Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial

TITLE

PlAtelet Transfusion versus standard care after acute stroke due to spontaneous Cerebral Haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial

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SUMMARY

Background – Platelet transfusion might reduce death or dependence for people taking antiplatelet therapy who suffer acute spontaneous primary intracerebral haemorrhage (ICH).

Methods – Multicentre, randomised, open, masked endpoint parallel group trial at 60 hospitals in The Netherlands, UK, and France. People were eligible if they were aged ≥18 years, within six hours of supratentorial ICH symptom onset, had used antiplatelet therapy for ≥7 days beforehand, and had a Glasgow Coma Scale score ≥8. Collaborators randomised participants using a secure web-based system (1:1, stratified by hospital and type of antiplatelet therapy) to receive standard care vs. standard care with platelet transfusion within 90 minutes of diagnostic brain imaging. The primary outcome of death or dependence was rated using the modified Rankin Scale (mRS) score at three months masked to treatment allocation, and analysed by ordinal logistic regression analysis of the shift of all categories of the mRS adjusted for stratification variables and the ICH score. We performed the primary analysis in the intention-to-treat population and the safety analysis in the as-treated population. PATCH was registered with the Netherlands trial register (NTR1303) and is now closed.

Findings – Between February 2009 and October 2015, 97 participants were randomised to platelet transfusion and 93 to standard care. The odds of death or dependence at three months were higher after platelet transfusion compared to standard care (adjusted common OR 2·05, 95% CI 1·18 to 3·56, p=0·0114). Safety outcomes (severe adverse events, thrombo-embolic events, and transfusion reactions) were non-significantly more frequent after platelet transfusion.

Interpretation – Platelet transfusion seems inferior to standard care for people using antiplatelet therapy before ICH.

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INTRODUCTION

Haemorrhagic stroke accounts for 11-22% of incident strokes,[1] half of all stroke deaths, and ~47 million (42%) of the disability-adjusted life years lost due to stroke.[2] Spontaneous (non-traumatic) intracerebral haemorrhage (ICH) caused by cerebral small vessel diseases accounts for two-thirds of haemorrhagic stroke,[3] amounting to >2 million incident ICH worldwide each year.

Antiplatelet therapy may slightly increase the incidence of ICH.[4] In high-income countries, more than one quarter of people with incident ICH take antiplatelet therapy before ICH.[5] People taking antiplatelet therapy before ICH have a 27% (95% CI 10 to 47) increase in the odds of death in comparison to people with ICH who had not taken antithrombotic drugs.[6] Observational analyses suggest that pre-ICH antiplatelet therapy use and reduced platelet activity may worsen outcome by increasing the risk of early ICH volume growth,[7] which is an important determinant of outcome.[8]

Platelet transfusion is used prophylactically and therapeutically in many clinical settings, however there is a shortage of randomised trials investigating its effectiveness for active bleeding conditions.[9-11] Published observational studies have reported variable associations with outcome after platelet transfusion for acute ICH in people taking antiplatelet therapy[12-17] and the absence of randomised trials has prevented guidelines from recommending its use.[10,11] Yet platelet transfusion is commonly used in emergency departments, stroke units, and neurosurgical settings for acute ICH associated with antiplatelet therapy use.[18]

Therefore, we performed a randomised controlled trial of platelet transfusion for acute ICH associated with antiplatelet therapy use, in order to test the hypothesis that platelet transfusion would reduce death or dependence compared to standard care by reducing ICH growth.

METHODS

Study design

We performed a multicentre, randomised, open, masked endpoint parallel group trial at 36 hospitals in the Netherlands, 13 hospitals in the United Kingdom, and 11 hospitals in France. The trial was designed and coordinated by the Department of Neurology of the Academic Medical Centre (University of Amsterdam, The Netherlands). We registered the trial with the Netherlands Trial Register (NTR 1303, http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1303), published the trial protocol,[19] and placed case report forms on the trial website (www.strokeamc.nl/patch). We obtained research ethics committee approval from: the Academic Medical Centre Ethics committee (MEC08/006) and each participating hospital in the Netherlands; the Scotland A Research Ethics Committee (10/MRE00/36) in the United Kingdom; and the Comité de Protection des Personnes (CPP 12/43, 2012-A00209-34) in France. The trial was monitored by the Clinical Research Unit of the Academic Medical Centre in the Netherlands, the Clinical Research Unit of the Lille University Hospital in France, and the UK trial manager on behalf of The Academic and Clinical Central Office for Research and Development (www.accord.scot) in the UK.

