

1 **Ticagrelor-Aspirin versus Clopidogrel-Aspirin in *CYP2C19* Loss-of-Function**

2 **Carriers with Minor Stroke or TIA Stratified by Risk Profile**

3

4 **Abstract**

5 **Background and Objective:** Genotype data of the Clopidogrel with Aspirin in Acute
6 Minor Stroke or Transient Ischemic Attack (CHANCE) trial showed that efficacy of
7 clopidogrel-aspirin **depended** on *CYP2C19* genotype and risk profile. A stratification
8 of patients who carried *CYP2C19* loss of function (LOF) alleles according to risk of
9 recurrent stroke may be important for selecting optimal antiplatelet therapy. We aimed
10 to compare the efficacy and safety of ticagrelor–aspirin versus clopidogrel–aspirin in
11 *CYP2C19* LOF carriers with minor stroke or transient ischemic attack (**TIA**) stratified
12 by risk profile.

13 **Methods:** Data were obtained from Ticagrelor or Clopidogrel with Aspirin in High
14 Risk Patients with Acute Nondisabling Cerebrovascular Events II (CHANCE-2) trial.
15 Low and high risk **profiles were** defined by Essen Stroke Risk Score (ESRS) (<3 [low
16 risk] and ≥ 3 [high risk], respectively).

17 **Results:** A total of 6,412 *CYP2C19* LOF carriers were enrolled, ticagrelor–aspirin
18 was associated with a reduced risk of primary outcome (new stroke **within 90-day**
19 **follow-up**) in patients at low risk (hazard ratio [HR], 0.65; 95% confidence interval
20 [CI], 0.48-0.82), but not in those at high risk (HR, 0.97; 95% CI, 0.73-1.29),
21 compared with clopidogrel–aspirin ($P=0.02$ for interaction). Secondary outcomes
22 generally went in the same direction as the primary outcome. The primary safety

23 outcome of severe or moderate bleeding did not differ based on risk profile ($P=0.24$
24 for interaction), though the incidence of total bleeding was greater with
25 ticagrelor–aspirin than clopidogrel–aspirin among patients at low risk ($P<0.01$ for
26 interaction). Analysis in the per-protocol population yielded similar results.

27 **Discussion:** This **post-hoc** analysis of CHANCE-2 trial showed that *CYP2C19* LOF
28 **carriers** with minor stroke or TIA at low risk of recurrent stroke received a greater
29 benefit from ticagrelor–aspirin **than clopidogrel–aspirin.**

30 **Classification of Evidence:** This study provides **Class II evidence** that *CYP2C19*
31 **LOF carriers with minor stroke or TIA at low risk, but not at high risk, of recurrent**
32 **stroke (by ESRS score) received a greater benefit from ticagrelor–aspirin than**
33 **clopidogrel-aspirin.**

34 **Keywords:** CHANCE-2; Stroke; Ticagrelor; Clopidogrel; Essen Stroke Risk Score

35 **Clinical trial Registration:** URL: <http://www.clinicaltrials.gov>. Unique identifier:
36 NCT04078737

37 **Introduction**

38 Among patients with an acute minor stroke or transient ischemic attack (TIA), the risk
39 of another stroke within 3 months after the initial event is approximately 5 to 10%.¹⁻³
40 Clinical trials have shown that early initiation of dual antiplatelet therapy with
41 clopidogrel–aspirin compared to aspirin alone significantly reduced the **incidence** of
42 stroke events during the first 3 months follow-up.^{4, 5} However, clopidogrel is a
43 prodrug requiring conversion into its active metabolite by hepatic cytochrome p450
44 (CYP). Clopidogrel is less effective for the secondary prevention of stroke in carriers
45 of *CYP2C19* loss-of-function (LOF) alleles, which are presented in 25% of white
46 patients and in 60% of Asian patients.^{6, 7} Genotype data from the Clopidogrel with
47 Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) trial showed
48 that efficacy of clopidogrel-aspirin **was** further influenced by risk profile assessed by
49 the Essen Stroke Risk Score (ESRS).⁸ The ESRS is an easy-to-use 9-point scale
50 derived and validated from the datasets of large clinical trials, and it can help
51 physicians predict the risk of recurrent stroke and cardiovascular events in patients
52 with acute ischemic stroke.^{9, 10} The results **of CHANCE trial** showed that *CYP2C19*
53 LOF carriers who were at high risk (ESRS \geq 3) received a greater benefit from
54 clopidogrel-aspirin.⁸ These findings indicated that stratification of patients who
55 carried *CYP2C19* LOF alleles according to risk of recurrent stroke may possibly be
56 important for selecting optimal antiplatelet therapy.

