Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Delayed Dual Antiplatelet Treatment in Ischemic Stroke.

Contents:

Participating sites and investigators in the INSPIRES Trial

No.	Participating sites	Investigators
1	Weihai Wendeng District People's Hospital	Jinguo Zhao
2	Sui Chinese Medical Hospital	Ying Li
3	Qinghe People's Hospital	Yingzhuo Zang
4	Biyang People's Hospital	Shuo Zhang
5	Jiyuan Chinese Medical Hospital	Hongqin Yang
6	The First Affiliated Hospital of Xi'an Jiaotong University	Jianbo Yang
7	The Affiliated Shuyang Hospital of Xuzhou Medical University	Yuanwei Wang
8	Mengzhou People's Hospital	Dali Li
9	Hejian People's Hospital	Yanxia Wang/ Dongqi Liu
10	Xiuwu People's Hospital	Guangming Kang
11	Taizhou First people's Hospital	Zhimin Wang
12	Xinmi Chinese Medical Hospital	Jianmin Guo
13	The Second Hospital of Hebei Medical University	Xiujuan Song
14	Liaocheng City Second People's Hospital	Xinqiang Wang
15	Weishi Central Hospital	Weifeng Lu
16	Suxitong Science and Technology Industrial Park People's Hospital	Panbing Huang
17	Pingyu People's Hospital	Feng Li
18	The Second Hospital of Harbin Medical University	Lihua Wang
19	Shijiazhuang Ping'an Hospital	Weigang Xiao
20	Tangshan Workers' Hospital	Yibin Cao
21	Xuzhou Mining Group General Hospital	Liangqun Rong
22	China-Japan Union Hospital of Jilin University	Ying Xing
23	Beijing Tiantan Hospital, Capital Medical University	Yilong Wang
24	Kaifeng Central Hospital	Lili Ma
25	Panjin Central Hospital	Yanhua Zhou
26	Tianjin Xiqing Hospital	YuQing Han
27	The First people's Hospital of Nanyang	Jingxian Fang

28	Luoyang New District People's Hospital	Jie Liu
29	The Second Affiliated Hospital of Henan University of Science and Technology	Wen Shangguan
30	North China University of Science and Technology Affiliated Hospital	Bin Liu
31	The First Hospital of Fangshan District	Jianhua Li
32	Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine	Yan Han
33	Benxi Central Hospital	Chengguang Song
34	Heilongjiang Agricultural Reclamation Bei'an Administration Central Hospital	Xuhong Song
35	General Hospital of Fushun Mining Bureau of Liaoning Health Industry Group	Yuanfeng Lv
36	Dongguan Kanghua Hospital	Changqing Xu
37	Luoyang Central Hospital	Congmin Ma/Zhihui Duan
38	Nanle Zhongxing Hospital	Yungao Pan
39	Shenzhen Second People's Hospital	Lijie Ren
40	Guantao People's Hospital	Bin Li
41	Zhoukou Yongshan Hospital	Jinqi Fan
42	Mishan People's Hospital	Yuanren Zhang
43	Yuanyang People’s Hospital	Jingfang Li
44	Baotou Central Hospital	Baojun Wang
45	Rudong People's Hospital	Jun Gu
46	Affiliated Hospital of Jiujiang College	Xiaoping Yin
47	Zouping People's Hospital	Xiao Wang
48	The Third People’s Hospital of Liaocheng	Liguo Chang
49	Shimen People's Hospital	Kaoling Gong
50	Zhoukou Renhe Hospital	Wenhua Zhang
51	Chongqing Donghua Hospital	Yu Che
52	Fengqiu People's Hospital	Yinyuan Wan
53	The Sixth People's Hospital of Hengshui	Linying Gui

54	The Second People's Hospital of Guiyang	Ping Sun
55	Mengjin People's Hospital	Zhonghai Jia
56	The Fourth People's Hospital of Shangqiu	Haichao Liu
57	Gucheng People's Hospital	Qinglian Meng
58	Dengzhou People’s Hospital	Donghe Chai
59	Zhenping People’s Hospital	Lei Zhang
60	Ruyang People's Hospital	Guofeng Li
61	Changzhou Wujin Traditional Chinese Medicine Hospital	Huafeng Jin
62	Changge People's Hospital	Gexia Liu
63	Affiliated Nanhua Hospital, University of South China	Yonghong Tang
64	Luoning People's Hospital	Xiaomin Mei
65	Ningde People's Hospital	Guoping Zou
66	Nanshi Hospital of Nanyang	Yuefeng Yang
67	Gaomi People's Hospital	Quanhao Li
68	Baoding NO.1 Hospital	Xiju Tian
69	The Central Hospital of Jiamusi	Hong Chen
70	The Second People's Hospital of Xi	Jialiang Xiao
71	Mianchi Chinese Medical Hospital	Xiaoming Song
72	Huadu District People's Hospital of Guangzhou	Guangning Li
73	The First Hospital of Harbin Medical University	Guozhong Li
74	Ningjin People's Hospital	Chunjie Yang
75	Liaocheng Central Hospital	Xiting Zhang
76	The First people's Hospital of Ruzhou	Chun Wang
77	Taikang People's Hospital	Jizheng Hu
78	Anshan Central Hospital	Wei Hu/Zhen Jiao
79	Wuxi Xishan People's Hospital	Yunnan Lu
80	Liaocheng People's Hospital	Zhangyong Xia
81	Heping Hospital affiliated to Changzhi Medical College	Yufen Wang
82	Xuchang Central Hospital	Yinshan Wang
83	Anyang District Hospital	Jinxing Qi
84	Jixi People's Hospital	Xiaoping Wang/Shuqin Liu

