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Baseline characteristics of the 3096 patients recruited into the 'Triple Antiplatelets for Reducing Dependency after Ischemic Stroke' trial

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Abstract

Background: The risk of recurrence following ischemic stroke or transient ischemic attack is highest immediately after the event. Antiplatelet agents are effective in reducing the risk of recurrence and two agents are superior to one in the early phase after ictus.

Design: The triple antiplatelets for reducing dependency after ischemic stroke trial was an international multicenter prospective randomized open-label blinded-endpoint trial that assessed the safety and efficacy of short-term intensive antiplatelet therapy with three agents (combined aspirin, clopidogrel and dipyridamole) as compared with guideline treatment in acute ischemic stroke or transient ischemic attack. The primary outcome was stroke recurrence and its severity, measured using the modified Rankin Scale at 90 days. Secondary outcomes included recurrent vascular events, functional measures (cognition, disability, mood, quality of life), and safety (bleeding, death, serious adverse events). Data are number (%) or mean (standard deviation, SD).

Results: Recruitment ran from April 2009 to March 2016; 3096 patients were recruited from 106 sites in four countries (Denmark 1.6%, Georgia 2.7%, New Zealand 0.2%, UK 95.4%). Randomization characteristics included: age 69.0 (10.1) years; male 1945 (62.8%); time onset to randomization 29.4 (11.9) h; stroke severity (National Institutes for Health Stroke Scale) 2.8 (3.6); blood pressure 143.5 (18.2)/79.5 (11.4) mmHg; IS 2143 (69.2%), transient ischemic attack 953 (30.8%).

Conclusion: Triple antiplatelets for reducing dependency after ischemic stroke was a large trial of intensive/triple antiplatelet therapy in acute ischemic stroke and transient ischemic attack, and included participants from four predominantly Caucasian countries who were representative of patients in many western stroke services.

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Introduction

The risk of recurrence following an ischemic stroke (IS) or transient ischemic attack (TIA) is very high over the first hours and days after the event,[1,2] reaching up to ~10% by 90 days and then declining, with a total of about 40% by five years. Typically, recurrent events are more severe than index events and thus increased dependency, disability, cognitive impairment and dementia, poor quality of life, and institutionalization are all more likely.[3,4]

The long-term risk of recurrence can be reduced through lifestyle changes (smoking cessation and reducing weight, salt, saturated fat, and high alcohol intake) and proven, cost-effective pharmacological (antihypertensives and statins) and surgical interventions (carotid endarterectomy or stenting in large vessel disease).[1–8] Oral anticoagulation is established for patients following cardioembolic stroke[9–12] while the majority of patients with non-cardioembolic ischemic events (stroke and TIA) require antiplatelet therapy.[13–20] In long-term secondary stroke prevention, dual antiplatelet therapy with aspirin and dipyridamole reduced recurrent events by 23% as compared with either aspirin or dipyridamole in isolation, and without increasing bleeding risk.[17,19] However, the combination of aspirin and clopidogrel given chronically was not superior to either drug alone, and dual therapy resulted in increased bleeding as compared with clopidogrel alone.[21–23]

In contrast, more intensive antiplatelet therapy may give improved prophylaxis in the acute phase of stroke or TIA. While early antiplatelet therapy with aspirin following acute IS is effective at reducing early recurrence,[15,16,24] dual antiplatelet therapy started within 72 h of onset reduced early recurrence risk more than monotherapy in a meta-analysis of small studies.[25] Moreover, the type of agents used was less important than using dual rather than monotherapy. This was supported by the findings of the large CHANCE trial; dual antiplatelet therapy with aspirin and clopidogrel was superior to aspirin alone in preventing stroke recurrence by 90 days when commenced within 24 h of minor IS or TIA.[26,27] One potential benefit of using multi-antiplatelet agents is the mitigation of treatment resistance seen individually with aspirin and clopidogrel monotherapy.[28–30]

If dual antiplatelet therapy reduces stroke recurrence following acute IS or TIA as compared to monotherapy, then triple/intensive antiplatelet therapy with combined aspirin, clopidogrel, and dipyridamole might be even more effective, providing the risk of recurrence is high and bleeding is not excessive. Several laboratory studies and clinical trials have assessed this concept.[31–35] Triple therapy in vitro was most effective in inhibiting leucocyte activation, platelet–leucocyte conjugation, and platelet aggregation.[31–33] Phase I and II multiway crossover trials compared short-term administration of single, dual, and triple antiplatelets and found that aspirin and clopidogrel, with or without dipyridamole, were most effective at inhibiting platelet function in healthy volunteers and those with previous stroke or TIA.[34,35] A parallel group trial comparing long-term triple antiplatelet therapy with aspirin alone in participants with stroke found that intensive treatment was feasible to administer for up to 24 months, but there was a non-significant trend to increased bleeding.[36] In addition, chronic use of triple antiplatelet therapy in patients with a very high risk of recurrence following events on dual therapy appeared to be effective in minimizing further events without increasing bleeding.[37]

Based on these preclinical and clinical data showing feasibility, tolerability, apparent safety and potential efficacy for triple antiplatelet therapy, the triple antiplatelets for reducing dependency after ischemic stroke (TARDIS) trial tested the overall safety and efficacy of short-term intensive antiplatelet therapy in comparison with guideline treatment. The protocol and statistical analysis plan have been published previously.[38,39]

Methods

Eligibility and consent

The full inclusion and exclusion criteria are published[38] and listed in the latest version of the protocol (online Appendix A, B). Adults aged >50 years with non-cardioembolic TIA or stroke within 48 h of onset were eligible. Those whose index event was a TIA had:

- Resolved limb weakness and/or dysphasia.
- Symptom duration between 10 min and 24 h.

