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Time Course for Benefit and Risk With Ticagrelor and Aspirin in Individuals With Acute Ischemic Stroke or Transient Ischemic Attack Who Carry *CYP2C19* Loss-of-Function Alleles

A Secondary Analysis of the CHANCE-2 Randomized Clinical Trial

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Key Points

Question

What is the time course for benefit and risk with dual antiplatelet therapy for individuals with minor ischemic stroke or transient ischemic attack (TIA) who carry *CYP2C19* loss-of-function (LOF) alleles?

Findings

In this secondary analysis of the Ticagrelor or Clopidogrel With Aspirin in High-risk Patients With Acute Nondisabling Cerebrovascular Events II (CHANCE-2) randomized clinical trial, the benefit with ticagrelor and aspirin was predominately present in the first week and persisted throughout the 21-day period of dual antiplatelet therapy with ticagrelor and aspirin in patients with a minor stroke or TIA who carried *CYP2C19* LOF alleles.

Meaning

The findings suggest that the benefit with ticagrelor and aspirin found in CHANCE-2 among patients with a minor ischemic stroke or TIA carrying *CYP2C19* LOF alleles was predominant in the first week, with a small benefit observed in the following 2 weeks.

Abstract

Importance

Dual antiplatelet therapy (DAPT) with ticagrelor and aspirin has been found to be effective for secondary prevention after minor ischemic stroke or transient ischemic attack (TIA) in individuals who carry *CYP2C19* loss-of-function (LOF) alleles; however, uncertainties remain about the time course of benefit and risk with ticagrelor and aspirin in these patients.

Objective

To obtain time-course estimates of efficacy and risk with ticagrelor and aspirin after minor stroke or TIA in individuals with *CYP2C19* LOF alleles.

Design, Setting, and Participants

The Ticagrelor or Clopidogrel With Aspirin in High-risk Patients With Acute Nondisabling Cerebrovascular Events II (CHANCE-2) randomized clinical trial enrolled patients 40 years and older from 202 hospitals in China with acute minor stroke or TIA who carried *CYP2C19* LOF alleles between September 23, 2019, and March 22, 2021, and were followed up for 90 days. All 6412 patients enrolled in the CHANCE-2 trial were included in this secondary analysis. Data were analyzed in October 2021.

Interventions

Ticagrelor (180 mg on day 1 followed by 90 mg twice daily on days 2-90) or clopidogrel (300 mg on day 1 followed by 75 mg daily on days 2-90). All patients received aspirin (75-300 mg on day 1 followed by 75 mg daily for 21 days).

Main Outcomes and Measures

The efficacy outcome was major ischemic event, defined as the composite of ischemic stroke or nonhemorrhagic death. Safety outcomes included moderate to severe bleeding and any bleeding.

Results

A total of 6412 patients were included (3205 in the ticagrelor and aspirin group and 3207 in the clopidogrel and aspirin group). The median (IQR) age was 65 (57-71) years, and 4242 patients (66%) were men. The reduction of major ischemic events with ticagrelor and aspirin predominately occurred in the first week (absolute risk reduction, 1.34%; 95% CI, 0.29 to 2.39) and attenuated but remained in the next 3 weeks (absolute risk reduction in the second week, 0.11%; 95% CI, −0.24 to 0.45; absolute risk reduction in the third week, 0.14%; 95% CI, −0.11 to 0.38; absolute risk reduction in the fourth week, 0.04%; 95% CI, −0.18 to 0.25). The risk of moderate to severe bleeding was consistently low in the ticagrelor and aspirin group. The absolute increase in any bleeding seen in the first week (0.87%; 95% CI, 0.25 to 1.50) remained in the next 3 weeks (absolute increase in the second week, 1.21%; 95% CI, 0.75 to 1.68; absolute increase in the third week, 0.33%; 95% CI, −0.05 to 0.72; absolute increase in the fourth week, 0.23%; 95% CI, −0.03 to 0.49).