85	Beijing Hepingli Hospital	Bo Li
86	Xuchang Hospital of Traditional Chinese Medicne	Yinghui Li
87	Zhangjiagang Traditional Chinese Medicine Hospital	Yaming Sun
88	Wuhan Central Hospital	Ping Jing
89	Tianjin Huanhu Hospital	Jialing Wu
90	Luzhou Chinese Medical Hospital	Bo Yang
91	Zhecheng Chinese Medical Hospital	Jinghua Zhang
92	Xun People’s Hospital	Tianxia Zhang
93	Luohe Central Hospital	Chunling Zheng
94	Wuxi Affiliated Hospital of Nanjing University of Chinese Medicine	Lejun Li
95	The Third People's Hospital of Luohe	Huimin Li
96	The Second People's Hospital of Wuxi	Yunnan Lu
97	The Second People's Hospital of Mudanjiang	Fumin Yu
98	Sanmenxia Central Hospital	Shufang Yao
99	Xinyang Central Hospital	Jianjun Chang
100	Yingkou Central Hospital	Dongqun Li
101	The first Affiliated Hospital of Henan University of Science and Technology	Ganqin Du
102	Tongzhou District 8th People's Hospital of Nantong City	Yi Zhao
103	Pingyao People's Hospital	Pengfei Liang
104	Dehong Prefecture People's Hospital	Ming Wang
105	The First Affiliated Hospital of Soochow University	Qi Fang
106	The First Hospital of Nanchang	Youqing Deng
107	Xinxiang Central Hospital	Xuzhao Gao
108	Inner Mongolia People's Hospital	Runxiu Zhu
109	Zhangjiakou Xuangang Hospital	Yimin Xie
110	Anyang People's Hospital	Yanshu Liu
111	The Third Xiangya Hospital of Central South University	Yi Yuan
112	The First People's Hospital of Zhangjiagang	Qiuyi Wu
113	General Hospital of Angang Group Company	Guimei Zhao
114	Qi People's Hospital	Yan Yang

115	Xi People’s Hospital	Yong Lu
116	Mianchi People’s Hospital	Weidong Zhao
117	Xingyang People's Hospital	Tianbao Chen
118	The First people's Hospital of Xinxiang	Deng Pan
119	The Fourth People's Hospital of Xinyang	Min Yang
120	Mengzhou Chinese Medical Hospital	Baoguo Xue
121	Luoyang Dongfang Hospital	Ge Zhang
122	Suiping Renan Hospital	Yanjiang Zhao
123	The Second Affiliated Hospital of Guangxi Medical University	Yunfei Wei
124	The Second People's Hospital of Changzhou	Wenwei Yun
125	Huangzhou District People's Hospital	Xiaoqi Chen
126	The Fifth People's Hospital of Shanghai	Danhong Wu
127	Changzhi People's Hospital	Lifang Zhang
128	The First Affiliated Hospital of Jiamusi University	Baoying Sheng
129	The Third People's Hospital of Datong	Zhigang Cui
130	The Second People's Hospital of Jiaozuo	Xiangdong Xie
131	Kangping People's Hospital	Guanghui Cheng
132	The First People's Hospital of Lingbao	Yifei Zhang
133	Henan Shenhuo Group staff General Hospital	Ruiming Zhu
134	Ningbo Medical Center Li Huili Hospital	Yong Chen
135	Cangzhou Hospital of Integrated TCM-WM Hebei	GuoHua Liu
136	Zaozhuang Mining Group Zaozhuang Hospital	Lei Feng
137	Zhumadian Central Hospital	Zhihua Long
138	Northern Theater General Hospital	Huisheng Chen
139	The First Affiliated Hospital of Xinxiang Medical College	Ping Zhang
140	Tanghe People’s Hospital	Yuanliang Cui
141	Wenxian People's Hospital	Yongli Zhang
142	Qinyang People's Hospital	Yazhou Han/Yajie Bai
143	Affiliated Hospital of Yangzhou University	Tieyu Tang
144	Xi'an First Hospital	Songdi Wu

145	Shengzhou People's Hospital	Wenping Gong
146	Nanxishan Hospital of Guangxi Zhuang Autonomous Region	Jun Wang
147	Shenzhen Luohu People's Hospital	Zhishan Zhu
148	The Second People's Hospital of Mengjin	Xiaoyan Ma
149	Baofeng People’s Hospital	Leyi Yao
150	The Affiliated Central Hospital of Shenyang Medical College	Runhui Li
151	Shenzhen Longhua District People's Hospital	Shuanggen Zhu
152	Handan Central Hospital	Juntao Li
153	Jilin Electric Power Hospital	Xiuhui Qi
154	Dongying District People's Hospital	Zhongping Jiang
155	Yantai Yuhuangding Hospital	Zhigang Liang
156	Dazhou Central Hospital	Chunping Liu
157	Dongyang People's Hospital	Dongjuan Xu
158	The First People's Hospital of Zigong	Tao Qiu
159	Linfen People’s Hospital	Chunping Chen
160	First hospital of Changsha city	Hong Tan
161	Chongqing Three Gorges Central Hospital	Shengli Chen
162	Shenzhen Nanshan District People's Hospital	Chunshui Yang
163	The First People's Hospital of Yibin	Wei Jun
164	Xuzhou NO.1 People's Hospital	Qing He
165	Zibo Municipal Hospital	Zengqiang Sun
166	Dalian Central Hospital	Shen Li
167	Liaocheng People's Hospital	Cunju Guo
168	The Sixth People's Hospital of Nantong	Hongliang Wang
169	Second Hospital of Shanxi Medical University	Dongfang Li
170	General Hospital of Shanxi Lu'an Mining (Group) Co., Ltd	Hongbin Wu
171	Dalian Friendship Hospital	Wenxu Zhen
172	The Fourth Central Hospital of Tianjin	Lijun Wang
173	The Second Hospital of Ningbo	Wenke Hong
174	The First Hospital of Qiqihar	Xuerong Qiu

175	Yellow River Central Hospital of Yellow River Water Conservancy Commission	Xinxia Wei
176	Shandong Province Third Hospital	Yongtao lv
177	Xihua People's Hospital	Xiangyang Feng
178	Zhengzhou Central Hospital	Gaiqing Yang
179	Shenzhen Traditional Chinese Medicine Hospital	Songjun Lin
180	The Second Affiliated Hospital of Luohe Medical College	Aihua Cao
181	The Third People's Hospital of Shenzhen	Dejin Sun
182	Shenzhen Longhua District Central Hospital	Pengcheng Fu
183	Jiangxi People's Hospital	Wenfeng Cao
184	The First People's Hospital of Pingdingshan	Wenjun Xue
185	Jilin People's Hospital	Haiyan Liu/Shanshan Li
186	The Second People's Hospital of Dalian	Fang Qu/Zhengguo Zhou
187	Dali Bai Autonomous Prefecture People's Hospital	Ping Liu
188	Tieling Central Hospital	Lixia Wang
189	The First Hospital of Handan	Yiping Wu
190	Qingyun People's Hospital	Jinxing Liu
191	The First Hospital of Jilin University	Xin Sun
192	University of Chinese Academy of Sciences Shenzhen Hospital	Qingyong Wang
193	Shenzhen Longgang District People's Hospital	Xiaomei Li
194	Shenzhen Bao'an District Shajing People's Hospital	Qizhang Wang
195	Beijing University of Chinese Medicine Shenzhen Hospital	Yongxiong Wu
196	The Second Affiliated Hospital of Soochow University	Chunfeng Liu
197	Shanghai Tenth People's Hospital	Yanxin Zhao
198	Peking University Shenzhen Hospital	Zhijian Lin
199	Nanyang Zhangzhongjing Hospital	Rui Ma
200	Nanyang Yuxi Union Hospital	Jiedan Li
201	Sheqi People’s Hospital	Zhishun Zhu