57

58 The Ticagrelor or Clopidogrel with Aspirin in High Risk Patients with Acute

59 Nondisabling Cerebrovascular Events II (CHANCE-2)¹¹ trial was conducted among
60 patients with minor stroke or TIA who carried *CYP2C19* LOF alleles and showed that
61 the risk of stroke within 90 days was modestly lower with ticagrelor–aspirin than with
62 clopidogrel–aspirin. However, whether the benefit of ticagrelor–aspirin compared
63 with clopidogrel–aspirin for patients who carried *CYP2C19* LOF alleles differed by
64 risk profiles remains unascertained. Therefore, our study utilized data from the
65 CHANCE-2 trial to investigate whether the efficacy and safety of ticagrelor–aspirin
66 versus clopidogrel–aspirin therapy were stratified by risk profile assessed using the
67 ESRS in *CYP2C19* LOF carriers with minor stroke or TIA.

68

69 **Methods**

70 **Study Population**

71 This study was a post-hoc analysis of the CHANCE-2 trial. The detailed study design
72 of the CHANCE-2 trial has been described elsewhere.¹² Briefly, the CHANCE-2 trial
73 is a multicenter, randomized, double-blind, placebo-controlled trial conducted at 202
74 centers in China from September 23, 2019 to March 22, 2021. The study was
75 designed to compare dual antiplatelet therapy with ticagrelor plus aspirin (placebo
76 clopidogrel plus a 180 mg loading dose of ticagrelor on day 1, followed by 90 mg
77 twice daily on days 2-90) with clopidogrel plus aspirin (placebo ticagrelor plus a 300
78 mg loading dose of clopidogrel on day 1, followed by 75 mg daily on days 2-90)
79 among 6,412 patients with minor stroke or TIA within 24 hours of symptom onset and
80 who carried *CYP2C19* LOF alleles. The study protocol and statistical analysis plan

81 are available in the Supplement.

82

83 **Risk Stratification by ESRS**

84 Based on the baseline information of the CHANCE-2 trial, the ESRS was calculated

85 for all patients at the time of admission: 2 points for age >75 years and 1 point each

86 for age 65-75 years, hypertension, diabetes mellitus, myocardial infarction, other

87 cardiovascular disease (except myocardial infarction and atrial fibrillation), peripheral

88 arterial disease, current or past smoking, and previous TIA or ischemic stroke. The

89 ESRS with a range from 0 to 9 was categorized as low risk (<3) and high risk (≥3).⁸⁻¹⁰

90 In addition to the components of ESRS, the modified ESRS was generated by adding

91 1 point each for waist circumference ≥90 cm, stroke subtype except small artery

92 occlusion, and men. The modified ESRS with a range from 0 to 12 was also

93 categorized as low risk (<6 in men and <5 in women) and high risk (≥6 in men and ≥5

94 in women), which was used in the sensitivity analysis.^{13, 14}

95

96 **Outcomes Assessment**

97 The primary outcome was new ischemic or hemorrhagic stroke within 90 days.

98 Secondary outcomes included new stroke within 30 days, a vascular event (a

99 composite of stroke, TIA, myocardial infarction, or death from vascular causes)

100 within 90 days, and ischemic stroke within 90 days. The primary safety outcome was

101 severe or moderate bleeding as defined by the Global Utilization of Streptokinase and

102 Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria

103 **within** 90 days.¹⁵ Secondary safety outcome was any bleeding through 90 days of
104 follow-up. All efficacy and safety outcomes were confirmed by an independent
105 clinical-event adjudication committee, whose members were unaware of the
106 trial-group assignments. The committee members classified ischemic stroke subtypes
107 on the basis of available medical records, including imaging **data**.