Participants

Inclusion criteria were: age ≥18 years; non-traumatic supratentorial ICH confirmed by brain imaging; Glasgow Coma Scale score 8-15; platelet transfusion could be initiated within six hours of symptom onset (or last seen well) and within 90 minutes of brain imaging; use of antiplatelet therapy with a cyclooxygenase (COX) inhibitor (aspirin or carbasalate calcium), or adenosine diphosphate (ADP) receptor inhibitor (clopidogrel), or an adenosine reuptake inhibitor (dipyridamole) for at least seven days preceding ICH; and pre-ICH modified Rankin Scale score of 0 (no symptoms) or 1 (no significant disability despite symptoms; able to carry out all usual duties and activities). Exclusion criteria were: blood on brain imaging suggestive to the treating physician of epidural or subdural haematoma, or an underlying aneurysm or arteriovenous malformation; planned surgical evacuation of ICH within 24 hours of admission; intraventricular blood more than sedimentation in the posterior horns of the lateral ventricles; previous adverse reaction to platelet transfusion; known use of vitamin K antagonist (unless INR≤1.3) or history of coagulopathy; known thrombocytopenia $<100x10^9$/L; lacking mental capacity by national legal standards before ICH; or death appeared imminent. We did not include participants with infratentorial or large intraventricular haematomas, because they are more likely to undergo surgical procedures which might confound the effects of platelet transfusion on outcome. Collaborating clinicians on the delegation log at each hospital site recruited participants, and obtained written informed consent from the participant or their legal representative.

Randomisation and masking

Participants were randomly assigned in a 1:1 ratio to receive standard care either with or without platelet transfusion by a secure, web-based, computerised randomisation system that concealed allocation (TENALEA, Clinical Trial Data Management system), stratified by study hospital and type of antiplatelet therapy pre-ICH (COX inhibitor alone, ADP receptor

inhibitor alone, COX inhibitor with an adenosine reuptake inhibitor, or COX inhibitor with an ADP receptor inhibitor). Participants and local investigators giving interventions were not masked to treatment allocation, but outcome assessors and investigators analysing data were masked to treatment allocation.

Procedures

The web-based randomisation system asked investigators to check eligibility criteria and required investigators to record participant age and pre-ICH antiplatelet therapy. Investigators recorded all other participant characteristics at the time of enrolment. Stroke severity was scored on the National Institutes of Health Stroke Scale (NIHSS, ranging 0-42 with higher scores indicating more severe stroke). Brain imaging was performed at admission using either computed tomography (CT) or magnetic resonance imaging (MRI) according to routine clinical practice. All participants received standard care, which was not defined in the protocol, but was assumed to be given according to contemporary European[20] and national guidelines. Leucocyte-depleted platelet transfusions, either buffycoat-derived or collected by apheresis, were supplied by national or regional blood supply organisations, issued by the hospital transfusion laboratory, and administered according to local hospital protocols for transfusion. The protocol required platelet transfusion to be initiated within six hours of ICH symptom onset and within 90 minutes of diagnostic brain imaging. Participants using a COX inhibitor with or without adenosine reuptake inhibitor received one platelet concentrate, whereas participants using an ADP receptor inhibitor with or without another antiplatelet agent received two platelet concentrates. The different dosages of platelet concentrates were chosen based on in-vitro experiments.[21] Investigators recorded whether platelet transfusion started within 0-3 hours or 3-6 hours after symptom onset. Data on paper case report forms were collected at the trial coordinating centre in each country (Amsterdam, The Netherlands;

Edinburgh, UK; and Lille, France). Good Clinical Practice (GCP)-compliant internet-based remote data capture (Oracle Clinical) was used for entering, managing, and validating the data from hospital sites.

Outcomes

The primary outcome was functional outcome at three months scored with the Modified Rankin Scale (mRS, ranging from 0 [no symptoms] to 6 [death]), rated by a neurologist or research nurse, who was trained and masked to treatment allocation and was not involved in participants' medical treatment. Each country's trial coordinating centre organised collection of the primary outcome so that it could be obtained in participants' first language by either structured telephone interview or face-to-face consultation. Secondary clinical outcomes at three months were survival, poor outcome defined as mRS 4-6, and poor outcome defined as mRS 3-6. The secondary explanatory outcome was median absolute ICH growth in mL on repeat brain imaging, using the same modality as the diagnostic study, performed as a trial procedure at 24±3 hours after randomisation. Diagnostic and 24-hour brain imaging studies were obtained in DICOM format from trial sites, anonymised, and analysed centrally in Amsterdam. The images were assessed for ICH location (deep or lobar) and intraventricular extension. We used an automated planimetric method to segment ICH on unenhanced baseline imaging[22] to calculate ICH volume in mL; these measurements were manually checked by MIB masked to treatment allocation and supervised by one of two independent neuroradiologists (CBM, LFB not involved in design and conduct of the trial) and adjusted where necessary. Investigators recorded the occurrence of any serious adverse events and other safety outcomes occurring during hospital admission and the date and destination of discharge. Safety outcomes were complications of platelet transfusion (transfusion reactions, thrombotic complications) and for other severe adverse events the treating physician was

