Efficacy of Dual Antiplatelet Treatment in Minor stroke or TIA Patients with Multiple Acute Infarctions and Lower Level of Stress Hyperglycemic Marker – A Post-hoc Analysis of a Randomized Control Trial

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Abstract

Background We intended to investigate how the interaction between glycemic status and infarction pattern affected the efficacy and safety of dual antiplatelet treatment in minor stroke or transient ischemic attack (TIA) patients.

Methods This post-hoc analysis of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) study included 797 patients with complete data of stress hyperglycemia markers (fasting plasma glucose (FPG)/glycated albumin (GA) ratio) and Magnetic Resonance Imaging work-up. The primary outcome is a 90-day new stroke (ischemic or hemorrhagic). Other endpoints included combined vascular events and bleeding events at 90 days. We used multivariable Cox regression models to evaluate the influence of stress hyperglycemia status × infarction pattern (Multiple acute infarctions (MAI), Single acute infarction (SAI) and No acute infarction (NAI)) on the efficacy and safety of clopidogrel plus aspirin treatment.

Results Among 797 patients, the median age was 63.1 years, and 64.9% of the patients were male. Within the 90-day after randomization, 73 (9.2%) new strokes 75 (9.4%) combined vascular events, and 17 (2.1%) bleeding events occurred. Dual antiplatelet treatment significantly reduced new stroke and combined vascular events in patients with lower FPG/GA ratio (lower than the median of FPG/GA ratio) and multiple acute infarctions, after adjusted for all potential confounders (11.9% vs. 23.3%, adjusted HR(95% confidence interval, CI): 0.240(0.080–0.713)). No significant reductions of recurrence or occurrence of combined vascular events were seen in the other three groups (NAI or SAI with lower FPG/GA ratio; NAI or SAI with higher FPG/GA ratio and MA with higher FPG/GA ratio). The proportion of bleeding events was similar among treatment groups regardless of the FPG/GA ratio or infarction pattern.

Conclusions Clopidogrel plus aspirin treatment was associated with reduced 90-day new stroke or combined vascular events in patients with multiple acute infarctions and lower FPG/GA ratio, without increasing the risk of bleeding events.

Trial Registration

URL: https://clinicaltrials.gov/ct2/show/NCT00979589; Unique Identifier: NCT00979589

Background

The risk of recurrence after minor stroke or transient ischemic attack (TIA) is high, ranging from 3.7–16.8%.[1–4] The dual antiplatelet treatment combining aspirin and clopidogrel was efficient in reducing new stroke in a 90-day period after minor stroke or TIA according to the result of the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) study.[5] The result was further validated in the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial[6], thus, the dual antiplatelet treatment was recommended by the 2018 guidelines for the early management of patients with acute ischemic stroke for the treatment of minor stroke or TIA.[7] Up to 40% of the acute stroke patients who had hyperglycemia at admission.[8] Hyperglycemia was associated with worse outcomes of stroke patients, such as death[9], infarct volume growth[10, 11] or hemorrhagic transformation[12]. Stress hyperglycemia, as one of the phenotypes of the heterogeneous entity of hyperglycemia, increased 90-day new stroke after minor stroke or TIA.[13] Potential mechanisms of stress hyperglycemia-induced ischemic injury includes oxidative stress, systematic endothelial malfunction or thromboinflammation.[14, 15] In diabetic rats, insulin treatment together with tissue plasminogen activator (tPA) alleviated brain tissue damage in an embolic stroke model.[16]

Furthermore, in the analysis of imaging subgroup of the CHANCE study, compared to mono antiplatelet treatment (aspirin-alone), the dual antiplatelet therapy (clopidogrel plus aspirin) reduced 50% recurrent stroke in patients with multiple acute infarctions (MAI), as one of potential imaging parameter of embolic stroke, while the superiority of this treatment was not seen in patients with single or none acute infarction (SAI or NAI).[17]

Whether clopidogrel plus aspirin regimen would reduce the risk of new stroke after minor stroke or TIA in patients with different glycemic levels as well as different infarction pattern remains unanswered.

