10 December 2020
EMA/CHMP/657331/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Plavix	clopidogrel
Iscover	clopidogrel

Procedure No. EMEA/H/C/xxxx/WS/1769

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE – Adverse event

AIS – acute ischemic stroke

ACS – acute coronary syndrome

ASA – acetylsalicylic acid

CI – Confidence interval

CVD – cardiovascular death

DAPT – Dual antiplatelet treatment

DSMB – Data and safety monitoring board

GUSTO - Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries

ITT – intention to treat

LD –loading dose

MI – myocardial infarction

NIHSS - National Institute of Health Stroke Score

SAE – Serious adverse event

TIA – Transient ischemic attack

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, sanofi-aventis groupe submitted to the European Medicines Agency on 8 January 2020 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication in combination with aspirin to include adult patients with moderate to high risk Transient Ischemic Attack (TIA) (ABCD2 score ≥4) or minor Ischemic Stroke (IS) (NIHSS ≤3) within 24 hours of either the TIA or IS event for Iscover and Plavix. The new indication is based on the results of two double-blind, randomised, placebo-controlled phase III trials (studies POINT & CHANCE); as a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated, the PL is updated accordingly. Version 2.3 of the RMP has also been submitted.

The worksharing procedure requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the WSA did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The WSA did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed Rapporteurs for the WS procedure:

Bruno Sepodes

Timetable	Actual dates
Submission date	8 January 2020
Start of procedure:	1 February 2020
CHMP Rapporteur Assessment Report	14 February 2020
Updated PRAC Rapporteur Assessment Report	31 March 2020
PRAC Outcome	17 April 2020
CHMP members comments	20 April 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	24 April 2020
Request for supplementary information (RSI)	30 April 2020
CHMP Rapporteur Assessment Report	19 August 2020
PRAC Rapporteur Assessment Report	19 August 2020
Updated PRAC Rapporteur Assessment Report	27 August 2020
PRAC Outcome	3 September 2020
CHMP members comments	7 September 2020
Updated CHMP Rapporteur Assessment Report	11 September 2020
Request for supplementary information (RSI)	17 September 2020
CHMP Rapporteur Assessment Report	10 November 2020
PRAC Rapporteur Assessment Report	19 November 2020
PRAC Outcome	26 November 2020
CHMP members comments	30 November 2020
Updated CHMP Rapporteur Assessment Report	4 December 2020
Opinion	10 December 2020

2. Scientific discussion

2.1. Introduction

Medicinal product

Clopidogrel belongs to the pharmacotherapeutic group of platelet aggregation inhibitors excluding heparin, ATC Code: B01AC-04. Clopidogrel is a prodrug, which is converted to its active metabolite by CYP450 enzymes, mainly CYP2C19. The mode of action is through irreversible antagonism at the platelet P2Y12 receptor, blocking binding of adenosine diphosphate (ADP) to the receptor and thereby inhibiting platelet aggregation

Clopidogrel is approved for the secondary prevention of atherothrombotic events in patients with non-ST-segment elevation acute coronary syndrome (ACS) and patients with acute ST-elevation myocardial infarction who are to be managed medically. Clopidogrel should be administered in combination with

acetylsalicylic acid (ASA) in these indications. In patients with established peripheral arterial disease or with a history of recent myocardial infarction or recent ischemic stroke, clopidogrel is indicated as monotherapy.

Problem statement

Stroke is clinically defined according to the World Health Organization as the sudden onset of focal neurological deficits of presumed vascular origin in patients with vascular risk factors that last more than 24 hours. Brain imaging exams like a brain computerized tomography or Brain resonance imaging can help to the diagnosis and define the area of ischemic damage. Neurological deficits resulting from ischemic stroke can be quantified using a clinical score. The most used clinical score is the National Institute of Health Stroke Scale (NIHSS). Patients are usually considered to have a minor stroke when the NIHSS score is equal or less than 4.

A transient ischemic attack (TIA) refers to the sudden onset of neurological deficits of presumed vascular origin that last less than 24 hours. It is a clinical diagnosis. There is currently some discussion regarding if patients that have symptoms that last less than 24 hours and have brain lesions in a brain imaging exams qualify as a TIA or minor stroke. This highlights the continuum between acute ischemic stroke (AIS) and TIA.

Stroke constitutes a major health concern world-wide. According to the Global Burden of Disease (GBD) Study 2016, the estimated global lifetime risk of stroke from the age of 25 years onward is approximately 25% in both men and women, with ischemic stroke accounting for three quarters of this risk. Regionally, the highest estimated lifetime risks are seen in East Asia, Central Europe, and Eastern Europe. Patients who have suffered AIS or TIA are at increased risk of recurrent stroke. The risk of stroke of recurrence is highest within the first two weeks after a TIA or stroke. Estimates from historical cohorts found a risk of new stroke and other vascular events at 90 days of 12% to 20%. The TIA registry.org international collaboration estimated a 1-year risk of recurrent stroke of approximately 5% (Kaplan-Meier estimate), with the majority of the risk pertaining to the first 30-90 days after the initial event. The lower event rates from more recent data may be explained by earlier implementation of secondary stroke prevention strategies (e.g., immediate initiation of antiplatelet drugs, oral anticoagulation if atrial fibrillation, urgent revascularization in patients with critical carotid stenosis, and other secondary prevention measures such as treatment with statins and blood pressure–lowering medicines).

The ABCD2 score is usually used in clinical practice to help to calculate the risk of stroke recurrence in TIA patients. The ABCD2 score is a clinical score that is used to calculate 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. Patients with a score equal or higher than 4 are at highest risk of stroke recurrence and should be admitted to the hospital to rapidly undergo etiological investigation.

Rationale for the use of clopidogrel in AIS and high-risk TIA

There are different causes of ischemic stroke or TIA. The most common stroke etiological classification that is used in clinical practice is the TOAST classification. This classification divides stroke etiologies in five main subgroups: cardioembolic, large vessels disease, small vessels disease, other determined (i.e. dissections, vasculitis) and undetermined causes. When patients present with a cardioembolic stroke or TIA related to atrial fibrillation or mechanic heart valves, anticoagulants should be used for secondary

stroke prevention. Antiplatelets are used for prevention of stroke recurrence in the remaining stroke etiologies. The early administration of ASA, within 24 to 48 hours after onset of AIS, is recommended standard practice for patients with presumed non-cardioembolic stroke.
The safety and benefit of ASA in patients with AIS were established by two placebo-controlled clinical trials administering daily doses between 160 and 300 mg/day. The findings were confirmed by a Cochrane review of ASA clinical trials. In patients with non-cardioembolic AIS, ASA is associated to an approximately 20% reduction in the rate of recurrent stroke. This value of efficacy is maintained across a wide range of doses. However, the risk of hemorrhage increases with higher doses of ASA. A low dose of 75-150 mg/day is therefore usually prescribed for chronic use in clinical practice.
Alternative antiplatelet agents, in particular the P2Y12 receptor antagonists clopidogrel, prasugrel, and ticagrelor have been studied in patients with AIS. Clopidogrel was originally approved based on the results from the CAPRIE study. This study included patients with atherothrombosis as manifested by recent myocardial infarction, recent ischemic stroke or established peripheral arterial disease. Clopidogrel 75 mg/day significantly reduced the incidence of the composite outcome, when compared to ASA 325 mg/day. Benefit of clopidogrel versus ASA could not be shown specifically for the subgroup of patients with recent ischemic stroke.
In the PRoFESS study, clopidogrel was tested versus low-dose ASA plus extended release dipyramidole in patients with non-cardioembolic stroke. Very similar stroke recurrence rates were observed in both treatment arms, but non-inferiority of clopidogrel as monotherapy could not be formally demonstrated.
Dual anti-platelet therapy (DAPT) with ASA and a P2Y12 antagonist can confer synergistic efficacy on the inhibition of platelet aggregation. The benefit of DAPT versus ASA alone on the composite endpoint of cardiovascular death, myocardial infarction, or stroke has been demonstrate in several clinical trials in patients with ACS. DAPT in ACS is part of the approved use of all marketed P2Y12 antagonists.
Clopidogrel and ASA are used together after coronary, carotid, and intracranial stenting, and appear to be well tolerated.
Clopidogrel has been studied in combination with aspirin in several trials of vascular disease, including 2 that included patients with stroke or TIA. Although results from these trials have not supported long-term use of clopidogrel combined with aspirin after stroke/TIA, the drug has never been tested as an acute therapy in this population; and the trials support that it may be more beneficial and particularly safe after minor stroke or TIA.
Early implementation of DAPT with clopidogrel plus ASA in selected patients with AIS or high-riskTIA may be beneficial for stroke prevention. Combination therapy with clopidogrel and ASA may provide greater protection against subsequent stroke than aspirin alone. This is an application for a type II variation, seeking to extend the indication for clopidogrel in combination with ASA, to patients with recent onset (within 24 hours) of minor NIHSS ≤3 AIS or high-risk ABCD2 score ≥4 TIA, to reduce the risk of recurrent stroke.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

This variation relates to an addition of a new therapeutic indication for clopidogrel to adult patients with high-risk transient ischemic attack or minor ischemic stroke. This medicine was authorised in 1998.

The applicant included an ERA in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2*), 2006.

Table 1 Summary of main study results

Substance (INN/Invented Name): clopidogrel					
PBT screening	***Method***	***Results***		***Conclusion***	
log K_{ow}	OECD 107 Shake Flask Method	Log Kow: 3.76±0.0013 ⩽ 4.5 Log Dow: 3.2 (pH=5) 1.5 (pH=7) -0.49 (pH=9).		PKa=4.55 Ion-corrected log Dow	
PBT-assessment					
Parameter		***Results***		**Conclusion**	
Bioaccumulation	log K_{ow}	⩾3		**B** Bioconcentration in fish	
Persistence	ready biodegradability	Not readily biodegradable		**P**	
Toxicity (*Pimephales promelas*)	NOEC	310 µg/L		**Not T**	
PBT-statement :	**not considered as vP and vB**				
Phase I					
Calculation	***Value***	***Unit***		***Conclusion***	
$PEC_{surfacewater}$	0.515	µg/L		⩾0.01 threshold	
$PEC_{groundwater}$	0.129	µg/L			
PECsediment	34.21	µg/kgdw			
Other concerns (e.g. chemical class)				**N**	
Phase II Physical-chemical properties and fate					
Study type	***Test protocol***	***Results***		***Remarks***	
Determination of adsorption coefficient (GLP)	OECD 106	Log Koc=3.23		Koc ≤4 threshold Four soils Activated sludge	
Biodegradability test	FDA 3.11	Not ready biodegradable			
Aerobic Transformation in Aquatic Sediment systems	OECD 308	Day 104: Water layer:parent compound: 0.0% Transformation products: 14.8% Sediment extract: parent compound: 0.0% Transformation products: 47.9%		⩾63 days Transformation product ⩾10 % - hydrolytic degradation product and carboxylic acid derivative of clopidogrel. NERs⩾10%	
Phase II-A Effect studies					
Study type	***Test protocol***	***End point***	***value***	***Unit***	***Remarks***
Green alga	OECD 201	Growth rate/ Biomass NOEC	850	µg/L	
Daphnia sp. Reproduction Test	OECD 211	Reproduction Growth NOEC	710	µg/L	

Fish, Early Life Stage Toxicity	OECD 210	NOEC	310	µg/L	**Most sensitive organism**
Bioconcentration in fish	OECD 305	BCF – BCF (whole fish)	358	mg/L	BCF⩾ 2000 threshold 5% lipid content basis
Activated Sludge, Respiration Inhibition Test (GLP)	OECD 209	EC50	582.6	mg/L	
Phase II-B Studies					
Sediment Dwelling Organism (Chironomus riparius)	OCDE 218	NOEC	1.9	mg/kg	10% organic carbon

Phase I: Estimation of Exposure

Screening for Persistence, Bioaccumulation and Toxicity

A study to determine the octanol:water partition coefficient according to OECD TG 107, has been referenced. Log Kow = 3.76 and the ion-corrected log Dow was calculated on the range of 3.2 (pH=5), 1.5 (pH=7) to -0.49 (pH=9).

Regarding the PBT assessment Clopidogrel does not meet the B-trigger (BCF≥2000)

Calculation of the Predicted Environmental Concentration (PEC)

The PECSURFACEWATER was calculated using a DOSEai of 300 mg and the Fpen value of 1%:PEC = DOSEai x Fpen / WASTEWinhab x D x 100 = 0.515 µg/L.

Environmental fate/effects estimation

Phase II, Tier A

The fate and effects studies were evaluated when the clopidogrel / acetylsalicylic acid fixed – dose combination was authorized (2010). It could be concluded that Clopidogrel is not biodegradable, reversibly bind to organic material is completely transformed in water layer / sediment extract on day 104. The transformation product (>10%) of parent concentration is SR26334, a pharmacologically inactive metabolite likely to be a hydrolytic degradation product and carboxylic acid derivative of clopidogrel. The fish is the most sensitive species in the aquatic effect studies, it does not bio concentrate in fish organism and not demonstrate bacterial activity. The evaluation of BCF expressed on a 5% lipid content basis is calculated to be 358 mg/L for the whole fish. The BCF values do not indicate any likelihood of significant bioconcentration of clopidogrel in the environment.

Phase II Tier B

PEC calculation for sediment

PECsediment, expressed on a dry weight basis (µg/kgdw) is calculated using equilibrium partitioning and REACH (EUSES) equations with characteristics for suspended matter. A Koc of 3020 L/kg was used as

well as a PECsurface water = 0.515 µg/L. The result is a PECsediment = 34.21 µg/kg. The PNECsediment was normalised to 10% organic carbon (o.c. sediment content of the test was 2.5%).

Table 2 Risk characterisation

Environmental compartment	PEC µg/L	PNEC µg/L	PEC/PNEC	Trigger value	Conclusion
Surface water	0.515	31	0.017	1	no risk
Groundwater	0.129	71	0.0018	1	no risk
Microorganism	0.515	5826	0.000088	0.1	no risk
Sediment	34.21(kgdw)	76	0.45	1	no risk

2.2.2. Discussion on non-clinical aspects

The applicant included an ERA in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2*), 2006. The applicant was asked to provide reports relevant to the present ERA; however, this information was already submitted and assessed in the variation EMEA/H/C/000174/II/91 and FUM29 (Plavix). All issues in need of clarification regarding the ERA were satisfactorily clarified during this procedure. This new indication is not expected to pose a risk to the environment.

2.2.3. Conclusion on the non-clinical aspects

Considering the above data clopidogrel is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The data that was presented is based in two phase 3 clinical trials, multicenter, double-blind randomized and controlled with placebo. These clinical trials were the CHANCE study and the POINT study. They evaluated the benefits and risks of the early institution of DAPT with clopidogrel plus ASA versus ASA alone in populations of patients with minor AIS or high-risk TIA

GCP

The studies were conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for Good Clinical Practice (GCP), all applicable laws, rules, and regulations.

The WSA has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 3 Tabular overview of clinical studies

Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (safety and efficacy)		
Study identifier Coordinating Investigator (and center) Number of centers	**[CHANCE] NCT00979589** Yongjun Wang (Beijing Tiantan Hospital, China) 114 centers	**[POINT] NCT00991029** S. Claiborne Johnston (University of California, San Francisco) 269 centers
Objective(s) of study Study design and type of control	Assess the effects of the clopidogrel plus aspirin group or aspirin alone group on the incidence of stroke in the first 90 days after acute minor stroke or high-risk TIA. Randomized, double-blind, placebo-controlled study	Determine whether clopidogrel 75 mg/day after a loading dose of 600 mg was effective in improving survival free from ischemic vascular events (ischemic stroke, MI, and ischemic vascular death) at 90 days when patients were randomized within 12 hours of time last known free of new ischemic symptoms in patients receiving aspirin 50-325 mg/day. Randomized, Multicenter, international, randomized, double-blind, placebo-controlled study
Test product(s): - Formulation - Dosage regimen - Route of administration	*Clopidogrel*: Day 1 300 mg oral tablet, Days 2-90 75 mg *Aspirin*: Day 1 75-300 mg oral tablet, Days 2-21 75 mg *Aspirin placebo*: Days 22-90 oral tablet	*Clopidogrel*: Day 1 600 mg oral tablet, Days 2-90 75 mg *Aspirin open-label*:*d* Days 1-5 162 mg oral tablet, Days 6-90 81 mg (recommended dose)
Reference therapy: - Formulation - Dosage regimen - Route of administration	*Clopidogrel placebo*: Days 1-90 oral tablet *Aspirin*: Day 1 75-300 mg, Days 2-90 75 mg	*Clopidogrel placebo*: Days 1-90 oral tablet *Aspirin open-label*:*d* Days 1 162 mg oral tablet, Days 2-90 81 mg (recommended dose)
Number of subjects - Total[a, b, c] - Gender[b] (M/F) - Race[b] - Age[b] median (range) - Treatment group[b]	- 5170/5170/4859 - 3420/1750 - 5170 (Asian) - Clopidogrel + Aspirin: 63 years (55-72) / Placebo + Aspirin: 62 years (54-71) - Clopidogrel + Aspirin: 2584 / Placebo + Aspirin: 2586	- 4881/2432/4557 - 2686/2195 - 3555 (White), 966 (Black), 144 (Asian), 73 (Other) - Clopidogrel + Aspirin: 65 years (55-74) / Placebo + Aspirin: 65 years (56-74) - Clopidogrel + Aspirin: 2432 / Placebo + Aspirin: 2449
Healthy subjects or diagnosis of patients	Patients with acute TIA or minor stroke	Patients with high-risk TIA or minor ischemic stroke randomized within 12 hours of time last known free of new ischemic symptoms.
Duration of treatment	90 days	90 days
Study status Type of report	Complete Full	Complete Full

a Randomized,
b Treated,
c Completed study drug according to Investigator (end-of-treatment form).
d The dose of aspirin was per investigator discretion and varied from 50 to 325 mg from Day 1-90. A dose of 150-200 mg/day for the first 5 days followed by 75-100 mg/day for remainder of participation in study was strongly recommended.
F: female, IQR: interquartile range, M: male, MI: myocardial infarction, TIA: transient ischemic attack.

2.3.2. Pharmacokinetics

The pharmacokinetics (PK) of clopidogrel are fully described in the approved product information [Plavix SmPC]. This description includes information on the impact of CYP2C19 metabolizer status on the transformation of clopidogrel to its active metabolite. The available data are considered fully applicable to the intended new target population, especially as clopidogrel for its currently approved use was investigated in populations that included a majority of elderly subjects with co-morbid cardiovascular conditions. No new PK data have been generated for this application.

2.3.3. Pharmacodynamics

The pharmacodynamic (PD) activity of clopidogrel, through its active metabolite, as an irreversible antagonist at the platelet P2Y12 ADP receptor is adequately summarized in the approved product information [Plavix SmPC]. No new PD data have been generated for this application.

2.3.4. PK/PD modelling

A maintenance dose of clopidogrel of 75 mg/day provides steady state levels of the active metabolite that result in an average inhibition of platelet aggregation between 40% and 60%. The 75 mg/day dose is the approved maintenance dose for all current indications [*Plavix SmPC*]. It was also the maintenance dose investigated in the studies pertinent to the current application.

In order to achieve faster onset of platelet aggregation inhibition, a loading dose of clopidogrel is used. A single 300 mg dose on the first day of treatment is currently recommended in the approved indications for clopidogrel when used as a component of DAPT. A number of clinical trials in patients within the spectrum of ACS have investigated a higher loading dose of clopidogrel of 600 mg and shown that this may be associated with increased early PD effects and a lower risk of recurrent cardiovascular events, without increasing the risk of haemorrhage. The higher loading dose is included as a treatment option in current consensus guidelines for the management of ACS.

2.3.5. Discussion on clinical pharmacology

No biopharmaceutical data specific to the intended new indication is being submitted. Marketed formulations of clopidogrel were used in the two clinical trials supporting this application [CHANCE (NCT00979589) and POINT (NCT00991029)]. Furthermore, no new pharmacokinetic or pharmacodynamic data have been generated for this application.

2.3.6. Conclusions on clinical pharmacology

The PK/PD information for clopidogrel is considered sufficient, and applicable to the intended new target population. The maintenance dose of 75 mg/day was used also in studies of patients with AIS or high-risk TIA, and is very well established regarding efficacy and safety for use within DAPT with concomitant ASA in patients with ACS. The clinical trials supporting this application variably used loading doses of 300 mg or 600 mg. The choice of loading dose is further discussed below (please refer to efficacy and safety evaluation).