108

109 **Statistical Analysis**

110 Baseline characteristics were compared between groups categorized by ESRS levels.
111 Continuous variables were presented in medians (interquartile ranges) and compared
112 between groups using the nonparametric Wilcoxon test. Categorical variables were
113 presented as percentages and tested by chi-squared test. Kaplan-Meier product limit
114 method was used to generate survival plots, and the significance of differences
115 between groups was tested by the log-rank test. Differences in the outcomes during
116 the 90-day follow-up period were assessed using a Cox proportional hazard regression
117 model, and hazard ratios (HRs) with 95% confidence intervals (CIs) were reported.
118 When there were multiple events of the same type, the time to the first event was used
119 in the model. Data from patients who had no event during 90-day follow-up were
120 censored at termination of the trial or nonvascular death. For each model, the
121 proportional hazards assumption was assessed by testing the interaction of treatment
122 by time in the model. Whether the treatment effect differed in different risk profile
123 categories was examined by testing the interactions of treatment by ESRS categories
124 in the Cox model. Sensitivity analyses were performed using modified ESRS **to**

125 **redefine risk profile** and in the per-protocol population. All statistical analyses were
126 performed with SAS statistical software, version 9.4 (SAS Institute Inc). All tests
127 were 2-sided, and $P < 0.05$ was considered statistically significant.

128

129 **Standard Protocol Approvals, Registrations, and Patient Consents**

130 The standard protocol and informed consent were approved by the ethics committee at
131 Beijing Tiantan Hospital (IRB approval number: KY2019-035-02) and all
132 participating centers. Written informed consent was provided by all the patients or
133 their representatives before enrollment. The trial was **registered at ClinicalTrials.gov**
134 **(Registration-URL: <http://www.clinicaltrials.gov>; unique identifier: NCT04078737).**

135

136 **Data Availability**

137 Data are available to researchers on request for purposes of reproducing the results or
138 replicating the procedure by directly contacting the corresponding author.

139

140 **Results**

141 **Baseline Characteristics**

142 Table 1 shows baseline characteristics of the study cohort stratified by ESRS levels
143 and treatment. **There were 3,899 patients (60.8%) at low risk (ESRS <3) and 2,513**
144 **patients (39.2%) at high risk (ESRS ≥3).** The differences in all study variables
145 between ticagrelor–aspirin group and clopidogrel–aspirin group were not significant
146 except time from symptom onset to randomization and previous antiplatelet therapy in

147 the low risk group, and ESRS in the high risk group. Baseline characteristics stratified
148 by modified ESRS and treatment are presented in eTable 1 in the Supplement. All the
149 characteristics were well balanced except history of myocardial infarction in the low
150 risk group and history of TIA or ischemic stroke in the high risk group.

151

152 **Efficacy Outcomes**

153 Within 90 days follow-up, recurrent stroke occurred in 198 patients (7.9%) in patients
154 at high risk and 236 patients (6.0%) in patients at low risk ($P=0.004$). The
155 relationships between treatment assignment and outcome differed by baseline risk
156 estimated by ESRS ($P=0.02$ for interaction). Ticagrelor–aspirin compared with
157 clopidogrel–aspirin was associated with a reduced **incidence** of new stroke in patients
158 at low risk (HR, 0.63; 95% CI, 0.48-0.82; $P<0.001$) but not in those at high risk (HR,
159 0.97; 95% CI, 0.73-1.29; $P=0.08$) (Table 2). Cumulative risk of new stroke among
160 patients at low or high risk by treatment **assignment** is shown in Figure 1; those at low
161 risk and treated with ticagrelor–aspirin experienced the lowest risk of new stroke
162 ($P<0.001$, log-rank test). Similar results were **observed** for the **secondary** outcomes of
163 new stroke within 30 days, combined vascular event and ischemic stroke within 90
164 days (Table 2). The results **were replicated** in the sensitivity analysis using modified
165 ESRS to **redefine** different risk **groups**, the **incidence** of new stroke was higher in
166 patients at high risk (100 patients, 8.95%) than that in patients at low risk (334
167 patients, 6.31%) ($P=0.001$) (eTable 2 and eFigure 1 in the Supplement). Results of the
168 per-protocol analysis were consistent with the intention-to-treat analysis (eTable 3-4

169 in the Supplement).

