ORIGINAL RESEARCH

Recurrent Stroke in Minor Ischemic Stroke or Transient Ischemic Attack With Metabolic Syndrome and/or Diabetes Mellitus

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***Background*—**We aimed to determine the risk conferred by metabolic syndrome (METS) and diabetes mellitus (DM) to recurrent stroke in patients with minor ischemic stroke or transient ischemic attack from the CHANCE (Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events) trial.

***Methods and Results*—**In total, 3044 patients were included. Patients were stratified into 4 groups: neither, METS only, DM only, or both. METS was defined using the Chinese Diabetes Society (CDS) and International Diabetes Foundation (IDF) definitions. The primary outcome was new stroke (including ischemic and hemorrhagic) at 90 days. A multivariable Cox regression model was used to assess the relationship of METS and DM status to the risk of recurrent stroke adjusted for potential covariates. Using the CDS criteria of METS, 53.2%, 17.2%, 19.8%, and 9.8% of patients were diagnosed as neither, METS only, DM only, and both, respectively. After 90 days of follow-up, there were 299 new strokes (293 ischemic, 6 hemorrhagic). Patients with DM only (16.1% versus 6.8%; adjusted hazard ratio 2.50, 95% CI 1.89–3.39) and both (17.1% versus 6.8%; adjusted hazard ratio 2.76, 95% CI 1.98–3.86) had significantly increased rates of recurrent stroke. No interaction effect of antiplatelet therapy by different METS or DM status for the risk of recurrent stroke (P=0.82 for interaction in the fully adjusted model of CDS) was observed. Using the METS (IDF) criteria demonstrated similar results.

***Conclusions*—**Concurrent METS and DM was associated with an increased risk of recurrent stroke in patients with minor stroke and transient ischemic attack. **(*J Am Heart Assoc*. 2017;6:e005446. DOI: 10.1161/JAHA.116.005446.)**

Key Words: diabetes mellitus • metabolic syndrome • prognosis • stroke

The metabolic syndrome (METS) refers to a cluster of highly interrelated metabolic risk factors.[1] Regardless of the details of several criteria by different organizations for its diagnosis,[2,3] it is generally accepted that the prevalence of METS in diverse racial populations is increasing (between 10% and 84%).[4,5] Previous prospective studies showed that the presence of METS identifies persons at an elevated risk for ischemic stroke or transient ischemic attack (TIA).[6,7] There are limited data, however, on the relationship between METS and the risk of stroke recurrence. Previous studies found that METS may not be predictive for stroke recurrence in patients with general ischemic stroke,[8,9] whereas another study demonstrated that METS was associated with higher risk of stroke recurrence in patients with ischemic stroke.[10] The relationship between METS and recurrence of stroke after a stroke or TIA remains controversial.

METS was defined for use in persons without diabetes mellitus (DM), but the definition has developed in recent decades to include those with DM.[11,12] Given a synergistic relationship among these components, the collective entity of METS provides better stroke risk estimates. Nevertheless, this integration of each component of METS made it difficult to understand the effect of DM or other components on stroke recurrence compared with the role of METS as an independent risk factor.

Minor ischemic stroke and TIA account for ≈65% of all acute ischemic cerebrovascular events[13] and lead to a risk of 10% to 15% stroke occurrence within 90 days.[14,15] Factors

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associated with a high risk of recurrence in patients with TIA or minor stroke were different from those of general stroke[16]; however, data from previous studies were derived from trials or cohorts in which patients were recruited weeks or months after their initial event and underestimated early recurrence, especially for minor stroke or TIA.[8,9,17] Consequently, the risks of recurrent stroke caused by METS and DM in patients with a minor stroke or TIA should be further examined.

We compared the risk of recurrent stroke in patients with different METS and DM status and minor stroke or TIA from the CHANCE (Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events) trial. Our hypothesis was that METS and DM were associated with an increased risk of recurrent stroke after a minor stroke or TIA.

Methods

Study Patients

The CHANCE trial was a randomized, double-blind, controlled trial that enrolled 5170 patients within 24 hours after onset of minor stroke (National Institutes of Health Stroke Scale [NIHSS] ≤3) or high-risk TIA ($ABCD^2$ ≥4) from 114 clinical centers in China.[18–20] In total, 73 (64%) of 114 participating hospitals voluntarily participated in the serum biomarker substudy in the CHANCE trial. The triglyceride and high-density lipoprotein levels, which are the significant items for the diagnosis of METS, were analyzed in the laboratory using collected serum. A total of 3044 patients in these 73 centers with available triglyceride and high-density lipoprotein levels were included in this analysis.

Standard Protocol Approvals, Registrations, and Patient Consents

The CHANCE trial is registered at ClinicalTrials.gov (identifier NCT00979589). The protocol and data collection of the CHANCE trial were approved by the ethics committee of Beijing Tiantan Hospital and all other study centers. All participants or his or her representatives provided written informed consent before being entered into the study.

