Comparison of prasugrel and clopidogrel in patients with non-cardioembolic ischaemic stroke: a phase 3, randomised, non-inferiority trial (PRASTRO-I)

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Summary

Background The effect of prasugrel in terms of the prevention of recurrence of ischaemic stroke is unknown. We investigated the non-inferiority of prasugrel to clopidogrel for prevention of ischaemic stroke, myocardial infarction, and death from other vascular causes in Japanese patients with non-cardioembolic stroke.

Methods In this phase 3 randomised, double-blind, non-inferiority trial, patients aged 20–74 years who had had a non-cardioembolic stroke in the previous 1–26 weeks were recruited from 224 hospitals in Japan. Eligible patients were randomly assigned (1:1) to receive prasugrel (3·75 mg/day) or clopidogrel (75 mg/day) orally for 96–104 weeks. Randomisation was stratified according to stroke subtype. The randomisation schedule was generated by an independent statistician who created a computer-generated random number sequence. Patients, investigators, and the funder were masked to treatment allocation. The primary endpoint was combined incidence of ischaemic stroke (fatal and non-fatal), myocardial infarction (fatal and non-fatal), and death from other vascular causes in the intention-to-treat population. The safety endpoint was incidence of bleeding events, comprising life-threatening bleeding, major bleeding, and clinically relevant bleeding. The safety analysis was done in the population excluding trial patients with serious Good Clinical Practice violations, and those who had not taken the trial drug. The predefined non-inferiority margin was an upper 95% CI limit for the risk ratio (RR) of 1·35. The trial was registered with the Japan Pharmaceutical Information Center (JapicCTI-111582).

Findings Patients were recruited between Sept 1, 2011, and June 12, 2015. 3747 patients (797 [21%] women) were enrolled, with a mean age of 62·1 (SD 8·5) years. 3753 patients were randomly assigned to treatment and, of these patients, 1885 in the prasugrel group and 1862 in the clopidogrel group were confirmed to have taken the trial drug at least once, and six patients withdrew from the trial before administration of the trial drug. Thus, a total of 3747 patients were included in the full analysis set. 73 (4%) of 1885 patients in the prasugrel group and 69 (4%) of 1862 patients in the clopidogrel group reached the primary endpoint (RR 1·05, 95% CI 0·76–1·44). The incidence of bleeding events was not significantly different between treatment groups; life-threatening bleeding was observed in 18 (1%) patients in the prasugrel group and 23 (1%) patients in the clopidogrel group (RR 0·77, 0·41–1·42).

Interpretation The non-inferiority of prasugrel to clopidogrel for the prevention of ischaemic stroke, myocardial infarction, and death from other vascular causes was not confirmed in Japanese patients with non-cardioembolic stroke. No safety concerns were identified.

Funding Daiichi Sankyo.

Introduction

Guidelines for the management of stroke recommend antiplatelet therapy for the secondary prevention of non-cardioembolic stroke. Currently, several antiplatelet agents, including clopidogrel and aspirin, are used;[1,2] however, even with the administration of these drugs, the risk of recurrent stroke is high (between 3% and 10% recurrence at 1 year after the index event).[3] Thus, further improvement of the efficacy of antiplatelet therapy is necessary. An issue yet to be resolved is the management of patients who respond poorly to aspirin and clopidogrel[4,5] who are at high risk of major adverse cardiovascular events with antiplatelet treatment.[6–8] Genetic polymorphisms of CYP2C19 have been identified as the major cause of poor responsiveness to clopidogrel.[9] Asian people have a much higher likelihood than white people of being poor metabolisers of CYP2C19;[10] this means that clopidogrel monotherapy might be less effective for secondary stroke prevention in Asia than in non-Asian population countries.

Prasugrel, a P2Y12 receptor antagonist, has the potential to inhibit platelet aggregation more rapidly, more consistently, and to a greater extent than clopidogrel, and independently of CYP2C19 genetic polymorphism status.[11–14] In the USA and European countries, prasugrel (10 mg/day as a maintenance dose) is contraindicated

Research in context

Evidence before this study

We searched PubMed from Feb 5 to 9, 2018, for relevant articles, using the search terms "antiplatelet therapy", "clopidogrel", "cilostazol", "aspirin", "ticlopidine", "stroke", "cerebral ischemia", and "cerebral infarction". We also manually searched references from original articles and pertinent reviews. Searches were restricted to completed trials in human beings with abstracts or full texts published in English.

Guidelines for the management of stroke recommend antiplatelet therapy for the secondary prevention of non-cardioembolic stroke, and the use of clopidogrel or aspirin (including the combination of aspirin and extended-release dipyridamole) is highly recommended worldwide. However, even under antiplatelet treatment, poor responders to aspirin and clopidogrel are at high risk for major adverse cardiovascular events. In Japanese patients with acute coronary syndrome, a once-daily dose of prasugrel (3·75 mg; approximately one-third of the approved maintenance dose in the USA and EU) in combination with aspirin was associated with a lower incidence of major adverse cardiovascular events and major bleeding compared with clopidogrel plus aspirin in a randomised controlled trial. In a multicentre, randomised, double-blind study, a significant reduction in P2Y12 reaction units was noted in patients with non-cardioembolic stroke after treatment with prasugrel at a dose of 3·75 mg/day, as compared with the predose value (ie, the value after clopidogrel administration and before prasugrel administration in a crossover study) after treatment with clopidogrel. However, the efficacy of prasugrel for the prevention of recurrent ischaemic stroke is unknown.

Added value of this study

To our knowledge, our study is the first large phase 3 trial to compare prasugrel at 3·75 mg/day with clopidogrel at 75 mg/day for secondary stroke prevention in Japanese patients with non-cardioembolic stroke.

Implications of all the available evidence

The non-inferiority of prasugrel (3·75 mg/day) to clopidogrel (75 mg/day) could not be confirmed in this population. However, in terms of number of events, prasugrel showed similar efficacy to clopidogrel; thus, it might be possible to switch clopidogrel in patients in whom clopidogrel was ineffective. Nevertheless, further studies are needed.