Conclusion and Relevance

Among patients with minor stroke or TIA who carried *CYP2C19* LOF alleles, benefit with ticagrelor and aspirin was present predominately in the first week, with additional small benefit accruing in the next 2 weeks.

Introduction

Patients with an acute minor ischemic stroke or transient ischemic attack (TIA) experience a high short-term risk of subsequent stroke of approximately 5% to 10% during the first 3 months.[1,2,3] Dual antiplatelet therapy (DAPT) with $P2Y_{12}$ inhibitors added to aspirin started within 24 hours after symptoms onset has been shown to be an effective secondary prevention strategy for patients with minor stroke or TIA.[4,5,6] The major concern in clinical practice is that DAPT with $P2Y_{12}$ inhibitors ticagrelor or clopidogrel added to aspirin also modestly increases the risk of bleeding.

The Ticagrelor or Clopidogrel With Aspirin in High-risk Patients With Acute Nondisabling Cerebrovascular Events II (CHANCE-2) randomized clinical trial[7] evaluated the efficacy and safety of DAPT with ticagrelor and aspirin vs clopidogrel and aspirin in patients with minor ischemic stroke or high-risk TIA who carried *CYP2C19* loss-of-function (LOF) alleles. CHANCE-2 demonstrated that, in comparison with clopidogrel and aspirin, 21 days of DAPT with ticagrelor and aspirin followed by ticagrelor alone for days 22 through 90 reduced the risk of subsequent stroke (ischemic or hemorrhagic) without increasing the risk of severe or moderate bleeding at 90 days. However, an increased risk of overall bleeding was observed in the ticagrelor and aspirin group and the main analysis ignored overlap in the primary efficacy and safety outcome measures, which may obscure a direct comparison of benefits and harms. Furthermore, concerns remained

regarding the duration of DAPT with ticagrelor and aspirin for 21 days in the CHANCE-2 trial,[7] because long-term duration of DAPT has been associated with an increased risk of bleeding.[8,9] Practitioners continue to be concerned about the increased risk of bleeding with ticagrelor and aspirin. Therefore, the benefit-risk profile of DAPT with ticagrelor and aspirin for these patients is still unknown. Whether a different treatment period than 21 days of DAPT with ticagrelor and aspirin would improve the benefit-risk ratio of for these patients is unclear. In this exploratory secondary analysis of the CHANCE-2 trial,[7] we aimed to assess the time course of benefit and risk with DAPT with ticagrelor and aspirin vs clopidogrel and aspirin in patients with a minor ischemic stroke or high-risk TIA who carried *CYP2C19* LOF alleles.

Methods

Study Design and Participants

Details on the design, protocol, and primary results of CHANCE-2 have been published elsewhere.[7,10] In brief, the CHANCE-2 trial[7] was a randomized double-blind active-controlled trial enrolling 6412 patients from 202 hospitals in China between September 23, 2019, and March 22, 2021, to assess the efficacy and safety of DAPT with ticagrelor and aspirin vs clopidogrel and aspirin in individuals with minor ischemic stroke or TIA who carried *CYP2C19* LOF alleles (with at least 1 *CYP2C19* LOF allele [*2 or *3])[11] identified using a rapid point-of-care genotyping system.[12] Eligible patients in the trial were 40 years and older and diagnosed with an acute minor noncardioembolic ischemic stroke (National Institutes of Health Stroke Scale score 3 or lower) or high-risk TIA (ABCD[2] score 4 or greater) within 24 hours after symptom onset. Patients were not eligible for the trial if they had received intravenous thrombolytic therapy or mechanical thrombectomy; surgery or interventional treatment requiring study drug cessation were scheduled; they had a history of intracranial hemorrhage or amyloid angiopathy; they were currently receiving treatment with heparin therapy or oral anticoagulation; or they had a contraindication to ticagrelor, clopidogrel, or aspirin. The protocol of the trial was approved by the ethics committee at Beijing Tiantan Hospital and each participating site. All participants or their representatives provided written informed consent before enrollment. The trial protocol has been published elsewhere.[7]

Randomization and Treatment

We randomly assigned patients within 24 hours after symptom onset in a 1:1 ratio to 1 of the 2 treatment groups in a double-blind active-controlled design. Patients were randomly assigned a number corresponding to a medication kit, and then the medication in the kit was administered to the patient.

