| Median | 5.0 | 4.5 | |
| Interquartile range | 4.0-5.0 | 4.0-5.0 | |

# Baseline characteristics

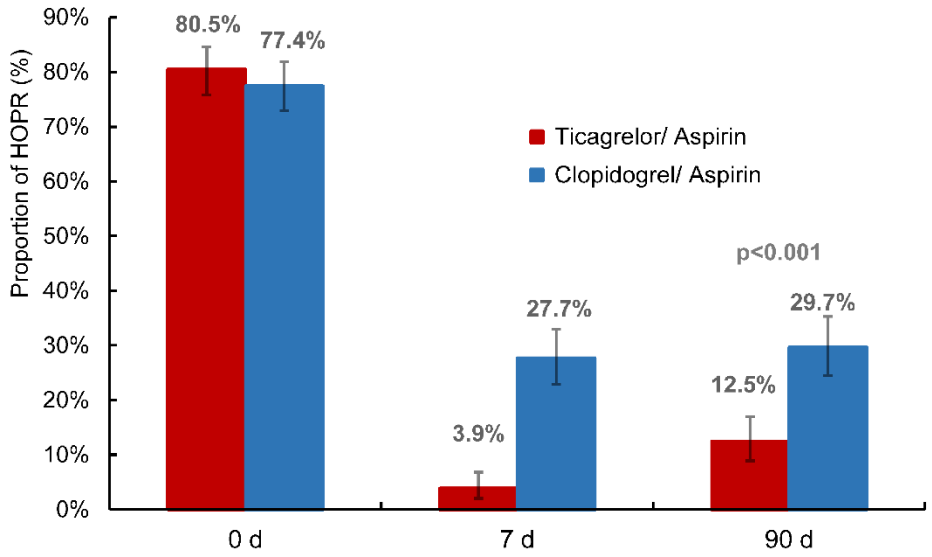
| Characteristic | Ticagrelor/Aspirin (n=336) | Clopidogrel/Aspirin (n=339) | P value |
|---|---|---|---|
| SSS-TOAST stroke subtype — no. (%) | | | 0.37 |
| Large-artery atherosclerosis | 151 (54.9) | 153 (52.9) | |
| Cardioaortic embolism | 8 (2.9) | 5 (1.7) | |
| Small-artery occlusion | 104 (37.8) | 109 (37.7) | |
| Other causes | 7 (2.5) | 9 (3.1) | |
| Undetermined causes | 5(1.8) | 13 (4.5) | |
| Unknown | 2 (0.7) | 7 (2.4) | |
| Unclassified | 3 (1.1) | 6 (2.1) | |

# Efficacy Outcome-PRU or HOPR

PRU

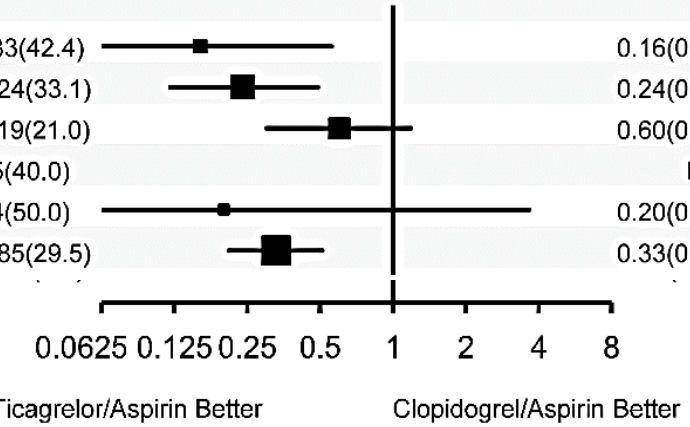



HOPR




# Effect of Tica/aspirin Vs. Clop/Asprin on 90-day by metabolizer status

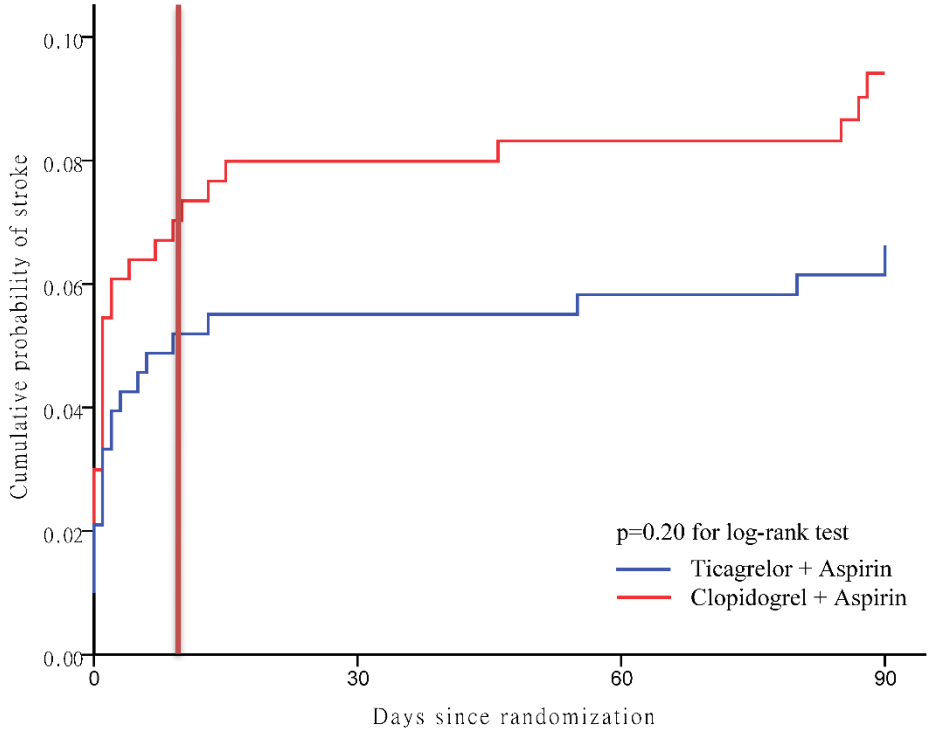
| Outcome | Phenotype | Ticagrelor /Aspirin n/N(%) | Clopidogrel /Aspirin n/N(%) | OR/HR (95%CI) | P value | P for interaction |
|---|---|---|---|---|---|---|
| HOPR at 90 days | | | | | | |
| | Poor | 4/38(10.5) | 14/33(42.4) | 0.16(0.05-0.56) | 0.004 | 0.29 |
| | Intermediate | 12/113(10.6) | 41/124(33.1) | 0.24(0.12-0.49) | <0.001 | |
| | Extensive | 16/117(13.7) | 25/119(21.0) | 0.60(0.30-1.19) | 0.14 | |
| | Ultra | 0/1(0.0) | 2/5(40.0) | NA | | |
| | Unknown | 1/6(16.7) | 2/4(50.0) | 0.20(0.01-3.66) | 0.28 | |
| | Total | 33/275(12.0) | 84/285(29.5) | 0.33(0.21-0.51) | <0.001 | |




