# Prasugrel
## nella prevenzione secondaria dell'ictus cerebrale ischemico non cardioembolico:
risultati dello studio PRASTRO-I

# 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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# Background

- 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; 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). 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**, who are at high risk of major adverse cardiovascular events with antiplatelet treatment. Genetic polymorphisms of CYP2C19 have been identified as the major cause of poor responsiveness to clopidogrel. Asian people have a much higher likelihood than white people of being poor metabolisers of CYP2C19; this means that clopidogrel monotherapy might be less effective for secondary stroke prevention in Asia than in non-Asian population countries.

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# Background

- **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.
- In the USA and European countries, prasugrel (10 mg/day as a maintenance dose) is contraindicated in patients with acute coronary syndrome who have received aspirin and have a history of stroke or transient ischaemic attacks: the results of the TRITONTIMI 38 study showed higher incidences of major adverse cardiovascular and bleeding events with prasugrel than with clopidogrel in this subgroup of patients.

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# Background

- 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 (PRASFIT-ACS study).
- 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 stroke is unknown.

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# Aim

The aim of **PRASTRO-I** phase 3 trial was 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.*

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# Methods

- **Randomised, double-blind, active-controlled, parallel group, multicentre, non-inferiority trial**, which enrolled patients with non-cardioembolic* stroke recruited from 224 hospitals in Japan between Sept 1, 2011, and June 12, 2015.

- 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;
✓ they had ischaemic lesions corresponding with the neurological symptoms confirmed by CT or MRI.

- Primary exclusion criteria were: presence of 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; 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.

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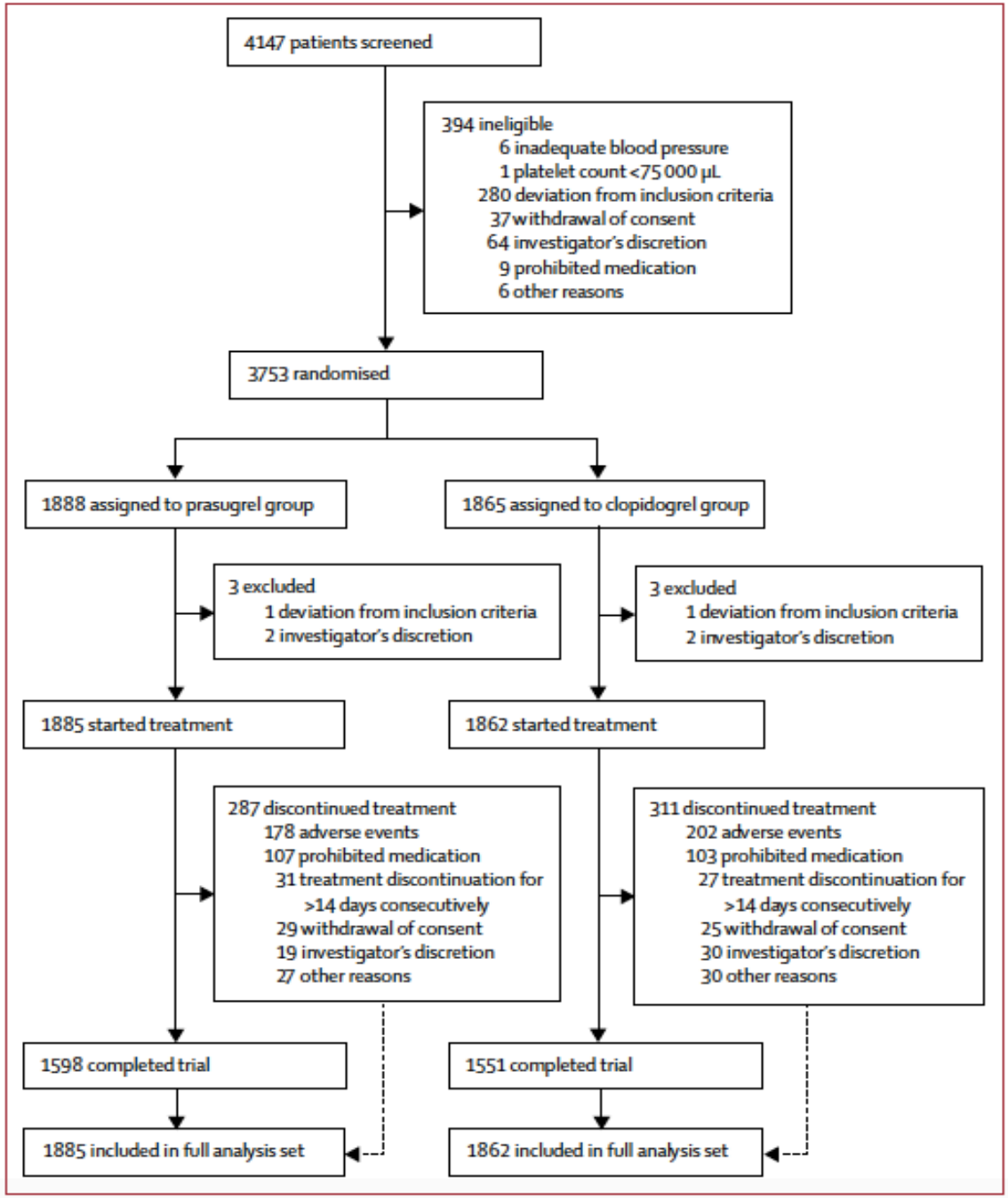
# Trial profile