- ABCD2 score[40] >4; and/or crescendo TIA; and/or already on dual antiplatelet therapy.

IS participants had:

- Ongoing limb weakness, or ongoing facial weakness with resolved limb weakness; and/or dysphasia; and/or ongoing isolated hemianopia (with positive neuroimaging of ischemia affecting the corresponding occipital lobe); and duration >1 h.
- Resolved limb weakness; and/or dysphasia; with duration >24 h after onset (i.e. resolution between 24 h and randomization).
- Note: Any severity of stroke could be recruited.

Patients gave written informed consent prior to enrolment; if they lacked capacity (e.g. due to dysphasia, confusion, or reduced conscious level) then proxy consent could be obtained from a relative, carer, or legal representative, and if not available then independent physician proxy consent was permitted. Neuroimaging was essential for IS to exclude intracranial hemorrhage and a non-stroke diagnosis. Patients who were thrombolyzed for stroke were eligible for inclusion following a delay of 24 h and providing neuroimaging excluded secondary intracranial hemorrhage. Neuroimaging was performed in patients presenting with a TIA at the discretion of local clinicians.

Randomization and data collection

After obtaining informed consent, the local investigator used a secure password-protected and data-encrypted web-based randomization system to enter a participant into the trial (a system derived from that used in the ENOS trial[41]). The system recorded baseline characteristics following validation of data using range and consistency checks, and then allocated the participant to a treatment group. To achieve optimal baseline matching between treatment groups and ensure concealment of allocation, randomization incorporated stratification (country, index event: stroke or TIA) and minimization (on baseline prognostic factors and additional criteria for TIA and stroke respectively, as highlighted in Tables 2 and 3); the minimization algorithm included a random element (simple randomization) in 5% of patients. Stratification and minimization allow for improved matching at baseline, stratification allows variable categories to be treated as trials in their own right, minimization increases statistical power,[42] and simple randomization reduces predictability. Following randomization, the local investigator was informed of the patient's treatment allocation to triple/intensive or guideline antiplatelet therapy; randomized treatment was taken for one month, after which participants on intensive antiplatelet therapy reverted to guideline therapy. The minimization variables will be used for adjustment of the primary and secondary analyses in the main publication,[39] as recommended.[42]

Investigational medicinal products

Trial interventions were given open label for one month (28 or 30 days depending on treatment pack size), a period chosen to cover the period of maximum risk of recurrence but minimize bleeding, and comprised:

- Aspirin: loading dose 300 mg then 50–150 mg daily; by oral, nasogastric tube (NGT) or rectal route.
- Clopidogrel: loading dose 300 mg then 75 mg daily; by oral or NGT route.
- Dipyridamole: 225–450 mg in divided doses; by oral (as 200 mg extended release capsules twice daily, or as 25–100 mg tablets three to four times daily) or NGT (as suspension or crushed tablets three to four times daily) route.

Participants were randomized to either:

- Intensive/triple antiplatelets (active): Combined aspirin, clopidogrel, and dipyridamole.
- Guideline/dual or mono antiplatelet(s): Combined aspirin and dipyridamole, or clopidogrel alone.

Throughout the trial, five protocol amendments were made covering multiple issues. The main change concerned an update of guidelines relating to antiplatelet agents after stroke. When the trial commenced, the National Institute for Health and Clinical Excellence (NICE) recommended aspirin and dipyridamole for secondary prevention,[43] which the initial protocol defined as guideline therapy. However, significant randomized evidence supporting the use of clopidogrel for secondary stroke prophylaxis, and widespread availability of generic inexpensive clopidogrel, resulted in NICE updating their guidance in 2010, this recommending that clopidogrel should be used first-line after non-cardioembolic IS.[44] Therefore, the trial protocol was updated allowing for use of either aspirin and dipyridamole, or clopidogrel monotherapy, as the guideline comparator (online Appendix C). Local investigators were able to choose whether randomization included either or both comparators, and this decision was made separately for stroke and TIA.