| HOPR [a] | Carriers [b] | | | Non-carriers [c] | | | p for interaction |
|---|---|---|---|---|---|---|---|
| | TicaNo.(%) (N=183) | ClopNo.(%) (N=189) | Odds ratio (95%CI) [d] | Tica No.(%) (N=137) | Clop No.(%) (N=137) | Odds ratio (95%CI) | |
| Baseline | 143/183(78.1) | 147/189(77.8) | 1.02 ( 0.63- 1.67) | 115/137(83.9) | 105/137(76.6) | 1.59 ( 0.87- 2.91) | 0.26 |
| **7 + 2 days** | **6/172(3.5)** | **66/182(36.3)** | **0.06 ( 0.03- 0.15)** | **6/129(4.7)** | **22/134(16.4)** | **0.25 ( 0.10- 0.63)** | **0.04** |
| **90±7 days** | **17/157(10.8)** | **57/161(35.4)** | **0.22 ( 0.12- 0.40)** | **16/118(13.6)** | **27/124(21.8)** | **0.56 ( 0.29- 1.11)** | **0.04** |

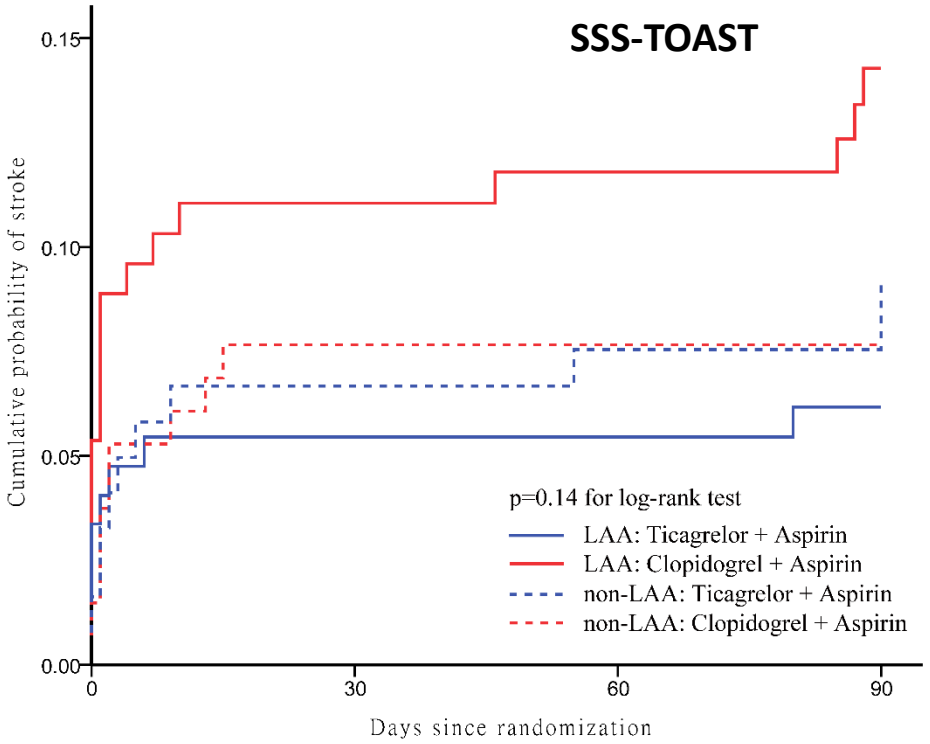
# Clinical efficacy outcome at 90 days

| Clinical outcome | Ticagrelor /Aspirin (n= 336 ) | Clopidogrel /Aspirin (n= 339 ) | HR ( 95%CI ) | P value |
|---|---|---|---|---|
| **Stroke** | **21/336 (6.3%)** | **30/339 (8.8%)** | **0.70 ( 0.40- 1.22)** | **0.20** |
| **Composite events** | 22/336 (6.5%) | 32/339 (9.4%) | 0.68 ( 0.40- 1.18) | 0.17 |