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in patients with acute coronary syndrome who have received aspirin and have a history of stroke or transient ischaemic attacks. The results of the TRITON-TIMI 38 study[15] showed higher incidences of major adverse cardiovascular and bleeding events with prasugrel than with clopidogrel in this subgroup of patients. To avoid such bleeding complications, prasugrel at 3·75 mg/day, approximately one-third of the approved maintenance dose in the USA and EU, was chosen for Japanese patients with acute coronary syndrome in the PRASFIT-ACS study.[16] In the PRASFIT-ACS study, low-dose prasugrel was associated with a lower incidence of major adverse cardiovascular events than clopidogrel: at 24 weeks, incidence of major adverse cardiovascular events was 9·4% in the prasugrel group and 11·8% in the clopidogrel group (risk reduction 23%; hazard ratio [HR] 0·77, 95% CI 0·56–1·07).[16] Low-dose prasugrel was also associated with a low incidence of thrombolysis in myocardial infarction major bleeding.[16] Moreover, 3·75 mg/day of prasugrel showed a higher inhibitory potency for adenosine diphosphate-induced platelet aggregation than did clopidogrel in Japanese patients with ischaemic stroke—a result that was independent of CYP2C19 genotype (unpublished). Thus, use of this low-dose prasugrel monotherapy might be another strategy for the prevention of stroke recurrence.

The results of a multicentre, randomised, double-blind study showed a significant reduction in P2Y12 reaction units in patients with non-cardioembolic stroke after treatment with 3·75 mg/day of prasugrel, as compared with the predose value (ie, the value after clopidogrel administration and before prasugrel administration in a crossover study), after treatment with clopidogrel.[17] However, the efficacy of prasugrel for the prevention of recurrent stroke is unknown.

We did this PRASTRO-I phase 3 trial to investigate the non-inferiority of 3·75 mg/day of prasugrel compared with 75 mg/day clopidogrel for the prevention of ischaemic stroke, myocardial infarction, and death from other vascular causes in Japanese patients with non-cardioembolic stroke.

Methods

Study design

In this randomised, double-blind, active-controlled, parallel group, multicentre, non-inferiority trial, patients with non-cardioembolic stroke were recruited from 224 hospitals in Japan between Sept 1, 2011, and June 12, 2015. The trial adhered to the ethical principles of the Declaration of Helsinki as well as Good Clinical Practice guidelines. The trial protocol was approved by the institutional review boards of the respective participating institutions (appendix), and all patients gave written informed consent. Full details of the trial protocol were previously published.[18]

See Online for appendix

Patients

Patients were eligible if they were aged 20–74 years at the time of providing consent; they weighed more than 50 kg; the interval from last stroke to time of consent was 1–26 weeks; and they had ischaemic lesions corresponding with the neurological symptoms confirmed by CT or MRI. A full list of exclusion criteria were previously published,[18] with the primary criteria being presence of

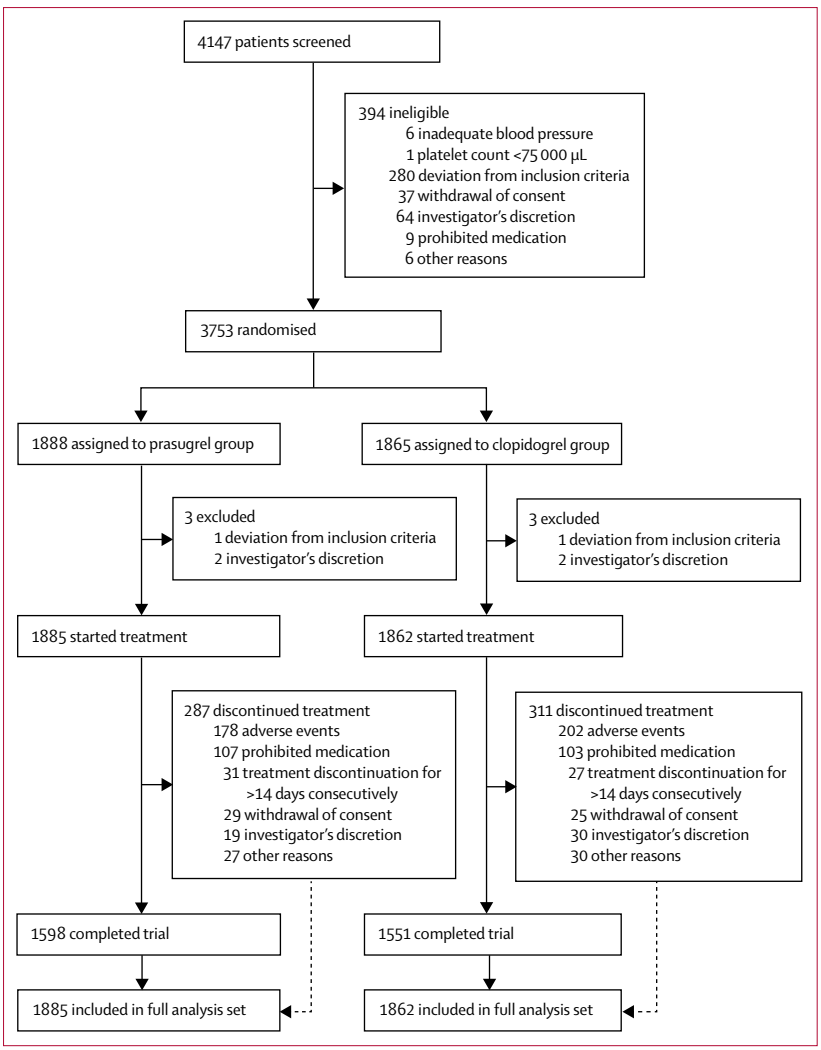

Figure 1: **Trial profile**

cardioembolic stroke or cardiovascular disease causing cardioembolic stroke, requirement for coadministration of other antiplatelet agents, current evidence or increased risk of intracerebral or subarachnoid haemorrhage, and poorly controlled hypertension.