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# Baseline characteristics (I)

| | 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%) |

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# Baseline characteristics (II)

| | Prasugrel group (n=1885) | Clopidogrel group (n=1862) |
|---|---|---|
| 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) |

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# Baseline characteristics (III)

| | Prasugrel group (n=1885) | Clopidogrel group (n=1862) |
|---|---|---|
| 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%) |

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# Primary and secondary efficacy assessments
## (full analysis set)

| | 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) |

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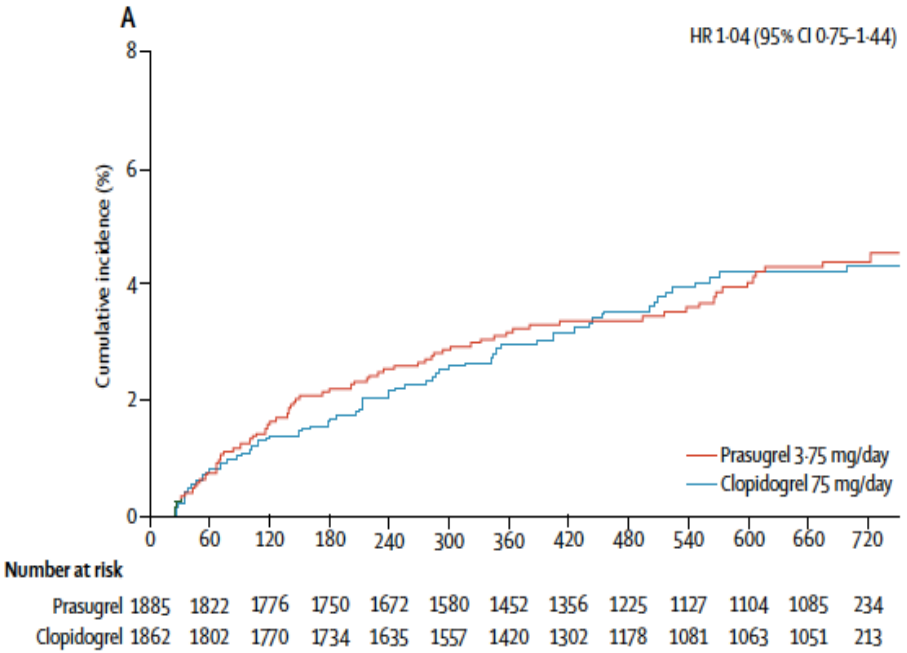
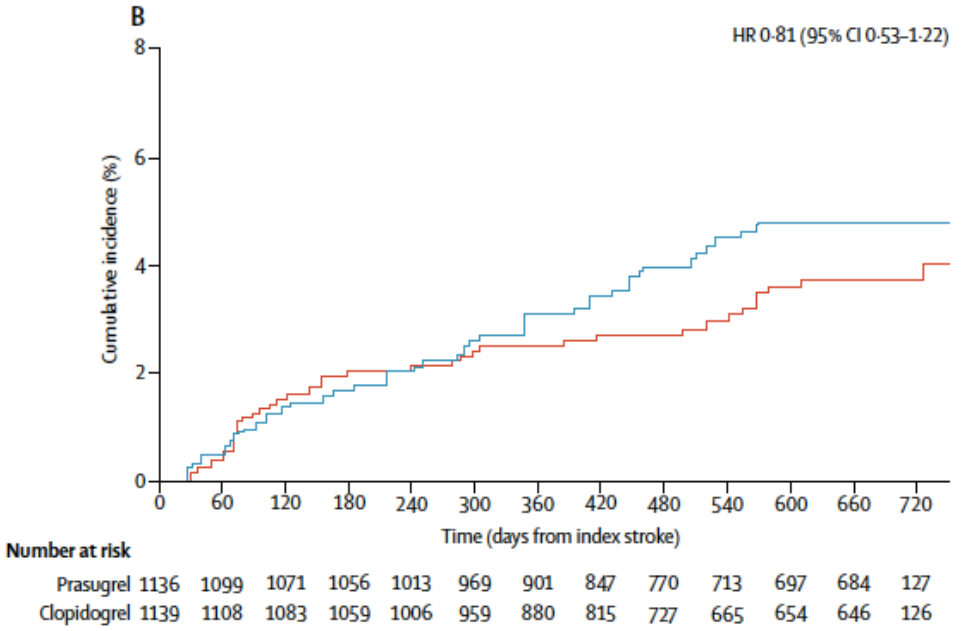
# Cumulative combined incidence of ischaemic stroke, myocardial infarction, and death from other vascular causes (the primary endpoint; A) and incidence in patients with large artery atherosclerosis or small artery occlusion at baseline (post-hoc subgroup analysis; B)