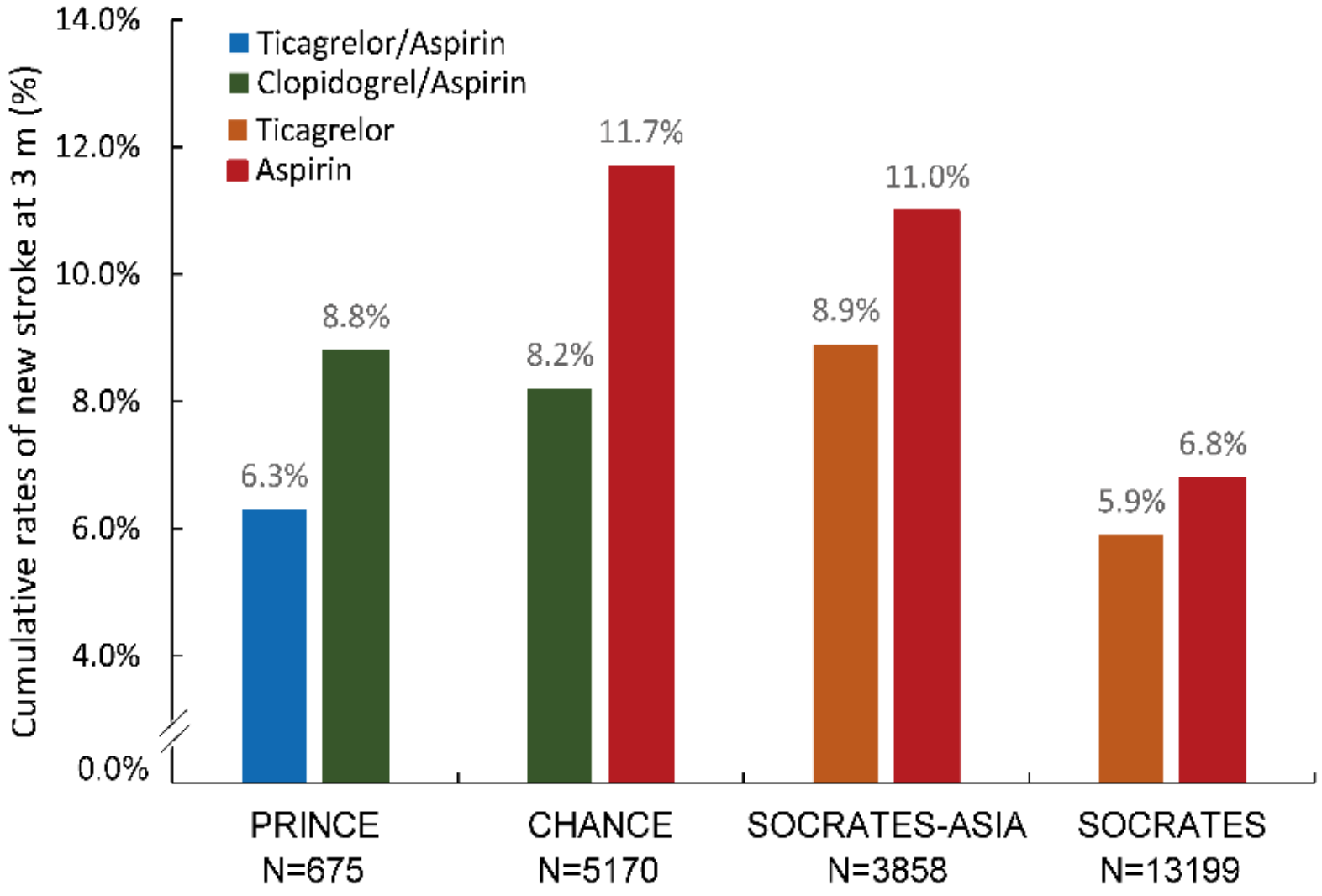


# Stroke at 90 days by stroke etiology (prespecified)

| Stroke etiology | Ticagrelor /Aspirin (n= 336 ) | Clopidogrel /Aspirin (n= 339 ) | HR ( 95%CI ) | P value | P for interaction |
|---|---|---|---|---|---|
| **LAA** | **9/151(6.0%)** | **20/153(13.1%)** | **0.45 ( 0.20- 0.98)** | **0.04** | **0.13** |
| **Non-LAA** | 10/124(8.1%) | 10/136(7.4%) | 1.10 ( 0.46- 2.63) | 0.84 | |



# Comparison of Stroke Recurrence at 90 Days among Different Trials



# Safety Outcomes

| Safety outcomes | Ticagrelor/ Aspirin (n=336) | Clopidogrel/ Aspirin (n=339) | Hazard Ratio ( 95%CI ) | P value |
|---|---|---|---|---|
| **Death (all cause)** | 3/336 (0.9%) | 2/339 (0.6%) | 1.50 (0.25-9.00) | 0.65 |
| **Major bleeding** | 5/336 (1.5%) | 4/339 (1.2%) | 1.27 (0.34-4.72) | 0.72 |
| **fatal/life-threatening** | 4/336 (1.2%) | 3/339 (0.9%) | 1.35 (0.30-6.03) | 0.69 |
| **other** | 1/336 (0.3%) | 1/339 (0.3%) | 1.01 (0.06-16.18) | 0.99 |
| **Minor bleeding** | 11/336 (3.3%) | 8/339 (2.4%) | 1.40 (0.56-3.47) | 0.47 |
| **Intracranial hemorrhage** | 3/336 (0.9%) | 2/339 (0.6%) | 1.27 (0.34-4.72) | 0.72 |
| **Minimal bleeding** | 64/336 (19.0%) | 36/339 (10.6%) | 1.86 (1.24- 2.80) | 0.003 |
| **Any bleeding** | 75/336 (22.3%) | 48/339 (14.2%) | 1.65 (1.15- 2.37) | 0.007 |

# AEs leading to study drug discontinuation

| AEs leading to study drug discontinuation | Ticagrelor/Aspirin (n=336) | Clopidogrel/Aspirin (n=339) | P value |
|---|---|---|---|
| **Dyspnea** | 14(4.2%) | 0(0.0%) | 0.0001 |
| **Epistaxis** | 6(1.8%) | 0(0.0%) | 0.04 |
| **Hemoptysis** | 3(0.9) | 0(0.0) | 0.24 |

# Limitations

- **Primary outcome is a surrogate endpoint and further study is needed to evaluate clinical efficacy.**
- **Surrogate endpoints (HOPR or PRU) are susceptible to missing data, which may introduce bias. Sensitivity analyses evaluated the robustness of the findings.**
- **Open-label design**
  - **Double-blinded unfeasible (cost, complexity of sham PFT results, etc)**
  - **Maybe affect the physician and pts' decision**

