ARTICLE

High-sensitive C-reactive protein and dual antiplatelet in intracranial arterial stenosis

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Abstract

Objective

To determine the relationship of high-sensitive C-reactive protein (hsCRP) and the efficacy and safety of dual antiplatelet therapy in patients with and without intracranial arterial stenosis (ICAS) in the Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial.

Methods

A subgroup of 807 patients with both magnetic resonance angiography images and hsCRP measurement was analyzed. Cox proportional hazards models were used to assess the interaction of hsCRP levels with the effects of dual and single antiplatelet therapy.

Results

A total of 358 (44.4%) patients had ICAS and 449 (55.6%) did not. The proportion of patients with elevated hsCRP levels was higher in the ICAS group than in the non-ICAS group (40.2% vs 30.1%, $p = 0.003$). There was significant interaction between hsCRP and the 2 antiplatelet therapy groups in their effects on recurrent stroke after adjustment for confounding factors in the patients with ICAS ($p = 0.012$), but not in those without ($p = 0.256$). Compared with aspirin alone, clopidogrel plus aspirin significantly reduced the risk of recurrent stroke only in the patients with ICAS and nonelevated hsCRP levels (adjusted hazard ratio 0.27; 95% confidence interval 0.11 to 0.69; $p = 0.006$). Similar results were observed for composite vascular events. No significant difference in bleeding was found.

Conclusions

Presence of both ICAS and nonelevated hsCRP levels may predict better response to dual antiplatelet therapy in reducing new stroke and composite vascular events in minor stroke or high-risk TIA patients. Further large-scale randomized and controlled clinical trials are needed to confirm this finding.

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Glossary

CHANCE = Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events; **CI** = confidence interval; **CRP** = C-reactive protein; **hsCRP** = high-sensitive C-reactive protein; **HR** = hazard ratio; **ICAS** = intracranial arterial stenosis; **MRA** = magnetic resonance angiography.

Higher rate of subsequent stroke has been reported in stroke patients with intracranial arterial stenosis (ICAS) despite treatment with antiplatelet medications,[1,2] which might be partly due to underlying inflammation.[3,4] The role of inflammation in pathogenesis of stroke has been addressed before.[5,6] Furthermore, the burden of vascular inflammation is suggested to be related to various mechanisms leading to thrombosis that are affected differently by antiplatelet treatment.[7–9] High-sensitive C-reactive protein (hsCRP) is a widely acknowledged inflammatory biomarker associated with recurrent vascular events,[10,11] and reflects intracranial atherosclerotic burden.[12] Moreover, it is indicated that hsCRP is associated with patient response to antiplatelet therapy[10,13,14] and could be a valuable marker for demarcating patients most likely to benefit from antiplatelet therapy in the primary and secondary prevention of cardiovascular disease.[7–9] However, among patients after stroke, the only 2 multicenter studies, which lacked consideration of neuroimaging features, yielded negative results regarding the role of C-reactive protein (CRP) in choosing antiplatelet therapy.[11,15]

The Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial found early and intensive antiplatelet treatment with clopidogrel plus aspirin was superior to aspirin alone in reducing recurrent stroke among patients with acute minor stroke or high-risk TIA.[16] We sought to investigate the relationship of hsCRP and the effects of dual and single antiplatelet therapy in patients with and without ICAS using the CHANCE trial cohort.

Methods

Study design

Details about the study design and methods of the CHANCE trial have been described.[16] Briefly, it was a randomized, double-blind, placebo-controlled clinical trial conducted in China, enrolling patients with acute minor stroke or TIA within 24 hours of symptom onset, to test the hypothesis that treatment with clopidogrel plus aspirin would reduce the 90-day risk of recurrent stroke as compared with aspirin alone. Patients enrolled with TIA were required to be at moderate to high risk of stroke (ABCD2 score of ≥4) and patients enrolled with minor stroke were required to have a score of 3 or less on the NIH Stroke Scale at the time of randomization. All eligible patients were randomized to either of the 2 antiplatelet treatment plans: (1) clopidogrel combined with aspirin for the first 21 days and clopidogrel alone on days 22 through 90; (2) placebo plus aspirin for 90 days.

Standard protocol approvals, registrations, and patient consents

All included patients or their legal proxies provided written informed consent. The CHANCE trial protocol was approved by the ethics committee at each study center.

The unique identifier was NCT00979589.