Non-cardioembolic stroke was defined as the composite of large artery atherosclerosis and small artery occlusion (lacunae), acute stroke of other determined aetiology, and stroke of undetermined aetiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[19]

Randomisation and masking

Patients were randomly assigned (1:1) to receive 3·75 mg/day of prasugrel or 75 mg/day of clopidogrel. Randomisation was done by use of the stratified randomisation method, according to stroke subtype of large artery disease and small artery disease. Other stroke subtypes were not considered for stratification during randomisation. The randomisation schedule was generated by an independent statistician, who used SAS software, version 9.2, to create a computer-generated random number sequence. Staff at the patient registration centre (Bell Medical Solutions, Tokyo, Japan) informed investigators of the numbers showing the randomisation schedule via a website, sequentially. Patients, investigators, and funder were masked to treatment allocation using the double-dummy design; ie, patients in the prasugrel group received prasugrel and indistinguishable placebo of clopidogrel and those in the clopidogrel group received clopidogrel and indistinguishable placebo of prasugrel.

Procedures

Patients received either prasugrel (3·75 mg) or clopidogrel (75 mg) orally once daily after breakfast for 96–104 weeks. During the trial, blood pressure was controlled, by measures that included antihypertensive medication at the discretion of the attending physician, to achieve a target level of less than 140/90 mmHg. Concomitant use of antiplatelet agents other than trial drugs, anticoagulants, thrombolytic agents, acidic non-steroidal anti-inflammatory drugs, and study drugs other than those the participant was randomly assigned to receive was prohibited throughout the trial period. Use of prohibited drugs was checked at weeks 2 and 4 after the treatment start, and every 4 weeks thereafter until the last visit.

Outcomes

The primary efficacy endpoint was the combined incidence of ischaemic stroke (fatal and non-fatal), myocardial infarction (fatal and non-fatal), and death from other vascular causes, occurring from administration of the first dose of trial drug to 1 day after the last dose of trial drug or to discontinuation. The secondary endpoints were the incidences of ischaemic stroke, myocardial infarction, death from other vascular causes, any stroke, and haemorrhagic stroke. The primary safety endpoint was the incidence of bleeding events, comprising life-threatening bleeding, major bleeding, and clinically relevant bleeding. The definitions of efficacy and bleeding events are provided in the appendix. The efficacy event committee and the bleeding event committee (appendix), both of which were independent from the funder, evaluated the efficacy events and bleeding events, respectively, under masked conditions. Adverse events were recorded throughout the study period. Adverse events were defined as any unfavourable and unintended sign (including an abnormal laboratory value or abnormal vital sign), symptom, or disease that developed between the start of study treatment and the end of the follow-up period, regardless of relationship to the study drug. Serious adverse events were defined as death or life-threatening adverse events, adverse events that required admission to hospital or prolongation of treatment in hospital, persistent or significant disability or incapacity (including potential disability), congenital anomaly

or birth defect, or serious cases that were considered equivalent to those already mentioned.

Subgroup analyses were done as prespecified in the protocol.[18] The composite of large artery atherosclerosis and small artery occlusion was selected post hoc.

Statistical analysis

Cumulative incidences for the primary efficacy endpoints were estimated by the Kaplan-Meier method. A Cox proportional hazard regression was also done with a model including a covariate for the number of days from the date of onset of the index stroke to the date the treatment started (<4 weeks, 4 to <12 weeks, or ≥12 weeks). The HR (95% CI) for prasugrel relative to clopidogrel was then calculated. Forest plots summarising treatment effects across subgroups were created by using the same Cox model (the $p_{interaction}$ value was calculated with the same model, with inclusion of an interaction term for the treatment group and subgroup factor).

Incidences and 95% CIs of the secondary efficacy endpoints were calculated for each treatment group, as well as risk ratios (RRs) and 95% CIs for the prasugrel group compared with the clopidogrel group. Incidences of the safety endpoints (bleeding events) were summarised with HR (95% CI) based on Cox proportional hazard regression without covariates. The efficacy analysis was done on the full analysis set, defined as the population excluding trial patients with major violations of the Good Clinical Practice guidelines, those who had not taken the trial drug, and those for whom there were no data after taking the trial drug. The safety analysis was done on the population excluding trial patients with serious Good Clinical Practice violations, and those who had not taken the trial drug.

In accordance with instructions from regulatory authorities, and because the participants of the present study were Japanese, we based the non-inferiority margin on event rates for aspirin and clopidogrel from Japanese studies. Based on the combined annual incidence of cerebral infarction and vascular event-related death (5·35%) in the aspirin group reported in the S-ACCESS study,[20] the annual incidence of cerebrovascular events in patients taking aspirin was estimated as 5·4%. Assuming the annual incidence of ischaemic stroke, myocardial infarction, and death from other vascular causes in patients taking clopidogrel as 4% at 1 year, based on the results of the Japanese phase 3 trial of clopidogrel,[21] the RR in patients taking aspirin relative to those taking clopidogrel was estimated as 1·35 (5·4% risk in patients receiving aspirin *vs* 4% risk in patients receiving clopidogrel). Consequently, and assuming the relative risk to remain stable over 2 years of treatment, the non-inferiority margin for our trial was determined to be 1·35.

We assumed a combined incidence of ischaemic stroke, myocardial infarction, and death from other vascular causes of 7% in 2 years of treatment with 75 mg/day of clopidogrel, on the basis of the results of the Japanese phase 3 trial of clopidogrel,[21] with 15% of the relative risk reduction for prasugrel 3·75 mg/day. With the non-inferiority margin (1·35), we calculated the number of patients for the conditions (one-sided α=2·5%) and statistical power of 80%, and determined the target number of patients as 2200. However, as of April 14, 2014,