170

171 **Safety Outcomes**

172 Patients at low (ESRS<3) or high risk (ESRS ≥3) in the ticagrelor–aspirin group and
173 the clopidogrel–aspirin group had a similar **incidence of** severe or moderate bleeding
174 (0.1% and 0.3% in low risk group vs 0.6% and 0.5% in high risk group; $P=0.24$ for
175 interaction) (Table 2). As the secondary safety outcome, the incidence of any bleeding
176 was higher in the ticagrelor–aspirin than in the clopidogrel–aspirin among patient at
177 low risk (5.8% vs 1.9%) but not among patients at high risk (4.6% vs 3.4%) ($P=0.01$
178 for interaction between ESRS categories and treatment). The results were similar for
179 the modified ESRS and in the per-protocol analysis (eTable 2-4 in the Supplement).

180

181 **Classification of Evidence:** This study provides Class II evidence that *CYP2C19*
182 LOF carriers with minor stroke or transient ischemic attack at low risk, but not at high
183 risk, of recurrent stroke (by ESRS score) received a greater benefit from
184 ticagrelor–aspirin than clopidogrel-aspirin.

185

186 **Discussion**

187 In this post-hoc analysis of the CHANCE-2 trial, we found that among patients with
188 minor stroke or TIA who were *CYP2C19* LOF **carriers**, ticagrelor–aspirin **versus**
189 clopidogrel–aspirin was associated with a significantly decreased risk of new stroke in
190 patients at low risk of recurrent stroke. Overall, among patients at low risk, the

191 incidence of total bleeding events was greater with ticagrelor–aspirin, mainly owing
192 to mild bleeding, but there was not an increased incidence of moderate or severe
193 bleeding. Our findings indicated that risk stratification by ESRS may provide
194 additional information on identifying patients who may receive greater benefit from
195 ticagrelor–aspirin therapy.

196

197 The prognosis of minor stroke or TIA is quite variable and is influenced by the
198 prevalence and levels of prognostic factors. Large population and clinical studies have
199 identified risk factors that are associated with poor clinical outcomes in patients with
200 stroke or TIA, including older age, smoking, hypertension, diabetes mellitus,
201 cardiovascular disease, and peripheral artery disease.^{9, 10, 16-18} Additionally, these risk
202 factors may influence the selection of antiplatelet therapy. For instance, the POPular
203 AGE trial showed in patients aged 70 years or older presenting with non-ST elevation
204 acute coronary syndrome, clopidogrel was a favorable alternative to ticagrelor.¹⁹ A
205 meta-analysis of randomized trials reported in smokers, patients with clopidogrel
206 received a better clinical benefit in reducing cardiovascular outcomes than those with
207 ticagrelor.²⁰ The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial
208 showed that in patients with acute coronary syndrome with or without ST-segment
209 elevation, ticagrelor as compared with clopidogrel significantly reduced the incidence
210 of cardiovascular death.²¹ Data from the Clopidogrel versus Aspirin in Patients at Risk
211 of Ischemic Events (CAPRIE) study reported that the absolute benefit of clopidogrel
212 over aspirin for subsequent combined vascular events was amplified in patients with a

213 history of diabetes or ischemic events.²² Based on these factors, ESRS was derived
214 from the patients with ischemic stroke in the large-scale CAPRIE⁹ trial and was
215 validated in the Reduction of Atherothrombosis for Continued Health (REACH)
216 registry population, and could predict the risk of recurrent stroke and cardiovascular
217 events in patients with acute ischemic stroke.¹⁰ Consistent with previous studies, our
218 study also found that a higher ESRS score was associated with a higher risk of
219 recurrent stroke within 90-day follow-up.

220

221 Previous studies suggested that in addition to modification of these stroke risk factors,
222 a stratification of patients according to risk of recurrent stroke assessed by ESRS may
223 **provide support to optimize** treatment regimens. Subgroup analysis of CAPRIE trial
224 showed that clopidogrel compared to aspirin **was** particularly beneficial to patients at
225 high risk, defining as >4% **per year** for recurrent stroke as assessed by the ESRS.⁹ A
226 prospective cohort study **conducted among** Chinese patients with TIA or ischemic
227 stroke admitted to 132 hospitals throughout China, **and suggested** that clopidogrel
228 may be preferable to aspirin in patients with an ESRS >3, and aspirin may be
229 preferred over clopidogrel for patients with an ESRS ≤3 for **the** secondary prevention
230 of non-cardioembolic ischemic stroke.²³ Except for risk profile, *CYP2C19* genotype
231 was also used to individualize antiplatelet therapy. A meta-analysis showed that
232 *CYP2C19* genetic testing **could** guide patients undergoing percutaneous coronary
233 intervention to select optimal antiplatelet therapy, thus may reduce the risk of major
234 adverse cardiovascular events.²⁴ Furthermore, post-hoc analysis of the CHANCE trial