202	The Sixth People's Hospital of Luoyang	Lili Guo
203	The Third People's Hospital of Luoyang	Bing Sun
204	The Third Affiliated Hospital of Xinxiang Medical College	Jun Tan
205	Henan Hongli Hospital	Ke Yang
206	The Fourth People's Hospital of Shanghai	Yong Bi
207	Liaoning Health Industry Group Fuxin Mine General Hospital	Yingjie Duan
208	The First People's Hospital of Yuanping	Shaochun Li
209	The Fourth Affiliated Hospital of Nanchang University	Xiaoliang Lou
210	Hunan Brain Hospital	Xiaosong Huang
211	Xinhua Hospital affiliated to Dalian University	Fucai Zang
212	Runan People's Hospital	Yonghua Dong
213	Sui People's Hospital	Jingyan Zhao
214	The First people's Hospital of Xiangcheng	Bin Li
215	Gongyi People's Hospital	Yanzeng Cui
216	Luyi Zhenyuan Hospital	Zili Zhang
217	Xinye People's Hospital	Yali Zhang
218	Yongcheng People's Hospital	Peng Yan
219	Dengfeng People's Hospital	Huixian Fan
220	Affiliated Hospital of Nantong University	Qiuhong Ji
221	The Forth People's Hospital of Hengsshui	Aisheng Wu
222	Kaifeng Central Hospital	Xinshen Han

Listing of committees in the INSPIRES Trial

Steering Committee:

Yilong Wang MD, PhD., Yongjun Wang MD., S. Claiborne Johnston MD, PhD., Pierre Amarenco MD., Philip M. W. Bath D.Sc., Xingquan Zhao MD, PhD., Liping Liu MD, PhD., and investigators from the participating hospitals.

Executive Committee:

Yilong Wang MD, PhD., Ying Gao MD., Jing Jing MD, PhD., Chunjuan Wang MD, PhD., Weiqi Chen MD., Xia Meng MD, PhD., Jinxi Lin MD, PhD., Lingling Jiang PhD., Yingying Yang MD., Tingting Wang MD., Shangrong Han MD.

Data and Safety Monitoring Board:

David Wang BA, MD., Hao Li MD, PhD., Haifeng Li MD, PhD.

Clinical Event Adjudication Committee:

James Wang MD, PhD., Yuming Xu MD, PhD., Kehui Dong MD, PhD., Xiaoling Liao MD, PhD., Hui Qu MD, PhD.

Clinical Coordinating Center:

Ying Gao MD., Jing Jing MD, PhD., Chunjuan Wang MD, PhD., Xia Meng MD, PhD., Jinxi Lin MD, PhD., Yingying Yang MD., Tingting Wang MD., Shangrong Han MD., Li Liu MM., Jie Song MM., Shuting Liu, Xiaoyu Che, Xianhong Liang, Shangzhi Li, Nan Qi, Xiaolei Chen, Zhiyuan Ji (SMO), Jianying Li (SMO), Jiawei Lu, Long Wang, Jiandong Yu, Xiaowu Zhang.

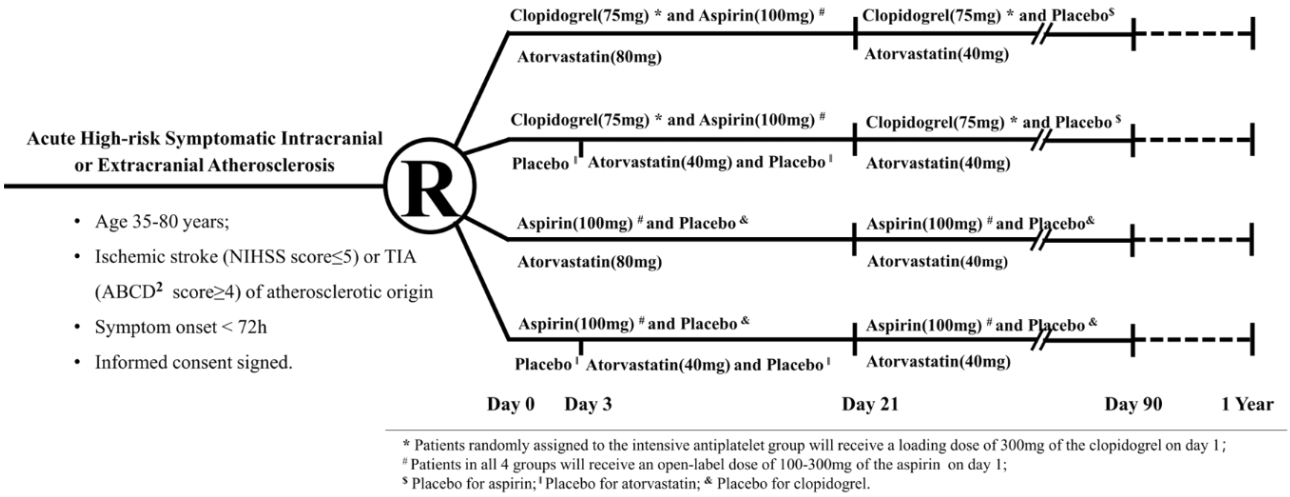
Statistical and Data Management Center:

Yuesong Pan PhD., Hongyi Yan MM., Aoming Jin PhD.

Drug Distribution Center: Haibo Wu (CRO)

Independent Medical Monitor: Haibo Wu (CRO)

Study design and treatment allocation



* Patients randomly assigned to the intensive antiplatelet group will receive a loading dose of 300mg of the clopidogrel on day 1;
# Patients in all 4 groups will receive an open-label dose of 100-300mg of the aspirin on day 1;
$ Placebo for aspirin; ! Placebo for atorvastatin; & Placebo for clopidogrel.