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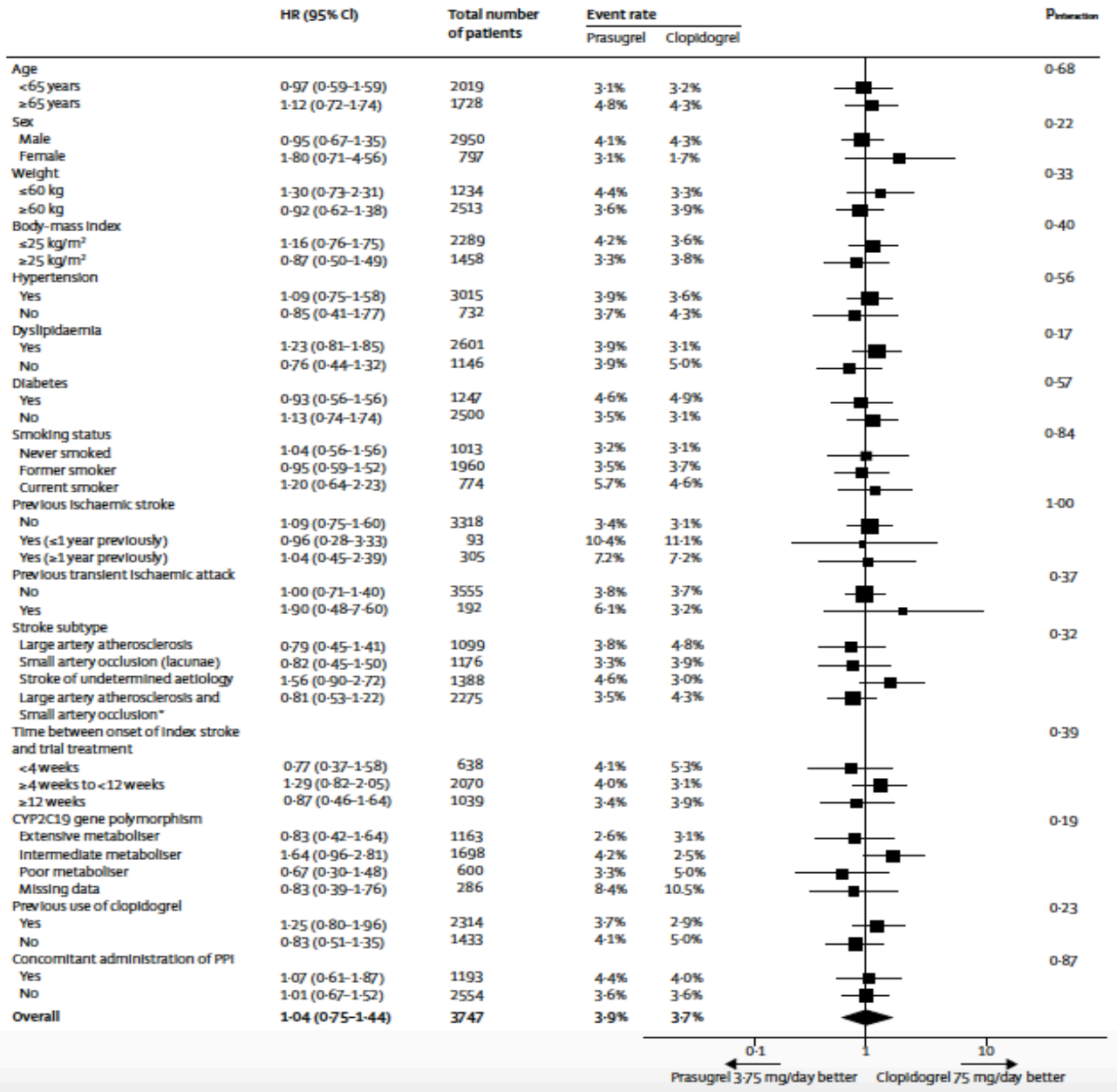
# Forest plot of hazard ratios for combined incidence of ischaemic stroke, myocardial infarction, and death from other vascular causes (the primary endpoint) according to predefined subgroups