235 showed that the benefit of clopidogrel in Chinese minor stroke or TIA patients
236 depended on both *CYP2C19* genotype and risk profile. Overall, *CYP2C19* LOF
237 carriers do not benefit from dual antiplatelet therapy with clopidogrel–aspirin, but
238 there is significant benefit for LOF carriers who are at high risk (ESRS ≥ 3).²⁵ Such
239 findings suggested that ticagrelor not reducing the risk of recurrent stroke over
240 clopidogrel in high risk *CYP2C19* LOF carriers. Similarly with these studies, our
241 analysis found that the efficacy of clopidogrel–aspirin was associated with a similar
242 incidence of recurrent stroke with ticagrelor–aspirin among *CYP2C19* LOF carriers at
243 high risk, but in patients at low risk, ticagrelor–aspirin was associated with a lower
244 risk of stroke.

245

246 The mechanisms underlying our findings are complex and multifactorial. First, it is
247 appropriate to speculate that patients at high stroke risk assessed by ESRS were more
248 likely to have thrombotic tendencies, systematic inflammation, and other basic
249 diseases related to stroke²⁶, antithrombotic treatment alone may not be sufficient for
250 adequate protection against ischemic events²⁷, thus there were not apparent
251 differences in the efficacy between ticagrelor–aspirin and clopidogrel–aspirin among
252 patients at high risk. Second, as previously reported⁸, stroke patients with *CYP2C19*
253 LOF alleles at high risk also received a significant benefit from clopidogrel–aspirin
254 treatment, which could explain why ticagrelor-aspirin did not exhibit a stronger effect
255 in reducing recurrent stroke over clopidogrel among these patients to some extent.
256 Additionally, the proportion of patients in the high risk group on antiplatelet therapy

257 prior to the index event was higher, and there was no washout period for the prior
258 anti-platelet treatment, which may lead to a higher antiplatelet load in these patients
259 and the unapparent benefit of ticagrelor-aspirin therapy. These findings suggest that
260 the risk profile, **according to ESRS levels**, should be taken into consideration in the
261 implementation of antiplatelet therapy in clinical practice, **ticagrelor-aspirin** is
262 associated with a lower risk of recurrent stroke in low risk *CYP2C19* LOF carriers
263 when compared to **clopidogrel-aspirin**.

264

265 Our study has several limitations. First, our cohort was made up of Chinese
266 population, a population has a higher incidence of intracranial-artery stenosis than
267 non-Asian population, and ticagrelor and clopidogrel may have different effects in
268 other population, which might limit generalizability. Second, this study was a
269 post-hoc analysis, thus the **results should** be interpreted with caution and **needed to be**
270 further confirmed by other studies. Third, the washout period of the prior antiplatelet
271 treatments was not available in our study, which may have influenced the benefits of
272 ticagrelor **in patients at low risk**.

273

274 **Conclusions**

275 This post-hoc analysis of CHANCE-2 trial found that among *CYP2C19* LOF carriers
276 with minor stroke or TIA, ticagrelor–aspirin was superior to clopidogrel-aspirin in
277 reducing the risk of subsequent stroke in those at low risk (ESRS<3). The risk of
278 severe or moderate bleeding did not differ between the two treatment groups across

279 different risk groups, but the risk of any bleeding was higher with ticagrelor–aspirin in
280 patients at low risk.