Patients were randomly assigned to receive either placebo clopidogrel plus ticagrelor (180-mg loading dose on day 1 followed by 90 mg twice daily for days 2 through 90) or placebo ticagrelor plus clopidogrel (300-mg loading dose on day 1 followed by 75 mg per day for days 2 through 90). All patients also received a 75- to 300-mg loading dose of aspirin followed by 75 mg daily for 21 days.

Outcomes

We collected efficacy and safety outcomes through face-to-face interviews by trained neurologists from participating sites. All ischemic and hemorrhagic events were verified by an independent central adjudication committee.[7] Stroke events were classified as ischemic or hemorrhagic, and bleeding events were classified as severe, moderate, or mild according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition.[7,13] The original primary efficacy outcome in the trial was new stroke (ischemic or hemorrhagic) at 90 days and the original primary safety outcome was severe or moderate bleeding according to the GUSTO definition at 90 days. In the present time-course benefit-risk analysis, we defined the efficacy outcome, major ischemic event, as the composite of ischemic stroke or nonhemorrhagic death[14] and included the safety outcomes of any bleeding and moderate to severe bleeding.[13] Severe bleeding was defined as fatal, intracranial, or other hemorrhage causing substantial hemodynamic compromise that required intervention. Moderate bleeding was defined as bleeding that did not lead to hemodynamic compromise requiring intervention but required transfusion of blood.[13] Net clinical benefit was also evaluated using the composite outcome of major ischemic event and moderate to severe bleeding, which included the combination of ischemic stroke, moderate to severe bleeding, and death. The outcomes of major ischemic event and moderate to severe bleeding were selected because they represent the expected main benefits and risks for antiplatelet drugs while avoiding double counting of events.[14]

Statistical Analysis

All efficacy and safety analyses were performed by the intention-to-treat principle based on the randomized treatment assignment. To determine the short-term temporal course of effect of ticagrelor and aspirin, we estimated the absolute number of events and absolute difference in proportions (clopidogrel and aspirin minus ticagrelor and aspirin) for the periods of each week for the first 5 weeks and sixth week through day 90 from randomization. This analysis covered the full period of treatment in the trial (90 days) and each week in the first 5 weeks (3 weeks with DAPT and 2 weeks with single antiplatelet therapy) in both arms.

Landmark analyses of ischemic benefit and hemorrhagic risk by week (the first 5 weeks and the sixth week through day 90) and periods from 0 to 21 days and 22 to 90 days (monoantiplatelet therapy was administered after 21 days in both arms) were performed in patients who were event free at the start of each period. For each interval with at least 1 event in each treatment group, the absolute risk differences in proportions (ticagrelor and aspirin minus clopidogrel and aspirin) and 95% CIs were estimated using generalized linear models, and hazard ratios (HRs) with 95% CIs were calculated using Cox proportional hazard models with study centers set as a random effect. We also evaluated the cumulative incidence of new events by treatment during cumulative periods of days 1 to 7, days 1 to 14, days 1 to 21, days 1 to 28, days 1 to 35, and days 1 to 90. Absolute risk differences in proportions and HRs with 95% CIs for each outcome were calculated for each cumulative period.