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Not applicable

2.4.2. Main study(ies)

Main studies – CHANCE and POINT

Table 4 CHANCE (Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events) – Study NCT00979589

Study ID	***Number of centres*** Locations	***Study start/Completion*** Total enrolled/randomised	***Design and duration***	***Study and control drugs***	***Patients by treatment*** (randomised/completed)	***Sex*** Median age (range)	***Diagnosis***	***Primary endpoint***
NCT00979589	*114* China	*October 2009/July 2012* 5170/5170	randomized, double blind, multicentre, placebo controlled trial	*ASA + clopidogrel* ASA + placebo	*ASA + clopidogrel* 2584/2402 ASA + placebo 2586/2425	*33.8% women* 62 years (?)	Adults with acute nondisabling ischemic stroke (National Institutes of Health Stroke Scale [NIHSS] ≤3 at the time of randomization) that can be treated with study drug within 24 hours of symptoms onset and with TIA (neurologic deficit attributed to focal brain ischemia, with resolution of the deficit within 24 h of symptom onset), that can be treated with study drug within 24 hours of symptoms onset and with moderate to high risk of stroke recurrence	Any new stroke event (ischemic or hemorrhagic) 3-months after minor stroke or high risk TIA

Methods

A Multicenter, randomized, double blind, placebo controlled trial to assess the effects of a 3-month regimen of clopidogrel initiated with a loading dose (LD) of 300 mg followed by 75 mg/day during the first 21 days versus a 3-month regimen of ASA 75 mg/day alone on reducing the 3-month risk of any new stroke (both ischemic and hemorrhagic, primary outcome) when initiated within 24 hours of symptom onset in high-risk patients with TIA or minor stroke.

Study participants

The study included patients from 114 sites in China. Patients were required to have a TIA (neurologic deficit attributed to focal brain ischemia, with resolution of the deficit within 24 hours of symptom onset) with moderate to high risk of stroke recurrence ($ABCD^2$ score ≥4 at the time of randomization). A certified, trained, licensed physician investigator was required to confirm the diagnosis of TIA or minor ischemic stroke and to calculate the $ABCD^2$ score for patients with TIA or an NIHSS score for patients with minor stroke.

Inclusion criteria:

- Adult subjects (male or female ≥40 years old).
- Acute nondisabling ischemic stroke (NIHSS ≤3 at the time of randomization) that could be treated with study drug within 24 hours of symptoms onset. Symptom onset was defined by the "last see normal" principle.
- TIA (neurologic deficit attributed to focal brain ischemia, with resolution of the deficit within 24 hours of symptom onset), that can be treated with study drug within 24 hours of symptoms onset and with moderate to high risk of stroke recurrence (ABCD2 score ≥4 at the time of randomization). Symptom onset is defined by the "last see normal" principle.
- Informed consent signed.

Exclusion criteria

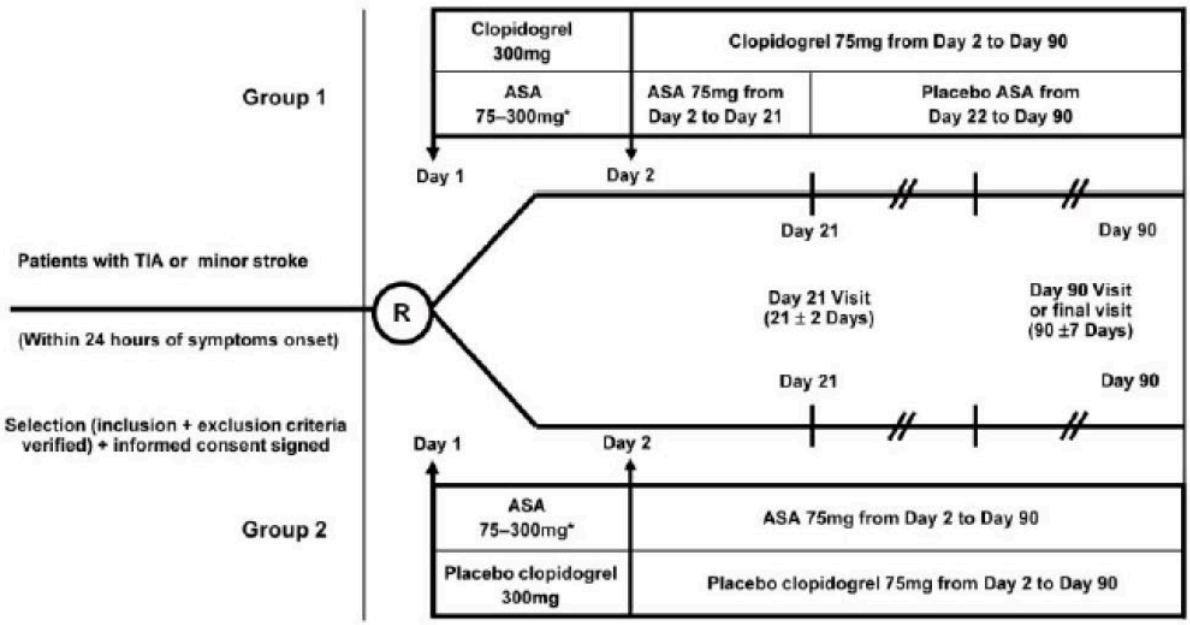
- Diagnosis of hemorrhage or other pathology, such as vascular malformation, tumor, abscess or other major nonischemic brain disease (eg, multiple sclerosis), on baseline head CT or MRI.
- Isolated or pure sensory symptoms (eg, numbness), isolated visual changes, or isolated dizziness/vertigo without evidence of acute infarction on baseline head CT or MRI.
- mRS score >2 at randomization (premorbid historical assessment).
- NIHSS ≥4 at randomization.
- Clear indication for anticoagulation (presumed cardiac source of embolus, eg, atrial fibrillation, prosthetic cardiac valves known or suspected endocarditis).
- Contraindication to clopidogrel or aspirin.
- Known allergy
- Severe renal or hepatic insufficiency
- Severe cardiac failure, asthma
- Hemostatic disorder or systemic bleeding
- History of hemostatic disorder or systemic bleeding

- History of thrombocytopenia or neutropenia
- History of drug-induced hematologic or hepatic abnormalities
- Low white blood cell (<2 × 109/L) or platelet count (<100 × 109/L)
- Use of thrombolysis within 24 hours before randomization
- History of intracranial hemorrhage.
- Anticipated requirement for long-term nonstudy antiplatelet drugs, or NSAIDs affecting platelet function.
- Current treatment (last dose given within 10 days before randomization) with heparin therapy or
- oral anticoagulation.
- Gastrointestinal bleed or major surgery within 3 months.
- Planned or likely revascularization (any angioplasty or vascular surgery) within the next 3 months (if clinically indicated, vascular imaging could be performed before randomization whenever possible).
- Scheduled for surgery or interventional treatment requiring study drug cessation.
- TIA or minor stroke induced by angiography or surgery.
- Severe noncardiovascular comorbidity with life expectancy <3 months.
- Women of childbearing age not practicing reliable contraception who did not have a documented negative pregnancy test result.
- Currently receiving an investigational drug or device.

Treatments

General study design

The general study design is outlined in the figure 1 below:



* Open label ASA: at the discretion of the investigator. This represents the total dose given on Day 1(between 75-300mg), including any ASA treatment taken by the patient, or given in the emergency unit on the same day.
R, Randomization; ASA, Aspirin

Figure 1 – General study design for the CHANCE trial

Study treatment and study dose

The first dose of study medication was given within 24 hours of symptom onset. Patients were randomized into 2 groups: the first group received an oral 300 mg loading dose of clopidogrel on the day of randomization, followed by oral clopidogrel 75 mg/day from day 2 to 3 months. Oral ASA was given in a total dose ranging between 75 and 300 mg (open label with dose determined by the treating physician) on the first day, followed by blinded 75 mg once a day from day 2 to 21. Between day-21 and 3-month visits, ASA 75 mg was replaced by a placebo of ASA 75 mg. The second group received open-label aspirin in a total dose ranging between 75 and 300 mg on the first day, followed by 75 mg once a day from day 2 to 3 months. A placebo for clopidogrel was given from the day of randomization until the 3-month visit. Study visits were performed on the day of randomization, at day 21, and at day 90.

Objectives

Primary objective: assess the effects of the two treatment regimens on the incidence of stroke in the first 90 days after acute minor stroke or high-risk TIA.

Outcomes/endpoints

The **primary efficacy outcome** was the percentage of patients with new stroke (ischemic or hemorrhage) at 3 months.

The **Secondary efficacy outcomes** were:

- Percentage of composite of any stroke, myocardial infarction, and vascular death within 3 months
- Percentage of patients at 3 months with new clinical vascular events (ischemic stroke/hemorrhagic stroke/TIA/myocardial infarction/vascular death) as a cluster and evaluated individually.
- mRS score changes (continuous) and dichotomized at percentage with score 0 to 2 versus 3 to 6 at 3-month follow-up;
- Impairment (changes in NIHSS scores at 3-month follow-up).
- EQ-5D.
- Efficacy endpoint were also to be analyzed stratified by etiologic subtypes (nonintracranial artery diseases vs intracranial artery diseases), by time randomization (<12 vs ≥12 hours), by qualifying event (TIA vs minor stroke), and by age (<65 years and ≥65 years).

The **primary safety outcome** was a moderate-to-severe bleeding event, according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition. Severe hemorrhage was defined as fatal or intracranial hemorrhage or other hemorrhage causing hemodynamic compromise that required blood or fluid replacement, inotropic support, or surgical intervention. Moderate hemorrhage was defined as bleeding that required transfusion of blood but did not lead to hemodynamic compromise requiring intervention.

Sample size

The minimum necessary sample size in the trial was established by the requirement to detect the smallest expected, clinically meaningful treatment difference comparing the treatment with placebo. Based on the pooled Northern California and Oxfordshire cohort study and FASTER trial, the 90-day risk of the stroke recurrence risk in placebo (ASA) group was 14% among high-risk TIA (ABCD2 score >4) or minor stroke patients treated with ASA within 24 hours of symptom onset. A relative risk reduction of 22% was the smallest difference that was attempted to detect.
A sample size of 5100 patients, has got a have 90% power to detect a relative risk reduction of 22% with a 2-sided α of 0.05 and 5% dropouts (medication nonadherence).

Randomisation

Patients meeting the enrollment criteria were randomly assigned to one of the two treatment groups with the use of a double-blind, double-dummy design.
Randomization was conducted by computer system (IVRS) and a randomization code was generated on 1st day after enrollment.
The site investigator called into an automated system that randomly assigned a number corresponding to a medication kit stored at the study site, and the medication in the kit was administered to the patient.

Blinding (masking)

CHANCE was a double-blind, placebo controlled trial.

75mg clopidogrel and placebo tablet used in this study were indistinguishable (identical on size, shape, color and appearance).

25/50 mg ASA and placebo tablet used in this study were indistinguishable (identical on size, shape, color and appearance).

The study staff, including the investigators, and patients were blinded to the study treatment. Unblinding by the investigator was only to occur if the patient had a serious adverse event for which unblinding of study drug information was very important for treatment. In such a case, details of the unblinding were to be recorded in written form.

Statistical methods

The primary null hypothesis of this trial was: in patients with TIA or minor ischemic stroke treated with ASA 75 mg/day, there was no difference in 90-day risk of stroke (ischemic or hemorrhagic) in those treated with a 3-month regimen of clopidogrel initiated with a loading dose of 300 mg followed by 75 mg/day compared with placebo when therapy was initiated within 24 hours of symptom onset.
The primary analysis was intention to treat, with inclusion determined by receipt of first study drug dose. Missing values were to remain missing, and patients were censored at their last follow-up assessment (time of clinical event, end of study, or last visit before loss to follow-up).
Reports were planned of Kaplan-Meier estimates of the cumulative risk of stroke (ischemic or hemorrhagic) event during maximum 90-day follow-up, with hazards ratios and 95% CI calculated using Cox proportional

hazards methods and the log-rank test to evaluate the treatment effect.
All statistics was 2-sided with $p<0.05$ considered significant.

Results

Participant flow

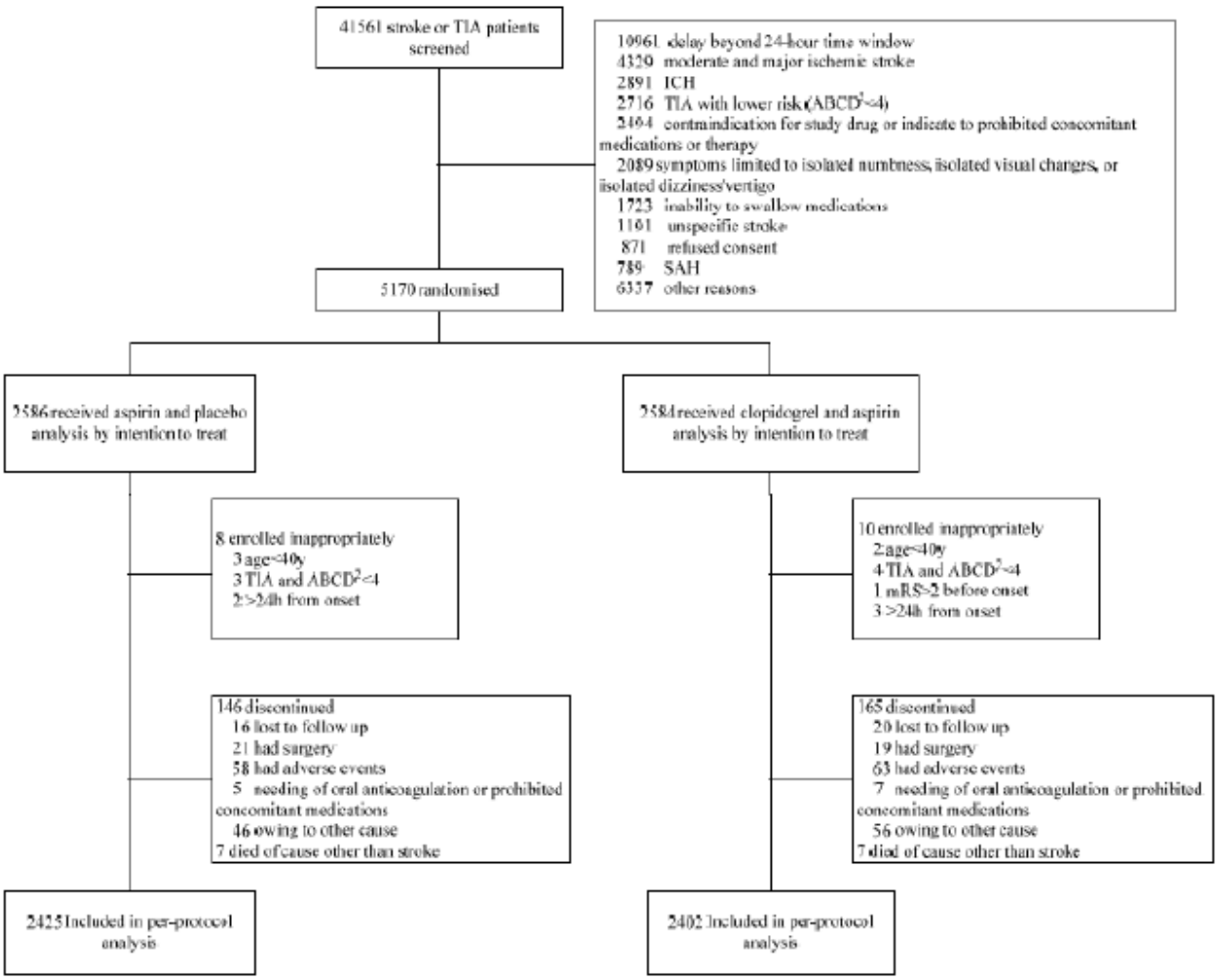


Figure 2 – Flow chart of patients included in the CHANCE study

Recruitment

Conduct of the study

Time until primary analysis censoring date

Protocol deviations

No protocol deviations were presented.

Treatment compliance

Treatment compliance was evaluated by counting returned tablets in the follow-up appointments. Investigator recorded usage and discontinuation of the study drug in the CRF.

Protocol amendments

No protocol amendments were reported.

Baseline data

The demographic and baseline characteristics of patients in the overall trial population were balanced between the two randomized treatment groups. A total of 5170 patients were included. The mean age of included patients was 62 years old and 33.8% were women. Tables 5 and 6 display the distribution of characteristics regarding demographics, previous pathologies and AIT and minor stroke characteristics in both arms.

Characteristic	Aspirin (N=2586)	Clopidogrel and Aspirin (N=2584)
Age — yr		
Median	62	63
Interquartile range	54–71	55–72
Female sex — no. (%)	898 (34.7)	852 (33.0)
Systolic pressure — mm Hg		
Median	150	150
Interquartile range	136–161	136–161
Diastolic pressure — mm Hg		
Median	90	90
Interquartile range	80–100	80–98
Body-mass index†		
Median	25	25
Interquartile range	23–27	23–26
Medical history — no. (%)		
Ischemic stroke	517 (20.0)	516 (20.0)
TIA	80 (3.1)	94 (3.6)
Myocardial infarction	53 (2.0)	43 (1.7)
Angina	87 (3.4)	97 (3.8)
Congestive heart failure	38 (1.5)	42 (1.6)
Known atrial fibrillation or flutter	48 (1.9)	48 (1.9)
Valvular heart disease	10 (0.4)	4 (0.2)
Hypertension	1683 (65.1)	1716 (66.4)
Diabetes mellitus	543 (21.0)	550 (21.3)
Hypercholesterolemia	283 (10.9)	290 (11.2)
Pulmonary embolism	1 (<0.1)	0
Current or previous smoking — no. (%)	1105 (42.7)	1116 (43.2)
Mean time to randomization — hr	13	13
Time to randomization — no. (%)		
<12 hr	1280 (49.5)	1293 (50.0)
≥12 hr	1306 (50.5)	1291 (50.0)
Qualifying event — no. (%)		
TIA	728 (28.2)	717 (27.7)
Minor stroke	1858 (71.8)	1867 (72.3)
ABCD² score‡		
Median	4	4
Interquartile range	4–5	4–5

Table 5 – Baseline characteristics of patients included in the CHANCE study distributed by the two arms

	Plus Aspirin (n=2586)	plus Aspirin (n=2584)	P Value
Surgical history			
Carotid stenting/angioplasty	21 (0.8%)	25(1.0%)	0.35
Clinical presentation			
Systolic blood pressure (mm Hg)	150.5 (22.1%)	150.8 (22.4%)	0.70
Diastolic blood pressure (mm Hg)	88.7 (13.0%)	88.3 (12.9%)	0.25
Body-mass index (kg/m^2)	24.7 (3.0%)	24.6 (3.0%)	0.18
Pulse rate (beats/min)	74.8 (9.4%)	74.7 (9.3%)	0.93
Symptoms present at randomization			
Loss of consciousness	2 (0.1%)	2 (0.1%)	1.00
Gaze	19 (0.7%)	18 (0.7%)	0.87
Hemianopia	29 (1.1%)	24 (0.9%)	0.49
Facial Paresis	959 (37.1%)	959 (37.1%)	0.98
Aphasia	357 (13.8%)	369 (14.3%)	0.62
Dysarthria	430 (16.6%)	467 (18.1%)	0.17
Weakness/paralysis	723 (28.0%)	755 (29.2%)	0.32
Paraesthesia/anaesthesia	485 (18.8%)	490 (19.0%)	0.85

Table 6 – Baseline characteristics of patients included in the CHANCE study distributed by the two arms

Concomitant medication

Combined treatment not allowed included:

- Open-label aspirin (except 1st day).
- NASIDs, Cox1, Cox2 inhibitor.
- Open-label clopidogrel or ticlopidine.
- Dipyridamole.
- Heparin.
- Oral anticoagulants.
- GP IIb/IIIa inhibitors.
- Thrombolysis drug.

Medications taken within 24 hours before hospital admission, between hospital admission and randomization, and within 90 days of treatment were all similar between the 2 treatment groups (p-values >0.05) with the exception of the concomitant medication dipyridamole, taken within 24 hours before hospital admission, taken by no patients in the clopidogrel + aspirin group and 4 (0.2%) patients in the placebo + aspirin group (p = 0.04). The most common medication taken within 24 hours before hospital admission or between hospital admission and randomization was aspirin in both treatment groups. The most common concomitant medications taken within 90 days of treatment were lowering-lipid drugs followed by antihypertensive drugs

Numbers analysed

The total number of patients that were planned to be included was 5100. The number of patients that were randomized was 5170. 5170 patients were evaluated regarding safety and efficacy.