281

282

283

284 **References**

- 285 1. Amarenco P, Lavallée PC, Labreuche J, et al. One-Year Risk of Stroke after
286 Transient Ischemic Attack or Minor Stroke. *The New England journal of medicine*
287 2016;374:1533-1542.
- 288 2. Shahjouei S, Sadighi A, Chaudhary D, et al. A 5-Decade Analysis of Incidence
289 Trends of Ischemic Stroke After Transient Ischemic Attack: A Systematic Review and
290 Meta-analysis. *JAMA neurology* 2021;78:77-87.
- 291 3. Pan Y, Elm JJ, Li H, et al. Outcomes Associated With Clopidogrel-Aspirin Use in
292 Minor Stroke or Transient Ischemic Attack: A Pooled Analysis of Clopidogrel in
293 High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE)
294 and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT)
295 Trials. *JAMA neurology* 2019;76:1466-1473.
- 296 4. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or
297 transient ischemic attack. *The New England journal of medicine* 2013;369:11-19.
- 298 5. Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and Aspirin in Acute
299 Ischemic Stroke and High-Risk TIA. *The New England journal of medicine*
300 2018;379:215-225.
- 301 6. Wang Y, Zhao X, Lin J, et al. Association Between CYP2C19 Loss-of-Function
302 Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients With
303 Minor Stroke or Transient Ischemic Attack. *Jama* 2016;316:70-78.
- 304 7. Pan Y, Chen W, Xu Y, et al. Genetic Polymorphisms and Clopidogrel Efficacy for
305 Acute Ischemic Stroke or Transient Ischemic Attack: A Systematic Review and

306 Meta-Analysis. *Circulation* 2017;135:21-33.

307 8. Xu J, Wang A, Wangqin R, et al. Efficacy of clopidogrel for stroke depends on
308 CYP2C19 genotype and risk profile. *Annals of neurology* 2019;86:419-426.

309 9. Diener HC, Ringleb PA, Savi P. Clopidogrel for the secondary prevention of
310 stroke. *Expert opinion on pharmacotherapy* 2005;6:755-764.

311 10. Weimar C, Diener HC, Alberts MJ, et al. The Essen stroke risk score predicts
312 recurrent cardiovascular events: a validation within the REduction of
313 Atherothrombosis for Continued Health (REACH) registry. *Stroke* 2009;40:350-354.

314 11. Wang Y, Meng X, Wang A, et al. Ticagrelor versus Clopidogrel in CYP2C19
315 Loss-of-Function Carriers with Stroke or TIA. *New England Journal of Medicine*
316 2021.

317 12. Wang Y, Johnston C, Bath PM, et al. Clopidogrel with aspirin in High-risk
318 patients with Acute Non-disabling Cerebrovascular Events II (CHANCE-2): rationale
319 and design of a multicentre randomised trial. *Stroke and vascular neurology*
320 2021;6:280-285.

321 13. Sumi S, Origasa H, Houkin K, et al. A modified Essen stroke risk score for
322 predicting recurrent cardiovascular events: development and validation. *International*
323 *journal of stroke : official journal of the International Stroke Society* 2013;8:251-257.

324 14. Chaudhary D, Abedi V, Li J, Schirmer CM, Griessenauer CJ, Zand R. Clinical
325 Risk Score for Predicting Recurrence Following a Cerebral Ischemic Event. *Frontiers*
326 *in neurology* 2019;10:1106.

327 15. investigators TG. An international randomized trial comparing four thrombolytic

328 strategies for acute myocardial infarction. *The New England journal of medicine*
329 1993;329:673-682.

330 16. Weimar C, Goertler M, Röther J, et al. Predictive value of the Essen Stroke Risk
331 Score and Ankle Brachial Index in acute ischaemic stroke patients from 85 German
332 stroke units. *Journal of neurology, neurosurgery, and psychiatry* 2008;79:1339-1343.

333 17. Ishkanian AA, McCullough-Hicks ME, Appelboom G, et al. Improving patient
334 selection for endovascular treatment of acute cerebral ischemia: a review of the
335 literature and an external validation of the Houston IAT and THRIVE predictive
336 scoring systems. *Neurosurgical focus* 2011;30:E7.

337 18. Alvarez-Sabín J, Molina CA, Montaner J, et al. Effects of admission
338 hyperglycemia on stroke outcome in reperfused tissue plasminogen activator--treated
339 patients. *Stroke* 2003;34:1235-1241.

340 19. Gimbel M, Qaderdan K, Willemsen L, et al. Clopidogrel versus ticagrelor or
341 prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary
342 syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. *Lancet*
343 (London, England) 2020;395:1374-1381.

344 20. Gagne JJ, Bykov K, Choudhry NK, Toomey TJ, Connolly JG, Avorn J. Effect of
345 smoking on comparative efficacy of antiplatelet agents: systematic review,
346 meta-analysis, and indirect comparison. *BMJ (Clinical research ed)* 2013;347:f5307.