# Conclusion

- **Ticagrelor plus aspirin reduced HOPR in more patients at 90 days, compared with clopidogrel plus aspirin in patients with minor stroke or high-risk TIA, especially for carriers of the CYP2C19 loss of function alleles**
- **There were numerically (not statistically significant) fewer strokes at 90 days, in patients on ticagrelor/ASA than clopidogrel/ASA, especially for LAA subtype**
- **More minimal bleeding events observed in the ticagrelor/ASA group, but not the major and minor bleeding events**
- **Higher incidence of study drug discontinuation was observed in Tica group, primarily because of respiratory disorders and minimal bleeding**

# Acknowledgements

**Executive Committee**

Yilong Wang, MD, PhD (Chairman, Coordinating Investigator); Xia Meng, MD, PhD; Weiqi Chen, MD, PhD (c); Yi Lin, MD, PhD; Yuesong Pan, PhD; Jing Jing, MD, PhD; Jinxi Lin, PhD; Wei Lv, MD; Yujing Peng, MD; Jiandong Yu, MD; Shanshan Chen, MD; Nan Qi, MD.

**Steering Committee**

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**Independent Data Monitoring Committee**

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**Clinical Event Adjudication Committee**

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# Acknowledgements

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# CLINICAL RESEARCH COORDINATOR


# CLINICAL RESEARCH ASSOCIATE


谢谢
THANKS
天坛医院
1958.8.23.

# PRINCE *VS.* SOCRATES ASIAN Subgroup

| Clinical outcome at 90days | PRINCE | | | SOCRATES Asian substudy | | |
|---|---|---|---|---|---|---|
| | Tica/ASA | Clop/ASA | Hazard Ratio ( 95%CI ) | Ticagrelor | Aspirin | Hazard Ratio ( 95%CI ) |
| Stroke | 21/336 (6.3%) | 30/339 (8.8%) | 0.70 (0.40-1.22) | 173/1933 (8.9%) | 211/1925 (11.0%) | 0.80 (0.66–0.98) |
| Ischemic stroke | 18/336 (5.4%) | 28/339 (8.3%) | 0.64 (0.35-1.16) | 172/1933 (8.9%) | 208/1925 (10.8%) | 0.81 (0.66–0.99) |
| Death | 3/336 (0.9%) | 2/339 (0.6%) | 1.50 (0.25-9.00) | 16/1933 (0.8%) | 11/1925 (0.6%) | 1.45 (0.67–3.12) |



***Stroke. 2017;48:167-173***

# PRINCE *VS.* SOCRATES *VS.* CHANCE

| Clinical outcome | PRINCE | | CHANCE | | SOCRATES | |
|---|---|---|---|---|---|---|
| | Ticagrelor/Aspirin | Clopidogrel/Aspirin | Clopidogrel/Aspirin | Aspirin | Ticagrelor | Aspirin |
| **Stroke** | 21/336 (6.3%) | 30/339 (8.8%) | 212/2584(8.2%) | 303/2586(11.7%) | 390/6589(5.9%) | 450/6610(6.8%) |
| **Ischemic stroke** | 18/336 (5.4%) | 28/339 (8.3%) | 204/2584 (7.9%) | 295/2586 (11.4%) | 385/6589 (5.8%) | 441/6610 (6.7%) |
| **Intracranial hemorrhage** | 3/336 (0.9%) | 2/339 (0.6%) | 8/2584 (0.3%) | 8/2586 (0.3%) | 12/6589 (0.2%) | 18/6610 (0.3%) |
| **Myocardial infarction** | 0/336 (0.0%) | 1/339 (0.3%) | 3/2584 (0.1%) | 2/2586 (0.1%) | 25/6589 (0.4%) | 21/6610 (0.3%) |
| **Cardiovascular death** | 1/336 (0.3%) | 2/339 (0.6%) | 6/2584 (0.2%) | 5/2586 (0.2%) | 41/6589 (0.6%) | 35/6610 (0.5%) |
| **Death** | 3/336 (0.9%) | 2/339 (0.6%) | 10/2584(0.4%) | /2586 (0.4%) | 68/6589 (1.0%) | 58/6610 (0.9%) |

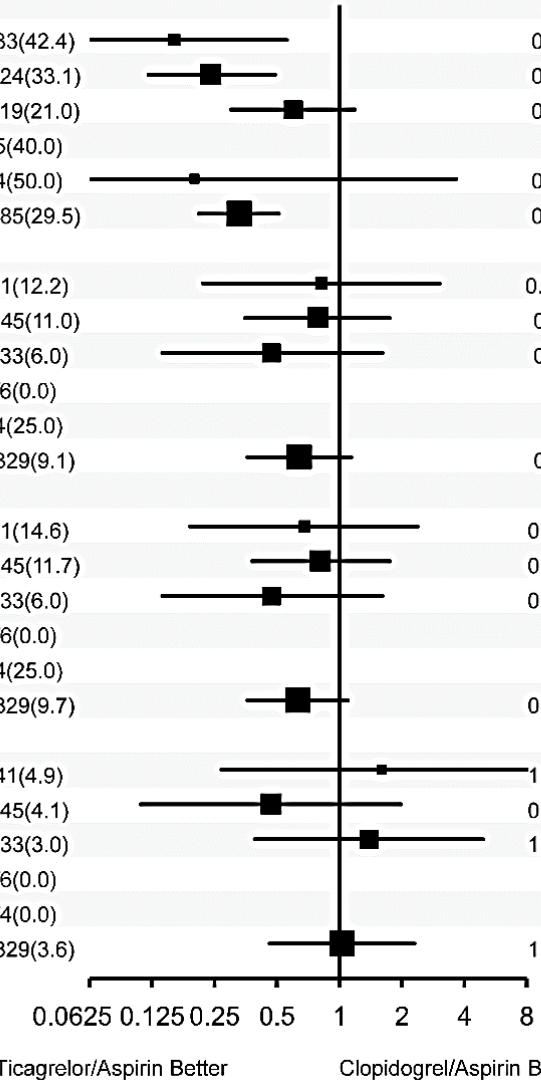
# Bleeding： PRINCE *vs.* SOCRATES ASIAN Subgroup