Outcomes and estimation

Efficacy results:

Primary endpoint: Stroke occurred in 212 patients (8.2%) in the clopidogrel-ASA group, as compared with 303 patients (11.7%) in the ASA group (hazard ratio, 0.68; 95% confidence interval [CI], 0.57 to 0.81; P <0.001). Fatal or disabling stroke occurred in 135 patients (5.2%) in the clopidogrel-ASA group and in 177 (6.8%) in the ASA group (hazard ratio, 0.75; 95% CI, 0.60 to 0.94; P = 0.01).

Secondary endpoint:

The composite outcome of vascular events occurred in 216 patients (8.4%) in the clopidogrel-ASA group, as compared with 307 patients (11.9%) in the ASA group (HR:0.69; 95% CI, 0.58 to 0.82; P <0.001), (Figure 3).

Ischemic stroke occurred in 204 patients (7.9%) in the clopidogrel-ASA group and in 295 (11.4%) in the ASA group (HR:0.67; 95% CI, 0.56 to 0.81; P <0.001).

Hemorrhagic stroke occurred in 8 patients in each of the two study groups (0.3% of each group) (HR1.01; 95%CI 0.38 to2.70; p=0.98).

Death from any cause occurred in 0.4% of the patients in each group. Vascular death (including death from hemorrhagic stroke) occurred in 6 patients (0.2%) in the clopidogrel-ASA group and in 5 (0.2%) in the ASA group (HR: 1.16; 95% CI, 0.35 to 3.79; P=0.81).

TIA occurred in 39 patients (1.5%) in the clopidogrel-ASA group and in 47 (1.8%) in the ASA group (HR:0.82; 95% CI, 0.53 to 1.26; P=0.36).

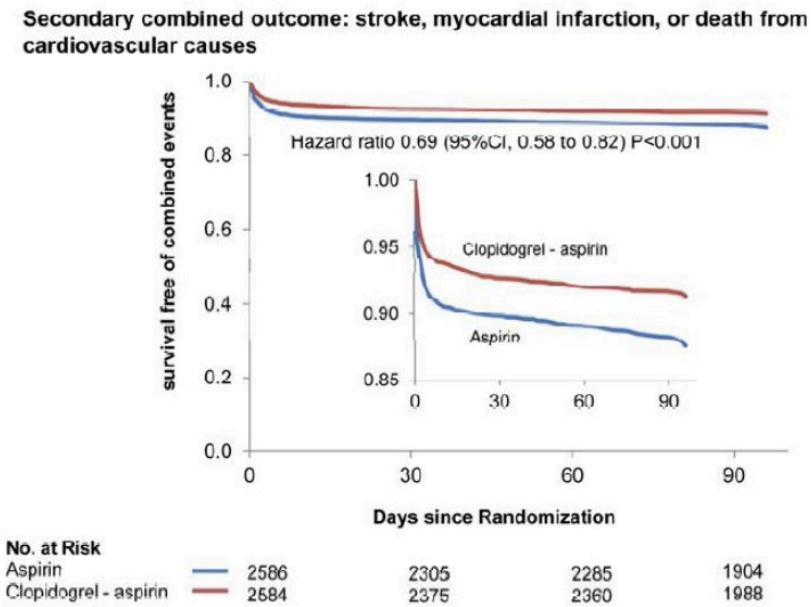


Figure 3 – Kapplan-meyer curve showing the composite outcome of vascular events in the CHANCE study

Ancillary analyses

The reduction in the rate of stroke and combined secondary vascular events with clopidogrel and ASA was consistent across all major subgroups. There were no significant interactions in any of the 11 predefined subgroups (P>0.10 for all comparisons) (Table 7).

Subgroup	No. of Patients	Aspirin	Clopidogrel–Aspirin	Hazard Ratio (95% CI)	P Value
		no. of events (%)			
Overall	5170	303 (11.7)	212 (8.2)	0.68 (0.57–0.81)	
Age					0.84
<65 yr	3029	164 (10.7)	110 (7.4)	0.67 (0.52–0.85)	
≥65 yr	2141	139 (13.2)	102 (9.4)	0.70 (0.54–0.90)	
Sex					0.37
Male	3420	190 (11.3)	130 (7.5)	0.65 (0.52–0.81)	
Female	1750	113 (12.6)	82 (9.6)	0.79 (0.59–1.05)	
Index event					0.91
Minor stroke	3725	223 (12.0)	159 (8.5)	0.69 (0.56–0.84)	
TIA	1445	80 (11.0)	53 (7.4)	0.65 (0.45–0.93)	
ABCD^2 score					0.47
4	747	33 (8.8)	27 (7.3)	0.69 (0.40–1.19)	
>4	698	47 (13.4)	26 (7.5)	0.60 (0.36–1.00)	
Previous stroke					0.49
Yes	1033	54 (10.4)	42 (8.1)	0.80 (0.52–1.21)	
No	4137	249 (12.0)	170 (8.2)	0.66 (0.55–0.81)	
Previous TIA					0.34
Yes	174	13 (16.2)	7 (7.4)	0.47 (0.15–1.44)	
No	4996	290 (11.6)	205 (8.2)	0.69 (0.58–0.83)	
History of hypertension					0.69
Yes	3399	220 (13.1)	158 (9.2)	0.70 (0.57–0.85)	
No	1771	83 (9.2)	54 (6.2)	0.63 (0.44–0.89)	
Previous diabetes					0.69
Yes	1093	74 (13.6)	56 (10.2)	0.75 (0.52–1.07)	
No	4077	229 (11.2)	156 (7.7)	0.67 (0.54–0.82)	
Systolic pressure					0.25
≥140 mm Hg	3790	250 (13.2)	165 (8.7)	0.65 (0.53–0.79)	
<140 mm Hg	1376	53 (7.6)	46 (6.7)	0.84 (0.56–1.26)	
Time to randomization					0.36
<12 hr	2573	162 (12.7)	125 (9.7)	0.73 (0.58–0.93)	
≥12 hr	2597	141 (10.8)	87 (6.7)	0.62 (0.47–0.81)	
Aspirin taken within 24 hr					0.91
Yes	597	38 (12.3)	26 (9.0)	0.66 (0.47–1.11)	
No	4573	265 (11.6)	186 (8.1)	0.68 (0.56–0.82)	

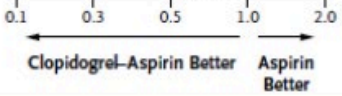


Table 7 - Hazard ratios for the primary outcome in prespecified subgroups in the CHANCE study

EFFICACY AND SAFETY OUTCOMES PER PROTOCOL

A total of 4854 patients per protocol were included in this analysis, 2402 patients in clopidogrel plus aspirin group and 2452 patients in the aspirin group. The per protocol outcomes are mainly consistent with results

in whole patients (Table 8).

Outcome	Aspirin Group (N=2452)		Clopidogrel-Aspirin Group (N=2402)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	%	no.	%		
Primary outcome: stroke	299	12.3	209	8.7	0.70(0.59-0.83)	<0.001
Secondary combined outcome: stroke, myocardial infarction, or death from cardiovascular causes	299	12.3	210	8.7	0.70(0.59-0.84)	<0.001
Other secondary outcomes						
Ischemic stroke	291	12.0	201	8.4	0.69(0.58-0.83)	<0.001
Hemorrhagic stroke	8	0.3	8	0.3	1.01(0.38-2.70)	0.98
Myocardial infarction	0	0.0	2	0.1	1.44(0.24-8.63)	0.69
Death from cardiovascular causes	2	0.1	3	0.1	1.28(0.22-8.23)	0.73
Death from any cause	2	0.1	3	0.1	1.28(0.22-8.23)	0.73
TIA	30	1.2	30	1.2	0.98(0.59-1.64)	0.95
Safety outcomes						
Bleeding, according to GUSTO						
Severe Bleeding	2	0.1	3	0.1	1.32(0.22-7.91)	0.76
Moderate Bleeding	1	0.0	1	0.0	0.97(0.06-15.44)	0.98
Mild Bleeding	10	0.4	14	0.6	1.38(0.61-3.11)	0.44
Any bleeding	22	0.9	30	1.2	1.35(0.78-2.34)	0.29

Table 8 – Efficacy and safety outcome per protocol in the CHANCE study

POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke)

Study ID	***Number of centres*** Locations	***Study start/Completion*** Total enrolled/randomised	***Design and duration***	***Study and control drugs***	***Patients by treatment*** (randomised/completed)	***Sex*** Median age (range)	***Diagnosis***	***Primary endpoint***
NCT00991029	350 sites in 10 countries (Australia, Canada, Finland, France, Germany, Mexico, New Zealand, Spain, United Kingdom, and the US) 82.8% enrolled in the US	*28 May 2010-9April 2018* 4881/4881	Multicenter, international, randomized, double-blind, placebo-controlled study	*ASA + clopidogrel* ASA + placebo	*ASA + clopidogrel* 2432/2276 ASA + placebo 2449/2281	*45%women* 65 years (?)	Age ≥18 years; minor (NIHSS ≤3) AIS or TIA (with ABCD^2 score ≥4); and randomized within 12 hours of the time patients were last known to be free of new ischemic symptoms Exclusion if received any thrombolytic therapy within 1 week; if candidates for thrombolysis, endovascular therapy, or endarterectomy interventions; planned use of non-study antiplatelet, NSAIDS, anticoagulation therapy	composite event of ischemic stroke, myocardial infarction (MI), or ischemic vascular death within 90 days

A prospective, Multicenter, randomized, double blind, placebo controlled trial to assess the effects of a 3-month regimen of clopidogrel initiated with a loading dose (LD) of 600 mg followed by 75 mg/day during the first 90 days versus a 3-month regimen of ASA 50-325 mg/day alone on reducing the 3-month risk of a composite event of ischemic stroke, myocardial infarction (MI), or ischemic vascular death within 90 days when initiated within 12 hours of symptom onset in high-risk patients with TIA or acute minor stroke.

Methods

Study participants

Patients of 18 years of age or older with high-risk TIA (ABCD2≥4) or minor ischemic stroke (NIHSS ≤3) randomized within 12 hours of the time patients were last known to be free of new ischemic symptoms.

Patients were enrolled from 350 sites in 10 countries (Australia, Canada, Finland, France, Germany, Mexico, New Zealand, Spain, United Kingdom, and the US). 82.8% were enrolled in the US.

A certified, trained licensed physician investigator was required to confirm the diagnosis of TIA (traditional definition) or minor ischemic stroke and to calculate the ABCD2 score and NIHSS score.

Inclusion criteria:

- Neurologic deficit (based on history or exam) attributed to focal brain ischemia and EITHER:

- High risk TIA: complete resolution of the deficit at the time of randomization AND ABCD2 score ≥4, OR
- Minor ischemic stroke: residual deficit with NIHSS ≤3 at the time of randomization.

- Ability to randomize within 12 hours of the time patients were last known to be free of new ischemic symptoms.
- Head CT or MRI ruling out hemorrhage or other pathology, such as vascular malformation, tumor, or abscess that could explain symptoms or contraindicate therapy.
- Ability to tolerate aspirin at a dose of 50 to 325 mg/day.

Exclusion criteria

- Age <18 years.
- TIA symptoms limited to isolated numbness, isolated visual changes, or isolated dizziness/vertigo.
- In the judgment of the treating physician, a candidate for thrombolysis, endarterectomy or
- endovascular intervention, unless the subject declines both endarterectomy and endovascular intervention at the time of evaluation for eligibility.
- Receipt of any intravenous or intra-arterial thrombolysis within 1 week prior to index event.
- Gastrointestinal bleed or major surgery within 3 months prior to index event.
- History of non-traumatic intracranial hemorrhage.
- Clear indication for anticoagulation (e.g., warfarin, heparin) anticipated during the study period (atrial fibrillation, mechanical heart valve, deep venous thrombosis, pulmonary embolism, antiphospholipid antibody syndrome, hypercoagulable state).
- Qualifying ischemic event induced by angiography or surgery.
- Severe non-cardiovascular comorbidity with life expectancy <3 months.
- Contraindication to clopidogrel or aspirin:
- Known allergy

- Severe renal (serum creatinine >2 mg/dL or 176.8 µmol/L) or hepatic insufficiency (prior or concurrent diagnosis, with an International Normalized Ratio [INR] >1.5, or any resultant complication, such as variceal bleeding, encephalopathy, or icterus)
- Hemostatic disorder or systemic bleeding in the past 3 months
- Current thrombocytopenia (platelet count <100 x109/L) or neutropenia/granulocytopenia (<1 x109/L)
- History of drug-induced hematologic or hepatic abnormalities
- Anticipated requirement for long-term (>7 day) non-study antiplatelet drugs (e.g., dipyridamole, clopidogrel, ticlopidine), or nonsteroidal anti-inflammatory drugs [NSAIDs] affecting platelet function (such as prior vascular stent or arthritis).
- Not willing or able to discontinue prohibited concomitant medications.
- Inability to swallow medications.
- At risk for pregnancy: premenopausal or post-menopausal woman within 12 months of last menses without a negative pregnancy test or not committing to adequate birth control (e.g., oral contraceptive, two methods of barrier birth control, or abstinence).
- Unavailability for follow-up.
- Signed and dated informed consent not obtained from patient.
- Other neurological conditions that would complicate assessment of outcomes during follow-up.
- Ongoing treatment in another study of an investigational therapy that may potentially interact with study drug, or treatment in such a study within the last 7 days.
- Previously enrolled in the POINT study.

Treatments

General study design

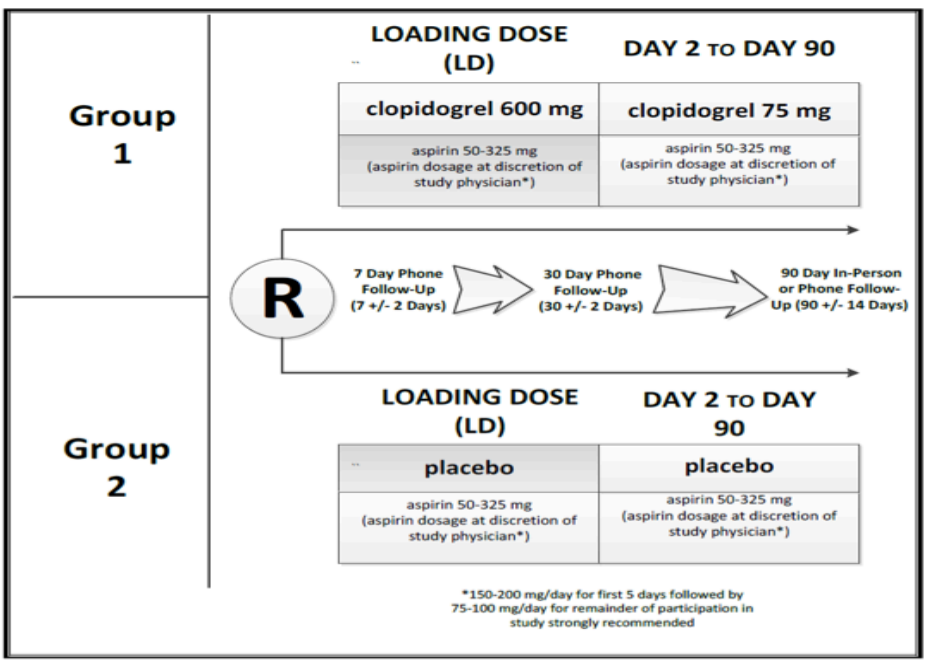


Figure 4 - General study design of the POINT study

Study treatment and study dose

Patients who met the enrolment criteria were randomly assigned in a 1:1 ratio to 1 of the 2 treatment groups (clopidogrel + ASA group or ASA alone group). Randomization was stratified according to clinical centre.

The clopidogrel + ASA group received a loading dose of 600 mg clopidogrel, followed by 75 mg/day clopidogrel from Day 2 to Day 90. The ASA alone group received 8 placebo tablets followed by 1 placebo tablet daily from Day 2 to Day 90. Both groups were given open-label ASA 50 to 325 mg/day as per the investigator's discretion: a dose of 162 mg daily for 5 days followed by the recommended 81 mg daily dose that was suggested in the protocol. The first dose of study drug was given as soon after randomization as possible, but no later than 12 hours from symptom onset. Each patient was followed for 90 days from randomization.

Objectives

The primary objective of POINT was to determine the effectiveness of clopidogrel (at a loading dose of 600 mg followed by 75 mg/day orally) over placebo when initiated within 12 hours of time last known free of new ischemic symptoms in patients receiving ASA therapy at 50 to 325 mg/day.

Outcomes/endpoints

The **primary efficacy measure** was the composite event of ischemic stroke, myocardial infarction (MI), or ischemic vascular death within 90 days.

The **primary safety outcome** was major hemorrhage. This variable was defined as symptomatic intracranial hemorrhage, intraocular bleeding causing vision loss, transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization or prolongation of an existing hospitalization, or death due to hemorrhage.

The **secondary outcomes for efficacy/net-benefit** included:

- Composite event of ischemic stroke, MI, or ischemic vascular death, or major hemorrhage
- Ischemic stroke
- Ischemic vascular death
- Myocardial infarction
- Composite event of ischemic stroke and hemorrhagic stroke

- Other **secondary safety/tolerability outcomes** included:
- All-cause death
- Hemorrhagic stroke
- Symptomatic intracerebral hemorrhage
- Other symptomatic intracranial hemorrhage (subarachnoid hemorrhage [SAH], subdural
- hemorrhage [SDH], or intraventricular hemorrhage [IVH])
- Major hemorrhage other than intracranial hemorrhage
- All minor hemorrhage (including asymptomatic intracranial hemorrhage)

Sample size

The minimum necessary sample size in the trial was established by the requirement to detect the smallest expected, clinically meaningful, treatment difference comparing the treatment with placebo. A relative risk reduction (RRR) of 23% was the smallest difference felt to be of clinical importance.
The initially defined total sample size for the study was 4150 patients (rounded up from 4142). With a sample size of 4150 patients, with 530 events, the study had 90% power to detect a RRR of 23% with a two-sided alpha of 0.05. The sample size was estimated based on a hazard ratio [HR] of 0.75 (equivalent to RRR of 23%) assuming an exponential survival distribution (assuming the proportion of patients with events in the placebo group was 0.1524 at 90 days), with inflation to account for two interim analysis for efficacy at equal intervals using O'Brien and Fleming stopping boundary using the Lan-Demets spending function and inflation for lost-to-follow-up and/or crossover.
The intention-to-treat (ITT) principle was applied to the analysis and the sample size was inflated to safeguard against lost-to-follow-up and/or crossover in the actual treatment received, which would dilute the effect size. From the FASTER (Fast Assessment of Stroke and Transient ischemic attack to prevent Early Recurrence) trial there were 12% crossovers and 2% losses to follow-up. Most events were expected to occur early in the follow-up period and hence a smaller fraction of events would be lost and a smaller total correction in sample size was required (5.0%).
Based on the observed event rate in the placebo + ASA group at the first interim analysis, the sample was increased to 5840 patients to provide the study with a power of 80% with other variables remaining unchanged in the calculation.

Randomisation

Randomization took place centrally and electronically via the WebDCU™ clinical trials management system housed at the POINT Statistics and Data Coordinating Center at MUSC.
Patients were randomized 1:1 (clopidogrel + ASA : placebo + ASA), balanced within clinical centers using the blocked-urn method. The randomization computer program made the treatment assignment based on the current status of treatment group distribution within each clinical center as well as overall balance of treatment assignment.
A "Real-Time" randomization procedure was implemented via the WebDCU™ system where the clinical center staff entered the eligibility information of a subject prior to enrollment. If the subject's eligibility status was confirmed, the computer program on the WebDCU™ server evaluated the treatment arm distribution and generated a study number based on the randomization scheme. The study number corresponded to a specific medication bottle already at the clinical center.

Blinding (masking)

The POINT study used a double-blind design. The 75-mg clopidogrel and placebo tablets used in this study were indistinguishable (identical taste, size, shape, color, and appearance). The study staff, including the investigators, and patients were blinded to the study treatment. Unblinding by the investigator was only to occur in an emergency need for unblinding. In such a case, details of the unblinding were to be recorded.

Statistical methods

The primary null hypothesis was that, in patients with TIA or minor ischemic stroke treated with aspirin 50 to 325 mg/day, there is no difference in the event-free survival at 90 days in those treated with clopidogrel (600 mg loading dose then 75 mg/day) compared with placebo when patients are randomized within 12 hours of time last known free of new ischemic symptoms.