Thus, we intended to investigate how the interaction between glycemic status and infarction pattern affected the efficacy of dual antiplatelet treatment in minor stroke or TIA patients.

Methods

Aim, design and setting of the study

This study derived data from the CHANCE trial, a placebo-controlled, double-blind, randomized clinical trial, which was conducted in 114 sites in China from October 2009 to July 2012. Detailed design and results were published elsewhere.[18-20] Sample size estimation were based on the requirement to detect the smallest expected, clinically meaningful treatment difference. In brief, eligible patients were randomly assigned into the two treatment arms: clopidogrel (initiated with a loading dose of 300mg and followed by 75mg per day) with aspirin (initiated with a range from 75

to 300mg and followed by 75mg per day in the first 21 days) arm; or aspirin arm (initiated with a range from 75 to 300mg and followed by 75mgper day for 90 days) by researchers who were blinded to the treatment regimen. Eligible patients included males or females with a ≥40 years of age, diagnosed as minor ischemic stroke (National Institutes of Health Stroke Scale, NIHSS ≤3) or moderate-to-high risk TIA (defined as the ABCD^2 (the age, blood pressure, clinical features, duration of symptoms, and presence of diabetes) score ≥4) and treatment could be received within 24 hours after symptom onset.

Among 5170 patients included in the CHANCE trial, 3044 patients from 73 study sites with experience of biological sample collection process management participated

in the prespecified biomarker sub-study. Meanwhile, 1342 patients from 45 sites participated in the imaging sub-study. Patients with both biomarker data as well as

imaging data will be included in the current research.

The CHANCE trial protocol was approved by the ethics committees of all study centers and registered on www.clinicaltrials.gov (registration number: NCT00979589).

All patients or their legal proxies had given written informed consent.

Data Collection

Trained research coordinators collected demographic and clinical characteristics at baseline including age, gender, modified Rankin Scale (mRS) prior to the event, history of ischemic stroke, TIA, myocardial infarction, atrial fibrillation, heart failure, hypertension and other important concurrent conditions, smoking habits, baseline blood pressure, through a face-to-face interview.

Measurement and Assessment of Stress Hyperglycemia

Overnight fasting venous blood was drawn within the first 24±12 hours after enrollment and preprocessed into plasma, serum, and other forms according to requirements in the protocol. Part of the plasma samples was tested for many items, including fasting plasma glucose (FPG) and low-density lipoprotein (LDL). And the serum specimens were shipped via overnight cold-chain transportation to Beijing Tiantan Hospital, Beijing, China, and stored in the −80°C condition. Before centralized testing for glycated albumin (GA) percentage in total serum albumin using the GA kit (catalog number 4085-717, Ruiyuan Bio-Technique Co. Ltd., Ningbo, China) by a Roche Modular P800 system in the clinical laboratory of Beijing Tiantan Hospital, the freezing and thawing circle were avoided. Laboratory technicians who performed the measurements were blinded to patients' baseline characteristics, treatment group and outcomes.[21]

In order to assess the stress glycemia situation by both random fasting glucose as well as background glucose level, FPG (mmol/L)/GA (%) ratio was calculated and defined as the indication of stress hyperglycemia.[13] Divided by the median value of the FPG /GA ratio, patients were categorized into two groups: FPG/GA ratio < median value and FPG/GA ratio > median value.

Imaging Interpretation

In the prespecified imaging sub-study, patients underwent Magnetic Resonance Imaging (MRI) (3.0or1.5T) examinations following the standard protocol, including diffusion-weighted imaging (DWI), 3-dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA), T1-weighted imaging and T2-weighted imaging.[17]

Infarction patterns were categorized into three groups: no acute infarction (NAI), single acute infarction (SAI), and multiple acute infarctions (MAI). SAI was defined as uninterrupted lesions visible in contiguous territories. MAI indicated more than one lesion "topographically distinct" from each other (separated in space or discrete on contiguous slices).[22] The study population was grouped as NAI or SAI vs. MAI in the current analysis.

