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Platelet function testing guided antiplatelet therapy for ischemic stroke: a phase II randomized controlled trial

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Article

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Abstract

High on-treatment platelet reactivity (HOPR) defined by platelet function testing (PFT), may weaken antiplatelet protection after ischemic stroke, but whether PFT can safely and effectively guide antiplatelet treatment is unclear. In this multicenter, open-label, blinded-endpoint trial, 1,224 adults who had recovered 1-3 months after a first-ever non-cardioembolic ischemic stroke and were receiving aspirin were randomized to PFT-guided antiplatelet therapy or continued aspirin trial at 26 hospitals in China. In the guided group, HOPR (maximal aggregation rate ≥35%) prompted switching from aspirin to clopidogrel and, if persistent, to ticagrelor. At 30 days, HOPR occurred in 93/602 of patients in the guided group and 129/604 patients in the usual care control group (adjusted relative risk 0.72, 95% CI 0.57-0.92; P=0.008). The secondary outcome of major ischemic events within 180 days occurred in 12/611 and 25/613 patients, respectively (hazard ratio 0.47, 95% CI 0.23-0.93; P=0.029), with no excess of serious bleeding. Trial registration: NCT06269432; ChiCTR2200066530.

Introduction

Antiplatelet therapy with aspirin, alone or with short-term clopidogrel in selected patients, is central to secondary prevention after non-cardioembolic ischemic stroke or transient ischemic attack.[1-3] However, laboratory high on-treatment platelet reactivity (HOPR), defined by platelet function testing (PFT), and often described as aspirin or clopidogrel resistance, is common and associated with recurrent ischemic cardiovascular events.[4,5] Whether acting on PFT information improves outcomes after an ischemic stroke is uncertain.

Modern point-of-care devices offer a simple and reliable approach to identifying patients with HOPR who may benefit from an alternative antiplatelet strategy to mitigate the risk of ischemic events whilst maintaining an acceptable bleeding risk.[6,7] The cardiology literature provides an important but incomplete precedent. In percutaneous coronary intervention (PCI) populations, early trials showed that routine platelet-function monitoring or high-dose clopidogrel could improve platelet reactivity but without a clear reduction in clinical events.[8,9] Later PCI studies and contemporary consensus statements have been more supportive of selective testing in higher-risk settings, particularly when the results guide a change in antiplatelet agent rather than a simple dose escalation.[7,10] These findings cannot be directly extrapolated to patients with ischemic stroke: PCI patients usually continue receive dual antiplatelet therapy for stent protection, whereas most patients with ischemic stroke transition from this to single antiplatelet therapy after the early high-risk period. A poor response to single long-term antiplatelet therapy may be more clinically consequential, with empirical intensification of therapy having the potential to expose patients to excessive bleeding risk.

Evidence for PFT-guided antiplatelet selection after ischemic stroke has so far been limited to observational studies, and with mixed results.[11-14] We initiated the first Precision Antiplatelet Therapy Guided by PFT in Patients with Ischemic Stroke (PATH STROKE) study, as a phase II randomized controlled trial to test whether a pragmatic PFT-guided switching algorithm for aspirin-treated patients 1-

3 months after first-ever non-cardioembolic ischemic stroke would reduce HOPR, and to explore its effects on recurrent ischemic and bleeding outcomes.

Results

Between July 21, 2023 and December 31, 2024, 1,416 patients with acute ischemic stroke were assessed for eligibility, and 1,224 were randomized: 611 to the PFT-guided group and 613 to the control group (continuation of standard low-dose aspirin therapy). In the guided group, 106 patients (17.3%) met criteria for aspirin resistance; 64 (10.5%) continued clopidogrel after repeat testing and 42 (6.9%) switched to ticagrelor. Baseline demographic, medical history and clinical characteristics of patients were well balanced between the two groups overall, and by age and sex (Table 1, Supplementary Appendix 2 Tables S4 and S5). Their mean age was 63.1 (SD 9.8) years and 417 (34.1%) were female, and randomization occurred a median of 45 days (IQR 36 to 63) after the index stroke and 32 days (IQR 20 to 46) after aspirin initiation. Primary outcome data at 30 days, and clinical outcome data at 6-months, were available for 1,206 (98.5%) and 1,197 (97.8%) patients, respectively (Fig. 1).