	Prasugrel group (n=1885)	Clopidogrel group (n=1862)
Age, years	61·9 (8·7)	62·4 (8·4)
Sex		
Female	386 (20%)	411 (22%)
Male	1499 (80%)	1451 (78%)
Weight, kg	65·8 (10·5)	65·4 (9·7)
Body-mass index, kg/m²	24·5 (3·2)	24·4 (3·0)
Time between onset of index stroke and trial treatment		
<4 weeks	316 (16·8)	322 (17·3)
≥4 weeks to <12 weeks	1038 (55·1)	1032 (55·4)
≥12 weeks	531 (28·2)	508 (27·3)
Type of stroke		
Large artery atherosclerosis	553 (29%)	546 (29%)
Small artery occlusion (lacunae)	583 (31%)	593 (32%)
Acute stroke of other determined aetiology	35 (2%)	49 (3%)
Stroke of undetermined aetiology*	714 (38%)	674 (36%)
Modified Rankin Scale grade		
0	444 (24%)	450 (24%)
1	1026 (54%)	1028 (55%)
2	291 (15%)	273 (15%)
3	88 (5%)	75 (4%)
4	36 (2%)	36 (2%)
History of atherosclerotic disease		
Ischaemic stroke	218 (12%)	211 (11%)
Transient ischaemic attack	99 (5%)	93 (5%)
Comorbidities		
Hypertension	1505 (80%)	1510 (81%)
Dyslipidaemia	1296 (69%)	1305 (70%)
Diabetes	611 (32%)	636 (34%)
Concomitant medication at baseline		
Statin	865 (46%)	893 (48%)
Insulin	60 (3%)	56 (3%)
Proton pump inhibitor	619 (33%)	574 (31%)
Angiotensin receptor blocker	907 (48%)	904 (49%)
Smoking status		
Never smoker	495 (26%)	518 (28%)
Former smoker	1005 (53%)	955 (51%)
Current smoker	385 (20%)	389 (21%)
Blood pressure, mmHg		
Systolic	134·3 (14·6)	134·5 (14·8)
Diastolic	79·9 (10·7)	79·5 (10·9)

(Table 1 continues on next page)

	Prasugrel group (n=1885)	Clopidogrel group (n=1862)
(Continued from previous page)		
CYP2C19 phenotype†		
Extensive metaboliser	581 (33%)‡	582 (34%)§
Intermediate metaboliser	861 (49%)‡	837 (49%)§
Poor metaboliser	300 (17%)‡	300 (17%)§
LDL cholesterol, mg/dL	109·2 (31·2)¶	110·0 (31·0)‖
HDL cholesterol, mg/dL	50·9 (15·0)¶	50·4 (14·3)‖
HbA_{1c} (NGSP)	6·01% (1·03%)**	6·05% (1·08%)††
Previously treated with clopidogrel	1155 (61%)	1159 (62%)

Data are mean (SD) or n (%). Percentages may not total to 100% because of rounding. HbA_{1c}=glycated haemoglobin. NGSP=National Glycohemoglobin Standardization Program. *Non-cardioembolic stroke, of undetermined aetiology (with two or more different origins), in patients with infarct area of more than 1·5 cm and less than 50% stenosis in a major artery. †CYP2C19 single nucleotide polymorphisms resulting in point mutations of 681G→A and 636G→A were detected with the Invader DNA assay (Third Wave Technologies, Madison, WI, USA). Genotypes were translated into star-allele genotypes and the patients were classified as extensive metaboliser (*1/*1), intermediate metaboliser (*1/*2, *1/*3), and poor metaboliser (*2/*2, *2/*3, *3/*3). ‡n=1742. §n=1719. ¶n=1882. ‖n=1855. **n=1882. ††n=1855.

Table 1: **Baseline characteristics**

	Prasugrel group (n=1885)		Clopidogrel group (n=1862)		Risk ratio (95% CI)
	Events (fatal events)	Incidence (95% CI)*	Events (fatal events)	Incidence (95% CI)*	
Primary endpoint					
Ischaemic stroke, myocardial infarction, and death from other vascular causes	73 (1)	3·9% (3·0–4·8)	69 (0)	3·7% (2·9–4·7)	1·05 (0·76–1·44)
Secondary endpoints					
Ischaemic stroke	69 (1)	3·7% (2·9–4·6)	64 (0)	3·4% (2·7–4·4)	1·07 (0·76–1·49)
Myocardial infarction	4 (0)	0·2% (0·1–0·5)	6 (0)	0·3% (0·1–0·7)	0·66 (0·19–2·33)
Death from other vascular causes	0 (0)	0·0% (0·0–0·2)	0 (0)	0·0% (0·0–0·2)	0
Any stroke	73 (2)	3·9% (3·0–4·8)	73 (1)	3·9% (3·1–4·9)	0·99 (0·72–1·36)
Haemorrhagic stroke	4 (1)	0·2% (0·1–0·5)	9 (1)	0·5% (0·2–0·9)	0·44 (0·14–1·42)

Data are n (n), unless otherwise indicated. *Incidence of both fatal and non-fatal events.

Table 2: **Primary and secondary efficacy assessments (full analysis set)**

the combined incidence of ischaemic stroke, myocardial infarction, and death from other vascular causes (ie, the primary endpoint) under masked conditions was lower than initially assumed, and a final incidence of around 4% was expected. Therefore, without changing any condition other than event incidence, the number of patients was recalculated, and the target reset at 3600. It was estimated that the incidence of the primary efficacy endpoint for the clopidogrel group would be 4·3%, and that the relative risk reduction with prasugrel would be 15% (based on the approximately 18% relative risk reduction in a phase 3 comparative study of prasugrel and clopidogrel in patients with acute coronary syndromes, done outside Japan[16]), with administration over a period of 2 years to a target study population of 3600 patients (1800 per group). With the primary endpoint occurring in each treatment group of 1800 patients at the expected incidence, the total number of these events was expected to be 143 (clopidogrel group n=77; prasugrel group n=66). Statistical analyses were done using SAS software, version 9.2.

Meetings of a data-monitoring committee, independent from the trial funder and trial investigators, were held once every 6 months. The role of this committee was to monitor the safety data and efficacy data to establish the feasibility of continuing the trial, and other matters, under unmasked assessment conditions.

The trial was registered with the Japan Pharmaceutical Information Center (JapicCTI-111582).

Role of the funding source

The study was designed and funded by Daiichi Sankyo (Tokyo, Japan), who collected all data and did all initial data analyses. The funder did further analysis and interpretation, with input from the authors and investigators. The initial draft of the report was reviewed and commented on by all authors and by employees of Daiichi Sankyo. The corresponding author and funder had full access to all data. The corresponding author had final responsibility for the decision to submit the paper for publication.

Results

Patients were recruited between Sept 1, 2011, and June 12, 2015. Of the 4147 patients from whom consent to participate in the trial was obtained, 394 were excluded before randomisation (figure 1). The reasons for exclusion were inadequate blood pressure (n=6), platelet count of less than 75 000 per µL (n=1), deviation from inclusion criteria (n=280), withdrawal of consent (n=37), discretion of the investigator (n=64), use of prohibited medication (n=9), and other reasons (n=6); there was overlap in reasons. 3753 patients were randomly assigned to treatment and, of these patients, 1885 in the prasugrel group and 1862 in the clopidogrel group were confirmed to have taken the trial drug at least once, and six (<1%) patients withdrew from the trial before administration of the trial drug. Thus, a total of 3747 patients were included in the full analysis set.