Readers of the imaging data were blinded to patients' baseline information, treatment assignment and outcomes.[17]

Efficacy and Safety Outcomes

The central adjudication committee, blinded to the treatment assignment, adjudicated all efficacy and safety outcomes/endpoints. All enrolled patients were interviewed by trained research coordinates at baseline and the 90-day visit[18] after randomization. All the adverse events, end-point events, mRS, medication use in the period between visits,

and related medical records were collected and submitted to the central adjudication committee.

The primary efficacy outcome was recurrent stroke (ischemic or hemorrhagic) within 90 days. The secondary efficacy outcomes included combined vascular events (consist of ischemic stroke, hemorrhagic stroke, myocardial infarction, and vascular death).[19] The primary safety outcome was any bleeding events according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition[23].

In this study, we focused on recurrent stroke, combined vascular events, and any bleeding event.

Statistical Analysis

The analysis was based on Intention-To-Treatment (ITT) principle. Baseline characteristics and outcomes were compared between groups according to FPG/GA ratio and infarction pattern. Categorical variables were presented by proportions and continuous variables as medians with interquartile ranges (IQRs). Categorical variables were compared using χ^2 statistics or Fisher exact test; continuous variables, using and were compared with the Wilcoxon rank-sum test.

The multivariable Cox regression was used in analyzing the association between different groups categorized by FPG/GA ratio × infarction pattern and efficacy of dual antiplatelet treatment in reducing efficacy endpoints and other outcomes after having a minor stroke or TIA. Crude and adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated (adjusted for all potential confound factors).

A 2-sided *p*-value, less than 0.05, was considered of statistical significance. We used SAS software, version 9.4 (SAS Institute Inc), to perform all the statistical analyses.

Results

Study participants and baseline characteristics

Among the 5170 enrolled patients in the CHANCE trial, 3026 patients (99.4% of the biomarker sub-study) with complete FPG and GA data, 1089 patients (81.1% of the imaging sub-study) who underwent MRI tests that met the requirements of sequences.

A total of 797 patients fulfilled the inclusion criteria with both complete data of FPG, GA, and imaging test. (Figure) The median age of all the included patients was 63.1 years; 64.9% of the patients were male. One hundred and ninety-two (24.1%) patients had multiple acute infarctions. Within the 90-day follow-up, 73 (9.2%) new strokes 75 (9.4%) combined vascular events and 17 (2.1%) bleeding events occurred. In the whole study population or in the NAI or SAI group after stratified by infarction pattern, patients with higher FPG/GA ratio were younger with higher body mass index (BMI), higher baseline LDL, and more likely to be current or former smokers (Table 1). In the MAI group, baseline characteristics and outcomes were well-balanced except for age and BMI.

Table 1
Baseline characteristics based on fasting glucose/GA and different infarction patterns.