asked to specify the presumed cause as following: due to complications of ICH (ICH enlargement, intraventricular extension, hydrocephalus, oedema, or brain herniation), epileptic seizures, infection (urinary tract or pneumonia), or others that investigators wished to record. Safety outcomes were independently verified with use of discharge letters. We did not perform the planned sub-studies of the spot sign on CT angiography and platelet function testing due to insufficient uptake in standard clinical practice. We did not investigate causes of poor outcome, functional outcome using the AMC Linear Disability score, or health economics due to insufficient funding.

Statistical analysis

The executive committee agreed on a statistical analysis plan with the trial statistician (RdeH) without knowledge of outcome data and before closing and un-masking the trial database; this statistical analysis plan was submitted in concise format to the Netherlands Trial Register on 14 March 2016 (published at www.trialregister.nl/trialreg/admin/rctview.asp?TC=1303 on 30 March 2016), was submitted in full to *Trials* on 21 March 2016, and the trial database was locked and un-masked on 31 March 2016. The statistical analysis plan describes the differences between the protocol and this final report; the principal change was from a fixed dichotomous analysis of the primary outcome (mRS 4-6) to an ordinal logistic regression analysis of the shift of all categories of the mRS, in view of the greater statistical efficiency of this analysis[23] and the hypothesised effect of platelet transfusion to shift all participants somewhat on a functional outcome scale by reduction of ICH growth. We originally based the target sample size of two groups of 95 participants (total 190) on an estimate of 70% frequency of the primary outcome of death or dependence (defined as mRS 4-6) with standard care,[24] a clinically important 20% absolute reduction of this risk to 50% with platelet transfusion (OR 0·43), 80% power and a two-sided level of significance of 0.05. However,

power increases to 91% to detect a common OR of 0·43 in an ordinal logistic regression analysis of all pairs of mRS categories, assuming a distribution of the mRS with standard care that is similar to the control group of a recent ICH trial.[25] We used the intention-to-treat population to describe baseline characteristics, compare the primary outcome using ordinal logistic regression (with adjustment for both the stratification variable of type of pre-ICH antiplatelet therapy as well as the ICH Score as a predictor of outcome after ICH[26]) and the secondary outcomes. Effect sized were expressed as OR with statistical uncertainties as 95% CI. We used both the intention-to-treat and the as-treated populations to compare the safety outcomes. We used parametric statistics when variables obeyed a normal distribution, and non-parametric statistics when they did not. If zero instances were reported, we added 0·5 to each cell to calculate an OR. We conducted three pre-specified subgroup analyses of the modification of the effect of platelet transfusion on the primary outcome using ordinal regression analyses: single vs. dual antiplatelet therapy pre-ICH; country of randomisation (The Netherlands vs. France vs. United Kingdom); and trichotomised ICH volume at baseline (≤7mL vs. >7-30mL vs. >30mL) in order to search for effects in small, medium, and large ICH. We performed a sensitivity analysis of the effect of platelet transfusion on the primary outcome at hospitals that included at least five participants in which we also adjusted for including centre. Analyses were performed using IBM SPSS statistics version 22 (Cleveland, Ohio). An independent data monitoring committee (appendix) oversaw the trial and agreed with the termination of the trial when it reached its pre-specified sample size in October 2015. A separate committee monitored the safety of participants included in France (see appendix).

Role of funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data from the trial and had final responsibility for the results on submission for publication.

RESULTS

Between 4 February 2009 and 8 October 2015, 41 sites enrolled 190 participants, all of whom were randomised, and none withdrew consent (Figure 1). 97 participants were randomly assigned to receive standard care with platelet transfusion (12 had intraventricular extension, two had infratentorial ICH, and one had not used antiplatelet therapy pre-ICH) and 93 were assigned to standard care without transfusion (20 had intraventricular extension and one had thrombocytopaenia $<100x10^9/L$).