347 21. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients
348 with acute coronary syndromes. *The New England journal of medicine*
349 2009;361:1045-1057.

350 22. Ringleb PA, Bhatt DL, Hirsch AT, Topol EJ, Hacke W. Benefit of clopidogrel
351 over aspirin is amplified in patients with a history of ischemic events. *Stroke*
352 2004;35:528-532.

353 23. Xu H, Ping Y, Lin H, He P, Li W, Dai H. Antiplatelet Strategies and Outcomes in
354 Patients with Noncardioembolic Ischemic Stroke from a Real-World Study with a
355 Five-Year Follow-Up. *Translational stroke research* 2017;8:228-233.

356 24. Galli M, Benenati S, Capodanno D, et al. Guided versus standard antiplatelet
357 therapy in patients undergoing percutaneous coronary intervention: a systematic
358 review and meta-analysis. *Lancet (London, England)* 2021;397:1470-1483.

359 25. Huang ZX, Chen LH, Xiong R, et al. Essen Stroke Risk Score Predicts Carotid
360 Atherosclerosis in Chinese Community Populations. *Risk management and healthcare*
361 *policy* 2020;13:2115-2123.

362 26. Grant PJ. Diabetes mellitus as a prothrombotic condition. *Journal of internal*
363 *medicine* 2007;262:157-172.

364 27. Alexopoulos D, Xanthopoulou I, Mavronasiou E, et al. Randomized assessment
365 of ticagrelor versus prasugrel antiplatelet effects in patients with diabetes. *Diabetes*
366 *care* 2013;36:2211-2216.

367

368

369

370 **Figure and legends**

371

372 **Figure 1. Cumulative Probability of Stroke According to treatment and risk**

373 **profile**

374 C denotes clopidogrel; ESRS denotes Essen Stroke Risk Score; T denotes ticagrelor.

Table 1. Baseline Characteristics According to Risk Profile

Characteristics	Low Risk, ESRS <3			High Risk, ESRS ≥3		
	Ticagrelor -Aspirin (N=1940)	Clopidogrel -Aspirin (N=1959)	<i>P</i> value	Ticagrelor -Aspirin (N=1265)	Clopidogrel -Aspirin (N=1248)	<i>P</i> value
Median age (IQR) -yr	60.5(54.4-66.5)	60.8(54.4-66.2)	0.74	70.9(65.8-77.2)	70.1(65.6-76.6)	0.05
Female sex - no. (%)	678 (34.9)	663 (33.8)	0.47	412(32.6)	417(33.4)	0.65
Median BMI (IQR), kg/m ²	24.5(22.7-26.7)	24.2(22.6-26.4)	0.05	24.5(22.6-26.6)	24.4(22.5-26.5)	0.42
Median ESRS (IQR)	2(1-2)	1(1-2)	0.61	3(3-4)	3(3-4)	0.03
ESRS components, no. (%)						
Age						
<65 yr	1347(69.4)	1370(69.9)	0.90	255(20.2)	280(22.4)	0.04
65-75 yr	517(26.6)	510(26.0)		571(45.8)	548(43.3)	
>75 yr	76(3.9)	79(4.0)		462(36.5)	397(31.8)	

Hypertension	910(46.9)	932(47.6)	0.68	1066(84.3)	1047(83.9)	0.80
Diabetes	272(14.0)	244(12.5)	0.15	536(42.4)	511(40.9)	0.47
Myocardial infarction	9(0.5)	4(0.2)	0.16	45(3.6)	38(3.0)	0.47
Other heart diseases	36(1.9)	44(2.2)	0.39	188(14.9)	194(15.5)	0.63
Peripheral vascular disease	2(0.1)	2(0.1)	0.99	4(0.3)	5(0.4)	0.72
Smoker	616(31.8)	643(32.8)	0.47	612(48.4)	587(45.4)	0.08
History of TIA or ischemic stroke	169(8.7)	151(7.7)	0.25	531(42.0)	567(58.5)	0.33
<i>CYP2C19</i> LOF carriers - no. (%)						
Intermediate metabolizers	1515(78.1)	1531(78.2)	0.96	971(76.8)	984(78.8)	0.21
Poor metabolizers	425(21.9)	428(21.8)		294(23.2)	264(21.2)	
Median time from symptom onset to randomization (IQR) — hr.	13.7(9.2-20.3)	14.9(9.2-21.0)	0.02	13.4(8.6-20.5)	13.2(8.3-20.0)	0.55
Qualifying event - no. (%)						
Ischemic stroke	1567(80.8)	1596(81.5)	0.58	1010(79.8)	985(78.9)	0.57