	Total patients, n = 797			Single or no acute infarction, n = 605			Multiple acute infarction, n = 192		
	Glucose/GA < median (0.33) n = 399	Glucose/GA ≥ median(0.33) n = 398	P value	Glucose/GA < median (0.33) n = 297	Glucose/GA ≥ median(0.33) n = 308	P value	Glucose/GA < median (0.33) n = 102	Glucose/GA ≥ median(0.33) n = 90	P value
Age, y, median (IQR)	65.9(57.5–74.1)	60.7(52.9–69.0)	< 0.0001	64.7(58.1–73.3)	60.5(53.0-68.6)	< 0.0001	68.3(57.3–75.2)	61.2(57.3–75.2)	0.0020
Men, n(%)	256(64.2%)	261(65.5%)	0.7108	194(65.3%)	194(63.0%)	0.5542	62(60.8%)	67(74.4%)	0.0471
mRS prior to current event, median (IQR)	0(0–0)	0(0–0)	0.0021	0(0–0)	0(0–0)	0.0358	0(0–0)	0(0–0)	0.0101
BMI, median (IQR), kg/m^2	24.1(21.8–26.0)	24.8(22.9–26.9)	< 0.0001	24.2(22.0–26.0)	24.6(22.9–26.7)	0.0011	23.7(21.8–26.0)	25.3(22.5–27.5)	0.0093
Medical history, n (%)									
Ischemic stroke	77(19.3%)	61(15.3%)	0.1601	55(18.5%)	48(15.6%)	0.3869	22(21.6%)	13(14.4%)	0.2613
TIA	11(2.8%)	15(3.8%)	0.4341	9(3.0%)	11(3.6%)	0.8214	2(2.0%)	4(4.4%)	0.4216
Myocardial infarction	10(2.5%)	3(0.8%)	0.0897	4(1.4%)	2(0.7%)	0.4430	6(5.9%)	1(1.1%)	0.1233
Congestive heart failure	11(2.8%)	5(1.3%)	0.2055	6(2.0%)	3(1.0%)	0.3321	5(4.9%)	2(2.2%)	0.4510
Known atrial fibrillation or flutter	10.(2.5%)	8(2.0%)	0.8124	293(98.7%)	302(98.1%)	0.7523	6(5.9%)	2(2.2%)	0.2865
Hypertension	258(64.7%)	262(65.8%)	0.7662	190(64.0%)	204(66.2%)	0.6088	68(66.7%)	58(64.4%)	0.7628
Dyslipidemia	53(13.3%)	52(13.1%)	1.0000	43(14.5%)	40(13.0%)	0.6371	10(9.8%)	12(13.3%)	0.5003
Diabetes mellitus	86(21.6%)	68(17.1%)	0.1271	54(18.2%)	55(17.9%)	1.0000	32(31.4%)	13(14.4%)	0.0064
Current or previous smoker, n (%)	151(37.8%)	187(47.0%)	0.0099	108(36.4%)	140(45.5%)	0.0256	43(42.2%)	47(52.2%)	0.1927
Baseline NIHSS score, median (IQR)	2(0–2)	2(1–2)	0.1860	1(0–2)	2(0–2)	01490	2(1–2)	2(1–3)	0.7108
Time from onset to randomization, n(%)			0.4786			0.4647			0.8844
<12 hours	202(50.6%)	212(53.3%)		146(49.2%)	161(52.3%)		56(54.9%)	51(56.7%)	
≥12 hours	197(49.4%)	186(46.7%)		151(50.8%)	147(47.7%)		46(45.1%)	39(43.3%)	
Qualifying events, n(%)			0.8065			0.6522			1.0000
Minor ischemic stroke	297(74.4%)	300(75.4%)		211(71.0%)	224(72.7%)		86(84.3%)	76(84.4%)	
TIA	102(25.6%)	98(24.6%)		86(29.0%)	84(27.3%)		16(15.7%)	14(15.6%)	
Treatment group			0.6202			0.8708			0.1927
Aspirin	197(49.4%)	204(51.3%)		154(51.9%)	157(51.0%)		43(42.2%)	47(52.2%)	

IQR indicates interquartile range; mRS, modified Rankin Scale; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale, GA, glycated albumin and LDL, low-density lipoprotein and NE, not estimable. Combined vascular events consist of ischemic stroke, hemorrhagic stroke, myocardial infarction, and vascular death. Bleeding events according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition.