| Safety outcome | PRINCE | | SOCRATES Asian | |
|---|---|---|---|---|
| | Ticagrelor/Aspirin | Clopidogrel/Aspirin | Ticagrelor | Aspirin |
| **Major bleeding** | **5/336 (1.5%)** | **4/339 (1.2%)** | **12/1914(0.6%)** | **16/1914 (0.8%)** |
| **fatal/life-threatening** | 4/336 (1.2%) | 3/339 (0.9%) | 9/1914 (0.3%) | 12/1914 (0.4%) |
| **other** | 1/336 (0.3%) | 1/339 (0.3%) | - | - |
| **Minor bleeding** | 11/336 (3.3%) | 8/339 (2.4%) | 30/1914(1.6%) | 19/1914(1.0%) |
| **Minimal bleeding** | 64/336 (19.0%) | 36/339 (10.6%) | - | - |
| | | | | |
| **Bleeding （PLATO definition）** | 75/336 (22.3%) | 48/339 (14.2%) | - | - |

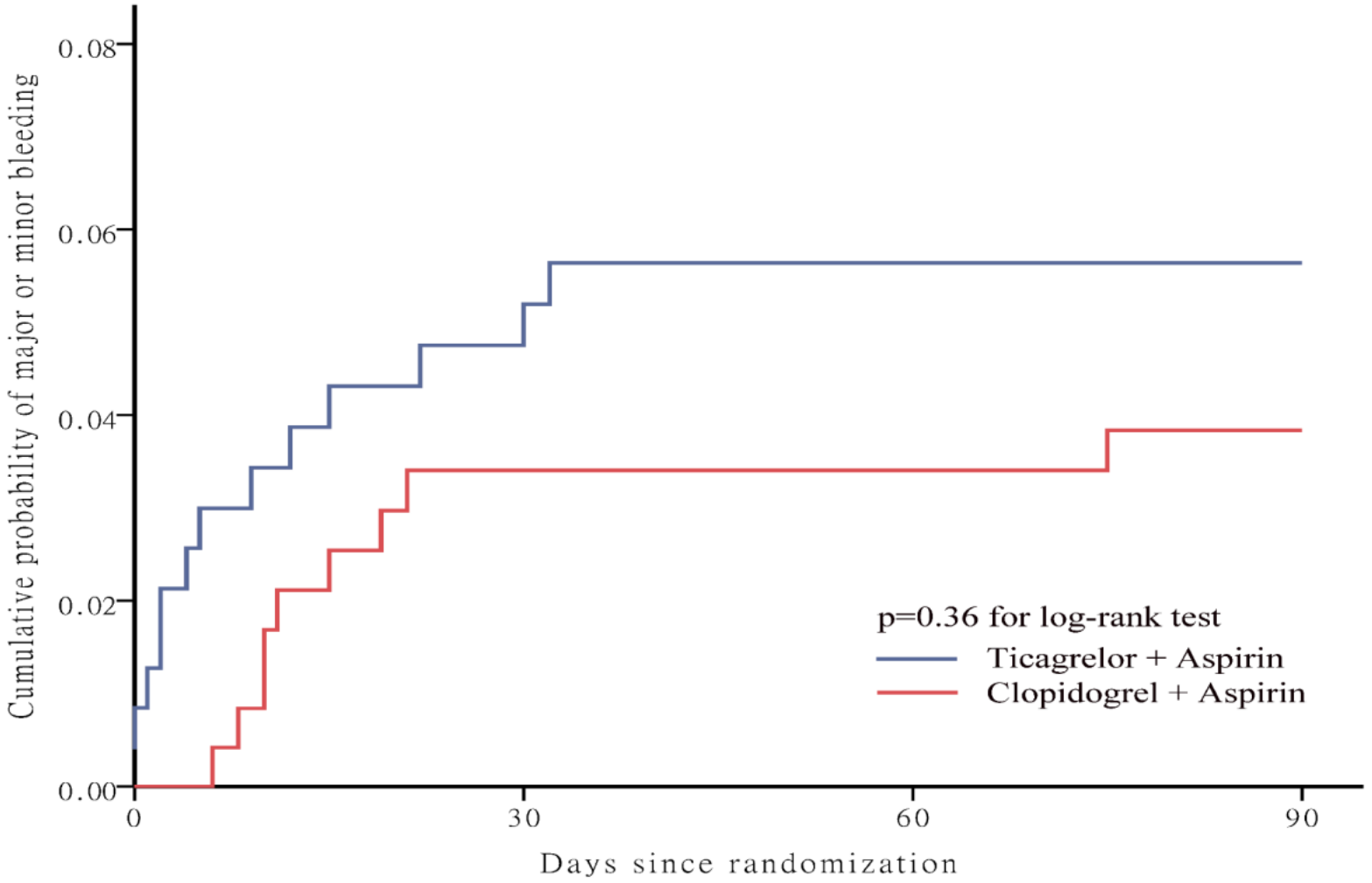
***Stroke. 2017;48:167-173***

# Effect of ticagrelor/aspirin Vs. on 90-day by metabolizer status

| Outcome | Phenotype | Ticagrelor /Aspirin n/N(%) | Clopidogrel /Aspirin n/N(%) | OR/HR (95%CI) | P value | P for interaction |
|---|---|---|---|---|---|---|
| HOPR at 90 days | | | | | | |
| | Poor | 4/38(10.5) | 14/33(42.4) | 0.16(0.05-0.56) | 0.004 | 0.29 |
| | Intermediate | 12/113(10.6) | 41/124(33.1) | 0.24(0.12-0.49) | <0.001 | |
| | Extensive | 16/117(13.7) | 25/119(21.0) | 0.60(0.30-1.19) | 0.14 | |
| | Ultra | 0/1(0.0) | 2/5(40.0) | NA | | |
| | Unknown | 1/6(16.7) | 2/4(50.0) | 0.20(0.01-3.66) | 0.28 | |
| | Total | 33/275(12.0) | 84/285(29.5) | 0.33(0.21-0.51) | <0.001 | |
| Stroke | | | | | | |
| | Poor | 4/39(10.3) | 5/41(12.2) | 0.82 ( 0.22- 3.05) | 0.77 | 0.96 |
| | Intermediate | 11/138(8.0) | 16/145(11.0) | 0.79 ( 0.35- 1.75) | 0.55 | |
| | Extensive | 4/136(2.9) | 8/133(6.0) | 0.47 ( 0.14- 1.62) | 0.23 | |
| | Ultra | 0/1(0.0) | 0/6(0.0) | NA | | |
| | Unknown | 0/7(0.0) | 1/4(25.0) | NA | | |
| | Total | 19/321(5.9) | 30/329(9.1) | 0.64 ( 0.36- 1.14) | 0.13 | |
| Composite events | | | | | | |
| | Poor | 4/39(10.3) | 6/41(14.6) | 0.68 ( 0.19- 2.39) | 0.54 | 0.97 |
| | Intermediate | 12/138(8.7) | 17/145(11.7) | 0.81 ( 0.38- 1.75) | 0.60 | |
| | Extensive | 4/136(2.9) | 8/133(6.0) | 0.47 ( 0.14- 1.62) | 0.23 | |
| | Ultra | 0/1(0.0) | 0/6(0.0) | NA | | |
| | Unknown | 0/7(0.0) | 1/4(25.0) | NA | | |
| | Total | 20/321(6.2) | 32/329(9.7) | 0.63 ( 0.36- 1.10) | 0.11 | |
| Major or minor bleeding | | | | | | |
| | Poor | 3/39(7.7) | 2/41(4.9) | 1.61 ( 0.27- 9.65) | 0.60 | 0.96 |
| | Intermediate | 3/138(2.2) | 6/145(4.1) | 0.47 ( 0.11- 1.98) | 0.30 | |
| | Extensive | 6/136(4.4) | 4/133(3.0) | 1.39 ( 0.39- 4.93) | 0.61 | |
| | Ultra | 0/1(0.0) | 0/6(0.0) | NA | | |
| | Unknown | 0/7(0.0) | 0/4(0.0) | NA | | |
| | Total | 12/321(3.7) | 12/329(3.6) | 1.03 ( 0.46- 2.30) | 0.94 | |



# Safety Outcome-Major or minor bleeding



# Bleeding： PRINCE *vs.* SOCRATES

| Safety outcome | PRINCE | | SOCRATES | |
|---|---|---|---|---|
| | Ticagrelor/Aspirin | Clopidogrel/Aspirin | Ticagrelor | Aspirin |
| **Bleeding （PLATO definition）** | 75/336 (22.3%) | 48/339 (14.2%) | - | - |