Measurements

Baseline demographics and clinical characteristics, including age, sex, medical history of ischemic stroke, TIA, myocardial infarction, angina, congestive heart failure, known atrial fibrillation or flutter, valvular heart disease, hypertension, DM, hypercholesterolemia, and baseline NIHSS and $ABCD^2$ scores were collected through face-to-face interviews by neurologists from clinical centers. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared (kg/m^2). Blood pressure was measured in the left arm of supine patients using a mercury or electronic sphygmomanometer. Venous blood was drawn from fasting patients 24±12 hours after randomization in 3044 patients of these 73 centers.[21] Plasma glucose after overnight fasting was then analyzed. The serum specimens were collected and shipped on ice by overnight courier from each participating hospital to Beijing Tiantan Hospital (China), where all data analyses were performed. The triglyceride and high-density lipoprotein levels were analyzed in the laboratory using collected serum by testing personnel blinded to clinical data in Beijing Tiantan Hospital. Data were analyzed with a Roche Modular P800 system.

DM was defined as a fasting glucose level ≥7.0 mmol/L (126 mg/dL), self-reported history of DM, or receiving treatment for DM. METS was defined using the definitions of the Chinese Diabetes Society (CDS),[3] which is the only official recommendation for the diagnosis of METS in the Chinese population, and International Diabetes Foundation (IDF).[2] We excluded patients with DM or fasting plasma glucose ≥7.0 mmol/L in both definitions of METS. Patients in our study were stratified into 4 groups: neither METS or DM, METS only, DM only, or both.

METS (CDS) was determined by the presence of ≥3 of the following metabolic risk factors: overweight or obesity (BMI ≥25); fasting plasma glucose of 6.1 to 6.9 mmol/L (110–125 mg/dL), 2-hour plasma glucose ≥7.8 mmol/L (140 mg/dL), or a history of DM with antidiabetic medication; elevated blood pressure (≥140/≥90 mm Hg) or a history of hypertension with antihypertensive medication; and dyslipidemia, which includes increased triglyceride levels (≥1.7 mmol/L [150 mg/dL]) or reduced high-density lipoprotein levels (<0.9 mmol/L [35 mg/dL] in men and <0.9 mmol/L [39 mg/dL] in women).[3]

METS (IDF) was defined by abdominal visceral obesity (increased waist circumference [WC], ≥90 cm in men and ≥80 cm in women for an Asian population) plus any ≥2 of the following factors: triglyceride level (≥150 mg/dL) or history of hyperlipemia with antihyperlipemia medication; reduced high-density lipoprotein level (<40 mg/dL in men and <50 mg/dL in women); elevated blood pressure (≥130/≥85 mm Hg) or a history of hypertension with antihypertensive medication; fasting plasma glucose of 100 to 125 mg/dL.[2] BMI ≥25 was used as a proxy for abdominal obesity because WC data are not available in the CHANCE study. METS (IDF) was used to perform sensitivity analysis.

Efficacy Outcomes

The primary efficacy outcome was a new stroke (ischemic or hemorrhagic) within 90 days.[18] Recurrent stroke was defined by the presence of a sudden new symptomatic neurological

deficit on a background of stability or improvement after the presenting event.[22] Secondary efficacy outcome contained composite events (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death).[18] All events were evaluated and confirmed by a central adjudication committee that was blinded to the study group assignments.

Statistical Analysis

Continuous variables of baseline characteristics were presented as medians with interquartile ranges and categorical variables as proportions. Baseline variables between patients included in and excluded from this analysis were compared with the Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables. Baseline variables among different METS and DM status (both, METS only, DM only, or neither) were compared with the Kruskal–Wallis test for continuous variables and the χ^2 test for categorical variables.

The interaction effect of METS and DM status with antiplatelet therapy group assignment was examined using METS/DM status by treatment group assignment in multivariable Cox models. We further assessed the relationship between METS and DM status and outcomes of minor stroke or TIA using multivariable Cox regression models with the *neither* group as reference. Adjusted hazards ratios (HRs) and their 95% CIs were calculated. All potential confounding

Table 1. Baseline Characteristics of the Patients Included in and Excluded From This Analysis

Characteristic	Included (n=3044)	Excluded (n=2126)	*P* Value
Age (y), median (IQR)	62.2 (54.7–71.2)	62.3 (54.6–71.3)	0.79
Female, n (%)	1017 (33.4)	733 (34.5)	0.42
Medical history, n (%)			
Ischemic stroke	582 (19.1)	451 (21.2)	0.06
TIA	95 (3.1)	79 (3.7)	0.24
Myocardial infarction	55 (1.8)	41 (1.9)	0.75
Angina	95 (3.1)	89 (4.2)	0.04
Congestive heart failure	54 (1.8)	26 (1.2)	0.11
Known atrial fibrillation or flutter	57 (1.9)	39 (1.8)	0.92
Valvular heart disease	10 (0.3)	4 (0.2)	0.34
Hypertension	1984 (65.2)	1415 (66.6)	0.30
Diabetes mellitus	613 (20.1)	480 (22.6)	0.03
Hypercholesterolemia	318 (10.5)	255 (12.0)	0.08
Smoking status, n (%)			0.96
Never	1739 (57.1)	1210 (56.9)	
Current	301 (9.9)	215 (10.1)	
Previous	1004 (33.0)	701 (33.0)	
Index event, n (%)			0.03
Minor stroke	2227 (73.2)	1498 (70.5)	
TIA	817 (26.8)	628 (29.5)	
NIHSS score on admission, median (IQR)	2 (0–2)	1 (0–2)	0.04
Mean time to randomization, h	12.0 (6.5–19.4)	12.0 (6.3–19.6)	0.80
Time to randomization, n (%)			0.91
<12 h	1513 (49.7)	1060 (49.9)	
≥12 h	1531 (50.3)	1066 (50.1)	
Antiplatelet therapy, n (%)			
Aspirin only	1526 (50.1)	1060 (49.9)	0.85
Clopidogrel plus aspirin	1518 (49.9)	1066 (50.1)	
Primary end points (stroke) at 90 days	299 (9.8)	216 (10.2)	0.69