The distributions of most baseline characteristics were similar, apart from a history of peripheral arterial disease (Table 1), which was not considered to be of major prognostic relevance to the primary outcome. Of the slightly imbalanced characteristics in the two treatment groups at baseline, some confer a better prognosis (more lobar ICH, fewer with intraventricular haemorrhage and fewer aged >80 years) and others confer a worse prognosis (larger ICH volume and two infratentorial ICH) in participants assigned to platelet transfusion, although median ICH Score was the same in both treatment groups. Baseline imaging was missing for centralised reading for two participants and ICH volume or intraventricular extension could not be measured for six participants because images were degraded by movement artefact.

Four participants assigned to platelet transfusion did not receive it and two participants assigned to standard care received platelet transfusion (Figure 1). Four protocol violations occurred in the platelet transfusion group (two participants did not receive the correct number of platelet concentrates and two received platelet transfusion out of pre-specified time window).

No participants were lost to clinical follow-up at three months and all were included in the final analyses after the last follow-up was completed on 6 January 2016. Follow-up imaging at 24 hours was missing for 17 participants in the platelet transfusion group (three omitted, five died, four performed >27 hours, and five poor quality) and for 20 participants in the control group (nine omitted, four died, two performed >27 hours, and five poor quality).

The odds of death or dependence at three months were higher following platelet transfusion compared to standard care in the intention-to-treat population (Figure 2) in ordinal regression analyses of the entire range of the mRS without adjustment (crude common OR 1·84, 95% CI 1·10 to 3·08, p=0·0200) and with adjustment for type of pre-ICH antiplatelet therapy and baseline ICH score (adjusted common OR 2·05, 95% CI 1·18 to 3·56, p=0·0114). A fixed dichotomous analysis of the secondary outcome of mRS 4-6 at three months gave similar statistically significant results, but there was no significant difference in survival, mRS 3-6, or ICH growth (Table 2). The distribution of the mRS was similar in participants receiving platelet transfusion within 3 hours vs. 3-6 hours of symptom onset (webappendix). There were no significant differences in safety outcomes in the intention-to-treat analyses, just one significant difference (in serious adverse events [SAE] due to ICH) in the as-treated analyses, and only one minor transfusion reaction (Table 3). There was no statistically significant interaction with the effect of platelet transfusion in sub-group analyses (Figure 3). Platelet

transfusion seemed inferior to standard care in a sensitivity analysis restricted to hospitals that included at least five participants (n=125, 65·8%) where the primary outcome was also adjusted for the hospital that included participants (adjusted OR 2·55, 95%CI 1·24 to 5·24, p=0·0107). In post hoc analyses, the primary outcome remained unchanged after also adjusting for ICH volume at baseline (adjusted common OR 1·90, 95% CI 1·08 to 3·36, p=0·0268) and after excluding the 36 participants who met at least one exclusion criterion (adjusted OR 2·22, 95% CI 1·20 to 4·09, p=0·0108).

DISCUSSION

This randomised trial of 190 people who suffered acute ICH while using antiplatelet therapy found that platelet transfusion seemed to increase the risk of death or dependence compared to standard care, that this effect was consistent in pre-defined sub-groups, and remained after adjustment for pre-ICH antiplatelet therapy and known prognostic factors. These surprising findings are contrary to our hypothesis that platelet transfusion would reduce ICH growth and improve functional outcome and are not consistent with small observational studies that have found better outcomes associated with the use of platelet transfusion.[12-14]

The PATCH trial has some strengths. PATCH is the first randomised trial to investigate the effects of platelet transfusion on acute ICH following the use of antiplatelet therapy, and is one of very few randomised trials to investigate the effect of platelet transfusion on active bleeding conditions.[9-11,16,17] In this multicentre trial, the effect of platelet transfusion on the primary outcome was consistent in three European countries, supporting the external validity of the trial (although its generalisability to low-middle income countries is unknown). The baseline characteristics and outcomes of the included participants were similar to previous

randomised trials for acute ICH.[25] Adherence to the assigned treatment was good and clinical follow-up for the primary outcome was complete (Figure 1). The trial achieved its target sample size.

This trial has some limitations. The sample size was small relative to other acute stroke trials, reflecting the incidence of acute stroke due to ICH, its clinical severity,[5] and the demanding eligibility criteria.[27] This small sample size resulted in some chance imbalances in baseline prognostic variables, although their direction of effect was not consistent: some of these imbalances may have biased the platelet transfusion group to a worse outcome and others may have biased it to a better outcome. Our findings could not be easily explained by chance imbalances in baseline characteristics, although residual confounding due to randomisation imbalances is possible especially in light of the small sample size. Most of the participants had taken aspirin and relatively few took ADP inhibitors, so it is unknown whether the findings are generalisable to the increasing numbers of people who take ADP inhibitors. PATCH investigators were not required to keep screening logs, so it is unknown if bias occurred by selective inclusion. Furthermore adherence to antiplatelet therapy for included participants was unknown and we relied on information supplied by the participants, care-givers, or medical charts. Too few hospitals were able to perform platelet function testing to investigate whether this modified treatment effect, as had been suggested by one observational study.[14] As is often the case in pragmatic trials in emergency settings, several participants (36/190 [19%]) met at least one exclusion criterion.[27] In particular, participants with intraventricular extension, more than sedimentation in the posterior horns of the lateral ventricles, were included possibly reflecting difficulty in interpretation of this criterion by clinicians. Because this protocol deviation was not equally distributed between treatment