Efficacy and safety outcomes

The primary efficacy outcome was a new stroke (ischemic or hemorrhagic) within 90 days and secondary efficacy outcome included composite vascular events (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death).[16] The safety outcome was any bleeding at 90 days according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries definition.[17] A central adjudication committee that was blinded to the study group assignments confirmed all reported efficacy and safety outcomes. Details about the definitions of all efficacy and safety outcomes have been described.[16]

Image analysis

The method of the imaging subgroup analysis has been described before.[1] Briefly, all eligible MRI of individual patients were collected from centers participating in the imaging subgroup analysis.[1] The following sequences were required in digital format for each patient: T1-weighted imaging, T2-weighted imaging, diffusion-weighted imaging, and 3D time-of-flight magnetic resonance angiography (MRA). Patients without any of the aforementioned sequences of baseline MRI examinations were excluded from the imaging subgroup. All images were centrally read by 2 readers (X. Zou and J.J.), who were blinded to patient information.[1] ICAS was determined by presence of 50%–99% stenosis according to Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial criteria[18] or occlusion of at least one of the following arterial segments: intracranial portion of internal carotid arteries, middle cerebral arteries (M1/M2), intracranial portion of vertebral arteries, and basilar artery.[1] The intrarater and interrater reliabilities of determining ICAS on MRA images at the reading center were 0.793 and 0.815, respectively.[19]

Measurement of hsCRP

As reported before, venous blood samples were obtained from fasting patients 24 ± 12 hours after randomization. Serum specimens were extracted and stored at −80°C without freezing and thawing circle before testing. hsCRP was centrally measured on a Roche Modular P800 analyzer (Basel, Switzerland) using a turbidimetric immunoassay method (Ji'en Technique Co. Ltd.; Shanghai, China) in the clinical

laboratory in Tiantan hospital by laboratory personnel blinded to the clinical data. The intra-assay and interassay coefficients of variation were 2.5% and 2.0%, respectively.[11]

Statistical analysis

The participants included in the current subanalysis of the CHANCE trial were classified into 2 subgroups, ICAS and non-ICAS groups, by presence or absence of ICAS. In each subgroup, baseline characteristics and the rates of efficacy and safety outcomes at 90 days were compared according to hsCRP levels, which were stratified by using relative risk category recommended by the Centers for Disease Control and Prevention and American Heart Association (low–medium risk, 0–3 mg/L; and high risk, >3 mg/L), originally recommended for the risk assessment of cardiovascular disease.[20] Proportions were used for categorical variables. Medians with interquartile ranges were used for continuous variables with skewed distribution. Categorical variables were compared with χ^2 statistics or Fisher exact test as appropriate. Continuous variables were compared by Wilcoxon rank sum tests.

The interactions of hsCRP levels with randomized antiplatelet therapy on the efficacy and safety outcomes were investigated with the use of crude and multivariable Cox proportional hazards models. Cox proportional hazards regression was also performed to analyze the difference between dual and single antiplatelet therapy in the rates of efficacy and safety outcomes. In the multivariable model, demographic variables of age and sex, behavioral risk factors of body mass index (the weight in kilograms divided by the square of the height in meters) and cigarette smoking, and clinical confounding factor of medical history of hypertension, diabetes mellitus, hypercholesterolemia, ischemic stroke, TIA, myocardial infarction, angina, congestive heart failure, known atrial fibrillation or flutter, and valvular heart disease were included. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. A 2-sided p value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with SAS software, version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Baseline characteristics

Of the 5,170 patients recruited to the CHANCE trial, 1,089 patients underwent baseline MRI examinations with all the sequences as required and 3,044 patients provided serum specimens. In total, 807 consecutive patients from 31 centers with both required MRIs and blood samples were included in this subgroup analysis. There was no missing baseline variable of interest. Baseline characteristics of patients included and those not included in this subgroup analysis were basically similar, except that patients included in this subgroup analysis had slightly lower body mass index, fewer of them had prior ischemic stroke, and more of them had minor stroke as a qualifying event and received antihypertensive agents and lipid-lowering agents during a 90-day follow-up period (table 1).