The log-rank test was used to compare the time from randomization to the first occurrence of any given endpoint. A Cox proportional hazards model to estimate the HR and 95% CIs. There was no adjustment for baseline covariates or for the ASA dose in the primary efficacy or safety analyses. Interactions between treatment assignment and pre-specified subgroups were evaluated in the Cox model. A P value<0.05 was considered to indicate statistical significance. A stratified Cox model was used according to the timepoint to perform a secondary analysis of the primary efficacy and primary safety outcomes comparing the treatment effect during four time periods: Days 0 to 7 versus Days 8 to 90 and days 0 to 30 versus Days 31 to 90.

Secondary efficacy outcome analyses were not adjusted for multiple comparisons and are considered to be exploratory. A post hoc Bonferroni calculation was made for reference purposes to derive an adjusted threshold for P values to account for multiple comparisons of secondary outcomes.

Unplanned secondary analysis

The absolute number of events was estimated using the life-table method for the following time periods: 1st week, 2nd week, 3rd week, 4th week, 5th week, and 6th week to 90 days. The effective sample size for each time period was calculated as the sample size at the start of the time interval minus one half the number of patients censored in the time interval. The absolute difference in proportions (ASA alone minus clopidogrel-aspirin) was calculated for each time period. The HR was evaluated at the midpoint of the 7-day intervals using the life-table method. Ischemic events with a binary treatment group indicator Z1 and a time-dependent indicator function in which Z2(t) = (Z1 if t > T and 0 if t ≤ T), where t is time in days and T is the cut point of the relative risk. To determine the optimal cut point for the piecewise proportional hazard model, a model with a cut point at every day from 7 to 45 days was used, and the optimal cut point was the day in which the partial log-likelihood was maximized.

A post hoc, exploratory analysis was conducted to estimate the treatment effect modeling a range of potential initiation times beyond 12 hours from symptom onset. All events through the optimal duration of treatment (21 days) were included in the analysis. By assuming that there was no accumulated benefit of antiplatelet effect, the treatment effect was modeled as follows: for each patient, the time from index event (TIA or minor stroke) onset to major ischemic events or censoring was derived. Beginning at 12 hours after onset, for every 6-hour period up to 168 hours (1 week), events and censoring time were left-truncated if the event or censoring occurred before the given time period by removing the participant from the numerator (event count) and the denominator (number at risk set) before calculating the proportion for each group. The absolute difference in proportions of events was calculated for each treatment group along the 95% (Wald) confidence intervals. The same approach was used to model major hemorrhage.

Interim analysis.

Two interimanalyses were planned. Enrollment in the POINT study was prematurely stopped after approximately 83% of the planned number of patients had been randomized. Of these patients, 4782

(98.0%) had been followed for at least 7 days, and 4557 (93.4%) had completed the 90-day trial visit or had died. The Data and safety monitoring board (DSMB) determined that the treatment effect observed had crossed the significance boundary for efficacy during an interim analysis.

Results

Participant flow

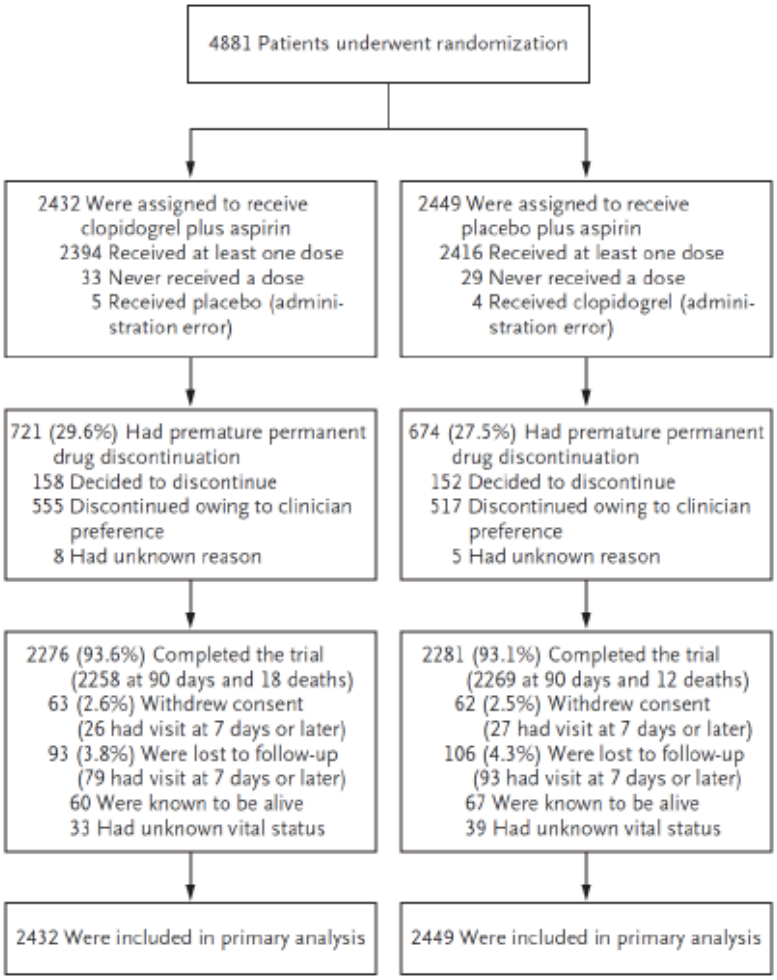


Figure 5 – Chart Flow of patients included in the POINT study

Discontinuation of the study medication occurred in 29.6% of the patients in the group receiving clopidogrel + aspirin and in 27.5% of those receiving placebo + aspirin. Rates of withdrawal from the study or loss to follow-up were 6.4% in the group receiving clopidogrel+ aspirin and 6.9% in the placebo + aspirin group.

Recruitment

Enrollment to the POINT study was prematurely stopped, as advised by the DSMB after approximately 83% of the planned number of patients had been randomized. At this time the DSMB recommended halting enrollment because of confirmation of significant excess in the number of patients with major haemorrhage in the DAPT group. At the same time, a planned analysis determined that a treatment effect had crossed the significance boundary for efficacy.

Conduct of the study

Time until primary analysis censoring data

4782 patients (98.0%) were followed for at least 7 days, and 4557 (93.4%) completed the 90-day trial visit or died.

Protocol deviations

The frequency of protocol deviations per type is shown in Table 9.

	N	% of Subjects
Failure to obtain signed informed consent prior to performing protocol-specific procedures	8	0.2%
Enrolled with invalid (i.e. not current) IC Form	119	2.4%
No documentation of IC process	164	3.4%
IC obtained by unauthorized personnel	36	0.7%
Missing original signed IC Form	12	0.2%
Missing signatures/dates on IC Form	35	0.7%
Unauthorized changes to IC Form	1	0.0%
Copy of IC Form not given to subject	4	0.1%
Other informed consent deviation(s)/violation(s)	229	4.7%
Failure to supervise loading dose	16	0.3%
Error in amount of loading dose	29	0.6%
Error in timing of loading dose	74	1.5%
Unblinding outside of the allowed protocol procedures	5	0.1%
Changes to protocol without prior IRB approval	0	0.0%
Other deviation(s)/violation(s)	474	9.7%
Randomization Errors	23	0.5%

Table 9 – Protocol deviations per type in the POINT study

In addition, data of 9 patients were removed from the clinical database due to the lack of documentation of informed consent.

One patient was re-enrolled. Only the data associated with the first enrollment was used in the primary analysis.

Five patients were randomized to clopidogrel and received placebo. Four patients were randomized to placebo and received clopidogrel.

Treatment compliance

Compliance with the study medication was assessed via the Morisky questionnaire at Days 7 and 90, and event phone call or in-person visit. The 4-question Morisky scale is a commonly used and validated adherence measure. A patient was considered compliant with the study medication if he/she reported at least medium compliance on the study adherence questionnaire. The Investigator was responsible for monitoring patient adherence.

In addition, compliance with the study drug was documented at the 90-day visit. Those patients taking

more than 80% of tablets on Days 2 to 90 (ie, 71 or more tablets) were considered adherent as assessed by pill count and patient/care-giver report. Since the loading dose was observed by the study Investigator or other member of the study team, patients were considered to be in compliance with the loading dose. Therefore, a patient was adherent if he/she took at least 79 tablets (8 at loading dose + 71 on Days 2 to 90).

In the clopidogrel + aspirin group, 76.3% of the study drug was taken by an overall of 2140 patients, while 77.8% of drug was taken in the placebo + aspirin group by an overall of 2164 patients.

Protocol amendments

The following changes were done to the planned analyses:

Sample Size Increase: Following the first interim analysis, the maximum sample size was re-estimated to be 5840 patients.

Trial Discontinuation: In August 2017, the pre-specified boundary for a safety signal of major hemorrhage was exceeded. It was decided to follow these events until a planned meeting of the DSMB in December 2017. At that meeting, the board recommended halting enrollment to the trial because of confirmation of a significant excess in the number of patients with major hemorrhage in the combined antiplatelet group, and a planned analysis determined that a treatment effect had crossed the significance boundary for efficacy.

There were 5 amendments to the protocol, of which 1 was introduced before the inclusion of any patients. The changes introduced by these amendments applied to all patients.

Baseline data

Demographic and patient characteristics at baseline were generally similar between treatments Arms (Table 10). The median age was 65 years in both treatment groups, and 45.1% of patients were women in the clopidogrel + ASA group versus 44.8% in the placebo + ASA group.

Characteristic	Placebo + Aspirin (N=2449)	Clopidogrel + Aspirin (N=2432)
Median age (IQR)-year	65.0 (56.0-74.0)	65.0 (55.0-74.0)
Female sex – no. (%)	1098 (44.8)	1097 (45.1)
Race – no./total no. (%)†		
White	1781/2378 (74.9)	1774/2360 (75.2)
Black	493/2378 (20.7)	473/2360 (20.0)
Asian	67/2378 (2.8)	77/2360 (3.3)
Other	37/2378 (1.6)	36/2360 (1.5)

Characteristic	Placebo + Aspirin (N=2449)	Clopidogrel + Aspirin (N=2432)
Hispanic ethnic group – no./total no. (%)†	146/2328 (6.3)	144/2320 (6.2)
Region – no. (%)		
United States	2029 (82.9)	2014 (82.8)
Other countries	420 (17.1)	418 (17.2)
Medical history – no./total no. (%)		
Ischemic heart disease	240/2443 (9.8)	257/2426 (10.6)
Hypertension	1680/2437 (68.9)	1693/2423 (69.9)
Diabetes mellitus	662/2447 (27.1)	678/2425 (28.0)
Medication use at presentation – no. (%)		
Aspirin	1397 (57.0)	1417 (58.3)
Clopidogrel	42 (1.7)	48 (2.0)
Time from presentation to randomization		
Mean time (±SD) – h	7.3 ±2.9	7.4 ±3.0
Interval – no./total no. (%)		
<6 h	789/2449 (32.2)	755/2431 (31.1)
≥6 h	1660/2449 (67.8)	1676/2431 (68.9)
Qualifying event – no. (%)		
TIA	1052 (43.0)	1056 (43.4)
Ischemic stroke	1397 (57.0)	1376 (56.6))
Median qualifying neurologic score (IQR)		
ABCD² for TIA‡	5.0 (4.0-5.0)	5.0 (4.0-6.0)
NIHSS for ischemic stroke	2.0 (1.0-2.0)	2.0 (1.0-2.0)
Systolic Blood Pressure		
Mean (SD)	162 (28)	162 (28)
Median	159	159
Min, max	89, 305	16, 267
Diastolic Blood Pressure		
Mean (SD)	88 (17)	88 (17)
Median	87	87
Min, max	35, 165	39, 202
Baseline Laboratory Values – Mean (SD)*		
Glucose, mg/dL	127 (50)	128 (54)
White blood cell count, x10/L	8 (3)	8 (2)
Red blood cell count, M/CUMM	5 (1)	5 (1)
Hemoglobin, gm/dL	14 (2)	14 (2)
Hematocrit, %	42 (4)	42 (5)
Platelet count, M/CUMM	234 (62)	235 (64)

Table 10 - Demographic and patient characteristics at baseline in the two arms of the POINT study

Medical history was similar between treatment groups (Table 11). The most frequent event in both treatment groups was hypertension (69.6% in the clopidogrel + aspirin group and 68.5% in the placebo + aspirin group).

Characteristic	Placebo + Aspirin (N=2449) N (% patients)	Clopidogrel + Aspirin (N=2432) N (% patients)
Congestive Heart Failure	62 (2.5)	64 (2.6)
Atrial Fibrillation	18 (0.7)	31 (1.2)
Ischemic Heart Disease	240 (9.7)	257 (10.5)
Valvular Heart Disease/Valve Replacement	34 (1.3)	49 (2.0)
Carotid Stenosis/Endarterectomy/Stent/Angioplasty	106 (4.3)	102 (4.1)
Hypertension	1680 (68.5)	1693 (69.6)
Diabetes Mellitus	662 (27.0)	678 (27.8)
Past/Present Smoking	1165 (47.5)	1171 (48.1)
Physician Diagnosis or Active Treatment of Peptic Ulcer	22 (0.8)	26 (1.0)
Current tobacco smoker – no. (%)	508 (20.8)	496 (20.4)

Table 11 – Past medical history of patients included in the two arms of the POINT study

Concomitant medication

Patients not willing or able to discontinue prohibited concomitant medications were not eligible to enroll in the study. However, if there was a clinical need that justified the added risk of these interventions in the setting of study drug use, they were employed at the discretion of the treating physician.

- Nonsteroidal anti-inflammatory drugs, Cox-1 inhibitors. If absolutely necessary, NSAIDs
- were given for as short a time as possible but not sooner than 8 days after randomization
- Anticoagulants (both oral and parenteral)
- Open-label thienopyridines (eg, ticlopidine, clopidogrel)
- Dipyridamole
- Other antiplatelets
- Thrombolytics (e.g., tPA)
- Vascular intervention (surgery and/or angioplasty of any vessel)

If the intervention was absolutely necessary within the three months after randomization, the study drug was stopped 5 days prior to the intervention. The study treatment was then restarted unless the patient needed to take open-label clopidogrel or ASA. In this case, the study drug was restarted only when treatment with an open-label antiplatelet therapy other than ASA had been stopped.

Concomitant medication use was similar in both treatment groups (Table 12). A similar proportion of patients in the clopidogrel + ASA group (22.1%) and placebo + ASA group (22.9%) took any prohibited medication since last visit. The most frequent prohibited medication taken in both treatment groups was anticoagulants (both oral and parenteral) (12.6% in the clopidogrel + ASA group and 13.3% in the placebo + ASA group).

Characteristic	Placebo + Aspirin (N=2403) N (% patients)	Clopidogrel + Aspirin (N=2380) N (% patients)
Patients taking any prohibited meds since last visit	551 (22.9)	526 (22.1)
Reported type of prohibited med taken since last visit		
Anticoagulants (both oral and parenteral)	321 (13.3)	301 (12.6)
NSAID	145 (6.0)	169 (7.1)
Thienopyridines	90 (3.7)	77 (3.2)
Thrombolytics	15 (0.6)	14 (0.5)
Other anti-platelets	57 (2.3)	51 (2.1)
Other prohibited medications	18 (0.7)	15 (0.6)
Patients taking any discouraged meds since last visit	308 (12.8)	311 (13.0)
Reported type of discouraged med taken since last visit		
Proton pump inhibitors	295 (12.2)	292 (12.2)
Other discouraged medications	18 (0.7)	24 (1.0)

Table 12 – Patients using concomitant medication by drug class in the POINT study

Numbers analysed

At the time the trial was stopped because of a significant excess in the number of patients with major hemorrhage in the clopidogrel + ASA group was confirmed, a total of 4881 patients had been enrolled, which represented 83.6% of the anticipated number of patients. Of these patients, 4782 (98.0%) had been followed for at least 7 days, and 4557 (93.4%) had completed the 90-day trial visit or had died.

Outcomes and estimation

The **primary efficacy outcome** in a time-to-event analysis was the risk of a composite of ischemic stroke, MI, or death from an ischemic vascular event, at 90 days. In patients with high-risk TIA or minor ischemic stroke, treatment with clopidogrel + ASA resulted in a statistically significant risk reduction of subsequent ischemic stroke, MI, or death from ischemic vascular causes (Figure 6). The composite primary efficacy outcome occurred in 121 patients (5.0%) receiving clopidogrel plus ASA and in 160 patients (6.5%) receiving placebo and ASA (HR: 0.75; 95% CI: 0.59-0.95; P = 0.02).

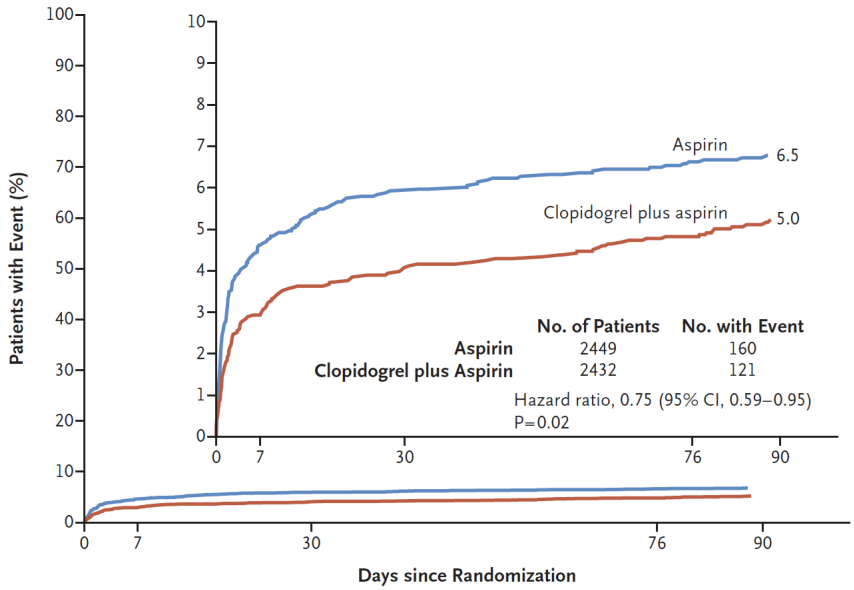


Figure 6 – Kaplan-Meyer curves documenting the primary efficacy outcome in the POINT study

Time course for benefit

All enrolled patients were included in this analysis. In the ASA group, 160 (6.5%) major ischemic events occurred within 90 days, with most events occurring in the first week (Figure 7). In the clopidogrel-ASA group, 121 (5.0%) major ischemic events occurred within 90 days, with most events also occurring in the first week. Major ischemic events were less frequent in patients randomly assigned to daily clopidogrel-ASA versus aspirin in the first 3 weeks after enrollment but not in subsequent weeks (Figure 7).

Time Period	Outcome	Clopidogrel-Aspirin (N=2432)		Aspirin (N=2449)		Hazard Ratio (95% CI)	P Value
		Patients with Event *no.*	Event Rate *%*	Patients with Event *no.*	Event Rate *%*		
0-7 days	Ischemic stroke, MI, or ischemic vascular death	70	2.9%	111	4.5%	0.74 (0.55 - 0.99)	0.04
	Major hemorrhage	7	0.3%	4	0.2%	1.82 (0.53 – 6.22)	0.34
8-90 days	Ischemic stroke, MI, or ischemic vascular death	51	2.1%	49	2.0%	1.03 (0.70-1.53)	0.88
	Major hemorrhage	16	0.7%	6	0.2%	2.69 (1.05 - 6.86)	0.04
0-30 days	Ischemic stroke, MI, or ischemic vascular death	96	3.9%	141	5.8%	0.73 (0.56 - 0.95)	0.02
	Major hemorrhage	12	0.5%	6	0.2%	2.05 (0.76 - 5.56)	0.16
31-90 days	Ischemic stroke, MI, or ischemic vascular death	25	1.0%	19	0.8%	1.30 (0.72 - 2.36)	0.39
	Major hemorrhage	11	0.5%	4	0.2%	2.77 (0.88 - 8.70)	0.08

Figure 7 – Number of events in the POINT distributed by time period

With the use of a model-based approach, the optimal cut point of relative risk for major ischemic events was 21 days (Figure 8). The hazard ratio of the primary efficacy outcome at 21 days was 0.65 (95%CI 0-50-0.85, p=0.0015) and at 22-90 days was 1.38 (95%CI 0.81-2.35,p=0.24).

