# Clinical trial results:
# REstart or STop Antithrombotics Randomised Trial (RESTART)

## Summary

| | |
|---|---|
| EudraCT number | 2012-003190-26 |
| Trial protocol | GB |
| Global end of trial date | 10 February 2021 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 19 September 2021 |
| First version publication date | 19 September 2021 |
| Summary attachment (see zip file) | RESTART Lancet Main Results (2019_The Lancet_RESTART main results with appendix.pdf)<br>RESTART Lancet Imaging results (2019_Lancet Neurol_RESTART imaging paper with appendix.pdf)<br>Results of final extended follow-up of RESTART (2021_JAMA Neurol_RESTART extended follow-up.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | RESTART13 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | ISRCTN71907627 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Academic and Clinical Central Office for Research and Development (ACCORD) |
| Sponsor organisation address | 47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ |
| Public contact | Head of Research Governance , Academic and Clinical Central Office for Research and Development (ACCORD), +44 0131 242 3330, enquiries@accord.scot |
| Scientific contact | Professor Rustam Al-Shahi Salman, University of Edinburgh, +44 0131 242 7014, rustam.al-shahi@ed.ac.uk |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 31 January 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 January 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 February 2021 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Research question: For adults surviving spontaneous (non-traumatic) intracerebral haemorrhage (ICH) who had taken an antithrombotic (i.e. anticoagulant or antiplatelet) drug for the prevention of vaso-occlusive disease before the ICH, does a policy of starting antiplatelet drugs result in a beneficial net reduction of all serious vascular events compared with a policy of avoiding antiplatelet drugs?

Primary objective of the pilot phase: To estimate the relative and absolute effects of antiplatelet drugs on the risk of recurrent symptomatic ICH associated with a policy of starting antiplatelet drugs after the acute phase of spontaneous ICH.

This entry on EudraCT relates to the main results of the trial, published in 2019. This entry also includes the final results after 2-year extended follow-up, published in 2021, as a summary attachment.

Protection of trial subjects:

RESTART was conducted in accordance with all relevant data protection, ethical and regulatory requirements to ensure the privacy and security of patient information and to ensure the rights, safety and well-being of the patients and the quality of the research data.

We sought support and advice from members of the patient reference group for the Research to Understand Stroke due to Haemorrhage (RUSH) programme for ongoing review of our study materials and on trial progress. We also included a member of this group as part of our Independent Steering Group.

We sought to minimise risk and the burden to the patient without compromising the scientific rigour of the trial. Risk was minimised by excluding patients in whom the risks were likely to be the greatest e.g. patients on anticoagulation. Annual follow-up questionnaires were kept to a minumum to avoid burden and a central helpline was available to support participants, families, general practitioners (GPs) and research staff.

Background therapy:

Any background therapy was determined for participants by the clinical teams at each of our 104 hospital sites.

Evidence for comparator:

The intervention in RESTART was standard care and antiplatelet therapy (any of aspirin, clopidogrel, or dipyridamole); the comparator was standard care without antiplatelet therapy.

The Antithrombotic Trialists' Collaboration meta-analysis of randomised controlled trials found that aspirin use for the secondary prevention of occlusive vascular disease reduces risk of major vascular events, even though it might increase the risk of intracranial haemorrhage (a composite of intracerebral, subarachnoid, or subdural haemorrhages). However, these trials excluded patients with intracerebral haemorrhage, the commonest subtype of intracranial haemorrhage with the worst outcome. We searched the Cochrane Stroke Group Register, the Cochrane Central Register of Controlled Trials, Ovid MEDLINE (from 1948), Ovid Embase (from 1980), online registries of clinical trials, and bibliographies of relevant publications on Jan 28, 2019, for randomised controlled trials of starting versus avoiding antiplatelet therapy after intracerebral haemorrhage, from database inception until Jan 28, 2019, without language restrictions. We found no completed randomised controlled trials. A meta-analysis of observational studies found no difference in the risk of haemorrhagic events and a lower risk of

occlusive vascular events associated with antiplatelet therapy resumption after any type of intracranial haemorrhage.

| | |
|---|---|
| Actual start date of recruitment | 04 March 2013 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy, Scientific research |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 537 |
| Worldwide total number of subjects | 537 |
| EEA total number of subjects | 0 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 86 |
| From 65 to 84 years | 376 |
| 85 years and over | 75 |

## Subject disposition

### Recruitment

Recruitment details:

Between May 22, 2013, and May 31, 2018, 562 patients were consented and 537 enrolled in 104 of 122 UK hospitals. 25 patients were not enrolled; 6 were ineligible; 7 had deterioration of health condition; in 11 cases the patients, clinician, carer or family member were not uncertain about antiplatelet use and 1 consented after recruitment ended.