In the modified intention-to-treat population with available primary outcome data, HOPR at 30 days occurred in 93/602 patients (15.5%) in the guided group and 129/604 patients (21.4%) in the control group (relative risk 0.72, 95% CI 0.57 to 0.92; *P*=0.008) (Table 2). Sensitivity and per-protocol analyses (1,184 patients) yielded similar results (Supplementary Appendix 2 Tables S7 and S8).

During 180 days of follow-up, the prespecified secondary outcome of major ischemic events occurred in 12/611 patients (2.0%) in the guided group and 25/613 patients (4.1%) in the control group (HR 0.47, 95% CI 0.23 to 0.93; *P*=0.029; Supplementary Appendix 2 Fig. S3). Overall stroke occurred in 15 (2.5%) and 25 (4.1%) patients, respectively (HR 0.57, 95% CI 0.30 to 1.09; *P*=0.089) (Table 2 and Supplementary Appendix 2 Fig. S4). and ischemic stroke occurred in 11 (1.8%) and 22 (3.6%) patients (hazard ratio 0.48, 95% CI 0.23 to 1.00; *P*=0.049) (Table 2 and Supplementary Figs. S4 and S5). Intracranial hemorrhage events were uncommon, occurring in 4 (0.7%) and 3 (0.5%) patients, respectively (Table 2 and Supplementary Appendix 2 Figs. S5 and S6). There was one (0.2%) death in the guided group and two (0.3%) deaths in the control group.

BARC type 2, 3 or 5 bleeding occurred in 5/603 (0.8%) patients in the guided group and 4/593 (0.7%) patients in the control group (Table 2). Any BARC type 1, 2, 3 or 5 bleeding occurred in 24/603 (4.0%) and 27/593 (4.6%) patients, respectively. Serious adverse events were reported in 32/604 (5.3%) and 34/596 (5.7%) patients (*P*=0.727) (Table 2 and Supplementary Table S9). The treatment effect on HOPR appeared larger in females than males (Fig. 2).

Discussion

In this multicenter randomized controlled trial of patients with recent first-ever non-cardioembolic ischemic stroke receiving aspirin, a PFT-guided switching strategy reduced HOPR at 30 days compared with continued aspirin. The strategy changed treatment only for patients with evidence of aspirin

resistance and was accompanied by fewer prespecified major ischemic events over 180 days, without an observed excess of BARC type 2, 3, or 5 bleeding. Because the study was powered for a pharmacodynamic primary rather than clinical endpoint, the recurrent-event findings should be interpreted as exploratory.

These findings should be viewed in the context of, but not directly extrapolated from, the cardiology literature. Early PCI trials did not show that routine platelet-function monitoring or intensified clopidogrel treatment clearly reduced major cardiovascular events, despite improvements in platelet reactivity.[8,9] More recent PCI studies, Chinese switching-strategy trials, and consensus statements suggest that PFT may be more useful when applied selectively and for test results that lead to a biologically plausible change in antiplatelet agent.[6,7,10] Stroke secondary prevention differs substantially from PCI: after the early high-risk period, many patients depend on a single antiplatelet agent rather than stent-driven dual therapy. Aspirin non-response may therefore be clinically relevant, but empiric escalation for all patients would expose many to unnecessary treatment intensity and potential bleeding risk.