During the trial period, 287 (15%) patients in the prasugrel group and 311 (17%) patients in the clopidogrel group discontinued treatment; 1598 patients in the prasugrel group and 1551 patients in the clopidogrel group completed the trial. The major reason for discontinuation for both groups was adverse events (prasugrel group, n=178; clopidogrel group, n=202), followed by concomitant use of prohibited drugs (prasugrel group, n=107; clopidogrel group, n=103). The median dosing period was

not different between the groups (prasugrel 673·0 days, IQR 392·0–705·0; clopidogrel 672·0 days, 384·0–700·0).

Baseline characteristics were similar between groups (table 1). Stroke of undetermined aetiology was the most frequent type to occur, accounting for nearly 40% of strokes. Large artery atherosclerosis and small artery occlusion (lacunae) accounted for around 30% each. The proportion of CYP2C19 poor metabolisers (ie, patients with reduced function of CYP2C19) was almost 20%. Seven (<1%) of 3753 patients were lost to follow-up during the trial period.

The incidences of the primary and secondary efficacy endpoints are shown in table 2. The combined incidence of ischaemic stroke, myocardial infarction, and death from other vascular causes (the primary endpoint) was 73 (4%) of 1885 patients in the prasugrel group and 69 (4%) of 1862 patients in the clopidogrel group. The RR was 1·05 (95% CI 0·76–1·44). The upper limit of the 95% CI of RR exceeded the predefined non-inferiority margin (1·35) for the primary endpoint; therefore, the results did not confirm the non-inferiority of prasugrel to clopidogrel. There were no major discrepancies between the full analysis set and per-protocol set in terms of the primary endpoint results. In the per-protocol set, 73 (4%) of 1867 patients in the prasugrel group and 68 (4%) of 1838 patients in the clopidogrel group met the primary endpoint. The RR was 1·05 (95% CI 0·76–1·46).

The cumulative incidence for the primary endpoint was similar between the two groups (figure 2; HR 1·04, 95% CI 0·75–1·44). The forest plot of HRs for the primary endpoint stratified according to predefined subgroups is shown in figure 3. The results for the primary endpoint were not significantly different between the two groups in any of the predefined subgroups.

In subgroups divided according to stroke type at baseline (as predefined in the statistical analysis plan), prasugrel reduced the primary endpoint by 21% (HR 0·79, 95% CI 0·45–1·41) in patients with large artery atherosclerosis, and by 18% (HR 0·82, 0·45–1·50) in patients with small artery occlusion, whereas an increase of 56% was observed in those with stroke of undetermined aetiology; however, none of these differences was statistically significant and there was not enough evidence to suggest an interaction effect ($p_{interaction}$=0·32). The cumulative incidence of the primary endpoint in patients with large artery atherosclerosis or small artery occlusion at baseline, both of which are considered consequences of platelet thrombus, is shown in figure 2 (HR 0·81, 0·53–1·22).

There were no significant differences in the effect of prasugrel depending on the CYP2C19 polymorphism subgroup (figure 3). The incidences of haemorrhagic stroke tended to be low in the prasugrel group but not significantly different, being at a level similar to that in the clopidogrel group (table 2).

The incidences and HRs of bleeding events assessed in the safety evaluation are shown in table 3. There was no statistically significant difference between the two groups in any of the events assessed. The HRs for the prasugrel group versus the clopidogrel group were low for life-threatening bleeding (0·77, 95% CI 0·41–1·42), and HRs between the two groups were almost the same for life-threatening bleeding, major bleeding, and clinically relevant bleeding (1·02, 0·79–1·33).

The incidences of adverse events during the trial are shown in table 4. There was no clinically significant difference between the two groups for any of the adverse events or drug-related adverse events. The incidences of drug-related serious adverse events are summarised in table 5.