IQR indicates interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

variables were adjusted. The proportional hazards assumption for the Cox models was examined by adding a time-dependent covariate with interaction of METS/DM status and a logarithmic function of survival time in the model.

In sensitivity analyses, the relationship between METS/DM status and patient outcomes was assessed by propensity score methods. The generalized propensity score for each METS/DM category was estimated using a nonparsimonious multivariable multinomial logistic regression model. All baseline variables were included to calculate the generalized propensity score. Then, HRs with their CIs were estimated by Cox regression models with adjustment of propensity score or weighting of inverse probability of METS/DM category.[23] We also performed a similar analysis using METS (IDF) criteria in a sensitivity analysis.

A 2-sided $P<0.05$ was considered to be statistically significant. All analyses were performed with SAS software version 9.4 (SAS Institute Inc).

Results

Baseline Characteristics

Among 5170 patients, a total of 3044 patients (59%) with minor stroke or TIA were included from these 73 centers, and 2126 patients (41%) were excluded because of missing data of triglyceride and high-density lipoprotein levels. The patients included in and excluded from the study were well balanced, except for a slightly higher proportion of DM and TIA and less severity in symptom presentation in excluded patients (Table 1). For the included patients, the baseline characteristics in the clopidogrel–aspirin and aspirin-alone groups were well balanced (Table 2).

The baseline characteristics of 3044 included patients are listed in Table 3. Of the 3044 participants, the average age was 62.2 years, and 1017 (33.4%) were female. Using the CDS definition of METS, 53.2%, 17.2%, 19.8%, and 9.8% of the

Table 2. Baseline Characteristics of the Patients Included in the Analysis by Treatment Group

Characteristic	Clopidogrel Plus Aspirin (n=1518)	Aspirin Only (n=1526)	*P* Value
Age (y), median (IQR)	62.4 (54.8–71.3)	62.2 (54.6–71.0)	0.65
Female, n (%)	493 (32.5)	524 (34.3)	0.28
Medical history, n (%)			
Ischemic stroke	295 (19.4)	287 (18.8)	0.66
TIA	49 (3.2)	46 (3.0)	0.73
Myocardial infarction	23 (1.5)	32 (2.1)	0.23
Angina	54 (3.6)	41 (2.7)	0.17
Congestive heart failure	30 (2.0)	24 (1.6)	0.40
Known atrial fibrillation or flutter	28 (1.8)	29 (1.9)	0.91
Valvular heart disease	4 (0.3)	6 (0.4)	0.76
Hypertension	996 (65.6)	988 (64.7)	0.62
Diabetes mellitus	304 (20.0)	309 (20.2)	0.88
Hypercholesterolemia	165 (10.9)	153 (10.0)	0.45
Smoking status, n (%)			0.16
Never	850 (56.0)	889 (58.3)	
Current	143 (9.4)	158 (10.4)	
Previous	525 (34.6)	479 (31.4)	
Index event, n (%)			0.66
Minor stroke	1116 (73.5)	1111 (72.8)	
TIA	402 (26.5)	415 (27.2)	
NIHSS score on admission, median (IQR)	2 (0–2)	2 (0–2)	0.04
Mean time to randomization, h	11.6 (6.2–19.4)	12.0 (6.5–19.5)	0.37
Time to randomization, n (%)			0.40
<12 h	766 (50.5)	747 (49.0)	
≥12 h	752 (49.5)	779 (51.0)	

IQR indicates interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Table 3. Baseline Characteristics of Patients According to METS (Chinese Diabetes Society) Status