Among the patients included in this subanalysis, patients with elevated levels of hsCRP were older, and more of them had prior hypertension and minor stroke as a qualifying event (table 2). Of the 807 patients, 358 (44.4%) had ICAS, while 449 (55.6%) did not. This prevalence of ICAS was almost identical with that of the recent large, multicenter study in China.[19] The proportion of patients with elevated hsCRP levels was higher in the ICAS group than that in the non-ICAS group (40.2% vs 30.1%, $p = 0.003$). The median hsCRP in the ICAS group and non-ICAS group were 2.2 mg/L and 1.7 mg/L, respectively ($p = 0.005$). In the ICAS group, more patients with elevated levels of hsCRP had prior hypertension compared with those with nonelevated hsCRP. In the non-ICAS group, patients with elevated levels of hsCRP were older and were more likely to have prior hypertension and lipid-lowering agents during follow-up period compared with those without elevated hsCRP levels (table 2). Other baseline characteristics were not significantly different between those with and without elevated levels of hsCRP in the ICAS and non-ICAS groups.

Interaction of hsCRP levels with antiplatelet therapy on efficacy outcomes

The primary efficacy outcome of recurrent stroke at 90 days occurred in 73 (9.0%) patients in the current subgroup analysis. Overall, the rate of recurrent stroke tended to increase in patients with elevated hsCRP levels, irrespective of the existence of ICAS (table 2).

Among the patients with ICAS, there was significant interaction between hsCRP and the 2 antiplatelet therapy groups in their effect on recurrent stroke.

Such interaction remained after adjustment for other confounding factors (table 3). Clopidogrel plus aspirin significantly reduced the risk of recurrent stroke (adjusted HR 0.27; 95% CI 0.11–0.69; $p = 0.006$) compared with aspirin alone in the patients without elevated hsCRP levels. However, such extra benefit of dual antiplatelet treatment was not observed in the patients with elevated hsCRP levels (table 3). Furthermore, since more patients with elevated levels of hsCRP had prior hypertension (table 2), and some lipid-lowering agents, such as statin, were shown to have anti-inflammation effect,[21] use of antihypertensive agents and lipid-lowering agents during 90-day follow-up period was further adjusted when analyzing the interaction of hsCRP with effects of randomized antiplatelet therapy. Such significant interaction persisted ($p = 0.014$). Similar results were found for the outcome of composite vascular events (table 3).

In the patients without ICAS, no significant interactions between hsCRP and antiplatelet therapy regimen on recurrent stroke and combined vascular events were observed (table 3). There was no significant difference in the effects of

Table 1 Baseline characteristics and outcomes of patients included vs not included in this subanalysis of the Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial

	Patients included (n = 807)	All other patients (n = 4,363)	*p* Value
Age, y, median (IQR)	63 (55–72)	62 (55–71)	0.083
Female, n (%)	282 (34.94)	1,468 (33.65)	0.491
BMI, median (IQR)	24 (22–26)	24 (23–26)	0.044[a]
Medical history, n (%)			
Ischemic stroke	140 (17.35)	893 (20.47)	0.044[a]
TIA	26 (3.22)	148 (3.39)	0.915
Myocardial infarction	14 (1.73)	82 (1.88)	0.888
Known atrial fibrillation or flutter	18 (2.23)	78 (1.79)	0.394
Hypercholesterolemia	105 (13.01)	468 (10.73)	0.059
Hypertension	527 (65.30)	2,872 (65.83)	0.778
Diabetes mellitus	155 (19.21)	938 (21.50)	0.146
Current or previous smoking, n (%)	343 (42.50)	1,878 (43.04)	0.786
Qualifying event, n (%)			0.045[a]
TIA	202 (25.03)	1,243 (28.49)	
Minor stroke	605 (74.97)	3,120 (71.51)	
Treatment			1.000
Aspirin	404 (50.06)	2,182 (50.01)	
Aspirin/clopidogrel	403 (49.94)	2,181 (49.99)	
Medications during follow-up			
Antihypertensive agents	359 (44.65)	1,455 (33.60)	<0.0001[a]
Hypoglycemic agents	110 (13.68)	546 (12.61)	0.421
Lipid-lowering agents	423 (52.61)	1,748 (40.37)	<0.0001[a]
Outcomes			
Stroke	73 (9.05)	442 (10.13)	0.371
Combined vascular events[b]	75 (9.29)	448 (10.27)	0.446
Bleeding	17 (2.11)	84 (1.93)	0.680

Abbreviations: BMI = body mass index (the weight in kilograms divided by the square of the height in meters); IQR = interquartile range.
[a] $p < 0.05$ compared with patients not included in this study.
[b] Combined vascular events were composed of ischemic stroke, hemorrhagic stroke, myocardial infarction, and vascular death.

clopidogrel plus aspirin and aspirin alone on the recurrent stroke and combined vascular events, regardless of hsCRP levels (table 3).