The intervention tested in PATH STROKE was intentionally targeted. Only 106 of 611 patients in the guided group had aspirin resistance; 64 continued clopidogrel after repeat testing and 42 were switched to ticagrelor. Thus, most patients avoided unnecessary exposure to more potent antiplatelet therapy, while those with persistent HOPR received a protocol-defined alternative. The PL-12 workflow also appeared feasible across 26 hospitals, with rapid point-of-care testing, standardized operator training, and high level of follow-up. A previous Chinese study reported higher recurrent stroke risk in aspirin-treated patients with HOPR identified by PL-12 than by VerifyNow or thromboelastography,[15] although assay-specific thresholds and performance characteristics are not interchangeable. These results support further evaluation of PL-12-guided antiplatelet optimization as a targeted adjunct to comprehensive secondary prevention, not as a replacement for established vascular risk-factor management.

The study has several strengths, including the random allocation, multicenter pragmatic design, blinded endpoint adjudication, prespecified treatment algorithm, standardized PL-12 testing with operator training and quality control, and near completeness of follow-up. However, several important limitations should temper interpretation. First, HOPR is a surrogate marker, and the trial was not powered to establish effects on recurrent stroke, disability, death, or bleeding. Second, the numbers of clinical and bleeding events were small, and secondary and subgroup analyses were not adjusted for multiplicity; these estimates should therefore be considered exploratory. Third, the open-label design may have influenced adherence, co-interventions, or event reporting, although endpoint adjudication was blinded. Fourth, baseline platelet function was not measured in the control group, limiting direct comparison of within-person changes in platelet reactivity. Finally, generalizability may be limited to patients similar to those enrolled, to Chinese health-care settings, and to centers using the PL-12 assay with the prespecified cut-off.

In summary, a PFT-guided antiplatelet switching strategy reduced HOPR after recent first-ever non-cardioembolic ischemic stroke and did not show an excess of clinically relevant bleeding in this pilot trial. The lower observed rate of major ischemic events is promising, but confirmation is needed in an adequately powered phase 3 trial with clinical outcomes, including recurrent stroke, disability, and bleeding, as primary or key secondary endpoints.

Methods

Study design

PATH STROKE was multicenter, parallel group, prospective, open-label, randomized controlled, blinded endpoint pilot trial conducted at 26 hospitals in China. Details regarding the rationale, design, and statistical analysis plan have been published and are available in Supplementary Appendix 1.[16] The aim was to determine whether modifying antiplatelet therapy according to platelet function is superior to continued low-dose aspirin for reducing HOPR at 30 days in patients with recent first-ever non-cardioembolic ischemic stroke. The protocol was approved by the Ethics Committee of Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital (Approval No. 2022-220-03, date June 16, 2022) and by the institutional review boards of each participating center. Written informed consent was obtained from each patient or a legally authorized representative before enrolment. Members of the Steering Committee designed the trial, supervised its conduct, and oversaw the data analysis. An independent Data and Safety Monitoring Board regularly reviewed the accumulating data in the study. The trial was conducted in accordance with the principles of the Declaration of Helsinki and followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.[17]

Participants

Eligible patients were between 18 and 80 years of age, had a first-ever acute ischemic stroke of non-cardioembolic origin diagnosed according to standard criteria 1-3 months previously, had no major ongoing disability (a modified Rankin scale [mRS] score ranging from 0 to 2), and had been taking aspirin 100 mg once daily for at least 8 days. Key exclusion criteria were intracerebral hemorrhage or hemorrhagic transformation, recurrent ischemic stroke, gastrointestinal or intracranial bleeding or another bleeding disorder, contraindication or intolerance to aspirin, clopidogrel or ticagrelor, severe comorbidity, or a presumed cardiac source of embolism, including atrial fibrillation, prosthetic cardiac valve or known or suspected endocarditis. Full criteria are provided in Supplementary Appendix 1.

Randomization and masking

After eligibility confirmation, patients were randomly assigned 1:1 to PFT-guided antiplatelet therapy or continued aspirin. Randomization was performed through a web-based central system with stratification by sex, age (<65 vs. ≥65 years) and baseline mRS score (0-1 vs. 2). To minimize ascertainment bias, an independent endpoint adjudication committee reviewed outcomes blinded to treatment allocation.