Characteristic	Total (n=3044)	Neither (n=1618)	METS Only (n=525)	DM Only (n=602)	Both (n=299)	*P* Value
Age (y), median (IQR)	62.2 (54.7–71.2)	63.0 (55.2–71.9)	58.7 (51.4–66.7)	64.2 (56.8–72.7)	60.2 (53.6–69.4)	<0.001
Female, n (%)	1017 (33.4)	534 (33.0)	137 (26.1)	250 (41.5)	96 (32.1)	<0.001
BMI, median (IQR)	24.5 (22.8–26.6)	23.7 (22.0–25.1)	26.7 (25.5–28.2)	24.0 (22.6–25.7)	26.7 (25.7–28.7)	<0.001
Medical history, n (%)						
Ischemic stroke	582 (19.1)	277 (17.1)	111 (21.1)	134 (22.3)	60 (20.1)	0.02
TIA	95 (3.1)	37 (2.3)	21 (4.0)	25 (4.2)	12 (4.0)	0.047
Myocardial infarction	55 (1.8)	19 (1.2)	6 (1.1)	17 (2.8)	13 (4.4)	<0.001
Angina	95 (3.1)	41 (2.5)	18 (3.4)	25 (4.2)	11 (3.7)	0.22
Congestive heart failure	54 (1.8)	25 (1.6)	9 (1.7)	14 (2.3)	6 (2.0)	0.65
Known atrial fibrillation or flutter	57 (1.9)	37 (2.3)	4 (0.8)	12 (2.0)	4 (1.3)	0.14
Valvular heart disease	10 (0.3)	8 (0.5)	0 (0.0)	1 (0.2)	1 (0.3)	0.31
Hypertension	1984 (65.2)	950 (58.7)	393 (74.9)	397 (66.0)	244 (81.6)	<0.001
DM	613 (20.1)	0 (0.00)	0 (0.00)	403 (67.0)	210 (70.2)	<0.001
Hypercholesterolemia	318 (10.5)	132 (8.2)	71 (13.5)	67 (11.1)	48 (16.1)	<0.001
Smoking status, n (%)						<0.001
Never	1739 (57.1)	910 (56.2)	264 (50.3)	396 (65.8)	169 (56.52)	
Current	301 (9. 9)	164 (10.1)	44 (8.4)	61 (10.1)	32 (10.70)	
Previous	1004 (33.0)	544 (33.6)	217 (41.3)	145 (24.1)	98 (32.78)	
Index event, n (%)						0.16
Minor stroke	2227 (73.2)	1179 (72.9)	375 (71.4)	461 (76.6)	212 (70.9)	
TIA	817 (26.8)	439 (27.1)	150 (28.6)	141 (23.4)	87 (29.1)	
NIHSS score on admission, median (IQR)	2 (0–2)	1 (0–2)	2 (0–2)	2 (1–3)	2 (0–2)	0.005
$ABCD^2$ score on admission, median (IQR)*	4 (4–5)	4 (4–5)	4 (4–5)	5 (4–6)	5 (4–6)	<0.001
Mean time to randomization, h	12.0 (6.5–19.4)	11.8 (6.5–19.0)	11.8 (6.3–19.7)	12.2 (6.50–19.8)	12.0 (6.3–18.6)	0.82
Time to randomization, n (%)						0.84
<12 h	1513 (49.7)	812 (50.2)	264 (50.3)	290 (48.2)	147 (49.2)	
≥12 h	1531 (50.3)	806 (49.8)	261 (49.7)	312 (51.8)	152 (50.8)	
Antiplatelet therapy, n (%)						0.46
Aspirin only	1526 (50.1)	793 (49.0)	278 (53.0)	302 (50.2)	153 (51.2)	
Clopidogrel plus aspirin	1518 (49.9)	825 (51.0)	247 (47.0)	300 (49.8)	146 (48.8)	

BMI indicates body mass index; DM, diabetes mellitus; IQR, interquartile range; METS, metabolic syndrome; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

*$ABCD^2$ stroke risk scores range from 0 to 7, with higher scores indicating higher risk. Data are provided only for the group of 817 patients for whom TIA was the qualifying event for inclusion in the trial.

patients met criteria for neither, METS only, DM only, and both conditions, respectively. Using the IDF criteria for METS, 44.6%, 20.8%, 18.8%, and 10.8% of the patients were diagnosed as neither, METS only, DM only, and both, respectively. Compared with patients with neither condition, patients with METS or DM had more vascular risk factors (such as higher BMI, history of ischemic stroke, TIA, hypertension, hypercholesterolemia) and higher NIHSS. Patients with DM had more history of myocardial infarction and higher $ABCD^2$ score (for TIAs only). Patients with DM only were more likely to be female and less likely to be current smokers, and those with METS only were younger (Tables 3 and 4).

As shown in Table 5, hypertension was the most prevalent metabolic component of METS (CDS), detected in 99.1% of the nondiabetic patients, followed by dyslipidemia (89.9%) and obesity (88.2%), whereas elevated fasting glucose was relatively uncommon (33.1%).