Interaction of hsCRP levels with antiplatelet therapy on safety outcome

The rate of any bleeding event at 90 days was low and not significantly different according to the levels of hsCRP (table 2).

There was no statistically significant evidence for the interaction between hsCRP levels and treatment allocation on any bleeding event, regardless of presence of ICAS (table 3). Clopidogrel plus aspirin did not increase the rate of hemorrhage compared with aspirin alone among patients with elevated and nonelevated hsCRP levels (table 3).

Discussion

In this subgroup analysis of the CHANCE trial, we found the role of hsCRP in discriminating the efficacy of dual and single antiplatelet therapy in patients with minor stroke or high-risk TIA only in the patients with ICAS, but not in those without.

Table 2 Characteristics of patients stratified by high-sensitive C-reactive protein (hsCRP) levels and presence of intracranial arterial stenosis (ICAS)

	All patients, n = 807			With ICAS, n = 358 (44.4%)			Without ICAS, n = 449 (55.6%)		
	hsCRP ≥3 mg/L, n = 279 (40.2%)	hsCRP <3 mg/L, n = 528 (59.8%)	*p* Value	hsCRP ≥3 mg/L, n = 144 (40.2%)	hsCRP <3 mg/L, n = 214 (59.8%)	*p* Value	hsCRP ≥3 mg/L, n = 135 (30.1%)	hsCRP <3 mg/L, n = 314 (69.9%)	*p* Value
Age, y, median (IQR)	66 (57–73)	62 (54–71)	0.001	67 (59–73)	66 (57–74)	0.268	63 (54–73)	60 (53–69)	0.009
Female, n (%)	94 (33.7)	188 (35.6)	0.641	50 (34.7)	86 (40.2)	0.319	44 (32.6)	102 (32.5)	1.0
BMI, median (IQR)	25 (22–27)	24 (22–26)	0.109	24 (22–27)	24 (22–26)	0.752	25 (22–27)	24 (22–26)	0.062
Medical history, n (%)									
Ischemic stroke	55 (19.7)	85 (16.1)	0.205	36 (25.0)	43 (20.1)	0.299	19 (14.1)	42 (13.4)	0.881
TIA	12 (4.3)	14 (2.7)	0.214	10 (6.9)	7 (3.3)	0.131	2 (1.5)	7 (2.2)	0.730
Myocardial infarction	6 (2.2)	8 (1.5)	0.574	4 (2.8)	6 (2.8)	0.988	2 (1.5)	2 (0.6)	0.587
Known atrial fibrillation or flutter	6 (2.2)	12 (2.3)	1.000	1 (0.7)	7 (3.3)	0.106	5 (3.7)	5 (1.6)	0.176
Hypercholesterolemia	38 (13.6)	67 (12.7)	0.742	19 (13.2)	28 (13.1)	1.0	19 (14.1)	39 (12.4)	0.647
Hypertension	209 (74.9)	318 (60.2)	<0.001	113 (78.5)	131 (61.2)	0.001	96 (71.1)	187 (59.6)	0.025
Diabetes mellitus	54 (19.4)	101 (19.1)	0.925	33 (22.9)	54 (25.2)	0.706	21 (15.6)	47 (15.0)	0.886
Current or previous smoking, n (%)	123 (44.1)	220 (41.7)	0.549	61 (42.4)	86 (40.2)	0.743	62 (45.9)	134 (42.7)	0.535
Qualifying event, n (%)									
TIA	58 (20.8)	144 (27.3)	0.049	28 (19.4)	55 (25.7)	0.202	30 (22.2)	89 (28.3)	0.200
Minor stroke	221 (79.2)	384 (72.7)	0.049	116 (80.6)	159 (74.3)	0.202	105 (77.8)	225 (71.7)	0.200
Treatment									
Aspirin	144 (51.6)	260 (49.2)	0.554	77 (53.5)	106 (49.5)	0.518	67 (49.6)	154 (49.0)	0.918
Aspirin/clopidogrel	135 (48.4)	268 (50.8)	0.554	67 (46.5)	108 (50.5)	0.518	68 (50.4)	160 (51.0)	0.918
Medications during follow-up									
Antihypertensive agents	130 (46.8)	229 (43.5)	0.412	67 (46.5)	105 (49.1)	0.667	63 (47.0)	124 (39.7)	0.174
Hypoglycemic agents	41 (14.7)	69 (13.1)	0.519	25 (17.4)	30 (14.0)	0.455	16 (11.9)	39 (12.5)	1.0
Lipid-lowering agents	157 (56.5)	266 (50.6)	0.119	76 (52.8)	116 (54.2)	0.829	81 (60.4)	150 (48.1)	0.018
Outcomes									
Stroke	31 (11.1)	42 (8.0)	0.156	19 (13.2)	26 (12.1)	0.871	12 (8.9)	16 (5.1)	0.139
Combined vascular events[a]	33 (11.8)	42 (8.0)	0.075	19 (13.2)	26 (12.1)	0.871	14 (10.4)	16 (5.1)	0.061
Bleeding	5 (1.8)	12 (2.3)	0.799	2 (1.4)	5 (2.3)	0.706	3 (2.2)	7 (2.2)	1.000

