Residual inflammatory risk predicts long-term outcomes following stenting for symptomatic intracranial atherosclerotic stenosis

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ABSTRACT

Background and purpose Residual inflammatory risk (RIR) can predict the unfavourable outcomes in patients with minor ischaemic stroke. However, the impact of preprocedural RIR on long-term outcomes in patients with symptomatic intracranial atherosclerotic stenosis (sICAS) who underwent stenting remains understudied.

Methods This retrospective, single-centre cohort study evaluated consecutive patients with severe sICAS who underwent intracranial stenting. Patients were categorised into four groups based on preprocedural high-sensitivity C-reactive protein (hs-CRP) and low-density lipoprotein cholesterol (LDL-C): residual cholesterol inflammatory risk (RCR, hs-CRP ≥3 mg/L and LDL-C ≥2.6 mmol/L), RIR (hs-CRP ≥3 mg/L and LDL-C <2.6 mmol/L), residual cholesterol risk (RCR, hs-CRP <3 mg/L and LDL-C ≥2.6 mmol/L) and no residual risk (NRR, hs-CRP <3 mg/L and LDL-C <2.6 mmol/L). The long-term clinical outcomes included recurrent ischaemic stroke and death. The long-term imaging outcomes consisted of in-stent restenosis (ISR) and symptomatic ISR (sISR) after stenting.

Results In this study, 952 patients were included, with 751 (78.9%) being male. Forty-six cases were categorised into the RCR group, 211 into the RIR group, 107 into the RCR group and 588 into the NRR group. Patients with RCR (adjusted HR 6.163; 95% CI 2.603 to 14.589; p<0.001) and RIR (adjusted HR 2.205; 95% CI 1.294 to 3.757; p=0.004) had higher risks of recurrent ischaemic stroke than those with NRR during the 54 months of median follow-up time. Patients with RCR (adjusted HR 3.604; 95% CI 1.431 to 9.072; p=0.007) were more likely to occur ISR, and patients in the RIR group showed a significant increase in the risk of sISR (adjusted HR 2.402; 95% CI 1.078 to 5.351; p=0.032) compared with those in the NRR group with a median follow-up time of 11.9 months.

Conclusions In patients with sICAS, preprocedural RIR may predict long-term recurrent ischaemic stroke, ISR and sISR following intracranial stenting.

INTRODUCTION

In patients with cerebrovascular diseases, elevated high-sensitivity C-reactive protein (hs-CRP) and low-density lipoprotein cholesterol (LDL-C) are both independent risk factors of recurrent stroke.1,2 For minor ischaemic stroke or transient ischaemic attack (TIA), lipid-lowering treatment can reduce new ischaemic stroke only in patients with LDL-C level >2.6 mmol. However, patients with LDL-C ≤2.6 mmol cannot benefit more from aggressive lipid-lowering treatment, possibly due to persist residual inflammatory risk (RIR) in this population.1 In recent years, the concepts of RIR and residual cholesterol risk (RCR) have come up and gradually become a hot topic in cardiovascular diseases research.3 The view of combination therapies targeting both lowering-LDL-C and anti-inflammation has also emerged and has shown efficacy in reducing the risk of cardiocerebral vascular diseases.4 Subsequently, the preliminary exploration of the relationship between RIR and cerebrovascular diseases has revealed that RIR can predict the poor prognosis in patients with minor ischaemic stroke or TIA.5 RIR, as well as RCR, shows promise as the next...
biomarker and potential therapeutic target in the field of cerebrovascular disease.

Intracranial atherosclerotic stenosis stands out as a major cause of ischaemic stroke in Asian, which imposes a huge economic burden on society.\(^6\)\(^7\) Inflammation facilitates the development and progression of atherosclerosis.\(^8\) The subgroup analysis of the CHANCE trial\(^9\) showed that high inflammatory state may affect the efficacy of dual antiplatelet therapy (DAPT) and elevate the likelihood of recurrent stroke in symptomatic intracranial atherosclerotic stenosis (sICAS).\(^10\) A subsequent retrospective study involving patients with severe (>70%) sICAS further found that elevated preprocedural hs-CRP can predict in-stent restenosis (ISR) and is closely related to recurrent ischaemic stroke after stent implantation.\(^11\) However, there is limited studies examining the impact of preprocedural residual cholesterol inflammatory risk (RCIR), RIR and RCR on the long-term clinical and imaging outcomes following stent implantation in sICAS. This current investigation aims to explore the connection between preprocedural residual risk and long-term outcomes after stenting for sICAS.