Outcomes

The primary and main secondary outcomes were collected centrally at day 90 by an assessor based in the national coordinating center who was blinded to treatment assignment. In the first instance, a check was

made that the patient was still alive, either via the general practitioner or using electronic records; the patient and/or carer was then contacted by telephone. Where telephone contact could not be made, outcome information was collected using a postal questionnaire. The primary outcome was the occurrence and severity of recurrent stroke and TIA, with severity measured using a six-level ordered categorical scale incorporating the modified Rankin Scale (mRS[45]): fatal stroke/severe non-fatal stroke (mRS 4 or 5)/moderate stroke (mRS 2 or 3)/mild stroke (mRS 0 or 1)/TIA/no stroke or TIA. Recurrent events and mRS were determined centrally by telephone by a trained assessor masked to treatment at day 90. Local investigators assessed and reported secondary, bleeding, and safety outcomes (including death) at days 7 and 35, and at hospital discharge (if admitted). Secondary outcomes were also collected at day 90, including bleeding, death, and measures of disability, cognition, mood, and quality of life.[38]

Use of the internet

The TARDIS trial used the internet to randomize and collect data in real-time on line:

- Trial website: www.tardistrial.org.
- Secure website for real-time data entry, validation and randomization: https://nottingham.ac.uk/~nszwww/tardis/tardistrialdb/tardis_login.php
- Demo website for local investigators to practice data entry: https://www.nottingham.ac.uk/~nszwww/tardis/tardistrialdb-demo/
- (log-in: demoinv1, password: Nottingham; pin: 8888)

Funding and governance

The TARDIS trial received two phases of funding:

- Start-up phase (April 2009 – September 2012): funding from the British Heart Foundation: 902 patients recruited.
- Main phase (October 2012 – March 2016, with funding through to end September 2017): funding from the NIHR Health Technology Assessment Programme; 2194 patients recruited. The overall aim was to recruit a total of 4100 patients.[38]

The trial was supervised by a Trial Steering Committee, with support from an International Advisory Committee; run by a Trial Management Committee (part of Nottingham Stroke Trials Unit); and monitored by an independent Data Monitoring Committee (DMC). The DMC met and assessed safety and efficacy on 13 occasions during the trial; prior to 2016, they recommended that the trial should continue with recruitment with no change to the protocol. Independent experts adjudicated brain scans and serious adverse events, blinded to treatment.

Results

Trial delivery

Recruitment progressed with a start-up phase in a limited number of sites, and then expanded to a main phase (Figure 1). During the trial's progress, a number of logistical issues arose (online Appendix C). The DMC recommended in March 2016 that the trial should stop recruitment; the TSC reviewed the same data and agreed to stop recruitment, complete follow-ups, and close the trial once data had been validated, the database locked and analyzed, and all sites closed. An explanation to the trial's early stopping will be provided in the main publication.

Baseline characteristics

The following data are given as number (%) or mean (standard deviation); 3096 participants were recruited between April 2009 and March 2016 from 106 sites (online Appendix D) across four countries in two continents: Denmark 51 (1.6%), Georgia 83 (2.7%), New Zealand 7 (0.2%), and UK 2955 (95.4%) (Table 1). Four sites recruited a high number of participants relative to other sites (Figure 2).

The baseline characteristics at the time of randomization are presented in Tables 2 and 3. Key features include: age 69.0 (10.1) years; male 1945 (62.8%); time from onset to recruitment 29.4 (11.9) h (Figure 3(a)); severity (National Institutes of Health Stroke Scale, NIHSS) 2.8 (3.6); mean blood pressure 143.5 (18.2)/79.5 (11.4) mmHg; IS 2143 (69.2%), TIA 953 (30.8%). In comparison with patients whose randomizing event was stroke, patients with TIA were more likely to have pre-morbid hypertension, hyperlipidemia, and a shorter time to randomization (Figure 3(b) and (c)), but were less likely to be current smokers.

Table 4 shows univariate relationships between several key baseline factors, including year of randomization into the trial. As the trial progressed, average NIHSS and ABCD2 scores, systolic blood pressure, time to randomization, and proportion of strokes (versus TIA) increased. Further, increasing time to randomization was associated with increased NIHSS score, stroke rather than TIA, and lower SBP; higher SBP was associated with increasing age, NIHSS, and ABCD2 scores; those with strokes were younger; and

Figure 1. Recruitment curve by time.