Table 4. Baseline Characteristics of Patients According to METS (International Diabetes Foundation) Status

Characteristic	Neither (n=1511)	METS Only (n=632)	DM Only (n=573)	Both (n=328)	*P* Value
Age (y), median (IQR)	62.9 (55.28–71.95)	59.7 (51.63–67.94)	64.2 (56.6–72.7)	60.4 (54.0–69.8)	<0.001
Female, n (%)	472 (31.2)	199 (31.5)	225 (39.3)	121 (36.9)	0.002
BMI, median (IQR)	23.4 (21.8–24.5)	27.0 (26.0–28.4)	23.7 (22.5–24.8)	27.0 (26.0–28.9)	<0.001
Medical history, n (%)					
Ischemic stroke	264 (17.5)	124 (19.6)	124 (21.6)	70 (21.3)	0.10
TIA	32 (2.1)	26 (4.1)	21 (3.7)	16 (4.9)	0.01
Myocardial infarction	19 (1.3)	6 (1.0)	16 (2.8)	14 (4.3)	<0.001
Angina	38 (2.5)	21 (3.3)	21 (3.7)	15 (4.6)	0.19
Congestive heart failure	21 (1.4)	13 (2.1)	11 (1.9)	9 (2.7)	0.33
Known atrial fibrillation or flutter	32 (2.1)	9 (1.4)	13 (2.3)	3 (0.9)	0.35
Valvular heart disease	8 (0.5)	0 (0.0)	1 (0.2)	1 (0.3)	0.22
Hypertension	899 (59.5)	444 (70.3)	375 (65.5)	266 (81.1)	<0.001
Diabetes mellitus	0 (0.0)	0 (0.0)	384 (67.0)	229 (69.8)	<0.001
Hypercholesterolemia	124 (8.2)	79 (12.5)	61 (10.7)	54 (16.5)	<0.001
Smoking status, n (%)					<0.001
Never	826 (54.7)	348 (55.1)	374 (65.3)	191 (58.2)	
Current	153 (10.1)	55 (8.7)	55 (9.6)	38 (11.6)	
Previous	532 (35.2)	229 (36.2)	144 (25.1)	99 (30.2)	
Index event, n (%)					0.12
Minor stroke	1099 (72.7)	455 (72.0)	441 (77.0)	232 (70.7)	
TIA	412 (27.3)	177 (28.0)	132 (23.0)	96 (29.3)	
NIHSS score on admission, median (IQR)	1 (0–2)	2 (0–2)	2 (1–3)	2 (0–2)	<0.001
$ABCD^2$ score on admission, median (IQR)*	4 (4–5)	4 (4–5)	5 (4–6)	5 (4–6)	<0.001
Mean time to randomization, h	12.0 (6.5–19.4)	11.0 (6.2–19.5)	12.0 (6.3–19.5)	12.0 (6.5–18.7)	0.64
Time to randomization, n (%)					0.53
<12 h	746 (49.4)	330 (52.2)	279 (48.7)	158 (48.2)	
≥12 h	765 (50.6)	302 (47.8)	294 (51.3)	170 (51.8)	
Antiplatelet therapy, n (%)					0.88
Aspirin only	748 (49.5)	323 (51.1)	292 (51.0)	163 (49.7)	
Clopidogrel plus aspirin	763 (50.5)	309 (48.9)	281 (49.0)	165 (50.3)	

BMI indicates body mass index; DM, diabetes mellitus; IQR, interquartile range; METS, metabolic syndrome; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

*$ABCD^2$ stroke risk scores range from 0 to 7, with higher scores indicating higher risk. Data are provided only for the group of 817 patients for whom TIA was the qualifying event for inclusion in the trial.

Association of METS Status With Risk of Recurrent Stroke

After 3 months of follow-up, there were 299 recurrent strokes, of which 293 (98.0%) were ischemic and 6 (2.0%) were hemorrhagic. There was no interaction effect of antiplatelet therapy by different METS (both criteria) and DM status for the risk of recurrent stroke (*P*=0.82 for interaction in the fully adjusted model of CDS criteria and *P*=0.97 for IDF criteria) (Tables 6 and 7).

Using the CDS criteria of METS, patients with DM only (16.1% versus 6.8%; adjusted HR 2.50, 95% CI 1.89–3.39) and both (17.1% versus 6.8%; adjusted HR 2.76, 95% CI 1.98–3.86) were associated with increased risk of recurrent stroke (FigureA). Using the IDF criteria of METS, patients with DM only (15.7% versus 6.5%; adjusted HR 2.53, 95% CI 1.89–3.37) and both (17.7% versus 6.5%; adjusted HR 3.08, 95% CI 2.22–4.28) were also associated with increased risk of recurrent stroke (FigureB). METS only did not show an increased risk of recurrent stroke in both definitions (adjusted

Table 5. Distributions of Metabolic Factors in Patients With or Without METS (Chinese Diabetes Society)

METS Category	Total	Non-METS	METS	*P* Value
Elevated blood pressure	1916 (89.4)	1396 (86.3)	520 (99.1)	<0.001
Elevated fasting glucose	241 (11.3)	67 (4.1)	174 (33.1)	<0.001
BMI ≥25	871 (40.6)	408 (25.2)	463 (88.2)	<0.001
Dyslipidemia	902 (42.1)	430 (26.6)	472 (89.9)	<0.001

BMI indicates body mass index; METS, metabolic syndrome.