**METHODS**

**Study design and population**

A professional panel comprising interventionists, neuroradiologists and radiologists, who were unaware of the study’s design, collected the baseline data (such as age, gender, atherosclerotic risk factors, medical history, modified Rankin Scale (mRS) score, qualifying events and so on). The implementation, safety and efficacy of the study were overseen by a data and safety monitoring committee operating independently.

Consecutive individuals who underwent stenting for severe sICAS from 2012 to 2019 were screened. The patients who meet the following criteria may be included:

1. 18–85 years old;
2. Severe stenosis (70%–99%) located in the middle cerebral artery (MCA), intracranial internal carotid artery (ICA), basilar artery (BA) or intracranial vertebral artery (VA).
3. Stenosis rate of culprit artery was measured by using the WASID (warfarin–aspirin symptomatic intracranial disease) method on the digital subtraction angiography (DSA)\(^12\); 
4. A lesion length ≤15 mm and target vessel diameter ≥2.0 mm; 
5. Ischaemic stroke or TIA within 3 months. Ischaemic stroke referred to a new focal neurological deficit persisting for over 24 hours or lasting for less than 24 hours accompanied by new infarction detected on imaging. TIA was defined as an acute onset of a focal neurological deficit that endures for less than 24 hours without any new infarction observed on imaging; 
6. Medical treatment resistance, encompassing both the management of risk factors and DAPT; 
7. More than one risk factor for atherosclerosis (including hypertension, hypercholesterolaemia, diabetes and tobacco usage); 
8. Procedural serum detection of both hs-CRP and LDL-C. Exclusion criteria included (1) acute ischaemic stroke within 2 weeks; (2) non-atherosclerotic stroke including cardiac cerebral embolism, artery dissection, vasculitis, moyamoya disease or muscle fibre dysplasia; (3) concurrent cerebral aneurysm, tumour or arteriovenous malformation; (4) A baseline mRS score more than 3; (5) concurrent infection or autoimmune disease.

**Laboratory analysis**

The levels of LDL-C, high-density lipoprotein cholesterol (HDLC) and hs-CRP level were detected at days before intracranial stenting. hs-CRP was measured by a Roche Modular P800 analyser (Roche, Basel, Switzerland). LDL-C and HDLC were measured by fully automatic biochemical analyser (model 008AS(SS), Hitachi). The CYP2C19 genotyping including genetic testing for CYP2C19*17 (-806C>T, rs12248560), CYP2C19*3 (636G>A, rs4986893) and CYP2C19*2 (681G>A, rs4244285) was implemented using the LightCycler480 (Roche). Patients with one or more loss-of-function allele (*2 or *3) were considered as CYP2C19 loss-of-function carriers. Professionals who were blinded to the design and results of this study collected and analysed the antecubital venous blood before interventional procedure.

Referring to previous reports,\(^5\)\(^15\) we define RCIR as hs-CRP ≥3 mg/L and LDL-C ≥2.6 mmol/L, RIR as hs-CRP ≥3 mg/L and LDL-C <2.6 mmol/L, RCR as hs-CRP <3 mg/L and LDL-C ≥2.6 mmol/L, and no residual risk (NRR) as hs-CRP <3 mg/L and LDL-C <2.6 mmol/L.