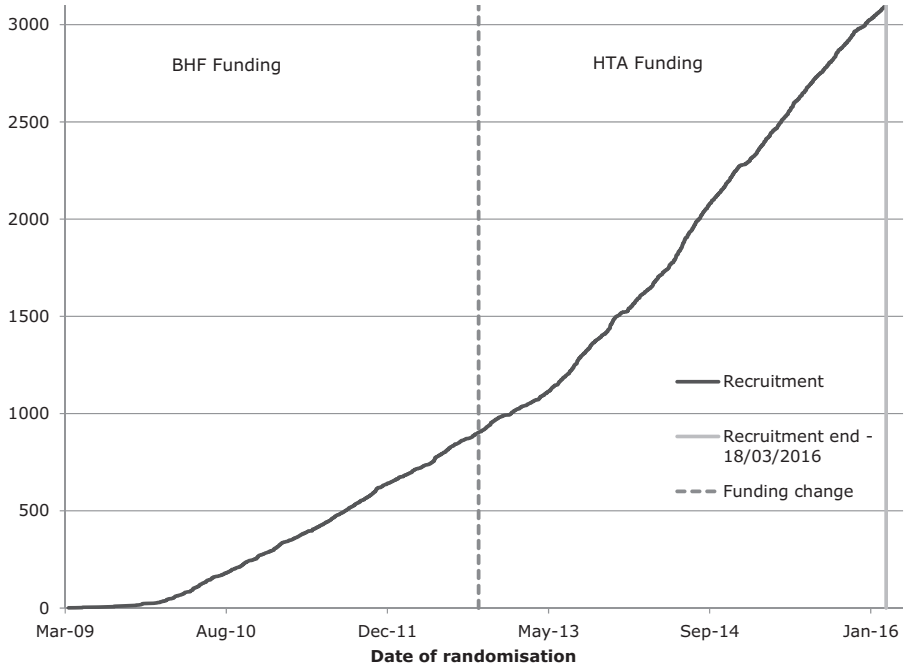

Table 1. Recruitment: Number of sites and patients by region and country

Regions	Countries	No. of sites (%)	No. of patients (%)
Australasia			
	New Zealand	1 (0.9)	7 (0.2)
Europe			
	Denmark	2 (1.9)	51 (1.6)
	Georgia	3 (2.8)	83 (2.7)
	UK	100 (94.3)	2955 (95.4)
Total		106 (100)	3096 (100)

Note: Data are number and percentage.

increasing age was associated with being female, higher ABCD2 score and SBP, and TIA rather than stroke.

Reporting of results

Following completion of data validation, the database will be locked and the trial unblinded and analyzed. It is intended to present the main results in late 2016/early 2017, with the main manuscript published in parallel. Multiple pre-specified secondary publications and analyses are described in the statistical analysis plan.[39]

TARDIS data will be shared with prospective individual patient data meta-analyses:

- Antiplatelet agents in acute stroke/TIA.
- Virtual international stroke trials archive (VISTA).[46]

Ultimately, a subset of data will be made available on the internet akin to the International Stroke Trial,[47] and anonymized neuroimaging data will be published.[48]

Discussion

TARDIS is the first trial to assess the safety and efficacy of intensive antiplatelet therapy based on three agents in comparison with guideline treatment; with 3096 patients, TARDIS is a large international trial. The characteristics of the participants justify several comments. First, although the trial was designed to run internationally, contracting issues, largely related to national sponsorship and availability of insurance (online Appendix C), led the trial to recruit predominantly a UK-population; with a large number of recruiting sites, it is therefore representative primarily of UK stroke services and their patients; however, participants also came from three other countries with predominantly Caucasian populations. Second, the proportion of

Figure 2. Recruitment by hospital sites.

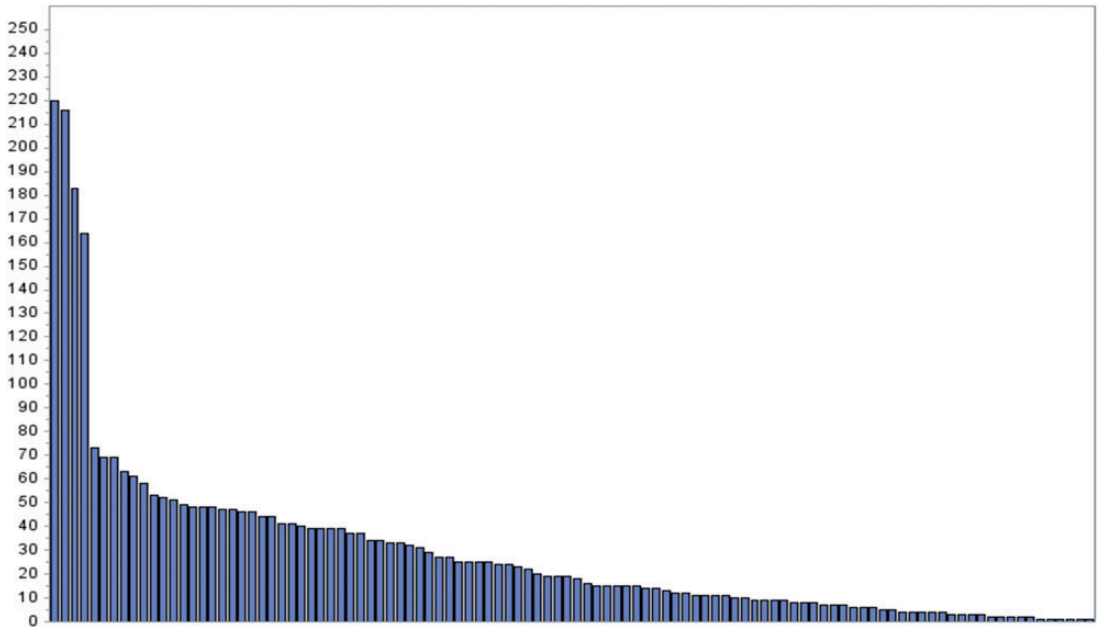

Table 2. Demographic characteristics and past medical history at time of randomization in TARDIS: Overall and by index event.