For the composite outcome of major ischemic event and moderate to severe bleeding, interactions between treatment assignment and prespecified subgroups were evaluated by including terms for treatment, subgroup, and treatment-by-subgroup interaction in the Cox model. In sensitivity analysis, we also calculated the net clinical benefit with ticagrelor and aspirin with different weights of the bleeding events for the total timeframe of the trial, periods by week, and periods from 0 to 21 days and from 22 to 90 days, respectively. The number of moderate to severe bleeding events and mild bleeding events (bleeding events other than moderate to severe bleeding) attributable to ticagrelor and aspirin was subtracted from the number of major ischemic events prevented by ticagrelor and aspirin with the weight of 0.5 to 1.2 and 0 to 0.5, respectively: net clinical benefit = (major ischemic event [clopidogrel and aspirin group] − major ischemic event [ticagrelor and aspirin group]) − weight (moderate to severe bleeding) × (moderate to severe bleeding [ticagrelor and aspirin group] − moderate to severe bleeding [clopidogrel and aspirin group]) − weight (mild bleeding) × (mild bleeding [ticagrelor and aspirin group] − mild bleeding [clopidogrel and aspirin group]). The weights account for the effects of a moderate to severe (weight [moderate to severe bleeding]) or mild (weight [mild bleeding]) bleeding event compared with a major ischemic event.[3,15,16] When the weight for mild bleeding was set to 0, the values corresponded to the net clinical benefit when only moderate to severe bleeding events considered. All analyses presented were exploratory. No adjustment for multiple comparisons was made, and all *P* values were nominal. All statistical analyses were performed with SAS version 9.4 (SAS Institute). Two-sided *P* values <.05 were considered statistically significant.

Results

A total of 6412 patients with minor ischemic stroke or TIA who carried *CYP2C19* LOF alleles were randomized in the CHANCE-2 trial,[7] including 3205 patients in the ticagrelor and aspirin group and 3207 in the clopidogrel and aspirin group. The median (IQR) age was 65 (57-71) years, and 4242 patients (66%) were men. All randomized patients were included in this secondary analysis.

The Figure shows the time-course distribution of the absolute treatment difference in major ischemic events and moderate to severe bleeding events. The largest reduction of major ischemic events by ticagrelor and aspirin occurred in the first week (4.2% vs 5.5%; absolute risk reduction, 1.34%; 95% CI, 0.29 to 2.39, with a number needed to treat of 75) and attenuated but remained in the next 3 weeks (absolute risk reduction in the second week, 0.11%; 95% CI, −0.24 to 0.45; absolute risk reduction in the third week, 0.14%; 95% CI, −0.11 to 0.38; absolute risk reduction in the fourth week, 0.04%; 95% CI, −0.18 to 0.25) (Figure; eTable in the Supplement). Cumulative analysis showed that the reduction of major ischemic events by ticagrelor and aspirin in the first week remained throughout the 90-day treatment period (Table 1). There were 2 fewer moderate to severe bleeding events in the ticagrelor and aspirin group, and risk was relatively constant during the 90-day treatment period. The absolute increase in any bleeding event in the first week (2.1% vs 1.2%; absolute risk increase, 0.87%; 95% CI, 0.25 to 1.50, with a number needed to harm of 115) remained in the next 3 weeks (absolute increase in the second week, 1.21%; 95% CI, 0.75 to 1.68; absolute increase in the third week, 0.33%; 95% CI, −0.05 to 0.72; and absolute increase in the fourth week, 0.23%; 95% CI, −0.03 to 0.49) (eTable in the Supplement). Cumulative analysis showed that the absolute increase in any bleeding event seen during the first week remained relatively constant in the following weeks (Table 1). Landmark analysis at 21 days showed that reduc-

tion of major ischemic events (4.7% vs 6.3%; absolute risk reduction, 1.56%; 95% CI, 0.44 to 2.67, with a number needed to treat of 64) and increase in any bleeding event (4.3% vs 1.9%; absolute risk increase, 2.37%; 95% CI, 1.52 to 3.22, with a number needed to harm of 42) was observed within the first 21 days (DAPT in both arms) but not during the period from day 22 to day 90 (single antiplatelet therapy in both arms) (Table 2).

The net clinical benefit with the composite outcome of major ischemic event and moderate to severe bleeding favored ticagrelor and aspirin in the first week (absolute risk reduction, 1.49%; 95% CI, 0.43 to 2.56) and remained in the next 3 weeks (absolute risk reduction in the second week, 0.04%; 95% CI, −0.32 to 0.40; absolute risk reduction in the third week, 0.10%; 95% CI, −0.15 to 0.35; absolute risk reduction in the fourth week, 0.07%; 95% CI, −0.16 to 0.29) (Table 1; eTable in the Supplement). The net clinical benefit was consistently observed across the prespecified subgroups, except that greater absolute net benefit was observed in patients without previous ischemic stroke or TIA than in those with previous ischemic stroke or TIA (eFigure 1 in the Supplement).