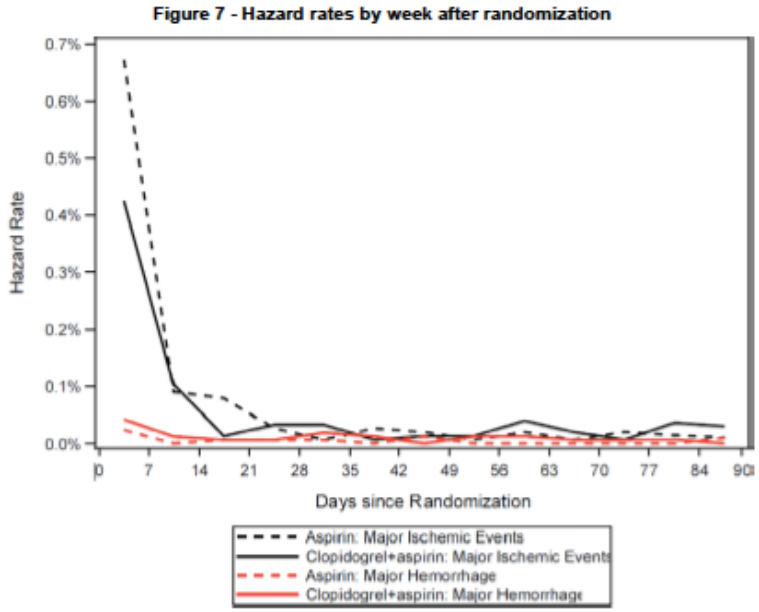


Figure 8 – Hazard rates by week after randomization

Secondary analyses

The **key secondary efficacy endpoints** included each component of the primary efficacy outcome, a composite of the primary efficacy outcome or major hemorrhage, and the total number of ischemic and hemorrhagic strokes.

The secondary outcome of ischemic stroke occurred in 112 patients (4.6%) receiving clopidogrel + ASA, and in 155 patients (6.3%) receiving placebo + ASA (HR: 0.72; 95% CI: 0.56-0.92; P = 0.01). Except for stroke, there were no significant differences between treatment groups in the other components of the composite primary efficacy outcome (Table 13).

The risk of total ischemic or hemorrhagic stroke was lower with clopidogrel + ASA than with placebo + ASA (HR: 0.74; 95% CI: 0.58-0.94; P = 0.01). A post hoc Bonferroni-corrected P value that incorporates five main secondary outcome comparisons is shown in Table 13.

Secondary efficacy outcomes	Placebo + Aspirin (N=2449)	Clopidogrel + Aspirin (N=2432)	Hazard Ratio (95% CI)	P value
Ischemic stroke	155 (6.3)	112 (4.6)	0.72 (0.56-0.92)	0.01*
Myocardial infarction	7 (0.3)	10 (0.4)	1.44 (0.55-3.78)	0.46*
Death from ischemic vascular causes	4 (0.2)	6 (0.2)	1.51 (0.43-5.35)	0.52*
Ischemic or hemorrhagic stroke	156 (6.4)	116 (4.8)	0.74 (0.58-0.94)	0.01*
Composite of ischemic stroke, myocardial infarction, death from ischemic vascular causes, or major hemorrhage	167 (6.8)	141 (5.8)	0.84 (0.67-1.05)	0.13*

Abbreviations: CI, confidence interval; N, no. of patients.
*Post hoc correction for multiple testing of five secondary end points by the Bonferroni method resulted in a P value of 0.01 to indicate a significant difference between treatment groups.

Table 13 – Secondary efficacy outcomes

The remaining pre-specified secondary and terciary analysis are shown in Table 14.

Outcome	Clopidogrel-Aspirin (N=2432)		Aspirin (N=2449)		Hazard Ratio (95% CI)	P Value
	Patients with Event *no.*	Event Rate *%*	Patients with Event *no.*	Event Rate *%*		
Secondary Analyses (as-treated sample)	**(N=2398)**		**(N=2421)**			
Primary Outcome: ischemic stroke, MI, or ischemic vascular death analyzed with the as-treated sample	102	4.3%	141	5.8%	0.73 (0.56 – 0.94)	0.01
Primary safety outcome: major hemorrhage analyzed with the as-treated sample	21	0.9%	6	0.2%	3.57 (1.44 – 8.85)	<0.01
Tertiary Analyses (Intent-to-treat sample)	**(N=2432)**		**(N=2449)**			
Primary Outcome: ischemic stroke, MI, or ischemic vascular death analyzed with adjustment for enrolling site	-	-	-	-	0.75 (0.60 – 0.95)	0.02
Primary Outcome: ischemic stroke, MI, or ischemic vascular death analyzed with adjustment for age, onset time, evidence of brain infarction, and enrolling site	-	-	-	-	0.74 (0.59–0.94)	0.01
composite event of ischemic stroke, TIA, MI, or ischemic vascular death	197	8.1%	250	10.2%	0.79 (0.65 – 0.95)	0.01
composite of ischemic stroke, MI, all-cause death, or major hemorrhage	149	6.1%	171	7.0%	0.87 (0.70 – 1.08)	0.21
TIA	89	3.7%	96	3.9%	0.93 (0.70 – 1.26)	0.63
Coronary Revascularization (with or without MI)	5	0.2%	5	0.2%	1.01 (0.29 – 3.48)	0.99
Vascular Death	9	0.4%	6	0.2%	1.51 (0.54 – 4.24)	0.43
Asymptomatic intracranial hemorrhage (ICH, SAH, SDH or IVH)	5	0.2%	2	0.1%	2.52 (0.49 – 13.00)	0.25
					Odds Ratio (95% CI)	
New handicap/disability defined as 90 day mRS (≥2) †	324	13.3%	335	13.7%	0.97 (0.82–1.14)	0.71*
	Median	**IQR**	**Median**	**IQR**		**P Value**
90 day mRS†	0	0-1	0	0-1		0.62**

Table 14 - Pre-specified secondary and terciary analysis in the POINT study

Ancillary analyses

Subgroup analysis

No significant treatment-by-subgroup interactions were observed in pre-specified subgroups, but the number of patients with available data for analysis limited the power to determine interactions (Figure 9). There was no difference in treatment effect according to the predominant daily aspirin dose received during the trial period.

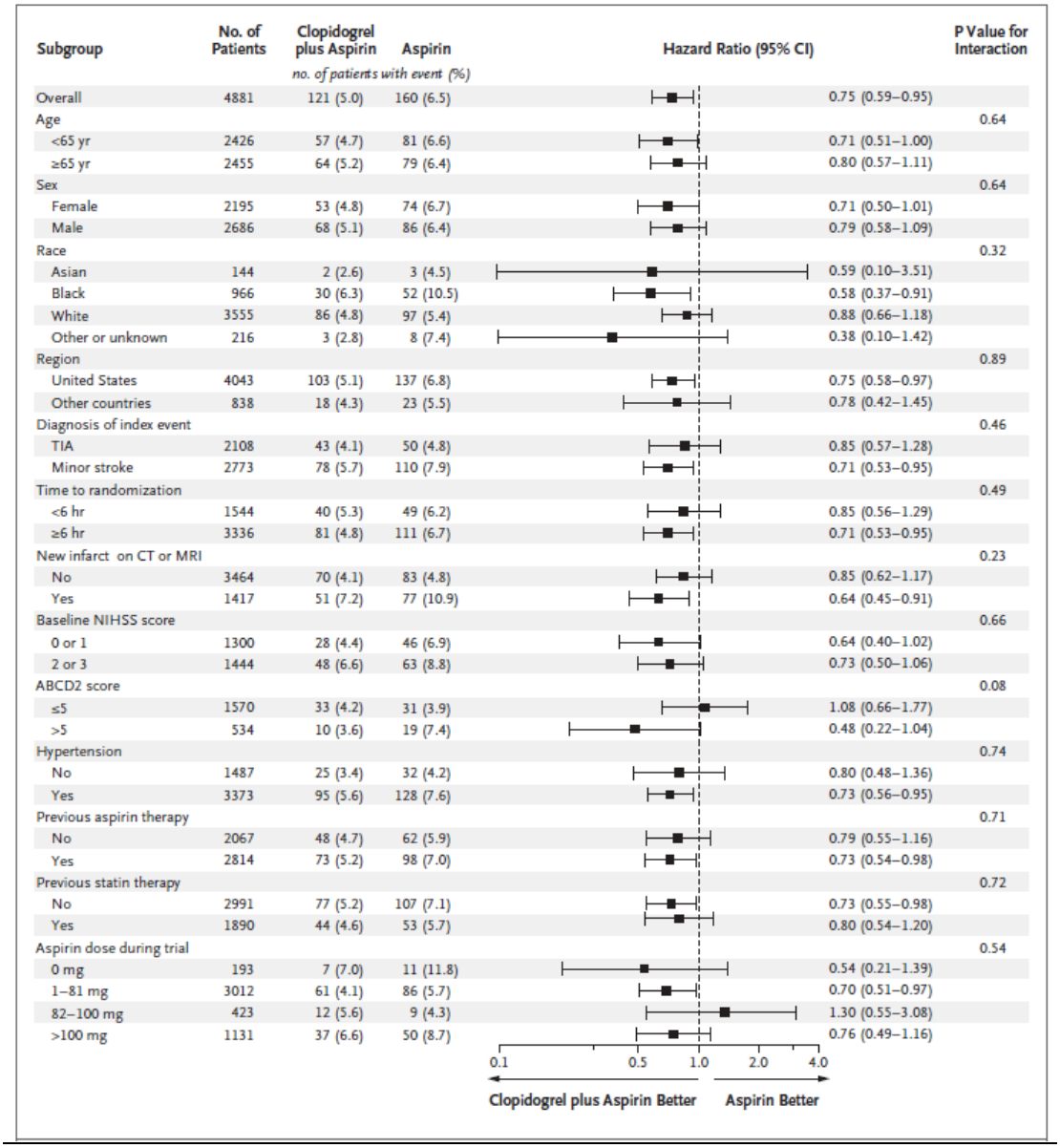


Figure 9 – Subgroup analysis regarding the main efficacy outcome in the POINT trial

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 15 Summary of Efficacy for trial CHANCE

Title: CHANCE (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events)				
Study identifier	NCT00979589			
Design	Multicenter, randomized, doubleblind, placebo controlled study conducted at 114 sites in China			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	2009-2012 34 months enrolment Not applicable		
Hypothesis	Superiority			
Treatments groups	ASA + clopidogrel	Clopidogrel: Day 1 300 mg, Days 2-90 75 mg ASA: Day 1 75-300 mg, Days 2-21 75 mg ASA placebo: Days 22-90 2584 patients randomized Follow-up 90 days		
	ASA + placebo	Clopidogrel placebo: Days 1-90 ASA: Day 1 75-300 mg, Days 2-90 75 mg 2586 patients randomized Follow-up 90 days		
Endpoints and definitions	Primary endpoint	Stroke	Ischemic or haemorrhagic stroke	
	Secondary endopoint	Stroke, MI or CV death		
	Secondary endpoint	Ischemic stroke		
	Secondary endpoint	Hemorrhagic stroke		
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	ASA + clopidogrel	ASA + placebo	HR (95% CI)
	Number of subject	2584	2586	5170
	Stroke	212 (8.2%)	303 (11.7%)	0.68(0.57 -0.81), p<0.001

Analysis description	**Secondary analysis**			
	Treatment group	ASA + clopidogrel	ASA + placebo	HR (95% CI)
	Number of subject	2584	2586	5170
	Composite of stroke, MI, CVD	216 (8.4)	307 (11.9)	0.69 (0.58-0.82), p<0.001
	Ischemic stroke	204 (7.9)	295 (11.4)	0.67 (0.56-0.81), p<0.001
	Haemorrhagic stroke	8 (0.3)	8 (0.3)	1.01 (0.38-2.70), p=0.98
	Myocardial infarction	3 (0.1)	2 (0.1)	1.44 (0.24-8.63), p=0.69
	Death from cardiovascular cause	6 (0.2)	5 (0.2)	1.16 (0.35-3.79), p=0.81
	Death from any cause	10 (0.4)	10 (0.4)	0.97 (0.40 – 2.33), p=0.94
	Transient ischemic attack	39 (1.5)	47 (1.8)	0.82 (0.53-1.26), p=0.36

Table 16 Summary of Efficacy for trial POINT

Title: POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke)			
Study identifier	NCT00991029		
Design	Multicenter, international, randomized, double blind, placebo controlled study conducted 350 sites in 10 countries (Australia, Canada, Finland, France, Germany, Mexico, New Zealand, Spain, United Kingdom, and the US)		
	Duration of main phase:	2010-2018	
	Duration of Run-in phase:	84 months enrolment	
	Duration of Extension phase:	Not applicable	
Hypothesis	Superiority		
Treatments groups	clopidogrel + ASA open label		Clopidogrel: Day 1 600 mg, Days 2-90 75 mg ASA open label: Day 1 50-325 mg, Days 2-90 50-325 mg 2432 patients randomized Follow-up 90 days
	Clopidogrel placebo + ASA open label		Clopidogrel placebo: Days 1-90 ASA open-label: Day 1 50-325 mg, Days 2-90 50-325 mg 2449 patients randomized Follow-up 90 days
Endpoints and definitions	Primary endpoint	Stroke, MI or ischemic CV death	
	Secondary endpoint	Ischemic stroke	
	Secondary endpoint	Ischemic or hemorrhagic stroke	
Results and Analysis			

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	ASA + clopidogrel	ASA + placebo	HR (95% CI)
	Number of subject	2432	2449	4881
	Stroke, MI or ischemic CV death	121 (4.98%)	160 (6.53%)	0.75 (0.59-0.95), p=0.02
Analysis description	**Secondary analysis**			
	Treatment group	ASA + clopidogrel	ASA + placebo	HR (95% CI)
	Number of subject	2432	2449	4331
	Ischemic stroke	112 (4.6)	155 (6.3)	0.72 (0.56-0.92), p=0.01
	Myocardial infarction	10 (0.4)	7 (0.3)	1.44 (0.55-3.78), p=0.46
	Death from ischemic vascular cause	6 (0.2)	4 (0.2)	1.51 (0.43-5.35), P=0.52
	Ischemic or haemorrhagic stroke	116 (4.8)	156 (6.4)	0.74 (0.58 – 0.94), p=0.01
	Composite of ischemic stroke, myocardial infarction, death from ischemic vascular cause or major hemorrhage	141 (5.8)	167 (6.8)	0.84 (0.67 – 1.05), p=0.13

Analysis performed across trials (pooled analyses and meta-analysis)

This analysis was based on individual patient data extracted directly from the databases of CHANCE and POINT, adhering to the ITT principle based on randomized treatment assignment. They included a total of 10,051 patients (5,016 assigned to clopidogrel plus ASA and 5,035 assigned to ASA alone).

The primary efficacy outcome in the pooled analysis was a new major ischemic event (ischemic stroke, myocardial infarction, or death from ischemic vascular causes) at 90 days. The secondary efficacy outcomes were each component of the primary efficacy outcome, a composite of primary efficacy outcome and major hemorrhage, and stroke (ischemic or hemorrhagic). The primary safety outcome was major hemorrhage at 90 days. Secondary safety outcomes were hemorrhagic stroke, minor hemorrhage, major or minor hemorrhage, and death from any cause.

The analysis included fixed effects for study and treatment assignment, and random effects rather than fixed effects for study site, in order to avoid the assumption of a common effect size between the two studies. If the interaction term was not significant, mixed effects Cox regression models were used with fixed effects for trial and treatment assignment, and random effects for study site to estimate the treatment

effects.

Three models were developed. The first model adjusted only for trial. The second model further adjusted for sex, age, race, history of congestive heart failure, known atrial fibrillation or flutter, ischemic heart disease, hypertension, diabetes mellitus, current or previous smoking, qualifying event type (ischemic stroke or TIA), and time to randomization. The third model further adjusted for lipid-lowering and antihypertensive treatments (sensitivity analysis only, due to missing data on such treatments).

Heterogeneity of treatment effect by prespecified, clinically-relevant variables was tested using mixed effects models with treatment-by-prespecified variable interaction terms. Prespecified variables included age, sex, race, previous ischemic heart disease, hypertension, diabetes mellitus, current or previous smoker, qualifying event, baseline NIHSS score, ABCD2 score, and time to randomization. All models were adjusted for the same covariates as the second model used for the primary analyses.

Two-sided p-values <0.05 were considered statistically significant.

Table 17 shows the baseline characteristics of the patients that were included in the pooled analysis.

Characteristics	Aspirin (n=5035)	Clopidogrel + Aspirin (n=5016)	Total (n=10051)	P-value
Age (yr), median (IQR)	63.0 (55.0-72.7)	63.6 (55.0-73.0)	63.2 (55.0-72.9)	0.16
Female, No. (%)	1996 (39.6)	1949 (38.9)	3945 (39.2)	0.42
Race, No. (%)				0.94
Asian	2653 (52.7)	2661 (53.1)	5314 (52.9)	
Black	493 (9.8)	473 (9.4)	966 (9.6)	
White	1781 (35.4)	1774 (35.4)	3555 (35.4)	
Other or unknown	108 (2.1)	108 (2.2)	216 (2.1)	
Medical history, No. (%)				
Congestive heart failure	100/5032 (2.0)	106/5012 (2.1)	206/10044 (2.1)	0.65
Known atrial fibrillation or flutter	66/5029 (1.3)	79/5008 (1.6)	145/10037 (1.4)	0.27
Ischemic heart disease	373/5029 (7.4)	385/5010 (7.7)	758/10039 (7.6)	0.61
Hypertension	3363/5023 (67.0)	3409/5007 (68.1)	6772/10030 (67.5)	0.23
Diabetes mellitus	1205/5033 (23.9)	1228/5009 (24.5)	2433/10042 (24.2)	0.50
Current or previous smoker, No. (%)	2765 (54.9)	2729 (54.4)	5494 (54.7)	0.61
Qualifying event, No. (%)				1.00
Minor Stroke	3255 (64.6)	3243 (64.7)	6498 (64.7)	
TIA	1780 (35.4)	1773 (35.3)	3553 (35.3)	
Median qualifying neurologic score (IQR)				
NIHSS for ischemic stroke	2 (1-3)	2 (1-3)	2 (1-3)	0.30
ABCD² for TIA	5 (4-5)	5 (4-5)	5 (4-5)	0.45
Time to randomization, No. (%)				0.95
<6 hrs	1346/5035 (26.7)	1329/5015 (26.5)	2675/10050 (26.6)	
6-11 hrs	2161/5035 (42.9)	2167/5015 (43.2)	4328/10050 (43.1)	
≥12 hrs	1528/5035 (30.4)	1519/5015 (30.3)	3047/10050 (30.3)	
Concomitant medication, No. (%)				
Anti-hypertensive agents[a]	1735/3862 (44.9)	1771/3821 (46.3)	3506/7683 (45.6)	0.21
Lipid-lowering agents	2961/4957 (59.7)	2966/4921 (60.3)	5927/9878 (60.0)	0.58

ABCD²: Age, Blood pressure, Clinical features, Duration of symptoms, and presence of Diabetes; IQR: interquartile range; N: no. of patients; NIHSS: NIH Stroke Scale; TIA: transient ischemic attack.

a Antihypertensive treatment was not collected in POINT before 2014.

Source: Pooled CHANCE and POINT Publication (19) Supplemental Table 2

Table 17 – Baseline characteristics of patients in the pooled analysis

In the pooled analysis, treatment with clopidogrel + ASA resulted in a statistically significant risk reduction of the composite outcome of ischemic stroke, MI, or death from ischemic vascular causes as well as individual components of ischemic stroke, ischemic or hemorrhagic stroke, disabling or fatal stroke (mRS>1), nondisabling stroke (mRS 0 or 1), and the composite of ischemic stroke, MI, death from ischemic vascular causes, or major hemorrhage (Table 18). A major ischemic event occurred in 328 patients (6.5%) receiving clopidogrel + ASA and in 458 patients (9.1%) receiving ASA alone at 90 days (adjusted HR: 0.70; 95% CI: 0.61 to 0.81; P <0.0001). New stroke (ischemic or hemorrhagic) occurred in 328 patients (6.5%) receiving clopidogrel + ASA and in 459 patients (9.1%) receiving ASA alone at 90 days (adjusted HR: 0.70; 95% CI: 0.61 to 0.80; P <0.0001). Further adjustment for lipid-lowing and antihypertensive treatments showed similar results.

No interaction of trial-by-treatment was observed for the composite primary efficacy outcome (8.0% versus 11.5% in CHANCE, 5.0% versus 6.5% in POINT; P = 0.45 for interaction) or for new stroke (8.2% versus 11.7% in CHANCE, 4.8% versus 6.4% in POINT; P = 0.56 for interaction).