Inclusion and exclusion criteria

Inclusion criteria:

1. Age 35-80 years;
2. At least one of the followings (a-b): a) Mild ischemic stroke (NIHSS score 4-5) within 24 hours after onset and either of the following imaging characteristics: i. Acute single infarction with ≥50% stenosis of a major intracranial or extracranial artery that likely accounts for the infarction and clinical presentation. ii. Acute multiple infarctions documented by head CT or MRI, attributed to large-artery atherosclerosis, including non-stenotic vulnerable plaques. b) Mild ischemic stroke (NIHSS score ≤5) or high-risk TIA ($ABCD^2$ score≥4) within 24 to 72 hours after onset and meet any of the following imaging characteristics: i. TIA with ≥50% stenosis of a major intracranial or extracranial artery that likely accounts for the clinical presentation. ii. Acute single infarction with ≥50% stenosis of a major intracranial or extracranial artery that likely accounts for the infarction and clinical presentation. iii. Acute multiple infarctions documented by head CT or MRI, attributed to large-artery atherosclerosis, including non-stenotic vulnerable plaques.
3. Written informed consent.

Exclusion criteria:

1. Presumed cardioembolic stroke or TIA (e.g. atrial fibrillation, heart valve prosthesis, atrial myxoma, endocarditis, etc.);
2. Other determined etiology of stroke or TIA (e.g. aortic dissection, cervico-cerebral artery dissection, vasculitis， vascular malformation, Moyamoya disease/syndrome, fibromuscular dysplasia, etc.);
3. Non-vascular neurological diseases (e.g. intracranial tumor, multiple sclerosis, etc.);
4. Index infarction affects >50% of a cerebral lobe (e.g. parietal, frontal, occipital);
5. Hemorrhagic transformation after onset;

6. Contraindications to clopidogrel, aspirin or atorvastatin: a) History of hypersensitivity; b) Severe heart failure (New York Heart Association classification: III- IV) or asthma; c) Coagulation disorder or systemic bleeding; d) History of drug-induced hematologic or hepatic abnormalities; e) Leukopenia (< 2×10^9/L) or thrombocytopenia (<100×10^9/L); f) Active liver disease; g) Pregnancy or lactation period
7. Pre-existing disability with modified Rankin Scale score >2；
8. Intra-arterial or intravenous thrombolysis, or endovascular therapy after onset;
9. Defibrinogen therapy (e.g. defibrase and lumbrokinase), anticoagulation therapy (e.g. argatroban), or antiplatelet therapy (e.g. ticagrelor, tirofiban) except for clopidogrel and aspirin after onset;
10. Creatine kinase > 5 times the upper limit of normal value of onset;
11. Drug use related to statin metabolism within 14 days before randomization (e.g. immune-suppressive drugs, antifungal agents, fibrates);
12. Severe hepatic insufficiency (alanine transaminase or aspartate transaminase > 2 times the upper limit of normal value) or renal insufficiency (creatinine > 1.5 times the upper limit of normal value or glomerular filtration rate < 40 ml/min/1.73 m^2);
13. Dual antiplatelet therapy with aspirin and clopidogrel within 14 days before randomization*;
14. High-intensity statin therapy within 14 days before randomization (e.g. atorvastatin ≥ 40mg/d, rosuvastatin ≥ 20mg/d);
15. History of intracranial hemorrhage (e.g. intracerebral or subarachnoid hemorrhage);
16. Gastrointestinal bleeding or major surgery within 90 days;
17. History of intracranial or extracranial angioplasty;
18. Planned long-term use of antiplatelet drugs or non-steroidal anti-inflammatory drugs except for study drugs;
19. Planned surgery or revascularization that may need to stop taking the study drugs within the next 90 days;
20. Anticipated life expectancy < 90 days;
21. Pregnant women, or patients of child-bearing potential with neither using birth control nor pregnancy test records;
22. Currently participating in any other investigational drug or device study;
23. Unable to complete the follow-up (e.g. dementia, alcoholism, substance abuse, severe mental disease).

Definitions of cardiac-cerebral vascular events

Event	Definition
Stroke	A sudden onset of focal or global brain, spinal cord or retinal vascular damage, resulting in symptoms and signs of acute nervous system defects, which is associated with cerebral circulation disorders.
Ischemic Stroke	Acute focal cerebral or retinal infarction meeting any of the following conditions: (1) Recurrent stroke: clinical signs or radiological evidence of acute onset of new focal neurological damage lasting longer than 24 hours, excluding other non-ischemic etiologies (such as brain infections, brain injuries, brain tumors, seizures, severe metabolic diseases, degenerative diseases of the nervous system and side effects of drugs); (2) TIA with infarction: acute cerebral or retinal ischemic events, excluding other non-ischemic etiologies, focal symptoms or signs sustaining less than 24 hours, but with radiological evidence of new infarction; (3) Progressive stroke: the worsening of pre-existing symptoms of vascular origin ischemic stroke (i.e. NIHSS increased ≥ 4 based on primary ischemic stroke, excluding the hemorrhagic transformation after infarction or symptomatic intracranial hemorrhage) persisting for more than 24 hours, with or without deterioration of ischemic lesions on MRI or CT. Etiologic typing is based on the TOAST criteria.
Transient Ischemic Attack	Neurologic deficit caused by sudden focal brain or retinal ischemia that can fully recover, lasting less than 24 hours, with no evidence of new cerebral infarction on imaging (CT or MR). Other non-ischemic causes (such as brain infections, brain injuries, brain tumors, epilepsy, severe metabolic diseases, or degenerative neurological diseases) are excluded.
Ordinal stroke or TIA	The type of vascular events and mRS score at 90 days were used to classify the new stroke and TIA on a six-level ordered category scale:

	5.Fatal stroke: stroke with subsequent death. 4.Severe stroke: stroke followed by mRS score of 4–5. 3.Moderate stroke: stroke followed by mRS score of 2–3. 2.Mild stroke: stroke followed by mRS score of 0–1. 1.TIA. 0.No stroke/TIA.
Hemorrhagic Stroke	Hemorrhagic stroke is defined as acute neurological dysfunction of the focal or whole brain or spinal cord caused by non-traumatic brain parenchymal, intraventricular, and subarachnoid hemorrhage.
Hemorrhagic Transformation after Cerebral Infraction	Any non-traumatic extravascular hemorrhage in acute / subacute infarcts, which could cause related neurological symptoms (symptomatic) or non-neurological symptoms (asymptomatic). Among them: (1) <u>Ischemic stroke transformed into symptomatic hemorrhagic stroke:</u> The following two conditions must be met at the same time: a. Imaging evidence (CT or MRI) of extravascular hemorrhage in the infarct area; b. Symptoms are related to hemorrhagic transformation. The hemorrhagic transformation must be able to partially explain the clinical manifestations of the patient's neurological performance, such as: i). Symptoms cannot be fully explained by infarct size and location ii). Clinical deterioration referring to an increase of 4 points or more in NIHSS score after the initial ischemic event, or death, which is caused by hemorrhagic transformation; iii). Clinical symptoms caused by volume effect secondary to hemorrhagic transformation; (2) <u>Ischemic stroke transformed into asymptomatic hemorrhagic stroke:</u> The following two conditions must be met at the same time: a. Imaging evidence (CT or MRI) of extravascular hemorrhage in the

	infarct area; b. Hemorrhagic transformation does not cause symptoms, or cause symptoms with an increase of less than 4 points in NIHSS score after the initial ischemic event.
Myocardial Infarction	Acute myocardial infarction diagnosed by the third universal definition.[1] If there is clinical evidence of myocardial necrosis consistent with acute myocardial ischemia (MI), acute MI should be diagnosed. It can be diagnosed if it meets any of the following criteria: (1) A rise and/ or fall of cardiac biomarkers (preferably troponin [cTn]) values with at least one value above the 99th percentile URL, and any of the followings is required: a. Clinical symptoms of myocardial ischemia; b. New myocardial ischemic changes in the ECG, including new ST-segment changes or left bundle branch block (LBBB) [According to whether there is ST-segment elevation in the ECG, it is classified as acute ST-segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI)]; c. Pathological Q wave detected in ECG; d. Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality; e. Coronary thrombosis confirmed by angiography or autopsy. (2) Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before cardiac biomarkers could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected. (3) Myocardial infarction related to percutaneous coronary intervention (PCI) is arbitrarily defined by elevation of cTn values >5×99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, any of the followings is required:

	a. Symptoms suggestive of myocardial ischemia; b. New ischemic ECG changes or new LBBB; c. Angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization; d. Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality. (4) Myocardial infarction related to stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL. (5) Myocardial infarction related to coronary artery bypass grafting (CABG) is arbitrarily defined by elevation of cardiac biomarker values ＞10×99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, any of the followings is required: a. new pathological Q waves or new LBBB; b. angiographic documented new graft or new native coronary artery occlusion; c. imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Vascular Death	Vascular death includes sudden cardiac death, death due to stroke, acute myocardial infarction, heart failure, pulmonary embolism, cardiac/cerebrovascular intervention or surgery (unrelated to acute MI) and other cardiovascular causes [e.g. arrhythmia irrelevant with sudden cardiac death, aortic aneurysm rupture, or peripheral artery disease]. Any death of unknown/unclear cause within 30 d after stroke, myocardial infarction, or cardio-cerebrovascular operation/surgery will be regarded as death due to stroke, myocardial infarction, or cardio-cerebrovascular operation/surgery, respectively.

Reference:

1. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581-98.

Additional Analyses

Figure S1. Caterpillar plot of the estimates by center.

Subcenters with fewer than 20 patients were pooled centers.

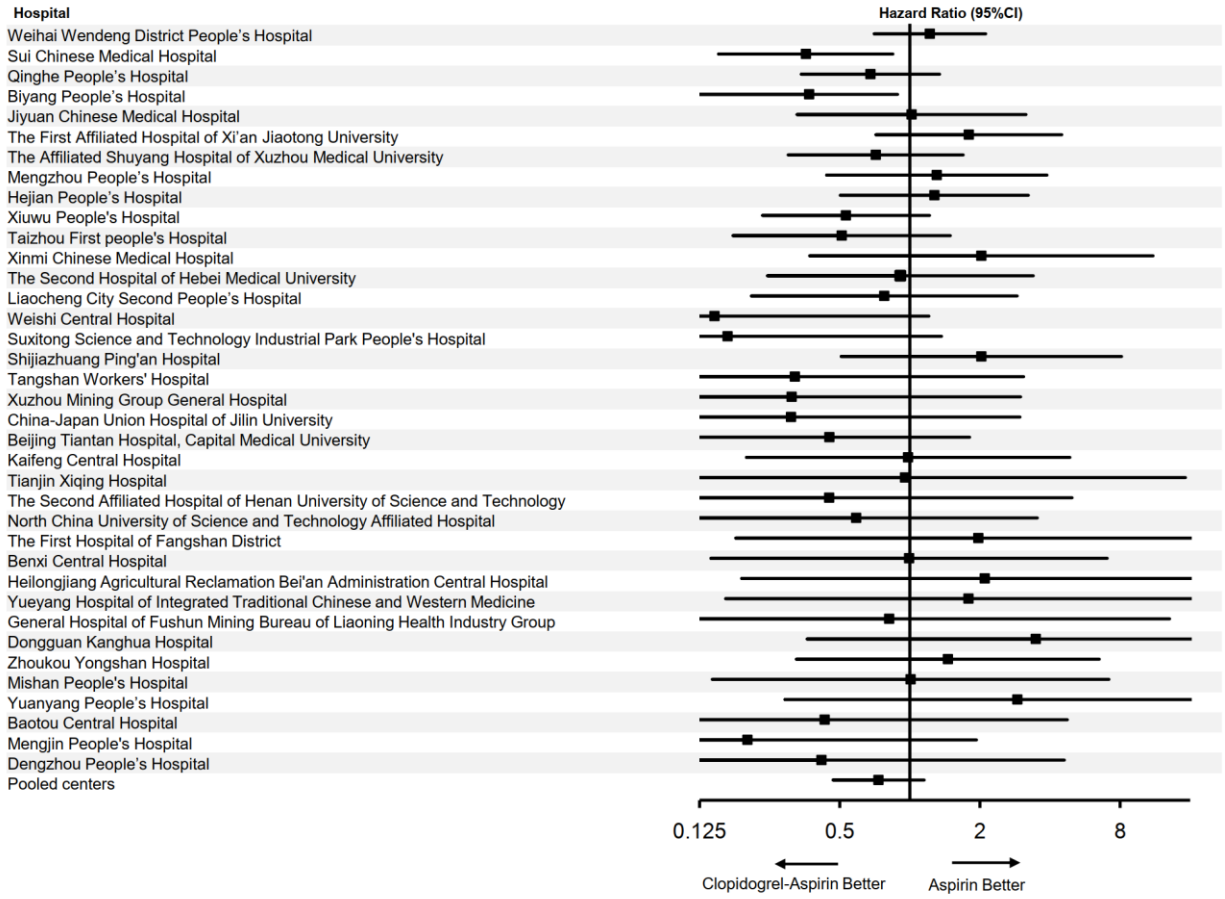


Figure S2. Hazard ratio for stroke in prespecified subgroups.