| **Major bleeding** | 5/336 (1.5%) | 4/339 (1.2%) | 31/6549(0.5%) | 38/6581(0.6%) |
| **fatal/life-threatening** | 4/336 (1.2%) | 3/339 (0.9%) | 22/6549 (0.3%) | 27/6581 (0.4%) |
| **other** | 1/336 (0.3%) | 1/339 (0.3%) | 9/6549 (0.1%) | 11/6581 (0.2%) |
| **Minor bleeding** | 11/336 (3.3%) | 8/339 (2.4%) | 75/6549 (1.1%) | 44 /6581(0.7%) |
| **Minimal bleeding** | 64/336 (19.0%) | 36/339 (10.6%) | - | - |

# Bleeding： PRINCE vs. CHANCE

| Safety outcome | PRINCE | |
|---|---|---|
| | Ticagrelor/Aspirin | Clopidogrel/Aspirin |
| Bleeding （PLATO definition） | 75/336 (22.3%) | 48/339 (14.2%) |
| Major bleeding | 5/336 (1.5%) | 4/339 (1.2%) |
| Major bleeding, fatal/life-threatening | 4/336 (1.2%) | 3/339 (0.9%) |
| Major bleeding ,other | 1/336 (0.3%) | 1/339 (0.3%) |
| Minor bleeding | 11/336 (3.3%) | 8/339 (2.4%) |
| Minimal bleeding | 64/336 (19.0%) | 36/339 (10.6%) |

| Safety outcome | CHANCE | |
|---|---|---|
| | Clopidogrel/Aspirin | Aspirin |
| Bleeding（GUSTO definition） | | |
| Severe or Life-threatening | 4/2564 (0.2%) | 4/2570 (0.2%) |
| Moderate | 3/2564 (0.1%) | 4/2570 (0.2%) |
| Mild | 30/2564 (1.2%) | 19/2570 (0.7%) |
| Any Bleeding | 60/2564 (2.3%) | 41/2570 (1.6%) |

# PLATO Bleeding Classification

**PLATO Major bleeding:**

*Fatal/ Life-threatening* – includes bleeding events that meet any of the following criteria:

- Fatal bleeding
- Intracranial
- Intrapericardial with cardiac tamponade
- Hypovolemic shock or severe hypotension due to bleeding and requiring pressors/inotropes or surgery
- Decline in haemoglobin of 5 g/dL or more (or, when Hgb is not available, a fall in hematocrit of ≥15%)
- Transfusion of 4 or more units (whole blood or PRBCs) for bleeding

*Major bleed-other* – includes bleeding events that meet any of the following criteria:

- Significantly disabling (eg, intraocular with permanent vision loss)
- Clinically overt or apparent bleeding associated with a decrease in Hgb of 3-5 g/dL (or, when Hgb is not available, a fall in hematocrit of 9 to <15%)
- Transfusion of 2-3 units (whole blood or PRBCs) for bleeding

**PLATO Minor bleeding:**

Bleeding that does not meet criteria for PLATO Major bleeding, **AND**

Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing)

**PLATO Minimal bleeding**

Bleeding that does not meet criteria for PLATO Major or Minor bleeding, **AND**

Includes all other bleeding events (e.g., bruising, bleeding gums, oozing from injection sites, etc) not requiring intervention or treatment

# Definitions of AEs that leading to study drug discontinuation

- **Any Bleeding:** Include all the bleeding events defined by PLATO classification.
- **Dyspnea:** Dyspnea is perceived to be difficulty of breathing or painful breathing.
- **Non-compliance to the study protocol :** Severe non-compliance to study protocol.
- **Death:** All cause of death.
- **Patient decision:** The patient is at any time free to discontinue treatment, without prejudice to further treatment.