**Interventional procedure and device selection**

Every patient was prescribed with a DAPT consisting of aspirin (100 mg/day) and clopidogrel (75 mg/day) for over 5 days or a loading dose of DAPT of 300 mg aspirin plus 300 mg clopidogrel before the procedure. The endovascular treatment was carried out by experienced neurointerventionists who performed over 240 intracranial artery interventional therapy annually. Before the procedure, general or local anaesthesia was chosen by professional anaesthesiologist based on preoperative assessment. After establishing vascular access, intravenous heparin was administered with an initial bolus of 75 U/kg, followed by half of the dose given after 1 hour. Subsequently, a percutaneous transluminal angioplasty and stenting was performed in every patient. The target lesions were divided into Mori A, Mori B or Mori C according to their length, angle or other morphological features.\(^18\) The device selection for stenting was based on the operator’s experience and inclinations, and the characteristics of the lesions. In cases of smooth arterial access or Mori A lesion, the balloon-mounted stent (Apollo stent (MicroPort Medical)) was used. For patients with curved arterial access or Mori C lesion, the preferred strategy involved balloon dilatation (Gateway balloon (Stryker)) followed by self-expanding stent (Wingspan stent (Stryker)). For some long and angular lesions with an exceedingly tortuous path, the Enterprise stent (Codman Neurovascular) or Neuroform EZ stent (Boston Scientific) was
chosen due to the good wall apposition, lower radial force and excellent conformability.\textsuperscript{15}

**Periprocedural management**
Prior to the procedure, all patients underwent fasting for at least 12 hours, and a post-procedure head CT was conducted to rule out intracranial haemorrhage. Patients were given antihypertensive drugs to ensure systolic blood pressure maintaining around 100–120 mm Hg if it was too high or unstable during 72 hours after stenting. Tirofiban may be used during the perioperative period to prevent and treat thromboembolic complications, taking into consideration the potential risk of acute thrombosis, the intraoperative operation and the operators’ experience.\textsuperscript{16,17}

**Aggressive medical management**
All patients were prescribed a combination of aspirin (100 mg/day) and clopidogrel (75 mg/day) for a period of 90 days after the procedure. After this period, the decision to discontinue either aspirin or clopidogrel was determined based on the results of resistance testing for antiplatelet drugs. Other risk factor management goals encompassed achieving systolic blood pressure below 140 mm Hg (or below 130 mm Hg for patients with diabetes mellitus), maintaining LDL-C below 1.81 mmol/L or achieving a 50% reduction, quitting smoking and adopting a healthier lifestyle.

**Clinical and imaging follow-up**
Enrolled patients were subjected to follow-up after discharge from the hospital. Trained staff, blinded to the study’s design, gathered and assessed follow-up data pertaining to clinical and imaging outcomes. Most of the clinical follow-ups were performed via in-person interview, with a few being carried out by telephone. MRI or CT was performed in patients experiencing new neurological symptoms. Long-term clinical outcomes were recurrent ischaemic stroke (device-related intracerebral haemorrhage or hyperperfusion syndrome within 30 days were excluded) and any death after stenting. The definition of ischaemic stroke was mentioned in the inclusion criteria.

CT angiography (CTA) or DSA was recommended for patients to evaluate the imaging outcomes after stent placement. The long-term imaging outcomes were consisted of ISR and symptomatic ISR (sISR). For CTA follow-up, if there was a good visualisation and wide patency of the whole stented segment as well as the proximal and distal parent vessel, it would be designated as no ISR (\textsuperscript{18}Figure 1A,B).\textsuperscript{18} Regarding DSA follow-up, ISR was defined as stenosis exceeding 50% within or immediately adjacent (within 5 mm) to the implanted stent or an absolute luminal loss more than 20% (\textsuperscript{18}Figure 1C,D).\textsuperscript{18} When CTA and DSA performed in the same period, the ISR interpretation depended on DSA. The symptomatic ISR (sISR) is defined as recurrent ischaemic events due to ISR. The evaluation of follow-up images was independently carried by two professional radiologists who were blinded to patients’ baseline characteristic and clinical follow-up outcomes, and the disagreements were determined by a third expert.

**Statistical analysis**
All included cases were divided into four groups: ‘RIR’, ‘RCR’, ‘RCIR’ or ‘NRR’ group. Shapiro-Wilk test was used to test the distribution normality of continuous variables. Normally distributed variables were expressed as mean±SD and compared among groups using one-way
analysis of variance. Non-normally distributed variables were presented as median (IQR), and group comparisons were conducted using Kruskal-Wallis H test. The distinction among the four groups in categorical variables was examined using χ² or Fisher’s exact tests. The Kaplan-Meier survival curve was plotted to describe the stroke occurrence, ISR and sISR among four groups, and the difference was tested by the log-rank univariate test. The Cox proportional hazards analysis was employed to examine the connection between residual risk with stroke occurrence, ISR and sISR. Variates with p<0.10 in the univariate analysis, as well as common atherosclerotic risk factors (eg, age, gender, diabetes mellitus, etc) and baseline NIHSS (National Institutes of Health Stroke Scale) score were adjusted for in multivariate Cox proportional hazards model. In the sensitivity analysis, a target cut-off level of 1.8 mmol/L for LDL-C was used to further evaluate the association between residual risk and recurrent ischaemic stroke. The unadjusted and adjusted HRs and their 95% CI were computed. Statistical significance was determined by a two-tailed p value <0.05. Statistical analyses were conducted using SPSS V.23.0 for Windows (IBM-SPSS).