| | HR (95% CI) | Total number of patients | Event rate | | $P_{interaction}$ |
|---|---|---|---|---|---|
| | | | Prasugrel | Clopidogrel | |
| Age | | | | | 0·68 |
| <65 years | 0·97 (0·59–1·59) | 2019 | 3·1% | 3·2% | |
| ≥65 years | 1·12 (0·72–1·74) | 1728 | 4·8% | 4·3% | |
| Sex | | | | | 0·22 |
| Male | 0·95 (0·67–1·35) | 2950 | 4·1% | 4·3% | |
| Female | 1·80 (0·71–4·56) | 797 | 3·1% | 1·7% | |
| Weight | | | | | 0·33 |
| ≤60 kg | 1·30 (0·73–2·31) | 1234 | 4·4% | 3·3% | |
| ≥60 kg | 0·92 (0·62–1·38) | 2513 | 3·6% | 3·9% | |
| Body-mass index | | | | | 0·40 |
| ≤25 kg/m² | 1·16 (0·76–1·75) | 2289 | 4·2% | 3·6% | |
| ≥25 kg/m² | 0·87 (0·50–1·49) | 1458 | 3·3% | 3·8% | |
| Hypertension | | | | | 0·56 |
| Yes | 1·09 (0·75–1·58) | 3015 | 3·9% | 3·6% | |
| No | 0·85 (0·41–1·77) | 732 | 3·7% | 4·3% | |
| Dyslipidaemia | | | | | 0·17 |
| Yes | 1·23 (0·81–1·85) | 2601 | 3·9% | 3·1% | |
| No | 0·76 (0·44–1·32) | 1146 | 3·9% | 5·0% | |
| Diabetes | | | | | 0·57 |
| Yes | 0·93 (0·56–1·56) | 1247 | 4·6% | 4·9% | |
| No | 1·13 (0·74–1·74) | 2500 | 3·5% | 3·1% | |
| Smoking status | | | | | 0·84 |
| Never smoked | 1·04 (0·56–1·56) | 1013 | 3·2% | 3·1% | |
| Former smoker | 0·95 (0·59–1·52) | 1960 | 3·5% | 3·7% | |
| Current smoker | 1·20 (0·64–2·23) | 774 | 5·7% | 4·6% | |
| Previous ischaemic stroke | | | | | 1·00 |
| No | 1·09 (0·75–1·60) | 3318 | 3·4% | 3·1% | |
| Yes (≤1 year previously) | 0·96 (0·28–3·33) | 93 | 10·4% | 11·1% | |
| Yes (≥1 year previously) | 1·04 (0·45–2·39) | 305 | 7·2% | 7·2% | |
| Previous transient ischaemic attack | | | | | 0·37 |
| No | 1·00 (0·71–1·40) | 3555 | 3·8% | 3·7% | |
| Yes | 1·90 (0·48–7·60) | 192 | 6·1% | 3·2% | |
| Stroke subtype | | | | | 0·32 |
| Large artery atherosclerosis | 0·79 (0·45–1·41) | 1099 | 3·8% | 4·8% | |
| Small artery occlusion (lacunae) | 0·82 (0·45–1·50) | 1176 | 3·3% | 3·9% | |
| Stroke of undetermined aetiology | 1·56 (0·90–2·72) | 1388 | 4·6% | 3·0% | |
| Large artery atherosclerosis and Small artery occlusion* | 0·81 (0·53–1·22) | 2275 | 3·5% | 4·3% | |
| Time between onset of index stroke and trial treatment | | | | | 0·39 |
| <4 weeks | 0·77 (0·37–1·58) | 638 | 4·1% | 5·3% | |
| ≥4 weeks to <12 weeks | 1·29 (0·82–2·05) | 2070 | 4·0% | 3·1% | |
| ≥12 weeks | 0·87 (0·46–1·64) | 1039 | 3·4% | 3·9% | |
| CYP2C19 gene polymorphism | | | | | 0·19 |
| Extensive metaboliser | 0·83 (0·42–1·64) | 1163 | 2·6% | 3·1% | |
| Intermediate metaboliser | 1·64 (0·96–2·81) | 1698 | 4·2% | 2·5% | |
| Poor metaboliser | 0·67 (0·30–1·48) | 600 | 3·3% | 5·0% | |
| Missing data | 0·83 (0·39–1·76) | 286 | 8·4% | 10·5% | |
| Previous use of clopidogrel | | | | | 0·23 |
| Yes | 1·25 (0·80–1·96) | 2314 | 3·7% | 2·9% | |
| No | 0·83 (0·51–1·35) | 1433 | 4·1% | 5·0% | |
| Concomitant administration of PPI | | | | | 0·87 |
| Yes | 1·07 (0·61–1·87) | 1193 | 4·4% | 4·0% | |
| No | 1·01 (0·67–1·52) | 2554 | 3·6% | 3·6% | |
| **Overall** | **1·04 (0·75–1·44)** | **3747** | **3·9%** | **3·7%** | |



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# Safety endpoints

| | 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) |

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# Adverse events

| | 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%) |

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| | 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%) |

# Drug-related serious adverse events

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# Conclusions

- 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.

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