	N	All	IS[a]	TIA[a]
Number of patients (%)	3096	3096 (100)	2143 (69.2)	953 (30.8)
Age (years)[b]	3096	69.0 (10.1)	68.5 (10.1)	70.2 (9.9)
Sex, male (%)[b]	3096	1945 (62.8)	1356 (63.3)	589 (61.8)
Geographical region[a]				
Europe, rest of	3096	134 (4.3)	109 (5.1)	25 (2.6)
UK	3096	2955 (95.4)	2032 (94.8)	923 (96.9)
World, rest of	3096	7 (0.2)	2 (0.1)	5 (0.5)
Ethnicity (%)				
White	3096	2939 (94.9)	2024 (94.4)	9156 (96.0)
Black	3096	63 (2.0)	58 (2.7)	5 (0.5)
East Asian	3096	2 (0.1)	2 (0.1)	0 (0.0)
South Asian	3096	46 (1.5)	29 (1.4)	17 (1.8)
South East Asian	3096	1 (0.0)	0 (0.0)	1 (0.1)
Other Asian	3096	11 (0.4)	7 (0.3)	4 (0.4)
Mixed: White and Black	3096	9 (0.3)	6 (0.3)	3 (0.3)

(continued)

Table 2. Continued

	N	All	IS[a]	TIA[a]
Mixed: Other	3096	2 (0.1)	2 (0.1)	0 (0.0)
Other	3096	12 (0.4)	7 (0.3)	5 (0.5)
Not Stated	3096	11 (0.4)	8 (0.4)	3 (0.3)
Dominant hand, Right (%)	3058	2798 (91.5)	1918 (90.6)	880 (93.5)
Source of referral				
Emergency department	3096	2037 (65.8)	1446 (67.5)	591 (62.0)
Outpatient clinic	3096	129 (4.2)	38 (1.8)	91 (9.5)
Ambulance	3096	586 (18.9)	435 (20.3)	151 (15.8)
General practitioner	3096	156 (5.0)	87 (4.1)	69 (7.2)
Inpatient ward	3096	94 (3.0)	55 (2.6)	39 (4.1)
Other	3096	94 (3.0)	82 (3.8)	12 (1.3)
Pre-stroke mRS [/6]	3096	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]
0 (%)	3094	2604 (84.2)	1781 (83.1)	823 (86.5)
1–2	3094	490 (15.8)	362 (16.9)	128 (13.5)
Medical history (%)				
Hypertension[b]	3096	1826 (59.0)	1241 (57.9)	585 (61.4)
Antihypertensives	3096	1742 (56.3)	1181 (55.1)	561 (58.9)
Hyperlipidaemia	2972	1315 (44.2)	874 (42.5)	441 (48.2)
Lipid lowering	3096	1387 (44.8)	929 (43.4)	458 (48.1)
Diabetes mellitus	3096	590 (19.1)	418 (19.5)	172 (18.0)
Treatment				
Insulin	3096	59 (1.9)	47 (2.2)	12 (1.3)
Oral agents	3096	347 (11.2)	232 (10.8)	115 (12.1)
Both	3096	79 (2.6)	64 (3.0)	15 (1.6)
Neither	3096	104 (3.4)	74 (3.5)	30 (3.1)
Antiplatelet agent				
Aspirin	3096	816 (26.4)	558 (26.0)	258 (27.1)
Aspirin/dipyridamole	3096	85 (2.7)	45 (2.1)	40 (4.2)
Clopidogrel	3096	162 (5.2)	117 (5.5)	45 (4.7)
Other	3096	17 (0.5)	14 (0.7)	3 (0.3)

(continued)

Table 2. Continued

	N	All	IS[a]	TIA[a]
Heparin	3096	7 (0.2)	5 (0.2)	2 (0.2)
Glycoprotein inhibitor	3096	0 (0.0)	0 (0.0)	0 (0.0)
Gastroprotection (PPI/H_2A)	3096	803 (25.9)	539 (25.2)	264 (27.7)
AF, current/previous	3096	1 (0.0)	0 (0.0)	1 (0.1)
Stroke	3096	349 (11.3)	255 (11.9)	94 (9.9)
Transient ischemic attack	3096	337 (10.9)	190 (8.9)	147 (15.4)
Ischemic heart disease	3096	402 (13.0)	289 (13.5)	113 (11.9)
Peripheral arterial disease	3062	70 (2.3)	50 (2.4)	20 (2.1)
Family history of young stroke	2901	170 (5.9)	120 (6.0)	50 (5.6)
Smoking, current (%)	3052	784 (25.7)	627 (29.7)	157 (16.7)
Alcohol intake, high (>21 upw)	3001	291 (9.7)	211 (10.2)	80 (8.6)
Qualifying event, final diagnosis (%)[c]				
Ischemic stroke	3095	2220 (71.7)	2055 (95.9)	165 (17.3)
TIA	3095	838 (27.1)	64 (3.0)	774 (81.2)
Crescendo	773	155 (20.1)	0 (0.0)	155 (20.1)
Dual antiplatelets	838	36 (4.3)	2 (3.1)	34 (4.4)
Non-stroke/TIA	3095	36 (1.2)	23 (1.1)	13 (1.4)
Onset to randomization [h][b]	3096	29.3 [21.8, 39.6]	32.1 [24.7, 41.2]	24.2 [17.5, 29.6]
By qualifying event				
Ischemic stroke	2143	32.1 [24.7, 41.2]	32.1 [24.7, 41.2]	–
TIA	953	24.2 [17.5, 29.6]	–	24.2 [17.5, 29.6]
Time, h (%)				
≤12	3096	314 (10.1)	151 (7.0)	163 (17.1)
13–24	3096	651 (21.0)	355 (16.6)	296 (31.1)
25–48	3096	2124 (68.6)	1630 (76.1)	494 (51.8)
>48[d]	3096	7 (0.2)	7 (0.3)	0 (0.0)
Mean (SD)	3096	29.4 (11.9)	31.8 (11.4)	24.1 (11.1)