HR 1.18, 95% CI 0.82–1.69 for CDS criteria; adjusted HR 1.34, 95% CI 0.96–1.87 for IDF criteria). All proportional hazards assumptions for the Cox models were met (*P*=0.11 for CDS criteria and *P*=0.23 for IDF criteria). In sensitivity analyses, we observed similar results using the propensity score method (Table 8). Similar results were observed in the secondary outcomes of composite events and ischemic stroke in both criteria.

Discussion

In this post hoc analysis of the CHANCE study, patients with DM only or concurrent METS and DM had higher recurrent stroke risk than those with neither condition; however, METS only was not associated with stroke recurrence in patients with minor stroke or TIA. There was no difference in the effect of antiplatelet treatment in reducing these events in patients with or without METS or DM.

As we hypothesized, DM only and concurrent METS and DM were significant risk factors of recurrent stroke in patients with minor stroke or TIA in present study. Different from what we expected, METS showed only a trend of increased risk of recurrent stroke and did not reach statistical significance. Even with medical intervention, minor stroke and TIA still led to a high risk of recurrence that could raise the disability rate.[14,15] METS was frequently found in patients with minor

Table 6. Risk of Stroke at 3 Months for Clopidogrel–Aspirin Combined Therapy Comparing With Aspirin Alone by METS (Chinese Diabetes Society) Status

	Aspirin		Clopidogrel–Aspirin		Model 1*			Model 2†		
METS Status	n	Events, n (%)	n	Events, n (%)	Adjusted HR (95% CI)	*P* Value	*P* Value for Interaction	Adjusted HR (95% CI)	*P* Value	*P* Value for Interaction
Neither	793	63 (7.9)	825	47 (5.7)	0.71 (0.49–1.04)	0.08	0.87	0.70 (0.48–1.02)	0.07	0.82
METS only	278	28 (10.1)	247	13 (5.3)	0.52 (0.27–1.00)	0.050		0.48 (0.24–0.93)	0.03	
DM only	302	59 (19.5)	300	38 (12.7)	0.63 (0.42–0.94)	0.03		0.60 (0.40–0.90)	0.01	
Both	153	31 (20.3)	146	20 (13.7)	0.67 (0.38–1.18)	0.16		0.71 (0.40–1.27)	0.25	

DM indicates diabetes mellitus; HR, hazard ratio; METS, metabolic syndrome.
*Model 1: adjusted for age and sex.
†Model 2: adjusted for age, sex, history of ischemic stroke, transient ischemic attack, myocardial infarction, angina, congestive heart failure, known atrial fibrillation or flutter, valvular heart disease, smoking status, index event and National Institutes of Health Stroke Scale on admission, and time to randomization.

Table 7. Risk of Stroke at 3 Months for Clopidogrel–Aspirin Combined Therapy Comparing With Aspirin Alone by METS (International Diabetes Foundation) Status

	Aspirin		Clopidogrel–Aspirin		Model 1*			Model 2†		
METS Status	n	Events, n (%)	N	Events, n (%)	Adjusted HR (95% CI)	*P* Value	*P* Value for Interaction	Adjusted HR (95% CI)	*P* Value	*P* Value for Interaction
Neither	748	59 (7.9)	763	39 (5.1)	0.65 (0.43–0.97)	0.04	0.98	0.66 (0.44–0.98)	0.04	0.97
METS only	323	32 (9.9)	309	21 (6.8)	0.67 (0.39–1.17)	0.16		0.63 (0.36–1.10)	0.11	
DM only	292	56 (19.2)	281	34 (12.1)	0.60 (0.39–0.92)	0.02		0.58 (0.38–0.90)	0.01	
Both	163	34 (20.9)	165	24 (14.5)	0.66 (0.39–1.12)	0.13		0.67 (0.39–1.15)	0.14	

DM indicates diabetes mellitus; HR, hazard ratio; METS, metabolic syndrome.
*Model 1: adjusted for age and sex.
†Model 2: adjusted for age, sex, history of ischemic stroke, transient ischemic attack, myocardial infarction, angina, congestive heart failure, known atrial fibrillation or flutter, valvular heart disease, smoking status, index event and National Institutes of Health Stroke Scale on admission, and time to randomization.