The trial was not powered to allow definite conclusions based on the results of the subgroup analyses. Distribution of criminal arterial stenosis data was missing in 436 cases due to the absence of both intracranial and extracranial arterial vascular assessments. Degree of symptomatic stenosis data was missing in 394 cases due to the absence of both intracranial and extracranial arterial vascular assessments; or subjects did not have occlusion in intracranial (or extracranial) arteries, but was missing in extracranial (or intracranial) vascular assessments. The body-mass index is the weight in kilograms divided by the square of the height in meters. TIA indicates transient ischemic attack; ICAS, intracranial artery stenosis; ECAS, extracranial artery stenosis.

Subgroup	No. of Patients	Clopidogrel to Aspirin	Aspirin	Hazard Ratio (95%CI)
		no. of events (%)		
Overall	6100	222(7.3)	279(9.2)	0.79(0.66 to 0.94)
Body to mass index				
<25	3520	131(7.3)	159(9.2)	0.78(0.62 to 0.98)
≥25	2580	91(7.3)	120(9.1)	0.79(0.61 to 1.04)
Qualifying event				
Ischemic stroke	5299	208(7.9)	266(10.1)	0.77(0.64 to 0.92)
TIA	801	14(3.5)	13(3.2)	1.09(0.51 to 2.32)
ABCD2 score in qualifying TIA				
≤5	641	10(3.1)	10(3.2)	0.97(0.40 to 2.32)
>5	160	4(5.5)	3(3.5)	1.60(0.36 to 7.17)
Distribution of criminal arterial stenosis				
No ICAS/ECAS/occlusion	1053	29(5.4)	31(6.0)	0.89(0.54 to 1.48)
ICAS/occlusion only	3408	109(6.4)	138(8.0)	0.80(0.62 to 1.02)
ECAS/occlusion only	445	21(8.6)	25(12.5)	0.68(0.38 to 1.21)
ICAS/occlusion and ECAS/occlusion	758	39(10.8)	61(15.3)	0.69(0.46 to 1.03)
Degree of symptomatic stenosis				
Non stenosis	1053	29(5.4)	31(6.0)	0.89(0.54 to 1.48)
50 to 99% stenosis	3315	109(6.6)	128(7.7)	0.86(0.67 to 1.11)
Occlusion	1338	63(9.5)	104(15.4)	0.60(0.44 to 0.82)

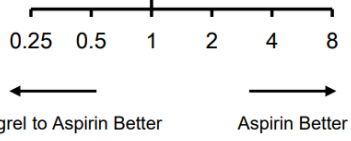


Table S1. Baseline characteristics of the patients. *

Characteristic	Clopidogrel-Aspirin (N=3050)	Aspirin (N=3050)
Ethnicity -no. (%) †		
Han	3003(98.5)	3008(98.6)
Zhuang	7(0.2)	8(0.3)
Hui	15(0.5)	10(0.3)
Manchu	9(0.3)	10(0.3)
Uygur	2(0.07)	3(0.1)
Others	14(0.5)	11(0.4)
Body-mass index, kg/m^2-Median (IQR)	24.4(22.6-26.5)	24.5(22.6-26.7)
Blood pressure, mmHg-Median (IQR) ‡		
Systolic	146(132-160)	146(133-160)
Diastolic	85(78-93)	85(78-94)
Medical history-no. (%)		
Previous TIA	48(1.6)	49(1.6)
Previous myocardial infarction	53(1.7)	60(2.0)
Coronary artery disease	337(11.1)	355(11.6)
Peripheral arterial disease	9(0.3)	8(0.3)
Application of drugs within 1 month before onset of symptoms-no. (%)		
Aspirin + clopidogrel	8(0.3)	14(0.5)
Statin	284(9.3)	281(9.2)
Antihypertensives	1521(49.9)	1508(49.4)
Antidiabetics	708(23.2)	694(22.8)
Distribution of criminal arterial stenosis/occlusion-no. (%) §,¶		
No intracranial/extracranial artery stenosis/ occlusion	537/2834(19.0)	516/2830(18.2)
Intracranial artery stenosis/ occlusion only	1692/2834 (59.7)	1716/2830 (60.6)
Extracranial artery stenosis/ occlusion only	245/2834 (8.7)	200/2830 (7.1)
Intracranial and Extracranial artery stenosis/ occlusion	360/2834 (12.7)	398/2830 (14.1)
Stenosis degree of symptomatic qualifying artery-no. (%) §,‖		
No stenosis/ occlusion	537/2842(18.9)	516/2864(18.0)
50-99% stenosis	1641/2842 (57.7)	1674/2864 (58.5)
Occlusion	664/2842(23.4)	674/2864 (23.5)
mRS score before the onset of symptoms-no. (%) #		
0	2401(78.7)	2421(79.4)
1	530(17.4)	490(16.1)
2	119(3.9)	138(4.5)

* IQR indicates interquartile range; TIA, transient ischemic attack.

† Ethnic group was reported by the patient and verified by identification card.

‡ Data was missing in 13 cases.

§ The stenosis degree of intracranial artery was defined on MRA, CTA or DSA by criteria from the Warfarin–Aspirin Symptomatic Intracranial Disease study and assessments of extracranial arteries stenosis degree was based on carotid duplex ultrasound, CTA, CE-MRA or DSA by standards from the North American Symptomatic Carotid Endarterectomy Trial. The criminal intracranial artery stenosis and extracranial artery stenosis were defined as more than 50% stenosis of intracranial and extracranial major arteries, respectively, which likely accounts for the infarction and clinical

presentation.

¶ Data was missing in 436 cases due to the absence of both intracranial and extracranial arterial vascular assessments.