[a]Stratification variable.
[b]Minimisation variable.
[c]Final hospital diagnosis may vary from diagnosis used at time of randomization
[d] Protocol violation.
AF: atrial fibrillation; H_2A: H_2 antagonist; mRS: modified Rankin Scale; PPI: proton pump inhibitor; TIA: transient ischemic attack; upw: units per week.
Note: Data are number (percentage), median [interquartile range] or mean (standard deviation).
Validation is ongoing and some data may undergo minor changes prior to data lock. These data have been partially validated and may undergo minor changes prior to data lock.

Table 3. Clinical characteristics at time of randomization in TARDIS: Overall and by index event

	N	All	IS[a]	TIA[a]
Number of patients	3096	3096	2143	953
Lesion side, right (%)	2789	1429 (51.2)	1021 (51.2)	408 (51.5)
Weakness (%)	3095	2789 (90.1)	1996 (93.1)	793 (83.3)
Sensory loss (%)	3096	1066 (34.4)	823 (38.4)	243 (25.5)
Dysphasia (%)	3096	1007 (32.5)	593 (27.7)	414 (43.4)
Isolated	3096	160 (5.2)	58 (2.7)	102 (10.7)
Neglect (%)	3096	331 (10.7)	299 (14.0)	32 (3.4)
Hemianopia (%)	3096	302 (9.8)	268 (12.5)	34 (3.6)
Isolated	3096	16 (0.5)	16 (0.7)	0 (0.0)
Dysarthria (%)	3096	1279 (41.3)	959 (44.8)	320 (33.6)
Posterior circulation (%)	3096	287 (9.3)	245 (11.4)	42 (4.4)
NIHSS (/42)[b]	3096	2.8 (3.6)	4.0 (3.8)	0.2 (0.7)
ABCD2 score [/7]	3096	5.0 [5.0, 6.0]	6.0 [5.0, 6.0]	5.0 [5.0, 6.0]
GCS [/15]	3096	15.0 [15.0, 15.0]	15.0 [15.0, 15.0]	15.0 [15.0, 15.0]
OCSP (%)[50]				
Total anterior †	3096	180 (5.8)	166 (7.7)	14 (1.5)
Partial anterior	3096	1412 (45.6)	837 (39.1)	575 (60.3)
Lacunar	3096	1289 (41.6)	952 (44.4)	337 (35.4)
Posterior	3096	213 (6.9)	188 (8.8)	25 (2.6)
TOAST (%)[c]				
Cardioembolic	3051	133 (4.4)	108 (5.1)	25 (2.7)
Large vessel	3051	490 (16.1)	389 (18.4)	101 (10.8)
Small vessel	3051	1225 (40.2)	896 (42.3)	329 (35.3)
Mixed	3051	22 (0.7)	19 (0.9)	3 (0.3)
Other	3051	1181 (38.7)	706 (33.3)	475 (50.9)
Hemodynamics				
Systolic BP (mmHg) [b]	3096	143.5 (18.2)	143.2 (18.2)	144.2 (18.0)
Diastolic BP (mmHg)	3096	79.5 (11.4)	79.6 (11.5)	79.2 (11.1)
Heart rate (bpm)	3096	73.1 (12.6)	73.6 (12.7)	71.8 (12.3)
Feeding status (%)				
Normal diet	3096	2874 (92.8)	1929 (90.0)	945 (99.2)

(continued)

Table 3. Continued

	N	All	IS[a]	TIA[a]
Soft diet	3096	168 (5.4)	161 (7.5)	7 (0.7)
NGT fed	3096	51 (1.6)	50 (2.3)	1 (0.1)
PEG/RIG fed	3096	3 (0.1)	3 (0.1)	0 (0.0)
IV/SC fluids	3096	0 (0.0)	0 (0.0)	0 (0.0)
Nothing	3096	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin (g/L)	3096	141.8 (14.7)	142.1 (15.0)	141.1 (14.2)
Blood glucose (mmol/L)	3050	6.8 (2.5)	6.9 (2.7)	6.5 (2.0)
Temperature (°C)	3058	36.5 (0.5)	36.5 (0.5)	36.5 (0.5)
Weight (Approx. kg)	3048	75.3 (16.6)	75.5 (16.5)	75.0 (16.9)
Brain imaging (%)				
Normal/no lesion	3089	1561 (50.5)	959 (44.9)	602 (63.2)
Ischaemic stroke	3089	1378 (44.6)	1175 (55.0)	203 (21.3)
Non stroke	3089	6 (0.2)	3 (0.1)	3 (0.3)
No brain scan	3089	144 (4.7)	0 (0.0)	144 (15.1)
Thrombolysis[b]	3096	341 (11.0)	336 (15.7)	5 (0.5)
Time [h]	341	2.3 [1.8, 3.0]	2.3 [1.8, 3.0]	2.3 [1.8, 2.5]