RESULTS
Baseline characteristics
We screened 1960 consecutive patients with sICAS undergoing intracranial stenting in our hospital from 2012 to 2019. Ultimately, 952 cases were enrolled in this study (figure 2). Among them, 46 cases were assigned to the RCR group, 211 to the RIR group, 107 to the RCIR group and 588 to the NRR group. The average age of the included patients was 59.45±8.46 years, and 78.9% (751/952) of them were male. For baseline characteristics, the proportion of hypertension was significantly different among the four groups (RIR (85.8%) > RCIR (80.4%) > NRR (78.6%) > RCR (71%); p=0.018). HDL-C in the RCIR, RCR and NRR groups was higher than that in the RIR group (1.10 vs 1.01 vs 0.98 vs 0.88; p<0.001). The median time from laboratory testing to stenting among the four groups had no significant difference (3.5 vs 4 vs 4 vs 4 days, p=0.132). The CYP2C19 genotyping was performed in 183 patients, and the detection rates of CYP2C19 genotyping had no significant difference among the four groups (13% vs 19% vs 24.3% vs 18.9%, p=0.660). There was an absence of statistical difference in the proportion of CYP2C19 loss-of-function carriers among the groups (table 1).

Technical and periprocedural characteristics
Significant difference (p=0.003) was found in the lesion location among the four groups (table 2). In the RCIR group, 5 (10.9%) responsible arteries were located in ICA, 3 (6.5%) in MCA, 19 (41.3%) in VA and 19 (41.3%) in BA. In the RIR group, 9.5% was located in ICA, 71.1% in MCA, 45.5% in VA and 37.9% in BA. The proportions were 6.5%, 14%, 41.1% and 38.3% in the RCR group and 15.3%, 15.5%, 34.2% and 35% in the NRR group, respectively. No significant disparity was observed in terms of Mori type, arterial stenosis (80% vs 80% vs 80% vs 80%; p=0.990), residual stenosis (10% vs 10% vs 10% vs 10%; p=0.858), length of lesion (7 vs 8 vs 7.5 vs 7 mm; p=0.724), length of stent (8.5 vs 13 vs 9 vs 9 mm; p=0.578), type of stent or the proportion of periprocedural use of Tirofiban (6.5% vs 11.4% vs 8.4% vs 10.7%, p=0.660) among the RCIR, RIR, RCR and NRR groups.

Follow-up characteristics
Out of 952 cases, clinical follow-up was completed by 811 (85.2%) individuals. The median follow-up time for the whole cohort was 54 (36.8–80.5) months, while the respective follow-up times of the 4 groups were 70.2, 59.9, 59.0 and 51.4 months (p=0.380, table 3). The blood pressure was assessed in 93.8% (761/811) of patients who completed the clinical follow-up, and no notable distinction was observed in the proportion of well-controlled systolic blood pressure among the four groups (74.3% vs 79.2% vs 77.4% vs 77.4%; p=0.926, table 3). During the follow-up, LDL-C was measured in 47.8% (388/811) of patients, and the level of LDL-C in the RCIR and RCR groups was found to be higher than that in the RIR and NRR groups (2.31 ± 2.08 ± 1.69 ± 1.65 mmol/L; p<0.001, table 3).
Associations of residual risk with long-term clinical outcomes

Recurrent ischaemic stroke occurred in 17.9% (145/811) of patients and the median time to stroke was 14.6 (3.3–50) months. Among 145 recurrent ischaemic strokes, 28 (24 caused by perforator occlusion and 4 caused by acute thrombosis) occurred within 30 days post-procedure, and 117 occurred beyond 30 days. Forty-three (5.3%) patients died. The rates of death among the four groups had no significant difference (RCIR vs RIR vs RCR vs NRR; 5.4% vs 5.0% vs 8.6% vs 4.8%; p=0.480).