‖Data was missing in 394 cases due to the absence of both intracranial and extracranial arterial vascular assessments; or subjects did not have occlusion in intracranial (or extracranial) arteries, but with the absence of extracranial (or intracranial) vascular assessments.

#The modified Rankin scale assesses measure functional recovery after stroke, with scores ranging from 0 to 6 and higher scores indicating more severe disability.

Table S2. Between-center variance component

	Variance*	95% Confidence Intervals
Study center	0.038	0.008 to 0.176

* The variance and 95% confidence intervals are on linear scale.

Table S3. Concomitant treatment within 90 Days

Concomitant Medication	Clopidogrel-Aspirin (N=3050)-no. (%)	Aspirin (N=3050) -no. (%)
Medicine use during hospitalization		
Antihypertensives	1643(53.9)	1648(54.0)
Diuretics	134(4.4)	127(4.2)
Calcium Antagonists	919(30.1)	943(30.9)
Angiotensin-Converting Enzyme Inhibitors	142(4.7)	155(5.1)
Angiotensin Receptor blockers	242(7.9)	259(8.5)
Adrenoceptor Antagonist	80(2.6)	73(2.4)
Antidiabetics	896(29.4)	896(29.4)
Oral Antidiabetics	594(19.5)	586(19.2)
Insulin	169(5.5)	164(5.4)
Medicine use at 90-day follow-up		
Antihypertensives	1569(51.4)	1583(51.9)
Diuretics	117(3.8)	120(3.9)
Calcium Antagonists	1238(40.6)	1242(40.7)
Angiotensin-Converting Enzyme Inhibitors	154(5.1)	142(4.7)
Angiotensin Receptor blockers	393(12.9)	412(13.5)
Adrenoceptor Antagonist	100(3.3)	107(3.5)
Antidiabetics	822(27.0)	791(25.9)
Oral Antidiabetics	740(24.3)	716(23.5)
Insulin	202(6.6)	198(6.5)

Table S4. Efficacy and safety outcomes in per-protocol population.

Outcome	Clopidogrel-Aspirin (N = 2788)		Aspirin (N = 2848)		Hazard Ratio/ Relative Risks * (95% CI)
	Patients with Event-no.	Event Rate†, %	Patients with Event-no.	Event Rate†, %	
Primary outcome					
Stroke (including ischemic and hemorrhagic stroke)	203	7.3	264	9.3	0.77(0.65 to 0.93)
Secondary outcomes					
Composite vascular event (stroke, myocardial infarction, or vascular death)	208	7.5	267	9.4	0.78(0.65 to 0.94)
Ischemic stroke	189	6.8	259	9.1	0.73(0.61 to 0.89)
Recurrent stroke	145	5.3	190	6.8	0.77(0.62 to 0.95)
TIA with infarction	5	0.2	11	0.4	0.46(0.16 to 1.31)
Progressive stroke	39	1.4	58	2.1	0.68(0.45 to 1.02)
Hemorrhagic stroke	15	0.5	5	0.2	3.07(1.12 to 8.45)
Myocardial infarction	3	0.11	2	0.07	1.53(0.26 to 9.17)
Vascular death	20	0.7	13	0.5	1.57(0.78 to 3.16)
Poor functional outcome (mRS 2-6) ‡	256/2788	9.2	307/2846	10.8	0.85(0.75 to 0.97)
TIA	11	0.4	26	0.9	0.43(0.21 to 0.87)
Ordinal stroke or TIA§					0.75(0.62 to 0.90)
Fatal stroke: score of 6 on mRS	19/2788	0.7	11/2847	0.4	
Severe stroke: score of 4 or 5 on mRS	27/2788	1.0	25/2847	0.9	
Moderate stroke: score of 2 or 3 on mRS	59/2788	2.1	96/2847	3.4	
Mild stroke: score of 0 or 1 on mRS	98/2788	3.5	131/2847	4.6	
TIA	11/2788	0.4	24/2847	0.8	
No stroke or TIA	2574/2788	92.3	2560/2847	89.9	
Primary safety outcome					
Moderate-to-severe bleeding¶	21	0.8	10	0.4	2.15(1.01 to 4.56)

Secondary safety outcomes					
Hepatotoxicity‖	22	0.8	25	0.9	0.90(0.48 to 1.67)
Muscle toxicity&	2	0.07	1	0.04	2.04(0.18 to 22.57)
All-cause mortality	29	1.0	25	0.9	1.19(0.69 to 2.02)
Any bleeding¶	60	2.2	52	1.8	1.18(0.81 to 1.71)
Mild bleeding	42	1.5	43	1.5	1.00(0.65 to 1.53)
Intracranial hemorrhage	17	0.6	8	0.3	2.17(0.94 to 5.03)

* The relative risks are shown for poor functional outcome, hepatotoxicity and muscle toxicity. The common odds ratio is shown for ordinal stroke or TIA. Hazard ratios are shown for other outcomes. The widths of the confidence intervals for secondary outcomes were not adjusted for multiplicity and may not be used for hypothesis testing.

† The event rates of poor functional outcome, ordinal stroke or TIA, hepatotoxicity and muscle toxicity are raw estimates, whereas the rates of other outcomes are Kaplan–Meier estimates of the percentage of patients with events at 90 days.

‡ The mRS score data at 90 days was missing in 2 patients in the aspirin group.

§ The severity of stroke or TIA is classified on a six-level ordered categorical scale combined vascular events with modified Rankin scale (mRS). The mRS score at 90days was missing in 1 patient in the aspirin group.

¶ Bleeding events were defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria.

‖ Hepatotoxicity was defined as alanine transaminase or aspartate transaminase >3 times the upper limit of normal value.

&Muscle toxicity was defined as creatine kinase >10 times the upper limit of normal value, or presence of muscle pain, myopathy or rhabdomyolysis.

Table S5. New stroke in population after further exclusion of patients with minor stroke (NIHSS score≤3) or TIA (ABCD^2 score ≥4) within 24 hours in per protocol population.