Procedures

Before site activation, key staff from participating hospitals were trained in trial procedures. Platelet function was assessed rapidly (within 12-15 min of sampling) using the PL-12 platelet analyzer (SINNOWA Co., Nanjing, China), a point-of-care device with stability and validity reported in previous clinical studies.[7,18] To ensure consistency, two or three full-time nurses at each participating site were trained and certified as designated platelet-function operators. The standardized operation and quality control protocol for PL-12 platelet function testing is presented in Supplementary Appendix 2 Table S3.

Patients assigned to PFT-guided therapy underwent immediate platelet-function testing. Patients without HOPR continued aspirin 100 mg once daily for 6 months. Patients with HOPR indicating aspirin resistance switched from aspirin to clopidogrel 75 mg once daily and underwent repeat platelet-function testing after 8 days. Patients without clopidogrel resistance continued clopidogrel until 6 months; patients with persistent HOPR switched to ticagrelor 90 mg twice daily for the remainder of the 6-month treatment period. HOPR was defined as a maximal platelet aggregation rate of 35% or more.[19,20] Patients assigned to the control group continued aspirin 100 mg once daily for 6 months.

To enhance generalizability and reflect routine clinical practice, antiplatelet agents were not limited to a specific manufacturer but were selected from formulations available at participating site. Antiplatelet regimens after the 6 month treatment period were at the discretion of treating physicians. Participants were scheduled for follow-up beyond the 6-month treatment period to collect longer-term clinical outcome data.

Outcomes

The primary outcome was HOPR, defined as maximal aggregation rate of 35% or more at 30±5 days post-randomization, according to thresholds established in the PRINCE trial.[19] Secondary outcomes were maximal aggregation rate, any major adverse cardiovascular event (a composite of any stroke including TIA, non-fatal myocardial infarction, and cardiovascular death), stroke, acute ischemic stroke, all-cause death, cardiovascular death, and non-vascular death; and scores on the mRS at 6 months. Safety outcomes were major bleeding events classified according to the Bleeding Academic Research Consortium (BARC) types 2, 3, or 5, any bleeding event classified according to the BARC types 1, 2, 3, or 5, and any serious adverse event (SAE) within 6 months.[21] SAEs were defined as events resulting in death, being life-threatening, requiring new or prolonged hospitalization, causing persistent disability, or otherwise judged to be medically important.

Statistical analysis

A sample of 1,018 patients was estimated to provide 90% power with a two-sided significance level of 0.05 to detect of a 40% lower rate of HOPR in the platelet function-guided group compared to the standard care control group, assuming a 20% incidence in the control group,[22] on the assumption of 5% loss to follow-up and 5% non-compliance (2.5% drop-in and 2.5% drop-out).

The primary analysis was undertaken on a modified intention-to-treat population, including all randomized patients with available primary outcome data. Multiple imputation was planned but not performed as the proportion of missing data was below the prespecified threshold of 5%. Generalized linear models with a binomial error distribution and log link function were used, with adjustment for the randomization stratification variables (sex, age [<65 vs. ≥65 years], and baseline mRS score [0-1 vs. 2]), and results reported as adjusted relative risk with 95% confidence intervals (CI). A per-protocol analysis was undertaken in patients without a major protocol violation who received the assigned treatment within the predefined time window and underwent platelet function testing. Secondary time-to-event outcomes were analyzed in Cox proportional hazards models, including all randomized patients with at least one post-randomization efficacy measurement, with results presented as hazard ratios (HR) and 95% CI. Kaplan–Meier curves and log-rank tests were used to compare cumulative event rates between the groups.