	Total patients, n = 797			Single or no acute infarction, n = 605			Multiple acute infarction, n = 192		
Clopidogrel plus aspirin	202(50.6%)	194(48.7%)		143(48.2%)	151(49.0%)		59(57.8%)	43(47.8%)	
FPG (mmol/L), median (IQR)	5.0(4.5–5.6)	5.7(5.1–6.8)	< 0.0001	5.0(4.6–5.6)	5.7(5.2–6.8)	< 0.0001	5.0(4.4–5.8)	5.7(5.0-6.9)	< 0.0001
GA (%), median (IQR)	**17.8(16.2–20.4)**	**15.0(13.6–17.1)**	**< 0.0001**	**17.7(16.2–20.0)**	**15.1(13.6–17.2)**	**< 0.0001**	**18.5(16.2–23.6)**	**14.8(13.5–16.8)**	**< 0.0001**
LDL (mmol/L)	3.1(2.4–3.7)	3.3(2.7–3.9)	< 0.0001	3.1(2.4–3.7)	3.3(2.7–3.9)	0.0063	3.0(2.2–3.7)	3.3(2.7–3.9)	0.0234
Outcomes at 90-day									
New stroke (Ischemic or hemorrhagic stroke)	33(8.3%)	40(10.1%)	0.3931	16(5.4%)	28(9.1%)	0.0865	17(16.7%)	12(13.3%)	0.5511
Combined vascular events	33(8.3%)	42(10.6%)	0.2777	16(5.4%)	29(9.4%)	0.0640	17(16.7%)	13(14.4%)	0.6722
Bleeding	11(2.8%)	6(1.5%)	0.3270	8(2.7%)	5(1.6%)	0.4114	3(2.9%)	1(1.1%)	0.6240

IQR indicates interquartile range; mRS, modified Rankin Scale; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale, GA, glycated albumin and LDL, low-density lipoprotein and NE, not estimable. Combined vascular events consist of ischemic stroke, hemorrhagic stroke, myocardial infarction, and vascular death. Bleeding events according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition.

Dual Antiplatelet Treatment Effects Stratified by Infarction Pattern and FPG/GA ratio

Clopidogrel plus aspirin significantly reduced new stroke occurrence and combined vascular events in patients with lower FPG/GA ratio and multiple acute infarctions, after adjusted for all potential confounders (11.9% vs. 23.3%, adjusted HR(95% confidence interval, CI): 0.240(0.080–0.713)). (Table 2) No significant reductions of recurrence or occurrence of combined vascular events were seen in the other three groups (NAI or SAI with lower FPG/GA ratio; NAI or SAI with higher FPG/GA ratio and MA with higher FPG/GA ratio).

Table 2
Effect of aspirin plus clopidogrel compared with aspirin alone on primary outcomes stratified by fasting FPG/GA and infarction pattern.

Outcomes	Aspirin*	Clopidogrel plus aspirin	Crude HR (95%CI)	Adjusted HR† (95%CI)	Adjusted p for interaction
Stroke					
Single or no acute infarction					0.9115
FPG/GA < median n = 297	9(5.8%)	7(4.9%)	0.835(0.311–2.242)	0.0970(0.353–2.666)	
FPG/GA ≥ median n = 308	14(8.9%)	14(0.3%)	1.050(0.501–2.203)	1.034(0.477–2.239)	
Multiple infarctions					**0.2610**
FPG/GA < median n = 102	10(23.3%)	7(11.9%)	0.478(0.182–1.255)	0.240(0.080–0.713)	
FPG/GA ≥ median n = 90	8(17.0%)	4(9.3%)	0.564(0.170–1.877)	0.940(0.222–3.982)	
Composite vascular event					
Single or no acute infarction					0.9798
FPG/GA < median n = 297	9(5.8%)	7(4.9%)	0.835(0.311–2.242)	0.970(0.353–2.666)	
FPG/GA ≥ median n = 308	15(9.6%)	14(9.3%)	0.979(0.472–2.027)	0.984(0.460–2.104)	
Multiple infarctions					**0.3914**
FPG/GA < median n = 102	10(23.3%)	7(11.9%)	0.478(0.182–1.255)	0.240(0.080–0.713)	
FPG/GA ≥ median n = 90	9(19.2%)	4(9.3%)	0.490(0.151–1.592)	0.623(0.154–2.514)	
Bleeding					
Single or no acute infarction					0.1448
FPG/GA < median n = 297	5(3.3%)	3(2.1%)	0.648(0.155–2.711)	0.651(0.143–2.970)	
FPG/GA ≥ median n = 308	1(0.6%)	4(2.7%)	4.165(0.466–37.263)	7.858(0.465-132.881)	
Multiple infarctions					NA
FPG/GA < median n = 102	0(0%)	3(5.1%)	NA	NA	
FPG/GA ≥ median n = 90	0(0%)	1(2.3%)	NA	NA	