### Pre-assignment

Screening details:

RESTART did not require sites to collect information about patients screened for eligibility, however we analysed screening logs at sites that kept them and published the results in Trials 2017;18:162 (https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-1909-4).

### Period 1

| | |
|---|---|
| Period 1 title | Baseline (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Staff following up the participants at the trial coordinating centre were masked to treatment allocation. Outcome event adjudicators were masked to participant identity, treatment allocation, and drug use.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Start Antiplatelet |

Arm description:

The intervention of starting antiplatelet therapy was restricted to the use of one or more of oral aspirin, dipyridamole, or clopidogrel, begun within 24 h of randomisation with doses determined at the discretion of the consultant responsible for the participant.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Aspirin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

As instructed by clinician

| | |
|---|---|
| Investigational medicinal product name | Dipyridamole |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

As directed by clinician

| | |
|---|---|
| Investigational medicinal product name | Clopidogrel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

As prescribed by randomising clinician

| | |
|---|---|
| **Arm title** | Avoid Antiplatelet |

Arm description:

The comparator was a policy of avoiding antiplatelet therapy. Participants were permitted to start or discontinue antiplatelet or anticoagulant therapy if clinically indicated by events during follow-up, regardless of treatment allocation.

| Arm type | No intervention |
|---|---|

No investigational medicinal product assigned in this arm

| **Number of subjects in period 1** | Start Antiplatelet | Avoid Antiplatelet |
|---|---|---|
| Started | 268 | 269 |
| Completed | 268 | 268 |
| Not completed | 0 | 1 |
| Consent withdrawn by subject | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Start Antiplatelet |
| Reporting group description: | |
| The intervention of starting antiplatelet therapy was restricted to the use of one or more of oral aspirin, dipyridamole, or clopidogrel, begun within 24 h of randomisation with doses determined at the discretion of the consultant responsible for the participant. | |
| Reporting group title | Avoid Antiplatelet |
| Reporting group description: | |
| The comparator was a policy of avoiding antiplatelet therapy. Participants were permitted to start or discontinue antiplatelet or anticoagulant therapy if clinically indicated by events during follow-up, regardless of treatment allocation. | |

| Reporting group values | Start Antiplatelet | Avoid Antiplatelet | Total |
|---|---|---|---|
| Number of subjects | 268 | 269 | 537 |
| Age categorical | | | |
| At baseline, participants in the two treatment groups were on average 76 years old | | | |
| Units: Subjects | | | |
| <70 years | 73 | 73 | 146 |
| ≥ 70 years | 195 | 196 | 391 |
| Age continuous | | | |
| Age Overall (median) | | | |
| Units: years | | | |
| median | 77.0 | 76.0 | |
| inter-quartile range (Q1-Q3) | 69.0 to 82.0 | 69.0 to 82.0 | - |
| Gender categorical | | | |
| As in many other randomised trials of intracerebral haemorrhage, most participants were male, which might be because of their propensity to be invited or consent rather than differences in incidence or outcome of intracerebral haemorrhage compared with women. | | | |
| Units: Subjects | | | |
| Female | 95 | 82 | 177 |
| Male | 173 | 187 | 360 |
| Ethnicity<br>Units: Subjects | | | |
| White | 251 | 242 | 493 |
| Asian | 12 | 18 | 30 |
| Black | 4 | 5 | 9 |
| Other | 1 | 4 | 5 |
| Probability of good 6-month outcome | | | |
| Predicted probability of being alive and independent at 6 months. See Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute and subacute stroke: development and validation of new prognostic models. Stroke 2002; 33(4):1041-1047 | | | |
| Units: Subjects | | | |
| <0.15 | 48 | 51 | 99 |
| >=0.15 | 220 | 218 | 438 |
| Location of intracerebral haemorrhage<br>Units: Subjects | | | |
| Non-Lobar | 102 | 103 | 205 |
| Lobar | 166 | 166 | 332 |
| Time since ICH symptom onset to | | | |