Safety outcomes (bleeding events and SAEs) were compared using generalized linear models, with adjustment for the same stratification factors used in randomization, and results reported as odds ratios (OR) with 95% CI. Prespecified subgroup analyses of the primary outcome were examined for any heterogeneity in the treatment effects according to age, sex, time from index event to randomization, duration of aspirin before randomization, and the presence of stroke-related comorbidities (including hypertension and diabetes). As the statistical analysis plan did not specify adjustment for multiple comparisons of the secondary outcomes and subgroup analyses, these results are reported as point estimates with 95% CI and should be interpreted as exploratory rather than confirmatory. Analyses were undertaken with SAS software (version 9.4; SAS Institute), STATA 18.0 (Stata Corp LP, College Station) and R software (version 4.4.1).

Declarations

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Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Contributors

JY and YL conceived the study and obtained funding. JY, XW and CSA supervised the planning, analyses, data interpretation, and writing of the report. YL and JY were responsible for the day-to-day running of the trial. GZ, QT and SH did the statistical analysis. YL and GZ wrote the first draft of the manuscript. All other authors contributed to data collection, analysis, interpretation, and report writing. All authors participated in the revisions of subsequent drafts. All authors read and approved the final version. GZ and SH directly accessed and verified the data. All authors were responsible for the decision to submit the manuscript for publication.

Declaration of interests

The SINNOWA Co. of Nanjing, China, donated the PL-12 platelet analyzers for the study but they had no role in the trial design, conduct or analysis. CSA reports grants from the National Health and Medical Research Council (NHMRC) and Medical Research Futures Fund (MRFF) of Australia outside of the study, expert consultancy fees from Astra Zeneca, Bayer, Merck, and Auzone Biotechnology Shanghai; he is President-elect of the World Stroke Organization and Editor-in-Chief of Cerebrovascular Diseases. JY has received grants from the National Natural Science Foundation of China, the Key R&D Project of Sichuan Provincial Department of Science and Technology, the Science and Technology Project of Sichuan Provincial Health Commission, Hospital-School Joint Fund of Chengdu Medical College.

Data sharing statement

Individual, de-identified participant data used in these analyses will be shared by request from any qualified investigator following approval of a protocol and signed data access agreement via the Research Office of The Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, China.

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Tables

Table 1. Baseline characteristics

	Function-guided antiplatelet therapy (n=611)	Standard antiplatelet therapy (n=613)
Age, years	64 ± 10	63 ± 10
Sex		
Female	204/611 (33.4)	213/613 (34.8)
Male	407/611 (66.6)	400/613 (65.3)
Ethnicity		
Han Chinese	610/611 (99.8)	610/612 (99.7)
Other	1/611 (0.2)	2/612 (0.3)
Location of residence		
Urban area	348/611 (57.0)	346/613 (56.4)
Non-urban area	263/611 (43.0)	267/613 (43.6)
Body mass index,* kg/m^2	24.0 (21.9 to 26.2)	24.4 (22.1 to 26.6)
Medical history		
Hypertension	465/611 (76.1)	462/612 (75.5)
Diabetes mellitus	188/610 (30.8)	171/611 (28.0)
Dyslipidemia	214/606 (35.3)	200/603 (33.2)
Medications		
Antihypertensive drugs	420/608 (69.1)	416/608 (68.4)
Antidiabetic drugs	175/609 (28.7)	157/610 (25.7)
Statins	594/611 (97.2)	587/610 (96.2)
Current smoker	223/607 (36.7)	223/609 (36.6)
Consumption of alcohol	195/607 (32.1)	192/609 (31.5)
Median time from the onset of symptoms to randomization, days	45 (36 to 66)	46 (36 to 61)
Median time from the initiation of aspirin to randomization, days	31 (17 to 45)	33 (23 to 46)
Level of disability on the modified Rankin scale†		
0	249/611 (40.8)	246/613 (40.1)

1	284/611 (46.5)	301/613 (49.1)
2	78/611 (12.8)	66/613 (10.8)
Median maximal aggregation rate	20.2 (14.6-30.1)	/

Data are mean (SD), n (%), median (IQR), or n/N (%)

*Body mass index is the weight in kilograms divided by the square of the height in meters.