groups, we performed a post hoc sensitivity analysis excluding these patients, in which the primary outcome remained the same.

These results contrast with the hypothesised mechanism of action of platelet transfusion. We did not find a clear mechanism to explain our findings amongst the reported safety outcomes (Table 3), although there was a non-significant difference in SAEs due to thromboembolism and complications of ICH were more common in the platelet transfusion group. Although we conjecture, it remains possible that some participants actually had haemorrhagic transformation of infarction rather than ICH or it is possible there is impaired collateral perfusion around the ICH resulting in cerebral ischaemia. Platelet transfusion might then increase the risk of thrombosis and result in lesion expansion In a large observational study, platelet transfusions to people with (pro-)thrombotic conditions such as thrombotic thrombocytopenic purpura and heparin induced thrombocytopenia were associated with increased mortality and myocardial infarction compared to non-transfused people.[28] Furthermore platelets have been shown to have pro-inflammatory effects and platelet transfusions may enhance vascular permeability associated with inflammation and platelet consumption.Platelets have also been shown to be activated when stored, resulting in increased pro-thrombotic and inflammatory properties.[29] It is also possible that platelet transfusion might not be beneficial, because the absolute increase in ICH growth associated with antiplatelet therapy is not large enough to be significantly modified by platelet transfusion, or that platelet transfusion is insufficient to reverse the effects of antiplatelet therapy on ICH growth. The majority of effective platelet transfusions are administered for prophylaxis of bleeding often in severe hypoproliferative thrombocytopenia in haemato-oncological patients.[30] The effect of platelet transfusions to stop or reverse ongoing bleeding may be beneficial or deleterious depending on the nature and location of the haemorrhage.

These potential effects, combined with some baseline imbalances, may explain the detrimental effect of platelet transfusion in our trial. However, even if platelet transfusion were not to be detrimental, our findings suggest that it is unlikely to be beneficial.

The implication of our findings for clinical practice is that platelet transfusion cannot be recommended for the treatment of acute ICH in people who had been using antiplatelet therapy and are similar to the participants in the PATCH trial, because platelet transfusion seemed to worsen their outcome. One other similar randomised trial is nearing completion (NCT00699621) and its results are needed to confirm our findings in acute ICH. Given the widespread use of platelet transfusion for other acute bleeding conditions despite a shortage of randomised evidence, the PATCH trial should lead to randomised trials for these other conditions, so that this potentially hazardous and costly intervention is only used for prophylactic or therapeutic indications supported by evidence from randomised controlled trials.

PANEL: RESEARCH IN CONTEXT

Systematic review

Before we initiated the PATCH trial in 2009, searches of clinicaltrials.gov and the Cochrane Central Register of Controlled Trials (CENTRAL) did not reveal published, ongoing, or planned randomised trials of platelet transfusion for acute ICH in people using antiplatelet therapy. On 1 April 2016, we searched MEDLINE (PubMed) from 1 January 1950, EMBASE from 1 January 1947, clinicaltrials.gov, CENTRAL from 1 January 1993 using textwords for platelet transfusion ("platelet" OR "blood platelet" OR "thrombocyte") AND the textword "transfusion" AND terms for ICH AND terms for randomised trials,[31] as well as bibliographies of relevant publications, for randomised trials of platelet transfusion for acute ICH in people using antiplatelet therapy, regardless of language of publication. We found one on-going randomised trial (NCT00699621), and one published randomised trial (dissimilar to PATCH) of platelet transfusion versus aspirin resumption for aspirin-sensitive people with acute basal ganglia ICH undergoing craniotomy.[32]

Added value of this study

This is the only completed randomised trial involving people taking antiplatelet therapy who suffer acute ICH, comparing the effects of platelet transfusion with standard care on functional outcome.

Interpretation of all the available evidence

In the PATCH trial, platelet transfusion seemed inferior to standard care for reducing death or dependence after acute ICH in people taking antiplatelet therapy. Therefore we cannot recommend platelet transfusion for this indication pending the results of another similar ongoing randomised trial.