HR indicated hazard ratio; FPG, fasting plasma glucose; GA, glycated albumin. Stroke included ischemic and hemorrhagic stroke.

Combined vascular events consist of ischemic stroke, hemorrhagic stroke, myocardial infarction, and vascular death. Bleeding events according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition.

*: As a reference.

†: Adjusted for age, sex, body mass index, current or previous smoking, low-density lipoprotein cholesterol, qualifying event, and medical history of hypertension, diabetes mellitus, hypercholesterolemia, ischemic stroke, TIA, myocardial infarction, congestive heart failure, and known atrial fibrillation or flutter.

Among patients in the NAI or SAI group or the MAI group, interactions between

infarction patterns and stress hyperglycemia status (FPG/GA ratio) were not significant for stroke recurrence and combined vascular events after adjustment of all

potential factors. (adjusted P for interaction: 0.9115 in NAI or SAI for new stroke. 0.2610 in MAI for new stroke, 0.9798 in NAI or SAI for combined vascular events and 0.3914 in MAI for combined vascular events). (Table 2)

Safety outcomes stratified by infarction pattern and stress hyperglycemia status

The proportion of bleeding events was similar among treatment groups (adjusted HR (95% CI): 0651 (0.143–2.970); 7.858(0.465-132.881) for lower and higher FPG/GA ratio in the NAI or SAI group, respectively) after adjusted for confounders. Because of the low occurrence of bleeding events, the

hazard ratio of dual antiplatelet treatment was not calculable. In accordance with the main findings of the safety outcome in the CHANCE trial, clopidogrel plus aspirin was not associated with elevated bleeding events in minor stroke or TIA patients regardless of infarction pattern or stress hyperglycemia status.

Discussion

In this post-hoc subgroup analysis, we observed that clopidogrel plus aspirin treatment was associated with reduced 90-day new stroke or combined vascular events in patients with multiple acute infarctions and lower FPG/GA ratio, without increasing the risk of bleeding events. Protection from recurrent stroke and combined vascular events at 90 days in patients with no acute infarction or single acute infarction regardless of the stress hyperglycemia status (measured by FPG/GA ratio) or patients with multiple acute infarctions and higher FPG/GA ratio were compromised. The interactions between infarction patterns and stress hyperglycemia status were not significant.

Previous sub-group analysis by the CHANCE investigators identified several modifiable factors, etiologic indicators, as well as genetic polymorphisms, which would

influence the efficacy of clopidogrel plus aspirin treatment. Among the studies of modifiable factors, elevated GA level (> 15.5%) was observed to be associated with a

higher incidence of recurrent stroke or combined vascular events.[21] Another analysis of the interaction of GA level and the *CYP2C19* loss-of-function (LOF) allele carrier status showed only in patients with a GA level lower than 15.5% and non-carrier of the

CYP2C19 LOF allele, dual antiplatelet significantly reduced total stroke or ischemic stroke recurrence and combined vascular events.[24] Furthermore, stress hyperglycemia, measured by FPG/GA ratio, was related to different outcomes among groups categorized by FPG/GA ratio quartiles. The highest quartile of glucose/GA ratio was associated with an increased 90-day stroke recurrence after adjusted for potential confounders, including fasting glucose.[13] In the imaging sub-analysis of the CHANCE study, a study focused on non-cardioembolic minor stroke or TIA patients, patients with MAI carried the highest risk of 90-day stroke risk compared to NAI or SAI patients. Notably, all MAI patients' index events' etiologic assignment of stroke subtypes were large artery atherosclerosis.[17] Mendelian randomization of single nucleotide polymorphisms (SNP) of type-2 diabetes (T2D) and other indicators of glycemic control, T2D may be causally associated with large artery atherosclerotic stroke.[25] Yet scarce evidence of stress hyperglycemia and imaging parameters with etiologic indication was reported.