†Scores on the mRS of functional recovery range from 0 (no symptoms) to 6 (death). A score of 0 indicates 'no symptoms' and a score 2 or less indicates functional independence. The mRS score before stroke onset was assessed by the treating physician with the use of information obtained from patients (if possible) or their family members

Table 2 Primary, secondary and safety outcomes in the intention-to-treat population

Outcome	Function-guided antiplatelet therapy (n=611)	Standard antiplatelet therapy (n=613)	Estimates (95% CI)†	*P* value
Primary outcome - high on treatment platelet reactivity at 30 days*	93/602 (15.5)	129/604 (21.4)	Relative risk 0.72 (0.57 to 0.92)	0.008
Secondary outcomes				
Major ischemic event within 6 months	12 (2.0)	25 (4.1)	Hazard ratio 0.47 (0.23 to 0.93)	0.029
Overall stroke event within 6 months	15 (2.5)	25 (4.1)	Hazard ratio 0.57 (0.30 to 1.09)	0.089
Ischemic stroke within 6 months	11 (1.8)	22 (3.6)	Hazard ratio 0.48 (0.23 to 1.00)	0.049
Intracerebral hemorrhage within 6 months#	4 (0.7)	3 (0.5)	Hazard ratio 1.23 (0.28 to 5.51)	0.786
Death from any cause within 6 months	1 (0.2)	2 (0.3)	Hazard ratio 0.49 (0.04 to 5.39)	0.557
mRS scores 3-5 at 6 months	5/602 (0.8)	6/594 (1.0)	Relative risk 0.79 (0.24 to 2.55)	0.688
EQ-5D-3L overall health utility¶				
No. of patients	603	594		
Score	0.96 (0.96 to 0.96)	0.96 (0.87 to 0.96)		
Safety outcomes				
BARC 2, 3, or 5 bleeding event within 6 months	5/603 (0.8)	4 /593 (0.7)	Relative risk 1.21 (0.33 to 4.48)	0.778
BARC 1, 2, 3, or 5 bleeding event within 6 months	24/603 (4.0)	27/593 (4.6)	Relative risk 0.89 (0.52 to 1.52)	0.663
Serious adverse event within 6 months	32/604 (5.3)	35/596 (5.9)		

At least one serious adverse event within 6 months - no. of patients (%)	32/604 (5.3)	34/596 (5.7)	Relative risk 0.92 (0.58 to 1.47)	0.727

Data are n/N (%), effect size, mean (SD), median (IQR) or p value. CI=confidence interval, BARC=Bleeding Academic Research Consortium, mRS=modified Rankin scale. The mRS evaluates global disability, with scores ranging from 0 (no symptoms) to 6 (death). A score of 3 to 5 indicates a major degree of disability.

*High on-treatment platelet reactivity is defined as a maximal platelet aggregation rate ≥ 35%.

#Including intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH).

¶The EuroQol 5-dimension 3-level (EQ-5D-3L) patient-reported questionnaire covers 5 domains of health-related quality of life: mobility, selfcare,

usual activities, pain and discomfort, and anxiety and depression. Each domain has 3 graded levels of response: no problems, moderate

problems, or extreme problems. Scores from these levels are combined to provide an overall health utility score that was calculated

according to population norms in China. A score of 1 represents perfect health, a score of 0 represents death, and negative scores represent

health states considered to be worse than death.

†Relative risk for binary outcomes. Hazard ratios for time to event in days. All model includes fixed effects of randomization group, sex, age (<65 vs. ≥65 years), and baseline mRS score (0–1 vs. 2).