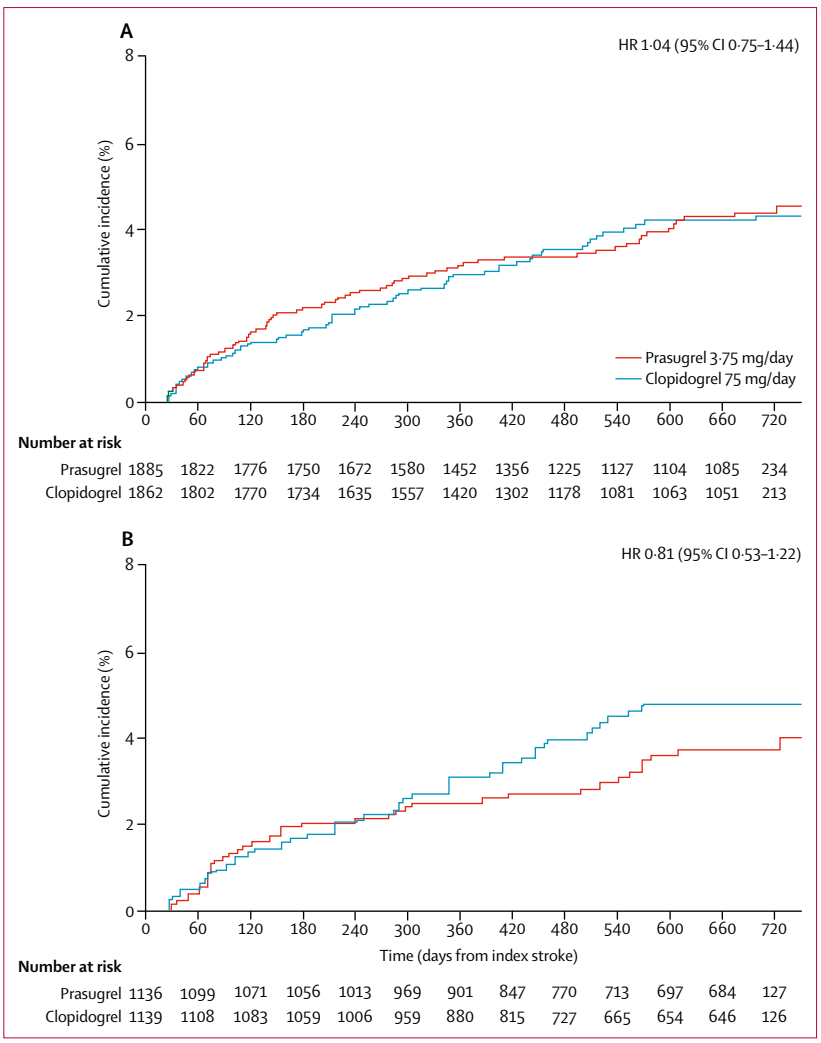

Figure 2: **Cumulative combined incidence of ischaemic stroke, myocardial infarction, and death from other vascular causes (the primary endpoint; A) and incidence in patients with large artery atherosclerosis or small artery occlusion at baseline (post-hoc subgroup analysis; B)**
Data from the full analysis set. HR=hazard ratio.

Discussion

This trial was done to investigate the safety and efficacy of 3·75 mg/day of prasugrel for the secondary prevention of non-cardioembolic ischaemic stroke as compared with

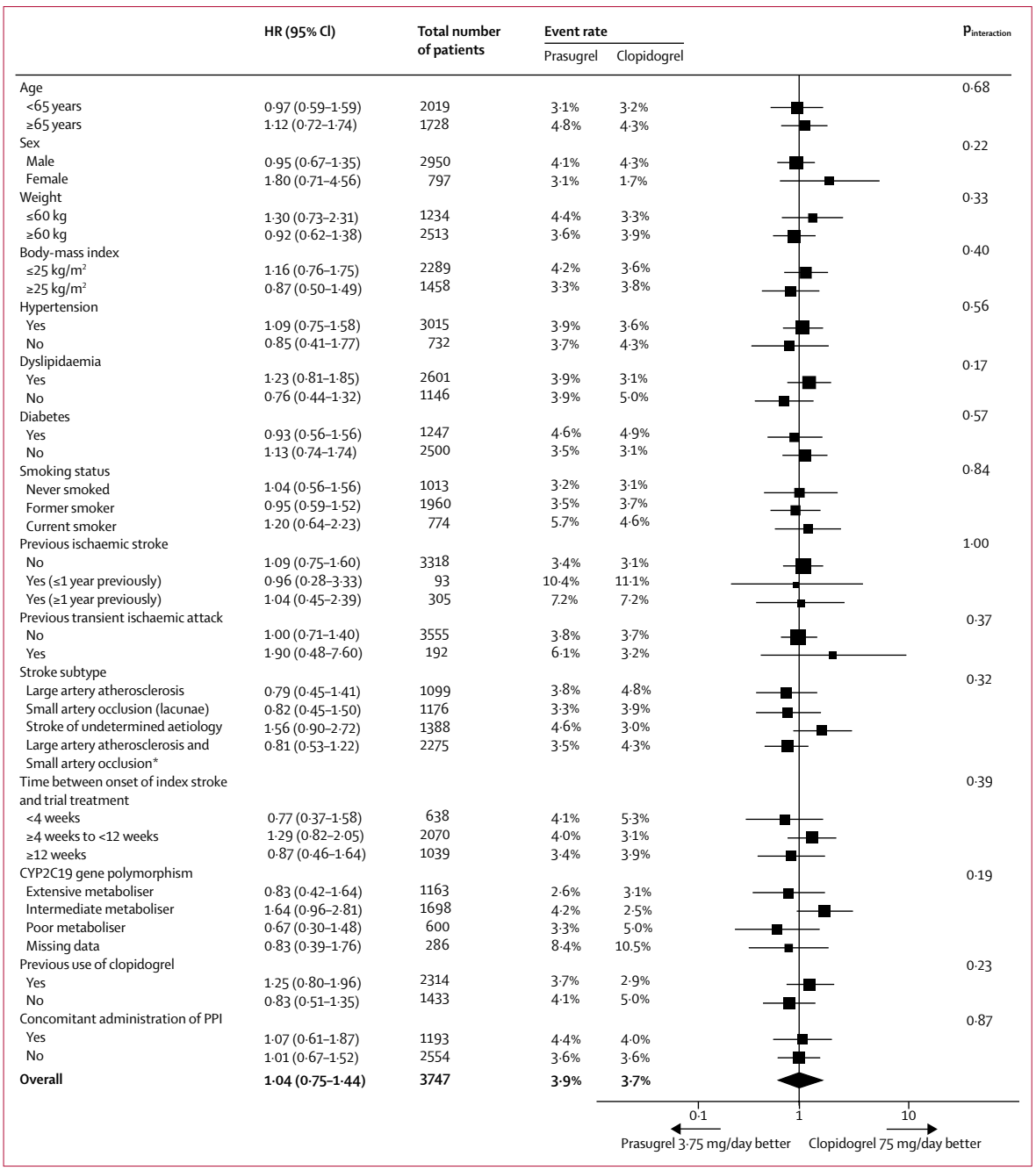

Figure 3: **Forest plot of hazard ratios for combined incidence of ischaemic stroke, myocardial infarction, and death from other vascular causes (the primary endpoint) according to predefined subgroups**
HR=hazard ratio. PPI=proton pump inhibitor. *Post-hoc analysis.

75 mg/day of clopidogrel. The results showed that the combined incidence of ischaemic stroke, myocardial infarction, and death from other vascular causes in the prasugrel group was similar to that in the clopidogrel group; however, the non-inferiority of prasugrel to clopidogrel was not confirmed. This was the largest phase 3 trial of prasugrel 3·75 mg/day (the approved dose in Japan) for secondary stroke prevention in Japanese patients. A post-hoc subgroup analysis showed that patients with large artery atherosclerosis or small artery occlusion (lacunae) had slightly lower event rates (although not significant). These results might be useful for the identification of patients most likely to benefit from antiplatelet therapy.