CONTRIBUTORS

MIB, CC, and RASS coordinated the trial and drafted the manuscript. MIB performed all analyses supervised by YBR and RJdH. CC and RASS obtained funding for the trial and recruited centres and supervised the trial in the United Kingdom and France respectively. KG was involved in the design of the trial, recruitment of participating centres, and coordinated the trial in The Netherlands. MMK was involved in the design of the trial and coordinated availability of platelet transfusion for Dutch centres. CBM and LFB were involved in the design of the study and supervised the performance of all radiological measurements and interpretation. HAM designed the radiological endpoints and was consulted for all technical aspects of analysing the radiological parameters. He supervised and performed importing of all imaging and automated measurements with interpretation. AB and MV were involved in the original design of the trial and critically reviewed the manuscript. PJN and RJdH were involved in the design of the trial, the statistical analyses involved, and critically reviewed the manuscript. YBR designed the trial, obtained funding, recruited centres, and supervised the entire trial.

DECLARATION OF INTERESTS

Prof. Cordonnier reports grants from Programme Hospitalier Recherche Clinique, during the conduct of the study; Prof. Al-Shahi Salman reports grants from Chest Heart and Stroke Scotland, during the conduct of the study; Dr. Nederkoorn reports fee for Advisory work for Metronic regarding AF registration in stroke, used for the AMC stroke reasearch group; and outside the submitted work; Dr. Marquering reports and Cofounder and shareholder of Nico-lab, Prof. Roos reports grants from ZonMW (170881002), grants from Sanquin, during the conduct of the study; All other authors declare no conflicts of interest.

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APPENDICES

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TABLE 1
Baseline characteristics of the intention-to-treat population

	Platelet transfusion (n=97)	Standard care (n=93)
Mean age (range), years	74·2 (49 – 94)	73·5 (40 – 92)
Female sex, n (%)	42/97 (43·3%)	36/93 (38·7%)
Vascular co-morbidities, n (%)		
Ischaemic stroke or TIA	38/94 (40·4%)	40/93 (43·0)
ICH	4/97 (4·1%)	5/92 (5·4%)
Hypertension	68/94 (72·3%)	67/92 (72·8)
Diabetes mellitus	15/97 (15·5%)	17/90 (18·9%)
Hypercholesterolaemia	46/94 (48·9%)	40/84 (47·6)
Ischaemic heart disease	23/96 (23·6%)	22/90 (24·4%)
Peripheral arterial disease	16/97 (16·5%)	4/91 (4·4%)
Coagulation disorder	1/96 (1·0%)	2/91 (2·2%)
Antiplatelet therapy pre-ICH, n (%)[#]		
COX inhibitor alone	71/97 (73·2%)	78/93 (83·9%)
COX inhibitor and dipyridamole	18/97 (18·6%)	13/93 (14·0%)
ADP inhibitor alone	4/97 (4·1%)	1/93 (1·1%)
COX inhibitor and ADP inhibitor	3/97 (3·1%)	1/93 (1·1%)
None	1/97 (1·0%)	0/93 (0%)
Statin therapy pre-ICH, n (%)	54/96 (56·3%)	48/92 (52·1%)
Median GCS score (IQR)	14 (13 – 15)	15 (13 – 15)
Median NIHSS score (IQR)	12 (7 – 19)	13 (7 – 17)
Mean platelet count, x10^9/L (range)	229 (120 – 622)	241 (91 – 461)
Country of inclusion n(%)[#]		
The Netherlands (27 centres)	63 (64·9%)	57 (61·3%)
France (9 centres)	19 (19·6%)	20 (21·5%)
United Kingdom (5 centres)	15 (15·5%)	16 (17·2%)
ICH location, n (%)		
Supratentorial deep	62/96 (64·6%)	70/92 (76·1%)
Supratentorial lobar	32/96 (33·3%)	22/92 (23·9%)
Infratentorial	2/96 (2·1%)	0
Median ICH volume, mL (IQR)	13·1 (5·4 – 42·4)	8·0 (4·4 – 25·8)
Intraventricular extension, n (%)	12/95 (12·6%)	20/92 (21·7%)
Median total ICH score (IQR)*	1 (0 – 2)	1 (0 – 1)
Age >80 years	28 (28·9%)	34 (36·6%)
GCS 5 – 12	19 (19·6%)	11 (11·8%)
3 – 4	1 (1·0%)	0
ICH volume >30ml	32 (34·0%)	19 (20·9%)
Intraventricular extension	12 (12·6%)	20 (21·7%)
Infratentorial ICH location	2 (2·1%)	0

* 3 missing in the platelet transfusion group and 2 missing in the standard care group. [#] Stratification variable. TIA = transient ischaemic attack, ICH = intracerebral haemorrhage, COX = cyclooxygenase, ADP = adenosine diphosphate, GCS = Glasgow Coma Scale, NIHSS = National Institutes of Health Stroke Scale.