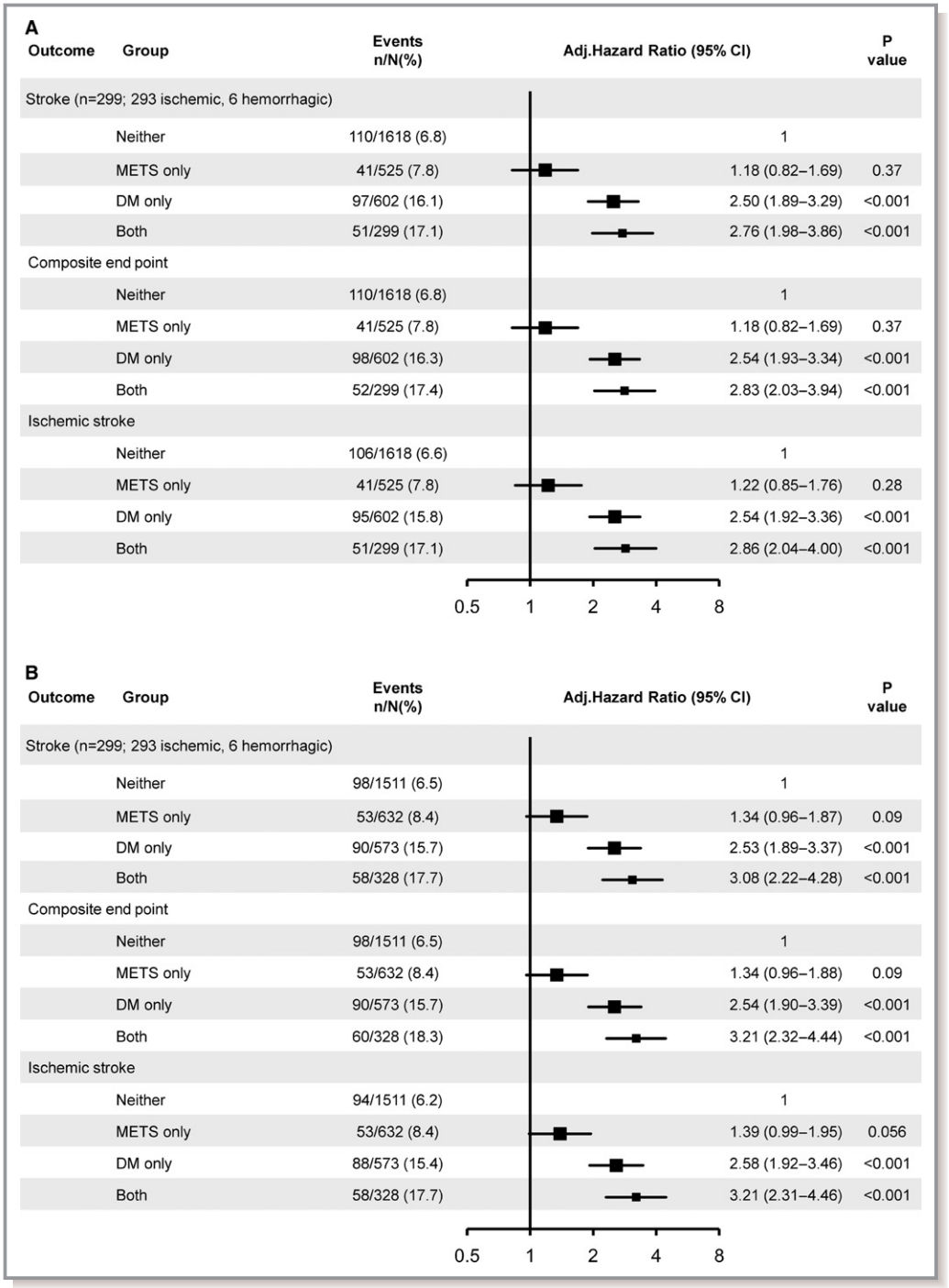

Figure. Adjusted hazard ratios of stroke recurrence according to METS (CDS and IDF) and DM status. A, METS defined by CDS. B, METS defined by IDF. Adjusted for age, sex, history of ischemic stroke, transient ischemic attack, myocardial infarction, angina, congestive heart failure, known atrial fibrillation or flutter, valvular heart disease, smoking status, index event and National Institutes of Health Stroke Scale on admission, time to randomization, and antiplatelet therapy. CDS indicates Chinese Diabetes Society; DM, diabetes mellitus; IDF, International Diabetes Foundation; METS, metabolic syndrome.

stroke and TIA.[5] It was reported that the prevalence of METS in different racial populations may be between 10% and 84%.[4,5] Our study added to the evidence that concurrent METS and DM was associated with an increased risk of new stroke in patients with minor stroke and TIA. It may be important to highlight early identification of patients at high risk of developing DM (eg, patients with METS) to predict the prognosis of patients with minor stroke or TIAs.

Table 8. Sensitivity Analysis of Hazard Ratios Estimated by Propensity Score Method