Figures

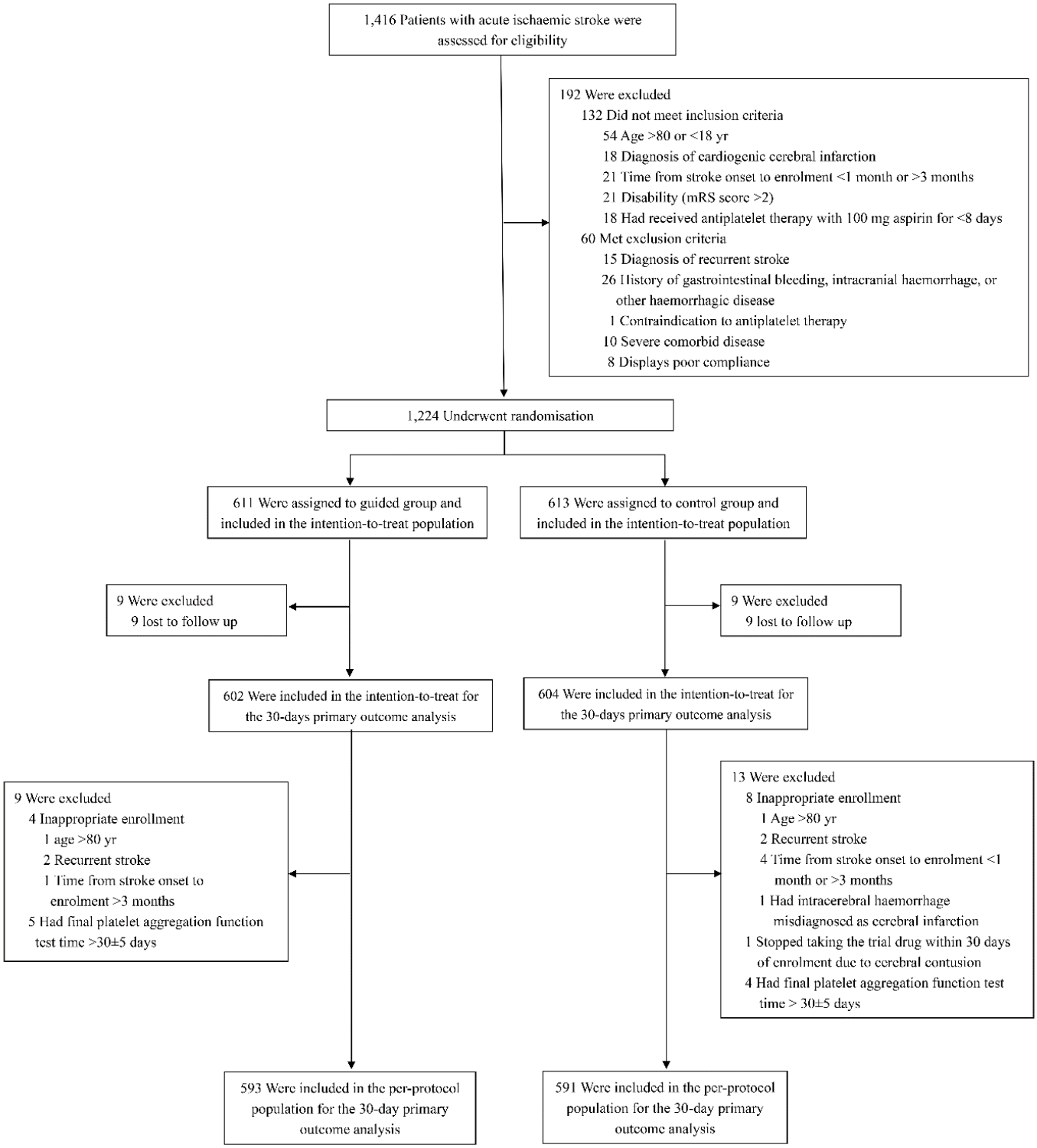


Figure 1

Enrollment and randomization of the patients.