[a]Stratification variable.
[b]Minimisation variable.
[c]Ischaemic patients only.
ABCD2: age, blood pressure, clinical features, duration, diabetes; BP: blood pressure; bpm: beats per minute; GCS: Glasgow coma scale; IV: intravenous; NGT: nasogastric tube; NIHSS: National Institutes of Health Stroke Scale; OCSP: Oxford community stroke project; PEG: percutaneous endoscopic gastrostomy; RIG: radiologically inserted gastrostomy; SC: subcutaneous; TIA: transient ischemic attack; TOAST: Trial of ORG 10172 in acute stroke treatment.
Note: Data are number (percentage), median [interquartile range] or mean (standard deviation). These data have been partially validated and may undergo minor changes prior to data lock.

stroke patients recruited as compared with TIAs was higher than intended; the proportion of stroke increased as the trial progressed, probably related to closure of other large stroke trials such as ENOS and SO_2S.[41,49] Third, in addition to more stroke patients being recruited over time, their severity, SBP, and time to randomization also increased, this reflecting differences in the types of participants recruited by sites who joined the trial later. Last, TIA patients were recruited much earlier than those with stroke as their index event, which may have implications for both efficacy and risk.

Although TARDIS is large, and definitive and significant results may help drive changes in clinical practice, it will still be necessary to merge individual patient data from TARDIS with other large trials of antiplatelet agents in acute IS and TIA to fully assess their effects in different patient subgroups.

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Figure 3. Histogram of recruitment by time from onset to randomization for: (a) all patients (median 29.3 h), (b) stroke (median 32.0 h), and (c) TIA (median 24.2 h).

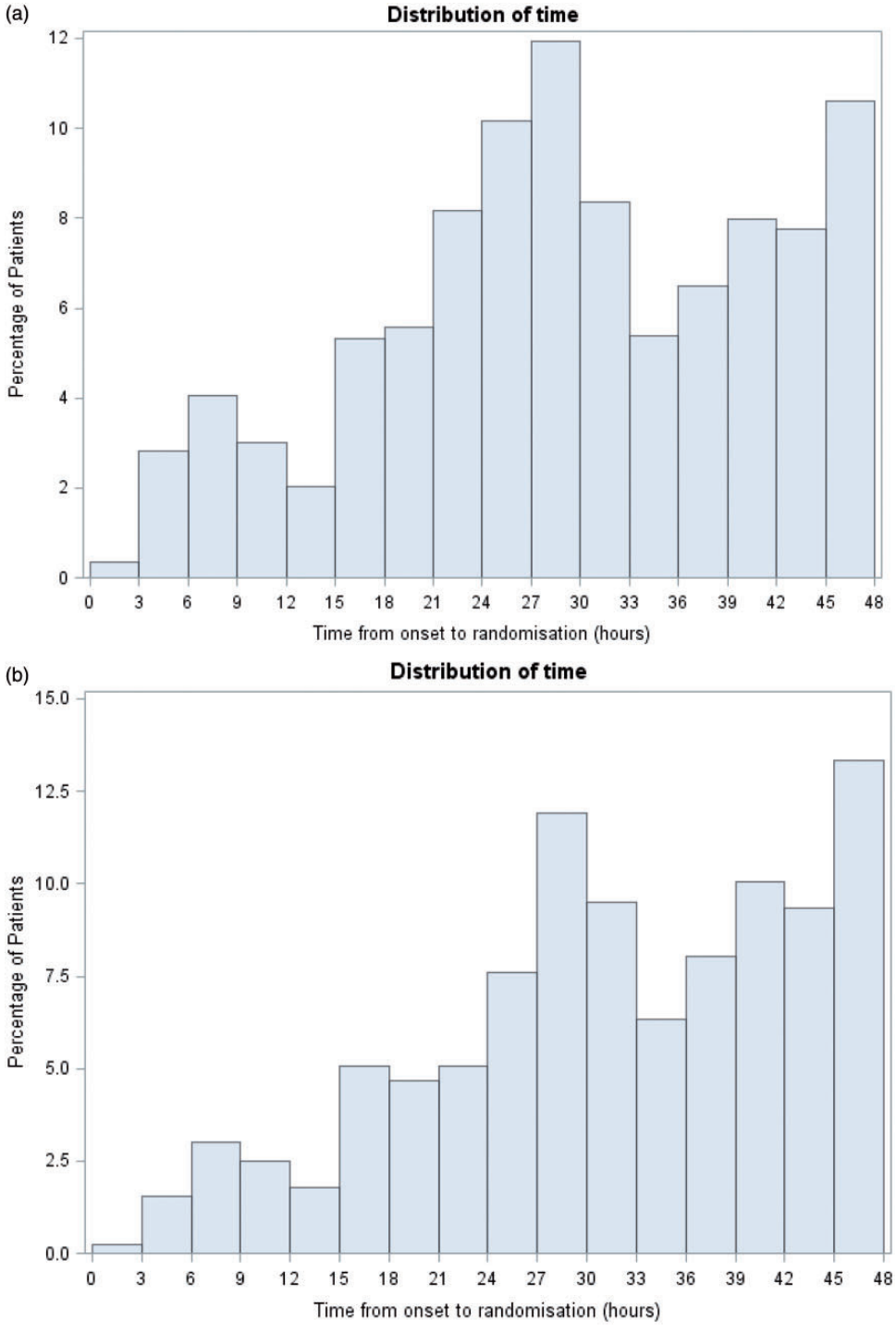

Figure 3. continued.