TABLE 2
Secondary outcomes in the intention-to-treat population

	Platelet transfusion n=97	Standard care n=93	OR, 95%CI	p-value
Survival at three months, n (%)	66 (68%)	72 (77·4%)	0·62, 0·33 to 1·19	0·15
mRS score 4-6 at three months, n (%)	70 (72·2%)	52 (55·9%)	2·04, 1·12 to 3·74	0·0190
mRS score 3-6 at three months, n (%)	86 (88·7%)	76 (81·7%)	1·75, 0·77 to 3·97	0·18
Median ICH growth at 24 hours, mL (IQR)#	2·01 (0·32 – 9·34)	1·16 (0·03 – 4·42)		0·81

* Median ICH growth tested with use of Mann Whitney U test. mRS = modified Rankin Scale, ICH = intracerebral haemorrhage. # n=80 in platelet transfusion group and 73 in standard care group.

TABLE 3
Safety outcomes occurring during hospital admission in the intention-to-treat and as-treated populations

	Intention-to-treat population			As-treated population		
	Platelet transfusion (n=97)	**Standard care (n=93)**	**OR, 95% CI**	**Platelet transfusion (n=95)**	**Standard care (n=95)**	**OR, 95% CI**
Any SAE, n (%)	41 (42·3)	27 (29·0)	1·79, 0·98 to 3·27	40 (42·1)	28 (29·5)	1·74, 0·96 to 3·17
Any fatal SAE, n (%)	24 (24·7)	15 (16·1)	1·71, 0·83 to 3·51	23 (24·2)	16 (16·8)	1·58, 0·77 to 3·22
SAE due to ICH, n (%)	24 (24·7)	13 (14·0)	2·02, 0·96 to 4·27	24 (25·3)	13 (13·7)	2·13, 1·01 to 4·50
ICH enlargement	15 (15·5)	13 (14·0)	1·13, 0·5 to 2·5	15 (15·8)	13 (13·7)	1·18, 0·53 to 2·64
Brain oedema	5 (5·2)	0	11·1, 0·61 to 204·0	5 (5·3)	0	11·6, 0·63 to 212·9
Brain herniation	2 (2·1)	0	4·90, 0·23 to 103·3	2 (2·1)	0	5·11, 0·24 to 107·8
Intraventricular extension	6 (6·2)	0	13·3, 0·74 to 239·2	6 (6·3)	0	13·9, 0·77 to 249·8
Hydrocephalus	3 (3·1)	2 (2·2)	1·45, 0·24 to 8·89	4 (4·2)	1 (1·1)	4·13, 0·45 to 37·7
SAE due to thromboembolism, n (%)	4 (4·1)	1 (1·1)	3·96, 0·43 to 36·1	4 (4·2)	1 (1·1)	4·13, 0·45 to 37·7
Ischaemic stroke	1 (1·0)	0	2·91, 0·12 to 72·3	1 (1·1)	0	3·03, 0·12 to 75·4
Myocardial infarction	1 (1·0)	1 (1·1)	0·96, 0·06 to 15·5	1 (1·1)	1 (1·1)	1·0, 0·06 to 16·2
Extremity embolism	2 (2·1)	0	4·90, 0·23 to 103·3	2 (2·1)	0	5·11, 0·24 to 107·8
Pulmonary embolism	1 (1·0)	0	2·91, 0·12 to 72·3	1 (1·1)	0	3·03, 0·12 to 75·4
SAE due to transfusion, n (%)						
Non-haemolytic	1 (1·0)	0	2·91, 0·12 to 72·3	1 (1·1)	0	3·03, 0·12 to 75·4
Anaphylactic	0	0		0	0	
Acute lung injury	0	0		0	0	
Post-transfusion purpura	0	0		0	0	
Graft-versus-host disease	0	0		0	0	
Transmitted bacterial infection	0	0		0	0	
SAE due to other causes, n (%)						
Infection (urinary/pulmonary)	14 (14·4)	12 (12·9)	1·14, 0·50 to 2·61	14 (14·7)	12 (12·6)	1·20, 0·52 to 2·74
Epileptic seizures	0	0	-	0	0	-
Other	6 (6·2)	5 (5·4)	1·16, 0·34 to 3·94	7 (7·4)	4 (4·2)	1·81, 0·51 to 6·40

SAE = serious adverse event. Participants could have more than one SAE. Some SAEs were deemed to be due to several causes.