The log-rank test indicated a significant connection between residual risk and recurrent ischaemic stroke (p=0.005), as shown in figure 3A. Patients with RCIR (32.4% vs 14.5%; HR 2.588; 95% CI 1.322 to 5.069; p=0.006) and RIR (25.1% vs 14.5%; HR 1.763; 95% CI 1.157 to 2.685; p=0.008) demonstrated a significantly elevated risk of recurrent ischaemic stroke compared with those with NRR (figure 3B). The association strengthened after accounting for confounding factors (adjusted HR 6.163; 95% CI 2.603 to 14.589; p<0.001; adjusted HR 2.205; 95% CI 1.294 to 3.757; p=0.004). The sensitivity analysis with a cut-off level of 1.8 mmol/L for LDL-C revealed that the association between residual risk and recurrent ischaemic stroke remained unchanged (figure 4).

Associations of residual risk with long-term imaging outcomes

A total of 472 cases underwent imaging follow-up, with a median follow-up time of 11.9 (6.3–18.8) months. The imaging follow-up time did not show any significant difference among the four groups (9.9 vs 12.2 vs 12.0 vs 11.6 months, p=0.332, table 3). Among the 472 cases, 28.6% (135) of vascular assessments were performed by DSA and 71.4% (337) by CTA. ISR was found in 103 (21.8%) cases and the median time to ISR was 11.8 (6.1–18.2) months, and sISR occurred in 7.0% (33/472) patients and the median time to sISR was 11.1 (6.7–22.3) months. Kaplan-Meier curves revealed residual risk was closely related to ISR (p=0.020, figure 5A) and sISR (p=0.024, figure 5B). Patients with RCIR (42.9% vs 20.1%; HR 2.854; 95% CI 1.292 to 6.357; p=0.004) and RIR (25.1% vs 14.5%; HR 1.763; 95% CI 1.157 to 2.685; p=0.008) exhibited a significantly elevated risk of ISR and sISR compared with those with NRR (figure 5B).
1.408 to 5.784; p=0.004) were more likely to occur ISR compared with those with NRR, even if adjusted for confounders (adjusted HR 3.604; 95% CI 1.431 to 9.072; p=0.007, figure 5C). Patients with RIR (12.6% vs 4.8%; adjusted HR 2.402; 95% CI 1.078 to 5.351; p=0.032) had an increased risk of sISR than those with NRR (figure 5D).

**DISCUSSION**

This study, owing the largest sample size of sICAS to date, mainly investigated the relationship between preprocedural residual risk and long-term clinical and radiological prognosis after stent implantation. Our finding that