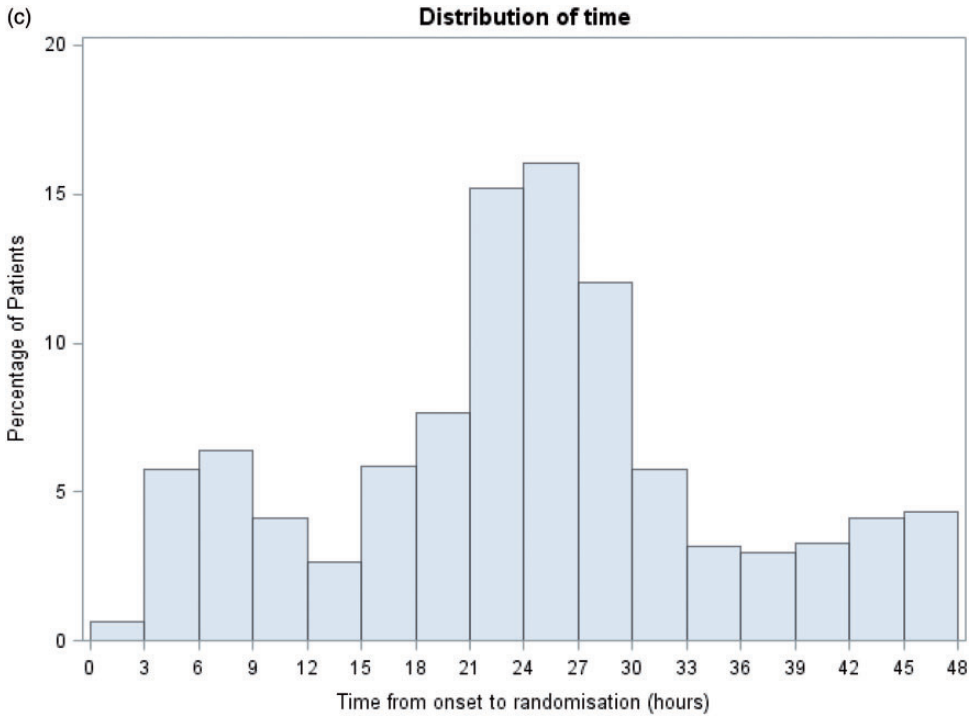

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Table 4. Univariate correlations between baseline characteristics for: age, sex, severity (NIHSS, ABCD2), qualifying event type (IS, TIA), systolic blood pressure (SBP), time to randomization, and year of randomization. Correlations by point biserial or Pearson's tests; data are regression coefficient (*p* value)

	Age	Sex, Male	NIHSS	ABCD2	Event type, Stroke	SBP	Onset to randomization	Year of randomization
Age	X	−0.134(<0.001)	−0.012(0.52)	0.271(<0.001)	−0.079(<0.001)	0.085(<0.001)	−0.023(0.21)	−0.017(0.34)
Sex	−0.134(<0.001)	X	−0.020(0.26)	0.008(0.67)	0.014(0.43)	0.019(0.29)	−0.011(0.56)	−0.012(0.49)
NIHSS	-0.012(0.52)	−0.020(0.26)	X	0.151(<0.001)	0.485(<0.001)	0.039(0.031)	0.167(<0.001)	0.047(0.0084)
ABCD2	0.271(<0.001)	0.008(0.67)	0.151(<0.001)	X	0.196(<0.001)	0.427(<0.001)	0.016(0.38)	0.047(0.0095)
Type	−0.079(<0.001)	0.014(0.43)	0.485(<0.001)	0.196(<0.001)	X	−0.024(0.19)	0.297(<0.001)	0.127(<0.001)
SBP	0.085(<0.001)	0.019(0.29)	0.039(0.031)	0.427(<0.001)	−0.024(0.19)	X	−0.112(<0.001)	0.062(<0.001)
Time	−0.023(0.21)	−0.011(0.56)	0.167(<0.001)	0.016(0.38)	0.297(<0.001)	−0.112(<0.001)	X	0.064(<0.001)
Year	−0.017(0.34)	−0.012(0.49)	0.047(0.0084)	0.047(0.0095)	0.127(<0.001)	0.062(<0.001)	0.064(<0.001)	X

ABCD2: age, blood pressure, clinical features, duration, diabetes; IS: ischemic stroke; NIHSS: National Institutes of Health Stroke Scale; SBP: systolic blood pressure; TIA: transient ischemic attack.

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Sites

The list of participating local investigators, sites and trial coordinating staff is given in online Appendix D.

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