Dabigatran Versus Acetylsalicylic Acid for Secondary Stroke Prevention in Patients with Embolic Stroke of Undetermined Source: Rationale, Design and Baseline Data from RE-SPECT ESUS™

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BACKGROUND

- Ischaemic strokes account for approximately 92% of all strokes, and around 25% of ischaemic strokes are cryptogenic.^{1,2}
- 'Embolic Strokes of Undetermined Source (ESUS)' are a subset of cryptogenic strokes defined as non-lacunar infarcts, without relevant arterial stenoses or cardiac sources, with no other specific known cause.²
- Antiplatelet agents, such as acetylsalicylic acid, are the standard of care for the prevention of secondary stroke in patients with cryptogenic stroke.³
- The optimal antithrombotic treatment for secondary stroke prevention in patients with ESUS has not been established.
- The direct oral anticoagulant dabigatran etexilate is commonly used for stroke prevention in patients with atrial fibrillation (AF)⁴ and may also be effective for the prevention of recurrent stroke in patients with ESUS.

OBJECTIVE

- The RE-SPECT ESUS™ trial will compare the efficacy and safety of dabigatran etexilate with acetylsalicylic acid for secondary stroke prevention in patients with ESUS.⁵

METHODS

Study Design

- RE-SPECT ESUS is a large-scale, phase III, double-blind, randomized trial.
- Patients were randomized 1:1 to receive dabigatran etexilate 150 mg twice daily (or 110 mg twice daily in those aged ≥ 75 years or with creatinine clearance ≥ 30 to < 50 mL/min) or acetylsalicylic acid 100 mg once daily (Figure 1).
- Patients were treated for a minimum of 6 months and for up to approximately 3 years.

Figure 1: Study design

Study Participants

- The main inclusion and exclusion criteria are shown in Table 1.

Table 1: Main inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
ESUS diagnosed within 3 months prior to randomization (6 months in patients aged ≥ 60 years with at least one additional risk factor for recurrent stroke)	Modified Rankin Score ≥ 4
Modified Rankin Score ≤ 3	Major-risk cardioembolic source of embolism
Patients aged ≥ 60 years, or 18–59 years with a stroke risk factor such as:	Any indication for anticoagulation
• Mild to moderate symptomatic heart failure	Other specific stroke aetiology
• Diabetes mellitus	Primary intracerebral haemorrhage on qualifying neuroimaging
• Hypertension	History of AF
• Patent foramen ovale	Conditions associated with increased bleeding risk
• Prior stroke or transient ischaemic attack	Symptomatic non-traumatic intracranial haemorrhage and renal impairment (creatinine clearance < 30 mL/min)
• CHA ₂ DS ₂ -VASC ≥ 3	

AF, atrial fibrillation; ESUS, Embolic Stroke of Undetermined Source.

Study Endpoints

- The main efficacy and safety endpoints are presented in Table 2.

Table 2: Efficacy and safety endpoints

Primary efficacy endpoint	Key secondary endpoints	Main safety endpoint
Time to first recurrent stroke (ischaemic, haemorrhagic or unspecified)	Ischaemic stroke	Time to first major bleed
	Composite endpoint of non-fatal stroke, non-fatal MI and CV death	

CV, cardiovascular; MI, myocardial infarction.

Statistical Analysis

- The trial was event-driven and would complete once at least 353 stroke events had been reported.
- The trial was powered to detect superiority. With 353 events the trial has approximately 92% power to show a 30% relative risk reduction, based on a yearly stroke rate of approximately 4.1% with acetylsalicylic acid.
- Originally 6000 patients were expected to be enrolled and the observational period was anticipated to be approximately 3 years. However, these were dependent on the actual event rate.
- Time-to-event endpoints will be analysed using the Cox proportional hazards regression model.

STUDY PROGRESS

- The study was initiated in December 2014. Randomization was completed in January 2018, at which time 5390 patients had been randomized.
- Patients were recruited from over 40 countries shown in Figure 2.