| randomisation Groups<br>Units: Subjects | | | |
|---|---|---|---|
| 0-6 days | 10 | 11 | 21 |
| 7-30 days | 59 | 59 | 118 |
| >30 days | 199 | 199 | 398 |
| Context of enrolment - Location<br>Units: Subjects | | | |
| Clinic | 181 | 173 | 354 |
| Hospital | 87 | 96 | 183 |
| Context of enrolment - Consent giver<br>Units: Subjects | | | |
| Proxy | 56 | 56 | 112 |
| Patient | 212 | 213 | 425 |
| History of intracranial or extracranial haemorrhage<br>Units: Subjects | | | |
| Yes | 22 | 25 | 47 |
| No | 246 | 244 | 490 |
| Indication for antithrombotic therapy before intracerebral haemorrhage | | | |
| Full category name;<br>> At least one occlusive vascular disease<br>----With atrial fibrillation<br>----Without atrial fibrillation<br>>No occlusive vascular diseases<br>----With atrial fibrillation<br>----Without atrial fibrillation | | | |
| Units: Subjects | | | |
| Occlusive vascular disease (with AF) | 42 | 50 | 92 |
| Occlusive vascular disease (without AF) | 194 | 189 | 383 |
| No occlusive vascular disease (with AF) | 19 | 23 | 42 |
| No occlusive vascular disease (without AF) | 13 | 7 | 20 |
| Time since ICH symptom onset to randomisation in days (Overall)<br>Units: day | | | |
| median | 80.0 | 71.0 | |
| inter-quartile range (Q1-Q3) | 29.5 to 148.5 | 29.0 to 144.0 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Start Antiplatelet |
| Reporting group description: | |
| The intervention of starting antiplatelet therapy was restricted to the use of one or more of oral aspirin, dipyridamole, or clopidogrel, begun within 24 h of randomisation with doses determined at the discretion of the consultant responsible for the participant. | |
| Reporting group title | Avoid Antiplatelet |
| Reporting group description: | |
| The comparator was a policy of avoiding antiplatelet therapy. Participants were permitted to start or discontinue antiplatelet or anticoagulant therapy if clinically indicated by events during follow-up, regardless of treatment allocation. | |

### Primary: Recurrent symptomatic spontaneous intracerebral haemorrhage

| | |
|---|---|
| End point title | Recurrent symptomatic spontaneous intracerebral haemorrhage |
| End point description: | |
| | |
| End point type | Primary |
| End point timeframe: | |
| First event after randomisation and before death or most recent follow up. | |

| End point values | Start Antiplatelet | Avoid Antiplatelet | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 268 | 268 | | |
| Units: Events | 12 | 23 | | |

### Statistical analyses

| Statistical analysis title | Adjusted Cox proportional hazards regression |
|---|---|
| Comparison groups | Start Antiplatelet v Avoid Antiplatelet |
| Number of subjects included in analysis | 536 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| P-value | = 0.06 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.51 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.25 |
| upper limit | 1.03 |

Notes:

[1] - Adjusted for minimisation variables: Qualifying ICH location of lobar versus non-lobar; Time since ICH symptom onset of 0-6 days versus 7-30 days versus over 30 days; Antiplatelet drug(s) that the patient's clinician would start if allocated to aspirin alone versus any other regimen; Participant's age at randomisation of less than 70 years versus 70 years or older; Predicted probability of a good six month outcome of less than 0.15 versus 0.15 or greater.