Abbreviations: BMI = body mass index (the weight in kilograms divided by the square of the height in meters); IQR = interquartile range.
[a] Combined vascular events were composed of ischemic stroke, hemorrhagic stroke, myocardial infarction, and vascular death.

With respect to the patients with both ICAS and nonelevated hsCRP levels, clopidogrel adding to aspirin reduced the risk of recurrent stroke by 73% compared with those on aspirin alone, without increased risk of hemorrhage.

In clinical practice, there is a substantial interest to find a simple and readily available marker, such as serum biomarkers, to predict patients' response to the preventive measures. A recent large trial using rosuvastatin by measuring hsCRP as a determinant in otherwise low-risk patients has illustrated such proof of concept.[22] As for antiplatelet treatment, an early observational study showed high CRP level was related to reduction in a first myocardial infarction by the use of aspirin.[7] Then subsequent studies including patients undergoing

Table 3 Effect of clopidogrel plus aspirin compared with aspirin on efficacy and safety outcomes stratified by high-sensitive C-reactive protein (hsCRP) levels and presence of intracranial arterial stenosis (ICAS)

Outcomes	Asprin	Asprin_clopidogrel	Unadjusted HR	Interaction, *p*	Adjusted HR[a]	Interaction, *p*[a]
Stroke						
With ICAS						
hsCRP <3 mg/L	18 (17.0)	8 (7.4)	0.41 (0.18–0.95)	0.029	0.27 (0.11–0.69)	0.012
hsCRP ≥3 mg/L	8 (10.4)	11 (16.4)	1.63 (0.65–4.05)		1.65 (0.63–4.36)	
Without ICAS						
hsCRP <3 mg/L	7 (4.5)	9 (5.6)	1.25 (0.47–3.35)	0.248	1.43 (0.51–4.00)	0.256
hsCRP ≥3 mg/L	8 (11.9)	4 (5.9)	0.50 (0.15–1.66)		0.42 (0.10–1.72)	
Combined vascular event[b]						
With ICAS						
hsCRP <3 mg/L	18 (17.0)	8 (7.4)	0.41 (0.18–0.95)	0.029	0.27 (0.11–0.69)	0.012
hsCRP ≥3 mg/L	8 (10.4)	11 (16.4)	1.63 (0.65–4.05)		1.65 (0.63–4.36)	
Without ICAS						
hsCRP <3 mg/L	7 (4.5)	9 (5.6)	1.25 (0.47–3.35)	0.137	1.43 (0.51–4.00)	0.132
hsCRP ≥3 mg/L	10 (14.9)	4 (5.9)	0.39 (0.12–1.25)		0.31 (0.08–1.15)	
Bleeding						
With ICAS						
hsCRP <3 mg/L	1 (0.9)	4 (3.7)	2.90 (0.30–27.93)	0.994	—	0.998
hsCRP ≥3 mg/L	0 (0)	2 (3)	—		—	
Without ICAS						
hsCRP <3 mg/L	3 (1.9)	4 (2.5)	1.29 (0.29–5.75)	0.507	1.50 (0.28–7.96)	0.500
hsCRP ≥3 mg/L	2 (3)	1 (1.5)	0.49 (0.05–5.43)		—	