TIA	373(19.2)	363(18.5)		255(20.2)	263(21.1)	
Median NIHSS score in patients with qualifying ischemic stroke (IQR) *	2(1-3)	2(1-3)	0.85	2(1-3)	2(1-3)	0.33
Median ABCD ² score in patients with qualifying TIA (IQR) †	4(4-5)	4(4-5)	0.28	5(4-6)	5(4-6)	0.05
Previous antiplatelet therapy - no. (%)‡	112(5.8)	85(4.3)	0.04	273(21.6)	278(22.3)	0.67
Previous lipid-lowering therapy - no. (%)‡	73(3.8)	56(2.9)	0.11	185(14.6)	185(14.8)	0.89

BMI denotes body mass index; ESRS denotes Essen Stroke Risk Score. IQR denotes interquartile range. IS denotes ischemic stroke. TIA denotes transient ischemic attack. LOF denotes loss-of-function.

* National Institutes of Health Stroke Scale (NIHSS) scores range from 0 to 42, with higher scores indicating more severe stroke.

† ABCD² score assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes, with scores ranging from 0 to 7 and higher scores indicating greater risk.

‡ Medication within 1 month before symptom onset.

1 Table 2. Efficacy and Safety Outcomes of Patients With Different Antiplatelet Therapies Stratified by Risk Profile

Outcome	Low risk, ESRS <3				High Risk, ESRS ≥3				<i>P</i> _{int}
	Ticagrelor -Aspirin, event rate (%)*	Clopidogrel -Aspirin, event rate (%)*	HR (95%CI)	<i>P</i> value	Ticagrelor -Aspirin, event rate (%)*	Clopidogrel -Aspirin, event rate (%)*	HR (95%CI)	<i>P</i> value	
Primary outcome									
Stroke	92 (4.7)	144 (7.4)	0.63(0.48-0.82)	<0.001	99 (7.8)	99 (7.9)	0.97(0.73-1.29)	0.08	0.02
Secondary outcomes									
Stroke within 30 days	78 (4.0)	126 (6.4)	0.62(0.46-0.82)	<0.001	78 (6.2)	79 (6.3)	0.97(0.70-1.34)	0.86	0.02
Composite vascular events†	111 (5.7)	167 (8.5)	0.66(0.52-0.84)	<0.001	118 (9.3)	126 (10.1)	0.92(0.71-1.19)	0.53	0.04
Ischemic stroke	92 (4.7)	142 (7.2)	0.64(0.49-0.83)	<0.001	97 (7.7)	96 (7.7)	0.98(0.73-1.30)	0.87	0.02
Primary safety outcome									
Severe or moderate bleeding‡	2 (0.1)	5 (0.3)	0.39(0.08-2.02)	0.26	7 (0.6)	6 (0.5)	1.27(0.42-3.81)	0.67	0.24
Secondary safety outcome									

Any bleeding	112 (5.8)	37 (1.9)	3.27(2.24-4.79)	<0.001	58 (4.6)	43 (3.4)	1.26(0.83-1.90)	0.28	0.01
--------------	-----------	----------	-----------------	--------	----------	----------	-----------------	------	------

2 CI denotes confidence interval. ESRS denotes Essen Stroke Risk Score. HR denotes hazard ratio. mRS denotes modified Rankin Scale. TIA
3 denotes transient ischemic attack.

4 * Event rates for ordinal stroke or TIA are raw estimates, whereas event rates for other outcomes are Kaplan-Meier estimates of the percentage
5 of patients with events at 90 days.

6 † Composite vascular events include ischemic stroke, hemorrhagic stroke, TIA, myocardial infarction, vascular death.

7 ‡ Severe or moderate bleeding and mild bleeding were defined according to GUSTO (Global Utilization of Streptokinase and Tissue
8 Plasminogen Activator for Occluded Coronary Arteries) criteria.

9