Outcome	Aspirin N (%) (n=5035)	Clopidogrel+ aspirin N (%) (n=5016)	Model 1[a]		Model 2[b]		Model 3[c]	
			Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Composite of ischemic stroke, myocardial infarction, or death from ischemic vascular causes	458 (9.1)	328 (6.5)	0.71 (0.61-0.81)	<0.0001	0.70 (0.61-0.81)	<0.0001	0.70 (0.60-0.82)	<0.0001
Ischemic stroke	450 (8.9)	316 (6.3)	0.69 (0.60-0.80)	<0.0001	0.69 (0.59-0.79)	<0.0001	0.69 (0.59-0.81)	<0.0001
Myocardial infarction	9 (0.2)	13 (0.3)	1.44 (0.62-3.38)	0.40	1.40 (0.60-3.29)	0.44	2.30 (0.60-8.93)	0.23
Death from ischemic vascular causes	7 (0.1)	9 (0.2)	1.28 (0.48-3.42)	0.63	1.22 (0.45-3.29)	0.69	0.83 (0.20-3.44)	0.80
Ischemic or hemorrhagic stroke	459 (9.1)	328 (6.5)	0.71 (0.61-0.81)	<0.0001	0.70 (0.61-0.80)	<0.0001	0.69 (0.59-0.81)	<0.0001
Disabling or fatal stroke (mRS>1)	307 (6.1)	232 (4.6)	0.75 (0.63-0.89)	<0.001	0.74 (0.62-0.87)	<0.001	0.72 (0.60-0.87)	<0.001
Non-disabling stroke (mRS 0 or 1)	152 (3.0)	96 (1.9)	0.63 (0.48-0.81)	<0.001	0.62 (0.48-0.80)	<0.001	0.63 (0.47-0.84)	0.002
Composite of ischemic stroke, myocardial infarction, death from ischemic vascular causes, or major hemorrhage	473 (9.4)	354 (7.1)	0.74 (0.64-0.85)	<0.0001	0.73 (0.64-0.84)	<0.0001	0.72 (0.62-0.84)	<0.0001

CI: confidence interval; HR: hazard ratio; mRS: modified Rankin Scale; N: no. of patients.

a Adjusted for trial, with study site as random effect variable in the model.

b Adjusted for trial, sex, age, race, history of congestive heart failure, known atrial fibrillation or flutter, ischemic heart disease, hypertension, diabetes mellitus, current or previous smoker, qualifying event, time to randomization, with study site as random effect variable in the model.

c Adjusted for trial, sex, age, race, history of congestive heart failure, known atrial fibrillation or flutter, ischemic heart disease, hypertension, diabetes mellitus, current or previous smoker, qualifying event, time to randomization, lipid-lowering and anti-hypertensive treatments, with study site as random effect variable in the model (only 7663 [76.2%] patients were included in the model because antihypertensive treatment was not collected in POINT before 2014).

Source: 5.3.5.1 Study CHANCE [Table 3]

Table 18 – Hazard ratio for the defined outcomes in the different models

Subpopulation in the pooled analysis

No evidence of heterogeneity of treatment effect was observed on major ischemic events across the prespecified subgroups (Figure 10).

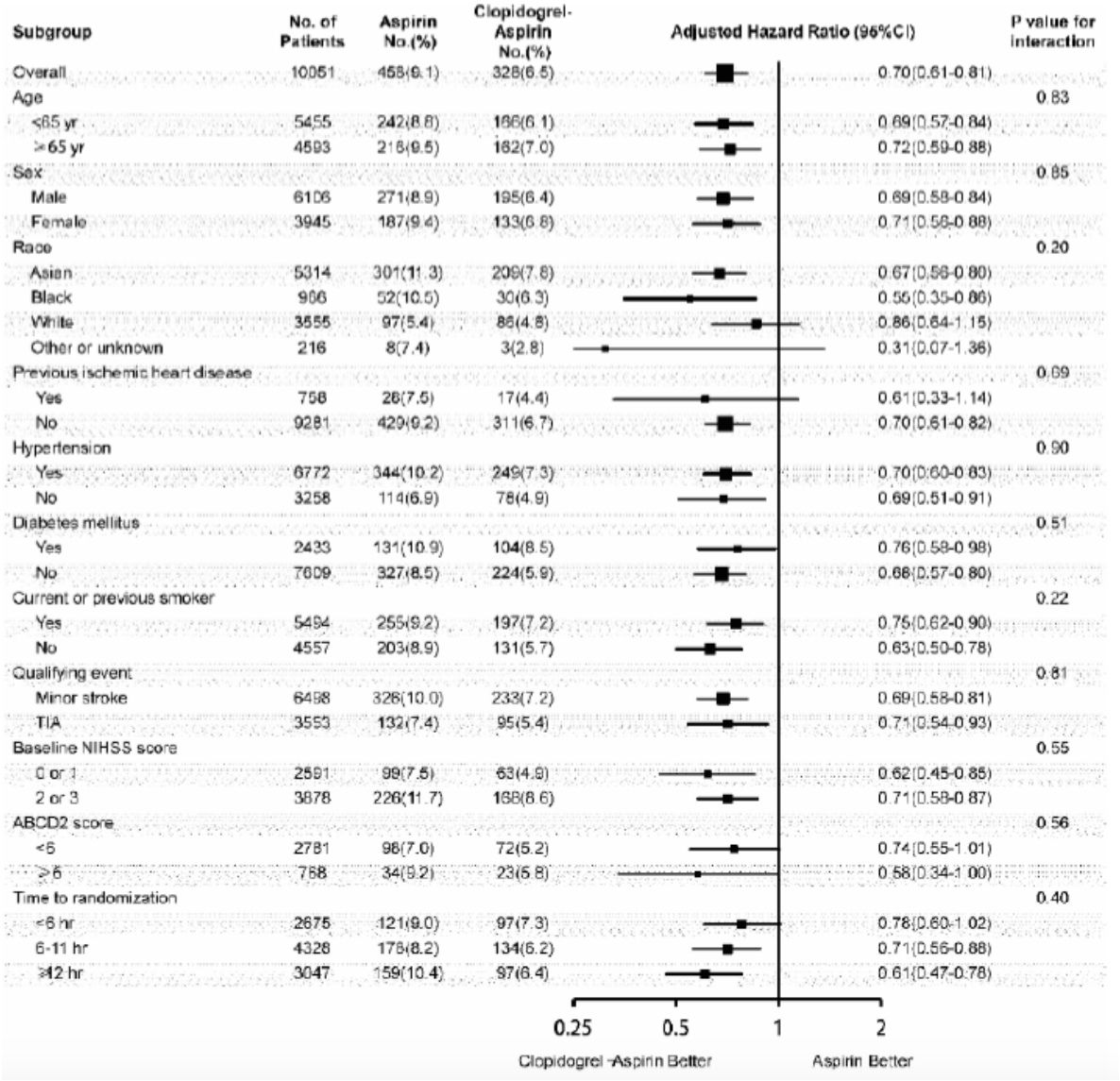


Figure 10 – Subgroup analysis for the outcome major ischemic events in the pooled analysis

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Both the CHANCE and POINT studies were phase 3 clinical trials, multicentre, double blind and controlled with placebo. The study population was adequate to study of the proposed new indication. Minor stroke and high risk TIA were defined according to the definitions more currently used in clinical practice (NIHSS<4 and ABCD2>=4).

The inclusion and exclusion criteria were similar in both studies. Patients with cardioembolic stroke that would need to be treated with anticoagulants were excluded.

In both studies, the mean age of included patients was 62 and 65 years respectively. This mean age is however relatively low taking into account that stroke is a disease with a prevalence that increased with advancing age.

The CHANCE trial included only patients of Chinese origin and the POINT study included patients that were 82.5% from the United States of America. Therefore, only a small portion of patients was from European origin. Clopidogrel is metabolized by CYP2C19. Some variants of CYP2C19 are associated with diminished platelet response to clopidogrel treatment and poorer cardiovascular outcomes.

Notwithstanding their different ethnic origin, CHANCE and POINT included patients with similar vascular risk factors, a medical history of hypertension in 65-70%, diabetes mellitus in 21-28%, and ischemic heart disease in approximately 10% of patients. The qualifying event was AIS in 72% in CHANCE versus 57% in POINT, with a median NIHSS of 2. The remaining patients were diagnosed with TIA, with a median ABCD2 score of 4-5. The mean time from symptom onset to randomization was 13h in CHANCE and 7.4h in POINT, which is consistent with their study protocols.
The primary efficacy endpoint in the CHANCE trial was stroke while in the POINT trial was a composite outcome of ischemic CV death, MI or stroke. These efficacy endpoints are clinically relevant to the population of patients under the proposed new indication. In the POINT trial the primary endpoint was a composite endpoint in which stroke was included and stroke and ischemic stroke and ischemic or haemorrhagic stroke were secondary endpoints. Both trials had an adequate sample size with statistical power to address the primary efficacy endpoint.

The length of DAPT in the CHANCE study was 21 days and in the POINT study was 90 days. In both trials the length of follow-up was 90 days. This short length of follow-up in both studies is considerate appropriate for an accurate account of stroke events because there is data supporting that the recurrence of TIA/minor stroke is highest in the first two weeks following the qualifying events.

The randomization process in both studies was sound and there was adequate masking.

In both clinical trials it was done an intention to treat analysis of data.

The POINT study was prematurely stopped because the DSMB determined that the treatment effect had crossed the significance boundary when 83% of the planned sample of randomized patients had been included.

Stroke recurrence depends not only on treatment with antiplatelets but also of control of other vascular risk factors. Data regarding anti-hypertensive treatment was not systematically collected in the POINT study and therefore it was not possible to adjust for it in the multivariable analysis.

A pooled analysis based on individual patient data extracted directly from the databases of CHANCE and POINT, adhering to the ITT principle based on randomized treatment assignment was done. This analysis included a total of 10,051 patients.

Efficacy data and additional analyses

In the CHANCE study the primary endpoint was stroke, while in the POINT trial the primary endpoint was a composed endpoint of stroke, MI and CVD.

In the CHANCE study there were less stroke events in the ASA + clopidogrel arm (212 (8.2%)) than in the ASA + placebo arm (303 (11.7%)), HR (95% CI) of 0.68 (0.57 – 0.81), p<0.001.

In the POINT study there were less events related to the composite endpoint in the ASA + clopidogrel arm (121 (4.98%)) than in the ASA + placebo arm (160 (6.53%)), HR (95% CI) of 0.75 (0.59 – 0.95), p=0.02. The POINT study was prematurely stopped because the DSMB determined that the treatment effect had crossed the significance boundary.

In the pooled analysis, treatment with clopidogrel + ASA compared to ASA alone resulted in a statistically significant risk reduction of ischemic stroke with a HR of 0.69 (95% CI 0.59 – 0.79), p<0.0001. The composite outcome of ischemic stroke, myocardial infarction or death from ischemic vascular causes was also lower in the clopidogrel + ASA group compared to ASA alone with a HR of 0.70 (95% CI 0.61 – 0.81), p<0.0001.

In POINT, all enrolled patients were included in a time to benefit analysis. In the ASA group, 160 (6.5%) major ischemic events occurred within 90 days, with most events occurring in the first week. In the clopidogrel-ASA group, 121 (5.0%) major ischemic events occurred within 90 days, with most events also occurring in the first week. Major ischemic events were less frequent in patients randomly assigned to daily clopidogrel-ASA versus ASA in the first 3 weeks after enrollment but not in subsequent weeks.

With the use of a model-based approach, the optimal cut-off point of relative risk for major ischemic events was 21 days. The hazard ratio of the primary efficacy outcome at 21 days was 0.65 (95%CI 0-50-0.85, p=0.0015) and at 22-90 days was 1.38 (95%CI 0.81-2.35,p=0.24).

In the pooled analysis, the secondary outcome disabling or fatal stroke (mRS>1) had a HR of 0.74 (95% CI 0.62 – 0.87), p<0.001. The composite of ischemic or haemorrhagic was lower in the ASA + clopidogrel arm than in the ASA alone arm with a HR of 0.70 (95% CI 0.61 – 0.80), p<0.0001. Death from ischemic vascular disease was not statistically different in the two arms although with a trend towards higher number of events in the ASA + clopidogrel arm with a HR of 1.22 (95% CI 0.45 – 3.29), p=0.69. Regarding the pooled subgroup analysis, no evidence of heterogeneity of treatment effect was observed on major ischemic events across the prespecified subgroups.

Assessment of paediatric data on clinical efficacy

Not applicable

2.4.4. Conclusions on the clinical efficacy

Two phase 3 clinical trials showed that among patients with high-risk TIA or minor ischemic stroke who were initially seen within 24 hours after symptom onset, treatment with clopidogrel plus aspirin for 21 days or 90 days, followed by clopidogrel alone for a total of 90 days, was superior to aspirin alone in reducing the risk of subsequent stroke events.

Both the CHANCE and POINT studies showed statistically significant reductions in the risk of ischemic stroke over 90 days with the DAPT regimen studied, compared with antiplatelet monotherapy with ASA.

In the Individual Patient Data Pooled Analysis, a HR of 0.69 (95% CI 0.60-0.80) was obtained. Efficacy was consistent in all the studied subgroups, including in patients with AIS or TIA as the qualifying event.

The treatment effect of DAPT with clopidogrel plus ASA versus antiplatelet monotherapy was established early, and, essentially, in the first few weeks of therapy in both studies.

2.5. Clinical safety

Introduction

There are several clinical studies describing the safety experience with clopidogrel, as monotherapy or in combination with ASA in other indications. The most common adverse reaction is bleeding. Platelet aggregation inhibition with clopidogrel as monotherapy does not increase bleeding risk compared with ASA in a general population with atherothrombotic disease, while DAPT with clopidogrel plus ASA in approved ACS indications is associated with an increased bleeding risk, compared with ASA alone. Similar findings were made in a more general population of patients with cardiovascular disease.
The safety profile of clopidogrel when used as a component of DAPT in patients with recent AIS or high-risk TIA is expects to be similar. Because patients with minor stroke or TIA generally have small areas of brain infarct or no evidence of infarct, the risk of hemorrhagic transformation of ischemic infarcts is considered to be low.

Patient exposure

Extent of exposure in clinical trials

The CHANCE study randomized 5170 patients to 21 days of DAPT with clopidogrel plus ASA followed by clopidogrel alone, or ASA for a follow-up treatment and observation period of 90 days. POINT enrolled 4881 patients for a 90-day period, contrasting DAPT with clopidogrel plus ASA versus ASA alone for the duration of the treatment period.
There are also individual Patient Data Pooled Analysis of the two studies. The MATCH,
FASTER, and SPS3 studies, which altogether enrolled approximately 11,000 patients, also provide safety-relevant information regarding the use of DAPT with clopidogrel plus ASA in patients with recent onset of symptomatic cerebral ischemic vascular disease.

Adverse events

Haemorrhages

In CHANCE, bleeding events were defined according to the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) criteria as:
- severe bleeding was defined as fatal or intracranial haemorrhage or other haemorrhage causing haemodynamic compromise that required blood or fluid replacement, inotropic support,
or surgical intervention;
- moderate bleeding as bleeding that required transfusion of blood but did not lead to haemodynamic compromise requiring intervention;
- mild bleeding as bleeding not requiring transfusion and not causing haemodynamic compromise (e.g.,

subcutaneous bleeding, mild haematomas, and oozing from puncture sites).

The **primary safety outcome** was a moderate-to-severe bleeding event, according to the GUSTO definition.

Other **Safety variables** were:
- Severe bleeding incidence (Global Use of Strategies to Open Occluded Coronary Arteries definition), including fatal bleeding and symptomatic intracranial hemorrhage;
- Incidence of symptomatic and asymptomatic intracranial hemorrhagic events at 3 months;
- Moderate bleeding (Global Use of Strategies to Open Occluded Coronary Arteries definition);
- Intracranial hemorrhage;
- Total mortality;
- Adverse events/severe adverse events reported by the investigators.
- Physical examination including nervous system evaluation on visit of 1st day, 21st day, 3 month;
- Adverse events collected in every visit; Lying position blood pressure and heart rhythm collected in every visit; ECG at baseline visit.

In POINT, the **primary safety outcome** was the risk of major haemorrhage, which was defined as symptomatic intracranial haemorrhage, intraocular bleeding causing vision loss, transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization or prolongation of an existing hospitalization, or death due to haemorrhage.

Other **secondary safety/tolerability outcomes** included:
- All-cause death
- Hemorrhagic stroke
- Symptomatic intracerebral hemorrhage
- Other symptomatic intracranial hemorrhage (subarachnoid hemorrhage, subdural
- hemorrhage, or intraventricular hemorrhage)
- Major hemorrhage other than intracranial hemorrhage
- All minor hemorrhage (including asymptomatic intracranial hemorrhage)

Safety results:

The haemorrhagic adverse events recorded in the two studies are shown in Table 19.

CHANCE	Clopidogrel + ASA (N=2584) Events, n (%)	ASA (N=2586) Events, n (%)	HR (95% CI)	p-value
Any bleeeding	60 (2.3)	41 (1.6)	1.41 (0.95–2.10)	0.09
Severe	4 (0.2)	4 (0.2)	0.94 (0.24–3.79)	0.94
Moderate	3 (0.1)	4 (0.2)	0.73 (0.16–3.26)	0.68
Mild	30 (1.2)	19 (0.7)	1.57 (0.88–2.79)	0.12
Haemorrhagic stroke	8 (0.3)	8 (0.3)	1.01 (0.38–2.70)	0.98
POINT	**Clopidogrel + ASA (N=2432)** Events, n (%)	**ASA (N=2449)** Events, n (%)	**HR (95% CI)**	**p-value**
Major haemorrhage	23 (0.9)	10 (0.4)	2.32 (1.10–4.87)	0.02
Death from haemorrhagic vascular cause	3 (0.1)	2 (0.1)		
Symptomatic intracerebral haemorrhage	2 (0.1)	2 (0.1)	1.01 (0.14–7.14)	0.99
Other symptomatic intracranial haemorrhage	2 (0.1)	0		0.16
Major hemorrhage other than intracranial hemorrhage	17 (0.7)	7 (0.3)	2.45 (1.01–5.90)	0.04
Minor hemorrhage	40 (1.6)	13 (0.5)	3.12 (1.67–5.83)	<0.001

Table 19 – Bleeding events in the CHANCE and POINT studies

In CHANCE, there was no statistical significant difference in the rate of bleeding including for moderate or severe bleeding between the two arms, with 7 patients (0.3%) in the clopidogrel + ASA group and in 8 (0.3%) in the placebo + ASA group (p = 0.73)

In the POINT study, major haemorrhage, as well as any extracranial bleeding events, occurred significantly more frequently in patients treated with DAPT with clopidogrel plus ASA, compared with ASA alone. Major hemorrhage occurred in 23 of 2432 patients (0.9%) receiving clopidogrel + ASA and in 10 of 2449 patients (0.4%) receiving placebo + ASA (HR, 2.32; 95% CI, 1.10 to 4.87; p = 0.02).
The POINT trials was prematurely stopped not only because the DSMB had determined that the treatment effect observed had crossed the significance boundary but also because the prespecified safety threshold for major haemorrhage had been crossed in the clopidogrel + ASA group in the interim analysis.
This difference between the two studies could have been due to the increased duration of DAPT in the POINT study (90 days) versus the CHANCE study (21 days). Also, the fact that the CHANCE only included Chinese patients, that have a higher prevalence of CYP2C19 non-function alleles may have contributed to

this results. The majority of bleeding events in both studies was mainly extracranial.

An analysis of the number of events in the POINT study distributed by time period was presented in Figure 7. It shows that the risk of hemorrhage with clopidogrel plus ASA versus ASA alone was greater during the period from 8 to 90 days than during the first 7 days (P = 0.04 for days 8 to 90 and P = 0.34 for days 0 to 7). There was not an increases risk of bleeding in the first days of treatment in which the loading was administered.

In the Individual Patient Data Pooled Analysis per time of CHANCE and POINT, major haemorrhages were more frequent in the clopidogrel + ASA group (0.6%) than in the placebo + ASA group (0.4%), but the difference was statistically nonsignificant (Table 20). There was not an increases risk of bleeding in the first days of treatment associated to the loading dose.

Period	Clopidogrel + ASA No. of Events/Total Patients (%)	ASA No. of Events/Total Patients (%)	Adjusted HR (95% CI)[a]	p-value
0-21 days	16/5016(0.3)	7/5035(0.1)	2.11(0.86-5.17)	0.10
0-10 days	13/5016(0.3)	6/5035(0.1)	1.97(0.74-5.26)	0.18
11-21 days	3/4682(0.06)	1/4624(0.02)	2.77(0.28-27.02)	0.38
22-90 days	14/4622(0.3)	11/4581(0.2)	1.28(0.58-2.81)	0.55
CHANCE	1/2362(0.04)	6/2305(0.3)	0.16(0.02-1.32)	0.09
POINT	13/2260(0.6)	5/2276(0.2)	2.63(0.94-7.40)	0.07
0-90 days	30/5016(0.6)	18/5035(0.4)	1.59(0.88-2.86)	0.12

Source: Pooled Meta Analyses Report Table 5

a Adjusted for trial, sex, age, race, history of congestive heart failure, known atrial fibrillation or flutter, ischemic heart disease, hypertension, diabetes mellitus, current or previous smoker, qualifying event, time to randomization, with study site as random effect variable in the model.