We found that in patients with a higher FPG/GA ratio, the efficacy of dual antiplatelet treatment was attenuated. There were several potential mechanisms underlying the results. In patients with myocardial ischemia, the presence of hyperglycemia accentuated the inadequate response to P2Y12 receptor antagonists, such as clopidogrel, by involving in the impairment of post-receptor, adenylate cyclase-dependent signaling.[26] Osmotic effect of hyperglycemia was associated with an increase of soluble

P-selectin and CD40-ligand leading to platelet hyperactivity.[27–29] Episodes of hyperglycemia could lead to the formation of advanced glycation end products (AGEs),

some of the AGEs was associated with the externalization of membrane phosphatidylserine in part of platelets causing thrombogenic state.[30]

In animal experiments, hyperglycemia was associated with infarct volume growth[10, 31–33] via toxic effects of lactic acidosis, excitotoxicity, and altered inflammatory responses.[34] Although the history of diabetes and the use of anti-diabetic medication were well-balanced among different infarction patterns group in the previous study[17], we observed that patients with MAI and higher FPG/GA ratio might be a group of optimal beneficiaries of clopidogrel plus aspirin treatment in minor stroke or TIA. Evidence of mechanisms underlying the relationship between stress hyperglycemia status and infarction pattern for ischemic stroke patients remained limited.

Certain limitations of this study needed to be stressed. Firstly, the relatively small size of study participants included (797 patients, 15.5%) might cause selection bias and insufficient statistical power. Except for more included patients who had a history of ischemic stroke, higher NIHSS at baseline, other factors were comparable between included and excluded patients. (see Additional file 1) Although the recurrence rate at 90-day in different treatment groups of MAI or NAI/SAI patients were comparable to the imaging sub-study of CHANCE[17], the recurrence rates were slightly lower than the CHANCE study.[18] Results of this study merit further evaluation in larger size prospective studies. Secondly, as all multiple acute stroke patients were large artery stroke in this non-cardioembolic study, the analysis of the dual antiplatelet treatment efficacy on MAI patients of other etiologies, such as paradoxical embolic MAI[35], is needed. Thirdly, only Chinese patients were enrolled in the CHANCE study. However, the distribution of different etiologic subtypes of stroke was highly different between

Asian and non-Asian patients.[36] A high prevalence of large artery stroke in the Chinese indicated that the generalizability of this study should be carefully interpreted.

Conclusions

In summary, clopidogrel plus aspirin treatment was associated with reduced 90-day new stroke or combined vascular events in patients with multiple acute infarctions and lower FPG/GA ratio, without increasing the risk of bleeding events.

Abbreviations

TIA: transient ischemic attack; CHANCE: the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events study; FPG: fasting plasma glucose (FPG); GA: glycated albumin; MAI: Multiple acute infarctions; SAI: Single acute infarction; NAI: No acute infarction; POINT: the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke trial; tPA: tissue plasminogen activator; NIHSS: National Institutes of Health Stroke Scale; the ABCD2 score: the age, blood pressure, clinical features, duration of symptoms, and presence of diabetes; mRS: modified Rankin Scale; LDL: low-density lipoprotein; MRI: Magnetic Resonance Imaging; DWI: diffusion-weighted imaging; 3D-TOF-MRA: 3-dimensional time-of-flight magnetic resonance angiography; GUSTO: the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; ITT: Intention-To-Treatment; IQRs: interquartile ranges; CIs: confidence intervals.