In sensitivity analysis, ticagrelor and aspirin had a positive net clinical benefit in the total period of 90 days and mainly in the first week, regardless of the weight of a moderate to severe bleeding event (between 0.5- to 1.2-fold greater) and the weight of a mild bleeding event (between 0- to 0.5-fold greater) compared with a major ischemic event (eFigure 2 in the Supplement; Table 3). Landmark analysis showed that ticagrelor and aspirin had a positive net clinical benefit within the first 21 days, but a negligible net benefit in the period from day 22 to day 90, regardless of the weights of the moderate to severe and mild bleeding events (eFigure 2 in the Supplement).

Discussion

In this post hoc exploratory analysis of CHANCE-2[7] including patients with minor ischemic stroke or TIA who carried *CYP2C19* LOF alleles, we found that the benefit with ticagrelor and aspirin compared with clopidogrel and aspirin predominately reduced the risk of major ischemic events in the first week, with additional attenuated benefit accruing in the second and third weeks of treatment. The overall risk of moderate to severe bleeding was low, but the increased risk of overall bleeding with ticagrelor and aspirin at the early stage persisted for the first 4 weeks. The net clinical benefit with ticagrelor and aspirin over clopidogrel and aspirin treatment may be predominant in the first week, with additional small benefit accruing in the second and third weeks.

Intensive antiplatelet therapy with potent platelet inhibition may reduce ischemic event rates but may also increase the risk of bleeding, which is a concern with $P2Y_{12}$ inhibitors added to aspirin in clinical practice.[17] Prolonged duration of DAPT is potentially associated with increased risk of bleeding in patients with ischemic stroke or TIA.[18] A previous time-course analysis[15] of the Clopidogrel With Aspirin in High-risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) trial[19] indicated that the net clinical benefit with DAPT with clopidogrel and aspirin in patients with minor stroke or TIA might be limited to the first 2 weeks. A secondary analysis[20] of the Platelet Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial[21] and the pooled analysis[3] of the CHANCE and POINT trials demonstrated that the benefit with DAPT with

clopidogrel and aspirin in patients with minor stroke or high-risk TIA occurred predominately within the first 21 days and that longer duration DAPT may increase hemorrhagic risk without additional ischemic benefit.

Clopidogrel is a commonly used antiplatelet agent but requires hepatic conversion that is influenced by *CYP2C19* genetic polymorphisms.[11,22] In contrast, ticagrelor reversibly blocks the platelet $P2Y_{12}$ receptor without requirement of metabolic activation.[23] Guidelines recommend ticagrelor as an alternative antiplatelet agent for use with aspirin, especially for patients who carry *CYP2C19* LOF alleles.[4] However, DAPT with ticagrelor and aspirin may also cause a small increase in bleeding. To our knowledge, no previous study has investigated the time course of benefit and risk with ticagrelor and aspirin vs clopidogrel and aspirin treatment in patients with minor stroke or TIA who carry *CYP2C19* LOF alleles. In addition to the overall effect of DAPT in the main analysis of the CHANCE-2 trial,[7] the present analysis directly compared and described the time course of the benefit (reduction in major ischemic events) and harm (increase in bleeding) with DAPT with ticagrelor and aspirin vs clopidogrel and aspirin in these patients. The results of the present study indicated that the net benefit with ticagrelor and aspirin treatment was largely realized in the first week but with additional small benefit accruing in the second and third weeks of treatment, regardless of whether mild bleeding events were considered. This demonstrated that the benefit with ticagrelor over clopidogrel was predominately present in the short term, which may be related to the fast action of ticagrelor. Nevertheless, numerical benefit and no evidence of harm were observed in the second and third weeks of treatment, although the trial was not powered to identify impacts in these periods. Whether DAPT with ticagrelor and aspirin should be administrated as a 1-week regimen needs further investigation with larger sample size.