**Table 2** Comparison of technical characteristics among the RCIR, RIR, RCR and NRR groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RCIR n=46</th>
<th>RIR n=211</th>
<th>RCR n=107</th>
<th>NRR n=588</th>
<th>P value</th>
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<tbody>
<tr>
<td>Lesion location, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>ICA</td>
<td>5 (10.9%)</td>
<td>20 (9.5%)</td>
<td>7 (6.5%)</td>
<td>90 (15.3%)</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>3 (6.5%)</td>
<td>15 (7.1%)</td>
<td>15 (14%)</td>
<td>91 (15.5%)</td>
<td></td>
</tr>
<tr>
<td>VA</td>
<td>19 (41.3%)</td>
<td>96 (45.5%)</td>
<td>44 (41.1%)</td>
<td>201 (34.2%)</td>
<td></td>
</tr>
<tr>
<td>BA</td>
<td>19 (41.3%)</td>
<td>80 (37.9%)</td>
<td>41 (38.3%)</td>
<td>206 (35%)</td>
<td></td>
</tr>
<tr>
<td>Mori type, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.769</td>
</tr>
<tr>
<td>Mori A</td>
<td>7 (15.2%)</td>
<td>36 (17.1%)</td>
<td>12 (11.3%)</td>
<td>104 (17.7%)</td>
<td></td>
</tr>
<tr>
<td>Mori B</td>
<td>29 (63%)</td>
<td>122 (57.8%)</td>
<td>69 (64.5%)</td>
<td>343 (58.3%)</td>
<td></td>
</tr>
<tr>
<td>Mori C</td>
<td>10 (21.7%)</td>
<td>53 (25.1%)</td>
<td>26 (24.3%)</td>
<td>141 (24%)</td>
<td></td>
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<tr>
<td>Arterial stenosis, median (IQR)</td>
<td>80 (80–90)</td>
<td>80 (75–90)</td>
<td>80 (75–90)</td>
<td>80 (74.5–90)</td>
<td>0.990</td>
</tr>
<tr>
<td>Residual stenosis, median (IQR)</td>
<td>10 (0–20)</td>
<td>10 (5–20)</td>
<td>10 (10–20)</td>
<td>10 (5–20)</td>
<td>0.858</td>
</tr>
<tr>
<td>Length of lesion, median (IQR)</td>
<td>7 (5–9)</td>
<td>8 (5.5–10)</td>
<td>7.5 (6–9)</td>
<td>7 (6–9.6)</td>
<td>0.724</td>
</tr>
<tr>
<td>Length of stent, median (IQR)</td>
<td>8.5 (8–15)</td>
<td>13 (8–15)</td>
<td>9 (8–15)</td>
<td>9 (8–15)</td>
<td>0.578</td>
</tr>
<tr>
<td>Diameter of stent, median (IQR)</td>
<td>3.0 (2.5–3.0)</td>
<td>3.0 (2.5, 3.0)</td>
<td>3.0 (2.5–3.0)</td>
<td>3.0 (2.5–3.25)</td>
<td>0.670</td>
</tr>
<tr>
<td>Type of stent, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.848</td>
</tr>
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</table>

**Table 3** Comparison of follow-up characteristics among the RCIR, RIR, RCR and NRR groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RCIR n=37</th>
<th>RIR n=179</th>
<th>RCR n=93</th>
<th>NRR n=502</th>
<th>P value</th>
</tr>
</thead>
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<tr>
<td>Time from stenting to clinical follow-up (months), median (IQR)</td>
<td>70.2 (38.6–89.5)</td>
<td>59.9 (35.3–82.4)</td>
<td>59.0 (38.0–73.7)</td>
<td>51.4 (37.1–77.8)</td>
<td>0.380</td>
</tr>
<tr>
<td>Time from stenting to imaging follow-up (months), median (IQR)</td>
<td>9.9 (6.3–12.6)</td>
<td>12.2 (6.8–23.5)</td>
<td>12.0 (6.3–15.6)</td>
<td>11.6 (6.2–18.9)</td>
<td>0.332</td>
</tr>
<tr>
<td>Systolic blood pressure at follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of evaluated, n (%)</td>
<td>35 (94.6%)</td>
<td>168 (93.9%)</td>
<td>84 (90.3%)</td>
<td>474 (94.4%)</td>
<td>0.561</td>
</tr>
<tr>
<td>Number of well controlled, n (%)*</td>
<td>26 (74.3%)</td>
<td>133 (79.2%)</td>
<td>65 (77.4%)</td>
<td>367 (77.4%)</td>
<td>0.926</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of evaluated, n (%)</td>
<td>15 (40.5%)</td>
<td>89 (49.7%)</td>
<td>41 (44.1%)</td>
<td>243 (48.2%)</td>
<td>0.661</td>
</tr>
<tr>
<td>Level (mmol/L), median (IQR)</td>
<td>2.31 (1.81–2.67)</td>
<td>1.69 (1.42–1.98)</td>
<td>2.08 (1.65–2.55)</td>
<td>1.65 (1.34–1.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from stenting to LDL-C (months), median (IQR)</td>
<td>10.9 (3.8–14.8)</td>
<td>12.4 (5.6–23.7)</td>
<td>9.8 (3.3–20.1)</td>
<td>11.7 (4.4–18.6)</td>
<td>0.491</td>
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</table>

*Well-controlled systolic blood pressure at follow-up was defined as systolic blood pressure <140 mmHg (or <130 mmHg in patients with diabetes mellitus). LDL-C, low-density lipoprotein cholesterol; NRR, no residual risk; RCIR, residual cholesterol inflammatory risk; RIR, residual inflammatory risk; RCR, residual cholesterol risk; VA, vertebral artery.
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Preprocedural RIR may simultaneously predict recurrent ischaemic stroke, ISR and sISR during long-term follow-up in sICAS population after stenting has not been well established in the previous literature.