Abbreviation: HR = hazard ratio.
[a] Adjusted for age, sex, body mass index, current or previous smoking, medical history of hypertension, diabetes mellitus, hypercholesterolemia, ischemic stroke, TIA, myocardial infarction, angina, congestive heart failure, known atrial fibrillation or flutter, valvular heart disease, and qualifying event.
[b] Combined vascular events were composed of ischemic stroke, hemorrhagic stroke, myocardial infarction, and vascular death.

percutaneous coronary intervention indicated the clinical benefit of dual antiplatelet therapy was greater in those with increased CRP levels.[8,9] There was relatively little evidence for the effect of CRP on the response to antiplatelet therapy among the patients with stroke. In a laboratory study including only 133 patients with acute ischemic stroke, CRP level was correlated with platelet reactivity.[23] In terms of clinical outcome, hsCRP predicted failure of antiplatelet treatment in stroke patients, but not response to dual antiplatelet therapy in 2 large intervention studies.[11,15] The reasons for these negative results are unknown, but negligence of certain key confounding factors, such as anatomical presentation of intracranial arterial diseases, should merit our attention. Atherosclerotic stenosis has been regarded as an inflammatory process and is a critical cause for recurrent vascular events.[1,24] A recent study recommended initiating urgent and intensive antiplatelet treatment in these patients.[25] However, inflammation has been suggested to be a common cause leading to poor response to antiplatelet therapy.[4,26] In our study, the addition of ICAS to hsCRP might improve resolution capability of the degree of vascular inflammation. The present study shed some light on how hsCRP measurement may be used by integration with neuroimaging tools in modifying future secondary preventive antiplatelet therapy for the patients with stroke.

On the other hand, we found that the protective effect of dual antiplatelet therapy was more apparent in ICAS patients without elevated hsCRP, which was consistent with the previous laboratory and clinical findings that nonelevated CRP levels were related to better response to antiplatelet therapy.[13,27] Indeed, early study have shown that inflammation could have a prothrombotic effect through increased platelet reactivity or reduced fibrinolysis, and eventually lead to incomplete inhibition of platelet function by antiplatelet therapy.[28,29] However, some previous cardiovascular research

proposed that increased CRP levels predicted greater benefit from antiplatelet treatment.[7–9] The reasons for this controversy were unclear. The differences in participants and the anatomy and function between coronary and intracranial arteries may be one side. The other explanation might be difference in vascular inflammation burden in this research. In the cardiovascular studies, either healthy participants or coronary artery disease patients with reduction in angiographic stenosis by percutaneous coronary intervention were included, which might represent a status of less vascular inflammatory burden. In our study, the presence of both ICAS and elevated hsCRP levels may suggest the settings of high-grade vascular inflammation, which might not be effectively alleviated by the dual antiplatelet therapy regimen of the CHANCE trial. However, because of the observational design and absence of systematic quantitative measures of specific vascular inflammation in our study, this hypothesis needs further validation.

Since hsCRP is an acute-phase reactant that increases with any infection or tissue injury, it is difficult to determine whether the elevation of hsCRP in our study is part of an acute inflammatory reaction to ischemia or a marker of chronic atherothrombotic process. However, we previously found hsCRP was not simply a short-term but also a long-term marker of risk of recurrent vascular events, even for 1 year later, and this association was not modified by the severity of stroke.[11] Moreover, the proportion of patients with elevated hsCRP levels was apparently higher in the ICAS group than in the non-ICAS group in the present study. These findings to some extent suggest the effects of hsCRP were probably mediated through a chronic inflammatory process rather than some acute-phase reactions or undetected acute illness at baseline.

There were some limitations to our study. First, it included only approximately 15% of patients with both MRIs and blood samples in the CHANCE trial. Limited statistic power could not be completely avoided. Second, digital subtraction angiography, the gold standard of diagnosis of ICAS, was not performed in our study. Though MRA is noninvasive, easily accessible, and therefore more suitable for large-scale studies compared with digital subtraction angiography, patients might have been misreported to have ICAS by MRA.[30] Third, we collected fasting venous blood when patients had already taken the first dosage of antiplatelet drug. Some studies have investigated the effect of antiplatelet therapy on hsCRP. One recent large trial randomizing patients to clopidogrel plus aspirin or placebo plus aspirin found that clopidogrel had no effect on hsCRP compared with placebo,[31] which was consistent with other previous studies.[32,33] In our study, all patients received antiplatelet therapy and the distribution of hsCRP levels was similar between the 2 antiplatelet therapy groups. Therefore, we supposed that the administration of first dosage of antiplatelet drug might rarely affect the effect of hsCRP in our study. Fourth, only 1 point measurement of hsCRP was available. A dynamic evaluation could be more informative. However, our results might promote further investigation to verify the application of this simple and economic laboratory measure in adjusting secondary preventive antiplatelet treatment in high-risk patients for recurrent stroke.