# Sample size

- We assume that about 45% of patients with minor stroke or TIA were HOPR defined as PRU>208 after 90-day clopidogrel/aspirin, and the relative risk of developing HOPR within 90 days would be reduced by 24% in ticagrelor/aspirin group. 10 Given that the testing power of 90% and the significance level of 5% (two sided), **a total of 952** (953.3patients for raw data) patients will be needed to detect the relative risk difference between the two therapy regimens, allowing for an approximate 10% dropout rate.

# Objectives

## Secondary Objectives - 2

- To compare the effects of ticagrelor/aspirin versus clopidogrel/aspirin on the proportion of patients with HOPR defined as $MA_{ADP}$ > 47 measured by Thrombelastography Platelet Mapping Assay (TEG) at 90 days.
- To compare the antiplatelet effects of ticagrelor/aspirin versus clopidogrel/aspirin at 2hours, 24hours, 7 days, 90 days inluding:

  PRU, ARU, IPA, $MA_{ADP}$ , $MA_{AA}$, TPI

  Δ PRU, ΔARU, Δ IPA, $\Delta MA_{ADP}$ , $\Delta MA_{AA}$, ΔTPI
- To compare the antiplatelet effects of ticagrelor/aspirin versus clopidogrel/aspirin in stratified subgroups defined by gender (male, female) and age (< 65 years, ≥ 65 years), index events (TIA, minor stroke), time from onset (>12 hours, ≤12 hours) etiology(large-artery atherosclerosis LAA, non-LAA), and (intracranial artery diseases ICAD, non-ICAD), et al.
- In further exploratory analysis, to evaluate impairment (change in NIHSS scores), disability(modified Rankin Scale) and Quality of Life (EQ-5D scale) among survivors.

# Sub-studies

- **Genetic sub-study**
- **Pharmacokinetic sub-study**

  **For Ticagrelor:** ticagrelor, active metabolite of ticagrelor(AR-C124910XX)

  **For Clopidogrel:** active metabolite (R-130964), intermediate metabolite (2-oxo-clopidogrel), and inactive metabolites of clopidogrel

  **For Aspirin :** acetylsalicylic acid, salicylic acid
- **Pharmacodynamics sub-study**

  VerifyNow, AspirinWorks, TEG and PL-11 platelet function tests
- **Dynamic biomarker sub-study**

  inflammation, thrombosis, metabolism, immune, oxidative stress biomarkers

  novel protein biomarkers for antiplatelet poor-responsiveness

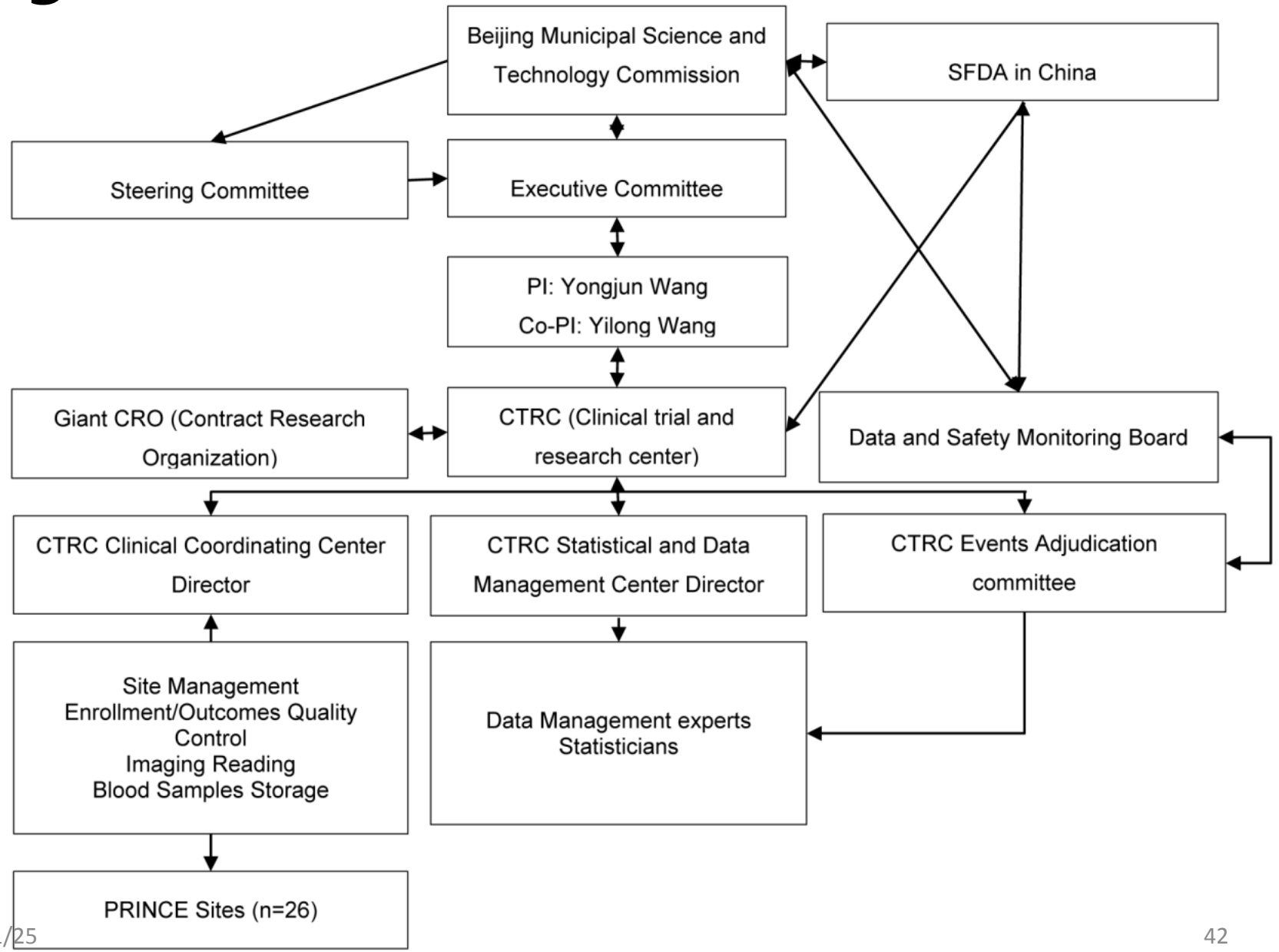
# Study population: Major exclusion criteria