FIGURE 1
Flow diagram of participants' progress through the phases of the PATCH trial

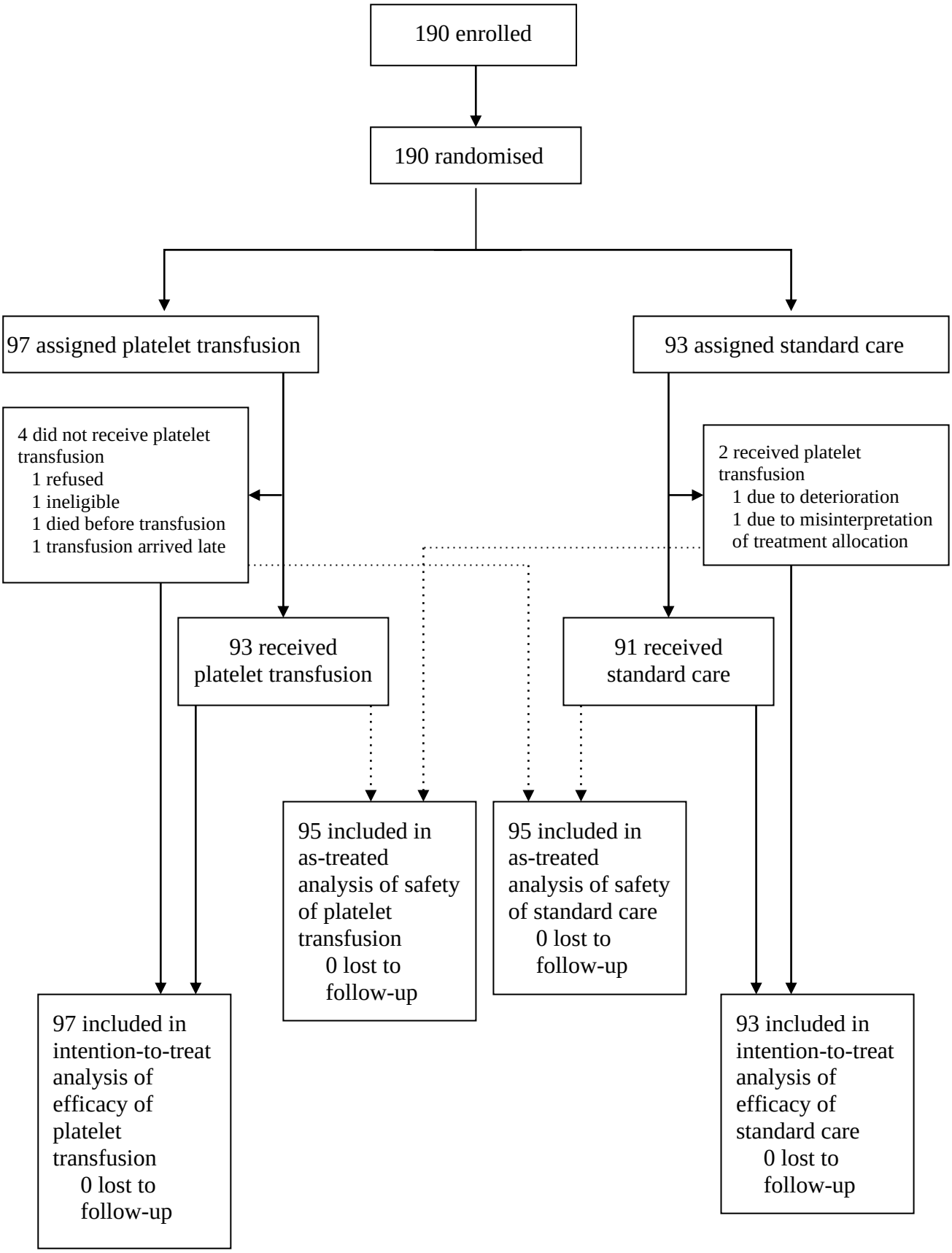

FIGURE 2
The distribution of the primary outcome of the modified Rankin scale (mRS) score at three months after randomisation, showing the number of participants in each category (percentage of each treatment group).

FIGURE 3
Effect of platelet transfusion on the primary outcome of the modified Rankin scale (mRS) score at three months after randomisation, in pre-specified sub-groups, quantified with the unadjusted common odds ratio (OR) and its 95% confidence interval (CI) from ordinal logistic regression analysis (testing interaction variable, adjusted for both component variables) of the shift of all categories of the mRS