The current subgroup analysis of the CHANCE trial showed that in the patients with acute minor stroke or high-risk TIA, presence of both ICAS and nonelevated hsCRP levels may predict better response to clopidogrel plus aspirin therapy in reducing new stroke and composite vascular events compared with aspirin alone. Further large-scale randomized and controlled clinical trials are needed to confirm this finding.

Author contributions

Dr. Jiejie Li: study concept and design, acquisition, analysis and interpretation of data, drafting of the manuscript. Dr. Anxin Wang: analysis and interpretation of data. Dr. Xingquan Zhao: acquisition of data, study supervision or coordination. Dr. Liping Liu: acquisition of data, study supervision or coordination. Dr. Xia Meng: acquisition of data, study supervision or coordination. Jinxi Lin: study supervision or coordination. Dr. Jing Jing: acquisition and interpretation of data. Dr. Xinying Zou: acquisition and interpretation of data. Dr. Yilong Wang: study concept and design, study supervision or coordination. Dr. Yongjun Wang: study concept and design, obtaining funding, study supervision or coordination.

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Disclosure

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FULL-LENGTH ARTICLE NPub.org/54s3tc

High-sensitive C-reactive protein and dual antiplatelet in intracranial arterial stenosis

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Study question

How are high-sensitive C-reactive protein (hsCRP) levels related to the efficacy of dual aspirin–clopidogrel therapy in patients with or without intracranial arterial stenosis (ICAS)?

Summary answer

Relative to aspirin alone, dual aspirin–clopidogrel therapy reduces recurrent stroke risk only in patients with ICAS and nonelevated hsCRP levels.

What is known and what this article adds

Patients with ICAS have an elevated recurrent stroke rate, possibly due to underlying inflammation. This study provides evidence that levels of the inflammatory biomarker hsCRP indicate which patients with ICAS will benefit from dual aspirin–clopidogrel therapy.

Participants and setting

The study comprised 807 participants (358 with ICAS and 449 without) from the Chinese multicenter Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial for whom MRI, magnetic resonance angiography, and hsCRP data were available. These patients had either TIA with a moderate to high stroke risk or minor stroke (NIH Stroke Scale score ≤3).

Design

In the double-blinded, placebo-controlled CHANCE trial, patients were randomly assigned to receive either aspirin alone or dual aspirin–clopidogrel therapy. CHANCE data with Cox proportional hazards models were retrospectively analyzed to calculate outcome hazard ratios (HRs).

Primary outcomes

The primary outcome was a new stroke within the 90-day trial period.

Main results and the role of chance

Relative to aspirin alone, dual aspirin–clopidogrel therapy reduced the recurrent stroke rate in patients with ICAS and nonelevated hsCRP levels ($p = 0.006$), but no such benefit was observed in patients with ICAS and elevated hsCRP levels or in patients without ICAS regardless of hsCRP levels. The table provides adjusted recurrent stroke HRs for dual aspirin–clopidogrel therapy vs aspirin alone in different patient groups.

	Patients with recurrent stroke, n (%)	Adjusted recurrent stroke, HR (95% CI)
ICAS with hsCRP <3 mg/L	26 (12.1%)	0.27 (0.11–0.69)
ICAS with hsCRP ≥3 mg/L	19 (13.2%)	1.65 (0.63–4.36)
Non-ICAS with hsCRP <3 mg/L	16 (5.1%)	1.43 (0.51–4.00)
Non-ICAS with hsCRP ≥3 mg/L	12 (8.9%)	0.42 (0.10–1.72)

Abbreviations: CI = confidence interval; HR = hazard ratio.

Bias, confounding, and other reasons for caution

This study included only ~15% of the CHANCE patients with available MRI and serologic data. ICAS diagnoses were not confirmed with gold standard procedures. Fasting venous blood was collected after initial antiplatelet drug administrations, which may have affected hsCRP levels. Furthermore, only single-point hsCRP measurements were available.

Generalizability to other populations

There is evidence that dual aspirin–clopidogrel therapy benefits patients with coronary artery disease and elevated hsCRP levels, so these results may not be generalizable to patients with nonischemic conditions.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