## Secondary: All major haemorrhagic events (all types of symptomatic spontaneous or traumatic intracranial haemorrhage, or symptomatic major extracranial haemorrhage)

| End point title | All major haemorrhagic events (all types of symptomatic spontaneous or traumatic intracranial haemorrhage, or symptomatic major extracranial haemorrhage) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

First event after randomisation and before death or most recent follow up.

| **End point values** | Start Antiplatelet | Avoid Antiplatelet | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 268 | 268 | | |
| Units: Events | 18 | 25 | | |

### Statistical analyses

| **Statistical analysis title** | Adjusted Cox proportional hazards regression |
|---|---|
| Comparison groups | Start Antiplatelet v Avoid Antiplatelet |
| Number of subjects included in analysis | 536 |
| Analysis specification | Pre-specified |
| Analysis type | other[2] |
| P-value | = 0.27 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.39 |
| upper limit | 1.3 |

Notes:

[2] - Adjusted for minimisation variables: Qualifying ICH location of lobar versus non-lobar; Time since ICH symptom onset of 0-6 days versus 7-30 days versus over 30 days; Antiplatelet drug(s) that the patient's clinician would start if allocated to aspirin alone versus any other regimen; Participant's age at randomisation of less than 70 years versus 70 years or older; Predicted probability of a good six month outcome of less than 0.15 versus 0.15 or greater.

## Secondary: All major occlusive vascular events (ischaemic stroke; myocardial infarction; mesenteric ischaemia; peripheral arterial occlusion; deep vein thrombosis; pulmonary embolism; or carotid, coronary, or peripheral arterial

| revascularisation procedures) | |
|---|---|
| End point title | All major occlusive vascular events (ischaemic stroke; myocardial infarction; mesenteric ischaemia; peripheral arterial occlusion; deep vein thrombosis; pulmonary embolism; or carotid, coronary, or peripheral arterial revascularisation procedures) |

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

First event after randomisation and before death or most recent follow up.

| End point values | Start Antiplatelet | Avoid Antiplatelet | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 268 | 268 | | |
| Units: Events | 39 | 38 | | |

### Statistical analyses

| Statistical analysis title | Adjusted Cox proportional hazards regression |
|---|---|
| Comparison groups | Avoid Antiplatelet v Start Antiplatelet |
| Number of subjects included in analysis | 536 |
| Analysis specification | Pre-specified |
| Analysis type | other[3] |
| P-value | = 0.92 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 1.6 |

Notes:

[3] - Adjusted for minimisation variables: Qualifying ICH location of lobar versus non-lobar; Time since ICH symptom onset of 0-6 days versus 7-30 days versus over 30 days; Antiplatelet drug(s) that the patient's clinician would start if allocated to aspirin alone versus any other regimen; Participant's age at randomisation of less than 70 years versus 70 years or older; Predicted probability of a good six month outcome of less than 0.15 versus 0.15 or greater.

| Secondary: All major haemorrhagic or occlusive vascular events | |
|---|---|
| End point title | All major haemorrhagic or occlusive vascular events |

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

First event after randomisation and before death or most recent follow up.

| End point values | Start Antiplatelet | Avoid Antiplatelet | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 268 | 268 | | |
| Units: Events | 54 | 61 | | |

### Statistical analyses

| Statistical analysis title | Adjusted Cox proportional hazards regression |
|---|---|
| Comparison groups | Start Antiplatelet v Avoid Antiplatelet |
| Number of subjects included in analysis | 536 |
| Analysis specification | Pre-specified |
| Analysis type | other[4] |
| P-value | = 0.43 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 1.24 |

Notes:

[4] - Adjusted for minimisation variables: Qualifying ICH location of lobar versus non-lobar; Time since ICH symptom onset of 0-6 days versus 7-30 days versus over 30 days; Antiplatelet drug(s) that the patient's clinician would start if allocated to aspirin alone versus any other regimen; Participant's age at randomisation of less than 70 years versus 70 years or older; Predicted probability of a good six month outcome of less than 0.15 versus 0.15 or greater.