Limitations

This study has several limitations. First, this secondary analysis of the temporal course of treatment is exploratory, although it does support the main trial design and findings. All patients were randomized to 21 days of DAPT followed by single antiplatelet therapy from day 22 to day 90. Moreover, the landmark analyses in each stratified period were hampered by low power with small sample size, especially for the event of moderate to severe bleeding. Second, the generalizability of these results was limited to patients with an acute minor ischemic stroke or high-risk TIA who carried *CYP2C19* LOF alleles. The results cannot be generalized to patients with major stroke who may be more at risk of hemorrhagic transformation[24] or those who metabolize clopidogrel normally. Third, the CHANCE-2 trial[7] enrolled exclusively Chinese patients, who may be more susceptible to bleeding,[25] have a high proportion of intracranial artery stenosis (30% to 50% in Asian vs 8% in non-Asian patients[26,27]), and more frequently carry of the *CYP2C19* LOF allele (eg, 60% in Asian individuals vs 25% in White individuals[22]). Secondary prevention practices also may differ in China compared with other countries. Therefore, the generalizability of these findings needs further validation in non-Chinese populations who have different demographic characteristics and disease patterns. Fourth, although sensitivity analysis of net clinical benefit was performed with different weighting assumptions, there is no definite weight of a bleeding event compared with a major ischemic event. Nonetheless, ischemic events produced permanent injury and most hemorrhages were mild and transitory.

Conclusions

In conclusion, this exploratory time-course analysis suggests that the ischemic benefit with ticagrelor and aspirin treatment occurring predominantly in the first week may outweigh the risk of bleeding throughout the 21-day period of DAPT in patients with minor ischemic stroke or TIA who carried *CYP2C19* LOF alleles. This analysis does not support shortening the 21-day regimen of DAPT with ticagrelor and aspirin demonstrated in the CHANCE-2 trial.[7]

Notes

Supplement.

eFigure 1. Absolute risk differences between ticagrelor-aspirin and clopidogrel-aspirin on composite of major ischemic event and moderate-severe bleeding in predefined subgroups

eFigure 2. Sensitivity analysis of net clinical benefit

eTable. Landmark analysis of benefit and risk by week after randomization

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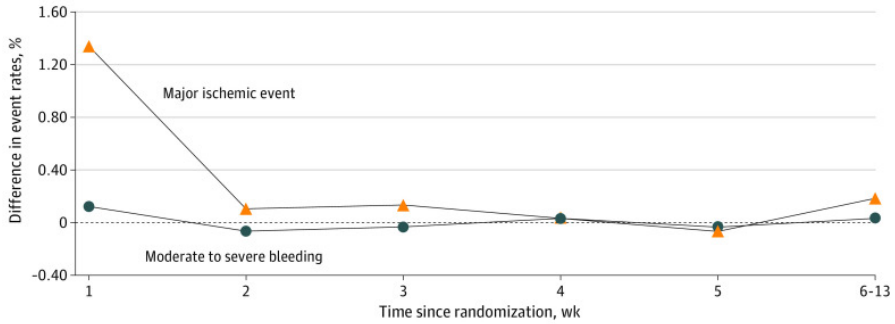
Figures and Tables

Figure.



Major ischemic event	Patient, No.	Total events	No. of events (event rate), wk 1	2	3	4	5	6-13
CLP + ASA	3207	247	176	16	9	6	2	38
TIC + ASA	3205	193	133	13	5	5	4	33
Difference	6412	54	43 (1.3%)	3 (0.1%)	4 (0.1%)	1 (0.04%)	-2 (-0.1%)	5 (0.2%)
Moderate to severe bleeding								
CLP + ASA	3207	11	7	0	0	1	0	3
TIC + ASA	3205	9	3	2	1	0	1	2
Difference	6412	2	4 (0.1%)	-2 (-0.1%)	-1 (-0.03%)	1 (0.03%)	-1 (-0.03%)	1 (0.03%)

Time Course of the Absolute Treatment Difference

Major ischemic event was defined as the composite of ischemic stroke and nonhemorrhagic death. Moderate or severe bleeding was defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria. ASA indicates aspirin; CLP, clopidogrel; TIC, ticagrelor.