Table 20 - Pooled analysis per time of bleeding events in the CHANCE and POINT studies

In a pooled analysis of the two trials, with calculation of the hazard ratios of bleeding adjusted for different confounders in three different analysis, although patients with DAPT tended to have a higher risk of bleeding than patients with ASA alone, the difference was only statistically significant for minor haemorrhage and combined major or minor haemorrhage (Table 21).

Outcome	Placebo + Aspirin n (%) (N=5035)	Clopidogrel + aspirin n (%) (N=5016)	Model 1[a]		Model 2[b]		Model 3[c]	
			Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Major hemorrhage	18 (0.4%)	30 (0.6%)	1.67 (0.93-2.99)	0.09	1.59 (0.88-2.86)	0.12	1.20 (0.61-2.39)	0.60
Hemorrhagic stroke	11 (0.2%)	13 (0.3%)	1.16 (0.52-2.60)	0.71	1.06 (0.47-2.40)	0.90	0.77 (0.30-1.95)	0.58
Minor hemorrhage	46 (0.9%)	93 (1.9%)	2.02 (1.42-2.88)	<0.0001	2.01 (1.41-2.86)	0.0001	1.87 (1.26-2.79)	0.002
Major or minor hemorrhage	64 (1.3%)	123 (2.5%)	1.91 (1.41-2.58)	<0.0001	1.88 (1.39-2.54)	<0.0001	1.66 (1.18-2.35)	0.004
Death from any cause	22 (0.4%)	28 (0.6%)	1.26 (0.72-2.21)	0.42	1.17 (0.66-2.05)	0.59	1.08 (0.54-2.16)	0.82

Abbreviations: CI: confidence interval; HR: hazard ratio.

a Adjusted for trial, with study site as random effect variable in the model.

b Adjusted for trial, sex, age, race, history of congestive heart failure, known atrial fibrillation or flutter, ischemic heart disease, hypertension, diabetes mellitus, current or previous smoker, qualifying event, time to randomization, with study site as random effect variable in the model.

c Adjusted for trial, sex, age, race, history of congestive heart failure, known atrial fibrillation or flutter, ischemic heart disease, hypertension, diabetes mellitus, current or previous smoker, qualifying event, time to randomization, lipid-lowing and anti-hypertensive treatments, with study site as random effect variable in the model (only 7663 [76.2%] patients were included in the model because antihypertensive treatment was not collected in POINT before 2014).

Table 21 – Adjusted Hazard ratios for bleeding in three different models

Subgroup analysis

In the subgroups analysed, no subgroup of patients was identified as having a higher bleeding risk in the clopidogrel + ASA group than the placebo + ASA group (all p-values >0.05) (Table 22).

Subgroup	No. of Patients	Aspirin n(%)	Clopidogrel-Aspirin n(%)	Adjusted Hazard Ratio (95%CI)	P-value for interaction
Overall	10051	18(0.4%)	30(0.6%)	1.59(0.88-2.86)	
Age					0.81
<65 yr	5455	7(0.2%)	10(0.4%)	1.50(0.57-3.97)	
≥65 yr	4593	11(0.5%)	20(0.9%)	1.67(0.79-3.50)	
Sex					0.50
Male	6106	11(0.4%)	15(0.5%)	1.30(0.60-2.84)	
Female	3945	7(0.4%)	15(0.8%)	1.91(0.77-4.75)	
Race					0.32
Asian	5314	9(0.3%)	8(0.3%)	0.90(0.35-2.35)	
Black	966	3(0.6%)	4(0.9%)	1.34(0.30-6.06)	
White	3555	5(0.3%)	17(1.0%)	2.75(1.00-7.57)	
Other or unknown	216	1(0.9%)	1(0.9%)	3.19(-)	
Previous ischemic heart disease					0.36
Yes	758	17(0.4%)	26(0.6%)	1.43(0.77-2.65)	
No	9281	1(0.3%)	4(1.0%)	4.35(0.47-39.95)	
Hypertension					0.47
Yes	6772	4(0.2%)	4(0.2%)	0.92(0.23-3.72)	
No	3258	14(0.4%)	25(0.7%)	1.77(0.92-3.41)	
Diabetes mellitus					0.69
Yes	2433	14(0.4%)	21(0.6%)	1.46(0.74-2.87)	
No	7609	4(0.3%)	9(0.7%)	1.94(0.58-6.47)	
Current or previous smoker					0.57
Yes	5494	7(0.3%)	14(0.6%)	1.36(0.62-2.96)	
No	4557	11(0.4%)	16(0.6%)	1.91(0.77-4.76)	
Qualifying event					0.58
Minor stroke	6498	12(0.4%)	17(0.5%)	1.41(0.67-2.96)	
TIA	3553	6(0.3%)	13(0.7%)	2.17(0.79-5.95)	
Baseline NIHSS score					0.67
0 or 1	2591	5(0.4%)	8(0.6%)	-	
2 or 3	3878	7(0.4%)	9(0.5%)	1.19(0.44-3.19)	
ABCD2 score					0.32
<6	2781	5(0.3%)	9(0.7%)	0.71(0.53-5.53)	
≥6	768	1(0.3%)	4(1.0%)	8.72(0.58-132.29)	

Table 22 – Subgroup analysis in the pooled analysis of the two trials

Serious adverse event/deaths/other significant events

Deaths

In CHANCE, 10 deaths were reported in each treatment group. No deaths due to haemorrhage were recorded.

In POINT, there were 19 deaths on clopidogrel plus ASA, compared with 12 deaths on ASA alone (HR: 1.51 (95% CI: 0.73–3.13). Death from haemorrhagic vascular causes occurred in 3 patients receiving clopidogrel plus ASA and in 2 patients receiving ASA alone (0.1% in each group). All cause deaths per body system in the POINT study are shown in Table 23.

		Treatment		Cohort		
		Placebo + Aspirin	Clopidogrel + Aspirin	TIA	Minor stroke	Total Patients
Total		12	19	9	22	31
Body System	MedDRA Preferred Term					
Cardiac disorders	Acute myocardial infarction	0	1	0	1	1
	Cardiac arrest	1	2	0	3	3
	Cardio-respiratory arrest	1	2	0	3	3
	Myocardial infarction	1	1	0	2	2
Gastrointestinal disorders	Intestinal obstruction	0	1	0	1	1
General disorders and administration site conditions	Cardiac death	0	1	1	0	1
Infections and infestations	Pneumonia	0	1	1	0	1
	Sepsis	0	1	0	1	1
Investigations	Aspiration bronchial	0	1	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to central nervous system	0	1	1	0	1
	Esophageal carcinoma	0	1	1	0	1
	Pancreatic carcinoma	0	1	0	1	1
Nervous system disorders	Cerebral hemorrhage	1	0	0	1	1
	Hemorrhage intracranial	1	1	1	1	2
	Hemorrhagic transformation stroke	0	1	1	0	1
	Ischemic stroke	2	1	2	1	3
Renal and urinary disorders	Renal failure acute	0	1	0	1	1
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	1	0	1	0	1
	Respiratory distress	2	1	0	3	3
	Respiratory failure	1	0	0	1	1
Vascular disorders	Aortic dissection	1	0	0	1	1

Table 23 – Distribution of death causes per body system in POINT

Other serious or clinically relevant adverse events

In the CHANCE study, the proportion of patients with SAEs was similar in both treatment groups (1.0% and 0.8% in the clopidogrel + ASA and placebo + ASA groups, respectively). The number of patients with haemorrhagic stroke was also similar in both arms as depicted in Table 24.

Outcome	Number (%) of patients	
	Placebo + Aspirin (n=2570)	Clopidogrel + Aspirin (n=2564)
Death	10 (0.4%)	10 (0.4%)
Hemorrhagic stroke	7 (0.3%)	6 (0.2%)
Others	4 (0.2%)	11 (0.4%)

Table 24 – Serious adverse events in the CHANCE study

In the POINT study, as per ITT analysis, SAEs occurred in a similar proportion of patients in the clopidogrel + ASA group (12.1%) and in the placebo + ASA group (11.1%)(Table 25).

Body System	Number (%) of patients	
	Clopidogrel-Aspirin (N=2432)	Aspirin (N=2449)
Total	295 (12.1%)	272 (11.1%)
Nervous system disorders	113 (4.6%)	115 (4.7%)
Cardiac disorders	48 (2.0%)	33 (1.3%)
Vascular disorders	17 (0.7%)	24 (1.0%)
Infections and infestations	24 (1.0%)	16 (0.7%)
Gastrointestinal disorders	24 (1.0%)	14 (0.6%)
Surgical and medical procedures	15 (0.6%)	19 (0.8%)
Respiratory, thoracic and mediastinal disorders	14 (0.6%)	14 (0.6%)
Psychiatric disorders	14 (0.6%)	13 (0.5%)
General disorders and administration site conditions	19 (0.8%)	5 (0.2%)
Injury, poisoning and procedural complications	12 (0.5%)	7 (0.3%)
Renal and urinary disorders	10 (0.4%)	7 (0.3%)
Neoplasms benign, malignant,d unspecified (incl cysts and polyps)	6 (0.2%)	9 (0.4%)
Metabolism and nutrition disorders	10 (0.4%)	4 (0.2%)
Musculoskeletal and connective tissue disorders	6 (0.2%)	4 (0.2%)
Skin and subcutaneous tissue disorders	8 (0.3%)	2 (0.1%)
Congenital, familial and genetic disorders	2 (0.1%)	2 (0.1%)
Hepatobiliary disorders	4 (0.2%)	0 (0.0%)
Investigations	3 (0.1%)	0 (0.0%)
Eye disorders	1 (0.0%)	2 (0.1%)
Blood and lymphatic system disorders	1 (0.0%)	2 (0.1%)
Ear and labyrinth disorders	1 (0.0%)	2 (0.1%)
Immune system disorders	1 (0.0%)	1 (0.0%)
Reproductive system and breast disorders	1 (0.0%)	0 (0.0%)

*There were no differences by treatment group except for general disorders and administration site conditions (p=0.004).

Table 25 – Distribution of SAE in POINT per body system

Nervous system disorder events (4.6% in the clopidogrel + ASA group and 4.7% in the placebo + ASA group) were the most frequent in each group.

Safety relationship with dose/regimen/treatment duration

Bleeding is the main safety concern with clopidogrel when used with ASA as DAPT.

Data from CHANCE and POINT shows that the overall bleeding risk during DAPT is associated to treatment duration (Figure 7). The loading dose of clopidogrel was not associated to a higher risk of bleeding during this period.

Overdose

There is no new information related to overdose.

Dependence or abuse potential

Not applicable

Rebound

There are no data to suggest a sudden rebound in the risk of thrombotic events upon discontinuation of clopidogrel. This is consistent with the action of clopidogrel as an irreversible antagonist at the P2Y12 receptor.

Safety in special populations

A review of special subgroup populations was not specifically assessed in the studies. A review is regularly performed as part of the Periodic Benefit Risk Evaluation Reports (PBRERs) for clopidogrel with or without aspirin. No concern has been identified up to the date of this report regarding intrinsic and extrinsic factors, overdose, drug abuse, withdrawal, or rebound in the current marketed indications, including clopidogrel monotherapy in recent stroke and DAPT (clopidogrel + aspirin) in the ACS indication.

Drug interactions for clopidogrel and aspirin are regularly updated and reflected in the Sanofi Company Core Safety Information (CCSI) where the increase risk of bleeding related to additive effect of these drug acting on homeostasis is mentioned.

Safety related to drug-drug interactions and other interactions

The CHANCE study was conducted in a Chinese population with an anticipated high prevalence of carriers of CYP2C19 loss-of-function alleles. It is not known if this could be associated to a lower risk of bleeding. A published substudy did not indicate significant differences in bleeding risk between carriers and non-carriers of such alleles.

POINT included mainly US subjects. It is not possible to conclude whether the higher bleeding rates on DAPT with clopidogrel plus ASA recorded in POINT may be related to the demographic composition of study participants.

Discontinuation due to adverse events

Discontinuations due to AEs were not collected in the AE dataset in the CHANCE or POINT studies.

Post marketing experience

There is no marketed experience with clopidogrel in the intended new target population.

Assessment of paediatric data on clinical safety

Not applicable

2.5.1. Conclusions on clinical safety

There are several clinical studies describing the safety experience with clopidogrel, as monotherapy or in combination with ASA in previous approved indications. The main safety concerning associated to use of clopidogrel is bleeding.

Specifically, the major safety concern of the new indication could be expected to be haemorrhagic transformation of the ischemic infarct in the first days after TIA/minor stroke. There was no previous evidence from clinical trials evaluating the use of loading doses of clopidogrel in patients with TIA/minor stroke. The CHANCE study used a loading dose of 300 mg and the POINT study a loading dose of 600 mg.

The definitions used to identify and define bleeding events in both studies were in accordance with generally accepted definitions and therefore appropriate. Data from both the POINT and CHANCE studies showed that there was no increased risk of bleeding in the initial days. This suggests that the loading dose of clopidogrel was not associated with an increased risk of bleeding when compared to the entire length of DAPT. Also, overall extracranial bleeding was more frequent than intracranial. In the pooled analysis, there was no statistically significant difference in both groups regarding haemorrhagic stroke. Eleven patients in the placebo + ASA group (0.2%) had hemorrhagic stroke versus thirteen patients in the clopidogrel + ASA group (0.3%).

In the CHANCE study, although patients in the clopidogrel + ASA had overall higher frequency of bleeding events than patients in the placebo + ASA group, this difference was not statistically significant. In the POINT study, major haemorrhage occurred significantly more frequently in patients treated with clopidogrel + ASA than in the placebo + ASA arm. Also, one the reasons why the POINT study was prematurely stopped was because the preespecified safety threshold for major haemorrhage had been crossed in the clopidogrel + ASA arm in the interim analysis. There are three possible explanations for this difference in bleeding in the two studies: a) The length of DAPT was 21 days in the CHANCE study and 90 days in the POINT study, c) CHANCE only included Chinese patients and these are known to have non-function allelic variants of CYP2C19 that may decrease the risk of bleeding, c) There is no reference to the dose of ASA that was used by the majority of patients in the POINT trial. The number of patients that had different dosages of ASA was not provided. The dose of ASA could be comprised according to protocol between 50-325 mg but there is no further information. Patients using the highest dose of ASA in combination with clopidogrel could theoretically have a higher risk of bleeding. The dose of ASA that was used in the CHANCE trial was 75 mg.

In the pooled analysis, no subgroup of patients was identified has having a higher bleeding risk in the clopidogrel + ASA arm than in the placebo + ASA arm. Nevertheless, the median age of patients that were included in this trial is lower than the mean age of stroke in the general population. There is previous evidence that older patients are at higher risk of bleeding with antiplatelets.

The number of deaths and SAEs were similar in both arms in both the POINT and CHANCE study. In the pooled analysis there is reference to death due to ischemic stroke in 3 patients (2 in the placebo + ASA arm and 1 in the clopidogrel + ASA arm).

The CHANCE and POINT studies did not generate any other safety concerns for clopidogrel not already included in the approved product information.

2.5.2. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP endorsed the Risk Management Plan version 2.3 with the following content:

Safety concerns

Summary of the safety concerns

Important identified risk	Major bleeding (including ICH[a])
Important potential risk	None
Missing information	None

a ICH is applicable especially in TIA/MS indication of DAPT for the first 21 days after TIA/MS events, this indication cumulating multiple risks of bleeding particularly in patients ≥75 years of age.

DAPT: Dual Antiplatelet Therapy; ICH: Intracranial Hemorrhage; MS: Multiple Sclerosis; TIA: Transient Ischemic Attack.

Pharmacovigilance plan

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection includes a specific targeted FUp questionnaire form for "major bleeding (including ICH)".

The safety profile of clopidogrel will continue to be further characterized in real clinical conditions of use through post-marketing safety surveillance, encompassing analysis of spontaneous reporting of adverse drug reactions in periodic safety reports and signal detection.

No additional pharmacovigilance activities are planned.

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Major bleeding (including ICH[a])	**Routine risk minimization measures:** SmPC: Labeled in section 4.3, 4.4 and 4.8 of ISCOVER and PLAVIX SmPC.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific targeted FUp questionnaire form. **Additional pharmacovigilance activities:** None
	PL: Labeled in section 2, 3 and 4 of ISCOVER and PLAVIX PL. **Additional risk minimization measures:** None	

a ICH is applicable especially in TIA/MS indication of DAPT for the first 21 days after TIA/MS events, this indication cumulating multiple risks of bleeding particularly in patients ≥75 years of age.

DAPT: Dual Antiplatelet Therapy; FUp: Follow-Up; ICH: Intracranial Hemorrhage; MS: Multiple Sclerosis; PL: Package Leaflet; SmPC: Summary of Product Characteristics; TIA: Transient Ischemic Attack.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA and has been found acceptable for the following reasons:

The present application for a new indication of clopidogrel in adult patients with high risk Transient Ischemic Stroke (TIA) (ABCD2 score ⩾4) or minor Ischemic Stroke (IS) (NIHSS ⩽3) does not bring any significant change to Patient Information Leaflet tested for Plavix® / Iscover® film-coated tablets 75 mg and 300 mg. Therefore, no readability testing was performed.

In view of the changes being introduced in the package leaflet as part of this new indication, the Applicant's justification is considered acceptable and therefore no readability testing is required.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

After a transient ischemic attack or minor stroke, patients are at increased risk of recurrence of ischemic cerebral events. This risk is highest in the first two weeks after the qualifying event. The ABCD2 score allows a stratification of stroke risk in TIA patients. Patients with an ABCD2>4 have the highest risk of

stroke recurrence. Stroke is considered clinically as minor when the patient presents with small neurological deficits. Neurological deficits resulting from ischemic stroke are usually quantified using the NIHSS scale. Patients are considered to have a minor stroke when the NIHSS score is lower or equal to 4.

3.1.2. Available therapies and unmet medical need

When considering secondary prevention of ischemic cerebral events two groups of patients are usually considered. The group of patients with a cardioembolic stroke etiology (atrial fibrillation, prosthetic heart valves) and the group of patients with non-cardioembolic stroke etiology. Patients with cardioembolic stroke etiologies should be treated with anticoagulants while patients with non-cardioembolic stroke etiologies are treated with antiplatelets. The only antiplatelet that was tested in acute ischemic stroke was ASA. Antiplatelet therapy with low-dose ASA is approved to reduce the risk of recurrent stroke in the target population. Secondary prevention with ASA instituted within 24-48h post-event has been shown to reduce the risk of a recurrent ischemic event by approximately 20%, compared with placebo. A combination of two antiplatelets that act by different mechanisms could theoretically further reduce the risk of recurrent ischemic stroke.

Main clinical studies

Two phase 3 clinical trials studied the proposed new indication. These studies were CHANCE and POINT. They investigated the benefits and risks of DAPT with clopidogrel plus ASA versus antiplatelet monotherapy. DAPT was initiated early after symptom onset, within 12h (POINT) to 24h (CHANCE), and continued for 21 days (CHANCE) to 90 days (POINT). Both studies enrolled in total approximately 10,000 patients.

3.2. Favourable effects

The main expected favourable effect was reduction in the risk of recurrent stroke during a follow-up period of 90 days.

Both the CHANCE and POINT studies showed statistically significant reductions in the risk of ischemic stroke and stroke over 90 days with the DAPT regimen studied, compared with antiplatelet monotherapy with ASA. The CHANCE study obtained a HR of 0.68 (95% CI 0.57-0.81) and the POINT study a HR of 0.75 95% CI 0.59-0.95) for stroke in DAPT versus ASA alone. Regarding the outcome ischemic stroke there were less events also in CHANCE and POINT in the DAPT arm compared to ASA alone with a HR of 0.67 (95%IC 0-56 – 0.81) and HR of 0.72 (95% CI 0.56-0.92) respectively.
In the Individual Patient Data Pooled Analysis for ischemic stroke recurrence, a HR of 0.69 (95% CI 0.59-0.79) was obtained. Efficacy was consistent in all the studied subgroups, including in patients with AIS or TIA as the qualifying event.
The treatment effect of DAPT with clopidogrel plus ASA versus antiplatelet monotherapy was established early, and, essentially, in the first few weeks of therapy in both studies.
In the POINT study, with the use of a model-based approach, the optimal cut-off point of relative risk for major ischemic events was 21 days. The hazard ratio of the primary efficacy outcome at 21 days in DAPT compared to ASA alone was 0.65 (95%CI 0-50-0.85, p=0.0015) and at 22-90 days was 1.38 (95%CI 0.81-2.35,p=0.24).