METS Definition	Outcome	METS Status	Propensity Score Regression Adjustment		Propensity Score Weighting	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
CDS	Stroke	Neither	1		1	
		METS only	0.99 (0.65–1.52)	0.97	1.02 (0.70–1.49)	0.92
		DM only	3.66 (2.61–5.14)	<0.001	3.09 (2.40–3.99)	<0.001
		Both	3.69 (2.32–5.86)	<0.001	2.88 (2.09–3.97)	<0.001
	Composite end point	Neither	1		1	
		METS only	0.99 (0.65–1.52)	0.99	1.02 (0.70–1.49)	0.92
		DM only	3.70 (2.64–5.18)	<0.001	3.10 (2.41–4.00)	<0.001
		Both	3.87 (2.45–6.12)	<0.001	2.96 (2.15–4.07)	<0.001
	Ischemic stroke	Neither	1		1	
		METS only	1.01 (0.66–1.55)	0.95	1.05 (0.72–1.53)	0.80
		DM only	3.74 (2.66–5.27)	<0.001	3.14 (2.43–4.06)	<0.001
		Both	3.82 (2.40–6.08)	<0.001	2.96 (2.14–4.08)	<0.001
IDF	Stroke	Neither	1		1	
		METS only	1.21 (0.76–1.94)	0.42	0.91 (0.61–1.36)	0.64
		DM only	3.80 (2.68–5.38)	<0.001	2.54 (2.09–3.10)	<0.001
		Both	4.76 (3.04–7.46)	<0.001	2.53 (1.87–3.44)	<0.001
	Composite end point	Neither	1		1	
		METS only	1.21 (0.76–1.94)	0.42	0.91 (0.61–1.36)	0.64
		DM only	3.80 (2.68–5.38)	<0.001	2.54 (2.09–3.10)	<0.001
		Both	5.02 (3.23–7.82)	<0.001	2.61 (1.93–3.54)	<0.001
	Ischemic stroke	Neither	1		1	
		METS only	1.25 (0.78–2.00)	0.36	0.92 (0.62–1.38)	0.69
		DM only	3.88 (2.73–5.52)	<0.001	2.35 (1.91–2.88)	<0.001
		Both	4.96 (3.16–7.79)	<0.001	2.57 (1.89–3.49)	<0.001

CDS indicates Chinese Diabetes Society; DM, diabetes mellitus; HR, hazard ratio; IDF, International Diabetes Foundation; METS, metabolic syndrome.

Patients with METS only did not have significantly higher risk of any recurrent stroke than those with neither condition. This finding might be associated with the fact that the definition of METS in our study did not include patients with DM. A previous study showed that METS likely played a crucial role in the development of recurrent ischemic stroke in patients with ischemic stroke or TIA.[10] The definition of METS in this study included DM; however, results of substudies of the SPARCL (Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial and the SPS3 (Secondary Prevention of Small Subcortical Strokes) study demonstrated that patients with METS only were not at an increased risk of recurrent stroke.[9,17] Unlike previous studies, the definition of METS in these 2 studies did not include DM, similar to our present study. Consequently, the definition of METS including DM or not might be a factor that influenced the relationship between METS and risk of stroke recurrence.

Several organizations formulated different criteria for METS diagnosis, but all showed 4 main categories of metabolic abnormalities: atherogenic dyslipidemia, increased blood pressure, abnormal glucose regulation, and obesity.[2,3] Among these factors, abnormal glucose regulation was an established risk factors of recurrent stroke in patients with stroke or TIA.[24] The physiology underlying the elevated risk of recurrent ischemic stroke in diabetic METS may be that it was a recognized risk factor of intracranial atherosclerosis.[25,26] Previous studies also reported that diabetic METS was associated with recurrent ischemic stroke in patients with large-vessel infarction or lacunar stroke,[10,17] which we were not able to examine in our study. Patients enrolled in the CHANCE trial primarily were minor stroke patients with stroke subtypes of large-artery atherosclerosis and small-vessel occlusion.[18,20] Therefore, patients with concurrent METS and DM had higher risk of recurrent stroke than

those with nondiabetic METS (METS only) and neither in our study.

In this post hoc analysis, we applied BMI rather than WC for definition of abdominal fat based on a previous study that showed WC and BMI can both be used in the prediction of abdominal visceral obesity for Chinese adults,[1] and the BMI cutoff for abdominal obesity was ≥25.[27–29] Even so, this still might be a bit inaccurate for the diagnosis of METS (IDF). Nevertheless, it is unlikely that using BMI as a proxy would alter the results because similar patients were diagnosed with METS regardless of whether BMI or WC was used.[30] Large epidemiologic studies have shown a high correlation between BMI and WC.[31] Furthermore, the association between obesity and insulin resistance was similar regardless of whether WC or BMI was used for obesity diagnosis.[32] Using METS with the IDF definition in a sensitivity analysis in our study, the results also demonstrated similar results.

Our study has some limitations. First, data on 2-hour plasma glucose, which is an item for assessment of METS (CDS), were not available in the CHANCE trial; therefore, we may have missed some patients who could be diagnosed as having METS. Second, only Chinese patients were enrolled in our study; further evaluation of METS in other races might be required. Third, the characteristics of minor stroke and TIA patients enrolled in this study were different from those of a typical minor stroke or TIA sample from population-based cohorts. This study enrolled only minor stroke patients with noncardiogenic embolism and high-risk TIA patients ($ABCD^2$ scores ≥4), which may have resulted in high events rates. Furthermore, large-scale population-based cohorts assessing the association of METS and recurrent stroke are needed to confirm this finding. Finally, duration of DM was not recorded in the CHANCE trial. The duration of DM might be associated with the prognosis of patients with stroke.[33]

Conclusions

The results from our study showed that patients with DM only or concurrent METS and DM were associated with an elevated risk of stroke among patients with minor ischemic stroke and TIA. Nondiabetic METS (METS only) was not observed to be associated with stroke recurrence in patients with minor stroke or TIA.

Appendix

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Disclosures

None.

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