Outcome	Clopidogrel-Aspirin (N=2536)		Aspirin (N=2585)		Hazard Ratio (95% CI)
	Patients with Event-no.	Event Rate, %	Patients with Event-no.	Event Rate, %	
Stroke (including ischemic and hemorrhagic stroke)	181	7.1	236	9.1	0.77(0.64 to 0.94)

Table S6. Number of patients with adverse events*† by system organ class (excluding strokes) up to 3-month visit

System Organ Class	Clopidogrel-Aspirin (N=3050) no. (%)	Aspirin (N=3050) no. (%)	P value
Overall	650(21.3)	648(21.3)	0.95
Blood and lymphatic system disorders	3(0.1)	3(0.1)	>0.99
Cardiac disorders	27(0.9)	25(0.8)	0.78
Arrhythmia	20(0.7)	12(0.4)	0.16
Coronary heart disease	4(0.1)	2(0.07)	0.69
Ear and labyrinth disorders	9(0.3)	3(0.1)	0.08
Endocrine disorders	0(0.0)	1(0.03)	0.32
Eye disorders	7(0.2)	6(0.2)	0.78
Gastrointestinal disorders	93(3.1)	79(2.6)	0.28
Gastrointestinal Hemorrhage	2(0.07)	0(0.0)	0.50
Gingival bleeding	5(0.2)	2(0.07)	0.45
General disorders and administration site conditions	9(0.3)	12(0.4)	0.51
Hepatobiliary disorders	18(0.6)	12(0.4)	0.27
Immune system disorders	8(0.3)	6(0.2)	0.59
Infections and infestations	66(2.2)	62(2.0)	0.72
Lung infection	18(0.6)	16(0.5)	0.73
Upper respiratory tract infection	17(0.6)	18(0.6)	0.87
Injury, poisoning and procedural complications	8(0.3)	8(0.3)	>0.99
Investigations	238(7.8)	279(9.2)	0.06
Metabolism and nutrition disorders	59(1.9)	70(2.3)	0.33
Musculoskeletal and connective tissue disorders	17(0.6)	18(0.6)	0.87
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	34(1.1)	12(0.4)	0.001
Nervous system disorders	93(3.1)	105(3.4)	0.39
Psychiatric disorders	35(1.2)	20(0.7)	0.042
Renal and urinary disorders	16(0.5)	11(0.4)	0.33
Reproductive system and breast disorders	10(0.3)	9(0.3)	0.82
Respiratory, thoracic and mediastinal disorders	19(0.6)	15(0.5)	0.49
Dyspnea	0(0.0)	1(0.03)	>0.99
Epistaxis	6(0.2)	5(0.2)	0.76
Skin and subcutaneous tissue disorders	19(0.6)	13(0.4)	0.29
Subcutaneous Hemorrhage/ Dermatorrhagia	6(0.2)	7(0.2)	0.78
Rash/Pruritus/Urticaria	11(0.4)	7(0.2)	0.35
Surgical and medical procedures	21(0.7)	16(0.5)	0.41
Vascular disorders	26(0.9)	22(0.7)	0.56

* Adverse events did not include serious adverse events. Includes adverse events with an onset date on or after the date of the first dose and up to the date of the last dose of study medication.

† Patients with multiple events of one type were counted once.

Table S7. Number of patients with serious adverse events* by system organ class (excluding strokes) up to 3-month visit

System Organ Class	Clopidogrel-Aspirin (N=3050) no. (%)	Aspirin (N=3050) no. (%)	P value
Overall	107(3.5)	89(2.9)	0.19
Blood and lymphatic system disorders	1(0.03)	0(0.0)	>0.99
Cardiac disorders	12(0.4)	10(0.3)	0.67
Ear and labyrinth disorders	0(0.0)	1(0.03)	>0.99
Eye disorders	1(0.03)	0(0.0)	>0.99
Gastrointestinal disorders	13(0.4)	5(0.2)	0.06
General disorders and administration site conditions	4(0.1)	7(0.2)	0.37
Hepatobiliary disorders	2(0.07)	2(0.07)	>0.99
Infections and infestations	8(0.3)	4(0.1)	0.25
Injury, poisoning and procedural complications	5(0.2)	4(0.1)	>0.99
Investigations	4(0.1)	2(0.07)	0.69
Metabolism and nutrition disorders	2(0.07)	0(0.0)	0.50
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3(0.1)	3(0.1)	>0.99
Nervous system disorders	46(1.5)	35(1.2)	0.22
Psychiatric disorders	1(0.03)	4(0.1)	0.37
Respiratory, thoracic and mediastinal disorders	4(0.1)	3(0.1)	>0.99
Skin and subcutaneous tissue disorders	0(0.0)	1(0.03)	>0.99
Surgical and medical procedures	10(0.3)	10(0.3)	>0.99
Vascular disorders	1(0.03)	3(0.1)	0.62

*Patients with multiple events of one type were counted once. Includes adverse events with an onset date on or after the date of first dose and up to the date of last dose of study medication.

Table S8. Number of patients with adverse events or serious adverse events leading to premature permanent drug discontinuation by system organ class up to 3-month visit

System Organ Class	Clopidogrel-Aspirin (N=3050) no. (%)	Aspirin (N=3050) no. (%)	P value
Blood and lymphatic system disorders	2(0.07)	0(0.0)	0.50
Cardiac disorders	12(0.4)	11(0.4)	0.83
Ear and labyrinth disorders	1(0.03)	0(0.0)	>0.99
Endocrine disorders	0(0.0)	0(0.0)	-
Eye disorders	1(0.03)	0(0.0)	>0.99
Gastrointestinal disorders	15(0.5)	12(0.4)	0.56
General disorders and administration site conditions	4(0.1)	2(0.07)	0.69
Hepatobiliary disorders	2(0.07)	0(0.0)	0.50
Immune system disorders	2(0.07)	0(0.0)	0.50
Infections and infestations	8(0.3)	5(0.2)	0.40
Injury, poisoning and procedural complications	2(0.07)	1(0.03)	>0.99
Investigations	11(0.4)	11(0.4)	>0.99
Metabolism and nutrition disorders	1(0.03)	0(0.0)	>0.99
Musculoskeletal and connective tissue disorders	2(0.07)	1(0.03)	>0.99
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4(0.1)	1(0.03)	0.37
Nervous system disorders	35(1.2)	30(1.0)	0.53
Psychiatric disorders	3(1.0)	1(0.03)	0.62
Renal and urinary disorders	1(0.03)	0(0.0)	>0.99
Reproductive system and breast disorders	0(0.0)	0(0.0)	-
Respiratory, thoracic and mediastinal disorders	5(0.2)	3(0.1)	0.73
Skin and subcutaneous tissue disorders	3(0.1)	1(0.03)	0.62
Surgical and medical procedures	21(0.7)	16(0.5)	0.41
Vascular disorders	6(0.2)	4(0.1)	0.53