3.3. Uncertainties and limitations about favourable effects

In the CHANCE study, DAPT was given during 21 days while in the POINT study DAPT was given during 90 days. Based on the time-to-event curves and the analysis by time period in the pooled analysis of the two studies a duration of DAPT of up to a maximum of 21 days after symptom onset, as done in CHANCE, appears reasonable from an efficacy perspective.

3.4. Unfavourable effects

The main unfavourable effect was bleeding. Specifically, for this new indication it was important to evaluate if DAPT was associated with a higher risk of haemorrhagic transformation of the ischemic infarct.
In the CHANCE study, although patients in the clopidogrel + ASA had overall higher frequency of bleeding events than patients in the placebo + ASA group, this difference was not statistically significant. In the POINT study, major haemorrhage occurred significantly more frequently in patients treated with clopidogrel + ASA than in the placebo + ASA arm. Overall extracranial bleeding was more frequent than intracranial. In the pooled analysis, no subgroup of patients was identified has having a higher bleeding risk in the clopidogrel + ASA arm than in the placebo + ASA arm.

An analysis of the number of events in the POINT study distributed by time period showed that the risk of haemorrhage with clopidogrel plus ASA versus ASA alone was greater during the period from 8 to 90 days than during the first 7 days (P = 0.04 for days 8 to 90 and P = 0.34 for days 0 to 7). There was not an increases risk of bleeding in the first days of treatment in which the loading was administered.
In the Individual Patient Data Pooled Analysis per time of CHANCE and POINT, major haemorrhages were more frequent in the clopidogrel + ASA group (0.6%) than in the placebo + ASA group (0.4%), but the difference was statistically nonsignificant.
The number of deaths and SAEs were similar in both arms in both the POINT and CHANCE study.

3.5. Uncertainties and limitations about unfavourable effects

Overall, a higher bleeding risk was observed in POINT than in CHANCE.

There are three possible explanations:

a) DAPT was given during 21 days in CHANCE and during 90 days in POINT. POINT was prematurely stopped in an interim analysis due to the fact that the established threshold for bleeding had been crossed. A DAPT length of 21 days is considered to be the appropriate duration.

b) The CHANCE study only included Chinese patients. Chinese patients have a higher frequency of non-functional allelic variants of CYP2C19. This could contribute to a lower risk of bleeding in these patients when compared to patients included in the POINT trial that were mainly from US origin.

c) There is no reference to the dose of ASA that was used by the majority of patients in the POINT trial. The number of patients that had different dosages of ASA is not provided. The dose of ASA could be comprised according to protocol between 50-325 mg but there is no further information. Patients using the highest dose of ASA in combination with clopidogrel could theoretically have a higher risk of bleeding. The dosage of ASA that was used in CHANCE was 75 mg.

Also, stroke prevalence increases with increasing age. The mean age of patients included in CHANCE and POINT was 62-65 years.

3.6. Effects Table

Table 26 Effects Table for DPAT with clopidogrel plus ASA

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Ischemic stroke	Recurrence	90 days KM % (FAS)	6.3	8.9	HR 0.69 (95% CI 0.59 – 0.79), p<0.0001	
CV outcome	Composite of ischemic stroke, myocardial infarction or death from ischemic vascular causes	90 days KM % (FAS)	6.5	9.1	HR 0.70 (95% CI 0.61 – 0.81), p<0.0001	
Stroke	Disabling or fatal (mRS<1)	90 days KM % (FAS)	4.6	6.1	HR 0.74 (95% CI 0.62 – 0.87), p<0.001	
Ischemic or haemorrhagic stroke		90 days KM % (FAS)	6.5	9.1	HR 0.70 (95% CI 0.61 – 0.80), p<0.0001	
Death from ischemic vascular cause		90 days KM % (FAS)	0.2	0.1	HR 1.22 (95% CI 0.45 – 3.29), p=0.69	
Unfavourable Effects						
Major haemorrhage		90 days KM % (FAS)	0.6	0.4	HR 1.59 (95% CI 0.88 – 2.86), p=0.12	
Hemorrhagic stroke		90 days KM % (FAS)	0.3	0.2	HR 1.06 (95% CI 0.47 – 2.40), p=0.90	
Minor haemorrhage		90 days KM % (FAS)	1.9	0.9	HR 2.02 (95% CI 1.42 – 2.88), p<0.0001	
Major or minor hemorhage		90 days KM % (FAS)	2.5	1.3	HR 1.88 (95% CI 1.39 – 2.54), p<0.0001	
Death from any		90 days KM %	0.6	0.4	HR 1.17 (95% CI 0.66 – 2.05), p=0.59	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
cause		(FAS)				

Abbreviations:

a Notes: Adjusted for trial, sex, age, race, history of congestive heart failure, known atrial fibrillation or flutter, ischemic heart disease, hypertension, diabetes mellitus, current or previous smoker, qualifying event, time to randomization, with study site as random effect variable in the model.

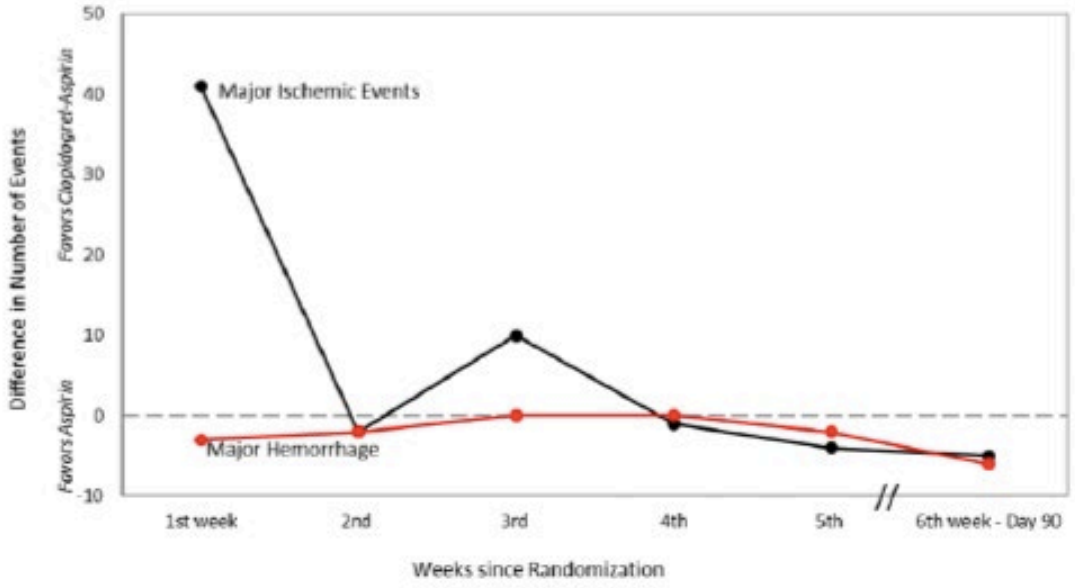
3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The current proposed new indication is prevention of stroke recurrence in patients with high risk TIA or minor stroke. Clinically relevant benefit of DAPT with clopidogrel plus low-dose ASA versus ASA alone in patients with recent symptom onset (within 24 hours) of minor AIS or high-risk TIA, to prevent recurrent ischemic stroke was demonstrated in the CHANCE and POINT studies. The efficacy benefit of DAPT with clopidogrel plus ASA was established early. This is consistent with what had been reported of high risk of recurrent ischemic events in the first weeks after the qualifying event.

The decrease in stroke recurrence was similar in the two studies. Extended use of DAPT in the POINT study for 90 days did not provide incremental benefit over the 21 days that were used in CHANCE.
Bleeding is the main unfavourable effect associated with DAPT with clopidogrel plus low-dose ASA. In this specific indication it was also important to consider intracranial bleeding including haemorrhagic transformation of ischemic infarcts and haemorrhagic stroke. There was trend to higher bleeding risk in CHANCE but this difference was not statistically significant. In the POINT study, major haemorrhage occurred significantly more frequently in patients treated with clopidogrel + ASA than in the placebo + ASA arm. In the pooled analysis there was a higher statistically significant risk of combined major and haemorrhagic bleeding and minor bleeding in patients with DAPT. However, there was no difference in haemorrhagic stroke. Overall, bleeding risk accumulated over time of treatment, and was not distinctly related to the loading dose of clopidogrel or associated with the period of highest risk of recurrent stroke and was manifested mainly by extracranial bleeds.

In POINT, the hazard rate of major ischemic events was highest within the first several weeks, but then decreased (Figure 11). In contrast, the HR of major haemorrhage was low but constant over time for both treatment groups. By day 28, the rate for ischemic events no longer decreased and was constant for both treatment groups.



Number of Events by week (% of effective sample size)

		Total Events	1st week	2nd week	3rd week	4th week	5th week	6th week - Day 90
Major Ischemic Events	Aspirin (n=2449)	160	111 (4.60%)	14 (0.63%)	12 (0.55%)	4 (0.19%)	1 (0.05%)	18 (1.02%
	Clopidogrel-aspirin (n=2432)	121	70 (2.93%)	16 (0.71%)	2 (0.09%)	5 (0.23%)	5 (0.23%)	23 (1.26%
	Difference	39	41 (1.67%)	-2 (-0.08%)	10 (0.46%)	-1 (-0.04%)	-4 (-0.18%)	-5 (-0.25%
	Effective Sample Size		4805	4475	4366	4345	4332	3587
Major Hemorrhage	Aspirin	10	4 (0.17%)	0 (0.00%)	1 (0.04%)	1 (0.04%)	1 (0.04%)	3 (0.16%)
	Clopidogrel-aspirin	23	7 (0.29%)	2 (0.09%)	1 (0.04%)	1 (0.04%)	3 (0.13%)	9 (0.48%)
	Difference	-13	-3 (-0.13%)	-2 (-0.09%)	0 (0%)	0 (0%)	-2 (-0.1%)	-6 (-0.32%
	Effective Sample Size		4800	4632	4547	4534	4525	3742

Figure 11 – Hazard rate of major ischemic events and major hemorrhages in the POINT study

In the POINT study, with the use of a model-based approach, the optimal cut point of relative risk for major ischemic events was 21 days (Figure 8). The hazard ratio of the primary efficacy outcome at 21 days was 0.65 (95%CI 0-50-0.85, p=0.0015) and at 22-90 days was 1.38 (95%CI 0.81-2.35, p=0.24).

The time course analysis of pooled data from the two studies is summarized in Table 27 and shows the early increase of major ischemic events and the lower number of events of major haemorrhage. These numbers indicate an efficacy benefit for clopidogrel plus ASA up to 21 days of treatment when compared to ASA alone (Figure 12). There was no initial peaking of haemorrhagic risk that could be related to the loading dose of clopidogrel.

Outcome	Treatment assignment	No. of events						
		Total	1st week	2nd week	3rd week	4th week	5th week	6th week-day 90
Major ischemic events	ASA (n=5035)	458	330	36	21	10	5	56
	CLP+ASA(n=5016)	328	217	30	14	10	9	48
	Difference	130	113	6	7	0	-4	8
Major Hemorrhage	ASA (n=5035)	18	4	2	1	1	1	9
	CLP+ASA(n=5016)	30	10	4	2	1	3	10
	Difference	-12	-6	-2	-1	0	-2	-1

Source: Pooled Meta Analyses Report Table 4. ASA: aspirin; CLP = clopidogrel

Table 27 - The time course analysis of events in the pooled analysis

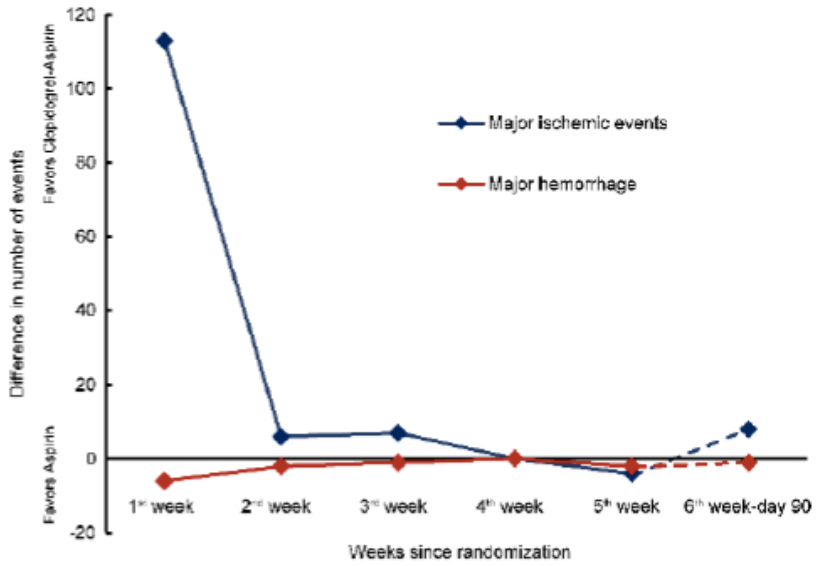


Figure 12 – Graphical analysis of the number of major ischemic and major hemorrhagic events

The benefit/risk is favourable for a limited duration of DAPT with clopidogrel plus low-dose ASA in patients with non-cardioembolic stroke with recent symptom onset of minor AIS (NIHSS 0-3) or high-risk TIA (ABCD2 score of at least 4).

Treatment should be within 24h of symptom onset, with a loading dose of clopidogrel of 300 mg, followed by 75 mg/day in combination with low-dose ASA. DAPT with clopidogrel plus low-dose ASA should be continued for up to of 21 days post-event and be followed by antiplatelet monotherapy with clopidogrel or ASA, as clinically indicated.

Treatment should thus limit to the minimum period associated with efficacy benefit. In the absence of data to support efficacy benefit of the higher loading dose of 600 mg in the proposed target population, and given the favourable benefit and bleeding rate data from CHANCE, the standard loading dose of 300 mg appears preferable.

3.7.2. Balance of benefits and risks

The benefit risk balance is positive for the use of clopidogrel plus aspirin for the prevention of stroke recurrence in a population of patients with moderate to high risk TIA or minor stroke of non-cardioembolic cause.

The studies showed that among patients with high-risk TIA or minor ischemic stroke who were initially seen within 24 hours after symptom onset, treatment with clopidogrel plus aspirin for 21 days, followed by clopidogrel alone for a total of 90 days, was superior to aspirin alone in reducing the risk of subsequent stroke events.

The pooled analysis showed a higher risk of combined major or minor haemorrhage and minor haemorrhage in patients that were treated with clopidogrel plus aspirin than with aspirin alone. The bleeding risk was higher in the POINT study than in the CHANCE study. Although there was a trend for higher bleeding in CHANCE in patients in DAPT than in patients treated with ASA alone, there was no statistically significant difference. Taking into account that both studies showed similar efficacy, the conditions of DAPT in the CHANCE study should be preferred. These included a loading dose of 300 of clopidogrel and a length of DAPT of 21 days.

The MAH attributed the increased bleeding risk in the POINT trial to the increased length of DAPT (90 days versus 21 days in CHANCE). Also, the CHANCE study only included Chinese patients. Chinese patients have a higher frequency of non-functional allelic variants of CYP2C19. This could contribute to a lower risk of bleeding in these patients when compared to patients included in the POINT trial that were mainly from US origin. The MAH acknowledges that there may be some issues that influence the external validity of the CHANCE trial, including the higher frequency of carriers of CYP2C19 loss of function alleles in the Chinese population than in Europeans. Nevertheless, CHMP agree with the MAH that the CHANCE study contributes information regarding the benefit/risk of short-term treatment with DAPT with clopidogrel plus ASA in patients with minor AIS/high-risk TIA that is also relevant also to a European population.

In the POINT trial, patients could be treated with doses of ASA ranging from 50-325 mg + clopidogrel while in the CHANCE trial only doses of 75 mg of ASA were administered plus clopidogrel. The CHMP requested a breakdown in the number of patients with corresponding bleeding incidence rates in the POINT trial treated with different doses of ASA. The great majority (at least 75%) of patients in the POINT trial were prescribed ASA at a maximum daily dose of 100 mg. There are no data to support augmented efficacy benefit of ASA doses higher than 75-100 mg/day as a component of DAPT with clopidogrel and, while the analyses from the POINT study do not indicate an increased excess of bleeding risk with DAPT with clopidogrel plus doses of ASA >100 mg/day, such excess risk cannot be excluded. As such in section 4.2 of the SmPC the maintenance dosage of ASA is restricted to 75-100 mg/daily as follows: "Adult patients with moderate to high-risk TIA or minor IS: Adult patients with moderate to high-risk TIA (ABCD2 score ≥4) or minor IS (NIHSS ≤3) should be given a loading dose of clopidogrel 300 mg followed by clopidogrel 75 mg once daily and ASA (75 mg-100 mg once daily). Treatment with clopidogrel and ASA should be

started within 24 hours of the event and be continued for 21 days followed by single antiplatelet therapy."

At the request of CHMP the number of patients according to age category and the age range in the overall sample was presented using the dataset from the Individual Patient Data Pooled Analysis of CHANCE and POINT. Patients ≥ 75 years represent 19% of the overall study population (close to 2000 patients, from which 980 received DPAT). The large majority of patients (75%) in the POINT were administered less than ≤100 mg/day of ASA. The benefit of using DPAT for secondary prevention of TIA or minor stroke was demonstrated to be similar in patients ≥75 years old and <65 years old. The incidence of bleeding events in general was, has expected, higher in patients ≥75 years old than in younger patients, irrespective of treatment allocation. However, as stated by the MAH neither POINT nor CHANCE were dimensioned for this type of subgroup analysis. This new indication for DAPT compared to the previous approved carries a novel potential risk of increased intracranial hemorrhage. The number of intracranial hemorrhages was double in patients with ≥65 years old compared with younger patients with a slighter higher number in patients treated with DAPT than ASA alone.

The benefit of using DAPT for the proposed indication in patients ≥75 years old was shown. However, it was associated to a higher bleeding risk compared to younger patients. DAPT should be used in these patients with a maintenance dose of ≤ 100 mg. The proposed indication compared to previous approved indications of DAPT is associated to an increased risk of intracranial haemorrhage in older patients. Therefore, the safety concern regarding the risk of major bleeding namely intracranial haemorrhage in patients ≥75 years old should be followed in the next PSUR of clopidogrel as an important potential risk.

Regarding subjects with severe renal impairment, it is noted that these subjects were excluded from both CHANCE and POINT; This is a population at increased bleeding risk. There is reference to renal impairment in the SmPC in sections 4.2 and 4.4 and the results of a study in subjects with severe renal impairment are detailed in SmPC Section 5.2. The safety profile of DAPT in the proposed indication for this specific population is considered to be the same as in the current approved indications.

Other important groups of patients for whom the risk of bleeding could be higher were excluded from participation in the CHANCE and POINT studies. These include in particular, patients with a history of (non-traumatic) intracranial haemorrhage and patients with a recent (within 3 months) gastro-intestinal bleed or major surgery. Section 4.4 of the SmPC was amended to reflect the lack of data regarding the benefit risk of using DAPT in adult patients with a past medical history of (non-traumatic) intracranial haemorrhage for moderate to high-risk TIA (ABCD2 score ≥4) or minor IS (NIHSS ≤3). Information was also added to the patient leaflet to the warning and precautions section: "If any of the situations mentioned below apply to you, you should tell your doctor before taking Plavix:

•*" if you had a past medical history of non traumatic intranial hemorrhage* "

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of DAPT with clopidogrel plus aspirin administered with a loading dose of 300 mg and maintenance with 75 mg of clopidogrel during 21 days in patients with minor stroke or moderate to high risk TIA is considered to be positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication in combination with aspirin to include adult patients with moderate to high risk Transient Ischemic Attack (TIA) (ABCD2 score ≥4) or minor Ischemic Stroke (IS) (NIHSS ≤3) within 24 hours of either the TIA or IS event for Iscover and Plavix. The new indication is based on the results of two double-blind, randomised, placebo-controlled phase III trials (studies POINT & CHANCE); as a consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated, the PL is updated accordingly. Version 2.3 of the RMP has also been submitted.

The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion WS1769-Iscover-Plavix-VAR_en