### Secondary: Major occlusive vascular events

| End point title | Major occlusive vascular events |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

First event after randomisation and before death or most recent follow up.

| End point values | Start Antiplatelet | Avoid Antiplatelet | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 268 | 268 | | |
| Units: Events | 45 | 52 | | |

**Statistical analyses**

| **Statistical analysis title** | Adjusted Cox proportional hazards regression |
|---|---|
| Comparison groups | Start Antiplatelet v Avoid Antiplatelet |
| Number of subjects included in analysis | 536 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.39 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.84 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 1.25 |

**Secondary: Major vascular events (as defined by the Antithrombotic Trialists' Collaboration)**

| End point title | Major vascular events (as defined by the Antithrombotic Trialists' Collaboration) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

First event after randomisation and before death or most recent follow up.

| **End point values** | Start Antiplatelet | Avoid Antiplatelet | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 268 | 268 | | |
| Units: Events | 45 | 65 | | |

**Statistical analyses**

| **Statistical analysis title** | Adjusted Cox proportional hazards regression |
|---|---|

Statistical analysis description:

Adjusted for minimisation variables: Qualifying ICH location of lobar versus non-lobar; Time since ICH symptom onset of 0-6 days versus 7-30 days versus over 30 days; Antiplatelet drug(s) that the patient'

s clinician would start if allocated to aspirin alone versus any other regimen; Participant's age at randomisation of less than 70 years versus 70 years or older; Predicted probability of a good six month outcome of less than 0.15 versus 0.15 or greater.

| | |
|---|---|
| Comparison groups | Start Antiplatelet v Avoid Antiplatelet |
| Number of subjects included in analysis | 536 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.025 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.44 |
| upper limit | 0.95 |

## Adverse events

### Adverse events information[1]

Timeframe for reporting adverse events:

Serious adverse events in the RESTART trial were collected for all participants from the period between randomisation and the end of the trial (unless they withdrew).

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Start Antiplatelet |

Reporting group description:

The intervention of starting antiplatelet therapy was restricted to the use of one or more of oral aspirin, dipyridamole, or clopidogrel, begun within 24 h of randomisation with doses determined at the discretion of the consultant responsible for the participant.

| | |
|---|---|
| Reporting group title | Avoid Antiplatelet |

Reporting group description:

The comparator was a policy of avoiding antiplatelet therapy. Participants were permitted to start or discontinue antiplatelet or anticoagulant therapy if clinically indicated by events during follow-up, regardless of treatment allocation.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Section 12.5 of the protocol states, "...safety assessments in RESTART are focussed on detecting: primary and secondary outcomes (all of which relate to the safety of antiplatelet drugs in this patient group) and any SAEs and SUSARs... PIs need not report to the TCC or sponsor any non-fatal AEs that are neither primary/secondary trial
outcomes nor SAEs nor SUSARs, and which are expected complications of ICH."