Table 1.

Cumulative Analysis of Benefit and Risk by Week After Randomization

Outcome	Time interval	Ticagrelor + aspirin, No. of events (n = 3205)		Clopidogrel + aspirin, No. of events (n = 3205)		Risk difference (95% CI), %	Hazard ratio (95% CI)	*P* value
Composite of major ischemic event[a] and moderate to severe bleeding[b]	Day 1-7	3205	135 (4.21)	3207	183 (5.71)	−1.49 (−2.56 to −0.43)	0.73 (0.58 to 0.91)	.005
	Day 1-14	3205	150 (4.68)	3207	199 (6.21)	−1.53 (−2.64 to −0.42)	0.74 (0.60 to 0.92)	.006
	Day 1-21	3205	156 (4.87)	3207	208 (6.49)	−1.62 (−2.75 to −0.49)	0.74 (0.60 to 0.91)	.005
	Day 1-28	3205	161 (5.02)	3207	215 (6.70)	−1.68 (−2.83 to −0.53)	0.74 (0.60 to 0.91)	.004
	Day 1-35	3205	165 (5.15)	3207	217 (6.77)	−1.62 (−2.78 to −0.46)	0.75 (0.61 to 0.92)	.005
	Day 1-90	3205	200 (6.24)	3207	257 (8.01)	−1.77 (−3.03 to −0.52)	0.77 (0.64 to 0.92)	.005
Major ischemic event[a]	Day 1-7	3205	133 (4.15)	3207	176 (5.49)	−1.34 (−2.39 to −0.29)	0.75 (0.59 to 0.93)	.01
	Day 1-14	3205	146 (4.56)	3207	192 (5.99)	−1.43 (−2.53 to −0.34)	0.75 (0.60 to 0.93)	.008
	Day 1-21	3205	151 (4.71)	3207	201 (6.27)	−1.56 (−2.67 to −0.44)	0.74 (0.60 to 0.92)	.006
	Day 1-28	3205	156 (4.87)	3207	207 (6.45)	−1.59 (−2.72 to −0.46)	0.74 (0.60 to 0.92)	.005
	Day 1-35	3205	160 (4.99)	3207	209 (6.52)	−1.53 (−2.66 to −0.39)	0.76 (0.61 to 0.93)	.008
	Day 1-90	3205	193 (6.02)	3207	247 (7.70)	−1.68 (−2.92 to −0.44)	0.77 (0.64 to 0.93)	.006
Moderate to severe bleeding[b]	Day 1-7	3205	3 (0.09)	3207	7 (0.22)	−0.13 (−0.32 to 0.07)	0.43 (0.11 to 1.68)	.23
	Day 1-14	3205	5 (0.16)	3207	7 (0.22)	−0.06 (−0.27 to 0.15)	0.72 (0.23 to 2.26)	.57
	Day 1-21	3205	6 (0.19)	3207	7 (0.22)	−0.03 (−0.25 to 0.19)	0.86 (0.29 to 2.56)	.79

[a] Major ischemic event was defined as the composite of ischemic stroke and nonhemorrhagic death.

[b] Moderate or severe bleeding was defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria.

Table 2.