In terms of safety, bleeding and adverse events were not significantly different between the two groups. The

occurrence of severe bleeding events, such as life-threatening bleeding and major bleeding, or haemorrhagic stroke, was generally within the same range in both treatment groups, which is similar to the results of earlier studies of the adjusted-dose regimen of prasugrel in patients undergoing percutaneous coronary intervention.[16,22]

In the predefined subgroup analysis, although the HRs for the primary endpoint according to the type of ischaemic stroke differed (0·79 for large artery atherosclerosis, 0·82 for small artery occlusion, and 1·56 for stroke of undetermined aetiology), there was not enough evidence to support an interaction effect. Studies published over the past 4 years have reported the effectiveness of platelet inhibition in the secondary prevention of stroke in patients with proven arterial stenosis. In the SOCRATES subgroup analysis,[23] ticagrelor (6·7%) was superior to aspirin (9·6%) in the reduction of stroke, myocardial infarction, and death in patients with ipsilateral carotid stenosis (HR 0·68, 95% CI 0·53–0·88; p=0·003). However, ticagrelor did not show superiority in patients with no ipsilateral carotid stenosis. In addition, the CHANCE subgroup analysis[24] showed that the clopidogrel plus aspirin group had a non-significant decrease in stroke incidence compared with the aspirin alone group in patients with intracranial arterial stenosis. By contrast, stronger antiplatelet therapy does not seem to be necessary for the management of lacunar stroke; the addition of clopidogrel to aspirin did not significantly reduce the risk of recurrent stroke after recent lacunar stroke.[25] All these results, and perhaps those of this trial, indicate that the degree of prevention of cardiovascular events, including stroke by antiplatelet agents, might depend on the type of stroke. A higher level of P2Y12 inhibition as compared with clopidogrel might be more effective for prevention of these events in patients with large artery atherosclerosis. Similarly, in patients with acute coronary syndrome who are undergoing percutaneous coronary intervention, and in whom the majority of acute events occur because of coronary atherosclerosis, two more potent P2Y12 antagonists, prasugrel and ticagrelor, reduced cardiovascular events more effectively than did clopidogrel.[15,26]

Prasugrel does not seem to be effective for patients with stroke of undetermined aetiology. A substantial number of patients with this subtype have been reported to have had covert atrial fibrillation,[18,27] and the concept of embolic stroke of undetermined source has been proposed.[28] Thus, there might be a random bias between the two groups in terms of event occurrence of stroke. The results of our trial would be clearer if participants had been restricted to patients with arteriosclerosis-associated stroke subtypes.

In the CYP2C19 poor metaboliser subgroup, patients receiving 3·75 mg/day of prasugrel had a 33% lower RR for the primary endpoint compared with those receiving 75 mg/day of clopidogrel (3·3% *vs* 5·0%), although this result was not statistically significant. The results of a previous study,[17] in which the influence of cytochrome P450 polymorphisms was investigated, showed that the antiplatelet effect was low in poor metabolisers. Considering the high prevalence of the CYP2C19 poor metaboliser phenotype in the Japanese population (at least 20%) and similar incidences of bleeding events between the prasugrel and clopidogrel groups in this trial, 3·75 mg/day of prasugrel might be useful for patients with this phenotype.

An uncommon exclusion criterion of this trial was age 75 years or older. The criterion was set to exclude patients at high risk of bleeding; however, it might have affected the results for efficacy endpoints. Additionally, blood pressure was well controlled throughout the trial period, which could also have reduced the event incidence as compared with a real-world population.

Regarding safety endpoints, prasugrel was as safe as clopidogrel. The findings were somewhat different from those of the TRITON-TIMI 38 study,[15] in which major bleeding was more common in patients with prasugrel. The main reason for this difference was the use of

	Prasugrel group (n=1885)		Clopidogrel group (n=1862)		Hazard ratio (95% CI)
	Events (n)	Incidence	Events (n)	Incidence	
Life-threatening bleeding, major bleeding, and clinically relevant bleeding	115	6·1% (5·1–7·3)	110	5·9% (4·9–7·1)	1·02 (0·79–1·33)
Life-threatening bleeding	18	1·0% (0·6–1·5)	23	1·2% (0·8–1·8)	0·77 (0·41–1·42)
Major bleeding	2	0·1% (0·0–0·4)	4	0·2% (0·1–0·5)	0·49 (0·09–2·66)
Clinically relevant bleeding	98	5·2% (4·2–6·3)	83	4·5% (3·6–5·5)	1·15 (0·86–1·55)
Bleeding event leading to treatment discontinuation	30	1·6% (1·1–2·3)	33	1·8% (1·2–2·5)	0·89 (0·54–1·46)

Table 3: **Safety endpoints**

	Prasugrel group (n=1885)	Clopidogrel group (n=1862)
Adverse event	1677 (89%)	1680 (90%)
Drug-related adverse event	617 (33%)	584 (31%)
Serious adverse event	347 (18%)	337 (18%)
Drug-related serious adverse event	45 (2%)	62 (3%)
Serious adverse event that led to death	10 (<1%)	11 (1%)
Drug-related serious adverse event that led to death	3 (<1%)	9 (<1%)
Death	10 (<1%)	11 (1%)
Drug-related death	3 (<1%)	9 (<1%)
Adverse event leading to discontinuation of trial treatment	221 (12%)	247 (13%)
Drug-related adverse event leading to discontinuation of trial treatment	62 (3%)	89 (5%)

Data are n (%).

Table 4: **Adverse events**

	Prasugrel group (n=1885)	Clopidogrel group (n=1862)
All	45 (2%)	62 (3%)
System organ class		
Infections and infestations	2 (<1%)	1 (<1%)
Neoplasms (benign, malignant, and unspecified, including cysts and polyps)	6 (<1%)	9 (<1%)
Psychiatric disorders	2 (<1%)	0
Nervous system disorders	10 (<1%)	17 (1%)
Eye disorders	3 (<1%)	1 (<1%)
Cardiac disorders	3 (<1%)	2 (<1%)
Vascular disorders	1 (<1%)	1 (<1%)
Respiratory, thoracic, and mediastinal disorders	2 (<1%)	3 (<1%)
Gastrointestinal disorders	14 (1%)	18 (1%)
Hepatobiliary disorders	1 (<1%)	4 (<1%)
Skin and subcutaneous tissue disorders	0	2 (<1%)
Musculoskeletal and connective tissue disorders	0	1 (<1%)
Renal and urinary disorders	1 (<1%)	1 (<1%)
General disorders and administration site conditions	0	2 (<1%)
Investigations	0	1 (<1%)
Injury, poisoning, and procedural complications	4 (<1%)	1 (<1%)