| Serious adverse events | Start Antiplatelet | Avoid Antiplatelet | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 268 (1.87%) | 5 / 269 (1.86%) | |
| number of deaths (all causes) | 54 | 50 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Prostate cancer | Additional description: Admitted with vomiting, meleana and haematuria. Investigations highly suggestive of metastic prostate carcinoma. | | |
| subjects affected / exposed | 0 / 268 (0.00%) | 1 / 269 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Colitis | Additional description: admitted following flexisigmoidoscopy with severe colitis and pain | | |
| subjects affected / exposed | 0 / 268 (0.00%) | 1 / 269 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Cardiac disorders | | | |
| Cardiac failure congestive | Additional description: Patient admitted with with shortness of breath - suspected mild pulmonary oedema and small pleural effusions. Diagnosed with congested cardiac failure . | | |
| subjects affected / exposed | 1 / 268 (0.37%) | 0 / 269 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorder | Additional description: syncopal episode after bowel prep for colonoscopy for change in bowel habit. Needed Mg replacement | | |
| subjects affected / exposed | 1 / 268 (0.37%) | 0 / 269 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Strangulated hernia repair | Additional description: admitted for repair of strangulated paraumbilical hernia | | |
| subjects affected / exposed | 1 / 268 (0.37%) | 0 / 269 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Postictal paralysis | Additional description: Admitted with right arm shaking,slurred speech was being treated as ischaemic stroke initially and started on Aspirin 300mg,MR scan later ruled out ischaemic stroke and is now thought to be Todds Paresis | | |
| subjects affected / exposed | 0 / 268 (0.00%) | 1 / 269 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hydrocholecystis | Additional description: cholecystis | | |
| subjects affected / exposed | 0 / 268 (0.00%) | 1 / 269 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pelvic fracture | Additional description: fractured pubic rami | | |
| subjects affected / exposed | 0 / 268 (0.00%) | 1 / 269 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | Additional description: Fractured L neck of femur following fall . Patient has had L dynamic hip screw | | |
| subjects affected / exposed | 1 / 268 (0.37%) | 0 / 269 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Start Antiplatelet | Avoid Antiplatelet | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 0 / 268 (0.00%) | 0 / 269 (0.00%) | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 31 January 2013 | AM01<br>Updated documents;<br>- Protocol v2.0<br>- Participant Consent form v2.0<br>- GPIL Letter v2.0<br>- Participant Annual Questionnaire v2.0<br>- Participant Prompt v2.0<br>- Participant Information Sheet v2.0<br>- Participant Legal Representative Consent form v2.0<br>- Regained Capacity Participant Information Sheet v2.0<br>- RIL Participant Information Sheet v2.0 |
| 22 April 2013 | AM04<br>New sites |
| 03 July 2013 | AM07<br>New sites<br>Changes PI |
| 11 July 2013 | AM05<br>New sites |
| 23 July 2013 | AM06<br>Updated documents;<br>- GP event form v2.1<br>- GPIL Letter v4.0<br>- Participant Annual Questionnaire v4.0<br>- Participant consent form V3.0<br>- GP follow up letter and questionnaire V3.0<br>- Patient Information Leaflet V3.0<br>- Participant annual questionnaire V4.0<br>- PLR consent form V3.0<br>- Protocol V4.0<br>- RIL V3.0<br>- Recovered PIL |
| 31 January 2014 | AM10<br>New sites<br>Changes PI |
| 11 March 2014 | AM11<br>New sites<br>Changes PI |
| 23 April 2014 | AM13<br>Updated documents;<br>- GP follow-up letter and questionnaire V4<br>- Participant annual questionnaire V5<br>- Protocol V5 |
| 18 July 2014 | AM15<br>New sites<br>Changes PI |

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|---|---|
| 06 December 2014 | AM09<br>New sites<br>Changes PI |
| 14 January 2015 | AM16<br>Changes PI |
| 16 April 2015 | AM18<br>Updated documents;<br>- RESTART consultant invitation letter to patient V1.2<br>- RESTART GP invitation letter to patient V1.2<br>- Protocol V6 |
| 19 June 2015 | AM19<br>Changes PI |
| 23 October 2015 | AM20<br>Changes PI |
| 28 January 2016 | AM23<br>Changes PI |
| 05 February 2016 | AM21<br>Updated documents;<br>- Participant consent form V4.0<br>- Participant consent form [Participant Consent Form] V4.0<br>- Participant consent form [Personal Legal Representative] V4.0<br>- Participant information sheet [PIS ] V4.0<br>- Participant information sheet [Relative IF] V4.0<br>- Participant information sheet [Recovered] V4.0 |
| 27 June 2016 | AM25<br>Changes PI |
| 07 October 2016 | AM26<br>Changes of PI |
| 11 January 2017 | AM27<br>Changes of PI's |
| 05 April 2017 | AM28 (REC reference AM29)<br>New site<br>Change of PI |
| 28 June 2017 | AM29 (REC reference AM30)<br>Change of PI |
| 05 September 2017 | AM30 (REC reference AM32)<br>Change of PI |
| 13 October 2017 | AM31 (REC reference AM31)<br>Updated documents<br>- Summary of Characteristics booklet v1.0<br>- Protocol Version v8.0 |
| 24 April 2019 | AM34<br>Change to SmPCs for Dipyridamole and Clopidogrel |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The main limitation of the trial was that it did not achieve its intended sample size.

Notes:

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/29282142

http://www.ncbi.nlm.nih.gov/pubmed/31129065

http://www.ncbi.nlm.nih.gov/pubmed/28381307

http://www.ncbi.nlm.nih.gov/pubmed/28253897

http://www.ncbi.nlm.nih.gov/pubmed/28245843

http://www.ncbi.nlm.nih.gov/pubmed/30909946

http://www.ncbi.nlm.nih.gov/pubmed/31128924

http://www.ncbi.nlm.nih.gov/pubmed/29506580