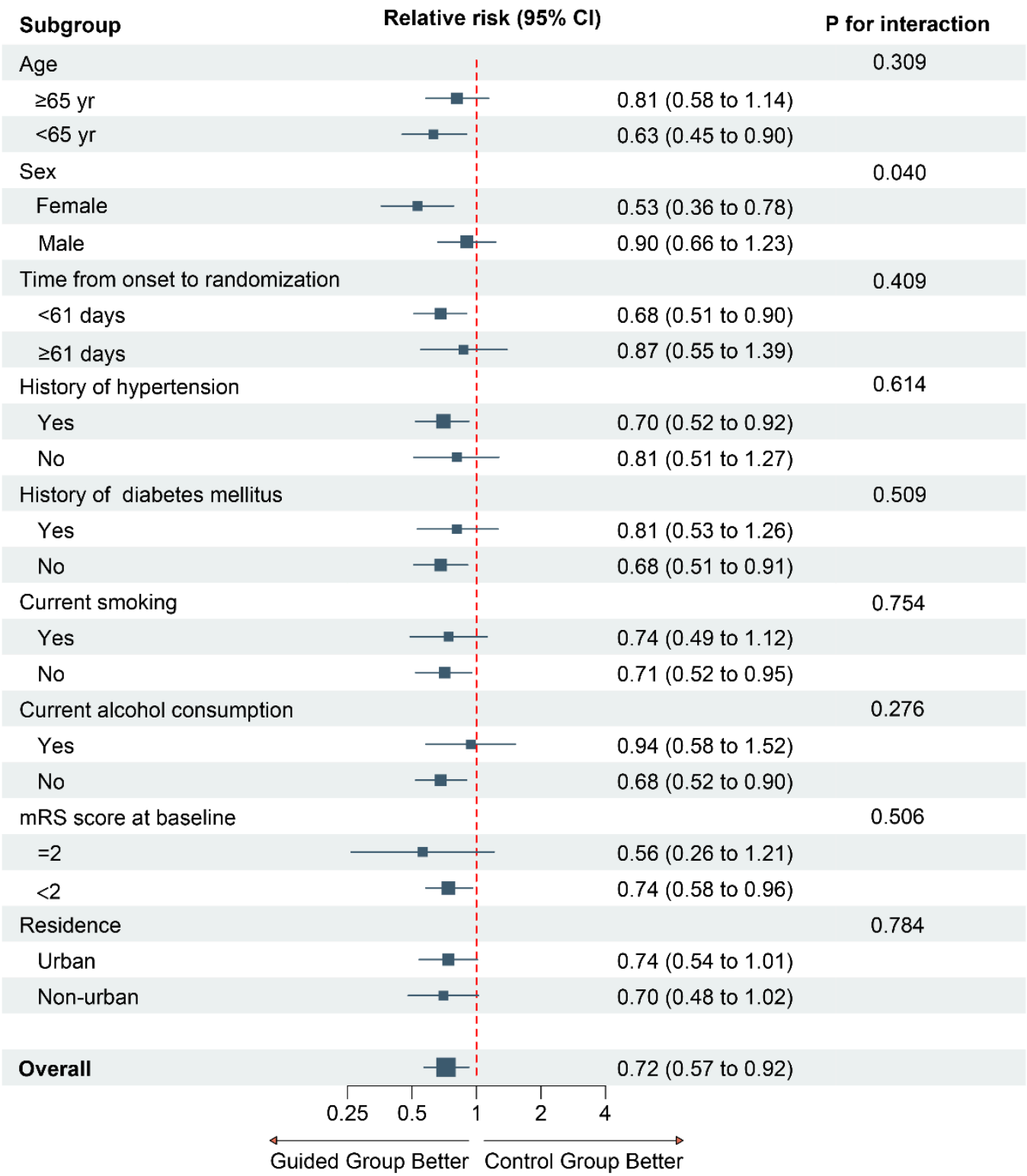


Figure 2

Relative risk for high on-treatment platelet reactivity in prespecified subgroups.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORTchecklist.docx
- Appendix2.docx
- Appendix1.docx