Data are n (%). Serious adverse events were classified by system organ classes in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

Table 5: **Drug-related serious adverse events**

prasugrel at a lower dose (3·75 mg) in this trial than the TRITON-TIMI 38 study[15] (10 mg). These results regarding safety endpoints are notable because our trial targeted Japanese patients with stroke, who are considered a population at high risk of intracranial haemorrhage.[29]

The first limitation of our trial was the inclusion of Japanese patients only, coupled with the use of a non-inferiority margin based on the results of Japanese studies; thus, our findings cannot necessarily be generalised to non-Japanese populations. This is particularly the case for white people, who are less likely to have the CYP2C19 poor metaboliser phenotype that has been identified as a cause of poor responsiveness to clopidogrel.[10] Second, patients aged older than 75 years or who weighed 50 kg or less were excluded. Thus, the results of our trial might not be generalisable to older patients or patients of low bodyweight; however, we are carrying out a similar comparison of prasugrel and clopidogrel in Japanese patients who have had a stroke and are aged older than 75 years or weigh 50 kg or less (JapicCTI-121901). A third limitation is that only about a fifth of patients were female. In Japan, the ratio of male to female patients with ischaemic stroke has been reported to be 3:2. The inclusion criteria of our study specified age younger than 75 years, which might have excluded a greater proportion of women because incidence of stroke in women generally increases after menopause. Moreover, our study excluded patients with cardioembolic stroke, which is relatively common in women. The criterion of body weight of more than 50 kg might also have contributed to the small proportion of women, because of their generally lower bodyweight compared to men.[30]

In conclusion, although the cumulative incidence of ischaemic stroke, myocardial infarction, and death from other vascular causes was similar between the 3·75 mg/day of prasugrel and 75 mg/day of clopidogrel groups, non-inferiority could not be confirmed in Japanese patients with non-cardioembolic stroke. Of note, the incidence of bleeding events, which was assessed as part of the safety evaluation, was not significantly different between groups. By examining the safety and efficacy of prasugrel and clopidogrel for each stroke subtype, we will be able to provide useful information to select an appropriate antiplatelet therapy.

Contributors

AO and YI were the principal investigators and advised on study design from medical viewpoints. The steering committee comprised KM, SU, NT, MM, and IN, who provided coordination of the participating institutions. KK, TK, TN, HY, and KT were members of the protocol committee, who developed and reviewed the protocol. KK, TK, and SN evaluated the efficacy events. MN and KT evaluated the bleeding events. All authors contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

AO reports personal fees from Daiichi Sankyo. KT reports personal fees from Daiichi Sankyo, Bayer Yakuhin, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, and Takeda Pharmaceutical. KK reports grants and personal fees from Daiichi Sankyo, Takeda Pharmaceutical, Nippon Boehringer Ingelheim, Sumitomo Dainippon Pharma, Astellas Pharma, Kyowa Hakko Kirin, Otsuka Pharmaceutical, Bayer Yakuhin, and Sanofi; personal fees from Mitsubishi Tanabe Pharma, Shionogi, Pfizer, and Bristol-Myers Squibb; and grants from AstraZeneca and Eisai. TK reports personal fees from Daiichi Sankyo; grants from Daiichi Sankyo and Sanofi; and grants and personal fees from Bayer Yakuhin. TN reports personal fees from Daiichi Sankyo. HY reports personal fees from Bayer Yakuhin, Daiichi Sankyo, Nippon Boehringer Ingelheim, and Stryker Japan; and grants and personal fees from Bristol-Myers Squibb. SU reports personal fees from Daiichi Sankyo; personal fees from Bayer Yakuhin, Nippon Boehringer Ingelheim, Sanofi, Takeda Pharmaceutical, AstraZeneca, Bristol-Myers Squibb, and Pfizer. MM reports grants and personal fees from Daiichi Sankyo; grants and personal fees from Sanofi, Bayer Yakuhin, Takeda Pharmaceutical, Otsuka Pharmaceutical, Nippon Boehringer Ingelheim, Sumitomo Dainippon Pharma, and Bristol-Myers Squibb; personal fees from Novartis Pharma; and grants from Mochida Pharmaceutical, Kyowa Hakko Kirin, Nihon Medi-Physics, MSD, Pfizer, Shionogi, Mitsubishi Tanabe Pharma, and Eisai. KM reports personal fees from Bayer Yakuhin, Otsuka Pharmaceuticals, Nippon Boehringer Ingelheim, AstraZeneca, Pfizer, Mitsubishi Tanabe Pharma, Stryker Japan, Kowa, Nihon Medi-Physics, Bristol-Myers Squibb, Sawai, Sumitomo Dainippon Pharma, Medico's Hirata, Kyowa Hakko Kirin, Sanofi, MSD, Eisai, Towa Pharmaceutical, and Nippon Chemiphar. MN reports grants and personal fees from Daiichi Sankyo, and personal fees from Sanofi. SN reports personal fees from Daiichi Sankyo. KA reports personal fees from Daiichi Sankyo. YI reports grants from Daiichi Sankyo. All other authors have nothing to disclose.

Data sharing

Deidentified individual participant data and relevant supporting clinical trial documents are available on request online. In cases in which clinical trial data and supporting documents are provided pursuant to Daiichi Sankyo company policies and procedures, Daiichi Sankyo will continue to protect the privacy of our clinical trial participants. Details of data-sharing criteria and the procedure for requesting access can be found online. Supporting information includes the study protocol, statistical analysis plan, and clinical study report. The access criteria are defined as follows: formal request from qualified scientific and medical researchers on individual participant data and clinical study documents from clinical trials supporting products submitted and licensed in the USA, the EU, or Japan from Jan 1, 2014, onwards for the purpose of legitimate research; this must be consistent with the principle of safeguarding study participants' privacy and consistent with provision of informed consent.

For the **deidentified individual participant data and relevant supporting clinical trial documents** see https://www.clinicalstudydatarequest.com/

For more on **data-sharing criteria and the procedure for requesting access** see https://vivli.org/ourmember/daiichi-sankyo

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