Atherosclerosis is a chronic inflammatory disease induced by lipid deposition in the intima of arteries. The mechanism of stroke recurrence in patients with symptomatic intracranial atherosclerosis is related to inflammatory activity and plaque progression. hs-CRP is a sensitive inflammatory marker which can predict major adverse cardiovascular and cerebral events (MACCE) in patients with atherosclerosis. Moreover, a previous study reported that hs-CRP, independently of LDL-C, was closely related to recurrent ischaemic stroke after intracranial stenting. In the current study, we found that preprocedural RIR is also strongly associated with an increasing risk of ischaemic stroke recurrence after stenting in intracranial atherosclerosis. The similar conclusion was proposed by Guedeney et al that persistent high RIR increases the risk of MACCE (adjusted HR 2.10; 95% CI 1.45 to 3.02; p<0.001) in patients undergoing percutaneous coronary intervention. In patients with minor stroke or high-risk TIA with large-artery atherosclerotic after dual antiplatelet combined with lipid lowering, RIR plays an important role in recurrent stroke occurrence even with a lower cut-off level of LDL-C target (1.8 mmol/L). We also use a target cut-off level of 1.8 mmol/L for LDL-C to perform sensitivity analysis, and the results revealed an increased association of RIR and recurrent ischaemic stroke, which suggested that the influence of RIR on stroke recurrence in patients with sICAS is dominant in patients who met the target of intensive lipid-lowering treatment. Therefore, it may be valuable to use RIR as a risk stratification indicator for recurrent stroke in sICAS, especially in stent-implanted patients.

Most studies focused on the medium-term results of around 1 years and lacked the long-term results of this association. In this study, we found that the preprocedural RIR is still relevant to ischaemic stroke recurrence at median follow-up of up to 5 years, which suggested that the impact of RIR on patients with sICAS who underwent stent implantation are perennial. Among patients with RIR at baseline, 71.3% (1028/1442) had a persistently elevated hs-CRP when remeasuring after a median interval of 16 (IQR 6–66) weeks, and this possibly means that the systemic inflammatory response after vascular events is not only present in the acute phase, but also a chronic, dynamic and
long-lasting process. Therefore, beyond intensively lowering LDL-C, previous study in cardiovascular diseases confirmed that achieving the dual target of low LDL-C and hs-CRP can reduce the risk of cardiovascular death, major coronary event or strokes compared with those who did not meet either target (38.9% vs 28.0%; adjusted HR 0.73; p<0.001). However, the efficacy of dual lower LDL-C and hs-CRP on secondary prevention of stroke recurrence in population with ischaemic stroke or sICAS is still unclear to date. A large randomised controlled trial aimed at investigating the efficacy of colchicine in the prevention of recurrent stroke among minor-to-moderate stroke or high-risk TIA patients with an elevated baseline hs-CRP is recently underway and may provide evidence on whether anti-inflammatory therapy benefits patients with cerebrovascular disease at high risk of inflammation. With the rising evidence on the impact of RIR on recurrent stroke in patients with cerebrovascular diseases, it is believed that clinical trials on the dual lower LDL-C and hs-CRP for stroke prevention will provide the answers in the near future.

Unlike previous studies on medical therapy for ischaemic stroke, all patients in our study refractory to medical therapy underwent intracranial stenting, and we found a semblable impact of residual risk on imaging outcomes that patients with RCIR had a higher rate of ISR than those with NRR, which has not been previously reported. Dual elevated level of preprocedural hs-CRP and LDL-C may imply an increased risk of ISR after procedure. In addition to the consideration of systemic inflammation and immune-mediated effects after stroke, local luminal inflammation induced by endothelial injury after stent implantation can lead to neointimal hyperplasia, which further facilitates the occurrence of ISR. Therefore, a high preprocedural inflammatory state may promote ISR, and high LDL-C are more prone to form vulnerable atherosclerotic plaques, which may further contribute to ISR in patients with high inflammatory burden. In other words, the identification of RCIR as a risk factor for ISR in our study underscores the synergistic driving of ISR by inflammation and lipid load.