Landmark Analysis of Benefit and Risk at 21 Days After Randomization

Outcome	Time interval	Ticagrelor-aspirin		Clopidogrel-aspirin		Risk difference (95% CI), %	Hazard ratio (95% CI)	*P* value
		No. of patients	No. of events (%)	No. of patients	No. of events (%)			
Composite of major ischemic event[a] and moderate to severe bleeding[b]	Day 1-21	3205	156 (4.9)	3207	208 (6.5)	−1.62 (−2.75 to −0.49)	0.74 (0.60 to 0.91)	.005
	Day 22-90	3049	44 (1.4)	2999	49 (1.6)	−0.19 (−0.81 to 0.43)	0.87 (0.58 to 1.31)	.50
Major ischemic event[a]	Day 1-21	3205	151 (4.7)	3207	201 (6.3)	−1.56 (−2.67 to −0.44)	0.74 (0.60 to 0.92)	.006
	Day 22-90	3052	42 (1.4)	3003	46 (1.5)	−0.16 (−0.76 to 0.45)	0.88 (0.58 to 1.34)	.56
Moderate to severe bleeding[b]	Day 1-21	3205	6 (0.2)	3207	7 (0.2)	−0.03 (−0.25 to 0.19)	0.86 (0.29 to 2.56)	.79
	Day 22-90	3196	3 (0.1)	3189	4 (0.1)	−0.03 (−0.19 to 0.13)	0.75 (0.17 to 3.36)	.71
Any bleeding	Day 1-21	3205	138 (4.3)	3207	62 (1.9)	2.37 (1.52 to 3.22)	2.30 (1.70 to 3.12)	<.001
	Day 22-90	3064	32 (1.0)	3134	18 (0.6)	0.47 (0.02 to 0.92)	1.75 (0.98 to 3.13)	.06

[a] Major ischemic event was defined as the composite of ischemic stroke or nonhemorrhagic death.

[b] Major hemorrhage was defined as moderate or severe bleeding according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria.

Table 3.

Sensitivity Analysis of Net Clinical Benefit by Week

Weight (moderate-severe bleeding)	Net clinical benefit[a]					
	1st wk	2nd wk	3rd wk	4th wk	5th wk	6th wk-day 90
0.5	45, 41.9, 29.5	2, −1.6, −16	3.5, 2.6, −1	1.5, 0.7, −2.5	−2.5, −2.5, −2.5	5.5, 4.7, 1.5
0.6	45.4, 42.3, 29.9	1.8, −1.8, −16.2	3.4, 2.5, −1.1	1.6, 0.8, −2.4	−2.6, −2.6, −2.6	5.6, 4.8, 1.6
0.7	45.8, 42.7, 30.3	1.6, −2, −16.4	3.3, 2.4, −1.2	1.7, 0.9, −2.3	−2.7, −2.7, −2.7	5.7, 4.9, 1.7
0.8	46.2, 43.1, 30.7	1.4, −2.2, −16.6	3.2, 2.3, −1.3	1.8, 1, −2.2	−2.8, −2.8, −2.8	5.8, 5, 1.8
0.9	46.6, 43.5, 31.1	1.2, −2.4, −16.8	3.1, 2.2, −1.4	1.9, 1.1, −2.1	−2.9, −2.9, −2.9	5.9, 5.1, 1.9
1.0	47, 43.9, 31.5	1, −2.6, −17	3, 2.1, −1.5	2, 1.2, −2	−3, −3, −3	6, 5.2, 2
1.1	47.4, 44.3, 31.9	0.8, −2.8, −17.2	2.9, 2, −1.6	2.1, 1.3, −1.9	−3.1, −3.1, −3.1	6.1, 5.3, 2.1
1.2	47.8, 44.7, 32.3	0.6, −3, −17.4	2.8, 1.9, −1.7	2.2, 1.4, −1.8	−3.2, −3.2, −3.2	6.2, 5.4, 2.2

[a] Net clinical benefit was calculated as: net clinical benefit = (major ischemic event [clopidogrel-aspirin group] − major ischemic event [ticagrelor-aspirin group]) − weight (moderate-severe bleeding) × (moderate-severe bleeding [ticagrelor-aspirin group] − moderate-severe bleeding [clopidogrel-aspirin group]) − weight (mild bleeding) × (mild bleeding [ticagrelor-aspirin group] − mild bleeding [clopidogrel-aspirin group]). The weights account for the effects of a moderate to severe (weight [moderate-severe bleeding]) or mild (weight [mild bleeding]) bleeding incident compared with a major ischemic event. Major ischemic event included ischemic stroke and nonhemorrhagic death. Data represented net clinical benefit with weight (mild bleeding) of 0, 0.1, and 0.5.