- 1. Hemorrhage or other pathology on baseline CT/MRI
- 2. Isolated sensory symptoms visual changes, dizziness/vertigo without evidence of acute infarction on baseline head CT or MRI.
- 3. Modified Rankin Scale Score > 2 at randomization
- 4. Contraindication to ticagrelor, clopidogrel or acetylsalicylic acid :
- 5. Clear indication for anticoagulation (presumed cardiac source of embolus, e.g., AF).
- 6. Continuous use of ticagrelor or clopidogrel over 5 days before randomization
- 7. Current treatment (last dose given within 10 days before randomization) with heparin or anti coagulation therapy
- 8. Receipt of intravenous/ intra-arterial thrombolysis or mechanical thrombectomy within 24 hours prior to randomization.
- 9. History of intracranial hemorrhage or cerebral artery amyloidosis.
- 10. History of aneurysm (including intracranial aneurysm or peripheral aneurysms)
- 11. Diagnosis or of acute coronary syndrome.
- 12. History of asthma or COPD (chronic obstructive pulmonary disease).

# Study population: Major exclusion criteria con't

- 13. High risk of bradyarrhythmia.
- 14. History of uric acid nephropathy.
- 15. Anticipated requirement for long-term (>7 days) non-study anti-platelet drugs, or
- NSAIDs (nonsteroidal antiinflammatory drugs) affecting platelet function.
- 16. History of previous symptomatic non-traumatic intracerebral bleed at any time, gastrointestinal (GI) bleed within the past 3 months, or major surgery within 30 days.
- 17. Qualifying TIA or minor stroke induced by angiography or surgery.
- 18. Planned or likely revascularization within the next 3 months.
- 19. Scheduled for surgery or interventional treatment requiring study drug cessation.
- 20. Severe non-cardiovascular comorbidity with life expectancy < 3 months.
- 21. Pregnancy or lactation, and women of childbearing age not practicing reliable contraception who do not have a documented negative pregnancy test.
- 22. Currently receiving an investigational drug or device.
- 23. Participation in another clinical study with an investigational product during the last 30 days.
- 24. Inability of the patient to understand and/or comply with study procedures and/or follow-up, in the opinion of the Investigator.

# Organization



# Efficacy Outcome-Secondary-early test

| | Visit | | Ticagrelor/Aspirin (n= 154 ) | Clopidogrel/Aspirin (n= 159 ) | p |
|---|---|---|---|---|---|
| **PRU** | 0h | N(Missing) | 153(1) | 155(4) | 0.48 |
| | | Mean±Std | 253.92±57.37 | 244.63±54.06 | |
| | 2h | N(Missing) | 149(5) | 151(8) | <.0001 |
| | | Mean±Std | 45.74±69.77 | 222.32±64.17 | |
| | 24 d | N(Missing) | 147(7) | 152(7) | <.0001 |
| | | Mean±Std | 36.71±40.26 | 182.67±74.09 | |
| **HOPR (PRU>208)** | 2h | Yes | 6(4.03) | 93(61.59) | <.0001 |
| | | No | 143(95.97) | 58(38.41) | |
| | 24h | Yes | 0(0.00) | 56(36.84) | <.0001 |
| | | No | 147(100.00) | 96(63.16) | |

# Efficacy Outcome-Secondary-TEG

| | Visit | | Ticagrelor/Aspirin (n= 140 ) | Clopidogrel/Aspirin (n= 142 ) | p |
|---|---|---|---|---|---|
| **$MA_{ADP}$** | 7 d | N(Missing) | 131(9) | 132(10) | <.0001 |
| | | Mean±Std | 23.24±14.27 | 38.02±16.39 | |
| | 90 d | N(Missing) | 122(18) | 120(22) | <.0001 |
| | | Mean±Std | 26.32±15.43 | 35.83±16.84 | |
| **HOPR ($MA_{ADP}$ >47)** | 7 d | Yes | 8(6.11) | 42(31.82) | <.0001 |
| | | No | 123(93.89) | 90(68.18) | |
| | 90 d | Yes | 15(12.30) | 35(29.17) | 0.0012 |
| | | No | 107(87.70) | 85(70.83) | |

# Efficacy Outcome-Secondary-PL-12

| | Visit | | Ticagrelor/Aspirin (n= 162 ) | Clopidogrel/Aspirin (n= 160 ) | p |
|---|---|---|---|---|---|
| **$MAR_{ADP}$** | 0 d | N(Missing) | 156(6) | 152(8) | 0.48 |
| | | Mean±Std | 43.17±16.55 | 44.75±18.31 | |
| | 90 d | N(Missing) | 135(27) | 128(32) | <.0001 |
| | | Mean±Std | 23.50±14.56 | 33.05±18.29 | |
| **HOPR** | 90 d | Yes | 5(3.70) | 19(14.84) | 0.0017 |
| **($MAR_{ADP}$≥55%)** | | No | 130(96.30) | 109(85.16) | |