A previous study revealing that the elevated hs-CRP was linked to a heightened of ISR after intracranial stenting in patients with ICAS may support the important role of inflammation in intracranial ISR. Interestingly, our study discovered the lack of correlation between RIR and ISR, leading us to speculate that inflammation...
may only exert its promoting effect on ISR when there is presence of pronounced underlying atherosclerotic burden. However, the potential bias due to relatively low rate of imaging follow-up may provide an alternative explanation for the absence of association. Given the retrospective nature of our study, further prospective studies are necessary to validate this finding.

With the gradual mature application of stent in intracranial artery, some clinical studies in recent years have shown a relatively low perioperative complication rate of stenting for sICAS,29–31 while stenting still did not show an advantage over medical treatment in the recent CASSISS trial.31 One potential reason is probably due to the failure in reducing the incidence of long-term ISR. It is well known that ISR increases the risk of non-procedural recurrent stroke after intracranial stenting.32 33 How to reduce the occurrence of sISR may be a breakthrough in stenting for ICAS. As shown in our results, the preprocedural level of RIR was an independent predictor of sISR, which reveals that inflammation plays an important role in the development of sISR in patients with standard LDL-C.

The underlying reason may be that the residual inflammation causes the progression and rupture of atherosclerotic plaques,34 which triggers clinical symptoms in patients with ISR. A randomised clinical trial demonstrated that drug-eluting stents (DES), when compared with bare-metal stents can markedly reduce the incidence of ISR (0.8% vs 6.9%; HR 0.10; p=0.03) by inhibiting local inflammatory response and neointimal hyperplasia.35 36 As a result, the incidence of ischaemic stroke recurrence during the period from day 31 to 1 year was correspondingly lower (0.8% vs 6.9%). DES might be a better choice for endovascular device in patients with RIR. The RIR may assist the neurointerventionist in stratifying the patients with high risk of ISR and sISR to provide a basis for decision-making for device selection and improve the efficacy of the intracranial stenting for sICAS.

Figure 5  (A) The Kaplan-Meier survival curve for probability of ISR within 36 months. (B) The Kaplan-Meier survival curve for probability of sISR within 36 months. (C, D) Hazard of ISR or sISR compared with NRR. Age (>60 or ≤ 60 years), gender, body mass index (>28 or ≤28 kg/m²), hypertension, diabetes mellitus, hypercholesterolaemia, coronary artery disease, smoking, baseline NIHSS (>3 or ≤3), baseline HDL-C level (>1.03 mmol/L or <1.03 mmol/L), periprocedural use of Tirofiban, lesion location and LDL-C during follow-up (>1.81 mmol/L or <1.81 mmol/L) were adjusted in the multivariate Cox proportional hazards model. HDL, high-density lipoprotein cholesterol; ISR, in-stent restenosis; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; NRR, no residual risk; RCR, residual cholesterol risk; RCIR, residual cholesterol inflammatory risk; RIR, residual inflammatory risk; sISR, symptomatic in-stent restenosis.
relevant conclusions may not be widely applicable to other ethnic groups. Second, this retrospective study analysed patients before 2019, when CHANGE 2 trial was not published. All patients received clopidogrel during the first 3 months postoperatively, according to the mainstream treatment for ICAS, ignoring the clopidogrel resistance. Although the proportion of clopidogrel resistance among the few patients who performed CYP2C19 genotyping was not statistically significant between groups, the majority of patients were not genotyped due to lack of recommendation at that time, which may impact the accuracy of our results. Third, DSA was not performed in all patients, although this is consistent with clinical practice and ethical considerations, and has been validated by other studies. However, the definition of ISR varied between CTA and DSA, which may lead to a heterogeneous evaluation of ISR. Finally, due to the nature of retrospective study, our conclusions need to be confirmed by further prospective studies.

CONCLUSIONS
In patients with sCAS, preprocedural RIR may predict long-term recurrent ischaemic stroke, ISR and sISR after stent implantation. Further prospective investigations are required to confirm our findings.

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