Declarations

Ethics approval and consent to participate

The CHANCE trial protocol was approved by the ethics committee of Beijing Tiantan Hospital and all the participating centers. All patients or their legal proxies had given written informed consent. Name of the ethics committee is the Institutional Ethical Review Board of Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

The approval number of this study is ky2009-002.

Consent for publication

Statement of that all collected data will be analyzed and prepared for publications was

listed in the patient informed consent. All patients or their legal proxies had given written informed consent.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Reporting Statement

This manuscript reporting adheres to CONSORT guidelines for reporting clinical trials.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YS interpreted the results of the analysis and drafted the manuscript. JJ analyzed and

interpreted the imaging data of patients. AXW and YJZ performed the statistical

analysis. HYZ, WC, YSP and HL reviewed the manuscript and data analysis process

and gave revision suggestions. LPL, XQZ, YLW and XM reviewed the manuscript and gave revision suggestions. YJW obtained funding, in charge of study concept and design, supervised and coordinated the study process. All authors read and approved the final manuscript.

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Disclosures

The authors of this study announced no disclosure.

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Figures

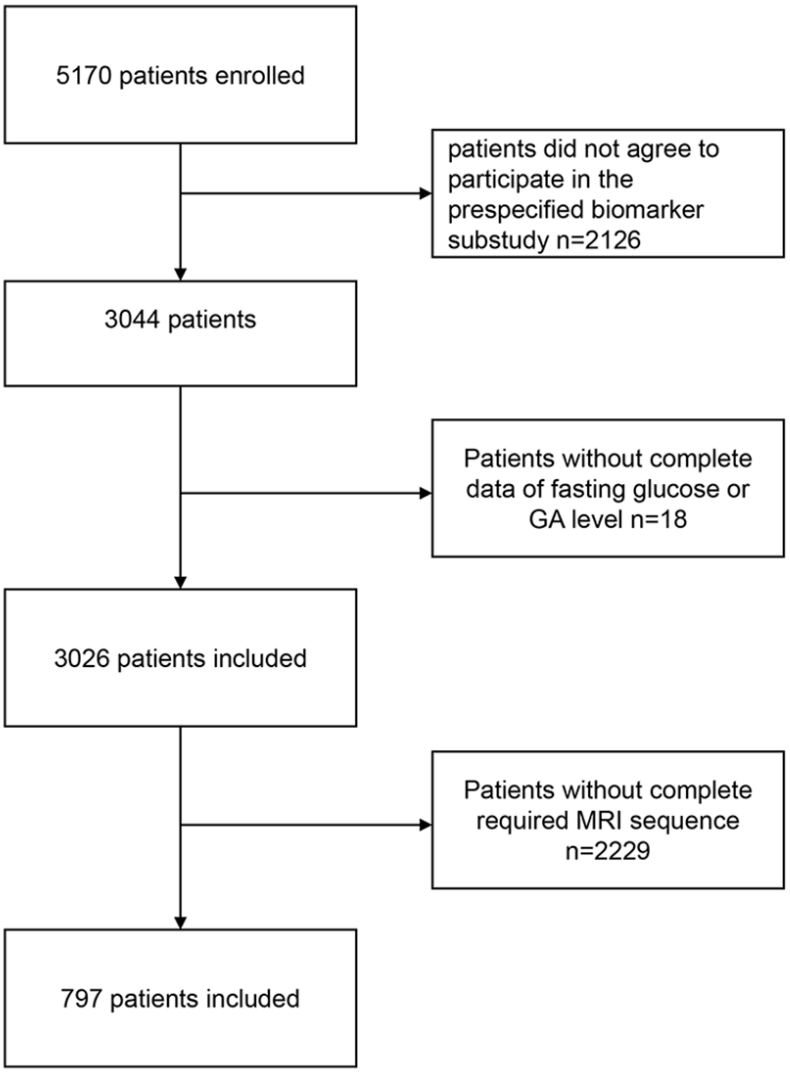

Figure 1

Flowchart of Patients' Inclusion. GA indicates glycated albumin, MRI, Magnetic Resonance Imaging.

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