Figure 2: Geographical distribution of participating countries

Patient Characteristics

- Data regarding baseline characteristics are available for 5390 patients (Table 3).
- Approximately 63% of patients were male.
- The median time from stroke to study entry was 44 days; the duration of cardiac monitoring before inclusion into the trial was 20–48 hours in 79% of patients; > 48–72 hours in 6% of patients and > 72 hours–7 days in 5% of patients.

Table 3: Baseline characteristics (data updated 19 April, 2018)

Number of patients, n	5390
Mean age, years	64.2 (11.4)
Male, %	63
Median time to study entry, days (IQR)	44 (21–80)
CHA ₂ DS ₂ -VASC score, mean (SD)	4.3 (1.3)
CHA ₂ DS ₂ -VASC scores, %	
2	6
3	26
4	28
5	23
≥ 6	18
TIA or stroke prior to index event, %	18
History of hypertension, %	74
Diabetes mellitus, %	23
Patent foramen ovale, %	13
Coronary artery disease, %	11
LV dysfunction/CHF, %	5

CHF, congestive heart failure; IQR, Interquartile range; LV, left ventricular; SD, standard deviation; TIA, transient ischaemic attack.

CONCLUSIONS

- Efficacy and safety data from the RE-SPECT ESUS trial will help to determine whether dabigatran is superior to acetylsalicylic acid for secondary stroke prevention in patients with ESUS.
- These findings will aid physicians to optimally treat patients with ESUS.

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ACKNOWLEDGEMENTS

This study was funded by Boehringer Ingelheim International GmbH. Editorial assistance was provided by PAREXEL with funding from Boehringer Ingelheim.

Disclosures and conflicts of interest:
H-C Diener has received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Abbott, Allergan, AstraZeneca (AZ), Bayer Vital, Bristol-Myers Squibb (BMS), Boehringer Ingelheim (BI), CoAxia, Corimund, Covidien, Daiichi Sankyo, D-Pharm, Fresenius, GlaxoSmithKline (GSK), Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, Medtronic, MindFrame, MSD, Neurobiological Technologies, Novartis, Novo Nordisk, Paion, Parke-Davis, Pfizer, Sanofi Aventis, Schering-Plough, Servier, Solvay, St Jude, Syngis, Talecris, Thrombogenics, WebMD Global, Wyeth and Yamamoto. Financial support for research projects was provided by AZ, BI, GSK, Janssen-Cilag, Lundbeck, Novartis, Sanofi Aventis, Syngis and Talecris. The Department of Neurology at the University of Duisburg-Essen received research grants from the German Research Council (DFG), the German Ministry of Education and Research (BMBF), the European Union, the National Institutes of Health (NIH), the Bertelsmann Foundation and the Heinz-Nixdorf Foundation. H-C Diener has no ownership interest and does not own stocks in any pharmaceutical company.
JD Easton has received research grant support from AZ for the SOCRATES trial (NCT01994720) and from the NIH/the National Institute of Neurological Disorders and Stroke (NINDS)/Sanofi as co-principal investigator for the Platelet-Oriented Inhibition in New TIA and minor ischaemic stroke trial (POINT) (U01 NS062835-01A1); POINT received free study drug and placebo from Sanofi (NCT00991029). JD Easton also receives support from BI and BMS as a consultant for the planning and conduct of the RE-SPECT ESUS trial (NCT02239120) and the phase 2 PARFAIT trial, respectively.
CB Granger has received consulting compensation from BI, BMS, GSK, Hoffmann La Roche, Eli Lilly, Pfizer, Sanofi Aventis, Takeda, The Medicines Company, AZ and Daiichi Sankyo. He has received research grants from BMS, GSK, Medtronic, Merck & Co., Pfizer, Sanofi Aventis, Takeda and The Medicines Company.
M Brueckmann, L Cronin, C Grauer and D Cotton are employees of BI.
RL Sacco is a past consultant of BI and the University of Miami currently receives support for his role on the steering committee of the RE-SPECT ESUS trial.

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